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MEETING ABSTRACTS

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Annual Meeting of the
American Society of Clinical Oncology

May 30-June 3, 2025

2025 Annual Meeting Abstracts

(a supplement to *Journal of Clinical Oncology*)

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2025 ASCO Annual Meeting Abstracts

Guide to Abstracts

Letter From the Editor

The *2025 ASCO Annual Meeting Abstracts* (a supplement to *Journal of Clinical Oncology*) is an enduring record of the more than 3,000 abstracts selected by the ASCO Scientific Program Committee for presentation as part of the ASCO Annual Meeting.

Publication-only abstracts are included in the online supplement to the June 1 issue of *Journal of Clinical Oncology* at ASCOPubs.org. Abstracts can be also accessed online through ASCO Meeting Experience (meetings.asco.org). Online abstracts include the full list of abstract authors and their disclosure information. All abstracts carry *Journal of Clinical Oncology* citations, for example:

J Clin Oncol 43:16s, 2025 (suppl; abstr 500).

Should you have any questions or comments about this publication, I encourage you to provide feedback by contacting abstracts@asco.org.

Sincerely,

Ryan D. Gentzler, MD, MS
ASCO Meeting Abstracts Editor, Journal of Clinical Oncology

Yara Abdou, MD
ASCO Meeting Abstracts Associate Editor, Journal of Clinical Oncology

ASCO Abstracts Policy

Public Release of Abstracts

The 2025 ASCO Annual Meeting Abstracts were publicly released by ASCO at 5:00 PM EDT on Thursday, May 22, 2025. Abstracts are publicly available online at asco.org/abstracts. Late-Breaking Abstracts, which include all Plenary Abstracts, will be publicly released according to the following schedule:

- Late-Breaking Abstracts presented in a scientific presentation on Friday, May 30, will be publicly released Friday, May 30, at 8:00 AM EDT.
- Late-Breaking Abstracts presented in a scientific presentation on Saturday, May 31, will be publicly released Saturday, May 31, at 8:00 AM EDT.
- Late-Breaking Abstracts presented in a scientific presentation on Sunday, June 1, will be publicly released Sunday, June 1, at 8:00 AM EDT.
- Late-Breaking Abstracts presented in a scientific presentation on Monday, June 2, will be publicly released Monday, June 2, at 8:00 AM EDT.
- Late-Breaking Abstracts presented in a scientific presentation on Tuesday, June 3, will be publicly released Tuesday, June 3, at 8:00 AM EDT.

In the unlikely event that ASCO publicly releases an abstract in advance of the scheduled time, the release will be publicly announced on https://www.asco.org/annual-meeting/abstracts-presentations/abstract-policies-embargoes-exceptions/embargo-abstract-release.

Conflict of Interest Disclosure

All financial relationships reported by contributors to this activity are provided to learners prior to the start of the activity. During planning and development of the activity, relevant financial relationships were mitigated for all contributors. Relationships are considered self-held and compensated unless otherwise noted (I = Immediate family member; Inst = My Institution). Disclosures are submitted per the ASCO Policy for Relationships with Companies.

LBA1 **Plenary Session**

Randomized trial of standard chemotherapy alone or combined with atezolizumab as adjuvant therapy for patients with stage III deficient DNA mismatch repair (dMMR) colon cancer (Alliance A021502; ATOMIC). First Author: Frank A. Sinicrope, Mayo Clinic Rochester, Rochester, MN

The full, final text of this abstract will be available at meetings.asco.org on the day of presentation and in the online supplement to the June 10, 2025, issue of the *Journal of Clinical Oncology*.

LBA2 **Plenary Session**

NIVOPOSTOP (GORTEC 2018-01): A phase III randomized trial of adjuvant nivolumab added to radio-chemotherapy in patients with resected head and neck squamous cell carcinoma at high risk of relapse. First Author: Jean Bourhis, CHUV, Bâtiment Hospitalier, Lausanne, Switzerland

The full, final text of this abstract will be available at meetings.asco.org on the day of presentation and in the online supplement to the June 10, 2025, issue of the *Journal of Clinical Oncology*.

LBA3 **Plenary Session**

Results from VERIFY, a phase 3, double-blind, placebo (PBO)-controlled study of rusfertide for treatment of polycythemia vera (PV). First Author: Andrew Tucker Kuykendall, Moffitt Cancer Center, Tampa, FL

The full, final text of this abstract will be available at meetings.asco.org on the day of presentation and in the online supplement to the June 10, 2025, issue of the *Journal of Clinical Oncology*.

LBA4 **Plenary Session**

Camizestrant + CDK4/6 inhibitor (CDK4/6i) for the treatment of emergent *ESR1* mutations during first-line (1L) endocrine-based therapy (ET) and ahead of disease progression in patients (pts) with HR+/HER2– advanced breast cancer (ABC): Phase 3, double-blind ctDNA-guided SERENA-6 trial. First Author: Nicholas C. Turner, Royal Marsden Hospital, London, United Kingdom

The full, final text of this abstract will be available at meetings.asco.org on the day of presentation and in the online supplement to the June 10, 2025, issue of the *Journal of Clinical Oncology*.

LBA5 **Plenary Session**

Event-free survival (EFS) in MATTERHORN: A randomized, phase 3 study of durvalumab plus 5-fluorouracil, leucovorin, oxaliplatin and docetaxel chemotherapy (FLOT) in resectable gastric/gastroesophageal junction cancer (GC/GEJC). First Author: Yelena Y. Janjigian, Gastrointestinal Oncology Service, Memorial Sloan Kettering Cancer Center, New York, NY

The full, final text of this abstract will be available at meetings.asco.org on the day of presentation and in the online supplement to the June 10, 2025, issue of the *Journal of Clinical Oncology*.

100 Clinical Science Symposium

Performance evaluation of a reflex blood-based methylated ctDNA multi-cancer early detection test in individuals with obesity. First Author: Dax Kurbegov, Sarah Cannon Research Institute, Nashville, TN

Background: Obesity increases risk of 13 distinct cancers, most without screening programs, and collectively representing 40% of all annual US cancer diagnoses.With recent CDC data (2023) showing that obesity rates exceed 35% in 23 U.S. states, multi-cancer early detection (MCED) testing represents a unique opportunity to address a critical screening gap in this population. In this case-control study, we examined the performance of a reflex blood-based ctDNA methylation MCED test in individuals with obesity (BMI $\geq$ 30 kg/m^2), evaluating cancer-specific intrinsic accuracy (sensitivity) and positive predictive value (PPV). **Methods:** We analyzed peripheral blood samples (NCT05435066) from individuals with obesity, including 424 treatment-naïve cancer patients and 458 non-cancer controls, using a reflex test by Harbinger Health. The test system consists of a primary methylome profiling test optimized for high sensitivity (rule-out), followed by a confirmatory reflex analysis utilizing an expanded methylation panel designed to achieve high PPV (rule-in) and tissue of origin (TOO) classification. Test performance metrics were derived using 10-fold cross-validation with patient-level stratification. Overall cancer incidence in the obese population was estimated at 1.6%. Prospective PPV for each TOO readout was calculated using cancer-specific intrinsic accuracy estimated from the case-control study in combination with incidence values. **Results:** In this cohort (mean age 57.1 $\pm$ 13.4 years; 63.3% female; 67.8% White; 22.4%, Black or African American), the test achieved an overall 29.7% (95CI, 25.3-34.6) correct-TOO sensitivity (66.1% false negative, 4.2% incorrect TOO) at 98.9% (95CI, 97.6-99.6) specificity and 98.9% negative predictive value (95CI, 98.85,99.0). Among a subset of cancers associated with obesity, TOO-specific PPVs were: hepatobiliary (HB: liver, biliary duct; 100%; 95CI, ND), CRC (87.5; 95CI, 61.1-96.9), upper gastrointestinal (UGI; 81.8; CI95, 48.6-95.5), uterine (66.7%; 95CI, 26.5-91.7), pancreaticobiliary (PB: pancreas, gallbladder; 17.6%; 95CI 3.1-59.0). Corresponding cancer group sensitivities (early stage, I-II) were: HB 50.0 (35.1), CRC 51.9 (28.6), UGI 40.9 (9.1), uterine 8.5 (3.8), PB 56.5 (25.0). In a modeled cohort of 100,000 tested individuals, the expected TOO readout counts (correct case-type odds) were: 23 for HB (23:0), 60 for CRC (7:1), 42 for UGI (9:2), 23 for uterine (2:1), 279 for PB (1:5). **Conclusions:** Inindividuals with obesity at increased risk for multiple cancers, especially those lacking established screening guidelines, the reflex ctDNA methylation MCED test demonstrated clinically meaningful PPV and early-stage sensitivity for each cancer type. These results warrant prospective validation to assess the test's clinical validity and utility in early-stage cancer detection in this high-risk population. Research Sponsor: None.

101 Clinical Science Symposium

Prognostic significance of blood-based multi-cancer detection in circulating tumor DNA (ctDNA): 5-year outcomes analysis. First Author: Robert Charles Swanton, Cancer Evolution and Genome Instability Laboratory, The Francis Crick Institute, London, United Kingdom

Background: In the case-control Circulating Cell-free Genome Atlas (CCGA) study (NCT02889978), a multi-cancer early detection (MCED) test was developed that uses next-generation sequencing to detect a cancer signal shared across $>$ 50 cancer types using ctDNA in blood. The concentration of ctDNA in blood is associated with cancer aggressiveness and prognosis. Previous analysis of participant outcomes in the second (cross-validation) CCGA substudy evaluated the prognostic value of cancer signal detection by an early version of the MCED test with 3-year follow-up. Participants with confirmed cancer and no cancer signal detected (NCSD) MCED test result had better 3-year survival than those with a cancer signal detected (CSD). In the present analysis, we evaluated the prognostic value of cancer signal detection by a refined version of the MCED test in the third (validation) CCGA substudy (CCGA3) using an updated statistical methodology with 5-year follow-up, a typical timeframe for cancer-survivor status. **Methods:** Participant blood samples collected during CCGA3 were analyzed using the MCED test. Participants with confirmed cancer were followed for up to 5 years and their overall survival stratified by cancer signal detection (CSD/NCSD). Observed survival was compared to the expected survival of a reference population calculated using Surveillance, Epidemiology, and End Results (SEER) data matched to the distribution of age, sex, cancer type, and stage in each signal detection group. A one-sample proportional hazard model was used to assess differences between observed and expected survival based on cancer signal detection status. **Results:** Follow-up data were available for 2475/2513 (99%) of participants with stageable, invasive cancer. Of these, 792 (32%) died during follow-up, 673/792 (85%) of whom had a CSD; of the 1683 (67%) participants alive at follow-up, 579/1683 (35%) had a CSD. Overall observed survival rates of both groups were higher than the expected survival rates based on SEER data matched for known clinical factors (43% vs 40% [CSD]; 88% vs 81% [NCSD]). Observed vs expected survival rates for participants with: stage I cancer were 66% vs 71% (CSD) and 90% vs 85% (NCSD); stage II cancer were 64% vs 67% (CSD) and 92% vs 83% (NCSD); stage III cancer were 48% vs 42% (CSD) and 79% vs 66% (NCSD); stage IV cancer were 22% vs 16% (CSD) and 56% vs 32% (NCSD). Overall HR for NCSD vs CSD across all stages was 0.60 (95% CI: 0.50-0.72; P = 6.18e-09). HRs for signal detection group vs SEER reference populations were $<$ 1 at all stages with NCSD; with CSD, HRs were $<$ 1 at stages III and IV and $\geq$1 at stages I and II. **Conclusions:** In CCGA3, 5-year follow-up confirmed that while CSD was associated with hazard of death, early-stage cases had long-term survival close to expected rates. These results suggest that a CSD MCED test result may inform prognosis and urgency of treatment. Clinical trial information: NCT02889978. Research Sponsor: GRAIL, Inc.

102 Clinical Science Symposium

A phase 1 study of intracerebroventricular (ICV) delivery of bivalent chimeric antigen receptor (CAR) T-cells targeting EGFR and IL13Ra2 in patients with recurrent glioblastoma (rGBM). First Author: Stephen Joseph Bagley, University of Pennsylvania, Philadelphia, PA

Background: Outcomes in patients with rGBM are poor, with historical median overall survival (OS) of 6-9 months. Here we report the results from the dose exploration phase of a phase 1 trial investigating ICV-delivered, bivalent CAR T-cells targeting EGFR epitope 806 and IL13Rα2 in rGBM. **Methods:** Patients with EGFR-amplified GBM that was recurrent/progressive following front-line radiotherapy were enrolled using a 3+3 design (dose levels: 5.0 x 10^6, 1.0 x 10^7, and 2.5 x 10^7 cells). Patients underwent surgery for (1) maximal safe resection and confirmation of viable tumor and (2) Ommaya reservoir placement. Post-operatively, patients received a single ICV dose of CART-EGFR-IL13Rα2 cells without lymphodepleting chemotherapy. Primary endpoints included dose-limiting toxicity (DLT) and determination of the maximum tolerated dose (MTD). Secondary endpoints included objective radiographic response, progression-free survival (PFS), and OS. Serial CSF samples were analyzed for CAR T-cell pharmacokinetics and single-cell RNA sequencing (scRNAseq). **Results:** Eighteen patientsreceived CART-EGFR-IL13Rα2 cells (n=6 per dose level). Median age was 57, 15 (83%) were male, 13 (72%) had MGMT unmethylated tumors, and 7 (39%) had $>$1 prior relapse. One DLT (grade 3 lethargy/fatigue) was observed at the MTD (2.5 x 10^7 cells). Acute neurotoxicity related to CAR T-cells occurred in all patients. Using immune effector cell-associated neurotoxicity syndrome (ICANS) grading, 10 of 18 patients (56%) experienced grade 3 neurotoxicity; none had grade 4-5 neurotoxicity. Using tumor-inflammation associated neurotoxicity (TIAN) grading, 2 of 18 patients (11%) had grade 3 and 1 patient (6%) had grade 4 neurotoxicity. Grade 1-2 fever occurred in all patients. Eleven of 13 patients (85%) with measurable disease at time of CAR T-cell infusion experienced tumor shrinkage, ranging from 1-62% reductions (median 35%, IQR 12 – 39%) in target lesions and with one confirmed partial response by modified RANO criteria. PFS and OS continue to mature and will be presented. CAR T-cell expansion in CSF was robust with a dose-response relationship observed. The CAR transgene remained detectable in CSF and blood 12 months post-CART infusion in a patient experiencing durable stable disease lasting for 17 months (ongoing at data cut-off). In patients undergoing repeat resection following treatment, CART-EGFR-IL13Rα2 cell infusion markedly increased the number of tumor-infiltrating lymphocytes. scRNAseq in post-treatment CSF revealed higher cytotoxicity and exhaustion scores in CD8+ CAR T-cells as compared to the infusion product, indicative of target cell engagement. **Conclusions:** ICV delivery of CART-EGFR-IL13Rα2 is feasible and appears safe. CART-EGFR-IL13Rα2 cells are bioactive and exhibit an encouraging early efficacy signal in rGBM. Clinical trial information: NCT05168423. Research Sponsor: Kite Pharma (a Gilead company).

103 Clinical Science Symposium

Neoadjuvant biomarker trial of pepinemab to enhance nivolumab or ipilimumab activity in resectable head and neck cancer. First Author: Conor Ernst Steuer, Emory University, Atlanta, GA

Background: Neoadjuvant treatment with immune checkpoint blockade (ICB) improves clinical benefit in patients with multiple types of cancers. Window of opportunity studies permit integrated assessments of safety and efficacy, including biomarker assessments of treatment effects and mechanisms of resistance in the tumor microenvironment. SEMA4D blocking antibody, pepinemab (pepi), has been reported to overcome resistance mechanisms including immune exclusion and myeloid suppression in preclinical and clinical studies. We conducted a neoadjuvant integrated biomarker study (NCT03690986) to evaluate the effect of pepi alone and in combination with ICB on the immune profile in the tumor and blood of patients with resectable head and neck squamous cell carcinoma (HNSCC). **Methods:** Patients were randomized to receive one dose of either pepi alone, pepi/ipilimumab (ipi), pepi/nivolumab (nivo), ipi, nivo (n = 6 patients/group), or no treatment (n = 4); followed by surgery within days 17-36. The primary objective is biomarker assessments; clinical endpoints include pathologic response (pMR), safety, surgical delays, RFS, and OS. Analysis of pretreatment and surgically resected tissue and blood to evaluate spatial distribution of tumor and immune populations employed high dimensional 36+ multiplex IHC and 32-color flow cytometry. Biomarker results were stratified by demographic and clinical outcome measures. **Results:** Thirty-four patients were enrolled (median age 63 (58-69); 70.6% male; 79.4% OC, 20.6% OP; 82.4% HPV/p16 Neg). All patients proceeded to surgery without delay; no additional or unexpected TRAEs were observed in pepi combinations; 9/10 patients who experienced TRAEs were Grade 1-2. Biomarker analysis was stratified by HPV status due to vast difference between highly infiltrated HPV+ compared to immunologically cold HPV- TME. Among 24 available HPV-resected tumors,an increase in the number of intratumoral tertiary lymphoid structures (TLS) was observed in pepinemab containing cohorts, whereas B cells lined the tumor edge and were generally excluded from tumor bed in cohorts lacking pepinemab. A significant increase in density of mature TLS (including CD21+ follicular DC and CD23+ germinal center B cells) was observed in patients treated with pepi+nivo compared with pepi or nivo alone and untreated patients. This finding was unexpected, as mature TLS are generally rare in poorly immunogenic HPV-negative HNSCC. Clinical assessments of pathologic response and RFS are being analyzed. **Conclusions:** Neoadjuvant treatment with pepi enhanced the density and maturity of TLS deep within the tumor which was most prominent in combination with nivo notably in HPV-negative disease. Pepi represents a novel strategy to boost tumor immunity and organization of functional TLS to overcome limitations of ICB in HPV- HNSCC. Clinical trial information: NCT03690986. Research Sponsor: Winship Cancer Institute of Emory University, Atlanta, GA.

104 Clinical Science Symposium

Efficacy and safety of IBI363 monotherapy or in combination with bevacizumab in patients with advanced colorectal cancer. First Author: Zhenyu Lin, Cancer Center, Union Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China

Background: The prognosis of patients (pts) with microsatellite stable/proficient mismatch repair (MSS/pMMR) colorectal cancer (CRC) who failed standard chemotherapy is poor, highlighting a significant unmet need. No immune-oncology therapy has succeeded in this indication due to the "cold" tumor nature. IBI363 is a PD-1/IL-2$^{\alpha\text{-bias}}$ bispecific antibody fusion protein that blocks PD-1 and stimulates tumor-specific T cells that could potentially turn "cold" tumors into "hot" tumors. **Methods:** The analysis of efficacy and safety data were from 68 pts treated with IBI363 monotherapy and 73 pts treated with IBI363 plus bevacizumab (beva), respectively. Eligible pts were locally advanced unresectable or metastatic CRC who failed or were intolerant to the standard treatment. Data cutoff date was Dec 6, 2024. **Results:** A total of 68 pts and 73 pts (None were confirmed as microsatellite instability-high/deficient mismatch repair [MSI-H/dMMR]; MSS/pMMR: 86.8% and 90.4%; unknown microsatellite/MMR status: 13.2% and 9.6%; liver metastases: 61.8% and 54.8%; *KRAS/NRAS* mutations: 42.6% and 41.1%; previous treatment lines ≥ 3: 63.2% and 53.4%; previous immunotherapy: 27.9% and 16.4%) were treated with IBI363 monotherapy (0.1 mg/kg to 3 mg/kg every week [QW], every 2 weeks [Q2W] or every 3 weeks [Q3W]) and IBI363 plus beva (0.6 or 1 mg/kg Q2W, 1.5, 2 or 3 mg/kg Q3W, plus beva 5 mg/kg Q2W or 7.5 mg/kg Q3W), respectively. Median follow-up time was 11.8 months (range: 0.4–22.5) for monotherapy and 5.1 months (range: 1.2–14.9) for combination. In efficacy-evaluable pts (n = 63 for monotherapy and n = 68 for combination), the objective response rate (ORR) was 12.7% (95% confidence interval [CI]: 5.6–23.5) and 23.5% (95% CI: 14.1–35.4). The median duration of response was 7.5 months (95% CI: 1.2–19.6) for monotherapy and not mature for combination. The median OS was 16.1 months (95% CI: 10.1–not reached) for monotherapy and not mature for combination. Especially, in pts without liver metastasis who received the combination therapy (n = 31), the ORR was 38.7% (95% CI: 21.9–57.8), the DCR was 83.9% (95% CI: 66.3–94.6), and median PFS was 9.6 months (95% CI: 4.1–12.2). Grade ≥ 3 treatment-related adverse events were reported in 16 (23.5%) pts with monotherapy and 22 (30.1%) pts with combination. Arthralgia, rash, and thyroid disorders were commonly reported immune-related adverse events. **Conclusions:** IBI363 monotherapy demonstrated prolonged overall survival in pts with advanced CRC compared to historic data of standard of care. IBI363 plus beva showed even more encouraging efficacy with acceptable safety and warrants further development. Clinical trial information: NCT05460767. Research Sponsor: None.

105 Clinical Science Symposium

Safety and efficacy of ABBV-706, a seizure-related homolog protein 6 (SEZ6)–targeting antibody-drug conjugate, in high-grade neuroendocrine neoplasms. First Author: Alissa Jamie Cooper, Department of Thoracic Oncology, Memorial Sloan Kettering Cancer Center, New York, NY

Background: SEZ6 is a potential neuroendocrine lineage marker that is expressed in small cell lung cancer (SCLC) and high-grade neuroendocrine neoplasms (NENs). NENs have a significant unmet need for novel effective targeted therapies. ABBV-706, a unique antibody-drug conjugate comprising a SEZ6-directed antibody conjugated to a potent topoisomerase 1 inhibitor payload, is being evaluated in a phase 1 study (NCT05599984) in patients (pts) with advanced solid tumors. Preliminary results from ABBV-706 monotherapy dose escalation showed a manageable safety profile with promising efficacy in SCLC and NENs (*J Clin Oncol* 2024;42[suppl 16]: abs 3001). Herein, updated safety and efficacy of ABBV-706 monotherapy in NENs are presented. **Methods:** Pts (≥18 yr) with relapsed/refractory high-grade NENs (well-differentiated grade [G] 3 neuroendocrine tumors [G3 NETs] and poorly differentiated neuroendocrine carcinomas [NECs]), atypical lung carcinoid, and medullary thyroid cancer (MTC) were enrolled in dose-escalation and -expansion cohorts of a phase 1, open-label study. Pts received ABBV-706 monotherapy IV at 1.3–3.5 mg/kg once every 3 weeks. Primary study objectives are assessment of safety, PK, and efficacy. SEZ6 expression is evaluated retrospectively. **Results:** As of Aug 27, 2024, 191 pts were enrolled overall, including 64 with NENs. In the NEN cohort, median age was 63 yr (range 33–86) and pts had received a median of 3 (range 1–8) prior therapies. NEN histologies were large cell NEC (LCNEC; 22%, n=14), gastro-enteropancreatic NEC (GEPNEC; 19%, n=12), MTC (9%, n=6), neuroendocrine prostate carcinoma (NEPC; 8%, n=5), G3 NETs (8%, n=5), and other NECs (34%, n=22). The safety profile for ABBV-706 was similar across NEN subtypes and aligned with the entire study population. For the overall study population, TEAEs occurred in 184 (96%) pts and G≥3 in 134 (70%). Most frequent hematologic TEAEs were anemia (58%; G≥3: 45%), neutropenia (44%; G≥3: 33%), and thrombocytopenia (35%; G≥3: 21%). Most frequent nonhematologic TEAEs were fatigue (45%; G≥3: 3%) and nausea (38%; G≥3: 2%). Unadjudicated pneumonitis/interstitial lung disease rate was 4% (G≥3 in 2 pts). For the entire NEN cohort, the objective response rate (ORR) was 31.3% (20/64) and the clinical benefit rate was 92.2% (59/64). ORR by NEN type was: LCNEC, 28.6% (4/14); GEPNEC, 16.7% (2/12); NEPC, 60.0% (3/5); G3 NET, 60% (3/5); MTC, 16.7% (1/6); other NEC, 31.8% (7/22). The median duration of response was 5.59 mo (95% CI: 4.24, not estimable) and median progression-free survival was 6.80 mo (95% CI: 5.45, 7.75). Correlation analysis of efficacy with SEZ6 expression is ongoing. **Conclusions:** ABBV-706 showed preliminary efficacy in several high-grade NENs with a high unmet need, supporting its further development in specific subtypes. Clinical trial information: NCT05599984. Research Sponsor: AbbVie Inc.; n/a

106 Clinical Science Symposium

Phase 1 study of SHR-1826, a c-MET–directed antibody-drug-conjugate (ADC), in advanced solid tumors. First Author: Yang Zhang, Sun Yat-sen University Cancer Center, Guangzhou, China

Background: MET alterations are key drivers of diverse oncogenic processes, including tumor invasion, growth, and metastasis, and are associated with poor prognosis. SHR-1826 is a novel ADC of a humanized c-MET-directed IgG2 monoclonal antibody attached to a topoisomerase I inhibitor payload via a tetrapeptide-based cleavable linker. We conducted a multi-center, first-in-human, phase 1 trial of SHR-1826 in advanced solid tumors, and here report preliminary results from the dose-escalation and expansion portions. **Methods:** Patients (pts) with advanced solid tumors harboring MET alterations (overexpression, amplification, or activating mutation) who had failed standard therapy or no available standard therapy, were enrolled. The study consisted of dose-escalation (i3+3 design), dose-expansion and efficacy-expansion phases, during which pts received SHR-1826 at 2.2–6.0 mg/kg, Q3W, iv. Primary objectives were to assess safety and tolerability. **Results:** As of Dec.5, 2024, 116 pts were enrolled and treated (NSCLC/CRC/GC/PC, n=72/32/10/2; median age, 59.2 yrs; ECOG PS 1, 87.9%; ≥3 lines of prior therapy, 44.0%; median c-MET H-score, 163 [range 9-300]). During dose-escalation, 1 DLT was observed at 6.0 mg/kg (grade 3 febrile neutropenia). Grade ≥3 TRAEs were reported in 56 (48.3%) pts, with the most common being decreased neutrophil count (32.8%), decreased white blood cell count (22.4%), anaemia (13.8%), and decreased platelet count (11.2%). Interstitial lung disease occurred in 3 (2.6%; grade 1-2, n=2; grade 3, n=1) pts. 2 (1.7%) pts discontinued treatment due to TRAE. There were no treatment-related deaths. Among 58 evaluable pts with NSCLC, ORR was 39.7% (95% CI 27.0–53.4) and DCR was 94.8% (95% CI 85.6–98.9; Table 1); response was observed across a range of c-MET expression levels, and in both *EGFR*-mutated and wild-type tumors. Median duration of response was not reached, with 21 of 23 responses ongoing. In all 72 NSCLC pts, median progression-free survival was 6.8 mo (95% CI 4.5–7.2). **Conclusions:** SHR-1826 demonstrated a manageable safety profile in pts with heavily pretreated advanced solid tumors. Promising anti-cancer activity was observed in MET-altered NSCLC, warranting further investigation in this population. Clinical trial information: NCT06094556. Research Sponsor: Jiangsu Hengrui Pharmaceuticals Co., Ltd.

Efficacy in pts with NSCLC.

	2.2 mg/kg (n=2)	4 mg/kg (n=24)	5 mg/kg (n=31)	6 mg/kg (n=1)	All patients (n=58)
Best overall response, n (%)					
Complete response	0	0	0	0	0
Partial response*	0	9 (37.5)	13 (41.9)	1 (100.0)	23 (39.7)
Stable disease	2 (100.0)	14 (60.9)	16 (51.6)	0	32 (55.2)
Progressive disease	0	0	2 (6.5)	0	2 (3.4)
Not evaluable	0	1 (4.2)	0	0	1 (1.7)
ORR*, % (95% CI)	0.0 (0.0–84.2)	37.5 (18.8–59.4)	41.9 (24.5–60.9)	100.0 (2.5–100.0)	39.7 (27.0–53.4)
DCR, % (95% CI)	100.0 (15.8–100.0)	95.8 (78.9–99.9)	93.5 (78.6–99.2)	100.0 (2.5–100.0)	94.8 (85.6–98.9)

Data are shown for pts with ≥1 post-baseline assessment.
*Including 6 unconfirmed responses across groups.

107 Clinical Science Symposium

Phase 1 trial of SHR-A2102, a nectin-4–directed antibody drug conjugate (ADC), in advanced solid tumors. First Author: Runbo Zhong, Shanghai Chest Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai, China

Background: Nectin-4 is a cell adhesion molecule that is highly expressed in a wide variety of cancers and is associated with poor prognosis. SHR-A2102 is a novel ADC consisting of a fully humanized Nectin-4–directed monoclonal antibody, bound to topoisomerase I inhibitor payload via a cleavable linker. We conducted a multi-center, phase 1 trial to evaluate SHR-A2102 in advanced solid tumors. **Methods:** Patients (pts) with Nectin-4 positive, locally advanced unresectable or metastatic solid tumors were enrolled. The study included dose-escalation (D-ESC), dose-expansion (D-EXP) and efficacy-expansion (E-EXP) phases. SHR-A2102 was given IV at 2–10 mg/kg, Q3W during D-ESC, and at 6 mg/kg and 8 mg/kg Q3W during D-EXP and E-EXP. The primary objectives were to assess safety and tolerability. **Results:** As of Dec. 20, 2024,369 pts were enrolled and treated (median age, 59 y; ECOG PS 1, 85.6%; ≥2 lines of prior therapy, 64.0%). During D-ESC, DLT occurred in 1 pt (10 mg/kg; grade 4 decreased platelet count). Overall, grade ≥3 TRAEs occurred in 167 (45.3%) pts, with the most common (≥3%) being decreased neutrophil count (25.5%), decreased white blood cell count (16.3%), anaemia (11.7%), decreased lymphocyte count (8.7%), decreased platelet count (4.9%), asthenia (3.5%) and nausea (3.3%). 2 (0.5%) pts discontinued treatment due to TRAE. ILD occurred in 1 (0.3%; grade 3) pt. In 304 evaluable pts for response, ORR was 35.2% (95% CI 29.8-40.9) and DCR was 84.2% (95% CI 79.6-88.1). As of data cutoff, 146 (39.6%) pts had disease progression or died; median PFS was 4.7 mo (95% CI 4.3-5.6). Efficacy in selected tumor types is shown in Table. **Conclusions:** SHR-A2102 demonstrated a manageable safety profile and promising activity across a variety of pretreated advanced solid tumors. Multiple trials are ongoing to further assess SHR-A2102 both as monotherapy and in combination therapy for solid tumors. Clinical trial information: NCT05701709. Research Sponsor: Jiangsu Hengrui Pharmaceuticals.

Efficacy in selected tumor types (efficacy evaluable set).

	EGFR-mut Nsq NSCLC (N=69)	*EGFR*-wt Nsq NSCLC (N=44)	Sq NSCLC (N=44)	HR+/HER2-BC (N=20)	TNBC (N=32)	HNSCC (N=12)	All patients† (N=304)
Best overall response, n (%)							
CR*	0	1 (2.3)	0	0	0	0	1 (0.3)
PR*	30 (43.5)	10 (22.7)	11 (25.0)	13 (65.0)	18 (56.3)	6 (50.0)	106 (34.9)
SD	28 (40.6)	21 (47.7)	33 (75.0)	4 (20.0)	9 (28.1)	5 (41.7)	149 (49.0)
PD	11 (15.9)	11 (25.0)	0	3 (15.0)	5 (15.6)	1 (8.3)	47 (15.5)
Not evaluable	0	1 (2.3)	0	0	0	0	1 (0.3)
ORR*, % (95% CI)	43.5 (31.6-56.0)	25.0 (13.2-40.3)	25.0 (13.2-40.3)	65.0 (40.8-84.6)	56.3 (37.7-73.6)	50.0 (21.1-78.9)	35.2 (29.8-40.9)
DCR, % (95% CI)	84.1 (73.3-91.8)	72.7 (57.2- 85.0)	100.0 (92.0-100.0)	85.0 (62.1-96.8)	84.4 (67.2-94.7)	91.7 (61.5-99.8)	84.2 (79.6-88.1)
PFS‡, mo (95% CI)	5.7 (5.1-NR)	4.3 (2.0-7.3)	4.5 (4.1-6.8)	5.6 (4.3-NR)	5.6 (4.3-7.1)	6.8 (2.4-6.8)	4.7 (4.3-5.6)

*Include responses to be confirmed.
†Other tumor types include ESCC, PAAD, CRC, CC and UC.
‡Evaluated in full analysis set (n=369).

LBA500 **Oral Abstract Session**

De-escalated neoadjuvant taxane plus trastuzumab and pertuzumab with or without carboplatin in HER2-positive early breast cancer (neoCARHP): A multicentre, open-label, randomised, phase 3 trial. First Author: Hong-Fei Gao, Department of Breast Cancer, Cancer Center, Guangdong Provincial People's Hospital (Guangdong Academy of Medical Sciences), Southern Medical University, Guangzhou, China

The full, final text of this abstract will be available at meetings.asco.org on the day of presentation and in the online supplement to the June 10, 2025, issue of the *Journal of Clinical Oncology*.

501 **Oral Abstract Session**

Predicting pathologic complete response (pCR) from clinicopathologic variables and HER2DX genomic test in stage II/III HER2+ breast cancer treated with taxane, trastuzumab, and pertuzumab (THP): Secondary results from the EA1181/CompassHER2 pCR trial. First Author: Nadine M. Tung, Beth Israel Deaconess Medical Center, Boston, MA

Background: EA1181 (NCT04266249) is a single-arm trial of neoadjuvant THP for patients with clinical anatomic stage II/III HER2+ breast cancer; patients with cT4 or cN3 disease were excluded . Assessing the primary endpoint, 3-year recurrence-free survival in patients with a pCR (ypT0/Tis, ypN0), requires longer follow-up. Here, we present results for the secondary objective of pCR rate and its relation to clinicopathologic factors and the HER2DX pCR likelihood score (Reveal Genomics) derived from gene expression and clinical features. **Methods:** Patients received 4 cycles of trastuzumab and pertuzumab (HP) with weekly paclitaxel (12 weeks) or docetaxel (q3w x 4), followed by surgery. Clinicopathologic features were assessed for all patients and HER2DX pCR score (stratified by ER status) was determined using the diagnostic biopsy in a representative subset of study participants. **Results:** 2175 patients were enrolled. Median age was 55 years (range 22-88 years); 58% had clinical stage IIA, 33% stage IIB, and 9% stage III. 45% had nodal involvement (mostly cN1). 781 tumors were HER2+/ER- and 1394 HER2+/ER+ (locally tested). 2141 patients started THP, for whom the pCR rate was 44% overall, 63.7% in HER2+/ER- and 32.4% in HER2+/ER+ tumors. Disease progressed during THP in 16 patients (0.7%). The pCR rate varied inversely to the proportion of cells staining for ER among patients with HER2+/ER+ breast cancer: 1-10%+, 62.5%; 11-69%, 51.6%; ≥70%, 22.5% ($p < 0.001$). The pCR rate was significantly associated with higher grade, especially in HER2+/ER+ disease. T and N stage did not significantly affect pCR rate. Among 569 patients assessed for the HER2DX pCR score, the pCR rate was significantly greater for patients with a higher vs lower score, regardless of ER status (Table). Further correlations and interactions will be presented. **Conclusions:** Neoadjuvant THP resulted in pCR in nearly two-thirds of pts with clinical stage II/III HER2+/ER- and in one-third with HER2+/ER+ breast cancer. There was no association with clinical stage. Lower ER expression and higher grade were associated with higher pCR rates. The HER2DX pCR score was a significant predictor of pCR, regardless of ER status. Clinical trial information: NCT04266249. Research Sponsor: National Cancer Institute; Breast Cancer Research Foundation; Susan G. Komen for the Cure.

	All Participants		HER2+/ER-		HER2+/ER+	
	# patients enrolled	pCR rate (95% CI)	# patients enrolled	pCR rate (95% CI)	# patients enrolled	pCR rate (95% CI)
Evaluable Cohort	2141	44% (42-46%)	774	64% (60-67%)	1367	32% (30-35%)
HER2DX Cohort	569	48% (44- 52%)	230	69% (63-75%)	339	34% (29-39%)
HER2DX pCR-high score	182 (32%)	68% (60-74%)	147 (64%)	70% (62-77%)	36 (11%)	58% (41-74%)
HER2DX pCR-medium score	161 (28%)	67% (59- 74%)	70 (30%)	74% (62- 84%)	89 (26%)	61% (50-71%)
HER2DX pCR-low score	226 (40%)	19% (14- 25%)	13 (6%)	31% (9-61%)	214 (63%)	18% (13-24%)
P-value HER2DX score	<0.001		0.010		<0.001	

502 **Oral Abstract Session**

Prediction of survival after de-escalated neoadjuvant therapy in HER2+ early breast cancer: A pooled analysis of three WSG trials. First Author: Monika Karla Graeser, West German Study Group and Ev. Hospital Bethesda, Breast Center Niederrhein, Moenchengladbach, Germany and Department of Gynecology, University Medical Center Hamburg, Hamburg, Germany

Background: Current treatment de-escalation strategies in HER2+ early breast cancer (eBC) aim to mitigate acute and late toxicities by reducing or entirely omitting systemic chemotherapy (sCTx). We analyzed the outcomes and investigated predictors of survival in three randomized de-escalation trials investigating short (12-week) neoadjuvant treatments (NAT) with and without sCTx (paclitaxel, pac) in HER2+ eBC. **Methods:** In total, 713 patients (pts) were analyzed. WSG-ADAPT-HR-/HER2+ (NCT01817452) compared trastuzumab and pertuzumab (T + P, n=92) vs. T +P + pac (n=42); WSG-ADAPT-HR+/HER2+ (NCT01779206) compared trastuzumab emtansine (T-DM1, n=118) vs. T-DM1 + standard endocrine therapy (ET, n=125) vs. T + ET (n=129); WSG-TP-II (NCT03272477) compared neoadjuvant/adjuvant T + P + ET (n=100) vs. T + P + pac (n=107). Omission of further sCTx was allowed in pts with pathological complete response (pCR, ypT0/is ypN0); sCTx was mandatory for non-pCR pts. pCR was the primary endpoint of each trial; survival was a secondary endpoint. Kaplan-Meier method and Cox regression were applied for survival analysis. **Results:** Median follow-up of 60.7 months was available for 713 pts (sCTx: n=149; sCTx-free NAT: n=564). 395 tumors (55%) were cT2-4, 414 (58%) were grade 3, and 223 pts (31%) were clinically node-positive. Ten (7%) and 74 (13%) pts had iDFS events, 8 (5%) and 51 (9%) had dDFS events, and 6 (4%) and 34 (6%) pts died in the sCTx and sCTx-free NAT groups, respectively. In the sCTx and sCTx-free NAT groups, the respective 5-year survival rates were 98% (95%CI 93, 99) and 97% (95%CI 95, 98) for OS (HR 0.88; 95%CI 0.36, 2.11; p=0.775) and 96% (95%CI 91, 98) and 88% (95%CI 85, 91) for iDFS (HR 0.56; 95%CI 0.29, 1.08; p=0.083). 95 (66%) and 171 (31%) pts had a pCR after sCTx and sCTx-free NAT, respectively. iDFS events occurred in 5 (5%) pts with pCR and 5 (10%) without pCR after sCTx and in 14 (8%) with pCR and 59 (16%) pts without pCR after sCTx-free NAT. 5-year iDFS rates in pts with pCR were 98% (95%CI 91, 99) after sCTx and 94% (95%CI 89, 97) after sCTx-free NAT (HR 0.76; 95%CI 0.27, 2.14; p=0.609). In univariate analysis, iDFS was associated with pCR (HR 0.18; 95%CI 0.04, 0.77) in the sCTx group and with cT (3-4 vs 1: HR 2.54; 95%CI 1.22, 5.28) and cN stage (cN+ vs cN-: HR 2.27; 95%CI 1.44, 3.58), grade (3 vs 1-2: HR 1.79; 95%CI 0.86, 3.74) and pCR (HR 0.47; 95%CI 0.26; 0.84) in the sCTx-free NAT group. Detailed subgroup analyses including the impact of standard chemotherapy on outcome will be presented at the meeting. **Conclusions:** This pooled analysis demonstrates that de-escalation trials in HER2+ eBC are feasible and safe for patients. 12× weekly paclitaxel + HER2 blockade is an effective and well-tolerated regimen with excellent 5-year survival. The favorable survival after pCR to sCTx-free NAT lays the groundwork for further de-escalation strategies, such as the currently ongoing WSG-ADAPT-HER2-IV evaluating T-DXd as NAT. Clinical trial information: NCT01817452, NCT01779206, NCT03272477. Research Sponsor: None.

503 **Oral Abstract Session**

Comparison of marking techniques for target lymph nodes in 2,596 patients with node-positive breast cancer treated with neoadjuvant chemotherapy: Results from the prospective multicenter AXSANA/EUBREAST-03/AGO-B-053 study (NCT04373655). First Author: Maggie Banys-Paluchowski, Department of Obstetrics and Gynecology, University Hospital of Schleswig Holstein, Campus Lübeck, Lübeck, Germany

Background: Surgical axillary staging in patients with node-positive (cN+) breast cancer scheduled for neoadjuvant chemotherapy (NACT) varies significantly, and includes axillary lymph node dissection (ALND), sentinel lymph node biopsy (SLNB), targeted axillary dissection (TAD), and target lymph node biopsy (TLNB). SLNB/TAD/TLNB aim at reducing surgical morbidity without loosing staging accuracy. Comparative data on marking techniques for TAD/TLNB are limited. Here, different marking techniques from the largest available international prospective cohort are critically evaluated. **Methods:** AXSANA is an ongoing cohort study investigating oncological and patient-reported outcomes after different axillary procedures in cN+ breast cancer treated with NACT. In the present analysis, the subgroup of patients receiving marking of their TLN is selected, and detection and removal rates are analyzed. The entire dataset is continuously and systematically monitored for data quality assurance. **Results:** 6,129 patients from 291 sites in 26 countries were included between June 2020 and January 6th, 2025. Of these, 2,596 had ≥ 1 TLN marked before NACT and had completed surgery at time of analysis. The mean number of suspicious nodes at diagnosis was 1.9 (≥ 4 in 13.4%). 2,484 patients (95.7%) received a minimally invasive biopsy of ≥ 1 node. TLN marking was performed using a clip in 2,003 patients (77.2%), a magnetic seed in 287 (11.1%), carbon ink in 192 (7.4%), radar marker in 119 (4.6%), radioactive seed in 18 (0.7%), radiofrequency identification device (RFID) in 12 (0.5%) or other methods in 2 (0.1%). > 1 type of marker was placed in 36 patients (1.4%). 1 TLN was marked in 2,427 patients (93.5%), followed by 2 TLNs in 138 (5.3%) and ≥ 3 in 27 patients (1%). The mean number of marked TLNs was highest if carbon ink was used (mean 1.21), followed by clip (1.07), magnetic seed (1.06) and radar marker (1.04); no patient received > 1 radioactive seed/RFID. 1,895 patients (73.0%) achieved ycN0 status. Targeted removal of the TLN was planned in 2,100 patients (80.9%): 2,076 (80.0%) were scheduled for a TAD and 24 (0.9%) for a TLNB. TLN was detected and removed during TAD/TLNB in 1,915 patients (91.2%). TLN detection rate was highest in patients whose TLNs were marked with probe-guided techniques (96.6%; radioactive seed: 100%, magnetic seed: 96.9%, radar marker: 96.1%, RFID: 90%), followed by carbon (94.9%) and clip (89.6%; $p < 0.001$). TAD/TLNB removed a median number of 3 nodes (mean 4.1, SD 2.77; carbon: median 4, mean 4.29, SD 3.52, probe-guided: median 3, mean 3.82, SD 2.63, clip: median 3, mean 4.15, SD 2.75). **Conclusions:** This large prospective analysis of patients with initially cN+ breast cancer receiving NACT demonstrates that probe-guided markers provide superior TLN detection rates. Clinical trial information: NCT04373655. Research Sponsor: AGO-B; AWOgyn; Claudia von Schilling Foundation for Breast Cancer Research; Ehmann Foundation Savognin; EndoMag; Merit Medical; Mammotome.

504 Oral Abstract Session

Predicting nodal burden after neoadjuvant chemotherapy (NAC) with circulating tumor (ct)DNA for surgical planning: Results from the I-SPY2 trial. First Author: Rita Mukhtar, Division of Surgical Oncology, Department of Surgery, University of California, San Francisco, San Francisco, CA

Background: Axillary surgery in breast cancer is used for staging and therapeutic purposes, but axillary lymph node dissection (ALND) confers high risk of complications including lymphedema. Accordingly, trials have focused on right-sizing axillary surgery, with options ranging from complete omission of surgery, sentinel lymph node (SLN) surgery, targeted axillary dissection (TAD), or ALND. Identifying a biomarker to reliably predict nodal burden would facilitate accurate selection of surgical management. We evaluated whether the presence or absence of ctDNA in the blood pre and post NAC is associated with residual nodal burden. **Methods:** I-SPY2 is a prospective, multicenter NAC trial for patients with clinical stage II-III high-risk breast cancer. Patients are randomized to novel NAC agents, with pathologic complete response being the primary endpoint. As part of the trial, serial ctDNA is assessed with a highly sensitive tumor-informed assay using up to 16 patient-specific tumor mutations (Signatera) at baseline, 3 weeks, 12 weeks, and post-NAC. We determined whether ctDNA positivity or negativity post-NAC, and the change in ctDNA status baseline/post-NAC (-/-, -/+, +/+, +/-) are associated with ypN category (N0, N1, N2). **Results:** ctDNA status was available post-NAC in 495 patients and change in ctDNA status from baseline was available in 493. At baseline, ctDNA was detected in 160/220 (72.3%) cN0 patients and 227/273 (83.2%) cN+ patients (p=0.006). Post-NAC, ctDNA was detected in 11/220 (5%) cN0 patients and 34/273 (12.5%) cN+ patients (p=0.004). While baseline ctDNA status was not associated with ypN category, there was a significant association between post-NAC ctDNA status and ypN category. For ctDNA + patients post-NAC, 33.3% were ypN0, 31.1% were ypN1, and 35.6% were ypN2 at surgery; in contrast, for ctDNA - patients post-NAC, 67.1% were ypN0, 23.1% were ypN1, and 9.8% were ypN2 ($p<0.0001$). Dynamic ctDNA changes were also associated with ypN category, with significantly more ypN0 patients among ctDNA -/- or ctDNA +/- cases, and more ypN2 patients in those who did not clear ctDNA (+/+) (p=0.0001, Table). **Conclusions:** To our knowledge this is the first study to demonstrate a significant relationship between ctDNA and ypN category, which has important surgical implications. CtDNA negativity was associated with low likelihood of ypN2 disease, making these patients excellent candidates for SLN surgery or TAD. Ongoing analyses will incorporate receptor subtype and timing of clearance of ctDNA. CtDNA in breast cancer may help tailor surgical management of the axilla, potentially reducing patient morbidity without compromising prognostic information. Research Sponsor: None.

ctDNA baseline/post-NAC	ypN0 (n=317)	ypN1 (n=116)	ypN2 (n=60)
ctDNA -/- (n=105)	72.4%	19.1%	8.6%
ctDNA -/+ (n=1)	0.0%	100.0%	0.0%
ctDNA +/+ (n=44)	34.1%	29.6%	36.4%
ctDNA +/- (n=343)	65.9%	23.9%	10.2%

505 Oral Abstract Session

15-year outcomes for women with premenopausal hormone receptor-positive early breast cancer (BC) in the SOFT and TEXT trials assessing benefits from adjuvant exemestane (E) + ovarian function suppression (OFS) or tamoxifen (T)+OFS. First Author: Prudence A. Francis, Peter MacCallum Cancer Centre, Melbourne, Australia

Background: Long-term follow-up of the SOFT and TEXT randomized trials has shown persistent reduction of recurrence from inclusion of OFS in adjuvant endocrine therapy, and clinically meaningful improvement in overall survival (OS) among patients at higher baseline risk of recurrence. We report a final update after a median follow-up of 15y in SOFT and 16.6y in TEXT. **Methods:** SOFT and TEXT enrolled premenopausal women with HR+ early BC from November 2003 to April 2011 (2660 in TEXT, 3047 in SOFT intention-to-treat populations). TEXT randomized women within 12 weeks of surgery to 5y E+OFS vs T+OFS; chemotherapy (CT) was optional and concurrent with OFS. SOFT randomized women to 5y E+OFS vs T+OFS vs T alone, within 12 weeks of surgery if no CT planned, or within 8 months of completing (neo)adjuvant CT. Both trials were stratified by CT use. The primary endpoint was disease free survival (DFS) which included invasive local, regional, distant and contralateral breast events, second non-breast malignancies and deaths. Secondary endpoints included invasive breast cancer-free interval (BCFI), distant recurrence free interval (DRFI) and OS. 20y data collection was completed in Q4'2024: 80% of surviving patients had final follow-up during or subsequent to 2020, for 70% it was during 2023-2024. 15y Kaplan-Meier estimates and hazard ratios (HR) with 95% CIs are reported. **Results:** There were 815 DFS events and 388 deaths reported in SOFT; and 669 DFS events and 325 deaths in TEXT. In SOFT, a moderate DFS benefit of T+OFS vs T (HR 0.85; 0.72-1.00) persisted, however 1/6 DFS events were not BC related; BCFI benefit was HR 0.82 (0.69-0.98). E+OFS vs T further reduced DFS events (HR 0.73; 0.61-0.86). The 15y DFS in SOFT was 67.0% for T, 70.5% for T+OFS and 73.5% for E+OFS. There were consistent but non-significant decreased hazards of death for T+OFS vs T (HR 0.87; 0.68-1.10) and E+OFS vs T (HR 0.85; 0.67-1.08). 15y OS was 85.3%, 86.7%, 86.9% respectively. For the TEXT+SOFT combined analysis of E+OFS vs T+OFS (n=2346 vs 2344) DFS, BCFI and DRFI continued as significantly improved for E+OFS over T+OFS. 15y DFS was 74.9% vs 71.3% (HR 0.82; 0.73-0.92). 15y OS was 87.8% vs 87.0% (HR 0.94; 0.80-1.11) respectively. 15y estimates by CT use are tabulated. **Conclusions:** The high level 15y final results of the SOFT and TEXT confirm a role for OFS- and aromatase inhibitor-containing adjuvant endocrine therapy for premenopausal women. Analysis is ongoing. Clinical trial information: NCT00066690 (SOFT) and NCT00066703 (TEXT). Research Sponsor: ETOP IBCSG Partners Foundation, BCRF, US NCI, Pfizer, Ipsen, et al have supported long-termfollow-up of the trials.

15y (%)	Events	SOFT Prior CT (n=1628)	SOFT no CT (n=1419)
	CT+noCT	T / T+OFS / E+OFS	T / T+OFS / E+OFS
DFS	536+279	60.9 / 63.0 / 66.3	73.9 / 79.1 / 82.1
DRFI	367+56	73.5 / 73.8 / 77.6	94.7 / 94.7 / 96.8
OS	318+70	77.4 / 79.4 / 79.8	94.4 / 95.1 / 95.2
		TEXT CT (n=1607)	**TEXT no CT (n=1053)**
		T+OFS / E+OFS	T+OFS / E+OFS
DFS	456+213	68.5 / 72.1	76.8 / 81.8
DRFI	286+69	79.0 / 81.3	91.6 / 94.6
OS	266+59	82.7 / 84.3	94.1 / 94.8

506 Oral Abstract Session

Updated survival outcomes and predictors of benefit from ovarian function suppression in premenopausal women with hormone-receptor–positive breast cancer: Results from the ASTRRA trial. First Author: Jai Min Ryu, Division of Breast Surgery, Department of Surgery, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, South Korea

Background: The ASTRRA trial previously demonstrated that adding ovarian function suppression (OFS) to tamoxifen (TAM) showed consistent disease free survival (DFS) benefit at 8-yr follow-up analysis in premenopausal women with hormone-receptor (HR)–positive breast cancer who remain premenopausal or resume menstruation after chemotherapy. Here, we aimed to update the survival outcomes and identify patients most likely to benefit from OFS to tailor clinical decision-making. **Methods:** A total of 1,282 premenopausal women were randomized 1:1 to receive either 5 years of TAM alone (TAM-only) or 5 years of TAM with OFS for 2 years (TAM + OFS). The primary endpoint was DFS, and the secondary endpoint was overall survival (OS). For the HER2-negative cohort, a composite risk score (range: 0–5) for breast cancer-free interval (BCFI) was calculated based on tumor size, nodal status, and tumor grade using a Cox regression model. The impact of OFS was analyzed by composite risk score and stratified by age. The events for BCFI were defined as local, regional, or distant recurrence; invasive contralateral breast cancer; or death resulting from breast cancer as the first event. **Results:** With a median follow-up of 117.6 months, the 10-year DFS rate was 83.7% in the TAM + OFS group compared to 75.9% in the TAM-only group (hazard ratio [HR], 0.68; 95% CI, 0.53-0.87). Meanwhile, there were no significant differences in 10-year OS: 94.6% in the TAM + OFS vs. 93.2% in the TAM-only group (HR, 0.79; 95% CI, 0.50-1.27). In the 776 patients with HER2-negative breast cancer, there were no significant differences in the distribution of age group (P = .320), tumor size (P = .572), lymph node status (P = .577), or histologic grade (P = .249) between TAM + OFS and TAM-only groups. Worse 10-year BCFI was significantly associated with younger age ($<$ 40 vs. 40-45 years, P = .026), larger tumor size ($\geq$ 2cm vs. $<$ 2cm, $P < .001$), lymph node positivity (positive vs. negative, $P < .001$), and aggressive histologic grade (III vs. II vs. I, P = .006), respectively. Among patients with a high composite risk score (4–5, n = 282, 36.3% of the HER2-negative cohort), the 10-year BCFI was significantly improved with OFS: 76.6% in the TAM + OFS group vs. 65.7% in the TAM-only group (HR, 0.62; 95% CI, 0.40–0.98). This benefit was particularly pronounced in patients aged 40–45 years. **Conclusions:** We demonstrated the consistent benefit of adding OFS for 2 years to TAM in improving 10-year DFS. In patients with HR-positive/HER2-negative breast cancer and a high composite risk score, the addition of TAM plus OFS resulted in a 10.9% improvement in the 10-year BCFI, suggesting this approach may be beneficial, especially for those aged 40-45 years. Clinical trial information: NCT00912548. Research Sponsor: National Research & Development Program for Cancer Control through the National Cancer Center funded by the Ministry of Health & Welfare, Republic of Korea; No. HA23C014400.

507 Oral Abstract Session

The impact of ovarian function suppression with adjuvant endocrine therapy on survival outcomes in young germline *BRCA* mutation carriers with breast cancer: Secondary analysis of an international cohort study. First Author: Paola Zagami, UNC Lineberger Comprehensive Cancer Center/University of Milan/European institute of Oncology IRCSS (IEO), Chapel Hill, NC

Background: In young women with hormone receptor-positive (HR+) breast cancer (BC), ovarian function suppression (OFS) has been shown to improve outcomes when combined with adjuvant endocrine therapy (ET). However, limited evidence exists on its efficacy in germline *BRCA (gBRCA)* carriers. Here we investigated the association between OFS plus ET and outcomes in the largest global cohort of young g*BRCA* carriers with BC. **Methods:** The BRCA BCY Collaboration (NCT03673306) is an international, multicenter, hospital-based, retrospective cohort study of women harboring germline *BRCA1/2* pathogenic/likely pathogenic variants, diagnosed between 2000 and 2020 with stage I-III invasive BC at age of $\leq$ 40 years. The analysis included patients with HR+ BC and available data on ET and OFS. The OFS group included patients treated with luteinizing hormone-releasing hormone agonists (LHRHa) and/or bilateral risk-reducing salpingo-oophorectomy (RRSO) within 1 year of BC diagnosis. Outcome analyses included disease-free survival (DFS), BC-free interval (BCFI) and overall survival (OS). Cox proportional hazard models, stratified for country, year of diagnosis, nodal status, and surgery type and adjusted for RRSO and bilateral risk-reducing mastectomy (time-dependent), were used to explore the association between OFS use (vs non-use) and outcomes. Sensitivity analysis explored OFS as time-dependent covariate. To address immortal time bias, an additional Cox model accounted for left truncation, considering differences in time to *BRCA* testing. **Results:** Among 5,660 patients from 109 centers, 1,865 patients with HR+ BC were included, of whom 1,071 (57%) received OFS plus ET (35% with an aromatase inhibitor [AI], 65% with tamoxifen [tam])and 794 (43%) received tam alone. Patients receiving OFS were more likely to have node-positive disease (56% vs 47%), receive treatment in recent years (36% vs 17%), undergo mastectomy (70% vs 57%) and be tested for g*BRCA* at diagnosis (46% vs 30%). With a median follow-up of 7.8 years (IQR 4.6-12.1), OFS combined with ET was associated with significantly improved DFS (adjusted HR [aHR] 0.79, 95% CI 0.66-0.94), BCFI (aHR 0.74, 95% CI 0.61-0.89) and OS (aHR 0.66, 95% CI 0.50-0.88) over tam alone. Sensitivity analysis using OFS as a time-dependent factor yielded consistent results. No significant interactions were observed between OFS use and specific g*BRCA* mutations or HER2 status. Sub-analyses by type of ET (OFS + AI vs. OFS + tam vs. tam alone) will be presented at the conference. **Conclusions:** In this global cohort of young *BRCA* mutation carriers, OFS combined with ET was associated with improved DFS, BCFI and OS versus tam without OFS. These findings support the consideration of OFS as a key component of adjuvant therapy in this population. Research Sponsor: None.

508 **Oral Abstract Session**

Efficacy and safety of elinzanetant for vasomotor symptoms associated with adjuvant endocrine therapy: Phase 3 OASIS 4 trial. First Author: Fatima Cardoso, ABC Global Alliance, Lisbon, Portugal

Background: Vasomotor symptoms (VMS) associated with adjuvant endocrine therapy (AET) impact quality of life and decrease treatment adherence, worsening breast cancer outcomes. There are few effective treatment options and none approved for this indication. **Methods:** The 52-week randomized phase 3 trial OASIS 4 (NCT05587296) evaluated the safety and efficacy of elinzanetant (EZN), a dual neurokinin-1 and -3 receptor antagonist, in women aged 18–70 years being treated for, or at high risk of developing, hormone receptor-positive (HR+) breast cancer and experiencing ≥35 moderate-to-severe VMS/week associated with AET. Women were randomized 2:1 to receive once-daily EZN 120 mg for 52 weeks or placebo (P) for 12 weeks followed by EZN for 40 weeks. Primary endpoints were mean change in moderate-to-severe VMS frequency from baseline to weeks 4 and 12 analyzed using mixed model with repeated measures (one-sided p-values). Secondary endpoints were mean changes from baseline in moderate-to-severe VMS frequency to week 1 and moderate-to-severe VMS severity to weeks 4 and 12. Treatment-emergent adverse events (TEAEs) were reported throughout the study. **Results:** Mean (standard deviation [SD]) baseline daily VMS frequency was 11.4 (6.9) in the EZN group (n=316) and 11.5 (6.4) in the P group (n=157). Reductions from baseline in VMS frequency were observed from week 1 (EZN: -4.0 [5.1]; P: -1.8 [3.8]). At week 4, mean (SD) VMS frequency reduced by -6.5 (6.1) with EZN and -3.0 (5.0) with P, with statistical significance between EZN and P (least squares [LS] mean difference [95% confidence interval (CI)]: -3.5 [-4.4, -2.6]; $p<0.0001$). At week 12, reductions in VMS frequency were -7.8 (6.2) with EZN and -4.2 (6.1) with P, with statistical significance between EZN and P (LS mean difference [95% CI]: -3.4 [-4.2, -2.5]; $p<0.0001$). Reductions in VMS severity were greater with EZN vs. P (week 4: -0.7 [0.6]; -0.4 [0.4], week 12: -1.0 [0.7]; -0.5 [0.6]). During the placebo-controlled period, 220 (69.8%) and 98 (62.0%) patients reported TEAEs in the EZN and P groups, respectively. Somnolence, fatigue, and diarrhea were more frequently reported with EZN (Table). Fewer TEAEs were reported in both groups during weeks 13–52. **Conclusions:** EZN was efficacious with a fast onset and well tolerated for the treatment of VMS associated with AET. TEAE frequency was as expected for this type of trial. Adequate VMS management can improve adherence to AET and, therefore, improve cancer outcomes and quality of life. Clinical trial information: NCT05587296. Research Sponsor: Bayer.

n (%)	EZN Week 1–12 n=315	P Week 1–12 n=158	Total EZN Week 1–52 N=465
Any TEAE	220 (69.8%)	98 (62.0%)	368 (79.1%)
Headache	30 (9.5%)	20 (12.7%)	56 (12.0%)
Arthralgia	20 (6.3%)	10 (6.3%)	52 (11.2%)
Fatigue	30 (9.5%)	8 (5.1%)	43 (9.2%)
Somnolence	34 (10.8%)	6 (3.8%)	42 (9.0%)
Diarrhea	16 (5.1%)	3 (1.9%)	32 (6.9%)
Back pain	10 (3.2%)	7 (4.4%)	29 (6.2%)
Nausea	19 (6.0%)	10 (6.3%)	29 (6.2%)
Any serious TEAE	8 (2.5%)	1 (0.6%)	33 (7.1%)

LBA509 **Rapid Oral Abstract Session**

NRG-BR003: A randomized phase III trial comparing doxorubicin plus cyclophosphamide followed by weekly paclitaxel with or without carboplatin for node-positive or high-risk node-negative TNBC. First Author: Vicente Valero, The University of Texas MD Anderson Cancer Center, Houston, TX

The full, final text of this abstract will be available at meetings.asco.org on the day of presentation and in the online supplement to the June 10, 2025, issue of the *Journal of Clinical Oncology*.

510 **Rapid Oral Abstract Session**

Prospective randomized phase II trial to assess the efficacy and safety of neo-adjuvant olaparib/carboplatin (OC) in comparison to docetaxel/epirubicin/cyclophosphamide (TAC) in patients with early triple-negative breast cancer (TNBC) with homologous recombination deficiency (HRD): Primary results from the ABCSG 45 trial. First Author: Christian F. Singer, Department of Obstetrics and Gynecology and Center for Breast Health, Comprehensive Cancer Center, Medical University of Vienna and Austrian Breast and Colorectal Cancer Study Group, Vienna, Austria

Background: Carboplatin-based regimen are effective in patients (pts) with eTNBC, and olaparib improves the outcome of pts with *BRCA1/2* pathogenic variants (PV), but the safety / efficacy of OC co-treatment in HRD-positive TNBC is unknown. ABCSG 45 (EU CT 2024-512821-10) is a prospective multicenter phase II study investigating the efficacy and tolerability of OC compared to conventional chemotherapy in HRD-positive eTNBC. **Methods:** Pts with HRD (Myriad genetics)-positive eTNBC were randomized to 6 cycles of olaparib (100 mg bid, days 4-16) / carboplatin (AUC 5) q3w, or 6 cycles of docetaxel/epirubicin/cyclophosphamide (75/50/500) q3w (TAC). In an initial dose-finding phase, 100 mg bid was identified as olaparib combination dose. Stratification factors were tumoral *BRCA1/2* and menopausal status. Primary endpoint was centrally assessed residual cancer burden (RCB), pCR and QoL were secondary endpoints. Planned sample size was 90 pts, randomized 1:1 to achieve 80% power (two-sided alpha=0.05) to detect a RCB 0/I difference of 31%. Differences between treatment arms were assessed with a two-sided Cochran Mantel-Haenszel test using stratification factors. Pre-defined subgroup analysis was performed with logistic regression. **Results:** A total of 90 pts (OC: n=46; TAC: n=44), of whom 42 (47%) were *BRCA1/2* PV carriers, were randomized between November 2019 and December 2023. Median age was 50.5 years (range 27.0-80.0). 40% had cT1, 55.6% cT2, and 4.4% cT3/4 tumors, and 60% of pts were clinically N0. 94.4% of tumors were G3, and Ki67 was >60% in 71.1%. Overall, the RCB0/I rate with OC was 52.2% vs. 70.5% with TAC (stratified risk difference = -18.8% (95%CI: -39.6% to 2.0%); p=0.068). In pts with *BRCA1/2* PV, RCB0/I rates were comparable: 77.3% (OC) vs. 65.0% (TAC), while in 47 pts with *BRCA1/2* wild type (WT), OC was significantly less effective: RCB0/I of 29.2% vs 73.9% in TAC (interaction p=0.008). pCR was achieved in 47.8% (OC) vs 59.1% (TAC; p=0.231). In pts with a *BRCA1/2* PV, OC resulted in 77.3% pCR rate, vs. TAC 65.0%, in *BRCA1/2 WT* pts pCR was achieved by 20.8% (OC) vs. 56.5% (TAC) (interaction p=0.021). OC treatment resulted in more ≥ grade 3 hematologic toxicities with 30% vs 3% thrombocytopenia and 43% vs 18% neutropenia but caused fewer non-hematological toxicities. **Conclusions:** In this prospective randomized study in HRD-positive TNBC, 6 cycles of TAC resulted in strikingly high RCB0/I and pCR rates, independent of *BRCA1/2* status. 6 cycles of OC achieved a pCR rate of >77% in BRCA1/2 PV but were less effective in pts with *BRCA1/2* WT disease. These results may help to optimize neoadjuvant treatment strategies in TNBC. This research was conducted with support from AstraZeneca Austria GmbH. Clinical trial information: 2024-512821-10. Research Sponsor: None.

511 **Rapid Oral Abstract Session**

A phase 2 study of response-guided neoadjuvant sacituzumab govitecan and pembrolizumab (SG/P) in patients with early-stage triple-negative breast cancer: Results from the NeoSTAR trial. First Author: Rachel Occhiogrosso Abelman, Massachusetts General Hospital Cancer Center, Harvard Medical School, Boston, MA

Background: Sacituzumab govitecan (SG) is a TROP-2 directed antibody-drug conjugate (ADC) approved for metastatic triple negative breast cancer (TNBC). Pembrolizumab (P), an anti-programmed death 1 monoclonal antibody, is approved for early-stage TNBC and metastatic PD-L1 positive TNBC. However, safety and efficacy of SG+P in early TNBC is not known. We published results of Arm A1 investigating neoadjuvant SG monotherapy in early TNBC (Spring et al. Annals of Onc 2024). Here we present results from Arm A2 of the NeoSTAR study investigating the combination of neoadjuvant SG + P in early-stage TNBC (NCT04230109). **Methods:** Patients (pts) with early TNBC (tumor size ≥2 cm or node positive) with no prior treatment were eligible. Pts received SG at starting dose of 10mg/kg on days 1,8 of a 21-day cycle for 4 cycles with P 200 mg given on day 1 of each cycle. After trial regimen, pts underwent imaging to determine residual radiographic disease per RECIST v1.1. A biopsy was performed if residual disease (RD) was suspected. Additional neoadjuvant chemotherapy (ANACT) was at discretion of the treating physician prior to definitive surgery. The primary objective was rate of pathologic complete response (pCR) with neoadjuvant SG/P. Secondary objectives included need for ANACT, radiographic response (RR), safety and tolerability (adverse events [AEs] per CTCAE v5.0) and event-free survival. A Simon two-stage design and standard descriptive statistics were utilized, including 95% binomial confidence intervals for all rates estimated. **Results:** From 5/19/23-8/13/24, 50 pts were enrolled (median age: 57 years, range 23-77). Clinical anatomic stage was II in 48 pts (96%) and III in 2 pts (4%). 64% of pts were node negative at diagnosis. 44 pts (88%) completed the trial regimen (5 pts had toxicity, 1 pt progressed on treatment). In interim analysis, 5/15 had pCR and so the remaining 35 were enrolled. The pCR rate per protocol (pts with pCR at surgery directly after SG/P without ANCT) was 16/50 (34%, 95% CI 19.5-46.7). The RR rate (complete CR or partial response PR) was 66% (95% CI 50-78%), 30% CR and 36% PR. Of 26 pts who received ANACT, 9 experienced pCR (2 biopsy-confirmed RD, 6 negative or non-diagnostic RD biopsy, 1 no biopsy). Overall, 25 (50%, 95% CI 35.5-64.5) pts had pCR at surgery. Of 5 pts with pathogenic BRCA mutations, 3 (60%) had pCR after SG/P, and 1 pt had pCR after ANACT. 20 pts (40%) had grade 3 or higher AEs. The most common AEs were nausea (28, 56%), alopecia (26, 52%), fatigue (23, 46%), and diarrhea (22, 44%). Dose reductions of SG occurred in 4 pts (8%). Updated survival and biomarker data will be presented at the meeting. **Conclusions:** In the first trial to investigate the SG/P combination in early TNBC, 34% of pts had pCR. Additional research is needed to determine the optimal duration and sequence of neoadjuvant SG/P and chemotherapy for pts with TNBC. Clinical trial information: NCT04230109. Research Sponsor: None.

512 Rapid Oral Abstract Session

The Promise study: A presurgical randomized clinical trial of CE/BZA vs placebo in postmenopausal women with ductal carcinoma in situ. First Author: Swati Kulkarni, Northwestern University Feinberg School of Medicine, Chicago, IL

Background: Conjugated estrogen/bazedoxifene (CE/BZA), the first tissue selective estrogen complex, was developed as an alternative to combination estrogen and progesterone therapy to treat hot flashes and osteoporosis. Preclinical studies found that CE/BZA reduced mammary ductal proliferation and increased expression of anti-tumorigenic markers in breast stroma. Our study aimed to determine if a pre-surgical window-of-opportunity intervention with CE/BZA in women with ductal carcinoma in situ (DCIS) had a protective effect on the duct epithelium and stroma of DCIS lesions without impacting quality of life. Differences between CE/BZA and placebo arms for the primary endpoint, change in Ki-67 protein expression, and quality-of-life endpoints are reported here. **Methods:** This multicenter, randomized, double-blind placebo-controlled Phase 2 trial was conducted between 9/19/17 and 8/21/24. Postmenopausal women with estrogen receptor positive (ER+) DCIS undergoing surgery were randomized to CE 0.45 mg /BZA 20 mg or placebo for 28 +/-7 days. Percentage of nuclei staining for Ki-67 was evaluated on slides from the baseline core biopsy and surgical specimen. Changes were compared between arms using the two-sample t-test, while changes within arms were analyzed using paired t-test. Analyses were done on log2 scale to satisfy the normality assumption. The Breast Cancer Prevention Trial Eight Symptom Scale (BESS) and Menopause-Specific Quality of Life (MENQOL) surveys were self-administered by patients before and after the intervention. Wilcoxon's signed-rank and rank-sum tests were used to perform within- and between-arm comparisons, respectively. **Results:** Of the 171 patients consented,141 enrolled, and 117 completed the study. Ninety-four patients (46= CE/BZA, 48=placebo) took >80% of the medication and had Ki-67 evaluated at baseline and post-intervention. The BESS and MENQOL surveys were completed by 100 and 108 patients, and 125 patients were evaluated for toxicity. The mean absolute change in Ki-67 was -5.62 (SD=10.2; p=0.003) in the CE/BZA arm and -1.07 (SD=10.8; p=0.6) in the placebo arm, with a greater reduction in CE/BZA arm (p=0.016). There was no difference between arms in the BESS score across all 8 domains or in the MENQOL score. However, within each arm, vasomotor symptoms decreased in the CE/BZA arm (p=0.002) but not in the placebo arm (p=0.4). No grade > 3 treatment related adverse events were reported. **Conclusions:** In this prospective randomized clinical trial, CE/BZA significantly reduced epithelial proliferation in ER+ DCIS with no impact on quality of life compared to placebo. These results support consideration that CE/BZA is a safe option to manage menopausal symptoms for women concerned about their risk of developing breast cancer, and provide supportive evidence that CE/BZA may reduce the risk of developing invasive breast cancer. Clinical trial information: NCT02694809. Research Sponsor: U.S. National Institutes of Health; 1R01CA218436-01.

513 Rapid Oral Abstract Session

The WinPro trial: A window of opportunity study of endocrine therapy with and without prometrium in postmenopausal women with early stage hormone receptor-positive breast cancer. First Author: Lucy Haggstrom, St Vincent's Hospital Sydney and University of New South Wales, Sydney, NSW, Australia

Background: Preclinical evidence has shown that progesterone is a tumour suppressor in estrogen receptor positive (ER+) breast cancer. Prometrium is bioidentical to human progesterone, currently used for treating menopausal symptoms. **Methods:** The WinPro trial is a randomised, multi-centre, phase 2, window of opportunity trial of preoperative endocrine therapy in post-menopausal women with early-stage, ER+, progesterone receptor (PR) +, HER2- breast cancer. Patients (pts) were randomised 1:1:1 to letrozole (let) 2.5mg daily, letrozole 2.5mg daily + prometrium (pro) 300mg daily, or tamoxifen (tam) 20mg daily + prometrium 300mg daily for 11-17 days before surgery. The primary endpoint was the percent proportional reduction in Ki67 between biopsy and surgery ('Ki67 suppression') in let vs let + pro in the per protocol population. Other endpoints were safety, changes in ER, PR and androgen receptor (AR) via immunohistochemistry (IHC) and H-scores, spatial transcriptomics and RNA sequencing. **Results:** From Feb 2018 to June 2024,244 pts were enrolled across 6 Australian sites. 239 pts were randomised to let (n=78, 32.6%), let + pro (n=79, 33.1%), and tam + pro (n=82, 34.3%). 189 pts completed per protocol: let (n=66, 34.9%, let + pro (n=64, 33.9%), and tam + pro (n=59, 31.2%). Baseline characteristics were well balanced across arms. There was no significant difference in Ki67 suppression between let (88.2%) vs let + pro (89.2%) (p = 0.4). Ki67 suppression appeared inferior with tam + pro (61.5%). Treatments were well tolerated, with hot flushes less frequent in let + pro (13.3%) vs let (22.4%) or tam + pro (20.5%). IHC analyses showed no change in ER% after treatment, a decrease in PR% after treatment with let and let + pro, and a decrease in AR% after treatment in all groups. H-score, spatial transcriptomics, RNA sequencing and PAM50 analyses are underway. **Conclusions:** The WinPro trial showed that the addition of pro to let in post-menopausal women with ER+, PR+, HER2- breast cancer was safe, reduced hot flushes and led to similar reduction in Ki67 as let alone. Ongoing translational analyses are underway which will examine the changes in gene expression in malignant, immune and stromal cells at sub-cellular resolution and provide further insight into the mechanisms of response and resistance to endocrine therapy. Clinical trial information: ACTRN12618000928213. Research Sponsor: Cancer Council New South Wales; National Health and Medical Research Council, Australian Government; Besins Healthcare.

	Baseline			Surgery		
	Let N = 67	Let + pro N = 64	Tam + pro N = 60	Let N = 67	Let + pro N = 64	Tam + pro N = 60
Ki67% suppression, median (Q1, Q3)	-	-	-	88.2 (74.6, 93.0)	89.2 (78.3, 93.9)	61.5 (32.3, 75.9)
Ki67%, median (Q1, Q3)	8.5 (4.5, 16.0)	10.5 (5.0, 16.3)	10.8 (6.0, 17.0)	1.0 (0.5, 2.5)	1.0 (0.5, 2.0)	3.5 (2.0, 7.5)
ER%, median (Q1, Q3)	95 (95, 95)	95 (95, 95)	95 (95, 95)	95 (95, 95)	95 (95, 95)	95 (95, 95)
PR%, median (Q1, Q3)	90 (50, 95)	90 (35, 95)	90 (50, 95)	20 (4, 70)	20 (2, 70)	90 (33, 95)
AR%, median (Q1, Q3)	40 (10, 90)	28 (8, 80)	70 (20, 90)	15 (2, 60)	10 (2, 75)	10 (1.3, 45)

514 Rapid Oral Abstract Session

Early results of the French multicenter, randomized SHARE trial comparing whole breast irradiation versus accelerated partial breast irradiation in postmenopausal women with early-stage low risk breast cancer: Analysis of toxicity and cosmetic outcomes. First Author: Yazid Belkacemi, AP-HP, Department of Radiation Oncology and Henri Mondor Breast Center, Henri Mondor University Hospital, University of Paris Est Creteil (UPEC), Paris, France

Background: Locoregional management of early stage breast cancer (BC) has evolved from maximal tolerable to minimal effective therapies. Significant advancements in radiation therapy (RT), such as limited target volumes and hypofractionation, have led to accelerated partial breast irradiation (APBI). This study reports on toxicity and cosmetic outcomes of APBI in post-menopausal women with unifocal pT1-N0-M0 invasive BC. **Methods:** The SHARE trial (NCT01247233) is a non-inferiority, multicenter, randomized trial comparing local control of APBI versus Whole Breast Irradiation (WBI). Eligible patients were postmenopausal women over 50 years who had lumpectomy with surgical margins > 2mm. Only patients who had at least 4-5 clips placed in the tumor bed during surgery were eligible. Patients were randomized to receive either WBI (50Gy in 25 fractions (fr) with optional 16Gy-boost or 40Gy in 15 fr, or 42.5Gy in 16fr) or APBI (38.5Gy or 40Gy in 10fr twice daily). Primary endpoint was local recurrence. Secondary endpoints included grade >2 toxicity (NCI-CTCAE-v4) and cosmetic outcomes (good/excellent versus intermediate/poor) evaluated by both patients and doctors, over the follow-up time. We estimated the cumulative incidences (CI) using the Kalbfleisch-Prentice method due to competing events, and cause-specific Hazard Ratios (cs-$HR_{APBI/WBI}$) from Cox models adjusted on stratification factors. **Results:** Among 1006 patients (503 per arm) enrolled between December-2010 and July-2015, with a median follow-up of 5.8 years, 28 deaths and 11 local recurrences were reported. The risk of severe toxicity appeared significantly reduced in the APBI-arm when considering all type of toxicity (cs-$HR_{APBI/WBI}$=0.74, [95%-CI: 0.61-0.89], p=0.001; 3-year CI=45% [41-49] in WBI vs 36% [32-40] in APBI), or only breast skin toxicity (cs-HR=0.55 [0.44-0.70], p<0.001; 3-year CI=36% [32-40] vs 21% [18-25], respectively). Conversely, for non skin breast toxicities, WBI was less toxic: cs-$HR_{APBI/WBI}$=2.06 (1.49-2.86), p<0.001). We observed no significant difference of patient-reported cosmetic results: cs-$HR_{APBI/WBI}$=1.08 (0.85-1.37), p=0.54. Findings were similar for doctor-evaluated results. Rib fractures incidence was nearly double in APBI compared to WBI. **Conclusions:** The SHARE trial showed that APBI is associated with reduced severe and skin-related toxicities compared to WBI, with no significant difference in cosmetic outcomes. Conversely, WBI was less toxic concerning non-skin breast toxicity, mainly breast fibrosis. The question that currently remains open on a practical level is how to consider APBI in the context of the widespread adoption of the "Fast Forward" regimen for patients at low risk of recurrence. Clinical trial information: 2010-A00243-36. Research Sponsor: French Ministry of Health PHRC-2010 Cancérologie; La Ligue contre le cancer.

515 Rapid Oral Abstract Session

Dalpiciclib (Dalp) plus endocrine therapy (ET) as adjuvant treatment for HR+/HER2− early breast cancer (BC): The randomized, phase 3, DAWNA-A trial. First Author: Zhi-Ming Shao, Fudan University Shanghai Cancer Center, Shanghai, China

Background: Dalp, a potent CDK4/6 inhibitor, has demonstrated significant improvements in PFS when combined with ET in both first-line and later-line settings for HR+/HER2− advanced BC. We conducted a randomized, double-blind, phase 3 trial (DAWNA-A) to further evaluate Dalp with ET as adjuvant therapy for high-risk, early HR+/HER2− BC and here present findings from the pre-specified first interim analysis (IA1). **Methods:** Women aged 18-75 y, with stage II-III, HR+/HER2− BC, who had completed definitive local therapy (surgery and/or radiotherapy) and had pathologically confirmed ipsilateral axillary lymph node involvement, were enrolled. Patients (pts) were randomized (1:1) to receive oral Dalp (125 mg QD; 3-wk on/1-wk off, for 2 y) + ET (letrozole 2.5 mg/anastrozole 1 mg/tamoxifen 10 mg/toremifene 60 mg QD, for 5 y) or placebo + ET. Pre/perimenopausal pts received LHRH agonists (perimenopausal use at investigator's discretion). Stratification factors were menopausal status (pre/peri vs post), clinical stage (II vs III), number of involved nodes (<4 vs ≥4), and adjuvant chemo (y vs n). The primary endpoint was invasive disease-free survival (iDFS). IA1 was pre-planned at ~254 iDFS events (~50% of total expected). As of Oct 25, 2024, 268 iDFS events occurred and IA1 was performed; the actual superiority boundary was a 1-sided p <0.00205 (Lan-DeMets [O'Brien-Fleming] boundary). **Results:** Between Apr. 30, 2021 and Jul. 19, 2024, 5274 pts were randomized (Dalp, n=2640; placebo, n=2634). As of data cutoff, median follow-up was 20.3 mo (range 0.0–41.9). Dalp + ET significantly prolonged iDFS vs placebo + ET (HR 0.56, 95% CI 0.43–0.71; 1-sided p <0.0001); iDFS benefits with Dalp were generally consistent across stratification factors and other baseline subgroups. DFS and distant DFS (DDFS) also favored Dalp + ET over placebo + ET (Table). TRAEs led to discontinuation of Dalp in 2.1% of treated pts in Dalp arm and of placebo in 0.8% in placebo arm. Tr-SAE occurred in 3.7% and 1.5%, respectively. There was no death due to TRAEs. **Conclusions:** Addition of Dalp to ET as adjuvant treatment significantly improved iDFS, with a tolerable safety profile. These data support the use of Dalp for treating HR+/HER2- early BC. Clinical trial information: NCT04842617. Research Sponsor: Jiangsu Hengrui Pharmaceuticals Co., Ltd.

Efficacy outcomes.

		Dalp + ET (n=2640)	Placebo + ET (n=2634)
iDFS	Event, n (%)	98 (3.7)	170 (6.5)
	3-y rate*, % (95% CI)	89.1 (85.8–91.7)	86.2 (83.3–88.6)
	HR† (95% CI); p value‡	0.56 (0.43–0.71); p <0.0001	
DFS	Event, n (%)	108 (4.1)	195 (7.4)
	3-y rate*, % (95% CI)	88.0 (84.5–90.7)	83.8 (80.5–86.6)
	HR† (95% CI); p value‡	0.53 (0.42–0.67); p <0.0001	
DDFS	Event, n (%)	93 (3.5)	149 (5.7)
	3-y rate*, % (95% CI)	90.2 (87.2–92.6)	88.7 (86.2–90.8)
	HR† (95% CI); p value‡	0.60 (0.46–0.78); p<0.0001	

*Kaplan–Meier method. †Stratified Cox proportional hazards model. ‡Stratified Log-rank test (1-sided).

516 Rapid Oral Abstract Session

Efficacy and safety of ribociclib (RIB) + nonsteroidal aromatase inhibitor (NSAI) in NATALEE: Analysis across menopausal status and age. First Author: Kevin Kalinsky, Winship Cancer Institute at Emory University, Atlanta, GA

Background: The NATALEE trial demonstrated significant invasive disease–free survival benefit with RIB + NSAI vs NSAI alone in patients (pts) with stage II/III HR+/HER2− early breast cancer (EBC) at high risk of recurrence. Here, we report outcomes by menopausal status and age. **Methods:** Pts were treated with RIB + NSAI or NSAI alone in NATALEE; premenopausal (PreM) women also received goserelin. Men were excluded from this analysis. Efficacy, safety, and quality of life were analyzed by menopausal status (assessed at randomization or start of adjuvant endocrine therapy, whichever was first) and age (PreM [<40 y, ≥40 y]; postmenopausal [PostM; <60 y, ≥60 y]). Data cutoff was April 29, 2024. **Results:** A greater portion of PreM vs PostM pts had ECOG performance status 0 (86.8% vs 80.1%), Ki-67 >20% (39.9% vs 34.4%), N1-N3 nodal stage (63.4% vs 56.9%), and T3/T4 tumors (28.7% vs 24.0%) at diagnosis. There was consistent treatment benefit with RIB + NSAI vs NSAI alone across groups and ages (median follow-up, 44.2 months) (Table). Fewer PreM pts discontinued RIB due to AEs vs PostM (16.1% vs 22.9%); reductions due to AEs were similar (22.4% vs 23.6%). Of pts who discontinued due to AEs, more PreM pts did so without a dose reduction vs PostM (75.4% vs 67.5%). Within menopausal groups, fewer pts in the younger cohorts discontinued RIB due to AEs (Table). Alanine aminotransferase elevation was the most common AE leading to discontinuation in the PreM (6.2%) and PostM groups (8.0%). Time to deterioration in global and physical functioning scales of the EORTC QLQ-C30 was similar between treatment arms for all subgroups. **Conclusions:** RIB + NSAIprovides treatment benefit to a broad range of pts with stage II/III HR+/HER2− EBC across menopausal status and age. In younger PreM pts, who typically have more aggressive disease characteristics, treatment favored RIB + NSAI, and these pts were least likely to discontinue RIB due to AEs. Clinical trial information: NCT03701334. Research Sponsor: None.

	PreM (n = 2238)			PostM (n = 2844)		
Hazard ratio[a] (95% CI)	All RIB = 1115 NSAI = 1123	<40 y RIB = 237 NSAI = 276	≥40 y RIB = 878 NSAI = 847	All RIB = 1424 NSAI = 1420	<60 y RIB = 703 NSAI = 735	≥60 y RIB = 721 NSAI = 685
Invasive disease–free survival	0.671 (0.518-0.870)	0.690 (0.419-1.137)	0.662 (0.488-0.897)	0.746 (0.607-0.917)	0.835 (0.619-1.128)	0.673 (0.506-0.896)
Distant disease–free survival	0.655 (0.498-0.861)	0.647 (0.383-1.091)	0.659 (0.478-0.908)	0.759 (0.612-0.941)	0.854 (0.625-1.168)	0.681 (0.506-0.916)
Recurrence–free survival	0.641 (0.486-0.845)	0.723 (0.429-1.220)	0.610 (0.439-0.846)	0.735 (0.588-0.919)	0.811 (0.590-1.114)	0.668 (0.487-0.915)
Disposition in RIB arm, n (%)						
RIB discontinuation due to AE	179 (16.1)	25 (10.5)	154 (17.5)	326 (22.9)	125 (17.8)	201 (27.9)
RIB reduction due to AE	248 (22.4)	64 (27.0)	184 (21.1)	332 (23.6)	169 (24.2)	163 (22.9)

[a]Hazard ratios between treatment arms (RIB + NSAI; NSAI alone), stratified by stage, prior chemotherapy, and geographic region.

517 Rapid Oral Abstract Session

The TRADE study: A phase 2 trial to assess the tolerability of abemaciclib dose escalation in early-stage HR+/HER2- breast cancer. First Author: Erica L. Mayer, Medical Oncology, Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA

Background: The CDK4/6 inhibitor abemaciclib (abema) is approved with adjuvant endocrine therapy (ET) for high-risk node positive hormone receptor positive (HR+) HER2- breast cancer. This regimen reduces cancer recurrence, yet therapy may be complicated by toxicity, limiting patient (pts) ability to maintain dose or continue medication. In the phase III monarchE study, 25.8% of pts discontinued abema early for reasons other than recurrence, 18.5% for adverse events (AEs), and 43.6% required dose reduction. Experiences with other targeted therapies suggest initial dose escalation may reduce toxicity and discontinuation. TRADE is a prospective, single-arm, phase 2 study evaluating whether a dose-escalation strategy of adjuvant abema improves drug tolerability. **Methods:** Eligible pts had node-positive HR+/HER2- breast cancer and were candidates for adjuvant abema with ET. All pts started abema at 50 mg BID for 2 weeks (wks), escalated to 100 mg BID for 2 wks, then escalated to final dose of 150 mg BID onwards. Escalation required absence of ongoing grade 3/4 or persistent grade 2 toxicity; anti-diarrheal medication was used as needed. The primary endpoint, measured at 12 wks, was a composite rate of discontinuation of abema for any reason or inability to reach or maintain the 150 mg dose. Based on assumptions from monarchE, the experimental hypothesis was that a dose-escalation schedule of abema would significantly reduce rate of the composite primary endpoint at 12 wks from 40%. **Results:** 90 pts enrolled, 89 evaluable for the primary endpoint (1 progression before 12 wks). Median age was 58 [range 24-78], 4% were Black, 3% were Hispanic. 48% had stage II disease, 52% had stage III, all received AI, 14% concurrent OFS. The study achieved the predefined primary endpoint with 26 pts (29.2%; 90% CI [21.3-38.2]; p=0.046) meeting the composite endpoint at 12 wks: 6 (6.7%) for early discontinuation (3 [3.4%] for toxicity), 8 (9.0%) for inability to reach 150 mg, and 12 (13.5%) for dose reduction from 150 mg. The most frequent >grade 2 treatment related AEs by 12 wks were neutropenia (23.3%), diarrhea (22.2%), and fatigue (20%). Rates of clinically significant diarrhea (> grade 2) within 0-4, 4-8, and 8-12 wks were 5.6%, 14.6%, 15.3%, in contrast to rates from monarchE of 20.5%, 12.1%, 7.3% in the same periods. **Conclusions:** The TRADE study is a positive trial meeting its primary endpoint. Use of an adjuvant abema dose escalation strategy allowed a greater number of pts (70.8%) to reach and maintain the 150 mg dose at 12 wks than in monarchE. Early discontinuation was infrequent, and 93.3% were continuing therapy at 12 wks. Reduced incidence and severity of clinically important toxicity such as diarrhea was observed. This dosing strategy could be considered when initiating adjuvant abemaciclib. Further follow-up will assess long-term tolerability, dosing maintenance beyond 12 wks, and correlative analyses. Clinical trial information: NCT06001762. Research Sponsor: Lilly.

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Impact of chemotherapy on financial toxicity in African-American breast cancer patients: Early findings from the navigator-assisted hypofractionation (NAVAH) phase I clinical trial. First Author: Maya J. Stephens, Medical College of Georgia, Augusta, GA

Background: With the rising cost of chemotherapy, the financial toxicity (FT) of systemic therapy can substantially impair patient quality of life. FT is also associated with various socioeconomic factors, one being race. Patients of African American race often bear the worst burden of cancer treatment-related FT, with a 40% increased mortality from breast cancer. The degree to which chemotherapy prior to radiation therapy (RT) impacts FT has yet to be formally quantified. We report early FT findings among African American breast cancer patients prior to receipt of adjuvant RT on the ongoing Navigator-Assisted Hypofractionation (NAVAH) Phase I clinical trial (ClinicalTrials.gov ID: NCT05978232) to assess the impact of chemotherapy on FT. **Methods:** African-American breast cancer patients undergoing RT were eligible if age 18+ with pathologically confirmed breast cancer following resection. As part of the trial, patients were assisted by a patient navigator during and after treatment. FT was measured using the validated 12-item COmprehensive Score for financial Toxicity-Functional Assessment of Chronic Illness Therapy (COST-FACIT) survey instrument. COST-FACIT scoring was used to find FT in patients before receipt of RT. Values from 26-44 represent Grade 0 FT (none), values from 14-25 represent mild Grade 1 FT (mild), values from 1-13 represent Grade 2 FT (moderate), and values of 0 represent Grade 3 FT (severe). The chi-square test was used to identify statistically significant differences ($p < 0.05$) between patients who received chemotherapy versus no chemotherapy prior to receipt of RT. **Results:** The first 32 enrolled patients completing the pre-RT COST-FACIT survey were evaluated. 53% of patients underwent chemotherapy before RT. Mild to moderate FT was apparent in 56% of patients. The mean and median COST-FACIT score (range 4.4-39) was 25 (+/- 10.4). 78% of patients who experienced some level of FT underwent chemotherapy and 22% of patients experiencing FT did not receive chemotherapy ($p = 0.0015$). Of patients who did not experience FT, 21% received chemotherapy and 79% of patients did not. In total, 82% of patients who underwent chemotherapy before RT reported mild to moderate FT. Grade 3 FT was not observed. **Conclusions:** The NAVAH study is the first to objectively compare FT among patients receiving chemotherapy before RT for early-stage breast cancer. Our findings indicate that more than 80% of patients who underwent chemotherapy experienced FT. Approximately 1 in 5 patients not experiencing FT received chemotherapy. The findings indicate that chemotherapy plays a significant role in patient quality of life, highlighting a subsection of patients who may benefit from proactive financial assistance to reduce the detrimental effect of FT on their livelihood. Clinical trial information: NCT05978232. Research Sponsor: Susan Komen Foundation; National Medical Fellowships.

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Out-of-pocket cost modeling of EUROPA trial arms for adjuvant breast cancer therapy: Five days of radiation versus five years of antiestrogen therapy. First Author: Ena Chinedum Oboh, The George Washington University School of Medicine and Health Sciences, Washington, DC

Background: Optimal adjuvant therapy following breast-conserving surgery in adults with low-risk, early-stage breast cancer remains uncertain. Cost and financial toxicity remain significant concerns for breast cancer patients. There is limited granular analysis of the role of insurance in the aggregate cost of five fractions of adjuvant radiotherapy (RT) versus adjuvant endocrine therapy (ET), as is being explored in the EUROPA Phase III trial. This study aims to disaggregate costs, estimate out-of-pocket (OOP) expenses by insurance plan, and increase transparency to better inform treatment decisions. **Methods:** Treatment protocols were aligned with the EUROPA trial arms. For our financial model, we used five-fraction RT and ET prescribed over 5 years, with follow-up after two years (consistent with EUROPA trial results) and five years (full duration of prescribed antiestrogen therapy). OOP costs, deductibles, and copays/coinsurance were calculated using Medicaid, Original Medicare, Medigap Plan G, and Medicare Part D plans. Data sources included medicare.gov, medicaid.oh.gov, aarpmedicareplans.com, and the CMS physician fee schedule. Price estimates reflect actual insurance plan costs rather than claims data. The model assumes a Medicare- and/or Medicaid-eligible patient aged ≥ 70 years with early-stage estrogen-receptor positive breast cancer after breast-conserving surgery. **Results:** Original Medicare beneficiaries face estimated OOP treatment costs of $1,049.06 for adjuvant ET at 24 months and $2,130.25 at five years. For five-fraction RT, the estimated OOP costs are $1,490.93 at 24 months and $2,320.12 at five years. Medigap Plan G beneficiaries incur lower OOP expenses: $682 for adjuvant ET at 24 months and $1,705 at five years, and $514 at 24 months and $1,285 at five years for five-fraction RT. In contrast, Medicaid beneficiaries have no OOP expenses for either treatment option, as Medicaid fully covers all treatments. **Conclusions:** The EUROPA trial highlights HRQOL outcomes at 24 months for endocrine therapy versus radiotherapy in women aged 70+ with luminal A-like early breast cancer. This cost analysis, based on actual cost estimates, provides a clear comparison of OOP expenses across Medicaid and Medicare plans. While RT has higher upfront OOP costs at 24 months under Original Medicare, the cost difference narrows over five years, with RT incurring slightly higher cumulative costs. This reflects RT's one-time nature versus the ongoing costs of ET, which more than doubles over the same period. Medigap Plan G beneficiaries experience significantly reduced OOP costs, favoring RT further at five years, while Medicaid eliminates OOP costs entirely for either treatment, ensuring equitable access to both options. These findings support the initial EUROPA trial results favoring RT over ET for HRQOL and treatment-related toxicity. Research Sponsor: None.

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Impact of body mass index (BMI) on efficacy and safety of abemaciclib in breast cancer patients (pts) treated in the monarchE trial. First Author: Christine Desmedt, Laboratory for Translational Breast Cancer Research, KU Leuven, Leuven, Belgium

Background: Two years (yrs) of adjuvant abemaciclib + endocrine therapy (ET) resulted in sustained improvement in invasive disease-free survival (IDFS HR=0.68, 5 yrs rates: 84% abemaciclib + ET vs 76% ET, 8% absolute benefit) in pts with hormone receptor positive, human epidermal growth factor receptor 2 negative, node-positive, high-risk early breast cancer (EBC). Obesity is an established factor influencing the biology and prognosis of breast cancer; however, the specific impact on treatment (tx) outcomes remains uncertain. Here we report efficacy and safety by BMI in monarchE. **Methods:** Pts were randomized 1:1 to receive ET for at least 5 yrs +/- abemaciclib for 2 yrs. Groups were defined by baseline BMI (kg/m^2): as obese ($\geq$30), overweight (25$<$30), and non-overweight ($<$25). IDFS/DRFS in each group was assessed using Kaplan-Meier method and unstratified Cox model. Safety was summarized by subgroup. **Results:** 1507 pts (27%) were obese, 1762 (32%) were overweight, and 2227 (41%) were non-overweight. Most obese pts were postmenopausal (67%), received aromatase inhibitor as first ET (75%) and a substantial proportion (47%) had $\geq$4 comorbidities, vs 60%, 69%, 34% among overweight pts and 47%, 63%, 30% among non-overweight, respectively. Pts $\geq$65 yrs constituted 18%, 17% and 12% of these groups. Disease characteristics were balanced across BMI groups. A consistent tx benefit in IDFS was observed with the addition of abemaciclib to ET across all 3 BMI groups: obese (HR = 0.67, 95% CI: 0.53, 0.85), overweight (HR = 0.73, 95% CI: 0.58, 0.91), and non-overweight (HR = 0.68, 95% CI: 0.55, 0.83), with an interaction p-value of 0.858. 5yr IDFS rates in the ET arm were lowest in obese pts (74%) and similar for overweight and non-overweight pts (77% in each). In the abemaciclib + ET arm, absolute improvements in IDFS were 8.8%, 5.8% and 7.9% across each respective BMI group. Similar findings were observed for DRFS. Obese pts had fewer grade$\geq$3 (G$\geq$3) neutropenia, and related dose hold/reductions. Despite higher G$\geq$3 diarrhea in obese pts, related dose reductions and discontinuations were similar in all 3 groups. G$\geq$3 ALT elevations were low in all groups. Serious AEs (SAEs) were more common in obese pts, across tx arms (Table). **Conclusions:** In pts with high-risk EBC, adjuvant abemaciclib + ET showed consistent and clinically meaningful tx benefit across BMI subgroups, along with a manageable safety profile. Additional analyses are planned to adjust for the impact of confounding factors such as comorbidities. Clinical trial information: NCT03155997. Research Sponsor: Eli Lilly and Company.

	Abemaciclib + ET			ET		
%	Obese n=723	Overweight n=886	Non-overweight n=1118	Obese n=784	Overweight n=876	Non-overweight n=1109
≥1AE Any grade	98	99	98	91	89	88
G ≥3	50	48	52	21	15	15
Neutropenia	14	19	24	0.1	0.5	2
Diarrhea	10	8	6	0.3	0.2	0.2
ALT	2	3	3	1	0.7	0.5
All tx discontinuation due to AE	7	6	5	2	0.3	0.5
Dose reductions related to any AE/diarrhea/ neutropenia	41/18/ 6	43/18/6	45/17/11	-	-	-
≥1 SAE	20	16	13	11	8	9
Fatal	3	2	1	2	1	1

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The effect of endocrine therapy omission on survival in ER-negative PR-low (1–10%) early-stage breast cancer treated with chemotherapy. First Author: Shawn Michael Doss, Medical College of Georgia, Augusta, GA

Background: The effect of endocrine therapy omission on outcomes in breast cancer (BC) with low progesterone receptor (PR) expression (1–10%) is unknown. Previously, omitting adjuvant endocrine therapy in estrogen receptor (ER)-low (1–10%) BC was associated with worse survival (1), but whether this is also true for PR 1–10% (PR-low) BC has not been studied. We analyzed outcomes for omission of endocrine therapy in patients with ER-negative PR-low stage I–III BC who received chemotherapy. **Methods:** We identified 46,704 patients from the National Cancer Database (diagnosed 2018–2020) with PR 1–10% stage I–III BC, of whom 3651 (7.8%) were ER-negative. Of these, 2,915 (79.8%) received chemotherapy. After excluding incomplete data for covariates, 2,796 remained for analysis. Cox proportional hazards models were used to analyze overall survival (OS). Multivariate Cox regression and propensity score matching were performed to account for confounding by age, stage, comorbidity score, HER2 status, year of diagnosis, and grade. This study protocol was developed and reviewed by oncology faculty prior to implementation. **Results:** Of the final cohort of 2,796 ER-negative PR-low BC patients, 73.6% were HER2-negative and 85.0% were high grade. Stage distribution was 34.8% stage I, 43.6% stage II, and 21.6% stage III. Endocrine therapy was omitted in 2,051 (73.4%). OS was 93.9% (95% CI 93.0–94.9%) at 2 years and 86.1% (95% CI 84.3–87.9%) at 4 years, with 267 total deaths. In the univariate (unadjusted) analysis, omission of endocrine therapy was associated with worse 4-year OS (hazard ratio [HR] 1.84, 95% CI 1.34–2.53, p$<$0.001). In the multivariate (adjusted) analysis, the HR was 1.72 (95% CI 1.25–2.37, p$<$0.001). Interaction testing for endocrine therapy and HER2 status was not significant. To account for possible pandemic impacts on OS, a sensitivity analysis of 2,639 patients (after excluding those who did not survive six months beyond definitive surgery) was performed and yielded a HR of 1.50 (95% CI 1.08–2.10, p=0.016). After propensity score matching of 1,490 ER-negative PR-low BC patients (matched by age, stage, comorbidity score, HER2 status, year of diagnosis, and grade), omission of endocrine therapy was still associated with worse 4-year OS (HR 1.63, 95% CI: 1.12–2.36, p=0.010). In contrast, omission of endocrine therapy in matched ER-negative PR-negative (instead of PR-low) BC patients was not associated with worse OS (HR 1.12, 95% CI: 0.92–1.37, p=0.27). **Conclusions:** In ER-negative PR-low (1–10%) early-stage BC treated with chemotherapy, omission of endocrine therapy may be associated with worse overall survival, suggesting that endocrine therapy could improve survival in ER-negative BC patients even with only low (1–10%) PR expression. Further investigation is recommended as this retrospective study design cannot establish causality. 1. Choong, 2024, *JCO*. Research Sponsor: None.

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Practice patterns related to ovarian function suppression in the SWOG S2010 clinical trial of young women with breast cancer. First Author: Norah Lynn Henry, University of Michigan Medical School, Ann Arbor, MI

Background: Addition of ovarian function suppression (OFS) to adjuvant endocrine therapy (ET) improves disease free survival for young patients at high risk of breast cancer recurrence. SWOG S2010, an ongoing clinical trial that has completed enrollment, is examining the benefit of active symptom monitoring for improving 18-month persistence with ET plus OFS. Because data are currently limited on the use of OFS and endocrine therapy in routine practice, this report of S2010 enrollees describes practice patterns related to the prescription of ET for young patients starting OFS plus ET for treatment of stage 1-3 hormone receptor-positive breast cancer. **Methods:** We characterized the baseline demographic, clinical, and pathologic data from the pre- and perimenopausal patients starting OFS plus ET for treatment of breast cancer enrolled in S2010 using descriptive statistics. **Results:** Of the 557 participants enrolled on S2010, median age was 44.5 years (range 23.5-57.1), 25% were Hispanic, 6% Black, 6% Asian, and 76% White. In addition, 39% were not college graduates, 9% were uninsured, and 58% worked full time. Most patients were overweight (34%) or obese (39%). Planned ET was aromatase inhibitor (AI) therapy for 423 (76%) and tamoxifen for 134 (26%). For OFS, 425 (80%) received GnRHa injections, 33 (6%) underwent bilateral salpingo-oophorectomy, and 74 (14%) had chemotherapy-induced ovarian failure (CIOF). Of the 32 (43%) participants with CIOF who were under the age of 45, 12 (38%) were planning to receive AI therapy without concomitant GnRHa therapy. There were 294 participants (55%) with anatomic stage 1 ER-positive breast cancer, of whom 127 (43%) did not receive chemotherapy. Of the 174 participants (33%) with anatomic stage 2 disease, 32 (18%) did not receive chemotherapy. **Conclusions:** Most participants on this clinical trial received GnRHa therapy as their method for OFS, and an AI for their endocrine therapy. We found that a small number of patients under the age of 45 with CIOF did not receive GnRHa therapy and planned to start AI therapy, even though such patients are at high risk of recovery of ovarian function. Additionally, approximately one-quarter of trial participants appeared to have low risk disease based on non-receipt of chemotherapy and anatomic Stage 1, despite NCCN guidance recommending that OFS be reserved for patients with higher risk features. These findings suggest that additional education about the optimal use of OFS in young women with hormone receptor-positive breast cancer may be warranted. Clinical trial information: NCT05568472. Research Sponsor: National Cancer Institute; R01CA266012; National Cancer Institute; UG1CA189974; Hope Foundation for Cancer Research.

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Beyond the 5-year mark: Adherence to and continuation of extended adjuvant endocrine therapy in non-metastatic breast cancer patients. First Author: Jenny Wei, Department of Hematology-Oncology, Kaiser Permanente San Francisco, San Francisco, CA

Background: Extending adjuvant endocrine therapy (AET) beyond five years has been shown to be beneficial for women with non-metastatic, hormone-responsive breast cancer. While many studies have examined adherence to (taking medication according to prescribed regimen) and continuation of (taking medication for prescribed duration) AET, most have focused on the first five years of use and data beyond that period are lacking. To address this knowledge gap, we conducted a large retrospective cohort study to determine adherence to and continuation of AET beyond the first 5 years among a cohort of non-metastatic breast cancer patients treated in a community setting. **Methods:** We estimated adherence to and continuation of extended AET (tamoxifen or aromatase inhibitor) among 13,675 women at Kaiser Permanente Northern California (KPNC), an integrated healthcare system caring for approximately 4.5 million members. The cohort consisted of women diagnosed with Stage I-III, estrogen receptor positive (ER+) breast cancer and were treated at KPNC from 2008 to 2017. Adherence was defined as medication possession ratio $>$80% for each 12-month period during follow-up. Continuation was defined as time to last pill possession date before a 180-day gap of AET and was based on the Kaplan-Meier estimator. Both adherence and continuation were examined for the 10-year period after initiation. **Results:** Of the 13,675 eligible women who initiated AET, 81% were 50 years or older, 61% were white and 76% had an Elixhauser Comorbidity Score of 2 or less. Most women had Stage I or II breast cancer (90.9%) that was progesterone receptor positive (79%) and HER2 negative (84%). We observed a gradual decline in adherence to AET each year from 79% in year 1 to 60% in year 5, followed by a dramatic drop to 23% in year 6. After year 6, annual adherence again dropped gradually and was 10% in year 10. Median AET continuation time was 5.1 years. Similarly, there was also a striking decline in AET continuation between year 5 and 6, with 52% continuing AET to the end of year 5 and 20% continuing to the end of year 6. Only 4.5% of the cohort continued to the end of year 10. **Conclusions:** We observed a substantial drop in both adherence to and continuation of AET following year 5 into year 6 with only 4.5% of the cohort continuing to the end of year 10. This period may represent an opportunity for intervention to improve use of extended AET. Future studies are needed to identify factors affecting adherence to and continuation with extended AET. Research Sponsor: None.

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Impact of initial chemotherapy dosing on subsequent dosing patterns and treatment completion in early-stage breast cancer. First Author: Maria Jose Monroy Iglesias, Memorial Sloan Kettering Cancer Center, New York, NY

Background: While breast cancer treatment guidelines provide dosing recommendations, some patients do not receive the full expected dose at outset. Preemptive dose reduction, often due to toxicity concerns, may influence subsequent reductions or early discontinuation. The impact of initial dose reductions on subsequent care delivery remains unclear. **Methods:** The Optimal Breast Cancer Chemotherapy Dosing (OBCD) study is a cohort of 34,109 women diagnosed with stage I-IIIA breast cancer at two U.S. integrated healthcare systems between 2004-2019. We examined associations between first-cycle dose proportion (FCDP), categorized as ≥95%, 90-95%, 85-90%, <85%, with average relative dose intensity (ARDI) categories and early discontinuation. Adjusted prevalence ratios (aPRs) were estimated using generalized linear models of the Poisson family to evaluate associations between FCDP (≥95% vs. <95%) and the likelihood of further dose reductions (based on ARDI) and early discontinuation. Analyses were performed overall and stratified by age, body mass index (BMI), and Charlson comorbidity index (CCI), as older age and comorbidities, including obesity, are linked to higher risk of dose reductions. **Results:** Among 9,724 women receiving adjuvant chemotherapy, 66% of those with FCDP ≥95% remained fully dosed throughout treatment. In contrast, 46% of patients in both the 90–95% and 85–90% FCDP groups stayed in the same category. The highest likelihood of early discontinuation was seen in patients with FCDP <85% (19%) compared to 13% in the FCDP ≥95% group (p <0.01). Multivariable analyses showed that women with FCDP <95% were more likely to experience further dose reductions (aPR 1.34; 95%CI 1.21-1.49), than those with FCDP ≥95%; but interactions with BMI, CCI, or age were not statistically significant. However, the associations between FCDP and early discontinuation (aPR 1.29; 95%CI 1.11-1.50) varied by BMI (p-interaction 0.02) and age (p-interaction 0.03). A lower FCDP was positively associated with early discontinuation in women with BMI 25-30kg/m^2 (aPR 1.62; 95%CI 1.27-2.07) and BMI 30-35kg/m^2 (aPR 1.50; 95%CI 1.16-1.94), but no association was observed for BMI <25 or >35 kg/m^2. Patients aged ≤49 years (aPR 1.84; 95% CI 1.39–2.45) and 50–64 years (aPR 1.25; 95% CI 1.07–1.46) with FCDP <95% were more likely to discontinue early, with no association observed in older adults. **Conclusions:** Women with breast cancer who have FCDP <95% are more likely to experience further dose reductions, regardless of age, BMI, or CCI, suggesting that initiating treatment with reduced doses may not prevent subsequent reductions. Early discontinuation was more likely among patients with FCDP <95%, particularly those with BMI 25–30 or 30–35 kg/m² or younger age. These findings may reflect frailty, treatment intolerance, or patient preferences. Understanding the drivers of these decisions is key to guide strategies that balance toxicity concerns with maintaining adequate dosing to reduce treatment cessation in at-risk groups. Research Sponsor: National Cancer Institute; R37CA222793, U24CA171524, U01CA195565, P30CA008748, and P01CA154292; Geoffrey Beene Cancer Research Center at Memorial Sloan Kettering Cancer Center; National Cancer Institute; R50CA211115.

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Chemotherapy (CT) declination among patients with early-stage hormone receptor positive breast cancer (BC) and high Oncotype DX recurrence scores (RS). First Author: Inimfon Jackson, The University of Texas MD Anderson Cancer Center, Houston, TX

Background: Among patients with hormone receptor positive, HER2-negative (HR+/HER2-) BC, the 21-gene Oncotype DX assay is both prognostic of recurrence risk and predictive of CT benefit. However, some patients decline CT despite their physician's recommendations. We investigated the factors associated with CT declination and its impact on overall survival (OS) among patients with early-stage HR+/HER2- BC and high RS. **Methods:** Patients (≥18 years) diagnosed with HR+/HER2- BC from 2018-2021, with pathologic (p) T1-T3, pN0-N1 disease and RS >25, were identified in the National Cancer Database. Multivariable logistic regression was used to examine the factors associated with CT declination. Furthermore, multivariable Cox proportional hazards regression was used to evaluate the association between CT declination and OS based on a propensity score matched 1:5 cohort using year of diagnosis, age, race/ethnicity, pT and pN. **Results:** Among 23,416 patients with early-stage HR+/HER2- BC and RS >25, 74.3% were non-Hispanic White (NHW) and 12.1% were Black. Overall, 2601 (11.1%) patients declined CT despite physician recommendation (median RS of 30). Among those declining CT, 15.8% also declined endocrine therapy. On univariate analysis, CT declination was associated with older age, Black race and lobular histology. After adjustment, each unit increase in RS was associated with lower odds of CT declination (aOR=0.97; 95%CI 0.96–0.97). A more recent year of diagnosis was associated with lower odds of CT declination while older age and Black race (aOR=1.33; 95%CI 1.17–1.51) were associated with higher odds. Additionally, patients on Medicaid (aOR=1.66; 95%CI 1.40–1.97) and Medicare (aOR=1.29; 95%CI 1.12–1.48) had higher odds of declination compared to those on private insurance. Having pN1 disease was associated with lower odds of declination than pN0 disease (aOR=0.74; 95% 0.66–0.83). There was no association between comorbidity and declination. Notably, CT declination was associated with an increased risk of death after a median follow-up of 3 years (aHR=1.28; 95%CI 1.02–1.61) among 10,909 matched patients. Sensitivity analyses among patients with RS >30 showed similar results. **Conclusions:** Though prospective studies have demonstrated the benefit of CT among patients with high RS, 11% of patients declined CT. We observed a decrease in CT declination over time, as well as with increasing RS. Of note, Black patients, and those on Medicaid or Medicare were more likely to decline chemotherapy. CT declination was associated with worse OS. While the reasons for treatment declination are multifactorial, research is needed to understand the underlying disparities and work toward improving cancer care delivery. Research Sponsor: Susan G. Komen Foundation; SAC220221; The Breast Cancer Research Foundation; 23-190.

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Treatment-related neutropenia as a predictor of response to adjuvant palbociclib in the PALLAS trial (ABCSG-42/AFT-05/BIG-14-13/PrE0109). First Author: Kristina Fanucci, Dana-Farber Cancer Institute, Boston, MA

Background: The PALLAS trial (NCT02513394) investigated the efficacy of the addition of palbociclib (palbo) to standard adjuvant endocrine therapy (ET) to reduce breast cancer recurrence. Previous analyses of this trial have not shown significant benefit of combination palbo+ET over ET alone. Given prior data showing that extent of neutropenia is associated with response to palbo and other cell cycle-specific therapies, we evaluated whether extent of neutropenia could identify responders to palbo in the adjuvant setting. **Methods:** PALLAS is a global, open-label, phase III trial that randomized patients (pts) with stage II-III hormone-receptor positive, HER2-negative breast cancer to receive ET for ≥5 years with or without standard-dose palbo for 2 years in 28-day cycles. The primary endpoint is invasive disease-free survival (iDFS). For this exploratory analysis, the palbo population was classified into pts with treatment-emergent high-grade neutropenia (HGN) with maximum grade ≥3 (absolute neutrophil count <1000), or low-grade/no neutropenia (LGN) with maximum grade <2; these groups were compared to each other and to the ET alone group for 5-year iDFS outcomes. Logistic regression examined individual baseline characteristics associated with HGN during the first 3 cycles within the palbo group. Impact of HGN during the first 3, 6, and 12 cycles on iDFS was tested using univariate and multivariable landmark Cox regression. **Results:** The safety population included 5736 pts, 2840 allocated to palbo+ET, 2896 to ET alone. Prior publications reported no new safety signals, low rates of serious infection, and no grade 5 treatment-related events. The palbo+ET group consisted of 1006 (35.4%) LGN and 1834 (64.6%) HGN. 5-year iDFS results are shown in the table. Pts who received palbo+ET and developed HGN by the end of cycle 6 had significantly improved 5-year iDFS compared to those who received ET alone (p=0.04), which remained statistically significant when adjusting for body mass index (BMI), prior chemotherapy, and race. Multivariable logistic regression showed lower BMI, prior chemotherapy, Asian race, and prior mastectomy were significantly associated with HGN (all p<0.05). **Conclusions:** In this exploratory analysis of the phase III PALLAS adjuvant trial, addition of palbo to ET appeared to be superior to ET alone in pts who developed HGN in the first 6 cycles of treatment but not in those who had LGN. These findings are consistent with observations in the metastatic setting suggesting that neutropenia could be a useful biomarker for palbo concentration and efficacy. Clinical trial information: NCT02513394. Research Sponsor: Pfizer.

Maximum grade neutropenia measured at end of cycle:	5-year iDFS				
	Palbo+ET HGN (%)	Palbo+ET LGN (%)	ET alone (%)	Hazard Ratio	p-value
3	84.9	84.4		1.06	0.54
	84.9		82.9	1.17	0.06
6	85.6	84.9		1.08	0.44
	85.6		83.4	1.19	0.04
12	86.3	85.9		1.06	0.57
	86.3		85.0	1.12	0.20

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Real-world (RW) analysis of characteristics and risk of recurrence (ROR) in Black patients (pts) with HR+/HER2− early breast cancer (EBC) eligible for NATALEE. First Author: Yara Abdou, Division of Oncology, Lineberger Comprehensive Cancer Center, The University of North Carolina at Chapel Hill, Chapel Hill, NC

Background: The NATALEE trial showed statistically significant and clinically meaningful invasive disease–free survival benefit with ribociclib + nonsteroidal aromatase inhibitor (NSAI) vs NSAI alone in pts with stage II/III HR+/HER2− EBC at high ROR that deepened even after all pts were off ribociclib. Prior RW analyses have shown clinically meaningful ROR at 5 y despite endocrine therapy (ET) among NATALEE-eligible pts. TAILORx and RxPONDER reported racial disparities in recurrence and outcomes; however, further understanding of characteristics and unmet needs in Black pts is needed. This RW analysis describes pt characteristics and outcomes among Black pts eligible for NATALEE and receiving ET. **Methods:** Data from the US Flatiron Health EHR-derived deidentified database (2011-2023) were used. Selection criteria included pts aged ≥18 y with anatomical stage I-III (AJCC) HR+/HER2− EBC who had primary tumor surgical resection and started adjuvant ET. Pt characteristics and treatment patterns were analyzed in Black vs White pts eligible for NATALEE. ET (any) adherence was defined as proportion of days covered ≥80%. Recurrence-free survival (RFS), distant recurrence–free survival (DRFS), and overall survival (OS) were assessed descriptively and using multivariate Cox regression analysis. **Results:** A total of7481 pts met selection criteria. Overall, 41.2% (242/588) of Black and 33.0% (1697/5142) of White pts met NATALEE eligibility criteria. Compared with White pts, Black pts were younger (median age, 59 y vs 62 y) and more likely to be premenopausal (29.3% vs 23.8%), have anatomical stage III disease (35.1% vs 25.7%), more extensive nodal involvement (19.8% N0, 54.1% N1, 14.0% N2, and 7.0% N3 vs 24.0% N0, 53.3% N1, 11.3% N2, and 6.2% N3), higher use of Medicaid (13.2% vs 3.6%), lower socioeconomic status (lowest socioeconomic status quintile, 33.9% vs 11.4%), higher obesity (body mass index ≥30, 52.9% vs 38.4%), and lower ET adherence (3 y ET adherence: 57.0% vs 65.2%; 5 y ET adherence: 48.3% vs 56.2%). Five-y RFS, DRFS, and OS rates were 74.3%, 77.6%, and 85.0%, respectively, in Black pts and 83.2%, 84.5%, and 90.9% in White pts. Compared to White pts, Black pts had worse RFS (hazard ratio, 1.5; *P*=0.0045), DRFS (hazard ratio, 1.4; *P*=0.0272), and OS (hazard ratio, 1.7; *P*=0.0023) after adjusting for age, menopausal status, body mass index, tumor size and grade, nodal status, chemotherapy use, and socioeconomic status index. **Conclusions:** In a RW dataset of pts eligible for adjuvant ribociclib based on NATALEE inclusion criteria, Black pts had a higher recurrence risk and worse survival compared with White pts, underscoring the opportunity to improve outcomes and address racial disparities in Black pts with HR+/HER2− EBC. Research Sponsor: None.

528 **Poster Session**

Real-world patterns of Oncotype DX (O-Dx) testing and chemotherapy (CT) use among patients with early-stage, hormone receptor−positive (HR+) breast cancer (BC). First Author: Marija Sullivan, The University of Texas MD Anderson Cancer Center, Houston, TX

Background: O-Dx, a 21-gene assay, has transformed the management of patients with early-stage, HR+, HER2-negative (HER2-) BC by guiding personalized treatment decisions regarding adjuvant CT. However, real-world patterns of CT use based on recurrence score (RS) remain a topic of interest. Using a large, hospital-based database, we evaluated testing patterns, factors associated with O-Dx testing, and examined predictors of CT use among patients by RS. **Methods:** Patients ≥18 years with early-stage, HR+/HER2- BC diagnosed from 2018-2021 who underwent surgery and had pT1-T3, pN0-N1 disease were identified in the National Cancer Database. Descriptive analyses were used to compare baseline sociodemographic, clinical and treatment characteristics by receipt of O-Dx testing. Multivariable logistic regression was used to examine factors associated with receipt of O-Dx testing and predictors of CT use, stratified by RS into 0-10 (low risk), 11-25 (intermediate risk) and > 25 (high risk). **Results:** Of 319,771 patients with early-stage, HR+/HER2- BC, 54% (172,491) received O-Dx testing. Median age was 61 among those who received testing and 65 among those who did not. Black (aOR = 0.93; 95%CI 0.90–0.95) and Hispanic patients (aOR = 0.89; 95%CI 0.86–0.92) were less likely to receive testing than White patients. Compared to private insurance, those on Medicare (aOR = 0.93; 95%CI 0.91–0.95), Medicaid (aOR = 0.89; 95%CI 0.86–0.92), or no insurance (aOR = 0.91; 95%CI 0.85–0.98) had lower odds of O-Dx testing. While older age, higher comorbidity scores and pN1 disease were associated with lower odds of testing, recent year of diagnosis, pT2 disease, lobular histology, higher grade and treatment in academic facilities were linked to higher odds of testing. Overall, 16% (51,213) of patients received CT. Of those, 17.3% did not have an O-Dx test, while 76% of those who received CT and testing had RS > 25. 4.2% of patients aged 18-49 years received CT despite RS 0-10. Among patients without a test, being Black (aOR = 1.19; 95%CI 1.12–1.26) or Hispanic (aOR = 1.08; 95%CI 1.01–1.16) was associated with higher odds of receiving CT. Black patients with RS > 25 (aOR = 0.84; 95%CI 0.76–0.93) were less likely to receive CT than White patients. Larger tumors, pN1 disease and higher-grade tumors were associated with greater odds of CT receipt while older age at diagnosis and lobular histology were associated with lower odds regardless of RS. **Conclusions:** O-Dx testing has been increasingly incorporated into clinical practice. Our findings highlight disparities in the receipt of O-Dx testing and CT use, particularly according to RS. Black patients who did not undergo O-Dx testing were more likely to receive CT, while those with RS > 25 were less likely to receive CT. Further research is needed to explore physician and patient decision-making regarding O-Dx testing and adjuvant CT. Research Sponsor: Susan G. Komen; SAC220221; Breast Cancer Research Foundation (BCRF); 23-190.

529 **Poster Session**

Estrogen receptor expression in residual breast cancer following neoadjuvant chemotherapy. First Author: Sarah K. Premji, Mayo Clinic, Rochester, MN

Background: Neoadjuvant chemotherapy (NAC) is commonly administered to patients (pts) with estrogen receptor alpha (ER) negative (immunohistochemistry [IHC] 0%) and ER-low (IHC 1-10%) breast cancer (BC). For pts without pathological complete response (pCR), ER expression may differ between baseline and residual BC following NAC. We previously demonstrated adjuvant endocrine therapy (ET) omission in ER-low early-stage BC was associated with significantly worse overall survival (OS); however, this effect was restricted to pts with residual BC following NAC and those with higher baseline ER levels (IHC 6-10%) (Choong et al., ASCO 2024). Here, we assessed how often ER was expressed in residual invasive BC for pts treated with NAC for ER-negative and ER-low BC. **Methods:** Weidentified pts with pre-treatment (tx) ER-negative and ER-low (regardless of HER2 expression) stage I-III BC treated with NAC who underwent BC surgery at Mayo Clinic Rochester between 2009 and 2023. ER IHC was performed in a CAP/CLIA laboratory. We evaluated ER expression in residual invasive BC for pts without pCR. The percent of pts with a post-tx change in ER status was estimated and reported with 95% Wilson confidence intervals. **Results:** 955 pts (838 [88%] pre-tx ER-negative; 117 [12%] pre-tx ER-low) met inclusion criteria, of whom 69% had HER2-negative and 31% HER2-positive BC. The median age at diagnosis was 52 (range: 24-86). 496 (52%) had residual BC. Residual BC was more common in HER2-negative versus (vs) positive tumors (56% vs 42%, p < 0.001) but did not differ significantly by ER status (ER-negative 51% vs ER-low 57%, p = 0.22). Of those with residual BC, 277/496 (56%) had ER re-testing. Rates of ER re-testing did not vary for pre-tx ER-negative vs -low (57% vs 51%, p = 0.37) but were significantly lower for HER2-positive vs HER2-negative tumors (39% vs 62%, p < 0.001). Among those with post-tx testing, 31/277 (11%, 95% CI: 8-15%) had an increase in ER expression from pretreatment levels (defined as ER IHC < 1% to either 1-10% or > 10%; or ER IHC 1-10% to > 10%). In these 31 pts, the original NAC was for either TNBC (21/31; 68%) or HER2+ BC (10/31; 32%). In pts with pre-tx ER-negative BC, 27/243 (11%, 95% CI: 8-16%) had ER expression in the residual BC including 14/243 (6%, 95% CI: 3-9%) with ER > 10% and 13/243 (5%, 95% CI: 3-9%) with ER 1-10%. For pts with baseline ER-low BC, 4/34 (12%, 95% CI: 5-27%) had ER > 10% in the residual BC. Among the 31 pts where ER increased following NAC, 21/31 (68%) received adjuvant ET, including 17/18 if ER was > 10% in the residual disease and 4/13 in those with ER 1-10%. **Conclusions:** In pts treated with NAC for ER-negative or ER-low BC not achieving pCR, we identified higher ER expression in the residual breast cancer in > 10% of pts. Given that omission of ET in ER-low BC with residual cancer following NAC is associated with worse survival, repeat biomarker testing should be considered in those without pCR, and ET individualized according to ER expression. Research Sponsor: None.

530 **Poster Session**

Molecular and immune profiling of breast cancer from pregnancy to postpartum: Insights into the tumour-immune landscape during breastfeeding from GEICAM EMBARCAM study. First Author: Regina Peña-Enriquez, Instituto Maimónides de Investigación Biomédica de Cordoba (IMIBIC)-Hospital Universitario Reina Sofia, Universidad de Cordoba, Córdoba, Spain

Background: Breast cancer (BC) is the most common malignancy among young women of childbearing age, with a rising incidence in this population. Pregnancy-associated breast cancer (PABC) is an aggressive entity linked to poor prognosis and elevated metastatic risk. Despite advances in BC research, the impact of pregnancy, breastfeeding, and postpartum mammary gland remodeling on tumor biology remains unclear, highlighting the need to explore their interaction with the tumor microenvironment for novel therapies. **Methods:** A gene expression and immune cell profiling analysis was conducted using the nCounter Breast Cancer 360 panel (NanoString) and CIBERSORTx (Newman 2019, Nat Biotechnol) on FFPE tumor samples from GEICAM/2017-07 EMBARCAM study (NCT04603820) PABC patients during the gestation (PABC_GS, n=21), breastfeeding (PABC_BF, n=21), and first-year postpartum (not during lactation period, PABC_FY, n=15) vs non-PABC tumours (n=49). Differential expression analysis per gene and biological signature was performed using the *limma* package. P-values were adjusted with the Benjamini-Yekutieli false discovery rate (FDR) method. Additionally, the LM22 matrix from CIBERSORTx was employed to quantify 22 immune cell types from normalized NanoString data. Statistical significance was set at 5%. **Results:** PABC clinical subtypes were 46% HR-positive/HER2-negative, 21% HER2-positive, and 33% triple-negative. Differential gene expression analysis identified similar significant enrichment pathways across all PABC groups compared to non-PABC: DNA repair-related signatures (HRD, BRCAness, BC p53) and BC proliferation (adj p<0.05), along with higher CDK4 expression and genomic risk (p<0.05). Conversely, key regulatory pathways such as apoptosis, TGF-Beta, and PD-L1 were downregulated (adj p<0.05). Nonetheless, it is noteworthy that the PABC_BF group showed a unique profile marked by increased immune activity and cell abundance (cytotoxic cells, CD8 T cells, T-reg, cytotoxicity), elevated SOX2 expression (adj p<0.05) and inflammatory chemokines levels (p<0.01) compared to non-PABC. The CIBERSORTx analysis supported these findings, demonstrating a significantly higher abundance of several immune cells in PABC_BF, remarkably CD8+ T-cells and T-regs, compared to all other groups (p<0.05). **Conclusions:** This GEICAM EMBARCAM sub-study reveals that PABC tumors display aggressive molecular features across all subtypes, contributing to poor prognosis. Notably, the breastfeeding-associated subset (PABC_BF) exhibits a highly active tumor-immune microenvironment with robust immune cell infiltration and inflammatory signalling, highlighting potential for targeted immunotherapy. These findings underscore the need for further clinical research to optimize immune-based strategies in PABC patients' management. Clinical trial information: NCT04603820. Research Sponsor: Instituto de Salud Carlos III (PI18/00817 and PI22/00969).; Fundacion Le Cado.

531 **Poster Session**

Prospective decision impact study of the Breast Cancer Index: Results from the BCI Registry study. First Author: Tara B. Sanft, Yale University, New Haven, CT

Background: The Breast Cancer Index (BCI) is a validated gene expression assay that provides an individualized risk of late distant recurrence and predicts the likelihood of benefit from extended endocrine therapy (EET) in HR+ early-stage breast cancer. The objective of this analysis was to assess the influence of BCI on clinical decision-making regarding EET. **Methods:** The BCI Registry study is a prospective, multi-institutional study investigating the long-term clinical outcome, decision impact, and quality of life in HR+ breast cancer patients receiving BCI testing as part of routine clinical care. Physicians and patients completed pre- and post-BCI test questionnaires to assess physician decision-making; physician confidence; and patient preferences and concerns for EET. Pre- and post-BCI responses were compared using McNemar's test and the Wilcoxon signed rank test. The BCI Registry Study is registered on ClinicalTrials.gov under NCT04875351. **Results:** In the current analysis,pre- and post-BCI testing questionnaires were completed for 2850 physicians and 2832 patients. 88.6% of patients were postmenopausal, 76.5% N0, 73.0% T1, 53.5% G2, and 13.0% HER2-positive. Following BCI testing, physicians changed treatment recommendations for EET in 41.2% (1175/2850) of patients (p<0.001). In cases where physicians recommended EET prior to BCI testing, 49.8% (775/1555) changed their recommendation to not treat with EET, while 31.2% (400/1280) of those who did not recommend EET prior to BCI testing changed their recommendation in favor of EET. Following BCI testing, 43.9% (1250/2850) of physicians felt more confident in their recommendation (p<0.001) and 43.2% (1223/2832) of patients felt more comfortable with their EET decision (p<0.001). The percentage of physicians having high confidence levels (confident or strongly confident) increased from 63.6% (N=1813) pre-BCI testing to 88.2% (N=2515) post-BCI testing. The percentage of physicians having low confidence levels (not at all confident, not confident, or ambivalent) decreased from 33.1% (N=943) pre-BCI testing to 11.0%(N=313) post-BCI testing. In BCI (H/I)-Low patients, 48.9% (868/1776) showed a decreased preference for EET (p<0.001). In BCI (H/I)-High patients, 34.6% (365/1056) showed an increased EET preference (p<0.001). After BCI testing, significantly more patients were less concerned about cost (23.9%, p<0.001), drug safety (25.7%, p<0.001), and EET benefit (30.9%, p<0.001). No significant change in concern regarding side-effects was observed (p=0.58). **Conclusions:** Incorporating BCI into clinical practice resulted in significant changes in physician recommendations for EET, while at the same time increasing physician confidence. Knowledge of the BCI result improved patient preference, satisfaction and reduced patient concerns regarding cost, drug safety and benefit of EET. Research Sponsor: None.

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HER2DX prognostic value in older patients with HER2-positive early breast cancer: A correlative analysis from the RESPECT phase III trial. First Author: Kazuki Nozawa, Department of Advanced Clinical Research and Development, Nagoya City University, Graduate School of Medical Sciences, Nagoya, Japan

Background: HER2DX, the first multigene assay specifically designed for HER2+ breast cancer, has demonstrated potential to guide treatment decisions. However, its validation in the context of de-escalated chemotherapy regimens, including trastuzumab monotherapy, in older patients remains limited. In the RESPECT trial (NCT01104935, JCO 2020), 1-year of trastuzumab monotherapy was shown to be a clinically meaningful adjuvant option compared to de-escalated chemotherapy and trastuzumab in older patients with HER2+ early breast cancer. This exploratory analysis of HER2DX within the RESPECT trial (Trans-RESPECT study) aimed to evaluate the assay's prognostic value. **Methods:** The RESPECT Phase III trial enrolled patients aged 70–80 years with stage I–IIIA HER2+ early breast cancer. Participants were randomized to receive trastuzumab monotherapy (H group) or trastuzumab plus chemotherapy (H+CT group). Chemotherapy regimens included paclitaxel monotherapy (35.1%), anthracycline/cyclophosphamide alone (22.9%), CMF (19.8%), docetaxel monotherapy (14.5%), or docetaxel-carboplatin (3.1%). Risk stratification into HER2DX low- or high-risk groups used both the standard 50 cutoff (scale 1-99) and an exploratory 32 cutoff, previously reported in the APT trial (Tolaney et al., Lancet Oncol, 2023). The primary endpoint was relapse-free survival (RFS), with secondary endpoints including overall survival (OS). **Results:** Among 275 patients in the RESPECT trial, 154 tumors (56.0%) were profiled using HER2DX (H group: 74; H+CT group: 80). Baseline characteristics of the profiled cohort mirrored those of the overall trial population. Most patients (92.9%) had a performance status of 0, 28.6% were older than 75 years, 53.2% were HR-negative, 80.5% had node-negative disease, and the majority had pT1c (41.6%) or pT2 (44.8%) tumors. Using the HER2DX 50 cutoff, 40 patients (26.0%) were classified as high risk, and 114 (74.0%) as low risk. RFS was higher in the HER2DX low-risk group compared to the high-risk group (hazard ratio [HR] = 2.02, 95% CI: 0.97–4.19), with 5-year RFS rates of 92% and 77%, respectively. OS was also superior in the HER2DX low-risk group (HR = 2.74, 95% CI: 1.18–6.36), with 5-year OS rates of 97% and 84%. Using the HER2DX 32 cutoff, 81 patients (52.6%) were classified as high risk, and 73 (47.4%) as low risk. In the H group, 3- and 5-year RFS were 97% and 94% in the low-risk group, compared to 87% and 81% in the high-risk group. In the H+CT group, 3- and 5-year RFS were 95% and 95% in the low-risk group, compared to 93% and 83% in the high-risk group. **Conclusions:** The HER2DX genomic risk score demonstrates prognostic value in older patients with HER2+ early breast cancer, including those treated with trastuzumab monotherapy. This assay may aid in identifying patients suitable for treatment de-escalation strategies. Additional analyses will be presented at the conference. Clinical trial information: NCT01104935. Research Sponsor: Chugai Pharmaceutical Co., Ltd.

533 Poster Session

The difference of clinical and molecular characteristics between HR-positive/HER2-positive and HR-negative/HER2-positive early breast cancer: A secondary analysis of 11 clinical trials. First Author: Hongmei Zheng, Department of Breast Surgery, Hubei Cancer Hospital, Tongji Medical College, Huazhong University of Science and Technology; Hubei Provincial Clinical Research Center for Breast Cancer, and Wuhan Clinical Research Center for Breast Cancer, Wuhan, China

Background: HER2+ early breast cancer (EBC) are treated as an identical cluster of patients in clinical practice. However, the various status of hormone receptor (HR) leads to different outcomes. We aimed to clarify the difference of clinical and molecular characteristics between HR+/HER2+ and HR-/HER2+ EBC. **Methods:** This secondary analysis assessed pathologically complete response (PCR) and disease free survial (DFS) among HR+/HER2+ and HR-/HER2+ EBC patients enrolled in the 11 clinical trials. These studies included 16866 HER2+ EBC patients, with available immunohistochemistry and/or in situ hybridization results. There are five neoadjuvant trials (TRYPHAENA, Kristine, Neosphere, BERENICE and Peony) and six adjuvant trials (HERA, HannaH, Aphinity, Katherine, PrefHer and SafeHer). The primary endpoints of the trials were PCR, DFS, overall preference proportions and adverse event rates. Kaplan–Meier approach and Cox proportional hazards model were applied to estimate the association of treatment strategies with PCR and DFS among HR+ and HR- populations. The 11 trials were all registered with ClinicalTrials.gov, number NCT00976989, NCT02131064, NCT00545688, NCT02132949, NCT02586025, NCT00045032, NCT00950300, NCT01358877, NCT01772472, NCT01401166 and NCT01566721. **Results:** In the16866 HER2+ EBC patients, except for PrefHer and SafeHer trials, which has no information about HR status, there are 13801 patients with HR details, of which, HR+ 8004 (58.0%) and HR- 5713 (41.4%). In HER2+ EBC, the various status of HR leads to different outcomes. Our study revealed an interesting phenomenon that compared to HR-/HER2+ EBC, HR+/HER2+ EBC has a lower pCR rate. However, trials from adjuvant therapy studies suggested HR+/HER2+ EBC has a longer DFS, which is not consistent with other subtype patterns. The pCR rate is a near-term indicator that visualizes the response rate to a particular treatment, and the DFS is a distant indicator that reflects the overall biological behavior of the individual. The HR+/HER2+ EBC, despite its low pCR rate, potentially improves its long-term DFS due to the addition of adjuvant endocrine therapy postoperatively. **Conclusions:** Compared to HR-/HER2+ EBC, HR+/HER2+ patients has a lower pCR rate, but has a longer DFS, which deserve further exploration. Research Sponsor: None.

The stratification of the HER2+ early breast cancer patients according to HR status in the 11 clinical trials.

Trial	Total, n	HR+, n(%)	HR-, n(%)	Unknown, n
TRYPHAENA	225	114(50.6)	111(49.4)	0
Kristine	444	276(62.2)	168(37.8)	0
Neosphere	417	197(47.2)	219(52.5)	1
BERENICE	401	252(62.8)	140(34.9)	9
Peony	329	173(52.6)	156(47.4)	0
HERA	5099	2571(50.4)	2528(49.6)	0
HannaH	596	265(44.5)	257(43.1)	74
Aphinity	4804	3082(64.2)	1722(35.8)	0
Katherine	1486	1074(72.3)	412(27.7)	0
PrefHer	488	NA	NA	NA
SafeHer	2577	NA	NA	NA

HR, hormone receptor.

534 Poster Session

Patterns of early and late recurrence across breast cancer subtypes in the CCTGMA.32 trial. First Author: Ana Elisa Lohmann, University of Western Ontario, London, ON, Canada

Background: An ongoing constant risk of recurrence out to 20 years is well established in hormone receptor positive breast cancer (BC) less so in other BC subtypes. This study aims to describe patters of early ($\leq$ 5 years of BC diagnosis) and late recurrence ($>$ 5 years of BC diagnosis) across immunohistochemically defined BC subtypes - luminal (ER/PgR+HER2-), triple negative (TN: ER/PgR/HER2-) and HER2+ (any ER/PgR) in CCTGMA.32 (NCT01101438) which investigated metformin vs placebo in patients enrolled 2010-2013. **Methods:** 3649 patients with high-risk non-metastatic BC were enrolled and followed for first locoregional and distant recurrence, new primary cancers and death. Annual rates of these events were calculated in each BC subtype and averaged for early (years 0-5) and late (after 5 years) post randomization. **Results:** In luminal (n = 2104), TN (n = 925), HER2+ (n = 620) BC the median follow-ups were 96.2 (range 0.2 to 120.7), 94.5 (0.03 to 120.5), 95.2 months (0.03 to 119.8), respectively. Patterns of events varied across subtypes and early vs late. In luminal BC, the early vs late annual invasive cancer event rates (ICERs) was 3.04 vs. 2.31 % (late rate 0.76 of early rate). The annual early vs late rates of distant recurrence (DR) were 2.33 vs 1.72% (late rate 0.74 of early rate). Bone was the most common site of DR both early and late. In the TN BC, the early vs late annual ICERs were 4.6 and 1.21% (late rate 0.35 of early rate). Annual early vs late DR rates were 3.09 vs. 0.20 % (late rate 0.28 of early rate). Visceral metastases (lung, liver, CNS) were most common early. In HER2+, early vs late annual ICERs were 2.93 vs 1.47% (late rate 0.50 of early rate). Annual early vs late DR rates were 2.25 vs 0.71% (late rate 0.32 of early rate). Bone and visceral metastases were common early. CNS was rare after 5 years in all BC subtypes. Second primary cancers (new BC and non-primary BC) were frequent across BC subtypes, with no fall-off over time; they were responsible for the majority of late events in TN and HER2+ BC. **Conclusions:** In luminal BC, risk of late ICER remains high (annual rate about three-quarters of early rate), while risk of late events was lower in TN and HER2+BC (late rates one quarter to one-third of early rates). Risk of second primary cancers did not decrease over time, and second primaries were the most frequent late events in TN and HER2+BC. Clinical trial information: NCT01101438. Research Sponsor: London Health Sciences Foundation - Ontario, Canada; Canadian Cancer Society Research Institute; National Cancer Institute; The Breast Cancer Foundation - New York; Canadian Breast Cancer Foundation - Ontario, Canada; Ontario Institute for Cancer Research; Apotex Canada; Hold'em for Life Charity.

	Luminal		TN		HER2+	
	Annual event rate (%)		Annual event rate (%)		Annual event rate (%)	
	Year 0-5	Year 5+	Year 0-5	Year 5+	Year 0-5	Year 5+
Any Invasive Cancer Event	3.04	2.31	4.60	1.21	2.93	1.47
Locoregional Event	0.50	0.29	1.15	0.26	0.64	0.15
Distant Recurrence*	2.08	1.29	3.09	0.20	2.03	0.57
Sites of First Metastasis:						
Bone	1.40	0.88	1.13	0.10	0.65	0.42
Lung	0.59	0.56	1.73	0.20	0.83	0.07
Liver	0.71	0.56	0.73	0.00	0.50	0.21
CNS	0.18	0.06	0.65	0.00	0.61	0.00
Second Primary Cancer**	0.66	0.92	0.96	0.90	0.60	0.74

*Including distant recurrence after a local regional events.
**Non-breast cancer and new breast cancer events.

535 Poster Session

Real-world evidence of PARPi-related MDS/AML risk in breast cancer patients: An international collaborative network analysis. First Author: Michela Palleschi, IRCCS Istituto Romagnolo per lo Studio dei Tumori (IRST) "Dino Amadori", Meldola, Italy

Background: Poly (ADP-ribose) polymerase (PARP) inhibitors have emerged as a significant therapeutic advance in breast cancer treatment. However, concerns about therapy-related myeloid neoplasms, specifically myelodysplastic syndrome (MDS) and acute myeloid leukemia (AML), necessitate thorough investigation of their safety profile in real-world settings. **Methods:** Using the TriNetX Global Collaborative Network, we conducted a retrospective analysis comparing breast cancer patients treated with PARP inhibitors (PARPi) versus conventional chemotherapy only (anthracyclines and taxanes). Our primary analysis utilized propensity score matching (1,702 patients per group) accounting for age and race, to evaluate the risk of developing MDS/AML. Hazard ratio (HR) was used to compare the incidence of MDS/AML between the matched cohorts. Secondary analyses included an unmatched Cox proportional hazards model in a larger cohort (1,826 vs 36,257 patients), comparison between different PARP inhibitors, and assessment of mortality risk factors. **Results:** In the propensity score-matched analysis, PARPi treated patients demonstrated a statistically significant higher risk of developing MDS/AML versus chemotherapy only cohort (16 cases versus 10, HR=5.25; 95% CI: 1.96-13.92; p$<$0.0001). Treatment patterns differed notably, with PARPi-treated patients receiving more carboplatin (HR=1.73; 95% CI: 1.42-2.10) but less anthracycline therapy (HR=0.25; 95% CI: 0.20-0.31). The unmatched Cox regression analysis confirmed these findings with a higher risk of developing AML/MSD in the PARPi cohort (HR=3.47; 95% CI: 1.87-6.27) and identified age (HR=1.03; 95% CI: 1.02-1.05) and platinum therapy (HR=2.12; 95% CI: 1.26-3.59) as independent risk factors. Within the triple negative group, the data remains statistically significant (HR=3.14; 95% CI: 1.459-6.757). No significant differences in MDS/AML risk were observed between olaparib and talazoparib. While mortality was comparable between groups, prior platinum exposure emerged as a significant mortality risk factor (HR=2.39; 95% CI: 1.09-5.09). **Conclusions:** Our findings indicate a significantly increased risk of therapy-related myeloid neoplasms with PARP inhibitor treatment compared to conventional chemotherapy, particularly in the context of previous platinum exposure in breast cancer patients. These results underscore the importance of careful patient selection and monitoring during PARP inhibitor therapy, while highlighting the need for extended follow-up studies to fully characterize long-term safety profiles. Research Sponsor: None.

537 Poster Session

Extended endocrine therapy after 5 years of adjuvant LHRH-agonist in premenopausal patients with node-positive hormone receptor (HR)-positive early breast cancer. First Author: Carmine Valenza, Division of Early Drug Development, European Institute of Oncology IRCCS, University of Milan, Milan, Italy

Background: There is no evidence regarding the benefit of extended endocrine therapy (eET) beyond 5 years of adjuvant treatment with LHRH agonists (LHRHa) in premenopausal women with node-positive, HR-positive early breast cancer (eBC). **Methods:** We conducted a retrospective study on two prospectively maintained datasets (Young Women Study and IEO Breast Cancer Dataset) to evaluate the clinical benefit of eET in women who had completed 5 years of adjuvant LHRHa, remained premenopausal, and had no evidence of distant or locoregional recurrence. This study included <40y women at diagnosis (between 2006 and 2016) with node-positive HR+ eBC, with ductal, lobular, or mixed histological subtypes, receiving or not eET (tamoxifen monotherapy or LHRHa+tamoxifen/aromatase inhibitor [AI]). The primary endpoint was the invasive breast cancer-free survival (IBCFS), calculated from the 5th year of endocrine therapy (ET) and adjusted for dataset, age at diagnosis, histotype, stage, disease subtype, type of adjuvant chemotherapy and ET received. **Results:** 503 patients were included (see Table): 287 received eET for a median duration of 3.6 years (Interquartile Range: 2.1–5.0). At a median follow-up of 7.05 years (calculated from the 5th year of ET), 50 and 72 IBCFS events occurred in the eET and non-eET groups, respectively. The adjusted Hazard Ratio (HR) for IBCFS comparing the eET to the non-eET group was 0.60 (95% CI,0.41-0.88; p<0.001). For distant recurrence or death, 28 and 46 events occurred, respectively, and the adjusted HR for distant disease free-survival was 0.43 (95% CI, 0.27-0.71). Among patients receiving eET, the adjusted HR for IBCFS comparing tamoxifen monotherapy (n=137) with LHRHa+tamoxifen/AI (n=150) was 0.75 (95% CI, 0.41-1.38). **Conclusions:** Extending endocrine therapy beyond five years of LHRHa treatment resulted in significantly higher IBCFS and distant metastasis free-survival. Larger prospective studies are required to confirm this finding and determine the most effective eET strategy. Research Sponsor: None.

Patients' characteristics.

Characteristic	Extended endocrine therapy (N=287)	No extended endocrine therapy (N=216)
Age at diagnosis, median (IQR)	37 (35-39)	37 (33-39)
Dataset: IEO | YWS, n	273 | 14	212 | 4
Histotype: ductal | lobular | mixed, %	91 | 5 | 4	95 | 3 | 2
pT: pT1 | pT2 | pT3-4, %	37 | 48 | 15	41 | 52 | 7
pN: pN1 | pN2 | pN3, %	64 | 22 | 14	73 | 17 | 10
Luminal A-like | B-like (G3 or HER2+), %	47 | 53	49 | 51
LHRHa combination during years 1-5: tamoxifen | aromatase inhibitor, %	66 | 34	76 | 22
Previous chemotherapy, %	77	70
Previous radiotherapy, %	64	62

G3, grade 3; IEO, European Institute of Oncology; IQR, interquartile range; YWS, Young Women Study.

538 Poster Session

Patterns in male and female breast cancer care: A comparative analysis of stage at presentation, treatment, and survival in the Veterans Health Administration. First Author: Ariana Naaseh, Washington University in St. Louis School of Medicine, St. Louis, MO

Background: Male breast cancer (MBC) is a rare disease that is often managed using treatment protocols derived from female breast cancer (FBC). Given its rarity, limited large-scale national cohort data exists to inform clinical treatment decisions for MBC. This study aims to compare contemporary treatment trends and survival outcomes for MBC and FBC within the Veterans Health Administration (VHA). **Methods:** We conducted a retrospective cohort study of patients diagnosed with MBC and FBC between 2000 and 2022 using national data from the VHA Cancer Cube registry. Demographics, tumor characteristics, treatment (surgery, chemotherapy, hormone therapy, and radiation), and survival were compared between MBC and FBC patients. Descriptive statistics and chi-square tests compared the cohorts. Kaplan-Meier methods and Cox proportional hazards regression model were utilized to examine overall survival (OS). **Results:** Of the 14,018 total patients who met inclusion criteria, only 13.9% (n=1952) were males. MBC patients were significantly more likely to get diagnosed at an older age (MBC 68.8 vs. FBC 60.0 years; p≤0.001) and present with stage III or IV disease (25.8% vs. 12.9%; p<0.001). Compared to FBC patients, MBC patients had significantly higher rates of receiving hormone therapy (56.8% vs. 51.6%; p<0.001) and lower rates of chemotherapy (34.3% vs. 37.4%; p=0.007), radiation (21.2% vs. 47.3%; p <0.001), and surgery (92.1% vs 93.0%; p=0.01). MBC patients were significantly less likely to undergo breast-conserving surgery (BCS) (11.2% vs. 52.0%; p <0.001) than FBC patients. In a Cox proportional hazard model including age and stratified by stage, MBC patients had reduced OS (6.9 vs. 19.0 years; p<0.001) and higher risk-adjusted hazard of all-cause mortality (adjusted hazard ratio 1.40, 95% CI 1.30-1.49). OS for MBC was lower than FBC across all stages (Table). **Conclusions:** Our national cohort study is the largest series of patients with MBC and FBC in the VHA population to date. We demonstrate that MBC patients present with advanced-stage cancer, are less likely to receive aggressive treatments, are less likely to undergo BCS, and have reduced OS across all stages, compared to FBC patients. Our findings highlight the need for further research to optimize outcomes of MBC patients. Research Sponsor: National Cancer Institute; T32CA009621.

Stage and survival of the cohort.

Clinical Stage	All Patients (n=12066)	Males (n =1952)	Median Survival for Males (years)	Females (n=12066)	Median Survival for Females (years)	P-value
0	2518	141 (7.2%)	12.3	2377 (19.7%)	Not reached	<0.001
I	5877	601 (30.8%)	9.8	5276 (43.7%)	20.2	
II	3589	709 (36.3%)	7.1	2880 (23.9%)	17.5	
III	1324	314 (16.1%)	5.4	1010 (8.4%)	10.6	
IV	730	189 (9.7%)	1.9	541 (4.4%)	2.8	

539 Poster Session

Racial differences in the prognostic value of Oncotype (RS) and MammaPrint (MP) in postmenopausal, estrogen receptor (ER)–positive, node-negative (N0) breast cancer (BC) patients with low genomic risk: A National Cancer Database (NCDB) study. First Author: Prashanth Ashok Kumar, George Washington University Medical Faculty Associates, Washington, DC

Background: Postmenopausal patients with ER+, HER2 negative, N0 BC often rely on genomic testing, such as RS or MP, to determine the benefit of chemotherapy. However, the prognostic value of RS, particularly among ethnic minority patients, remains uncertain. **Methods:** We utilized the 2021 NCDB to include postmenopausal female BC patients aged >50 years. Inclusion criteria were ER+, HER2-negative patients with, stage T1-4, N0, RS <26, or MP low risk. Patients were stratified by race, Caucasian (W) and African American (AA). Univariate analysis was performed to evaluate patient and tumor characteristics. Five-year overall survival (OS) rates were constructed using Kaplan-Meier (KM) product limit estimation. Unadjusted and covariate adjusted associations between race and OS were evaluated using Cox proportional hazard (PH) regression. Associations between race and OS among subgroups were similarly evaluated to highlight disparities and trends within the population. Hazard ratios (HRs; AA: W), 95% confidence intervals (CIs) and p-values are reported. **Results:** 96,411 patients had an RS<26 [W- 89,105 (92.42%) AA-7,306(7.58%)] and 3,146 had MP low [W-2,929(93.1%) AA-217(6.9%)]. Over 93% of patients in both groups received endocrine therapy, ~75% underwent partial mastectomy and radiation, and 7% received chemotherapy. Significant racial differences in tumor size and grade were observed in the RS group: T1 tumors (AA: 75% vs. W: 78%), T2 tumors (AA: 23% vs. W: 20%, p<0.001), G1 (AA: 29% vs. W: 34%), and G3 (AA: 13% vs. W: 9.3%, p<0.001), but these differences were not seen in the MP group. At 5 years, survival for RS <26 was 95.5% (AA) vs. 97.1% (W), and for MP low, 96% (AA) vs. 96.7% (W). The adjusted HR for RS <26 showed worse outcomes for AA (HR: 1.2, 95% CI 1.1–1.31, p<0.001), especially in younger patients, grades 1–2 tumors, T1 stage, partial mastectomy and low income. For MP low, the HR was not significant (HR: 1.08, 95% CI 0.59–1.97, p=0.8). **Conclusions:** Our analysis shows that among ER+, HER2- N0 cohort with RS <26, AA patients have a 20% increase in the risk of death compared to W patients, after adjusting for patient- and tumor-related factors. In contrast, no survival disparities were observed in the MP low-risk group. These findings suggest that RS may not be fully prognostic for AA patients even when accounting for clinic-pathologic risk factors. Study limitations include its retrospective design, potential biases, and incomplete consideration of biological and socioeconomic factors. Research Sponsor: None.

540 Poster Session

The impact of racial and socioeconomic disparities on radiation therapy delays in breast cancer patients: A National Cancer Database analysis. First Author: Mehmet Murat Zerey, Miami Cancer Institute, Baptist Health South Florida, Miami, FL

Background: Despite advancements in breast cancer (BC) treatment, significant disparities in outcomes persist in the United States. Timely initiation of adjuvant radiation therapy (RT) is crucial, as delays are associated with increased recurrence. Using the National Cancer Database (NCDB), this study provides a larger-scale analysis of racial and ethnic (R/E) disparities, examining the role of socioeconomic (SE) factors, including education and income, on RT delays and overall survival (OS) differences. **Methods:** A retrospective analysis was conducted using data from the NCDB. The study included female patients (pts) ≥18 years with stage I-III BC diagnosed between 2004 and 2020. Pts who received chemotherapy were excluded. Pts were categorized by R/E into four groups: White (W), Black (B), Hispanic (H), and Other (O). SE variables, including income and education, were stratified into quartiles (Q1–Q4) as defined by the NCDB. A delay in RT initiation was defined as starting treatment more than 3 months (mos) after surgery. Kaplan-Meier (KM) analysis with the log-rank test was used to compare OS across groups. Cox proportional hazards regression was performed to estimate hazard ratios (HR) and assess the impact of income and education on delays in RT and survival outcomes. **Results:** A total of 395,328 female BC pts were included in the analysis. The median age of the cohort was 65. Most were W (85.2%), followed by B (7.4%), H (4.0%), and O (3.5%). Almost all pts had stage I (81.6%) BC. The majority of patients were in the highest (Q4) income and education quartiles (40.2% and 45.6% respectively). Higher RT delays (> 3 mos) were observed in B (11.07%) and H (11.38%) compared to W (5.31%), (p < 0.001). Pts in the lowest income and education quartiles (Q1) experienced delays more frequently (8.02% and 9.29%, respectively) compared to those in Q4 (5.72% and 5.27%, respectively p < 0.001). KM survival analysis revealed significant differences in OS for delayed RT, with median survival of 218 mos for 0–3 mos, 211 mos for 3–6 mos, and 209 mos for > 6 mos (p < 0.001). KM survival analysis also demonstrated worse survival for pts in Q1 income and education compared to Q4 (p < 0.001). Cox proportional hazards model, when adjusted for clinical, R/E and SE factors revealed that pts in Q1 for income (HR = 1.411, p < 0.001) and education (HR: 1.036, p < 0.001) had a significantly higher risk of mortality compared to Q4. **Conclusions:** This study highlights significant R/E and SE disparities in timely RT initiation and survival outcomes among BC pts. B, H, and pts with lower S/E status experienced greater RT delays, emphasizing the critical need for targeted interventions to address delays in care and improve equity in cancer treatment. Research Sponsor: None.

541 **Poster Session**

Association between chemotherapy use and clinical outcomes in young BRCA carriers with T1N0 breast cancer: Results from an international cohort study. First Author: Filipa Lynce, Dana-Farber Cancer Institute, Boston, MA

Background: Systemic treatment decisions for young BRCA carriers with small node-negative breast cancers present unique challenges due to limited evidence on the benefits of chemotherapy in this setting. This study evaluated chemotherapy use and survival outcomes among these patients. **Methods:** The BRCA BCY collaboration (NCT03673306) is an international, multicenter, hospital-based, retrospective cohort study that included carriers of germline pathogenic variants in *BRCA1/2* diagnosed with invasive breast cancer at the age of ≤40 years between January 2000 and December 2020. Among patients diagnosed with T1N0 disease, survival outcomes - disease-free survival (DFS) and overall survival (OS) defined from breast cancer diagnosis - were compared between patients who received chemotherapy and those who did not, using multivariate Cox models adjusted for propensity score (including age at diagnosis, histology, grade, country and year of diagnosis) and risk-reducing surgeries (bilateral risk-reducing mastectomy (RRM) and/or risk-reducing salpingo-oophorectomy (RRSO)), and accounting for the delayed entry at the time of BRCA testing (i.e. left truncation). Subgroup analyses were performed according to tumor subtype (HR+/HER2- vs triple negative breast cancer (TNBC)). **Results:** Out of 5660 from 109 centers, 1280 patients had T1N0 breast cancer: T1mic (n = 14, 1.1%), T1a (n = 92, 7.2%), T1b (n = 303, 23.7%), T1c (n = 778, 60.8%), and T1 size unknown (n = 93, 7.3%). Most patients received chemotherapy (80%), although use was less frequent over time. Among patients who received chemotherapy, the majority were treated with an anthracycline-containing regimen (83.6%) and in the adjuvant setting (85.7%). Patients who received chemotherapy were younger and more likely to have high grade, TNBC or larger tumors compared to those who did not. The median follow-up was 8.7 years (IQR 5.0-13.4 years), during which 428 had DFS events including second primary breast cancer (n = 174), locoregional (n = 130), distant relapse (n = 65), second primary non breast cancer (n = 53), and 88 had died. Overall, 8-year DFS was 69.4%. In multivariate analysis, no significant differences in DFS or OS were observed between patients who received chemotherapy and those who did not (DFS HR = 0.92, 95% CI 0.65-1.31; OS HR = 0.68, 95% CI 0.37-1.24). No significant difference in 8-year DFS was observed between patients with HR+/HER2- breast cancer (n = 474) treated with or without chemotherapy (HR 0.91: 95% CI 0.59-1.43), or between patients with TNBC (n = 637) treated with or without chemotherapy (HR 0.84: 95% CI 0.46-1.53). **Conclusions:** In this global study of young BRCA carriers with T1N0 breast cancer, chemotherapy was not associated with better DFS or OS overall. However, these patients remain at high risk of events and warrant investigation of additional risk-reduction strategies. Research Sponsor: None.

542 **Poster Session**

Long-term outcomes of patients with HER2-positive invasive lobular carcinoma in the ALTTO trial (BIG 2-06/NCCTG N063D [Alliance]). First Author: Guilherme Nader Marta, Medical Oncology, Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA

Background: Invasive lobular carcinoma (ILC) is the second most common histologic subtype of breast cancer (BC), representing 10–15% of cases. HER2 overexpression is rare in ILC, and there is limited data on the clinical characteristics and outcomes of patients (pts) with HER2-positive (HER2+) ILC treated with adjuvant trastuzumab. This study aims to investigate the prognostic value of ILC histology in this setting. **Methods:** ALTTO was a multicenter, randomized phase III trial evaluating the efficacy of trastuzumab, lapatinib, their sequence, or combination as adjuvant therapy in pts with HER2+ early BC. Pts with pure ILC or invasive BC of no special type (NST) who were enrolled in trastuzumab-containing arms of the ALTTO trial were included in this analysis. Central pathology review confirmed histologic subtype and was used for classification, while local pathology was used when centralized review was unavailable (USA and China). Survival outcomes, including disease-free survival (DFS), and overall survival (OS) were evaluated using Kaplan-Meier method and multivariate Cox regression adjusted for prognostic factors. Patterns of relapse were analyzed and compared across histological subtypes. Time to distant recurrence (TTDR) and time to CNS recurrence were summarized using cumulative incidence functions. **Results:** Among pts in the trastuzumab-containing arms (N = 6281), 84.4% underwent central pathology review, with a concordance rate of 67.4% for ILC diagnosis. A total of 61 pts with pure ILC (1.0% of the cohort) and 5981 pts with NST were included in the analysis. Pts with ILC were older (mean 54.8 vs. 50.9 years; p=0.002), more likely White (95.1% vs. 68.8%; p<0.001), and postmenopausal (72.1% vs. 56.3%; p=0.01). The proportion of pts with ILC (vs NST) was higher in Europe (67.2% vs 53.7%) and lower in Asia-Pacific (8.2% vs 30.6%) (p<0.001). A significantly higher proportion of ILC (vs NST) were hormone receptor-positive (80.3% vs. 57.4%; p<0.001), Grade 1-2 (51.7% vs. 39.3%; p=0.05). At a median follow-up of 9.8 years (IQR 6.9-10.0), no significant differences in DFS (hazard ratio [HR] 1.14, 95% CI 0.66-1.97; adjusted HR [aHR] 1.33,0.77–2.31), OS (HR 0.96, 0.43-2.15; aHR 1.09, 0.48–2.44), or TTDR (HR 1.67, 0.91–3.05) were observed between ILC and NST. Central nervous system (CNS) relapses were more frequent in ILC (13.6% at 10y, 95% CI 7.1–26.1%) than in NST (5.0%, 4.5–5.7%), with an HR of 3.14 (1.52–6.48) for CNS recurrences in ILC when compared to NST. **Conclusions:** Long-term outcomes were comparable between ILC and NST in HER2+ early BC treated with trastuzumab-containing regimens. The higher incidence of CNS metastases in ILC highlights its unique relapse pattern, necessitating further investigation to optimize treatment. High discordance between central and local pathology emphasizes the need for standardized histological review in trials and treatment decisions. Clinical trial information: NCT00490139. Research Sponsor: Novartis.

543 **Poster Session**

Cost-effectiveness of HER2/neu 655 genotyping in managing trastuzumab-induced cardiotoxicity risk in HER2-positive breast cancer patients. First Author: Isabel Blancas, Hospital Universitario Clínico San Cecilio / Medicine Department, Granada University / Instituto de Investigación Biosanitaria de Granada (ibs Granada), Granada, Spain

Background: Trastuzumab has significantly improved survival in HER2-positive breast cancer patients. However, around 20% of patients experience cardiotoxicity. Cardiotoxicity has been defined as a ≥10% drop in left ventricular ejection fraction (LVEF) or LVEF <50%, or the appearance of clinical cardiac insufficiency. The HER2/neu 655 A>G polymorphism has been linked to cardiotoxicity risk. This study evaluates the cost-effectiveness of HER2/neu 655 genotyping. **Methods:** Eighty-eight HER2-positive breast cancer patients treated for early disease with trastuzumab were retrospectively analyzed. All were genotyped for HER2/neu 655 A>G (AA: n=53, AG: n=32, GG: n=3). LVEF was monitored by echocardiography or isotopic ventriculography at baseline and regular intervals. Cardiotoxicity was defined as above. Logistic regression adjusting for hormonal status and anthracycline use estimated the association between genotype and cardiotoxicity. Cost data from the Andalusian Regional Health Service included diagnostic tests, cardiology visits, pharmacologic therapy, and hospitalizations. **Results:** Among the 53 patients with the AA genotype, 3.7% experienced a decrease in LVEF, while 9.4% developed clinical symptoms. For the AG genotype (32 patients), 9.3% showed an LVEF reduction, and 28.1% presented clinical symptoms. In the GG genotype group (3 patients), 1 patient (33.3%) developed clinical symptoms. AG carriers had a significantly higher risk of cardiotoxicity than AA patients (OR adjusted for hormonal status and anthracycline treatment =4.42; p=0.037). HER2/neu 655 A>G genotyping costs €38. Asymptomatic LVEF reductions usually required 3 cardiology visits including echocardiography (€121.05 each), and one year of pharmacological treatment (carvedilol and/or enalapril therapy; €84.72 total). Cardiac insufficiency costs range from €2,992.61 (grade 1) to €9,363.56 (grade 4). **Conclusions:** HER2/neu 655 genotyping is cost-effective for identifying patients at higher risk of trastuzumab-induced cardiotoxicity. The low cost of genotyping is outweighed by the potential savings in preventing severe cardiac events. Genotype-driven monitoring and proactive cardiac and targeted cardiovascular risk management in AG carriers could reduce both the incidence and severity of cardiotoxicity. Research Sponsor: None.

544 **Poster Session**

Neuromorphological effects of simultaneous exercise during neo-/adjuvant chemotherapy in breast cancer patients: The Exercise Cancer and Cognition (ECCO) study. First Author: David Kiesl, Ordensklinikum Linz - Elisabethinen, Linz, Austria

Background: Cancer-Related Cognitive Impairment (CRCI) is commonly experienced by breast cancer patients, often linked to chemotherapy. It manifests as deficits in learning, memory, reaction time, and concentration, with the hippocampus—a critical region for cognitive and affective functions—playing a central role. The hippocampus retains neurogenesis potential throughout life, with physical exercise shown to enhance hippocampal volume and memory function. High-intensity exercise appears to have superior cognitive benefits compared to moderate aerobic activity. The ECCO study aimed to assess the neuropsychological and brain morphological effects of high-intensity interval training (HIIT) in breast cancer patients, focusing here on imaging data subanalysis. **Methods:** The ECCO-study was designed as monocentric two-armed 1:1 randomized controlled trial (RCT), including a 12-month intervention group and a control group. Patients in the intervention group were instructed to perform strength- and low-intensity endurance training at least once a week at home according to the American College of Sports Medicine (ACSM) recommendations and to complete a supervised high-intensity interval training (HIIT) once a week at our health center. Patients in the control group were advised physical activity recommendations according to the World Health Organsiation (WHO). Participants randomized to the control arm received usual care and physical activity recommendations have been given according to usual standards. The volume measurements of the brain were performed with an automatic segmentation tool FreeSurfer version 7.4. The FreeSurfer algorithm performs an automatic segmentation of subcortical volumes and reconstructs the cortex after the elimination of non-brain tissue. **Results:** MRI data were available at baseline and after 12 months for a total of 67 patients diagnosed with breast cancer. Randomized into an intervention arm (n = 35) and control arm (n = 32). The groups were comparable in all demographic factors such as age, BMI and VO2max. There were no statistically significant changes ($p < 0.05$) in the volumes between the baseline measurement and the 12-months-follow-up measurement. Other brain areas also showed no significant ($p < 0.05$) alterations between baseline and follow-up. No differences were found in the volume change between the exercise group and the control group. **Conclusions:** This analysis of the ECCO study revealed that there were no significant changes in hippocampal volume or in the more precise categorization into its subfields in either the intervention or control group of breast cancer patients. Contrary to hypotheses suggested in the literature, it was shown that breast cancer therapy does not lead to morphological changes in the hippocampus, indicating that CRCI is not based on morphological damage. Clinical trial information: NCT04789187. Research Sponsor: Verein zur Forschungsförderung der Krebshilfe OÖ.

545 **Poster Session**

Effect of a multidisciplinary intervention based on a supervised training program on cardiovascular risk and quality of life in early stage breast cancer patients. First Author: Maria Torrente, Hospital Universitario Puerta de Hierro-Majadahonda, Madrid, Spain

Background: There is growing evidence that physical activity can enhance cancer care. Exercise programs have been shown to help manage treatment side effects, improve functional outcomes, enhance overall quality of life, and reduce fatigue. Additionally, obesity and cardiovascular disease are among the most common comorbidities in breast cancer survivors. However, despite these benefits, exercise is still not widely prescribed to oncology patients. A multidisciplinary approach involving various healthcare professionals is crucial to ensuring that exercise interventions are tailored to individual needs. Our study aims to determine whether a 12-week exercise intervention can improve physical fitness and reduce cardiovascular risk in patients with early-stage breast cancer after completing oncologic treatment. For the first time, impact is assessed by measuring cardiorespiratory fitness (VO_2 max) and muscle strength, including range of motion, speed, and power. **Methods:** A total of 75 women with histologically confirmed Stage I-III primary breast cancer who have recently completed all cancer-related treatments were included. Through computer-generated simple randomization, participants were assigned to resistance training (RTG; two sessions/week for 12 weeks) or control (CG; general physical activity guidelines recommendations). Outcomes were evaluated at baseline and week 12. Muscular strength (including range of motion, speed, and power) was the primary outcome. Secondary outcomes included cardiorespiratory fitness (measured by VO_2 max-*maximum* rate of oxygen consumption attainable during exercise), cancer-related fatigue and HRQoL. All participants had Performance status 0 or 1 and completed the EUROQOL-5D 5L and EORTC-QLQ-C30 QoL online survey. **Results:** The expected number of 75 patients was enroled in the study (mean age 55.9 $\pm$ 7.4 years, all female). Patients assigned to the intervention had a significant positive change in HRQoL total score [mean difference 3.8; 95% confidence interval (CI) 0.2; 7.3; P = .038], body mass index [mean difference -0.7 kg/m2 (95% CI -1.3; -0.1); P = .022], muscle strength [mean difference 2.5 (95% CI 0.1; 5); P = .044; effect size 0.39], and cardiorespiratory fitness (VO2 max) [mean difference 2.7 (95% CI 0.8; 4.6); P = .007]. No significant changes were observed in the control group between week 0 and 12. **Conclusions:** This 12-week supervised exercise-based programme improved HRQoL, body mass index, muscle strength, range of motion, and power in loads while notably enhancing cardiorespiratory fitness. Integrating exercise into standard healthcare practice can significantly improve patient's quality of life and reduce cardiovascular risk. Research Sponsor: SPANISH SOCIETY OF MEDICAL ONCOLOGY.

546 **Poster Session**

Survival impact of adjuvant chemotherapy regimens for small (T1mi/a/b), node-negative (pN0), triple-negative breast cancer (TNBC). First Author: Kai Conrad Cecil Johnson, The Ohio State University - James Comprehensive Cancer Center, Columbus, OH

Background: While triple negative breast cancer (TNBC) represents an aggressive subtype of breast cancer worldwide, clinically low-risk cases are still encountered. When managing such cases, questions remain regarding the true added benefit of adjuvant chemotherapy on survival outcomes given the absence of dedicated prospective trials for this population. Additionally, in the event that systemic therapy is pursued for these patients, it remains unclear whether anthracycline-containing treatments lead to improved long-term outcomes. **Methods:** Given the rarity of stage 1 triple negative breast cancer, we extracted recurrence & survival data from within the ASCO-developed CancerLinQ database to perform an in-depth retrospective analysis involving women with small (pT1mi/a/b), node-negative (pN0), TNBC who underwent curative breast surgery and were diagnosed between the years 2002-2023. For the adjuvant chemotherapy recipients, only those who received a regimen of either taxane chemotherapy plus cyclophosphamide (TC) or an anthracycline & cyclophosphamide combined followed by taxane chemotherapy (AC-T) were included in this study. Our co-primary objectives were to compare the invasive recurrence-free survival (iRFS) and overall survival (OS) of patients who received adjuvant TC or AC-T versus those receiving locoregional therapy alone. Our secondary outcome included an iRFS comparison between AC-T, TC, & locoregional therapy. Clinicopathologic variables were compared with appropriate tests for the categorical and continuous variables. **Results:** Among the 159 patients identified with T1mi/a/b N0 TNBC who met inclusion criteria, 42 had undergone locoregional therapy alone, 77 had received TC chemotherapy, and 40 received AC-T. Baseline demographics found that the locoregional group had a higher proportion of T1mi/a vs T1b patients ($p < 0.001$) & a higher average age ($p < 0.002$). No differences were seen between groups in terms of germline mutations (BRCA1, BRCA1, PALB2, CHEK2, & ATM), tumor grade, lymphovascular invasion, surgery type, race, ethnicity, or average body-mass index. After a median follow up period of 57.2 months overall, we found there was a significant benefit in both iRFS (HR 2.52, 95% CI 1.1-5.83, p = 0.025) & OS (HR 6.95, 95% CI 1.62-29.79, p = 0.0027) for those who received adjuvant chemotherapy (TC or AC-T) compared to locoregional therapy alone. The 5-year iRFS was 89.9% with AC-T, 77.1% with TC, & 69.1% with locoregional therapy, whereas the 5-year OS was 96.9%, 96.3%, 85.8%, respectively. **Conclusions:** These findings suggest that a recurrence & survival benefit is seen with the application of adjuvant chemotherapy, even among this clinically low-risk population. However, whether it needs to be AC-T or TC appears less significant. Research Sponsor: None.

547 **Poster Session**

Obesity, chemotherapy dosing, and toxicity: Results from the Optimal Breast Cancer Chemotherapy Dosing study. First Author: Elizabeth Kantor, Memorial Sloan Kettering Cancer Center, New York, NY

Background: ASCO guidelines state that most cytotoxic drugs should be dosed according to full body surface area (BSA) without limiting the dose on the basis of obesity. This approach is supported by a lack of evidence to suggest that patients with obesity, when fully-dosed, experience higher risk of toxicity. Indeed, historical evidence suggests that obese, fully-dosed patients may experience lower risk of neutropenia than normal weight patients. However, questions remain regarding the representativeness of historical trial data on which this evidence is based. We examined this issue in the Optimal Breast Cancer Chemotherapy Dosing (OBCD) Study. **Methods:** The OBCD Study is a real-world cohort of 34,109 women diagnosed with stage I-IIIA breast cancer at Kaiser Permanente Northern California and Kaiser Permanente Washington between 2004-2019. Among women receiving the full dose of chemotherapy at treatment initiation ($\geq$90% of intended dose, n = 7,644), we examined risk of toxicities in women with obesity (BMI $\geq$30 kg/m^2) compared to non-obese women (BMI 18.5-$<$ 30 kg/m^2). We examined hematologic (neutropenia, anemia, thrombocytopenia) and non-hematologic (nephrotoxicity, hepatotoxicity, neuropathy, and cardiotoxicity) toxicities. Hazard ratios (HR) and 95% confidence intervals (CI) were calculated using Cox proportional hazards regression, adjusted for covariates including prevalent comorbid conditions. Secondary analyses examined associations pertaining to specific BMI groups and also stratified by administration schedule (standard vs dose-dense). **Results:** Fully-dosed patients with obesity experienced lower risk of neutropenia (HR: 0.80; 95% CI: 0.73-0.88) and any hematologic toxicity (HR: 0.83; 95% CI: 0.75-0.91) but increased risk of neuropathy (HR: 1.34; 95% CI: 1.18-1.52), cardiotoxicity (HR: 2.30; 95% CI: 1.13-4.67), and non-hematologic toxicities overall (HR: 1.31; 95% CI: 1.15-1.48). The strength of these associations increased with increasing BMI category. The inverse association between obesity and hematologic toxicity was evident for standard administration schedules (HR: 0.54; 95% CI: 0.45-0.66) but not dose-dense schedules. However, the positive association between obesity and non-hematologic toxicities persisted regardless of administration schedule. **Conclusions:** Women with obesity given the full BSA-determined chemotherapy dose are less likely to experience neutropenia than fully-dosed non-obese women. Importantly, this holds among patients with more severe obesity, but not when restricted to newer dose-dense administration schedules. Findings also suggest that fully-dosed patients with obesity may experience higher risks for neuropathy and cardiotoxicity. These findings highlight the importance of better understanding the risks and benefits of dosing strategies as treatments and patient populations continue to evolve. Research Sponsor: National Cancer Institute; R37CA222793; National Cancer Institute; U24CA171524; National Cancer Institute; U01CA195565; National Cancer Institute; P30CA008748; National Cancer Institute; P01CA154292; Geoffrey Beene Cancer Research Center at Memorial Sloan Kettering Cancer Center; National Cancer Institute; R50CA211115.

548 **Poster Session**

Clinical outcomes of patients with stage I triple-negative breast cancer (TNBC) treated with or without chemotherapy: The Mayo Clinic experience. First Author: Sumeet Kumar Yadav, Mayo Clinic Health System, Mankato, MN

Background: TNBC is associated with higher risk of recurrence and poorer survival rates than other breast cancer subtypes. For node-positive TNBC or tumors larger than 0.5 cm, chemotherapy is generally recommended. For stage I TNBC, the benefit from chemotherapy, the optimal regimen, and whether to administer it in the neoadjuvant versus adjuvant setting remain controversial. Here, we report the treatment patterns and clinical outcomes of patients with stage I TNBC treated at Mayo Clinic. **Methods:** Using the Mayo Clinic Tumor Registry data, we identified patients with stage I TNBC treated between 2010 and 2021. We used the pathologic tumor (T) category for patients treated with upfront surgery and the clinical T category for patients receiving neoadjuvant chemotherapy. We used the Kaplan-Meier method and log-rank test to compare recurrence-free survival (RFS) according to treatment groups, measured from the day of surgery. RFS was reported at a median follow-up of 3.9, 6.2, and 7.3 years for patients who received chemotherapy neoadjuvantly, adjuvantly, and surgery alone with no chemotherapy, respectively. **Results:** A total of 602 patients with Stage I TNBC were included, with a median age of 62 years. 290 (48%) underwent upfront surgery followed by adjuvant chemotherapy (pT1a: 2%, pT1b: 25%, pT1c: 74%), 127 (21%) received neoadjuvant chemotherapy followed by surgery (cT1a: 2%, cT1b: 11%, cT1c: 87%), and 185 (31%) underwent primary surgery without any chemotherapy (pT1mi/T1a: 33%, pT1b: 32%, pT1c: 35%). Most patients treated with neoadjuvant therapy received anthracycline/cyclophosphamide + taxane (70%), while most patients treated in the adjuvant setting received a non-anthracycline containing regimen (60%). The 5-year RFS was 96% (95% CI: 93-100%) for patients who received chemotherapy neoadjuvantly, 95% (95% CI: 92-98%) for those who received chemotherapy adjuvantly, and 85% (95% CI: 80-91%) for those treated with surgery alone and no chemotherapy ($P < 0.0001$). 71 (56%) of the 127 patients who received neoadjuvant therapy achieved a pCR, with only 1 RFS event (at 14 months) in that group, compared to 4 RFS events among those not achieving pCR (at 12, 20, 28 and 75 months, respectively). Among patients not receiving chemotherapy (either adjuvantly or neoadjuvantly), the 5-year RFS rates were 94% for pT1mi/T1a, 92% for pT1b and 72% for pT1c (T1mi/a/b vs T1c, $P = 0.009$). **Conclusions:** In this large cohort of stage I TNBC, patients who received chemotherapy (adjuvantly or neoadjuvantly) had better 5-year RFS compared with those treated with locoregional therapy only. Among patients receiving chemotherapy, 5-year RFS was nearly identical regardless of whether chemotherapy was administered before or after surgery. Interestingly, patients undergoing upfront surgery were more likely to receive an anthracycline-sparing chemotherapy regimen. Research Sponsor: Mayo Clinic Breast Cancer SPORE P50CA 116201; ASCO, the Conquer Cancer - Breast Cancer Research Foundation Advanced Clinical Research Award.

549 Poster Session

Clinical validation of a multi-modal Ataraxis AI platform for recurrence prediction in early-stage breast cancer across multiple patient cohorts. First Author: Jan Witowski, Ataraxis AI, New York, NY

Background: Breast cancer (BC) treatment selection is traditionally guided by clinical characteristics. However, as clinical characteristics cannot capture the complexity of a disease, genomic tools have been developed. Recent advances in artificial intelligence (AI) have allowed pathology imaging to be used to build more accurate and comprehensive prognostic/predictive models. In this study, we validated an AI test, powered by a pan-cancer histopathology foundation model, that integrates digital pathology images with clinical variables to predict breast cancer recurrence. **Methods:** The Ataraxis AI prognostic model (ATX) was developed using 4,659 stage I-III BC patients from 10 distinct cohorts. Ataraxis AI platform first extracts novel morphological features from digitized H&E slides using a pre-trained AI foundation model. These morphological features are then integrated with common clinical characteristics, such as TNM staging, ER/PR/HER2 status, age at diagnosis, or lobular or ductal histology to generate a risk score between 0 and 1. We evaluated ATX on 3,502 patients from 5 external cohorts, including 858 patients with available Oncotype DX (ODX) scores. The primary endpoint of this study was disease-free interval (DFI), defined as the time until first recurrence, with deaths prior to recurrence censored. **Results:** Across 3,502 patients spanning five validation cohorts, ATX accurately predicted DFI with a C-index of 0.71 [0.68-0.75] and hazard ratio (HR) of 3.63 [3.02-4.37, $p < 0.01$], computed for every 0.2 unit increase in the test score. Compared to ODX (n = 858), the ATX was more accurate, achieving a C-index of 0.67 [0.61-0.74] versus 0.61 [0.49-0.73]. Additionally, ATX added independent prognostic information to ODX in a multivariate analysis (HR: 3.11 [1.91-5.09, $p < 0.01$]). ATX demonstrated robust accuracy in TNBC (n = 230, C-index: 0.71 [0.62-0.81], HR: 3.81 [2.35-6.17, p = 0.02]) and HER2+ (n = 353, C-index: 0.67 [0.55-0.80], HR: 2.22 [0.99-5.01, p = 0.05]) groups. **Conclusions:** (1) ATX is predictive of breast cancer recurrence, (2) ATX improves upon the accuracy of ODX, (3) ATX demonstrates robust performance in all main BC subtypes. Research Sponsor: Ataraxis AI.

ATX evaluated across 5 cohorts individually and pooled, for both Harrell's C-index and hazard ratio.

Cohort	N	C-index	HR
Karmanos	168	0.62 [0.49-0.75]	3.82 [1.33-10.98, p=0.01]
Basel	269	0.67 [0.58-0.77]	3.98 [1.92-8.25, p<0.01]
TCGA	911	0.70 [0.63-0.77]	3.0 [2.1-4.28, p<0.01]
Providence	1733	0.74 [0.7-0.79]	4.02 [3.09-5.23, p<0.01]
Chicago	421	0.70 [0.60-0.80]	3.25 [1.45-7.31, p<0.01]
Pooled	3502	**0.71 [0.68-0.75]**	**3.63 [3.02-4.37, p<0.01]**

550 Poster Session

Pathologic complete response to neoadjuvant chemotherapy in early-stage male breast cancer across molecular subtypes and racial/ethnic groups. First Author: Jincong Q. Freeman, Department of Public Health Sciences, The University of Chicago, Chicago, IL

Background: Male breast cancer (mBC) accounts for ~1.0% of all breast cancers in the U.S. Neoadjuvant chemotherapy (NACT) is often used to downsize locally advanced tumors and/or allow for lumpectomy in early-stage breast cancer. However, data on pathologic complete response (pCR) after NACT in mBC is scarce. This study aimed to explore how pCR in male patients with early-stage breast cancer differed by molecular subtype and by race/ethnicity. **Methods:** This retrospective study analyzed data from the 2004-2021 U.S. National Cancer Database registry. Patients were eligible if they were male sex, aged ≥18 years, diagnosed with stage I-III disease, and underwent NACT. pCR (achieved/did not achieve) was defined as ypT0/TisypN0. Molecular subtypes included HR+/HER2−, HR+/HER2+, HR−/HER2+, and TNBC. Racial/ethnic groups included Asian or Pacific Islander, Black, Hispanic, White, and Other. We performed multivariable logistic regression, adjusting for age, race/ethnicity, molecular subtype, clinical T/N, and tumor grade. **Results:** Of 1428 patients, the mean age was 58.5 years (SD=12.8); 69.3% identified as White, followed by 18.8% as Black, 6.2% as Hispanic, 3.4% as Asian or Pacific Islander, and 2.4% as Other. Most (87.2%) patients had invasive ductal carcinoma. 51.3% were HR+/HER2−, 31.9% were HR+/HER2+, 11.7% were TNBC, and 5.1% were HR−/HER2+. Overall, the rate of pCR was 10.9%. Patients with HR−/HER2+ tumors achieved the highest pCR rate (37.3%) compared to 33.8% with TNBC, 14.9% with HR+/HER+, and only 3.7% with HR+/HER2− tumors ($p<.001$). The pCR rate trended higher in Asian or Pacific Islander (14.6%) or Hispanic (13.6%) patients than in Black (11.2%), White (10.4%), or Other (8.8%) patients, though not statistically significant ($p=.728$). On multivariable regression analysis, patients with HR+/HER2+ (adjusted odds ratio [aOR] 3.89, 95% CI: 2.24-6.76; $p<.001$), TNBC (aOR 8.80, 95% CI: 4.76-16.28; $p<.001$), or HR−/HER2+ (aOR 13.45, 95% CI: 6.40-28.28; $p<.001$) tumors had greater odds of having achieved pCR than those with HR+/HER2− tumors. No significant differences in odds of pCR by race/ethnicity were found. Additionally, older age (aOR 0.84 [per 10-year increase], 95% CI: 0.72-0.98; $p=.026$) and grade 1/2 (*vs* grade 3) tumors (aOR 0.39, 95% CI: 0.25-0.60; $p<.001$) were associated with lower odds of pCR. **Conclusions:** In early-stage mBC, the post-NACT pCR rate varied significantly across molecular subtypes, with the lowest rate in HR+/HER2− tumors, mirroring patterns observed in female breast cancer in the neoadjuvant setting. pCR rates were similar by race/ethnicity but lower among patients who were older or had low-grade tumors. These data suggest pCR dependence on tumor biology and could help neoadjuvant treatment selection to achieve optimal outcomes for early-stage mBC. Future research could investigate survival outcomes by pCR in this mBC population. Research Sponsor: National Institute on Aging; T32AG000243; Susan G. Komen Breast Cancer Foundation; TREND21675016.

551 Poster Session

Artificial intelligence (AI) based spatial assessment of tumor-infiltrating lymphocytes (TIL) and pathologic complete response in early HER2+ breast cancer (BC): Secondary analysis of NSABP B-41. First Author: Ilana Schlam, Dana-Farber Cancer Institute, Boston, MA

Background: Manual quantitative assessment of stromal TILs has shown promise as a biomarker in HER2+ BC. We present an AI-powered single-cell TIL assessment. **Methods:** Manual TIL assessment was completed per guidelines. Zero-shot, AI-powered pipeline (Case45) was used to analyze tumor microenvironment (TME) from H&E slides, focusing on TILs and their spatial interplay with cancer cells. The algorithm identified all cells, deriving three metrics: pct_lymphocyte (lymphocytes/total cells), AI_TIL (adjacent-tumor lymphocyte to stromal cell ratio), hotspot_immune (normalized fraction of immune cell aggregates in relation to cancer/tissue). Spearman correlation coefficients evaluated correlations; logistic regression models assessed the relationship between TIL measurements and pCR, with and without gene expression adjustments. AUC assessed predictive performance, and univariate Cox models examined TILs' association with event-free survival (EFS). **Results:** Our analyses included tumors of 262 patients with early-stage HER2+ BC, 67% estrogen receptor (ER) positive, 51% positive lymph nodes. Poor histologic grade ($p<0.001$), non-luminal (p=0.006), and ER- tumors (p=0.003) were associated with higher manual TILs. Manual TILs were moderately associated with pct_lymphocyte (r= 0.34) and AI_TIL (r= 0.43). Perthe table, manual TILs were positively associated with pCR, the association was numerically stronger in ER- tumors (Interaction p=0.38). pct_lymphocyte and AI_TIL were positively associated with pCR, regardless of ER status. hotspot_immune was strongly associated with pCR (OR=1.26 for all, 1.29 in ER-, 1.22 in ER+, $p=<0.001$). TILs and *ESR1 and ERBB2* provided complementary prognostic utility in pCR in trastuzumab-treated patients (AUC: 0.699-0.757). Among all subjects, there was no association between manual TILs and EFS (p=0.2); there was a marginal association between AI_TIL and EFS (p=0.06). **Conclusions:** The spatial characterization of TILs using an AI-powered tool shows promise as a prognostic biomarker in both HER2+/ER+ and HER2+/ER- BC, manual TIL assessment is prognostic in HER2+/ER- BC. The assessment of immune aggregates appears to be highly predictive of pCR. Further validation through prospective-retrospective studies, focused on the spatial immune heterogeneity in the TME, is required before integrating these biomarkers into routine clinical practice. Clinical trial information: NCT00486668. Research Sponsor: BCRF; BCRF 21-156.

TILs measurements and pCR.

Variable (continuous)	Cohort	OR (95% CI)	p-value
Manual TILs %	All	1.13 (1.04, 1.23)	0.004
(10-unit inc.)	ER-	1.16 (1.02, 1.31)	0.02
	ER+	1.07 (0.95, 1.21)	0.27
Percentage of Lymphocyte	All	2.00 (1.30, 3.07)	0.002
(10-unit inc.)	ER-	1.75 (0.95, 3.21)	0.07
	ER+	1.93 (1.02, 3.62)	0.04
AI TILs	All	1.22 (1.06, 1.40)	0.005
(one-tenth inc.)	ER-	1.19 (0.98, 1.44)	0.09
	ER+	1.19 (0.97, 1.46)	0.10

552 Poster Session

Ultrasensitive circulating tumor DNA (ctDNA) detection for prognostication in triple-negative breast cancer (TNBC) post-neoadjuvant chemotherapy (NAC). First Author: Luc Cabel, Institut Curie, Paris and Saint-Cloud, France

Background: NAC +/- immune checkpoint inhibitors is the standard of care for most early-stage TNBC patients. After NAC and breast surgery, adjuvant treatment decisions rely on pathological complete response (pCR) status, which does not inform on the presence of distant micrometastases. Blood-based assays for ctDNA enable non-invasive monitoring of residual disease levels at sensitivities down to 1 part-per-million (PPM). We report the prognostic value of ultrasensitive ctDNA detection during NAC in patients with TNBC. **Methods:** Early-stage TNBC patients treated with NAC in the SCANDARE prospective study were evaluated for ctDNA before, during, after NAC/pre-surgery and during post-surgical follow-up. Plasma ctDNA was profiled using NeXT Personal (Personalis), an ultrasensitive tumor-informed MRD assay that tracks up to 1,800 patient tumor-specific variants based on whole genome sequencing to attain sensitivity down to 1-3 PPM with >99.9% specificity. **Results:** Plasma ctDNA was analyzed for 279 samples from 84 TNBC patients (Stage I: 2%, II: 77%, III: 20%), of whom 35 (42%) achieved pCR after NAC. After a median follow-up of 53 months, 16 patients (19%) developed distant metastases, and 18 patients (21%) died. ctDNA was detected before NAC in all 82 patients with an available sample (median=3461 PPM, IQR: 1168-22078), with pretreatment levels in the ultrasensitive range (<100 PPM) in 12%. Most ctDNA detections during (51%) and post-NAC (55%) were <100 PPM. Patients with rates of early on-treatment ctDNA reduction faster than the median, or clearance, had significantly improved distant relapse-free interval (DRFI, log-rank $P=7.7x10^{-3}$) and overall survival (OS, log-rank $P=7.9x10^{-3}$). Patients with post-NAC, pre-surgery ctDNA clearance had significantly improved DRFI (log-rank $P=3.5x10^{-7}$) and OS (log-rank $P=1.4x10^{-11}$), and were enriched for pCR (59% vs 9%, OR=13.9, 95% CI [2.8,137.2], Fisher's exact $P=1.4x10^{-4}$). Multivariable Cox models including pCR and ctDNA detection post-NAC, pre-surgery performed significantly better than models including only pCR for predicting DRFI (LRT $P=8.0x10^{-4}$) and OS (LRT $P=6.6x10^{-4}$). ctDNA detection significantly stratified survival outcomes among patients without pCR (DRFI HR=8.2, 95% CI [1.8,37.0], Cox $P=6x10^{-3}$), with 60% of ctDNA-positive patients developing distant metastases vs 10% of ctDNA-negative patients. During follow-up, all plasma samples from non-relapsing patients were ctDNA-negative. In relapsed patients, ctDNA was detected in 95% of samples collected at relapse or tumor progression. **Conclusions:** Ultrasensitive ctDNA detection informs on the outcome of early TNBC treated by NAC, independently of pCR status. These results, obtained with samples taken post-NAC but before-surgery warrant investigating the benefit of implementing ctDNA detection in an interventional setting. Research Sponsor: Agence National de la Recherche; Site de recherche intégré contre le cancer (SiRIC).

553 Poster Session

Association of immune, proliferation gene signatures and stromal tumor infiltrating lymphocytes (sTILs) with outcomes in patients with stage I triple-negative breast cancer (TNBC). First Author: Paolo Tarantino, Dana-Farber Cancer Institute, Boston, MA

Background: Approximately one third of all TNBC diagnoses are stage 1. No validated biomarker is routinely utilized to guide treatment at this early stage. **Methods:** Samples from patients with stage I TNBC or ER-low (1-10%) breast cancer undergoing surgery at Dana-Farber/Brigham Cancer Center between 2016 and 2021 were identified. The 10-gene Core Immune Gene (CIG) signature and the 4-gene proliferation signature (both part of the TNBC-DX tool) were derived from extracted RNA. Central evaluation of sTILs was conducted at Dana-Farber, with 5% and 20% used as thresholds. All markers were tested for prediction of recurrence free survival (RFS) using the Kaplan-Meier method. **Results:** We identified 253 patients with stage I TNBC (n=218) or ER-low tumors (n=35) treated at Dana-Farber. Median age was 61 (31 – 85), most tumors were ductal (89%), high-grade (73%), 48% were >1 cm and 65% received chemotherapy. 5-year RFS in the overall cohort was 86.8%, with numerical variation by tumor size (T1a 100%, T1b 93.8%, T1c 81.7%, p=0.26). Gene signatures and sTILs were obtained for 117 and 123 patients, respectively (both for 110 patients), with their association with outcomes described in Table 1. Median follow-up was 3 years. A total of 20/117 patients (17.1%) had medium-high CIG score, with none experiencing RFS events prior to year 5. Similarly, no recurrence was observed prior to year 5 in 29 patients (24.8%) at the upper CIG quartile (vs 83-88% 5-year RFS in other quartiles). Worse outcomes were seen among patients in the upper quartile of proliferation (5-year RFS 83%, vs 88-100% in other quartiles). Overall, 33/123 patients (26.8%) had high sTILs (>20%) and experienced the highest 5-year RFS (97%, vs 78% if low sTILs). OS data will be presented. **Conclusions:** High expression of the 10-gene CIG immune signature or high sTILs are associated with numerically improved outcomes in patients with stage I TNBC that did not reach statistical significance, warranting further study as prognostic tools. Research Sponsor: None.

3- and 5-year recurrence free survival (RFS) according to gene signatures and sTILs. P values were obtained via Cox proportional hazard models.

	N	3-year RFS	5-year RFS
CIG score			
- Low	97	91% (85%, 98%)	89% (80%, 98%)
- Med-High	20	100% (100%, 100%)	100% (100%, 100%)
CIG score (quartiles)			
- ≤25%	49	94% (87%, 100%)	88% (74%, 100%)
- 25-50%	10	83% (58%, 100%)	83% (58%, 100%)
- 50-76%	29	87% (74%, 100%)	87% (74%, 100%)
- >75%	29	100% (100%, 100%)	100% (100%, 100%)
Proliferation score			
- Low	58	96% (89%, 100%)	90% (78%, 100%)
- Med-High	59	90% (82%, 99%)	90% (82%, 99%)
Proliferation score (quartiles)			
- ≤25%	30	100% (100%, 100%)	88% (67%, 100%)
- 25-50%	29	90% (77%, 100%)	90% (77%, 100%)
- 50-76%	29	100% (100%, 100%)	100% (100%, 100%)
- >75%	29	83% (68%, 100%)	83% (68%, 100%)
sTILs			
- 1-5%	62	94% (87%, 100%)	78% (63%, 98%)
- >5-20%	28	91% (81%, 100%)	91% (81%, 100%)
- >20%	33	97% (90%, 100%)	97% (90%, 100%)

554 Poster Session

Association of ImPrintTN signature with survival outcomes by race in basal-type triple negative breast cancer (TNBC): FLEX registry analysis. First Author: Priyanka Sharma, University of Kansas Medical Center, Westwood, KS

Background: ImPrintTN is a triple negative breast cancer (TNBC) immune classifier signature that has been associated with pathological complete response (pCR) to immunotherapy (IO) plus chemotherapy in ISPY2. Real Word data (RWD) from FLEX was utilized to assess the association of ImPrintTN with self-reported race and its impact on clinical outcomes in early stage TNBC. **Methods:** Patients (pts) enrolled in the FLEX (NCT03053193) trial diagnosed with early-stage TNBC and BluePrint Basal molecular subtype with available survival data, who self-identified as Black or White, were eligible for this analysis. ImPrintTN results (+/-) were acquired through whole transcriptome profiling. Chi-squared and Fisher's exact tests assessed differences in clinical characteristics. Association of pCR outcomes and ImPrintTN+/- were tested by binary logistic regression. Recurrence-free survival (RFS) was compared between race and ImPrintTN+/- using Kaplan-Meier estimates and log rank tests. Cox proportional hazards model was used to analyze the association of ImPrintTN, race, and clinical features with RFS. **Results:** Among 279 eligible patients with early stage Basal TNBC, 23.7% were Black, 76.3% were White, 27.7% had node positive disease, 49.8% received neoadjuvant therapy, 47.3% adjuvant therapy, 2.5% IO, and median follow-up was 3 years. 56.6% of pts were ImPrintTN+, similarly distributed by race (Black: 60.6%, White: 55.4%, p=0.761). Among pts treated with neoadjuvant therapy (n=139) no significant differences in pCR rates were observed by race (Black: 26.5%; White: 35.2%; p=0.46). However, a higher pCR rate was achieved in ImPrintTN+ vs ImPrintTN- cancers (39.3% vs 22.0%; OR=2.29, 95% CI [1.04-5.08]; p=0.039). The 3-year RFS was similar for Black (82.5%) and White (83.5%; p=0.91) pts. Significantly improved 3-year RFS was associated with ImPrintTN+ (87.9%) compared to ImPrintTN- (77.5%; p=0.01). Among ImPrintTN+, RFS was similar for Black (89.7%) and White (87.3%; p=0.30) pts. However, ImPrintTN- observed a trend towards lower 3-year RFS in Black (71.1%) compared with White (79.2%; p=0.24) pts. In a multivariate model, RFS probability was significantly associated with ImPrintTN (ImPrintTN+ vs ImPrintTN-: HR= 0.41, 95% CI [0.22-0.75]; p=0.004) and nodal status (LN+ vs LN-: HR= 2.98, 95% CI [1.66-5.37,]; p<0.001), while race and neo/adjuvant therapy were not. **Conclusions:** The analysis found that 56.6% of Basal TNBCs in the FLEX trial were ImPrintTN+, with similar proportions observed among Black and White pts. ImPrintTN status was prognostic for both pCR and RFS in TNBC and was associated with significantly improved RFS across racial groups. However, the negative prognostic impact of ImPrintTN- appeared more pronounced among Black compared with White pts. Ongoing research is focused on exploring biological differences within the ImPrintTN- subgroup by race. Clinical trial information: NCT03053193. Research Sponsor: Agendia, Inc.

555 Poster Session

Real-world (rw) ctDNA testing trends and associated outcomes in patients (pts) with early stage breast cancer (EBC). First Author: Erin Fidyk, Flatiron Health, New York, NY

Background: Emerging evidence from prospective studies underscores the prognostic potential of ctDNA to inform risk stratification and clinical decision-making in EBC (stage I-III). However, its use and correlation with outcomes in routine clinical practice remains less understood. We describe tumor-informed ctDNA testing trends and the association of test results with recurrence risk among pts with EBC in the rw setting. **Methods:** Pts with an EBC diagnosis (dx) after 1/1/2018 who had documented HR/HER2 status at initial dx, surgery, and ≥1 commercial ctDNA test in the early stage setting were selected using machine learning models from the Flatiron Health US-nationwide EHR-derived, deidentified, longitudinal database of >750 000 pts with BC (data cutoff 8/31/2024). ctDNA positivity (ctDNA+) was defined as having ≥1 positive test in EBC. Baseline characteristics were stratified by EBC subtype and ctDNA status. To examine the association of ctDNA status with recurrence, unadjusted Kaplan-Meier (KM) plots and adjusted Cox proportional hazards models were performed to assess recurrence-free survival among ctDNA-tested pts, controlling for age, race/ethnicity, stage, ECOG status, dx year, insurance status, practice type, and neoadjuvant/adjuvant treatment. Recurrence was indexed to surgery date and defined as locoregional or metastatic recurrence or death. **Results:** In a cohort of 195 279 pts with EBC, 14 496 ctDNA tests were performed in 4639 pts (median 2 per pt) with most in stage I (43.3%) and II (37.1%). Testing prevalence was highest in HR-/HER2- (4.9%), followed by HR-/HER2+ (3.5%), HR+/HER2+ (2.9%), and HR+/HER2- (1.9%). Testing increased from 1.6% (n = 450) of EBC pts dx in 2020 to 4.25% (n = 1278) in 2023 with a decrease in median time to first test pre- and post-2022 (35 vs 8 months respectively). Among tested pts, 921 (19.9%) had ≥1 positive test and were more likely to be younger (58 vs 64 years) and have stage III disease compared to non-tested pts. ctDNA+ patients had a worse 3-year overall survival (OS) as well as a strong association with recurrence (Table). **Conclusions:** In the largest rw study of ctDNA testing in EBC to date, pts with ctDNA+ disease across all subtypes were more likely to recur, highlighting the potential prognostic value of ctDNA testing to inform pt counseling, monitoring and treatment strategies. These rw results, coupled with findings from prospective randomized trials, support the case for ctDNA+ as a distinct risk category in the management of EBC. Research Sponsor: Flatiron Health, Inc.

	Unadjusted 3-year OS probability (95% CI)		
EBC Subtype	**ctDNA- pts**	**ctDNA+ pts**	**Adjusted HR (95% CI) All with *P* <0.01**
HR+/HER2- N = 2786	0.98 (0.97-0.99)	0.76 (0.7-0.82)	10.7 (7.08-16.1)
HR-/HER2- N = 1002	0.96 (0.95-0.98)	0.61 (0.52-0.72)	10.7 (6.34-18.1)
HR+/HER2+ N = 592	0.97 (0.95-0.99)	0.85 (0.77-0.94)	11.8 (4.54-30.8)
HR-/HER2+ N = 259	0.97 (0.94-1)	0.78 (0.62-0.97)	8.94 (1.72-46.4)

556 Poster Session

Association of genetic predisposition to low-grade systemic inflammation with cancer-related fatigue in women receiving chemotherapy for non-metastatic breast cancer in URCC07012 and URCC10055. First Author: Ayo Olowofela, Department of Radiation Oncology, Medical College of Wisconsin, Milwaukee, WI

Background: Cancer-related fatigue (CRF) is reported by ~75% of patients receiving chemotherapy for breast cancer. CRF has been linked to inflammation. Chronic, low grade systemic inflammation is a polygenic trait, and a polygenic risk score for inflammation (iPRS) might be associated with risk of CRF. **Methods:** Using data from the UK Biobank,we developed an iPRS using the INFLA-score, a composite measure of serum C-reactive protein, white-cell count, platelet count, and neutrophil-lymphocyte ratio. The iPRS was evaluated for association with CRF among women with non-metastatic breast cancer enrolled in one of two completed multi-site clinical trials of the University of Rochester Cancer Center NCI Community Oncology Research Program (NCORP) Research Base. CRF was measured before and after standard-of-care chemotherapy using the Multidimensional Fatigue Symptom Inventory-Short Form (MFSI-SF). Linear regression evaluated the change in MFSI-SF score from pre- to post-chemotherapy; logistic regression evaluated a binary outcome of any vs no worsening of scores. Analyses were adjusted for patient and treatment factors. **Results:** The NCORP cohort included 802 women who received chemotherapy (anthracycline-based = 51.8%; previous surgery = 85.0%) at a median age of 55 years (range = 22 to 81). There was an increase in MFSI in 55% of the women, with a mean increase of 8 (range=-64 to 71) from prechemotherapy (mean=8, range = -24 to 83) to post-chemotherapy (mean=15.3, range = -24 - 88), indicating an overall increase in CRF. The iPRS was associated with a significant decrease in MFSI-SF (β=-3.29; 95%CI=-6.25 to -0.34; *P*=0.029; covariate-adjusted β=-2.71; 95%CI=-5.50 to 0.08; *P*=0.057) and lower odds of worsening CRF (OR=0.66; 95%CI=0.47-0.93; *P*=0.016; covariate-adjusted OR=0.67; 95%CI=0.47 to 0.96; *P*=0.029). The negative relationship between the iPRS and change in CRF was partially explained by the finding that women with an iPRS in the highest quartile have worse pre-chemotherapy MFSI-SF scores (β=4.33; 95%CI=0.23 to 8.43; *P*=0.038). **Conclusions:** Women with genetic predisposition to low-grade systemic inflammation, indicated by a higher iPRS, have worse CRF pre-chemotherapy that does not worsen, and may improve, over the course of treatment while women with a lower iPRS have less CRF pre-chemotherapy and are at greatest risk of developing new or worsening CRF during treatment. If validated, the iPRS could identify patients in need of supportive care interventions to reduce CRF. This work was supported by the National Institutes of Health National Cancer Institute Contract No. HHSN261201500003I, Task Order No. HHSN261000039 and by UG1CA189961, URCC NCORP Research Base. Research Sponsor: National Cancer Institute/U.S. National Institutes of Health; Contract No. HHSN261201500003I, Task Order No. HHSN261000039.

557 **Poster Session**

Assessment of ovarian function suppression (OFS)-containing adjuvant endocrine therapy in premenopausal women by Breast Cancer Index. First Author: Ruth O'Regan, University of Rochester, Rochester, NY

Background: Breast Cancer Index (BCI) previously identified that premenopausal patients with *HOXB13/IL17BR* ratio (H/I)-Low tumors derived greater benefit than BCI(H/I)-High tumors from OFS-containing adjuvant endocrine therapy vs tamoxifen alone in the Suppression of Ovarian Function Trial (SOFT). This translational study of the Tamoxifen and Exemestane Trial (TEXT) was conducted to assess the predictive benefit of BCI (H/I) from exemestane (E) plus OFS over tamoxifen (T) plus OFS and validate the prognostic performance of BCI. **Methods:** Blinded BCI testing was performed in all available tumor samples from patients enrolled in TEXT, of which 1782 of 2660 had BCI successfully assessed and BCI categories assigned per established clinical cutpoints. Primary endpoints were breast cancer–free interval (BCFI) for predictive and distant recurrence–free interval (DRFI) for prognostic analyses. Per pre-specified SAP, a secondary analysis of predictive benefit combined the two OFS arms common to TEXT and SOFT (2896 of 4690 patients); clinicopathologic subgroup analyses were conducted in the combined TEXT+SOFT cohort. Cox proportional hazards models, stratified by chemotherapy use and nodal status, that included treatment assignment, BCI(H/I) status, and interaction term were used to assess BCI predictive performance by testing for treatment-by-BCI(H/I) interaction. The median follow-up was 13 years. **Results:** Among TEXT patients, 58% had BCI(H/I)-Low tumors.Patients with BCI (H/I)-Low tumors exhibited a 6.6% absolute benefit in 12-year BCFI (HR=0.61 [95% CI, 0.44-0.85]) for E+OFS versus T+OFS while those with BCI(H/I)-High tumors had an 6.3% absolute benefit (HR=0.78 [95% CI, 0.57-1.07]) (P-interaction = 0.29). Results were consistent in the combined TEXT+SOFT cohort and adjusting for clinicopathological variables. Clinical subgroup analyses consistently showed benefit of E+OFS vs T+OFS for BCI(H/I)-Low tumors, and more variable relative treatment effects among BCI(H/I)-High tumors, including by age. Post-hoc exploratory time-varying estimates suggested the treatment-by-BCI relationships may differ in years 0-5 vs >5 years. BCI and BCIN+ as continuous indices were prognostic for distant recurrence in N0 (P = 0.0004) and N1 (P < 0.0001) cancers. The 12-year DRFI was 96.3%, 90.3% and 84.9% for BCI-low, intermediate and high-risk N0 cancers, respectively. **Conclusions:** BCI was confirmed as prognostic in premenopausal women with HR+ early breast cancer enrolled in TEXT. BCI(H/I) status did not clearly predict differential benefit from E+OFS vs T+OFS. The TEXT results complement the prior results from SOFT, indicating premenopausal patients with BCI(H/I)-Low tumors benefit from more intensive endocrine therapy. Research Sponsor: Biotheranostics, Inc., a Hologic company.

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Dynamic changes in circulating tumor DNA among Taiwanese early breast cancer patients undergoing upfront surgery: Results from the VGH-TAYLOR study. First Author: Chi-Cheng Huang, Taipei Veterans Genreal Hospital, Taipei City, Taiwan

Background: Circulating tumor DNA (ctDNA) has emerged as a promising prognostic marker in breast cancer. Post-treatment ctDNA detection is associated with increased recurrence risk and reduced long-term survival. This study evaluated dynamic ctDNA changes in early breast cancer patients with distinct immunohistochemical (IHC) subtypes. **Methods:** Liquid biopsies were performed using the Oncomine Breast cfDNA Assay v2. Samples were collected at baseline (pre-surgery, visit 1), after adjuvant therapy (visit 2), and every six months thereafter (visit 3 and subsequent visits) for patients in the upfront surgery (Group 1A) arm of the VGH-TAYLOR study. Pre-operative and follow-up ctDNA detectability and its impact on recurrence-free survival (RFS) were evaluated. **Results:** A total of 577 early breast cancer patients with at least one ctDNA test were analyzed; the majority (74%, n=425) were hormone receptor (HR)-positive/human epidermal growth factor receptor 2 (HER2)-negative. Among 500 pre-operative samples, ctDNA was detected in 24% (n=121) of patients, with *TP53* (21%, n=106) and *PIK3CA* (6%, n=28) being the most prevalent mutations. During follow-up (visit 2 and later), ctDNA was detected in only 3% (n=13) of patients; all harbored *TP53* mutations, with one case also exhibiting an *ERBB3* mutation. All patients with detectable follow-up ctDNA had also tested positive pre-operatively (Table 1). Five-year RFS was 94% in the ctDNA-positive group (n=121) and 95% in the ctDNA-negative group (n=319). Among HR-negative/HER2-positive and HR-negative/HER2-negative subtypes, ctDNA positivity was associated with numerically worse RFS (90% vs. 94% and 88% vs. 89%, respectively). **Conclusions:** Following surgery and adjuvant therapy, most pre-operative ctDNA-positive cases became undetectable (89%, 108/121). Although ctDNA positivity showed a trend toward compromised RFS, particularly in HR-negative/HER2-positive and HR-negative/HER2-negative subtypes with *TP53* mutations, the high clearance rate of pre-surgery ctDNA positivity warrants longer follow-up to fully evaluate its prognostic value and the impact of liquid biopsy in early breast cancer. Clinical trial information: NCT04626440. Research Sponsor: Yonglin HealthCare Foundation.

Dynamic changes of circulating tumor DNA before surgery and after treatment across immunohistochemical subtypes among early breast cancer.

Subtype	Pre-surgery ctDNA positive	Post-treatment/follow-up ctDNA positive
HR+/HER2+	26%(9/35)	0%(0/35)
HR+/HER2-	22.8%(84/369)	1.9%(7/369)
HR-/HER2+	25%(7/28)	7.1%(2/28)
HR-/HER2-	30.8%(20/65)	6.2%(4/65)

HR: hormone receptor, HER2: human epidermal growth factor receptor II, ctDNA: circulating tumor DNA.

559 **Poster Session**

Impact of germline *BRCA* status on clinical outcomes of patients with HR+/HER2- early breast cancer. First Author: Antonio Marra, Division of Early Drug Development for Innovative Therapies, European Institute of Oncology IRCCS, Milan, Italy

Background: Germline pathogenic variants (PVs) in the *BRCA1* and *BRCA2* (g*BRCA1/2*) genes increase the risk for breast cancer (BC) development.The prognostic significance of *gBRCA1/2* in patients with hormone receptor-positive/HER2-negative (HR+/HER2) early BC is still controversial. **Methods:** This cohort study derived from a prospectively-maintained institutional database of all consecutive patients with BC who underwent germline testing, including *BRCA1*, *BRCA2* and *PALB2*, at the European Institute of Oncology (May 2002-Jan 2024). The study population comprised patients with stage I-III HR+/HER2- (estrogen receptor expression >1%) invasive BC who underwent surgery and (neo)adjuvant treatment, as endocrine therapy (ET) +/- chemotherapy (CT) (Jan 2000-Dec 2022). Primary endpoints were distant relapse-free interval (DRFI) and invasive disease-free survival (iDFS) by STEEP 2.0. Univariate and multivariate Cox proportional-hazard models were employed for survival analyses, with left-truncated models to account for the time from BC diagnosis to germline testing. **Results:** A total of 1,730 patients were included in the analyses, with 52 (3%) *BRCA1*, 180 (10%) *BRCA2*, and 9 (0.5%) *PALB2* PV carriers. Compared to non-carriers, patients with *gBRCA*1/2 and *gPALB2* PVs were younger (median age: 39 vs 42 yrs, p<.001), had advanced disease stage (stage II-III: 71% vs 58%, p<.001), higher tumor grade (G3: 54% vs 26%, p<.001) and Ki-67 expression (median: 26% vs 20%, p<.001). Patients with *gBRCA*1/2 and *gPALB2* PVs were also more likely to receive neoadjuvant (13% vs 6%, p<.001) and/or adjuvant CT (56% vs 36%, p<.001) and mastectomy (56% vs 45%, p=.002). All patients received adjuvant ET, as tamoxifen or aromatase inhibitor +/- GnRH analogue. No patient received adjuvant olaparib or CDK4/6 inhibitor. At a median follow-up of 9.7 (IQR 6-13.9) years, 335 (19%) patients experienced local relapse, 316 (18%) distant metastasis, and 124 (7.2%) died due to BC. At multivariate analyses, *gBRCA2* P/LPVs were independently associated with shorter DRFI (HR 1.46, 95%CI 1.04–2.06, p=.028) and iDFS (HR 1.34, 95 CI 1.01–1.78, p=.045), regardless of stage, nodal status, (neo)adjuvant CT, type of surgery and adjuvant ET, whereas *gBRCA1* were not. Exploratory analyses showed that among 232 *gBRCA1/2* carriers, 47 (20%) and 96 (41%) were eligible for adjuvant olaparib or abemaciclib therapy per OlympiA and monarchE criteria, respectively, with 37 (16%) eligible for both therapies. Additional analyses to unravel interaction of *gBRCA* status with adjuvant treatment are underway. **Conclusions:** Patients with HR+/HER2- early BC harboring *gBRCA2* PVs had a significantly increased risk of recurrence, with a potentially distinct impact of *BRCA2* vs *BRCA1*. Only a small proportion of this population currently qualify to adjuvant treatment escalation with targeted therapies, underscoring the need of expanding the therapeutic options in this setting. Research Sponsor: None.

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Cadence of circulating tumor DNA (ctDNA) testing for molecular surveillance in early-stage breast cancer (eBC). First Author: Marla Lipsyc-Sharf, UCLA Health Jonsson Comprehensive Cancer Center, Los Angeles, CA

Background: Post-surgical detection of molecular residual disease (MRD) via plasma ctDNA testing is strongly associated with recurrence of eBC. Our prior real-world data suggests that adjuvant MRD testing impacts clinical care for most patients (pts) with positive ctDNA (ctDNA+) results. Ongoing trials are studying whether adjuvant ctDNA testing improves eBC outcomes. While serial testing is known to improve MRD detection rates, the optimal cadence of testing is unknown. Here, we investigated the role of timing, cadence, and quantitative results of real-world ctDNA testing on detection of clinical recurrence of eBC. **Methods:** We identified eBC pts with available recurrence-free survival data who had adjuvant plasma MRD testing via a clinically validated, personalized, tumor-informed mPCR-NGS ctDNA test (Signatera, Natera, Inc.). All tests were ordered in the United States in the real-world clinical setting between 2019-2024; clinical records were reviewed. The cumulative incidence of clinical recurrence after each ctDNA test was used to calculate negative predictive value (NPV) for recurrence within 3, 6, 12, 18, 24, and 30 months (mo) post-test. ctDNA levels at different timepoints prior to recurrence were analyzed separately by ER and HER2 status. **Results:** For 819 pts with stage I-III eBC (ER+/HER2-: 249, HER2+: 68, triple-negative [TNBC]: 502), there were 4689 total plasma samples obtained in the adjuvant setting (median 5.7 time points per patient). Median time of first adjuvant ctDNA testing was 7 mo after surgery (range: 0.1-214.9). Median follow-up was 18.1 mo (range: 0.7-239.4). For pts with ER+/HER2- tumors, median time to first test was 14.6 mo (range: 0.3-214.9) versus 16.1 mo (range: 0.3-151.8) in HER2+ and 7.1 mo (range: 0.1-178.8) in TNBC. Among pts with multiple adjuvant ctDNA tests, median interval between tests was 2.8 mo (consistent across subtypes). For ER+ and TNBC tumors NPV (95%CI) gradually decreased over time from 99.5% (98.8-99.8) and 99.7% (99.2-99.9) at 3 mo to 97.7% (96.7-98.4) and 97.8% (96.6-98.5) at 30 mo, respectively. Among ctDNA+ TNBC pts, quantitative ctDNA levels were higher among those who recurred < 3 mo after a +ctDNA test than those with recurrence in 3-6 mo; median ctDNA levels were lowest in pts who recurred > 6 mos after a ctDNA+ test (median [range], 2.7 [0.03-1089.6] vs 2.0 [0.1-15.3] vs 0.3 [0.3-1.7] MTM/mL, p = 0.0041 and p = 0.0071, respectively). This trend was less pronounced in ER+HER2- disease between pts who relapsed < 6 mo, 6-9 mo, and > 9 mo after a ctDNA+ test (median [range], 11.6 [0.26-299.4] vs 4.5 [0.2-27.0] vs 3.8 [2.3-124.5] MTM/mL, p = 0.5, p = 0.8). **Conclusions:** The data from this real-world analysis of tumor-informed ctDNA testing in pts with eBC during surveillance demonstrate a high NPV for both ER+ and TNBC disease. These data guide future prospective ctDNA-guided studies aimed at therapeutic interception to improve clinical outcomes. Research Sponsor: Conquer Cancer, the ASCO Foundation; Natera, Inc.

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Association of lifestyle factors and pathological characteristics in patients with early breast cancer and overweight/obesity: Results from the Breast Cancer Weight Loss (BWEL) trial. First Author: Caterina Sposetti, Dana-Farber Cancer Institute, Boston, MA

Background: Obesity and other lifestyle factors are associated with breast cancer (BC) risk and outcomes. These relationships appear to vary in pre- vs postmenopausal women. Here we explore associations between pathological features, diet quality and physical activity (PA) in patients (pts) with BC enrolled in the BWEL (Alliance for Clinical Trials in Oncology A011401) trial, stratifying for menopausal status. **Methods:** BWEL is a phase III trial evaluating the impact of a weight loss intervention on disease outcomes in 3180 pts with stage II-III HER2– BC and body mass index ≥27 kg/m^2. The first 542 BWEL pts underwent assessment of PA (7-Day PA Recall) and diet (24-hour Diet Recall) at enrollment. Healthy Eating Index 2020 (HEI) score (0-100, higher value = healthier diet) and minutes/week (min/wk) of moderate/vigorous PA (MVPA) were calculated. Estrogen receptor (ER) and progesterone receptor (PR) expression level (%) were abstracted from pathology reports. Analyses of links between HEI score, MVPA min/wk, % ER/PR, stratified by menopausal status, were conducted using t-tests; differential associations by menopausal status used linear regression models with interaction term. **Results:** In 523 pts with available pathology data, 76.5% had ER/PR+ BC, 56.2% were postmenopausal. Median HEI score was 50.1 (range 18.1-96.4), median MVPA min/wk was 0 (range 0-630), median time from diagnosis to enrollment was 10.0 months (range 2.4-13.1). In postmenopausal pts, higher diet quality was linked to increased % ER and PR (HEI above vs below median, mean % ER 78.0 vs 66.1, p=0.012; mean % PR 57.7 vs 43.1, p=0.004). The relationship between HEI score and % ER/PR differed significantly by menopausal status (interaction term of menopausal status and % ER: p=0.006; and % PR: p=0.012); there were no significant associations between HEI scores and % ER/PR in premenopausal pts. There were no significant associations between PA and % ER/PR. **Conclusions:** Healthier diet was associated with higher % ER and PR in postmenopausal pts with BC, but no relationship was seen in premenopausal pts. These data suggest that lifestyle factors may influence BC pathologic features related to outcomes in older women. Support: U10CA180821, U10CA180882, UG1CA189823, U24CA196171, https://acknowledgments.alliancefound.org. Clinical trial information: NCT02750826. Research Sponsor: National Cancer Institute/U.S. National Institutes of Health; U10CA180821; National Cancer Institute/U.S. National Institutes of Health; U10CA180882; National Cancer Institute/U.S. National Institutes of Health; UG1CA189823; National Cancer Institute/U.S. National Institutes of Health; U24CA196171; National Cancer Institute/U.S. National Institutes of Health; U10CA180820; National Cancer Institute/U.S. National Institutes of Health; U10CA180868; National Cancer Institute/U.S. National Institutes of Health; U10CA180863; National Cancer Institute/U.S. National Institutes of Health; UG1CA189974; National Cancer Institute/U.S. National Institutes of Health; CCS 707213; Italian Association for Cancer Research (AIRC) / Gianni Bonadonna.

	% ER mean (SD)	*p value*	% PR mean (SD)	*p value*
Post-Menopausal				
HEI* score				
≤50.1 [n=134]	66.1 (43.3)	*0.012*	43.1 (41.8)	*0.004*
>50.1 [n=156]	78.0 (36.8)		57.7 (41.0)	
MVPA† min/wk				
0 [n=147]	74.5 (39.3)	*0.37*	50.0 (41.8)	*0.41*
≥1 [n=147]	70.3 (41.2)		53.0 (42.0)	
Pre-Menopausal				
HEI* score				
≤50.1 [n=124]	70.5 (38.5)	*0.15*	53.5 (41.1)	*0.43*
>50.1 [n=103]	65.5 (43.0)		49.1 (43.0)	
MVPA† min/wk				
0 [n=112]	66.3 (41.0)	*0.99*	49.5 (41.4)	*0.59*
≥1 [n=113]	66.3 (41.2)		52.6 (42.7)	

*Healthy Eating Index.
†Moderate/Vigorous Physical Activity.

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Association of infiltration of hematopoietic stem cells (HSC) with cell proliferation and patient survival in breast cancer. First Author: Masanori Oshi, Roswell Park Comprehensive Cancer Center, Buffalo, NY

Background: HSCs, also known as blood stem cells, are self-renewable cells that can develop into all types of blood cells. They are found in bone marrow and peripheral blood. However, the clinical relevance of HSCs in the BC TME remains unknown.To elucidate the clinical significance of HSC infiltration in the tumor microenvironment (TME) of breast cancer (BC). **Methods:** In silico analyses were conducted on 5,176 BC patients, including large independent cohorts; The Sweden Cancerome Analysis Network-Breast (SCAN-B) and the Molecular Taxonomy of Breast Cancer International Consortium (METABRIC), as well as multiple single-cell sequenced cohorts. HSC were identified through the xCell algorithm, and patients with high HSC levels were defined as those with HSC expression above the median in each cohort. **Results:** Fraction of HSCs ranged from 0.04-0.50% of all cells in BC TME by single cell transcriptome analyses. HSC infiltration was not correlated with its lineage cells, common myeloid progenitor cells and common lymphoid progenitor cells, but was associated with high infiltration of dendritic cells and stromal-related cells and low infiltration of Myeloid-related cells; M1-macrophages, and eosinophils, and lymphoid-related cells; Th1 cells, Tregs, NK T cells, and memory B cells. HSC high BC enriched TGF-β signaling, myogenesis, coagulation, and angiogenesis gene sets. On the other hand, all the cell proliferation-related gene sets in Hallmark collection; E2F targets, G2M checkpoint, MYC targets-v2, and mitotic spindle, enriched to low HSC BC, and HSC infiltration was significantly lower in high histological grade BC and in Ki67 high expression BC. HSC high patients were significantly associated with better overall survival compared to low patients in ER+/HER2- (both $p<0.02$), but not in TNBC in both cohorts. Interestingly, there was no survival difference by HSC infiltration in ER+/HER2- when neoadjuvant chemotherapy (NAC) was used. Together with our finding that HSC in the TME markedly reduced by NAC, we cannot help but speculate that the loss of HSCs by NAC may have contributed to lose their benefit in patient prognosis. Lastly, high levels of HSC were associated with significantly lower risk of lung metastasis and better survival, but not with brain and bone metastases. **Conclusions:** This is the first report that quantified HSCs using transcriptome in TME and demonstrated that they are rare, associated inversely with cell proliferation and with better survival in ER+/HER2- BC patients. Survival benefit of HSC infiltration was lost with NAC that reduce its infiltration. HSC high BC was associated with lower risk of lung metastasis and with better survival, but not with brain nor bone metastasis. Research Sponsor: National institutes of healthes.

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MRI-based radiomic signature and its association with genomic complexity in breast tumor heterogeneity. First Author: Joonoh Lim, Inocras Inc., San Diego, CA

Background: Breast cancer is inherently heterogeneous, posing challenges for effective treatment. Uncovering the relationship between imaging features and genomic profiles could improve patient stratification. In this study, we evaluated whether radiomic features can capture the underlying genomic complexity of breast tumors, potentially offering a non-invasive means to better characterize tumor heterogeneity. **Methods:** We analyzed 284 breast cancer patients using an integrated radiogenomic approach. MRI-derived radiomics features were extracted and clustered using unsupervised learning methods, resulting in 12 distinct clusters. We then analyzed these clusters against matched whole-genome sequencing and transcriptome data, focusing on heterogeneity-related radiomics features. Clustering was performed using dynamic tree cutting after hierarchical clustering of 10 principal components derived from 214 radiomic features. **Results:** We identified distinct patterns of tumor heterogeneity among the 12 identified clusters, named according to descending cluster size (range: 10-46). Clusters 9, 4, and 3 exhibited the highest homogeneity (in that order), with cluster 9 being the most homogeneous overall. Cluster 12, 11, 8, 7, and 5 showed varying degrees of heterogeneity, while clusters 1 and 2 were moderately heterogeneous. Cluster 1-3 were HER2-enriched (PAM50). Clusters 1 and 2 together had *ERBB2* amplifications (33%; Fisher's exact test, $P = 0.056$), whereas cluster 3 was HER2-positive (IHC) without amplifications. Cluster 1 leaned toward the basal-like subtype, while 3 leaned toward luminal A. Cluster 2 was enriched in luminal B (50%; $P = 0.012$). Cluster 1-3 were distinguishable by their degree of radiomics-quantified heterogeneity. Cluster 4 was enriched in high *Myc* expression (17%; $P = 0.059$). Cluster 5 was enriched in whole-genome-based HRD (40%; $P = 0.01$) and basal-like (52%; $P = 0.001$). Cluster 6 was deprived of *TP53* mutations (37%; $P = 0.04$), had low tumor mutational burden, and was characterized by small volume but higher surface-volume ratio, suggesting irregular shape. Cluster 8 was enriched in *PIK3CA* mutations (60%, $P = 0.046$), cluster 10 was enriched in *CHEK2* mutations (9%; $P = 0.039$), cluster 11 showed high *TERT* (40%, $P = 0.005$) and *CDKN2A* (40%; $P = 0.048$) expression, cluster 12 was predominantly post-menopausal (80%; $P = 0.47$), and both clusters 10 and 12 exhibited low *ESR1* expression (20%; $P = 0.035$). **Conclusions:** This comprehensive radiogenomic analysis demonstrates that MRI-based radiomics features can effectively capture tumor heterogeneity patterns that correlate with specific genomic alterations in breast cancer. The identification of 12 distinct clusters, each with characteristic genomic features, provides new insights into the biological basis of tumor heterogeneity, potentially opening new avenues for breast cancer subtyping. Research Sponsor: None.

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Pregnancy-associated breast cancer: Tumor infiltrating lymphocytes TILting the balance? First Author: Carsten F.J. Bakhuis, University Medical Center Utrecht, Utrecht, Netherlands

Background: Pregnancy-Associated Breast Cancer (PABC), which includes breast cancer diagnosed during pregnancy (PrBC) or postpartum (PPBC), is often more aggressive and diagnosed at more advanced stage compared to breast cancer in non-pregnant young women. The aggressive tumor growth in PABC may be influenced by the maternal shift towards immunotolerance during pregnancy, aimed at safely harboring the semi-allogenic fetus. Potentially, this shift allows cancer cells to evade immune detection. In recent years, the importance of stromal tumor-infiltrating lymphocytes (sTILs) as a marker of the anti-cancer immune response has become evident. Given the aforementioned relevance of immunotolerance in PABC development, we have evaluated the presence and prognostic importance of sTILs in PrBC and PPBC patients in this most extensive study to date. **Methods:** We assessed tumor tissues from the Dutch Pregnancy-Associated Breast Cancer Cohort, which includes PrBC and PPBC (≤1 year postpartum) patients diagnosed between 1988 and 2022. Whole slide images (H&E) of tumors from 200 patients were uniformly reviewed, and sTILs were scored according to international guidelines. Given the lack of previous sTIL cutoffs for PABC, a data-driven approach was chosen. **Results:** Our initial analysis revealed a clear survival benefit for a sTIL score of at least 20%. Therefore, our PrBC/PPBC patient group was divided into a "Low sTILs" ($<$ 20%, n = 153) and a "High sTILs" (≥20%, n = 47) group. High sTIL scores were associated with a higher histologic grade (89% grade III versus 73% in the low sTIL group, p = 0.043) and more frequent triple negativity (68% versus 43%, p = 0.021) Despite this more aggressive histopathology, higher sTILs were associated with a significantly better 5-year overall survival (OS) probability (94% versus 69%, $p < 0.001$). In a multivariable analysis, correcting for disease stage, intrinsic subtype and tumor grade, high sTIL scores remained a strong prognostic indicator in PABC (HR 7.3, 95% CI 2.24 – 23.9). In a subgroup analysis for triple negative disease only (n = 93), patients with a high sTIL score (n = 30) showed a better 5-year OS probability (93% versus 60%, p = 0.002), which also persisted in a multivariable analysis (HR 4.7, 95% CI 1.4 – 15.7). **Conclusions:** Despite the immunotolerance in pregnancy, this study demonstrates the presence and prognostic importance of sTILs in PABC. Importantly, patients with high sTILs (≥20%) had a markedly better prognosis despite having more aggressive disease characteristics, regardless of subtype. Therefore, sTILs may be an important prognostic indicator and may aid in selecting patients to forgo adjuvant systemic therapy, especially during pregnancy. Research Sponsor: A Sister's Hope for Breast Cancer Research; Private philantropist (unrestricted funding for this project).

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Effect of allostatic load and measures of segregation on cancer detection and false positive rate after screening mammography. First Author: Niam Abeysiriwardena, Massachusetts General Hospital, Boston, MA

Background: Allostatic load (AL), a cumulative stress measure and residential segregation (MRSs) have been associated with breast cancer (BC) outcomes. We assess the association of AL and MRSs on breast screening outcomes. **Methods:** From the Mass General Brigham Biobank, we retrospectively identify women aged ≥40, who underwent screening mammography from Jan 1, 2021 to Dec 31, 2021. We collected age, self-reported race/ethnicity, and zip code. Five MRSs were computed: Dissimilarity, Isolation (BI), Delta Index, Absolute Centralization, and Spatial Proximity. To compute AL, we assessed cardiovascular, metabolic, immune and renal lab values. AL was assigned one point for each lab value in the worst quartile and summed. We assessed any false positive (FP) and cancer diagnoses within 12 months after the index screen. Multiple imputation was performed for missing covariates. Multivariable logistic regression models were constructed to assess age, race, AL, and each MRSs association with cancer detection and FP rates. Rubin's rules were applied to estimate overall odds ratios (OR), confidence intervals (CI), and p-values for all covariates. **Results:** Of 13,754 women assessed, 1.2% (n=169) women received a cancer diagnosis. Most of the women were White (87.6%), 2.6% Asian, 5.3% Black; 1.5% self-identified as Hispanic; mean age, 64.4±11.3SD. Each point increase in AL increased the risk of cancer detection after screening mammography by 15% (OR=1.15,95% CI[1.06, 1.25],p=0.001). No association was detected between each MRS and cancer detection (all p>0.22). BI, the expected proportion of neighbors belonging to the same group, was associated with FP rate, with BI > 0.6 increasing the odds of FPs (OR=2.80[1.13-6.92],p=0.026). After adjusting for AL and MRSs, age and race were not significantly associated with cancer detection, but 5-year changes in age were associated with lower FP rate (OR=0.82[0.80, 0.84],p<0.001). **Conclusions:** AL was associated with an increased risk of cancer detection after screening mammography after adjusting for age, race, and MRSs. The MRS BI above 0.6 was associated with an increased false positive rate. Further work is needed to confirm these observations. Clinical Relevance Statement: AL and MRS (i.e., BIS) may represent potential biomarkers for personalized mammographic screening for BC. Research Sponsor: None.

566 Poster Session

Prognostic value of systemic inflammation in early-stage breast cancer in the CANTO cohort (SIM-CANTO). First Author: Julia Dixon-Douglas, Peter MacCallum Cancer Centre, Hobart, Australia

Background: The importance of host anti-tumor immunity in early-stage breast cancer (eBC) is now well recognised. Neutrophil / lymphocyte ratio (NLR) is a peripheral blood-based measure of systemic inflammation and immune status that has been associated with prognosis in other tumour types.We aimed to evaluate the prognostic value of NLR in a large prospective cohort of eBC. **Methods:** Patients with eBC (stage I-III) in the national French CANTO (NCT01993498) cohort with baseline peripheral blood counts (obtained after diagnosis and before any eBC treatment, including surgery) were included, regardless of systemic (neo)adjuvant therapy. The independent variable of interest was baseline NLR assessed as a continuous variable. Outcomes included invasive- and distant-disease-free survival (iDFS, DDFS) and overall survival (OS). We performed univariable analysis followed by multivariable Cox regression models sequentially adjusting for age, biologic subtype, TNM stage and treatment. Main analyses were conducted in the overall cohort, while additional analyses explored the role of NLR in subtypes (ER+/HER2-, HER2+, TNBC). For a cohort of patients receiving neoadjuvant therapy we tested the impact of NLR or pCR using Wilcoxon test. Sensitivity analyses used NLR as a categorical variable (using median NLR as cutoff to define high vs low NLR). **Results:** Overall, 10 470 patients were included. Median follow-up was 6.7 years (5.1 – 8.5). The median age at diagnosis was 56.4 years. Most (78%) of patients had stage I/II eBC, 77% ER+/HER2-, 13% HER2+ and 9% TNBC. The median NLR was 2.03. In the univariate analysis, there was a significant association between increasing NLR and worse DDFS in the overall cohort (HR: 1.1, p = 0.004; 95% CI:1.1 – 1.16) and in the ER+/HER2- cohort (HR: 1.1; p = 0.03; 95%CI:1.1 – 1.2). In a model adjusted by age and biologic subtype, NLR showed significant associations with DDFS (HR 1.07; p = 0.04) in the global cohort, but these associations did not maintain significance after further adjustment for TNM stage and treatment. Similarly, in the ER+/HER2- cohort, NLR was significantly associated with DDFS when adjusted for age (HR 1.08; p = 0.02), which was no longer significant after adjusting for TNM stage. No statistically significant differences were observed across other subtypes for DDFS, iDFS or OS, nor for pCR in the neoadjuvant cohort. Sensitivity analysis showed consistent results, in particular low NLR was significantly associated with improved DDFS (HR: 0.8, p = 0.03; 95%CI: 0.7 – 0.9) in the ER+/HER2- subgroup. **Conclusions:** Systemic inflammation, as measured by baseline NLR, was associated with significantly shorter DDFS in the overall CANTO cohort and in the ER+/HER2- subgroup in univariable and age- adjusted analysis. However, this association disappeared after adjustment for known clinicopathologic prognostic characteristics. Research Sponsor: None.

567 Poster Session

Exploring tumor genomics and clinical outcomes in in adolescent and young adult (AYA) breast cancer. First Author: Faris Tamimi, King Hussein Cancer Center, Amman, Jordan

Background: Breast cancer in adolescents and young adults (AYAs, defined as individuals aged 39 or younger) often exhibits aggressive biological behavior and distinct clinical patterns compared to older patients. This research investigates the somatic mutations and clinical features that distinguish AYA breast cancer, aiming to uncover unique genomic and prognostic characteristics. **Methods:** We analyzed data from the METABRIC cohort using cBioPortal, focusing on 173 genes sequenced from 2,509 breast cancer cases. The dataset included information on copy number variations, gene expression, and long-term clinical outcomes. Tumor characteristics, mutation frequencies, and relapse-free survival (RFS) outcomes were compared between AYAs and older patients. Statistical methods employed included Chi-square tests for categorical data, Wilcoxon Rank-Sum tests for medians, and Cox regression for survival analysis. The 10 most commonly altered genes across the dataset were examined. **Results:** Of 2,498 patients included in the analysis, 143 were AYAs (5.7%) and 2,355 were older patients (94.3%). Compared to older patients, AYAs demonstrated: Lower ER-positive rates (37.8% vs. 74.9%), Higher ER-/HER2- subtype prevalence (25.2% vs. 11.6%), Greater lymph node positivity (52.4% vs. 41.3%), and Worse Nottingham Prognostic Index scores (median 5.04 vs. 4.04). Genomic analysis revealed significantly higher TP53 mutation frequencies in AYAs (58.9% vs. 33.2%, p < 0.01) and lower PIK3CA alterations (28.1% vs. 42.1%, p < 0.01). Other significantly altered genes in AYAs included TG, TRPS1, CASC8, POU5F1B, MYC, CASC11, NDRG1, and LINC02912. However, stratification by receptor subtypes (ER-/HER2-, ER+/HER2-, HER2+) showed no significant differences in TP53 or PIK3CA alterations between AYAs and older patients. AYA status (< 40 years) was associated with worse recurrence-free survival (RFS) in univariable analysis and remained a significant predictor in multivariable analysis, adjusting for ER status, HER2 status, and nodal involvement (HR: 1.33, 95% CI: 1.00–1.77, p = 0.048). **Conclusions:** AYA breast cancer is marked by distinct genomic and clinical features, including higher TP53 mutation rates, lower PIK3CA mutation rates, more aggressive subtypes such as ER-/HER2-. While some genomic differences are less pronounced within biomarker-matched subgroups, AYAs remain at higher risk for recurrence. These findings highlight the urgent need for age-specific therapeutic strategies to improve outcomes in this population. Research Sponsor: None.

Gene alteration event frequency by age group (AYA versus >39 years).

Gene	AYA	>39	p-Value	q-Value
TP53	58.90% (86/146)	33.16% (780/2352)	<0.001	<0.001
PIK3CA	28.08% (41/146)	42.05% (989/2352)	<0.001	0.0442
TG	35.62% (52/146)	23.72% (558/2352)	<0.01	0.0645
NDRG1	29.45% (43/146)	19.56% (460/2352)	<0.01	0.126
TRPS1	30.82% (45/146)	23.04% (542/2352)	0.0347	0.340
CASC8	30.14% (44/146)	21.51% (506/2352)	0.0178	0.231
LINC02912	29.45% (43/146)	20.88% (491/2352)	0.0167	0.229
CASC11	30.14% (44/146)	21.73% (511/2352)	0.0235	0.268
MYC	30.14% (44/146)	21.68% (510/2352)	0.0234	0.268

568 Poster Session

Global trends and regional disparities in young-onset breast cancer: Age-specific patterns from 1990 to 2021. First Author: Muzamil Khan, The George Washington University School of Medicine and Health Sciences, Washington, DC

Background: Young-onset breast cancer (YOBC), defined as breast cancer in women under 40, is a growing global health concern with unique biological and clinical implications. Analyzing its patterns and distribution is essential for developing effective healthcare strategies and ensuring efficient resource allocation. **Methods:** Data on incidence, prevalence, mortality, and morbidity indicators (DALYs, YLD, and YLL rates per 100,000) were obtained from the Global Burden of Disease (GBD) 2021 database for women under 40 from 1990 to 2021. The dataset, covering 204 countries, was stratified into five age groups: 35–39, 30–34, 25–29, 20–24, and < 20 years. Linear regression was used to calculate average annual percent change (AAPC) and 95% confidence intervals (CI) for each indicator and age group. Statistical significance was set at p < 0.05. **Results:** Between 1990 and 2021, YOBC accounted for 16,783,674 deaths globally. Incidence increased across all age groups, with the largest increases in women under 30. AAPC for incidence was 2.27 (95% CI: 2.21–2.33) in those under 20, 2.18 (95% CI: 2.11–2.24) for ages 20–24, and 1.60 (95% CI: 1.51–1.70) for ages 25–29 (all p < 0.0001). Prevalence showed similar increases: 2.35 (95% CI: 2.29–2.41), 2.24 (95% CI: 2.18–2.30), and 1.64 (95% CI: 1.54–1.73), respectively (all p < 0.0001). Mortality AAPCs were 1.54 (95% CI: 1.46–1.61) for under 20, 1.35 (95% CI: 1.23–1.46) for ages 20–24, and 0.68 (95% CI: 0.59–0.76) for ages 25–29, while older cohorts saw declines, including -0.38 (95% CI: -0.53 to -0.23, p < 0.0001) for ages 35–39. DALYs also increased in younger groups, with AAPCs of 1.56 (95% CI: 1.49–1.63) for under 20 and 1.37 (95% CI: 1.26–1.48) for ages 20–24 but declined in older cohorts. Regionally, Turkey had the highest AAPCs across metrics, Malawi had the highest incidence and YLL for those under 20, and Zimbabwe, Yemen, and Lesotho reported the highest incidence, prevalence, YLL, and DALY. In contrast, Ukraine, Mariana Island and Armenia experienced the greatest declines in incidence, prevalence, YLL, and DALY. **Conclusions:** The global burden of YOBC has risen sharply, especially in the youngest cohorts (< 20 and 20–24 years), with significant increases in low- and middle-income regions like Turkey, Sub-Saharan Africa, and the Middle East. Age-specific interventions, early detection, and preventive measures are needed to address the growing YOBC rates. Research Sponsor: None.

569 **Poster Session**

Interferon signaling and outcomes in triple-negative breast cancer (TNBC) in FinXX, CALGB 40603 (Alliance) and real-world clinico-genomic data. First Author: Saranya Chumsri, Mayo Clinic Florida, Jacksonville, FL

Background: Several studies established the prognostic role of both the amount and locations of tumor-infiltrating lymphocytes (TILs) in TNBC. Three distinct immunotypes were described based on the amount and locations of TILs: immune enriched (IN), immune excluded, and immune desert. Using single-cell spatial transcriptomic analysis in the Mayo Clinic TNBC cohort, our previous studies showed the central role of interferon (IFN) signaling in IN phenotype. Herein, we evaluated the association between IFN and outcomes in TNBC in 3 independent datasets. **Methods:** NanoString IO360 was performed in 114 samples from FinXX (NCT00114816) to generate 22-gene IFNα and 33-gene IFNγ signatures. RNA sequencing was performed in 388 samples from CALGB 40603 (NCT00861705). 3038 TNBC samples were tested by WTS (NovaSeq; Caris Life Sciences, Phoenix, AZ). Median values were used as cut-offs for high vs low IFNγ RNA expression and 18-gene IFNγ signature scores. Caris Life Science CODEai was used to evaluate real-world overall survival (OS) obtained from insurance claims and calculated from tissue collection to last contact using Kaplan-Meier estimates. Chi-square, Mann-Whitney U, ANOVA, and Cox regression were used. **Results:** A high 22-gene IFNα signature score was associated with significantly improved recurrence-free survival (RFS) in FinXX (hazard ratio [HR] 0.32, 95% confidence interval [CI] 0.14-0.74, p 0.007) and OS (HR 0.28, 95%CI 0.12-0.66, p 0.003). Similar findings were observed with 33-gene IFNγ signature with significant improvement in RFS (HR 0.21, 95%CI 0.09-0.51, p $<$ 0.001) and OS (HR 0.18, 95%CI 0.08-0.44, p $<$ 0.001). Furthermore, in CALGB 40603, both IFNα and IFNγ scores were positively associated with pathologic complete response (pCR: IFNα p 0.019 and IFNγ p 0.007) and residual cancer burden (RCB: IFNα p 0.044 and IFNγ p 0.013). Using the Caris data platform to further validate, we identified 2899 TNBC patients (pts) with genomic and clinical outcome data. High IFNγ expression was associated with significant improvement in OS (25.95 vs 17.43 months; HR 0.65, 95% CI 0.59 – 0.72, p $<$ 0.001). Similarly, pts with high IFNγ signature scores had significant improvement in median OS (25.79 vs 16.22 months; HR 0.66, 95% CI 0.6 – 0.73, p $<$ 0.001). **Conclusions:** This study underscores the pivotal role of IFN signaling in TNBC. High IFNα and IFNγ signatures were consistently associated with improved RFS, OS, higher pCR rates, and lower RCB across clinical trial cohorts and real-world data. These findings signify IFN signaling as a potential key biomarker and therapeutic target in TNBC. Support: U10CA180821, U10CA180882, U24CA196171; Breast Cancer Research Foundation, Mayo Clinic Breast Cancer SPORE (P50CA116201-17), Bankhead Coley, W81XWH-15-1-0292, P50CA015083, R35CA253187; https://acknowledgments.alliancefound.org. Genentech. Clinical trial information: NCT00114816 and NCT00861705. Research Sponsor: U.S. National Institutes of Health; U10CA180821, U10CA180882, U24CA196171; Mayo Clinic Breast Cancer SPORE (P50CA116201-17), P50CA015083, R35CA253187; Bankhead Coley; Breast Cancer Research Foundation; U.S. Department of Defense; W81XWH-15-1-0292; Genentech.

570 **Poster Session**

MHC class I expression and outcomes in breast cancer in the real-world clinico-genomic data and the FinXX trial. First Author: Yi Liu, Department of Quantitative Health Sciences, Mayo Clinic, Phoenix, AZ

Background: Major histocompatibility complex class I (MHC I) plays a critical role in immune surveillance by binding peptides derived from intracellular proteins and presenting them on the cell surface for recognition by CD8+ T cells. Loss or downregulation of MHC I expression has been identified as a key mechanism of immune evasion in cancers. Here, we evaluated MHC I expression and outcomes in all subtypes of breast cancer (BC). **Methods:** 9,038 BC samples were analyzed via NGS (592-gene panel, NextSeq; WES/WTS, NovaSeq; Caris Life Sciences, Phoenix, AZ), including triple-negative BC (TNBC) 3,038, HER2-positive (HER2+) 1,082, and hormone receptor-positive (HR+HER2-) 4,918. Immune cell fractions were estimated using WTS deconvolution (Quantiseq). MHC I (*HLA-A*/*HLA-B*/*HLA-C*)-high (H) and -low (L) were classified by RNA expression above or below the 25th percentile. Real-world overall survival (OS) was derived from insurance claims and calculated from tissue collection to last contact using Kaplan-Meier. NanoString IO360 was performed in 114 samples from the FinXX trial (NCT00114816). Statistical significance was assessed using chi-square, Mann-Whitney U, ANOVA, and Cox regression with multiple comparison adjustments (q$<$.05). **Results:** TNBC had higher expression of *HLA-A* and *HLA-B* (median TPM: 169 and 191) compared to HER2+ (146.6 and 170, q$<$0.05) and HR+HER2- (141.7 and 157.5, q$<$0.05). However, there was no significant difference in *HLA-C* expression across 3 BC subtypes. In TNBC, MHC I-H tumors had higher frequencies of PD-L1 positivity (66.2% vs. 13.1%) as well as higher infiltration of B cells (4.5% vs. 3.2%), M1 macrophages (5% vs. 1.5%), M2 macrophages (4% vs. 2.1%), Tregs (2.8% vs. 0.8%), $CD8^+$ T cells (1.8% vs. 0%), dendritic cells (3.2% vs. 2.8%), higher T-cell inflamed score (137 vs. -144), and IFN*g* score (0.02 vs. -0.49) compared to MHC I-L TNBC (all q$<$.05). MHC I-H TNBC was associated with significant improvement in median OS (30.1 vs. 15.2 months, HR 0.55, 95% CI 0.46-0.65, p$<$0.0001). However, this survival difference was not observed in patients with MHC I-H vs. MHC I-L in HER2+ (HR 1.04, 95% CI 0.74-1.47, p = 0.81) and HR+HER2- (HR 0.87, 95% CI 0.75-1.02, p= 0.09) BC subtypes. We further validated the MHC I expression in the FinXX trial. Similarly, patients with MHC I-H had significant improvement in recurrence-free survival (HR 0.27, 95%CI 0.11-0.66, p = 0.002) and OS (HR 0.23, 95% CI 0.09-0.57, p = 0.0005) compared to MHC I-L. **Conclusions:** Our findings demonstrate that higher MHC I expression is associated with higher immune infiltration and improved outcomes in TNBC but not in HER2+ or HR+HER2- BC subtypes. These results suggest that MHC I expression plays a critical role in the tumor microenvironment of TNBC. Future studies are needed to evaluate the prognostic value and potential therapeutic target of MHC I in TNBC. Support: Breast Cancer Research Foundation, Bankhead Coley, W81XWH-18-1-0564. Clinical trial information: NCT00114816. Research Sponsor: None.

571 **Poster Session**

Impact of HER2 low status on pathologic response after neoadjuvant chemotherapy in TNBC: A large scale retrospective cohort study. First Author: Julia Tchou, University of Pennsylvania, Philadelphia, PA

Background: HER2 low status, defined as HER2 1+ or HER2 2+ and nonamplified by in-situ hybridization, has demonstrated the ability to identify a population of patients with triple-negative disease who benefit from trastuzumab deruxtecan in the metastatic setting. The implications of HER2 low status in the early-stage setting is unclear. This study evaluated whether HER2 low status impacts rates of pathologic complete response in response to neoadjuvant chemotherapy (NAC). **Methods:** Using the national cancer database (NCDB), patients with clinically invasive non-metastatic breast cancer between 2010-2021 were retrospectively identified (n=1,926,979). Patients with unknown receptor status or who did not have triple negative breast cancer (n=1,755,897) and those who did not have surgery (n=9,849) were excluded. Clinicopathologic, treatment, and outcome variables were compared using chi-square and anova tests. Subgroup analysis was performed among patients who received NAC and had available pathologic response results. Multivariable binary logistic regression was performed to assess clinical variables associated with pCR after NAC. Cox proportional hazards model was performed to assess clinical variables associated with overall survival (OS) in TNBC receiving NAC. **Results:** Of the 161,233 individuals eligible for analysis, 79,268 (49.4%) had HER2 low disease. The proportion of HER2 0, HER2 1+ and HER2 2+/ish negative (HER2 2+) were 50.6, 34.8, and 14.6% respectively. Overall, 49,994 (31%) individuals received NAC with an overall pCR rate of 42.9%. The pCR rate was significantly lower in those with HER2 2+/ish negative compared to those with HER2 0 TNBC at 39.9 vs. 44.2%, p $<$0.001. On multivariable analysis, HER2 1+ status trended towards a lower likelihood of pCR R 0.95, 95% CI 0.91-1.00, p=0.06) while HER2 2+/ish negative status was significantly associated with a lower likelihood of pCR (OR 0.87, 95% CI 0.82-0.94, p$<$0.001) compared to HER2 0 disease. Cox proportional hazards model analysis demonstrated that the strongest clinical factor for worse OS was non-pCR with HR 3.76, 95% CI 3.48 – 4.05, p$<$0.001 while neither HER2 1+ or HER2 2+/ish negative was associated with worse OS. **Conclusions:** In this analysis, tumors that were HER2 2+/ish negative were associated with a significantly lower pCR rate after NAC compared with HER2 0 tumors. This is the first large-scale study to demonstrate that HER2 low status may be prognostically unfavorable in early-stage TNBC. Examination of novel neoadjuvant therapeutic approaches tailored based on HER2 status including trastuzumab deruxtecan may be warranted to improve pCR rates and outcomes in patients with HER2-low early-stage breast cancer. Research Sponsor: None.

pCR rate stratified by HER2 low status.

	HER2 0		HER2 1+		HER2 2+	
n	81605		56109		23519	
Neoadjuvant	26458	32.4%	16841	30.0%	6695	28.5%
pCR	11690	44.2%	7064	41.9%	2672	39.9%

572 **Poster Session**

Reframing hormone-positive DCIS management: Effects of adjuvant therapies and surgical extent on any invasive recurrence. First Author: Thomas O'Keefe, University of California, San Francisco, San Francisco, CA

Background: The treatment of DCIS is still primarily informed by trials that are now decades old. We have learned since then that only invasive subsequent events, not in situ ones, increase a woman's risk of eventual metastasis and breast cancer mortality, and may necessitate more aggressive systemic treatment. This suggests a need for the reassessment of the impact of adjuvant therapies. **Methods:** Women diagnosed with a first breast cancer of unilateral hormone positive DCIS undergoing breast conserving surgery were identified in the Surveillance, Epidemiology and End Results Program registry. Propensity-matching was performed between treatment groups using age, race, lesion size and grade. Competing risks methods were used to estimate the cumulative incidence of any invasive event at 10 years and subdistribution hazard ratios (sHRs) were calculated from multivariate models adjusting for the same covariates used for matching. **Results:** A total of 14,189 patients diagnosed from 2007 to 2011 were eligible for matching, among whom 900 (6.3%) suffered a subsequent invasive event.A cohort was developed by matching from the smallest treatment group, lumpectomy with endocrine therapy. There were 2,996 matched patients, among whom 511 (17.1%) had an invasive subsequent event. Adjuvant endocrine therapy was associated with reduced risk of any invasive event (sHR=0.38, p$<$0.001) compared to patients undergoing lumpectomy without adjuvant therapy. Radiotherapy alone was not associated with reduced risk (sHR=1.03, p=0.81): it was associated with reduced risk of an ipsilateral invasive event (sHR=0.65, p=0.006) but an increased risk of a contralateral invasive event (sHR=1.50, p=0.01). In subgroup analyses, lumpectomy with radiation therapy was noted to be non-significantly associated with increased risk of any invasive disease in patients younger than 60 years (sHR=1.38, p=0.053) and with decreased risk in patients 60 years or older (sHR=0.79, p=0.12). **Conclusions:** Our results suggest that endocrine therapy may confer the greatest risk reduction to the development of any subsequent invasive recurrences, and whole-breast radiotherapy may be associated with increased risk for younger women. The risk posed by DCIS as a high-risk marker may outweigh its risk as a premalignant lesion. Research Sponsor: None.

Any invasive subsequent breast cancer, and subgroup analyses by age. Only treatment effect shown, but results are adjusted for race, grade, age, and lesion size.

	Any Invasive, Any Age		Any Invasive, < 60 years old		Any Invasive, ≥ 60 years old	
	sHR (95% CI)	p	sHR (95% CI)	p	sHR (95% CI)	p
Treatment						
BCS	Ref	-	Ref	-	Ref	-
BCS + ET	0.38 (0.29-0.51)	$<$0.001	0.34 (0.21-0.54)	$<$0.001	0.40 (0.28-0.58)	$<$0.001
BCS + RT	1.03 (0.82-1.28)	0.81	1.38 (1.00-1.91)	0.053	0.79 (0.59-1.07)	0.12

sHR = Subdistribution hazard ratio.
BCS=Breast conservation surgery.
ET=Endocrine therapy.
RT=Radiation therapy.

574 **Poster Session**

Impact of postmastectomy radiotherapy on health-related quality of life and safety in breast cancer patients undergoing breast reconstruction: A multi-center cross-sectional study (Reborn-02). First Author: Hirohito Seki, Department of Breast Surgery, Kyorin University School of Medicine, Tokyo, Japan

Background: Postmastectomy radiotherapy (PMRT) is the standard treatment for improving the prognosis of patients with high-risk breast cancer. Expanded indications for breast reconstruction (BR) will likely increase the number of patients undergoing BR who require PMRT, but combining BR with PMRT raises concerns about complications and aesthetics. Evaluating the impact of PMRT on the health-related quality of life (HR-QOL) in Japanese patients is essential for shared decision-making (SDM). This study assessed differences in postoperative HR-QOL and complications between patients who underwent BR with or without PMRT. **Methods:** We conducted a multicenter cross-sectional study using a questionnaire survey of patients with primary breast cancer who underwent BR between January 2008 and December 2022 at participating institutions, which was approved by the respective institutional review boards. We used the Japanese version of the BREAST-Q questionnaire and questions on patient backgrounds. **Results:** We included 1078 patients with primary breast cancer. The questionnaire response rate was 77.0% (830/1078). The non-PMRT and PMRT groups comprised 616 and 214 patients, respectively. The PMRT group had higher rates of axillary lymph node dissection (11.7% vs. 52.4%; $P<0.001$), adjuvant hormonal therapy (67.2% vs. 90.6%; $P<0.001$), and perioperative chemotherapy (31.8% vs. 84.0%; $P<0.001$) than the non-PMRT group. Moreover, the overall complication rate (45.3% vs. 76.2%, $P<0.001$) and the rates of dermatitis (9.9 vs. 48.1%; $P < 0.001$), skin necrosis (2.9 vs. 9.8%; $P<0.001$), breast asymmetry (17.0% vs. 24.3%; P=0.002), capsular contracture (4.9 vs. 16.4%; $P<0.001$), and lymphedema of the upper limb (1.1% vs. 7.5%; $P<0.001$) were higher in the PMRT group. Multivariate analysis revealed PMRT as an independent risk factor for dermatitis, skin necrosis, and capsular contracture. In the BREAST-Q assessment, the PMRT group showed lower satisfaction with the breast (55 vs. 49; $P<0.001$), and with physical (85 vs. 76; $P<0.001$), psychosocial (55 vs. 49; $P<0.001$), and sexual well-being (36 vs. 34; P=0.021) than the non-PMRT group. Multiple regression analysis revealed PMRT as an independent factor associated with low BREAST-Q scores for breast satisfaction and physical and psychosocial well-being in patients with BR. **Conclusions:** This is the first large-scale, multi-institutional study to use patient-reported outcomes to assess the effects of PMRT on HR-QOL in Japanese patients with breast cancer who underwent BR. PMRT was associated with an increased risk of complications and decreased HR-QOL in patients with BR. Of note, these findings do not negate the role of PMRT in patients undergoing BR, but highlight the importance of SDM based on realistic HR-QOL expectations after breast reconstruction surgery with PMRT. Research Sponsor: None.

575 **Poster Session**

Development and validation of prediction models for 5-year and 10-year ipsilateral breast tumor recurrence after breast-conserving surgery. First Author: Yasuaki Sagara, Department of Breast Surgical Oncology, Social Medical Corporation Hakuaikai Sagara Hospital, Kagoshima, Japan

Background: Ipsilateral breast tumor recurrence (IBTR) remains a critical concern for patients undergoing breast-conserving surgery (BCS). Reliable prediction tools for IBTR risk can support personalized surgical strategies and adjuvant treatment decisions, especially in the era of evolving systemic therapies. This study aimed to develop and validate prediction models for 5-year and 10-year IBTR. **Methods:** This multi-center retrospective cohort study included 10,089 women who underwent partial mastectomy for invasive breast cancer between 2008 and 2017. Cases involving conversion to mastectomy, use of neoadjuvant chemotherapy, bilateral/multiple cancers, or missing key data were excluded. Prediction models were developed using Cox proportional hazards regression and validated via bootstrap resampling. Model performance was assessed using Harrell's C-index, Brier scores, calibration plots, and goodness-of-fit tests. The cumulative incidence of IBTR, which served as the baseline for the prediction model, was calculated using the Fine and Gray model, treating death as a competing risk. **Results:** The median age of patients was 55 years [interquartile range (IQR): 46–65]. During a median follow-up of 8.9 years (IQR: 6.4–10.8), IBTR occurred in 292 patients (3.1%). The initial model, based on variables from Sanghani et al. (JCO 2010), achieved a Harrell's C-index of 0.70. Incorporating hormonal receptor status, HER2 status, radiotherapy, and targeted therapy as predictors reduced the C-index to 0.60, despite their clinical relevance. Importantly, the inclusion of these factors improved calibration, demonstrating better alignment between predicted and observed IBTR probabilities. The final Cox model exhibited strong clinical and statistical robustness ($p < 0.001$), providing individualized IBTR risk estimates. Cox-Snell residual analysis confirmed goodness-of-fit, with the cumulative hazard closely following the 45-degree line up to 0.3, indicating reliable model performance for observed events. While hazard ratios (HRs) for chemotherapy and radiotherapy were consistent with results of EBCTCG meta-analyses (MA), HR for endocrine therapy was lower than reported in MA. Consequently, HRs from MA were adopted to account for treatment effects in our prediction model. **Conclusions:** We have developed and validated a new prediction model for 5-year and 10-year IBTR using Cox regression and bootstrap methods. A web-based tool is under development to enable individualized risk assessment and treatment planning. Future research will focus on external validation and the integration of genetic and novel therapeutic data to enhance model robustness and clinical utility. Research Sponsor: Japanese Breast Cancer Society.

576 **Poster Session**

Regional node recurrence after sentinel lymph node biopsy for ycN0 patients treated with primary chemotherapy in cT1-3N1M0 breast cancer (second report from SHARE study). First Author: Shigeru Imoto, Kyorin University, Mitaka, Japan

Background: Axillary management after sentinel lymph node biopsy (SLNB) is still debated for clinically node-positive breast cancer (BC) patients treated with neoadjuvant chemotherapy (NAC). The Japanese Society for Sentinel Node Navigation Surgery conducted a prospective non-randomized phase 2 study (SHARE study, UMIN000030558). False-negative rate (FNR) as the primary endpoint was reported at ASCO2023. In brief, it was 11.5% (90% confidence interval, 5.5% and 20.5%). When multimodal imaging, 1 nodal metastasis, multiple tracers, multiple sentinel lymph nodes were considered for subset analysis, the FNR was 12.1%, 9.1%, 11.1%, and 10.6%, respectively. Here we report a short-term prognosis of ycN0 BC patients. **Methods:** Clinical T1-3N1M0 BC was eligible. Nodal metastasis was histologically confirmed. In case of ycN0 BC, SLNB was planned and lymphatic mapping depended on each institutional practice. In cases of pN0(sn), pN0(i+)(sn) and pN1mi(sn), SLNB followed by lymph node sampling (LNS) had been allowed instead of axillary lymph node dissection (ALND). **Results:** Between February 2018 and May 2021, 185 patients from 19 institutes were registered. Twenty-seven cases were excluded by protocol deviation, non-ycN0 or withdrawal of SLNB. Among the 158 ycN0 cases, sentinel lymph nodes were detected in 153 cases. The median age was 52 years old. Clinical stage was IIA in 40 cases, IIB in 105 and IIIA in 8. Luminal subtype classified by ER, PR and HER2 expression was found in 60 cases, HER2 in 34, Luminal-HER2 in 35 and triple-negative in 24. SLNB alone was performed in 37 cases, SLNB and LNS in 72 and SLNB followed by ALND in 44. Regional nodal irradiation was planned in 63 cases. At the median follow-up of 24 months, 13 cases relapsed and 5 died of BC. Regional node recurrence-free survival rate at 2 years after surgery, disease-free survival rate and overall survival rate were 98.6%, 92.6% and 97.3%, respectively. **Conclusions:** SLNB-guided axillary management is feasible and safe in ycN0 BC after NAC. Clinical trial information: 000030558. Research Sponsor: The Japanese Society for Sentinel Node Navigation Surgery.

577 **Poster Session**

Preoperative axillary US and MRI in early-stage breast cancer: Potential to prevent unnecessary axillary surgery. First Author: Xin Wang, West China Hospital (China), Chengdu, China

Background: Recent studies, including the INSEMA and SOUND trials, have demonstrated that omitting sentinel lymph node (SLN) biopsy does not adversely affect survival outcomes. Notably, patients with positive axillary findings on ultrasound (US) tended to show more extensive axillary nodal metastasis on final histopathological examination. Thus, we aimed to focused on the advanced utility of preoperative axillary US and Magnetic Resonance Imaging (MRI) in preventing unnecessary axillary surgery in a large series of patients with early-stage breast cancer treated with both breast surgery and SLN biopsy. **Methods:** Between January 2012 to December 2023, a total of 7879 patients who underwent breast surgery for clinical T1–2/N0 cancers and SLN biopsy with or without axillary lymph node dissection were included. Preoperative axillary US and MRI findings were compared with clinical-pathologic variables, considering the presence of SLN metastasis. Patients with positive results routinely underwent US-guided fine needle aspiration biopsy (FNAB), and negative FNAB results were also considered. Multivariate logistic regression analysis was used to identify factors associated with SLN metastasis. **Results:** A total of 7879 eligible patients (47.48% with clinical T1 cancer and 52.52% with T2 cancer) were included in our study. Among them, 2048 (25.99%) had positive SLN biopsy, and 1971 (25.02%) underwent axillary lymph node dissection due to positive SLN biopsy. Patients with SLN metastasis were younger and had a higher frequency of positive axillary findings on US and MRI, as well as clinical T2 stage ($P<0.05$). At multivariate analysis, positive axilla at US (P =0.001), positive axilla at MRI (P =0.02), clinical T2 stage (P =0.004), grade 3 (P =0.004) and lymphovascular invasion (P=0.001) were significantly associated with SLN metastasis. The number of nodal metastases increase with increasing tumor size. Among 3595 (45.06%) patients with negative axilla at US and MRI and clinical T1 stage cancer, 698 (8.75%) had SLN metastasis. For these people, the median follow-up was 73.6 months. The estimated 5-year invasive disease–free survival rate was 96.8%, while the 5-year overall survival rate was 98.6%. The analysis of the first primary-outcome events (occurrence or recurrence of invasive disease or death from any cause), showed apparent differences between the positive axilla at US and MRI and clinical T1 stage cancer group and negative axilla at US and MRI and clinical T1 stage cancer group in the incidence of recurrence (4.7% vs. 3.2%) and death (2.0% vs. 1.4%). **Conclusions:** Preoperative axillary US and MRI results, along with clinical T stage are significant predictors of SLN metastasis in patients with early-stage breast cancer. The results of this study suggest that preoperative axillary US and MRI can help select patients at minimal risk of SLN metastasis, for whom axillary surgery could be omitted. Research Sponsor: National Natural Science Foundation of China; National Clinical Research Center for Geriatrics, West China Hospital, Sichuan University; Natural Science Foundation of Sichuan Province.

578 Poster Session

Use of local estrogen therapy among breast cancer patients in SEER-MHOS database. First Author: Olivia Mitchel, University of Arizona- College of Medicine Tucson, Tucson, AZ

Background: Anti-hormonal therapy with tamoxifen or aromatase inhibitors is a key component in the treatment of hormone receptor-positive breast cancers. One of the adverse effects of this type of therapy is genitourinary syndrome of menopause, which may be treated with vaginal estrogen. It remains unclear whether local vaginal estrogen use carries any increased risk of recurrence or mortality in patients with a history of breast cancer. This has led to conflicting advice in the clinical setting and potentially unnecessary avoidance of hormone-based products that could possibly provide women symptomatic relief. Further exploration of the relationship between local estrogen therapy and breast cancer outcomes is warranted. **Methods:** A retrospective cohort study of 18,620 female breast cancer patients $\geq$ 65 years of age diagnosed between 2010-2017 in the SEER-MHOS registry was performed, comparing the breast cancer patients who used local vaginal estrogen (n=800) to those who did not (n=17,820), to assess whether local vaginal estrogen exposure was associated with any difference in overall survival as a primary outcome. Breast cancer specific survival was analyzed as a secondary outcome. Missing data was excluded by complete case analysis. Wilcoxon rank-sum tests were performed to compare continuous variables, Chi-square tests to compare categorical variables, Kaplan-Meier estimation to summarize overall survival, and sub-distribution hazard regression was performed to evaluate breast cancer specific survival by group. Multivariate regression models controlled for age, race, cancer stage, treatment (i.e. surgery, radiation, anti-hormonal therapy), and year of diagnosis. The research protocol was approved by our Scientific Review Committee and submitted for IRB approval. **Results:** There was a statistically significant increase in overall survival (HR=0.56, $p<0.0001$) as well as breast cancer-specific survival (HR=0.53, p=0.014) among breast cancer patients who used vaginal estrogen compared to those who did not. Among those who used vaginal estrogen, there was a statistically significant increase in overall survival for those with a duration of use >7 years (median duration of use) compared to those with a duration of use <7 years (HR=0.01, $p<0.0001$). Subset analysis restricted to patients with hormone positive breast cancer showed a statistically significant increase in overall survival for those who used vaginal estrogen compared to those who did not (HR=0.62, p=0.0007), and a nonsignificant increase in breast cancer specific survival (HR=0.62, p=0.08). **Conclusions:** The use of vaginal estrogen among this SEER-MHOS cohort of breast cancer patients showed improved survival outcomes. These findings add to a rising contemporary paradigm shift that local hormone therapy is not associated with increased risk to overall or breast cancer specific survival, which has important clinical implications. Research Sponsor: Departmental funding from the University of Arizona College of Medicine - Tucson Department of Surgery.

579 Poster Session

Efficacy and safety of post-mastectomy radiation therapy for patients with breast cancer after breast reconstruction: A retrospective multicenter cohort study (Reborn-03). First Author: Wakako Tsuji, Department of Breast Surgery, Shiga General Hospital, Moriyama Shiga, Japan

Background: A cornerstone of multidisciplinary treatment for breast cancer, breast reconstruction has recently been extended to high-risk patients with breast cancer who require post-mastectomy radiation therapy (PMRT). PMRT reduces the 10-year risk of locoregional recurrence; however, its association with postoperative complications remains unclear. This study aimed to evaluate the efficacy and safety of PMRT in patients with high-risk breast cancer who underwent breast reconstruction. **Methods:** This retrospective cohort study included patients with high-risk breast cancer who underwent immediate or delayed breast reconstruction after mastectomy between 2008 and 2018. High-risk patients were defined as those with positive axillary lymph nodes, clinical tumor size of >5 cm, chest wall invasion, or skin invasion. Patient data were collected from participating institutions and analyzed retrospectively. **Results:** Of the 1,138 patients, 427 (37.5%) underwent PMRT and 711 (62.5%) did not. The median age at surgery was 46 years (range, 23–76years), and the median follow-up period was 8 years. The number of patients meeting more than two high-risk criteria was 149 (23.9%) and 81 (11.4%) in the PMRT and non-PMRT cohorts, respectively. Breast reconstruction using silicone breast implants (SBI) was performed in 70% and 71.4% of patients in the PMRT and non-PMRT cohorts, respectively. The locoregional recurrence rates were 7.7% and 12.7% in the PMRT and non-PMRT cohorts, respectively (P=0.034). Multivariate analysis revealed that PMRT was an independent predictive factor for reducing locoregional recurrence ($P<0.001$) (Table 1). Complications occurred in 130 patients (30.4%) in the PMRT cohort and 168 (23.6%) in the non-PMRT cohort (P=0.016). The reoperation rates due to complications were 46 (35.4%) in the PMRT cohort and 61 (36.3%) in the non-PMRT cohort (P = 0.100). In the PMRT cohort, 62 patients (14.5%) experienced grade 2 radiation-induced dermatitis, and three patients (0.7%) developed grade 2 radiation-induced pneumonia. **Conclusions:** Although the incidence of adverse events was slightly higher in the PMRT cohort, the reoperation rates due to complications were comparable between the cohorts. PMRT is a safe and effective modality that provides substantial benefits for locoregional recurrence reduction in patients with high-risk breast cancer undergoing breast reconstruction. Research Sponsor: None.

Multivariate analysis for locoregional recurrence in patients with high-risk breast cancer who underwent breast reconstruction.

Factors	Hazard ratio	95% Confidence interval	P-value
PMRT	0.40	0.251-0.623	<0.001
Neoadjuvant therapy	3.43	2.29-5.12	<0.001
pT (>5 cm)	1.95	1.25-3.03	0.003
Surgical margin	1.96	1.01-3.81	0.047

580 Poster Session

Implications for sentinel lymph node biopsy (SLNB) omission in patients with early-stage node-negative HR+/HER2- breast cancer undergoing mastectomy. First Author: Jennifer Hechao Chen, The University of Texas MD Anderson Cancer Center, Houston, TX

Background: The SOUND and INSEMA trials demonstrated non-inferiority of SLNB omission in HR+/HER2- early-stage breast cancer (BC) patients with negative axillary ultrasound (AUS) undergoing breast conserving therapy (BCT). However, it remains unclear if this approach may be applied to patients receiving mastectomy. We evaluated outcomes in a similar patient population receiving BCT versus mastectomy. **Methods:** Using an institutional database (2010-2023), we identified patients with cT1N0M0 HR+/HER2- unifocal invasive ductal carcinoma with negative AUS who underwent upfront BCT (breast conserving surgery + Radiation therapy [RT]) or mastectomy +/- RT. All patients underwent SLNB. Clinicopathologic and treatment characteristics were compared by surgery type as well as clinical outcomes. **Results:** Among 1,506 patients, median age was 59 years (IQR 51-67), and 80% were postmenopausal. BCT was performed in 78.2% (n=1,178) while 21.8% (n=328) underwent mastectomy. Patients who underwent mastectomy were more likely to be younger, premenopausal, with larger and higher grade tumors (Table). SLN positivity rate was 7.7% with no significant differences by surgery type (7.6% vs 8.2%, p=0.684). Only 4 (1.2%) and 2 (0.2%) patients had pN2 disease in the mastectomy and BCT cohorts, respectively. More patients undergoing mastectomy had axillary lymph node dissection compared to patients undergoing BCT (6.96% vs 0.3%, $p<0.001$). Among mastectomy patients, 10.1% received RT with higher rates in node-positive patients (52.9% vs 5.1%, $p<0.0001$). Similarly, chemotherapy use was higher among node-positive mastectomy patients (76.5% vs 22.5%, p=0.0001). Among SLN-positive postmenopausal patients with 21-gene recurrence score (RS) <25, chemotherapy use was 16.6% (2/12) after BCT and 0% (0/4) after mastectomy. When RS was >26, chemotherapy use was 60% (27/45) after BCT and 85.7% (12/14) after mastectomy. Median follow up was 25.3 months (IQR 13.2-58.9). There were 3 (0.2%) axillary recurrences with 2 recurrences after mastectomy (1 of whom received RT). There were 7 (0.46%) distant recurrences, with 2 following mastectomy. **Conclusions:** Among patients with cT1N0M0 HR+/HER2- invasive ductal carcinoma with negative AUS, positive SLNs were identified in 7.7% with only 0.46% having pN2 disease. Low axillary and distant recurrence rates were observed regardless of surgery type. However, given that nodal status impacts RT use among mastectomy patients, further research investigating omission of SLNB in this cohort is warranted. Research Sponsor: None.

	BCT (N, %)	TM (N, %)	p-value
Age (median, IQR)	60.8 (53.2-67.8)	55.7 (46.9-64.9)	<0.00001
Premenopausal	198 (16.8)	101 (30.8)	<0.00001
Grade 3	146 (16.7)	66 (22.8)	0.035
cT stage			0.002
T1mic	14 (1.2)	12 (3.7)	
T1a	56 (4.8)	19 (5.8)	
T1b	376 (31.9)	80 (24.4)	
T1c	732 (62.1)	217 (66.1)	
pT size (median, IQR)	1.4 (0.9-4)	1.35 (0.8-2.1)	0.022

581 Poster Session

Serial circulating tumor DNA (ctDNA) monitoring in early-stage, HR+/HER2-, invasive lobular carcinoma (ILC) of the breast and impact on clinical outcomes. First Author: Julia Foldi, University of Pittsburgh Medical Center (UPMC), Pittsburgh, PA

Background: ILC accounts for ~10-15% of breast cancer (BC) cases in the US with difficult-to-diagnose patterns of metastasis. Loss of E-cadherin (*CDH1*) is the pathognomic feature of ILC. Tumor-informed ctDNA assays detect molecular residual disease in patients who completed definitive therapy for early-stage BC. However, little is known about the ctDNA dynamics and its prognostic relevance in ILC specifically. Here, we assessed actionable genomic alterations and correlated ctDNA dynamics with clinical outcomes in patients with HR+/HER2- ILC. **Methods:** We utilized Natera's proprietary real-world database linked to commercially available claims data and commercial ctDNA testing via a clinically validated, personalized, tumor-informed mPCR-NGS ctDNA assay (Signatera, Natera, Inc.) to identify patients with early-stage, HR+/HER2- ILC. Tumors with *CDH1* truncated alterations from tumor whole exome sequencing were categorized as ILC. HR+/HER2- tumors were categorized using treatment regimens from insurance claim codes. Targetable alterations in *PIK3CA*, *AKT*, *PTEN*, *BRCA1*, *BRCA2*, *ESR1*, NF1, and *ERBB2* were assessed. ctDNA positivity rates and distant recurrence-free survival (DRFS) were evaluated using longitudinal ctDNA status (ctDNA + or -). The timing of ctDNA+ after primary BC surgery was divided into two categories: <2 years (y) and >2y. **Results:** 430 patients with early-stage HR+/HER2- ILC and ctDNA testing were identified. The most common targetable alterations co-mutated with *CDH1* were in *PIK3CA* (54.4%), *AKT1* (5.1%), *NF1* (4.9%), and *ERBB2* (4.6%). The first ctDNA test was performed on 258 (59.3%) and 172 (39.5%) patients within or after 2y surgery, respectively. Of 430 patients, 88 (20.2%) had >1 ctDNA+ test. A ctDNA+ result was reported in 31/258 (12%) and in 57/172 (33.1%) patients with testing within or after 2y surgery, respectively. Longitudinal ctDNA+ was associated with DRFS based on distant secondary malignant neoplasm claim codes. Among patients with a ctDNA- test within 2y, only 2.83% (6/212) presented a DRFS event compared to 48% (12/25) of ctDNA-+ cases (Odds ratio 31, p-value=1.42E-9). In patients with a ctDNA- test after 2y, only 2.06% (2/95) presented a DRFS event compared to 37.5% (9/24) of ctDNA+ cases (Odds ratio 27, p-value=4.92E-6). **Conclusions:** To our knowledge, this is the first large-scale analysis of the landscape of targetable genomic alterations and matching longitudinal ctDNA and outcomes in patients with early-stage, HR+/HER2- ILC. We find that *PIK3CA* is most frequently co-mutated with *CDH1*, and a comparison with the *CDH1* wildtype cohort will be presented. These data provide insights into the ability of ctDNA to detect recurrence earlier, including sites associated with challenges in the interpretation of imaging results in the early-stage ILC setting. Research Sponsor: None.

582 **Poster Session**

TROP2 overexpression as predictor of outcome in patients with early triple-negative breast cancer. Exploratory analysis from the GEICAM_CIBOMA trial. First Author: Federico Gustavo Rojo Todo, Hospital Universitario Fundación Jiménez Díaz; CIBERONC-ISCCIII; GEICAM Spanish Breast Cancer Group, Barcelona, Spain

Background: Antibody-drug conjugates (ADCs) have emerged as a promising therapeutic strategy for triple-negative breast cancer (TNBC), a subtype with limited treatment options and poor prognosis. Understanding the biological and prognostic/predictive implications of biomarkers for these ADCs could help refine appropriate adjuvant treatment for high-risk TNBC. TROP2-targeted ADC sacituzumab govitecan has demonstrated significant improvements in progression-free and overall survival in clinical trials involving the advanced TNBC setting. We sought to explore the prognostic/predictive value of TROP2 expression by immunohistochemistry (IHC) in early TNBC patients (pts) from the GEICAM_CIBOMA trial (NCT00130533). **Methods:** We evaluated TROP2 expression by IHC using an anti-TROP2 monoclonal antibody (clone ERP20043, Abcam) in tumors from a subset of 70 TNBC pts included in the trial. These patients received either 6 months therapy with capecitabine (n=35) or observation (n=35) after receiving standard (neo)adjuvant chemotherapy (trial recruitment between 2006 and 2011). Semi-quantitative Histoscore (H-score) was estimated to consider the following TROP2 expression categories: H-score 0 to $<$100: TROP2 low; H-score 100-200: TROP2 medium; H-score $\geq$200: TROP2 high. Median TROP2 H-score was also explored for pts categorization. Cox regression models were assessed to predict DRFS (primary endpoint), DFS and OS (secondary endpoints). Multivariate models were adjusted for confounding factors, including histological grade, stage, chemotherapy regimen, and treatment. **Results:** The TROP2 H-score median value was 165. Medium/high TROP2 expression (H-score $\geq$100) was observed in 27 (77%) pts treated with capecitabine, and 25 (71%) in the observation group. Higher TROP2 expression was associated with higher histological grade (p=0.032). Medium/high TROP2 expression significantly associated with better DRFS (univariate analysis, HR=0.41; 95%CI 0.19-0.90; p=0.026; multivariate analysis, HR=0.24; 95% CI 0.10-0.60; p=0.002). This prognostic value was confirmed at DFS (multivariate analysis, HR=0.33; 95%CI 0.14-0.77; p=0.010) and OS (multivariate analysis, HR=0.29; 95%CI 0.11-0.76; p=0.011). High TROP2 expression by median value (H-score $\geq$165) was also associated with better clinical outcome (DRFS univariate analysis, HR=0.43; 95%CI 0.19-0.97; p=0.041; multivariate analysis, HR=0.44; 95%CI 0.19-1.02; p=0.057). TROP2 expression categorization did not demonstrate predictive value of capecitabine benefit (DRFS interaction with treatment, p=0.852). **Conclusions:** In this GEICAM_CIBOMA trial sub-study, TROP2 overexpression by IHC was observed in 74% of the analyzed cases and significantly associated with better clinical outcome in early TNBC pts, in terms of DRFS, DFS, and OS. Clinical trial information: NCT00130533. Research Sponsor: Sociedad Española de Oncologia Medica SEOM (SEOM/FECMA Grant 2022).

583 **Poster Session**

Disparities in demographics and outcomes of breast cancer in females undergoing mastectomy in rural vs. urban teaching centers. First Author: Harkaran Shergill, Maulana Azad Medical College, New Delhi, India

Background: Breast cancer (BC) sensitization, awareness, and increased screening have led to significant improvements in prevention, management, and survival rates over the last three decades. Recent reports have shown that the use of prophylactic and therapeutic mastectomy is on the rise. Previous studies have revealed healthcare disparities between rural (RC) and urban teaching centers (UTC), which may influence outcomes. In this retrospective study, we propose to explore the presence of similar disparities among BC patients undergoing mastectomy in rural hospitals vs. UTC. **Methods:** For this study, we extracted procedures of mastectomy among BC females through the hospitalization records of the National Inpatient Sample (NIS). We stratified our sample into procedures performed at RC and UTC. Procedural and postprocedural complications were compared through multivariable regression models. **Results:** We studied 75915 BC patients who underwent mastectomy between 2016 and 2022. Around 93.2% of our sample involved procedures performed at UTC, with 6.8% conducted at RC. Procedures at RC involved an older group(mean age 66.18 years vs. 57.19 years, $p < 0.01$), with a higher Charlson Comorbidity Index (CCI) score(mean score 3.79 vs. 3.53, $p < 0.01$). An estimated 91.6% of all procedures were performed on an elective basis(88.8% of rural and 91.9% of UTC, $p < 0.01$). Metastasis was present in 25.5% of all cases (25.4% of UTC and 25.8% of rural cases, p = 0.591). Mastectomies performed at RC had higher odds of bleeding (aOR 1.170, 95% CI 1.075-1.272, $p < 0.01$), sepsis (aOR 2.163, 95% CI 1.557-3.004, $p < 0.01$), postprocedural respiratory failure (PPRF) (aOR 2.667, 95% CI 1.479-4.808, $p < 0.01$), need for mechanical ventilation (MV) (aOR 2.732, 95% CI 1.845-4.046, $p < 0.01$), ischemic stroke (aOR 5.073, 95% CI 2.884-8.922, $p < 0.01$), and cardiac arrest (aOR 8.443, 95% CI 4.861-14.666, $p < 0.01$). Acute kidney injury events were similar (aOR 1.160, 95% CI 0.945-1.423, p = 0.155). The odds of all-cause death were higher among RC procedures (aOR 5.401, 95% CI 3.456-8.442, $p < 0.01$). **Conclusions:** The findings of this study have significant implications for healthcare policies. BC patients undergoing mastectomy in rural areas were significantly older and had a higher CCI score. Moreover, rural procedures reported higher risks of bleeding, sepsis, stroke, cardiac arrests, PPRF, MV use, and death. These results highlight the need for additional studies to establish the causes of these disparities, which may reflect the need for improving healthcare services in rural areas. Furthermore, encouraging RC to set up review protocols on their adverse events through Ishikawa diagrams may help identify probable healthcare inequities compared to UTC, which can then be remedied. This research has the potential to influence policy changes that could improve outcomes for rural BC patients. Research Sponsor: None.

584 **Poster Session**

Changes in the degree of satisfaction and quality of life in breast cancer patients who are candidates for breast conservation but opted for mastectomy: A single-center prospective study. First Author: Changhoon Lee, Department of Surgery, Seoul National University Hospital, Seoul National University College of Medicine, Seoul, South Korea

Background: Randomized trials have shown that breast-conserving surgery (BCS) and total mastectomy (TM) provide comparable survival outcomes for early breast cancer patients. Consequently, the choice of surgery is now considered a preference-based shared decision-making process. While studies have examined quality of life (QoL) in TM and BCS patients, it remains unclear how choosing TM over BCS affects postoperative QoL and satisfaction. This single-center prospective trial investigated the longitudinal impact of TM on QoL and satisfaction in the BCS-eligible patients who voluntarily opted for TM. **Methods:** We prospectively screened newly diagnosed breast cancer patients who are eligible for BCS based on the preoperative clinical assessment between Nov 2021 and June 2024 at Seoul National University Hospital. Patients were allowed to choose between TM and BCS through the shared decision-making process, and were enrolled according to the selected surgical method. A series of surveys were conducted using the BREAST-Q questionnaire and Decision Regret Scale (DRS) before and between 6-24months following surgery and then compared the results between two groups. **Results:** A total of 68 patients were enrolled; 28 opted for TM, and 40 underwent BCS, with two patients lost to follow-up in the TM group. The TM group was significantly older than the BCS group (57.92 vs. 51.43 years, p=0.015), and had larger preoperative tumor sizes (25.77mm vs. 17.88mm, p=0.001). Postoperatively, satisfaction with the breast (62.0 vs. 53.3, p=0.013) and physical well-being (chest) (83.9 vs. 77.5, p=0.004) decreased significantly. Satisfaction with the breast was significantly lower in the TM group compared to BCS (62.7 vs. 38.7, $p<0.001$). Psychosocial well-being (80.3 vs. 58.1, $p<0.001$), sexual well-being (55.3 vs. 24.2, $p<0.001$), and physical well-being (80.9 vs. 72.9, p=0.043) were all lower in the TM group. When comparing pre- and postoperative scores, the TM group experienced greater declines in breast satisfaction (-1.38 vs. -21.34, p=0.007), psychosocial well-being (5.71 vs. -8.40, p=0.004), and sexual well-being (1.55 vs. -17.83, p=0.004). The TM group also had significantly higher DRS scores (21.92 vs. 13.52, p=0.036), indicating greater regret. **Conclusions:** Our data demonstrates that patients who opted for TM over BCS for their breast cancer surgery may experience more profound decline in QoL and higher degree of regret after their surgery. These findings should be incorporated into the shared decision-making process when choosing optimal surgical treatment in early breast cancer patients who are eligible for BCS. Research Sponsor: None.

585 **Poster Session**

Bilateral mastectomy and breast cancer morality for invasive lobular carcinoma: A SEER-based study. First Author: Richa Jaiswal, Women's College Hospital, University of Toronto, Toronto, ON, Canada

Background: Many women with unilateral breast cancer opt for bilateral mastectomy. While removing the unaffected contralateral breast lowers the risk of second primary cancers, there is no benefit on breast cancer mortality. Studies have not investigated whether this holds true for invasive lobular carcinoma (ILC). To estimate the 20-year risk of breast cancer mortality in women with stage I-III unilateral ILC and compare survival outcomes between unilateral lumpectomy, unilateral mastectomy and bilateral mastectomy. **Methods:** This retrospective cohort study used the Surveillance, Epidemiology, and End Results (SEER) database to identify women diagnosed with unilateral invasive lobular carcinoma (ILC) between 2000 and 2020. The cohort was followed for up to 20 years to assess contralateral breast cancer and breast cancer-specific survival. We estimated crude mortality rates, 20-year cumulative breast cancer mortality, and hazard ratios by surgical treatment group. Kaplan-Meier was used for cumulative risk, and Cox proportional hazards models for unadjusted and adjusted hazard ratios with 95% confidence intervals. P-values < 0.05 were considered significant. **Results:** We identified 58,861 women with unilateral ILC. Of which, 34,561 (59%) had lumpectomy, 18,894 (32%) had unilateral mastectomy, and 5406 (9.1%) had bilateral mastectomy. The mean age (in years) was 64 $\pm$11 for unilateral lumpectomy, 62 $\pm$13 for unilateral mastectomy, and 57$\pm$11 for bilateral mastectomy ($p < 0.0001$). The mean tumour size was smallest in the lumpectomy group (1.9$\pm$1.5 cm) compared with 3.6$\pm$ 3 cm in both unilateral and bilateral mastectomy groups ($p < 0.0001$). The 20-year cumulative invasive contralateral breast cancer risk was 7.3% for lumpectomy, 7.5% for unilateral mastectomy, and 0.3% for bilateral mastectomy. The 20-year cumulative breast cancer mortality was 13.4% in the lumpectomy group, 30.2% in unilateral mastectomy group and 24.3% in bilateral mastectomy group. However, after adjusting for demographic, clinical, and treatment variables, we observed no difference in breast cancer mortality rates among unilateral mastectomy patients versus lumpectomy patients (adjusted hazard ratio [aHR], 1.01; 95% CI, 0.94–1.08), and a statistically significant reduction in breast cancer mortality rates among bilateral mastectomy patients compared to lumpectomy patients (aHR, 0.90; 95% CI, 0.82–1.00; p value 0.04). **Conclusions:** In this cohort of invasive lobular breast cancer, bilateral mastectomy patients had a significantly lower risk of contralateral breast cancer and, after adjusting for differences in the surgical treatment groups, had a 10% lower rate of breast cancer mortality as compared to lumpectomy patients. Research Sponsor: None.

586 Poster Session

Evaluating the outcome of cardiovascular risk factors in breast cancer patients. First Author: Michelle Koifman, The Brooklyn Hospital Center, Brooklyn, NY

Background: Breast cancer patients are at increased risk of cardiovascular disease due to factors such as treatment-related toxicity and shared comorbidities. This study analyzes demographics and outcomes of cardiovascular risk factors in hospitalized breast cancer patients using nationwide data to guide improved care strategies. **Methods:** We used the National Inpatient Sample Database (2016 to 2020) to perform the analysis. ICD-10 codes were used to make the primary diagnosis of patients with breast cancer admitted to hospitals, and secondary diagnosis of various cardiac risk factors. We used the chi-square test and the student's T-test to analyze categorical and continuous variables. Multivariable regression analysis was used to adjust for confounders and calculate adjusted odds ratio (aOR). Statistical significance was set at $p < 0.05$. **Results:** A total of 855394 patients were detected with primary diagnosis of breast cancer. Out of them, 11% had coronary artery disease (CAD), 13% had congestive heart failure (CHF), 6% had atrial fibrillation, 1% had ventricular arrhythmias and 0.06% had endocarditis. The prevalence of cardiac risk factors was mostly in older adults. The mean age of patients with CAD and CHF was 73 years, atrial fibrillation was 75 years, ventricular arrhythmias was 69 years and endocarditis was 71 years. The mortality was found to be higher in patients with cardiac risk factors as well. The patients with coronary artery disease had aOR of 1.9 (p-value 0.02), congestive heart failure had 1.3 (p-value <0.001), atrial fibrillation had aOR 1.1 (p-value 0.001), for ventricular arrhythmias was 3 (p-value <0.001) and for endocarditis was 1.4 (p-value 0.3). **Conclusions:** Breast cancer patients with cardiovascular risk factors experience significantly higher mortality rates compared to those without. These findings emphasize the need for early cardiovascular risk assessment and proactive management in breast cancer patients to improve outcomes and reduce complications. Research Sponsor: None.

Outcomes of cardiovascular disease in breast cancer patients.

Mortality	With Cardiac Risk Factors	Without Cardiac Risk Factors	Adjusted Odds Ratio	Adjusted Odds Ratio
Coronary Artery Disease	4.7%	4.5%	1.9	0.02
Congestive Heart Failure	6.6%	4.3%	1.3	<0.001
Atrial Fibrillation	5.5%	4.5%	1.1	0.01
Ventricular arrhythmias	12%	4.5%	3.0	<0.001
Endocarditis	6.6%	4.6%	1.4	0.3

587 Poster Session

Gene expression signatures (GES) derived from digital histology to predict pathologic complete response (pCR) to neoadjuvant chemotherapy (CT) in ISPY2 and other trial/real world cohorts. First Author: Frederick Matthew Howard, University of Chicago, Chicago, IL

Background: GES predictive of response to therapy across multiple breast cancer subtypes are commercially available or in development. Deep learning models can predict GES from digital histology, and may serve as a lower-cost alternative immediately available at the time of biopsy. **Methods:** Transformer-based models trained to predict 38 distinct breast cancer signatures from pathology (all with Pearson correlation > 0.5 versus true GES) were previously developed using cases from The Cancer Genome Atlas. These models were applied to digital H&E from pre-treatment biopsies from HER2- cases treated with CT or CT + immunotherapy (IO) from the ISPY2 trial. The histology-derived GES most predictive of pCR in ISPY2 (as per area under the ROC curve [AUROC]) was tested in two external neoadjuvant cohorts - a subset of a trial from Yale of durvalumab + CT (NCT02489448) with TIL annotations, and patients receiving standard of care CT at University of Chicago. AUROC significance was assessed with 1000x bootstrapping, with Benjamini Hochberg correction applied in ISPY2 to account for testing multiple GES models. Tertiles of predicted expression calculated in ISPY2 defined groups with low, medium, and high likelihood of pCR; these cutoffs were tested in the external cohorts. **Results:** Accuracy for pCR prediction was tested in 578 patients from seven arms of ISPY2 – with breakdown by treatment and hormone receptor (HR) status shown in Table. A histology model for a GES defined by estrogen regulated genes (Oh et al, JCO 2006) – including proliferation, apoptosis, and interferon-response genes – predicted pCR with the highest AUROC (0.794) in ISPY2, and outperformed a logistic regression fit on grade, HR status, and tumor / nodal stage (AUROC 0.705, p for comparison 0.0001). Tertiles of predicted expression for this GES (computed in ISPY2) identified groups with low / high pCR rates which were robust to treatment, HR status, and consistent in validation cohorts (Table). This digital signature (AUROC 0.737) compared favorably to pathologist TIL annotation (AUROC 0.664) from the external Yale cohort. An explainability tool demonstrated that patterns of lymphocytic infiltrate and poor differentiation contributed to high signature predictions from histology. **Conclusions:** A digital histology-derived GES consistently identifies patients at low / high likelihood of pCR with neoadjuvant CT or CT + IO, and may improve treatment personalization. Research Sponsor: National Cancer Institute/U.S. National Institutes of Health.

Subgroup	n	AUROC	p	% pCR (low expression)	% pCR (mid expression)	% pCR (high expression)
ISPY2	579	0.794	2×10^{-28}	7.6	26.7	58.6
ISPY2, CT + IO	459	0.810	3×10^{-26}	8.0	28.2	64.1
ISPY2, CT only	120	0.726	0.001	6.4	20.0	36.8
ISPY2, HR-	239	0.704	4×10^{-7}	14.8	29.2	58.4
ISPY2, HR+	340	0.817	1×10^{-15}	6.5	24.8	59.0
UChicago HR-	151	0.746	3×10^{-7}	11.1	27.3	55.1
UChicago HR+	63	0.847	1×10^{-5}	5.5	12.0	70.0
Yale HR-	41	0.737	0.005	0.0	50.0	61.5

588 Poster Session

Neoadjuvant penpulimab combined with taxanes and carboplatin in triple-negative breast cancer: A single-arm, open-label, multi-center phase II clinical study (neoTAPPL). First Author: Wenting Yan, Department of Breast and Thyroid Surgery, Southwest Hospital, Army Medical University; Key Laboratory of Minimally Invasive Surgery and Precision Treatment for Breast Cancer of Chongqing Municipal Health Commission, Chongqing, China

Background: The integration of immunotherapy with neoadjuvant chemotherapy has been shown to enhance pathologic complete response (pCR) and survival outcomes in patients with triple-negative breast cancer (TNBC). Nonetheless, additional research is required to ascertain the optimal neoadjuvant regimen. Here we present a prospective phase II NeoTAPPL trial in which evaluated the efficacy and safety of penpulimab (anti-PD-1 antibody) in combination with taxanes and carboplatin for TNBC patients. **Methods:** In this open-label, multi-center phase II study, patients with untreated, histologically confirmed TNBC in stage II-III were enrolled. Patients received 6 cycles of neoadjuvant therapy with penpulimab (200 mg, d1, q3w) plus taxanes (docetaxel 75 mg/m^2 or nab-paclitaxel 260 mg/m^2, d1, q3w) and carboplatin (AUC=6, d1, q3w). Patients who either completed or discontinued the neoadjuvant treatment would undergo breast surgery. Adjuvant chemotherapy and immunotherapy were at the discretion of the treating physician, and radiation therapy was per standard of care. The primary endpoint was the rate of pCR based on the definition of ypT0/Tis ypN0. Secondary endpoints included residual cancer burden (RCB), event free survival (EFS), overall survival (OS), adverse events (AE), and immune response biomarkers. **Results:** 50 patients were enrolled, among which 37 patients received neoadjuvant treatment and underwent breast surgery. The median age was 51 years (range, 32-72). 33 (89.2%) patients had stage II breast cancer at diagnosis. 21 of the 37 patients achieved pCR (56.7%; 95% CI, 40.9%-71.3%), and 29 patients achieved RCB 0-1 (78.4%; 95% CI, 62.8%-88.6%). The ORR and DCR were 86.5% (95% CI, 72.0%-94.1%) and 91.9% (95% CI, 78.7%-97.2%), respectively. Subgroup analysis showed that 60.6% (20/33) patients with stage II had achieved pCR, 25% (1/4) patients with stage III reached this outcome. The pCR rate was 56.5% (13/23) in patients with negative lymph nodes, and 57.1% (8/14) in those with positive lymph nodes. Treatment-emergent adverse events (TEAEs) of any grade occurred in all 37 pts, in which 20 (54.1%) were grade ≥3. The most common grade ≥3 TEAEs were neutropenia (43.2%), leukopenia (24.3%), anemia (21.6%), and thrombocytopenia (18.9%). 15 patients (40.5%) experienced immune related adverse events (irAEs), all of which were hypothyroidism. **Conclusions:** In this trial, we demonstrated that an anthracycline-free neoadjuvant regimen consisting of penpulimab, carboplatin and taxanes in TNBC showed promising antitumor efficacy and manageable safety profile. The study is still ongoing. Clinical trial information: ChiCTR2300071925. Research Sponsor: Development Center for Medical Science & Technology National Health Commission of the People's Republic of China WKZX2023CX010002.

589 Poster Session

Neoadjuvant low-dose carboplatin and docetaxel in combination with toripalimab for early or locally advanced triple-negative breast cancer (NeoTOP): A single-arm phase 2 trial. First Author: Jun Tang, Sun Yat-sen University Cancer Center, Guangzhou, China

Background: Neoadjuvant immunotherapy combined with chemotherapy improves the rate of pathological complete response (pCR) and prognosis of triple-negative breast cancer (TNBC). However, chemo-immunotherapy treatment is frequently associated with adverse events, resulting in dose reduction and delays. Approaches to deescalate chemo-immunotherapy without compromising outcomes for TNBC patients are needed. Evidence suggests that low-dose carboplatin potentiates the anti-tumor effect of PD-1 inhibitors through many mechanisms. The NeoTOP trial aimed to assess the efficacy and safety of low-dose carboplatin and docetaxel in combination with toripalimab as neoadjuvant therapy for early or locally advanced TNBC. **Methods:** This is a single-arm, open-label, phase 2 trial. Patients with untreated stage IIA-IIIC TNBC were enrolled. Eligible patients received carboplatin (AUC=4), docetaxel (75 mg/m^2) and toripalimab (240 mg), every 21 days for a total of 6 cycles. Toripalimab (240mg, every 3 weeks) continued post-operatively for a further 11 cycles. The primary endpoint was the rate of pCR (ypT0/Tis ypN0). The secondary endpoints included safety, objective response rate (ORR), residual cancer burden (RCB) rate, event-free survival and overall survival. This study used Simon's two-stage design. **Results:** From January 2022 to September 2024, 51 patients were enrolled. Among them, 29 patients (56.9%) had stage II, and 22 (43.1%) had stage III. Four patients prematurely discontinued study treatment due to adverse events (three patients) or tumor progression (one patient), including two discontinued toripalimab only and two discontinued both toripalimab and chemotherapy. One of the four patients who discontinued treatment achieved a pCR when proceeding to surgery. One patient achieved clinical CR after neoadjuvant therapy and refused to receive surgery. After surgery, pCR in both breast and lymph nodes was achieved in 29 of 50 patients, resulting in a pCR rate of 58.0%. For all the 51 patients who received at least one dose of neoadjuvant therapy, the ORR was 90.2%. The proportions of RCB-0, RCB-1, RCB-2, and RCB-3 were 58%, 12%, 22%, and 8%. All 51 (100%) patients reported any grade of treatment-related adverse events (TRAEs). Grade ≥3 TRAEs occurred in 23 (45.1%) patients. Serious adverse events were reported in 5 (9.8%) patients. The regimen was well tolerated, and no new toxicity signals were noted. **Conclusions:** The combination of low-dose carboplatin, docetaxel, and toripalimab showed promising efficacy and manageable safety, suggesting the feasibility of this regimen in the neoadjuvant setting for TNBC. Further randomized phase III trials are warranted. Clinical trial information: NCT06618014. Research Sponsor: None.

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Post-treatment MRI to predict pathological complete response in triple-negative breast cancer following neoadjuvant chemoimmunotherapy. First Author: Toulsie Ramtohul, Institut Curie, Paris, Ile de France, France

Background: Neoadjuvant chemoimmunotherapy (NACI) has significantly improved pathological complete response (pCR) rates in early-stage triple-negative breast cancer (TNBC). However, the predictive accuracy of post-treatment MRI for pCR remains unexplored. Our objective was to assess the performance of post-treatment MRI in predicting pCR in TNBC patients treated with NACI. **Methods:** In this prospective, multicenter study (August 2021–June 2024), women with early-stage TNBC were recruited from three centers. Post-treatment dynamic contrast-enhanced (DCE) MRI data were analyzed across multiple vendors. The predictive performance of radiological complete response (rCR) on MRI for pCR was evaluated using the area under the curve (AUC) of receiver operating characteristics. A multivariable logistic regression model incorporating rCR, nodal involvement, and Ki-67 levels was developed and validated. For patients with residual enhancement, a radiomics score was generated using first-order and shape-based features. **Results:** The study included 175 women in a training set from centers #1 (mean age 49 ± 11 years) and 84 in an external test set from centers #2 and #3 (mean age 52 ± 12 years). MRI rCR achieved an AUC of 0.83 (95% CI: 0.75–0.92) for pCR prediction. A combined model with rCR, nodal status, and Ki-67 levels yielded an AUC of 0.88 (95% CI: 0.81–0.96) in the test set. Among patients with rCR, no nodal involvement, and Ki-67 >30%, the false-positive rate was 3.6% and 3.5% in the training and test sets, respectively, with all cases limited to Residual Cancer Burden-I. For patients with residual enhancement, a model incorporating a radiomics score and lesion count achieved an AUC of 0.80 (95% CI: 0.69–0.90). **Conclusions:** Post-treatment MRI effectively predicts pCR in early-stage TNBC after NACI, suggesting its potential role in identifying candidates for breast cancer surgery omission trials. Research Sponsor: Institut Curie.

Accuracy of rCR for predicting pCR.

Set	Subgroup	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	F1 score (%)
Training	N0 and Ki-67>30%	81 (54/67) [71,90]	86 (12/14) [67, 99]	96 (54/56) [92, 99]	48 (12/25) [28, 68]	88
External test	N0 and Ki-67>30%	82 (28/34) [70, 95]	92 (11/12) [76, 99]	97 (28/29) [90, 99]	65 (11/17) [42, 87]	89

Note-Unless otherwise specified, the data are presented as percentages, with the numbers of participants in parentheses and 95% CIs in brackets; pCR = pathological complete response; PPV = positive predictive value; NPV = negative predictive value.

591 Poster Session

Efficacy and safety of neoadjuvant TQB2102 in women with locally advanced or early HER2-positive breast cancer: A randomized, open-label, multi-centre phase 2 trial. First Author: Junjie Li, Shanghai Cancer Center, Shanghai, China

Background: Standard neoadjuvant regimens for HER2-positive breast cancer include trastuzumab and pertuzumab combined with chemotherapy, and the efficacy and safety of third-generation HER2-direted antibody-drug conjugate (ADC) is unknown. TQB2102 is an anti-HER2 antibody-drug conjugate that targets two non-overlapping epitopes of HER2 (ECD2 and ECD4). It consists of a humanized HER2 IgG1 bispecific antibody conjugated to a topoisomerase I inhibitor via a cleavable linker, and the DAR value is 6. **Methods:** This open-label, randomized, multi-centre phase 2 study enrolled HER2-positive patients aged 18-75 years with stage II–III disease. Patients were randomly assigned to receive neoadjuvant TQB2102 6mg/kg every 3 weeks for 6 cycles or for 8 cycles. The primary endpoint was pathological complete response (pCR). Safety was analysed in patients who received at least one dose of study medication. **Results:** Between 05 February 2024 and 24 Sep 2024, we randomly assigned 52 patients to neoadjuvant TQB2102 6 cycles (Arm A, n=26), 8 cycles (Arm B, n=26). The baseline characteristics were well balanced; approximately 50% of the patients were hormone receptor (HR)-positive, and 63% of the patients were stage III. The pCR rate was 57.7% in Arm A (95%CI 36.9%-76.7%), 76.9% in TQB2102 Arm B (95%CI 56.3%-91%). In patients with HR positive disease, the pCR rate was 53.8% in Arm A and 58.3% in Arm B; in patients with HR negative disease, the pCR rate was 61.5% and 92.9%. Grade 3 or higher adverse events occurred 23.1% in Arm A, and 30.8% in 8 Arm B, 7.69% with increased alanine aminotransferase and aspartate transferase. Dose reduction rate and discontinuation was 3.8% and 19.2% in Arm A, 3.8% and 23.1% in Arm B, and no treatment-related deaths occurred. **Conclusions:** This is the first study to report the efficacy and safety of third-generation duel-HER2-directed ADC in the neoadjuvant setting for HER2-positive breast cancer. TQB2102 is highly efficient and well tolerated. Clinical trial information: NCT06198751. Research Sponsor: None.

pCR in All patients and by HR status.

	6 cycles	8 cycles
All	57.7%	76.9%
HR positive	53.8%	58.3%
HR negative	61.5%	92.9%

592 Poster Session

Early on-treatment (on-Rx) tumor volume reduction (TVR) to predict response to the KEYNOTE-522 (KN-522) regimen in early stage triple negative breast cancer (TNBC). First Author: Clinton Yam, The University of Texas MD Anderson Cancer Center, Houston, TX

Background: Monitoring clinical response by breast ultrasound (US) during neoadjuvant therapy is considered standard of care. We previously demonstrated that suboptimal on-Rx TVR after neoadjuvant doxorubicin and cyclophosphamide (AC) predicts non-pCR after sequential taxane-based chemo. However, it is unknown if on-Rx TVR has the similar predictive value in pts receiving the KN-522 chemo-immunotherapy regimen. **Methods:** Pts with early stage TNBC planned to receive the KN-522 regimen were enrolled on the prospective ARTEMIS trial (NCT02276443). Breast US was performed at baseline and after 6 weeks of paclitaxel + carboplatin + pembrolizumab. TVR was defined as the percent reduction of tumor volumes calculated using 3 perpendicular measurements of the index breast lesion. Pathological complete response (pCR) was defined as ypT0/isN0. Logistic regression was used to examine associations between covariates and pCR. Receiver operating characteristic (ROC) analyses were utilized to assess the predictive value of TVR and determine an optimal TVR threshold. **Results:** 150 pts were included. Clinicopathological characteristics are described in Table 1. The pCR rate was 63%. In uni- and multi-variable analyses, TVR was the only covariate to demonstrate statistically significant association with pCR (aOR:1.9 per 10% TVR, p<0.001). In ROC analyses, the area under the ROC curve (AUC-ROC) was 0.74 (95% CI: 0.66-0.82). TVR>50%, selected based on the Youden index, predicted pCR with the following performance characteristics: positive predictive value: 73%; negative predictive value: 79%; sensitivity: 94%; specificity: 41%. **Conclusions:** Early on-Rx TVR by breast US outperforms clinicopathological covariates in the prediction of pCR in pts with TNBC receiving the KN-522 regimen and should be leveraged for risk stratification and design of response-adapted neoadjuvant clinical trials for pts with TNBC. Clinical trial information: NCT022766443. Research Sponsor: Conquer Cancer, the ASCO Foundation; 12238.

	pCR (n=95)	Non-pCR (n=55)	Odds ratio (OR)	p value (univariable)	Adjusted OR (aOR)	p value (multivariable)
Median 6w TVR – % (interquartile range [IQR])	84 (72-90)	69 (38-83)	1.5	**<0.001**	1.9	**<0.001**
Median age – years (IQR)	51 (40-61)	51 (43-64)	0.98	0.25	1.0	0.73
	N (%)					
Ethnicity						
White	50 (53)	33 (60)	1		1	
Black	15 (6)	10 (18)	1.1	0.84	0.9	0.91
Hispanic/Latino	25 (26)	6 (11)	2.4	0.08	1.9	0.32
Asian	5 (5)	6 (11)	0.6	0.36	0.2	0.12
T stage						
T1/2	79 (83)	46 (84)	1		1	
T3/4	16 (17)	9 (16)	1.0	0.94	1.2	0.77
Nodal status						
Positive	31 (33)	24 (44)	1		1	
Negative	64 (67)	31 (56)	1.60	0.18	1.4	0.55
Germline *BRCA* status						
Mutant	8 (8)	2 (3)	1		1	
Wild Type	84 (88)	51 (93)	0.41	0.27	0.3	0.31
Unknown	3 (3)	2 (4)				
Histology						
Ductal	87 (92)	48 (87)	1		1	
Metaplastic	3 (3)	5 (9)	0.33	0.14	0.3	0.26
Other	4 (4)	2 (4)	1.1	0.91	2.0	0.59
Unknown	1 (1)	0				
Histologic grade						
2	13 (14)	14 (25)	1		1	
3	81 (85)	41 (75)	2.1	0.08	2.0	0.59
Unknown	1 (1)	0				
Ki67						
≤35%	5 (5)	8 (15)	1		1	
>35%	67 (71)	38 (69)	2.82	0.09	4.6	0.09
Unknown	23 (24)	9 (16)				

593 Poster Session

Use of artificial intelligence (AI)–powered spatial analysis to predict pathologic complete response (pCR) in HR+ HER2- breast cancer (BC) patients treated with neoadjuvant chemotherapy (NAC). First Author: Dae-Won Lee, Seoul National University Hospital, Seoul, South Korea

Background: In the KEYNOTE(KN)-756 study, adding pembrolizumab to NAC increased pCR in high-risk HR+ HER2- BC. There is an unmet need to discover who will benefit from adding immune checkpoint inhibitors (ICIs). This study aims to investigate the role of pCR in HR+ HER2- BC and to identify whether AI-powered TIL analysis could predict pCR in patients treated with NAC without ICIs. **Methods:** This is a single-center study conducted in Seoul National University Hospital, Korea. H&E whole-slide images (WSIs) of archival breast tumor tissues at diagnosis were analyzed by Lunit SCOPE IO, an AI-powered spatial TIL analyzer. Tumors with a high proportion of area with high intratumoral TIL were classified as immune-inflamed, those with a high proportion of area with low intratumoral but high stromal TIL as immune-excluded, and the remaining as immune-desert. Recurrence risk prediction AI model was trained and validated on independent 1,552 H&E WSIs to predict OncotypeDx score. Patients with histologic grade 3 and tumor size ≥2 cm with node-positive status, or tumor size ≥5 cm were classified as those eligible for KN-756 study. **Results:** A total of 425 BC patients who were treated with NAC without ICIs between January 2015 and October 2018 were included. The median age was 47 (range 24-80), 67.1% had stage III disease, 93.6% had node-positive disease, and 23.5% were eligible for KN-756 study. pCR was achieved in 57 (13.4%) patients and was higher in patients with whom were eligible for KN-756 study (20% vs 11.4%, p= 0.041). Patients who achieved pCR had better 5-year event free survival (EFS, 92.9% vs 77.7%, p= 0.010). AI-powered spatial analysis was performed in 340 patients. There were 125 (36.8%) with immune-desert tumor, 138 (40.6%) with immune-excluded tumor, and 77 (22.6%) with immune-inflamed tumor. Patients with inflamed tumor had higher pCR rate compared to those with immune-excluded or immune-desert in the whole population (Table) and in patients not eligible for KN-756 study (25.6% vs 11.9% vs 5.7%, p = 0.013). Patients with inflamed or excluded tumor had better EFS compared to desert group (80.9% vs 71.2%, p = 0.0275). In addition, recurrence prediction model showed that those who were predicted to have OncotypeDx score ≥ 26 had higher pCR rate (18.2% vs 4.3%, p= 0.002). **Conclusions:** Achieving pCR was associated with favorable EFS in HR+ HER2- patients treated with NAC. Patients with immunogenic tumor microenvironment had higher pCR rate and better EFS. Investigating the role of immune checkpoint inhibitors according to tumor microenvironment may be promising. Research Sponsor: None.

	Desert (N=125)	Excluded (N=138)	Inflamed (N=77)	p-value
pCR	8 (6.4%)	18 (13.0%)	23 (29.9%)	<0.001
Stage III	85 (68.0%)	88 (63.8%)	51 (66.2%)	0.32
LN +	114 (91.2%)	132 (95.7%)	72 (93.5%)	0.34
HG 3	21 (16.8%)	31 (22.5%)	38 (49.4%)	<0.001
KN-756 eligible	20 (16.0%)	29 (21.0%)	34 (44.2%)	<0.001

594 **Poster Session**

SHR-A1811 as neoadjuvant therapy for HR-positive, HER2-low breast cancer: A single-arm, phase II clinical study. First Author: Zhenzhen Liu, Department of Breast Disease, Henan Breast Cancer Center, The Affiliated Cancer Hospital of Zhengzhou University & Henan Cancer Hospital, Zhengzhou, China

Background: Human Epidermal Growth Factor Receptor (HER2)-low breast cancer accounts for approximately 55% of all breast cancer cases, and it is more prevalent in hormone receptor-positive (HR+) breast cancer. Recent breakthroughs in anti-HER2 antibody-drug conjugates (ADCs) have revolutionized the therapeutic landscape for breast cancer treatment, particularly for HER2-low breast cancer. SHR-A1811 is an anti-HER2 ADC and has demonstrated acceptable tolerability and encouraging antitumor activity in HER2-low advanced breast cancer. Therefore, we conducted the phase 2 trial to investigate the efficacy and safety of SHR-A1811 as a neoadjuvant treatment in patients with HR+/HER2-low breast cancer. **Methods:** This is an open-label, two-stage, phase II clinical trial. In the first stage, 35 participants will be enrolled, and if at least 18 participants achieve an objective response rate (ORR), the trial will proceed to the second stage, enrolling an additional 31 subjects. Eligible patients are women aged 18-70 years; treatment-naive; histologically confirmed invasive breast cancer stage cT2-3/N0-2M0; HR+/HER2-low, and the expression of Ki-67 exceeds 14%. Eligible patients receive SHR-A1811 as neoadjuvant therapy. SHR-A1811 is administered intravenously at a dose of 6.4 mg/kg once every three weeks for a total of eight cycles. The primary endpoint is ORR. Secondary endpoints include safety, residual cancer burden (RCB) 0-1, and pathologic complete response (pCR). **Results:** A total of 66 patients enrolled in this study. The median age was 49 years, with 84.8% (56/66) aged $\geq$ 40 years. Of all patients, 66.7% (44/66) were premenopausal, 66.7% (44/66) had node-positive disease, 86.4% (57/66) had stage II, 13.6% (9/66) had stage IIIA, and 74.2% (49/66) had HER2 expression of IHC 2+/FISH-, while 25.8% (17/66) were IHC 1+. In the modified intention-to-treat population (mITT, patients who received at least one cycle of study treatment and at least one post-baseline MRI assessment), 81.5% (53/65) of patients achieved an ORR, and two patients achieved a pathological complete response, resulting in a pCR rate of 3.1% (2/65). Additionally, the proportion of patients with RCB 0 or RCB I was 9.3% (6/65). 97% (64/66) of patients experienced at least one treatment-related adverse event (TRAE). Grade 3 or higher TRAEs occurred in 39.4% (26/66) of patients, with the most prevalent being neutropenia (27.3%, 18/66), leukopenia (16.7%, 11/66), and anemia (13.6%, 9/66). No interstitial lung disease (ILD) and treatment-related deaths were reported. **Conclusions:** As a neoadjuvant treatment, SHR-A1811 achieves a significant improvement in ORR and brings both pCR and RCB 0-I benefits in patients with HR+/HER2-low breast cancer. These outcomes support further exploration of SHR-A1811 in this patient population. Clinical trial information: NCT05911958. Research Sponsor: None.

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Computational pathology-informed immune biomarker for trastuzumab benefit in HER2+ breast cancer: Validation in NSABP B-41 clinical trial. First Author: Satvika Bharadwaj, Wallace H. Coulter Department of Biomedical Engineering, Emory University and Georgia Institute of Technology, Atlanta, GA

Background: Trastuzumab, a targeted therapy, considerably improves survival outcomes in HER2+ breast cancer patients (pts). However, identifying pts most likely to benefit from trastuzumab and those who might avoid it, remains a challenge. Data from the NSABP B-41 randomized clinical trial which evaluated lapatinib-containing regimens against trastuzumab, each given concurrently with chemotherapy in the neoadjuvant setting, holds potential for computational pathology to uncover treatment response patterns. In this study, we present DeSTIL (Density and Spatial Architecture of Tumor Infiltrating Lymphocytes [TILs]), a predictive biomarker derived from Hematoxylin and Eosin (H&E) images, to evaluate the immune microenvironment and identify HER2+ pts that benefit from trastuzumab. **Methods:** Digitized and quality-controlled H&E slides from HER2+ pts in The Cancer Genome Atlas (TCGA; n=175) were used to develop DeSTIL and was independently validated on NSABP B-41 (n=221) pts. Following nuclei segmentation, TILs were identified, and their density and spatial architecture features were quantified. A lasso-regularized Cox proportional hazards model was used to select features and compute a continuous DeSTIL risk score, which was then dichotomized at the median into DeSTIL-positive and DeSTIL-negative groups in the training set. The locked model was validated on NSABP B-41 to predict event-free survival (EFS) in pts receiving neoadjuvant chemotherapy with trastuzumab, lapatinib, or a combination of trastuzumab and lapatinib. Within the DeSTIL-stratified groups, treatment-specific progression was analyzed to evaluate the potential benefit of trastuzumab-based therapies. **Results:** Among 221 HER2+ pts from the NSABP B-41 trial, 61 pts (28%) were classified as DeSTIL-positive and 160 (72%) as DeSTIL-negative, based on the median training threshold. DeSTIL-positive pts demonstrated a significant benefit with the trastuzumab-alone arm compared to the combination regimen (HR=0.09, 95% CI=0.01-0.77, p=0.0061) (interaction term p=0.024) and against lapatinib plus the combination regimen (HR = 0.11, 95% CI = 0.01-0.9, p = 0.01) (interaction term p = 0.05). In contrast, no significant benefit was observed in DeSTIL-negative pts when comparing trastuzumab to the combination regimen (HR=1.33, 95% CI=0.47-3.75, p=0.5840) or to lapatinib plus the combination regimen (HR=1.01, 95% CI=0.45-2.30, p=0.9701). **Conclusions:** DeSTIL, a biomarker based on the density and spatial architecture of TILs, may help identify HER2+ pts more likely to benefit from trastuzumab. Further validation through prospective trials is warranted. Additionally, this biomarker offers a practical framework for comparing HER2-targeted therapies, with the potential to minimize unnecessary treatments, reducing associated cardiotoxicity and financial burden. Research Sponsor: U.S. National Institutes of Health; R01CA268287A1, R01CA26820701A1, R01CA249992-01A1, R01CA202752-01A, 1R43 EB028736-011, R01CA208236-01A1, R01CA216579-01A1, R01CA220581-01A1, R01CA25 7612-01A1, 1U01CA239055-01, 1U01CA248226-01, 1U54CA254566-01, 1R01HL15127701A1, R01HL15807101A1, W81XWH-19-1-0668.; sponsored research agreements from Bristol Myers-Squibb, Boehringer-Ingelheim, Eli-Lilly and Astrazeneca.

596 **Poster Session**

Exploration of the new classification of hormone receptor-positive breast cancer: Based on the genomic landscape of 2111 early to mid-stage Asian patients. First Author: Cuiyun Zhang, The Affiliated Cancer Hospital of Zhengzhou University and Henan Cancer Hospital, Zhengzhou, China

Background: The molecular classification of breast cancer using omics data has led to varied prognoses; however, with the increase of targeted therapy options, current classifications may not adequately guide treatment strategies. **Methods:** This study analyzed 2,111 HR^+ Asian breast cancer patients using next-generation sequencing of 1,021 genes for targeted therapy classification. **Results:** The majority of patients had invasive ductal carcinoma (67.0%) and were at stages 0 to III (89.6%), with 29.7% being HER2 positive. Variations were widespread, with SNV/Indel mutations found in 99.4% and CNV detected in 44.6% of the samples, respectively. The key signaling pathways, including PAM, RTK/RAS, DDR, and TP53, each showed a prevalence of 50% or higher and co-existed. Interestingly, 76.1% of patients had actionable mutations, predominantly in the PAM (54.8%), RTK/RAS (22.2%), and DDR (11.7%) pathways, which were found to be mutually exclusive ($p < 0.01$). Subsequently, Patients were categorized into two groups, C and M, based on CNV presence, revealing significant differences in the prevalence of actionable genes and pathways. The C group stood out for its high prevalence of PAM (43.7%) and HER2 (38.4%), while the M group exhibited prominence in PAM (64.1%) and DDR (15.0%). Notably, responses to neoadjuvant treatment (NAT) varied as well, with higher pCR rates (51.9% vs. 22.1%, $p < 0.001$) for the combination of chemotherapy and HER2-targeted therapy (Chemo + HP) and lower pCR rates (6.0% vs. 15.2%, p = 0.017) for chemotherapy alone (Chemo) observed in the C group compared to those in the M group. Additionally, subsequent subgroup analyses based on actionable signaling pathways between the two groups showed similar patterns, with the $C\text{-}HER2^+$ subgroup having the highest pCR rate (64.1%) for Chemo + HP and $M\text{-}PAM^-\text{-}DDR^-$ subgroup showing the highest pCR rate (21.5%) for Chemo. Besides, clinical characteristics among the various groups and subgroups showed differences. For instance, the $M\text{-}PAM^-\text{-}DDR^+$ subgroup had an earlier onset ($p < 0.001$) and included more premenopausal individuals (p=0.034), along with higher ER and PR expression ($p < 0.001$) and lower Ki-67 levels ($p < 0.001$). Multivariate logistic regression analysis identified HER2 amplification, PR negativity, and TP53 mutation as independent risk factors for the efficacy of Chemo + HP NAT. **Conclusions:** The study suggested that classifying breast cancer patients based on CNVs and actionable pathways may enhance neoadjuvant pCR rates. This underscored the potential implications for expanding neoadjuvant treatment strategies and facilitating tailored precision treatment options based on distinct molecular profiles and therapy responses. Research Sponsor: None.

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Analysis of event-free survival (EFS) of stromal tumor infiltrating lymphocytes (sTILs), PD-L1 expression, and their early dynamics in the NeoTRIP trial. First Author: Giampaolo Bianchini, Università Vita-Salute San Raffaele, Milan, Italy

Background: We demonstrated that pre-treatment sTILs and PD-L1, and on treatment sTILs but not PD-L1 were associated with pathological Complete Response (pCR) to neoadjuvant therapy in patients (pts) with triple-negative breast cancer (TNBC) enrolled in NeoTRIP (NCT02620280) trial (Bianchini G ESMO 2020). Here we assess the association between the same biomarkers and EFS. **Methods:** NeoTRIP randomized 280 pts to nab-paclitaxel/carbo for 8 cycles (CT) or with atezolizumab (CT/A). As Per-Protocol Population, 258 pts were evaluable for EFS, the primary endpoint of the study.We collected samples at baseline (n=258/258; 100%) and on Day 1 Cycle 2 (D1C2) (n=230/258; 89.2%]. We centrally assessed sTILs (cut-off $\geq$30% to be considered high) and PD-L1 expression (SP142) on immune cells (IC) (IC$\geq$1% considered positive). Association with EFS was investigated. Imaging mass cytometry (IMC) (Wang Nature 2023) was used to investigate the biology linked to PD-L1 dynamic over-expression. **Results:** Median follow-up was 54 months. Pre-treatment high sTILs and PD-L1+ were associated with lower risk of recurrence in CT arm (HR 0.35 [0.12-0.99], p=0.049 and HR 0.31 [0.15-0.64], p=0.001, respectively). In CT/A arm neither pre-treatment marker was significantly associate with EFS. At D1C2 in CT arm, high sTILs but not PD-L1+ was significantly associated with lower risk of recurrence (HR 0.34 [0.15-0.81], p=0.015 and HR 0.65 [0.28-1.48], p=0.30, respectively). In CT/A arm both high sTILs and PD-L1+ were strongly associated with lower risk of recurrence (HR 0.23 [0.07-0.78], p=0.019 and HR 0.25 [0.11-0.57], p=0.001, respectively). Only in CT/A arm, on-treatment PD-L1 provided prognostic information independent of baseline biomarkers, on-treatment sTILs and pCR (adjHR = 0.25 [0.11-0.58], p=0.001). In patients with baseline PD-L1- tumors and paired D1C2 samples (n=87), conversion from PD-L1- to on-treatment PD-L1 positivity occurred in 64.3% and 17.8% in CT/A and CT arms, respectively ($p= 7.39x10^{-6}$). The tumors converted to PD-L1+ status were significantly associated with better outcome in CT/A arm (HR 0.23 [0.08-0.68], p=0.008) but not in CT arm (HR 0.82 [0.24-2.85], p=0.76). Notably, in CT/A arm, patients with baseline PD-L1- tumors had similarly low pCR rate regardless of PD-L1 status on D1C2 (20% and 25.9% in PD-L1- and PD-L1+ D1C2 groups, respectively). The IMC results for the biological characterization of tumors with induction of PD-L1+ will be presented. **Conclusions:** In NeoTRIP on-treatment high sTILs (both CT and CT/A arms) and PD-L1 positivity (only in CT/A arm) were significantly associated with lower risk of recurrence independently of pCR and baseline biomarkers. The findings suggest up-regulation of PD-L1 as new candidate pharmacodynamic biomarker of benefit from atezolizumab. Whether this observation hold also for pembrolizumab remain to be defined. Research Sponsor: Fondazione AIRC per la ricerca sul cancro (AIRC); IG 2018 - ID. 21787, Grant to GB; Breast Cancer Research Foundation (BCRF); 20-181, Grant to LG; Breast Cancer Research Foundation (BCRF); 18-181, Grant to LG; Fondazione AIRC per la ricerca sul cancro (AIRC); IG 2024 - ID. 30919, Grant to GB.

598 **Poster Session**

Long-term outcomes in triple-negative breast cancers (TNBC) treated with talimogene laherparepvec (TVEC) in combination with neoadjuvant chemotherapy (NACT). First Author: Hatem Hussein Soliman, H. Lee Moffitt Cancer Center and Research Institute, Tampa, FL

Background: TVEC is an engineered herpes simplex oncolytic virus (HSV OV) approved for the treatment of melanoma. We published a phase 1/2 trial combining TVEC with NACT in early stage TNBC demonstrating increased pathologic complete response (pCR) compared to expected rates with NACT. We are presenting updated long term follow up data on this cohort of both phase 1 and 2 evaluable patients. **Methods:** Stage II-III TNBC pts were enrolled into a single arm, optimal phase 1/2 trial with TVEC (10^6 PFU 1st dose then 10^8 PFU x 4 doses) weeks 1,4,6,8,10 + weekly paclitaxel (80mg/m2) IV x 12, followed by dose dense AC (doxorubicin/cyclophosphamide 60/600 mg/m2) IV q2weeks x 4 alone (wT-AC) given preoperatively. Primary endpoint was pCR rate. Secondary endpoints included 5 year disease free survival/overall survival rates (DFSR/OSR), safety, immune correlates. **Results:** Forty six patients were enrolled at Moffitt (5/2018 – 4/2020) and evaluable for response and outcomes. Study demographics: median age 49 (27-66), 69.5% White, 13% Black, 13% Hispanic, clinical stage II 80% and III 20%, node + 45%. The pCR rate for the phase 1/2 cohort was 45.6% (95% CI 30.9-60.9). Additionally, 10 patients had residual cancer burden (RCB) 1 responses (associated w/ favorable outcomes) 21.7% (95% CI 10.9-36.3%). At median follow up of 70 months (range 17-98), six patients have had a breast cancer recurrence DFSR=86.9% (95% CI 73.7-95.0) and four patients died OSR=91.3% (95% CI 79.2-97.6). DFSR in pCR group = 95.2% (95% CI 76.1 – 99.9) and non-pCR group = 80% (95% CI 59.3 – 93.1%). All but one of the recurrences occurred in patients with non-PCR responses (RCB 2-3) to TVEC+NACT. Clinical stages at presentation for patients with recurrences were 5 stage II and 1 stage III. No patients had any HSV reactivation or autoimmunity events during the post study surveillance period. Greater immune enrichment of B and T cell subsets in pCR vs. non-pCR tumors was observed during TVEC treatment. **Conclusions:** To our knowledge, this is the first report on longer term outcomes for early TNBC treated with OV. TVEC plus wT-AC demonstrates promising long term outcomes when compared to the more intensive KEYNOTE 522 checkpoint regimen. Additional investigation of oncolytic viruses administered during NACT for TNBC is warranted to confirm this benefit. Clinical trial information: NCT02779855. Research Sponsor: Amgen.

599 **Poster Session**

Neoadjuvant cadonilimab (anti-PD-1/CTLA-4 bispecific antibody) plus chemotherapy in early or locally advanced triple-negative breast cancer: A single-arm phase II trial (CABIN study). First Author: Tao Wu, Changde Hospital, Xiangya School of Medicine, Central South University, Changde, China

Background: Neoadjuvant chemotherapy for triple-negative breast cancer (TNBC) can improve surgical outcomes; however, many patients fail to achieve pathological complete response (pCR). Immune checkpoint inhibitors (ICIs) targeting PD-1/PD-L1 show promise, but responses are limited. This phase II trial evaluates cadonilimab (AK104), a bispecific PD-1/CTLA-4 antibody, combined with nab-paclitaxel and carboplatin in neoadjuvant TNBC to improve pCR rates and assess safety. **Methods:** This phase II, single-arm trial enrolled patients aged 18-75 with treatment-naïve, stage IA-IIIC triple-negative breast cancer (TNBC). Patients received cadonilimab (10 mg/kg) plus nab-paclitaxel (260 mg/m²) and carboplatin (AUC 4) every 3 weeks for six cycles, followed by surgery within 4 weeks. Biopsy specimens were collected before treatment for whole-exome sequencing. The primary endpoint was total pathological complete response (tpCR) rate (ypT0/is ypN0). Secondary endpoints included objective response rate (ORR), disease control rate (DCR), disease-free survival (DFS), event-free survival (EFS), overall survival (OS), and safety. **Results:** A total of 29 patients were enrolled from January 31, 2023, to January 20, 2025. The median age was 53 years, and 11 patients (37.9%) were premenopausal. The majority had positive nodal involvement (75.9%) and stage III (51.7%) disease. of the 29 patients, 19 (65.5%, 95% CI: 45.7-82.1) achieved total pathological complete response (tpCR), and 21 (72.4%, 95% CI: 52.8-87.3) achieved breast pCR (bpCR). Tumor downstaging occurred in 89.7% (T) and 62.1% (N) of patients. Radiological assessments showed an objective response rate (ORR) of 93.1% (95% CI: 77.2-99.2) and a disease control rate (DCR) of 100%. All patients experienced at least one treatment-related adverse event (TRAEs), with 51.7% having grade 3/4 events, most commonly neutropenia (37.9%), platelet count decrease (19.2%), and leukopenia (17.2%). Serious TRAEs occurred in 6.9%. Immune-related adverse events (irAEs) of any grade occurred in 14 (48.0%) patients, while those of grade $\geq$ 3 occurred in only one patient (3.4%). The most common irAE was hypothyroidism (44.8%, 13/29), all were grade 1 or 2. Notably, patients with *TASOR2* or *MST1R* mutation demonstrated a significantly lower pCR rate (both *P*=0.041). Additionally, *CCND1* amplification showed a non-significant negative trend with the pCR rate (*P*=0.051). **Conclusions:** The combination of cadonilimab, nab-paclitaxel, and carboplatin in neoadjuvant treatment for stage IA-IIIC TNBC showed promising efficacy, with high response rates and significant tumor downstaging, particularly in stage III patients. The regimen was well tolerated with manageable adverse events, supporting its further investigation as a potential neoadjuvant treatment for TNBC. Clinical trial information: ChiCTR2200067005. Research Sponsor: None.

600 **Poster Session**

Biomarkers of neoadjuvant dalpiciclib in patients with operable HER2-negative luminal B breast cancer in the DANCER trial. First Author: Yunxiang Zhou, Department of Breast Surgery and Oncology, The Second Affiliated Hospital of Zhejiang University School of Medicine, Hangzhou, China

Background: DANCER (NCT05640778) was a circulating tumor DNA (ctDNA)-directed, single-arm, phase II trial investigating the clinical activity of dalpiciclib combined with aromatase inhibitors as a neoadjuvant regimen for operable human epidermal growth factor receptor 2 (HER2)-negative luminal B breast cancer. Although a high complete cell cycle arrest (CCCA) rate (primary endpoint) of 86.7% (26/30) was achieved at 2 weeks (T1), some patients showed suboptimal clinical responses after neoadjuvant therapy. This underscores the importance of identifying biomarkers predictive of response to CDK4/6 inhibitors. **Methods:** Plasma samples collected at baseline (T0), T1, mid-therapy (T2), surgery (S), and postoperatively (PO) underwent ctDNA and Olink proteomic analyses. Tumor tissues obtained at T0, T1, and S were assessed for somatic variation profiling, immunohistochemical markers and MammaPrint index. Patients achieving CCCA at both T1 and S with a concurrent objective response by MRI at S were classified as Good Responders (GRs, *n* = 15); others were Moderate Responders (MRs, *n* = 15). **Results:** The baseline clinicopathological features of the patients were balanced between the GR and MR groups. Compared to MRs, the GRs at S exhibited significantly lower residual cancer burden (RCB) scores, preoperative endocrine prognostic index (PEPI) scores, histological tumor grades, Ki67 expressions, and CA153 levels. Additionally, GRs demonstrated significantly higher Miller-Payne grades, tumor-infiltrating lymphocyte levels, and tumor shrinkage rates. In terms of biomarkers, GRs had a higher rate of ctDNA clearance at and prior to T2 (100.0% vs 54.5%; $p = 0.045$), as well as higher levels of plasma CCL4 ($p = 0.029$), plasma CCL19 ($p = 0.020$), immunohistochemical pRb ($p = 0.044$), and immunohistochemical CDK4 ($p = 0.034$). Furthermore, *GSTM1* demonstrated a significant shift in its copy number pattern after treatment at S, with five previously detected baseline deletions no longer being identified and five de novo amplifications emerging ($p = 0.007$). Lack of early ctDNA clearance was also significantly associated with RCB class of III and PEPI score of $\geq$ 4. Besides, MammaPrint high-risk patients showed a significant increase in RCB and PEPI scores vs. low-risk patients. **Conclusions:** Patients with operable HER2-negative luminal B breast cancer who exhibit early ctDNA clearance, MammaPrint low-risk status, *GSTM1* deletion, increased pRb/CDK4 expression, and higher plasma CCL4/CCL19 levels may derive substantial benefit from neoadjuvant dalpiciclib therapy. Clinical trial information: NCT05640778. Research Sponsor: National Natural Science Foundation of China; the Key Research and Development Program of Zhejiang Province.

601 **Poster Session**

Patient outcomes in WSG-ADAPT according to NATALEE and MonarchE risk criteria. First Author: Oleg Gluz, West German Study Group and Ev. Hospital Bethesda, Breast Center Niederrhein, Moenchengladbach, Germany and University Hospital Cologne, Cologne, Germany

Background: In HR+/HER2- high-risk early breast cancer (eBC), abemaciclib and ribociclib improve the efficacy of standard endocrine treatment (ET), as shown in MonarchE (abemaciclib) and NATALEE (ribociclib). However, the absolute benefit varies according to prognostic factors. We analyzed the outcome of prognostic groups based on MonarchE and/or NATALEE inclusion criteria in the WSG-ADAPT trial considering Recurrence Score (RS, OncotypeDx) and Ki-67 response after preoperative ET. **Methods:** In WSG-ADAPT (NCT01779206), patients (pts) with clinically high-risk HR+/HER2- eBC (cT2-4 or cN+ or G3 or Ki67 $\geq$ 15%) initially received a 3-week standard ET before surgery or sequential biopsy. Pts with c/pN2-3 or G3 with Ki67 $>$ 40% were randomized directly to chemotherapy (CT trial) evaluating (neo)adjuvant 4 $\times$ paclitaxel q2w vs. 8 $\times$ nab-paclitaxel q1w, followed by epirubicin + cyclophosphamide q2w, followed by ET. pN0-1 pts with RS 0-11 or RS 12-25 with ET-response (central $Ki67_{postET} \leq$ 10%) received ET alone (ET trial); RS 12-25 pts without ET-response entered CT trial. Pts with N1-3 or T3 or T2, N0 with either Ki-67 $\geq$ 20% or G3 or RS $>$ 25 were classified as NATALEE high-risk, pts with N2-3 or N1 with either T3-4 or G3 or Ki-67 $\geq$ 20% were classified as MonarchE high-risk. **Results:** In the WSG-ADAPT ET trial, 303 (14.2%) and 784 (36.7%) of 2135 pts were classified as MonarchE and NATALEE high-risk, respectively. In the CT trial, 963 (43.2%) and 1572 (70.5%) of 2230 pts were classified as MonarchE and NATALEE high-risk. After 60 months of median follow-up, both high-risk vs. low-risk classifications were highly prognostic for iDFS and dDFS in ET and CT trials. However, low-risk pts (by both classifications) in the ET trial had 5-y iDFS and dDFS of 94.7% and 96.4%, respectively, vs. 90.1% and 93.6% for high-risk by just NATALEE but not by MonarchE criteria (p = n.s.) and vs. 88.3% and 88.9% in both NATALEE and MonarchE high-risk pts ($p < 0.001$). In the ET-only cohort, survival outcomes were similar between pN0 and pN1 pts at high-risk by NATALEE but not by MonarchE criteria (5-y iDFS of 87.7% vs. 90.2%; p = n.s. and 5-y dDFS of 91.7% vs. 91.9%; p = n.s.). In the CT trial, 5-y iDFS and dDFS rates were 93.9% and 94.9%, respectively, for NATALEE low-risk pts vs. 84.7% and 87.0% for high-risk by NATALEE but not by MonarchE criteria and vs. 77.7% and 79.6% for MonarchE high-risk pts. **Conclusions:** Among 4365 pts in the WSG-ADAPT trial, subgroups classified as high-risk by NATALEE and MonarchE criteria had poor outcomes. However, N0-1 pts who were high-risk by NATALEE but not MonarchE criteria and pts with RS $\leq$ 25 and/or ET response had only slightly inferior outcomes compared to low-risk pts with ET therapy alone. Assuming a hazard ratio of 0.7 for a ribociclib effect, as shown in NATALEE, an absolute benefit of approx. 2% fewer dDFS events after 5 years can be assumed in this group based on the WSG-ADAPT experience. Shared decision-making will be key in this intermediate-risk group. Clinical trial information: NCT01779206. Research Sponsor: Genomic Health (Exact Science); Celgene; Amgen; Allgemeine Ortskrankenkasse.

602 Poster Session

Racial disparities in clinical outcomes of early-stage triple-negative breast cancer treated with neoadjuvant chemoimmunotherapy: Insights from the NCDB. First Author: Zunairah Shah, Roswell Park Comprehensive Cancer Center, Buffalo, NY

Background: Triple-negative breast cancer (TNBC) is an aggressive breast cancer (BC) subtype, and Black patients (pts) with TNBC have worse survival outcomes after neoadjuvant chemotherapy, likely due to biological and socioeconomic factors. Neoadjuvant immune checkpoint inhibitors combined with chemotherapy, i.e. neoadjuvant chemoimmunotherapy (NACI) have improved pCR rates and overall survival (OS), but its efficacy by race is unclear. This study evaluates racial disparities in clinical outcomes for pts with early-stage TNBC treated with NACI, aiming to address this critical gap. **Methods:** We analyzed the National Cancer Database (NCDB) for pts with stage II/III TNBC treated with NACI from 2019 to 2022. Primary outcomes included pCR and OS, which were analyzed with race using univariate and multivariable logistic regression and Cox proportional hazards models, while adjusting for clinicopathologic variables (age, stage, grade, comorbidities (Charlson-Deyo Comorbidity Classification) and socioeconomic factors (residence (rural/urban area), insurance, income). P value $\leq$0.05 was considered statistically significant. **Results:** A total of 5,137 pts were included. Median age was 51 years (range:39-63); 69.9% were White, 20.5% Black, 9.6% Other, 49.3% had stage II and 50.7% had stage III TNBC. Median follow up was 26.6 months (3.3-61.9), pCR was achieved in 76.5% pts, (White: 77%, Black: 74%, Other: 76%; p = 0.113). Pts achieving pCR had significantly higher 3-year OS (92% vs 72%, p$<$0.001) and 5-year OS (84% vs 56%, p$<$0.001) compared to those without pCR. Racial disparities in survival were observed, with 3-year OS of 88%, 84%, and 85% (p $<$0.05) and 5-year OS of 83%, 77%, and 85% for White, Black, and Others, respectively (p$<$0.05). After adjusting for covariates, Black pts had a trend toward lower likelihood of pCR compared to White pts although not statistically significant (odds ratio (OR) 0.76 [95% CI: 0.54–1.07]. The factors independently associated with worse OS were residence in rural areas (HR 1.79 [95% CI: 1.00–3.19], p = 0.05), tumors $\geq$10 cm (HR 1.92 [95% CI: 1.21–3.06], p = 0.006), stage III disease (HR 1.91[95% CI: 1.47–2.49], p $<$ 0.001) and Black vs. White group (HR 1.42 [95% CI: 1.10–1.84], p = 0.007). **Conclusions:** Black pts with TNBC receiving NACI have worse OS than White pts, possibly due in part to social, structural, or biological determinants of health. Further research is needed to investigate personalized treatment strategies that address the unique challenges Black pts face in achieving long-term survival and improving overall prognosis. Research Sponsor: None.

Survival rates and hazard ratios by race.

Race	3-year survival rate (%)	5-year survival rate (%)	Hazard ratio
White	88%	83%	1.00
Black	84%	77%	1.42 [95% CI 1.10–1.84]
Other race	85%	85%	1.19 [95% CI 0.82–1.74]

603 Poster Session

Outcomes of neoadjuvant endocrine therapy (NAET) versus neoadjuvant chemotherapy (NAC) in stage II-III invasive lobular carcinoma (ILC). First Author: Jason A. Mouabbi, The University of Texas MD Anderson Cancer Center, Houston, TX

Background: ILC is a distinct subtype of breast cancer, accounting for up to 15% of cases, and is characterized by unique clinical and pathological features. ILC often yield poor responses to NAC. Case reports suggest that NAET yields favorable outcomes in ILC. However, no large-scale study has evaluated the impact of NAET in ILC patients. This is the first large study that aims to compare the outcomes of NAC versus NAET in stage II/III ILC. **Methods:** A retrospective analysis was performed on patients treated at MD Anderson Cancer Center with a diagnosis of anatomical stage II-III estrogen receptor-positive (ER+) HER2-ve ILC in our prospectively collected and curated electronic database. Data collected included demographics, receptor status (ER, PR, HER2), treatments received, clinical anatomic and pathologic stage, type of surgery, surgical pathology outcomes, and recurrence. Endpoints included pathologic complete response (pCR), modified Preoperative Endocrine Prognostic Index (mPEPI) score 0, endocrine therapy responsiveness (ETR; Ki67 $\leq$10%), rates of axillary downstaging (from node positive to negative), rate of lumpectomy, rate of axillary lymph node dissection (ALND), and 10-year distant recurrence-free survival (10y DRFS). For DFRS, NAC patients were compared to NAET patients who did not receive adjuvant chemotherapy (ACT). Univariate analysis identified variables associated with outcomes, and multivariate logistic regression was planned for significant factors (p $<$ 0.05). **Results:** We analyzed 611 patients among who the median age was 55 (range 30–91), with 77% White, 8.5% Hispanic, and 8.1% Black. 65% were postmenopausal and all patients received adjuvant ET. 509 (80%) received NAC, and 102 (20%) received NAET. Among NAET patients, 83% received a non-steroidal AI, while 98% of NAC patients received anthracycline-containing regimens. pCR was achieved in 13 NAC patients (2.5%) and 2 NAET patients (1.9%). mPEPI score 0 was attained by 10 NAET patients (9.8%), and the ETR rate was 83%. Axillary downstaging occurred in 11% of NAC patients and 5% of NAET patients. Rates of lumpectomy (17.1% in NAC vs. 17.6% in NAET) and axillary lymph node dissection (ALND) (68.6% in NAC vs. 62.6% in NAET) were comparable between the groups. With a median follow-up of 85 months, 10y DRFS was 55% for NAC and 65% for NAET (HR 0.57, 95% CI 0.33–0.98, P = 0.02). Univariate analysis for DRFS revealed no significant associations with age, race, or initial stage (all p $>$ 0.05), precluding multivariate analysis. **Conclusions:** This large-scale analysis highlights the limited efficacy of NAC in ILC, with minimal pCR rates. NAET yields promising results, including superior 10y DRFS. These findings underscore the potential of NAET as a viable neoadjuvant option for patients with stage II/III ER+ ILC. Research Sponsor: None.

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Serum estradiol (sE2) levels in premenopausal (PreM) women receiving neoadjuvant ovarian function suppression (OFS) with the oral SERD amcenestrant, alone, or in combination with letrozole or abemaciclib in the I-SPY2 Endocrine Optimization Pilot (EOP). First Author: Jo Chien, University of California, San Francisco, San Francisco, CA

Background: The addition of OFS to standard endocrine therapy (ET) improves iDFS for preM women with early-stage hormone receptor positive (HR+) breast cancer (BC). Incomplete OFS occurs in a subset of women, the long-term clinical significance of which is unclear. This study evaluates local sE2 levels in preM women receiving OFS with an oral SERD in the neoadjuvant (NA) setting. **Methods:** The EOP is a I-SPY2 sub-study investigating NA endocrine-based strategies in pts with HR+ HER2- Stage 2/3 BC predicted to have lower benefit from chemotherapy. Pts were randomized to oral amcenestrant 200 mg/d, alone or in combination with either letrozole 2.5 mg/d or abemaciclib 150 mg bid. Additional pts were randomized to a standard of care (SOC) arm consisting of an aromatase inhibitor. All PreM pts received OFS with monthly GnRHa up to 2 wks prior to C1D1 of study therapy. Pts were treated for 6 months prior to surgery. sE2 levels were collected locally prior to each GnRHa injection. Tumor Ki67 was assessed at 3 weeks and surgery, and associated with sE2 level. Statistical significance was determined using a two-sided Student's t-test and a significance level 0.05. **Results:** Between 5/2021-8/2022, 74 pts were enrolled to an amcenestrant containing arm, 40 of whom were preM. 38/40 pts had at least one local sE2 level measured in follow up. Of these 38 pts (median age 45 years), 37 suppressed sE2 into the postmenopausal (postM) range at one or more follow-up timepoints. Of the 37 pts that completely suppressed into the postM range, 6 pts had sE2 levels rebound into the preM range (mean 319 pg/mL, range 20-848 pg/mL) with peak sE2 levels occurring at a median of 12 weeks from C1D1. One pt never suppressed to the postM range (peak sE2 1227 pg/mL) and was found to have an ovarian cyst after 3 months on amcenestrant, requiring surgery. One additional pt had multiple ovarian cysts (sE2 84 pg/mL). Median age of the 7 pts who had sE2 rebound was 43 years. There was no significant difference in Ki67 at 3 weeks and surgery between pts whose sE2 levels remained suppressed (median Ki67 2.0%) compared to those whose estradiol rebounded into the preM range or never suppressed (median Ki67 1.5%). In the 5 pts whose sE2 rebounded to $>$ 200 pg/mL, all pts had tumor Ki67 $<$ 10% at 3 weeks and surgery. Between 12/2022 and 8/2023, 20 pts were enrolled to AI +/- OFS and 11 pts were preM. Of the 11 preM pts, all pts suppressed sE2 to the postM range. No SOC patients had sE2 levels rebound into the preM range. **Conclusions:** In this study of neoadjuvant oral SERD with monthly OFS, 7/38 (18.4%) preM pts had sE2 levels remain or rebound into the preM range. sE2 levels did not appear to impact Ki67 suppression on NA ET. Work up for ovarian cysts should be considered in pts with symptoms, or significantly elevated or persistent sE2 levels. Clinical trial information: NCT01042379. Research Sponsor: Quantum Leap Healthcare Collaborative.

605 Poster Session

Molecular insights into HR+/HER2+ early-stage breast cancer: Neoadjuvant therapy responses by MammaPrint and BluePrint genomic subtypes. First Author: Laila Samiian, Baptist MD Anderson Cancer Center, Jacksonville, FL

Background: Clinical HER2+ (cHER2+) early breast cancer (EBC) represents 15-20% of invasive EBC and is typically treated with Neoadjuvant HER2-targeted therapy (NHT) combined with chemotherapy, regardless of ER status. NBRST and I-SPY2 trials showed varied NHT responses in cHER2+ tumors based on genomically-defined molecular subtypes, emphasizing the importance of understanding tumor biology. Genomic assays MammaPrint (MP) and BluePrint (BP) predict therapy response and inform treatment decisions. Here, we explored the biological pathways underlying differential NHT response in triple positive (HR+HER2+) tumors using whole transcriptome analysis (WTA). **Methods:** Patients with HR+/HER2+ early-stage breast cancer treated with NHT (N = 720) were included from FLEX (NCT03053193). MP classified tumors as UltraLow (UL), Low, High 1, or High 2 Risk, while BP categorized them as Luminal A, Luminal B, HER2, or Basal. Differences in clinical characteristics and pathological complete response (pCR) rates were assessed by Chi-Square or Fisher's exact tests and proportional Z-test, respectively. Differential gene expression (DGE) analysis of WT profiles was performed between tumors with and without pCR, using limma package in R, followed by pathway enrichment analysis in Metascape. **Results:** Among 720 HR+/HER2+ EBCs, MP classified 19 (2.6%) as UL, 107 (14.9%) as Low, 385 (53.5%) as High 1, and 209 (29.0%) as High 2. BP classified 120 (16.7%) as Luminal A, 307 (42.6%) as Luminal B, 278 (38.6%) as HER2, and 15 (2.1%) as Basal. Compared to other BP subtypes (Luminal A/B), BP HER2 tumors were associated with younger age (54 vs 60, p $<$ 0.001), premenopausal status (p = 0.002), higher grade (G3: 54.7%, p $<$ 0.001), and T3 tumors (10.7% vs 3-4%, p $<$ 0.001). pCR rates with NHT were higher in BP HER2 tumors compared to Luminal A/B tumors (n = 41, 61.2% vs n = 18, 26.5%, respectively, p $<$ 0.001). WTA of BP HER2 tumors with pCR showed 23 genes with 2-fold change (not statistically significant after correction), 20 of which were upregulated and associated with regulation of bone morphogenic protein encoding genes and increased cell-substrate/cell matrix adhesion, compared to tumors that had residual disease. **Conclusions:** These data show heterogeneity within HR+/HER2+ tumors, with approximately 60% genomically reclassified as non-HER2-type by BP. Consistent with I-SPY2, BP HER2 cancers showed higher pCR rates than Luminal A/B, suggesting that additional therapeutic strategies are needed to increase the pCR rates in these cancers. Although WTA in BP HER2 tumors with and without pCR identified DGE, the findings were not statistically significant. Future analyses of WTA in larger numbers of BP subtypes within the HR+ HER2+ EBC patients who are being enrolled on the FLEX trial may elucidate the biology of the cancers with pCR vs non-pCR. Clinical trial information: NCT03053193. Research Sponsor: Agendia, Inc.

606 **Poster Session**

Results of the prospective randomized controlled trial VOG-01: Neoadjuvant endocrine therapy ribociclib + fulvestrant + GnRH-a versus chemotherapy 4 AC + 4 T for early HR+/HER2-negative breast cancer in premenopausal patients. First Author: Rashida Orlova, Saint Petersburg State University, Saint Petersburg, Russian Federation

Background: CDK4/6 inhibitors are used to treat HR+/HER2- metastatic breast cancer in combination with endocrine therapy. However, there is still a lack of evidence about combined endocrine therapy in neoadjuvant setting. VOG-01 is a phase II randomized trial that evaluated the effects of combination ribociclib plus fulvestrant and GnRH-a as neoadjuvant therapy in premenopausal patients. **Methods:** Premenopausal women with HR+/HER2-negative stage II-III were randomly assigned to Fulvestrant (500 mg on the 1st, 15th, 28th days of the first cycle, then once every 28 days), Triptorelin (3.75 mg every 28 days) and Ribociclib (600 mg daily, 3 weeks/4) during 16-24 weeks (NET), or Doxorubicin 60 mg/m2 + Cyclophosphamide 600 mg/m2 x4 21-day courses followed by Docetaxel 75 mg/m2 x4 21-day courses (NCT). Primary endpoint was objective response rate. Secondary endpoints were pathological response rate (RCB), frequency of breast-conserving surgery, severity of adverse events and the quality of life (EORTC QLQ-C30). **Results:** Eighty two patients were recruited. The objective response rate was 83% in the NET and 71% in the NCT (p = 0.2). Complete pathological response (RCB 0) was in 2 cases (5%) in the NET and in 4 cases (10%) in the NCT; RCB I was in 1 case (2.6%) in the NCT and did not occur in the NET; RCB II - 55% in the NET and 62% in the NCT, RCB III was in 40% and 26% respectively. Breast-conserving surgery were not so common in both groups: 37% in the NET and 32% in the NCT (p=0.5). Severe adverse events (CTCAE ver 5 G3-4) were 66% in the NET and 87% in NCT ($p < 0.019$). Quality of life significantly decreased during NCT compared with NET: the total score was 75.7 ± 22.2, 42.0 ± 19.7, 66.3 ± 12.9 in NCT at visits on 1-12-24- weeks and 76.4 ± 20, 70.7 ± 25.4, 76.1 ± 20.5 in NET at the same visits ($p < 0.05$). **Conclusions:** For the first time randomised trial comparing NET and NCT was conducted in premenopausal women with HR+/HER2-early breast cancer. NET was not inferior to standard NCT in terms of objective response rate, complete or pronounced pathological response rate and breast-conserving surgery. At the same time it was associated with a lower severity of adverse events and increased quality of life. Nevertheless new treatment approach requires confirmation of its effectiveness in large studies. Clinical trial information: NCT04753177. Research Sponsor: None.

607 **Poster Session**

HER2DX genomic test in HER2-positive breast cancer treated with 15 weeks of neoadjuvant paclitaxel, trastuzumab, and pertuzumab (THP): Final analysis from the BiOnHER clinical trial. First Author: Bartomeu Fullana Grimalt, Avinguda de la Granvia de l'Hospitalet, 199-203, L'hospitalet De Llobregat, Barcelona, Spain

Background: HER2DX is a 27-gene genomic assay providing prognostic and predictive insights in early-stage HER2-positive (HER2+) breast cancer. Although widely validated, less data exists for its performance in THP beyond the DAPHNe trial (JAMA Oncol 2023), which included 80 patients (pts). This study aimed to validate HER2DX for predicting pathological complete response (pCR) with THP and compare its performance to hormone receptor (HR) status. **Methods:** HER2DX (Reveal Genomics) was centrally evaluated on all tumor biopsies from the BiOnHER trial (NCT05912062), where pts with stage I-III HER2-positive breast cancer received 15 weeks of neoadjuvant THP at the Catalan Institute of Oncology. Biopsies were collected at pre-treatment baseline (D1) and day 8 (D8) after an HP loading dose but before initiating paclitaxel. HER2DX pCR group cutoffs were based on predefined thresholds for HER2DX low-, medium-, and high groups. Logistic regression and receiver-operating characteristic (ROC) curve analyses were used for statistical evaluation. The primary objective was to assess HER2DX pCR score for predicting pCR (ypT0/isN0). Secondary objectives included evaluating HER2DX performance by HR status, baseline TILs/Ki67, and additional insights from D8 data. **Results:** HER2DX was successfully evaluated in all 83 enrolled patients. The cohort included 65.1% T2 tumors, 62.7% cN0 status, 69.9% stage II disease, and 67.5% HR-positive tumors. The overall pCR rate was 45.8% (95% CI, 34.9–57.0%), and the ypT1miN0 rate was 54.2%. HER2DX pCR score was significantly associated with pCR (odds ratio [OR] = 5.26, $P < 0.001$), with an AUC of 0.835. Patients were categorized into 35.0% low, 37.5% medium, and 27.5% high HER2DX pCR score groups, with pCR rates of 13.3% (95% CI, 4.4–31.6%), 51.6% (95% CI, 33.4–69.4%), and 81.8% (95% CI, 59.0–94.0%), respectively. Among HR-negative tumors, pCR rates were 78.6% for high-pCR and 0.0% for low-pCR groups, while in HR-positive tumors, pCR rates were 87.5% and 13.8%, respectively. HR status alone was associated with pCR (OR = 0.125, P = 0.006) but lost significance in multivariable analysis including HER2DX. Baseline Ki67 (median: 35.0%) and TILs (median: 8.0%) were not associated with pCR. While D8 data offered biological insights, it did not improve predictive performance beyond baseline HER2DX. **Conclusions:** HER2DX is a robust predictor of pCR following neoadjuvant THP in stage I-III HER2-positive breast cancer, outperforming HR status. Baseline TILs and Ki67 were not predictive of pCR, and HER2DX D8 data did not improve predictive performance. Clinical trial information: NCT05912062. Research Sponsor: Instituto de Salud Carlos III (ISCIII); FIS PI20/00544.

609 **Poster Session**

Outcomes of elderly patients with early-stage triple-negative breast cancer treated with the KEYNOTE-522 regimen. First Author: Renata Colombo Bonadio, Instituto D'Or de Pesquisa e Ensino (IDOR), São Paulo, Brazil

Background: The KEYNOTE-522 regimen (neoadjuvant pembrolizumab combined with a four-drug chemotherapy backbone, followed by adjuvant pembrolizumab) is a standard of care for stage II-III triple-negative breast cancer (TNBC). However, the median age of TNBC diagnosis is 40–50 years, and elderly patients (pts) are underrepresented in clinical trials. **Methods:** The effectiveness and safety of the KEYNOTE-522 regimen were evaluated in patients aged ≥65 years (y) in the Neo-Real/GBECAM-0123 trial, a real-world, multicenter study conducted across ten institutions since July 2020. Pathological complete response (pCR) was assessed as the primary endpoint. Patients < 65y served as the control group. **Results:** Of the 413 pts included in the study, 45 (10.9%) were aged ≥65y. Compared to younger patients, elderly pts exhibited a higher proportion of special histological types (15.6% vs 6.8%, P = 0.055), lower-grade tumors (grade 1–2: 35.5% vs 13.6%, P = 0.001), lower Ki-67 index (< 50%: 46.7% vs 16.6%, P < 0.001), and fewer germline BRCA1/2 mutations (2.2% vs 13%, P = 0.039). The majority of patients in both groups had stage II disease (77.8% vs 69.3%, P = 0.574). Elderly pts were less likely to receive dose-dense anthracycline and cyclophosphamide (AC) (44.4% vs 55.4%, P = 0.027). Patients aged ≥ 65y had lower pCR rates compared to those < 65y (46.3% vs 64%; univariate logistic regression: OR 0.48, 95%CI 0.25–0.93, P = 0.030). However, this difference was not significant in multivariable analysis adjusted for histological type, tumor grade, Ki-67 index, BRCA status, and AC schedule (OR 1.80, 95% CI 0.74–4.37, P = 0.188). Elderly pts experienced significantly higher rates of safety concerns (Table 1). **Conclusions:** TNBC in elderly pts appears to have distinct biological characteristics, which may contribute to lower pCR rates with the KEYNOTE-522 regimen. Additionally, the higher incidence of safety issues in this population underscores the importance of personalized treatment strategies and careful patient selection. Further studies focused on elderly pts with TNBC are needed. Research Sponsor: None.

Safety outcomes of elderly patients treated with KN522 regimen.

	≥ 65y	< 65y	P
Drug discontinuation due to AE	33.3%	21.7%	0.140
AC discontinuation	17.8%	3.8%	0.001
Dose reduction	27.2%	12.2%	0.010
Delay for neoadjuvant treatment conclusion	42.2%	22.3%	0.006
Hospitalization due to AE	33.3%	15.2%	0.011
Antibiotics use	44.4%	25.5%	0.019
Grade ≥ 3 AE	48.9%	34.2%	0.137
Anemia	8.9%	2.4%	0.042
Neutropenia	35.5%	19.6%	0.020
Febrile neutropenia	22.2%	10.3%	0.026
Fatigue	6.7%	1.4%	0.046

610 **Poster Session**

Early adverse symptoms to predict response to treatment among patients in the I-SPY trial. First Author: Amrita Basu, University of California, San Francisco, San Francisco, CA

Background: The adverse event (AE) landscape in oncology is changing due to the introduction of immunotherapy and antibody drug conjugates. These AEs come with both short and long-term symptoms that significantly impact patient quality of life. Monitoring for early onset of symptoms could optimize therapy for a particular patient, maximizing potential efficacy while mitigating toxicity. It is also possible that some toxicities are directly associated with drug sensitivity. We sought to identify symptoms associated with pathologic complete response (pCR) using patient-reported outcomes (PROs) in early-stage high-risk breast cancer patients. **Methods:** Our study population included 288 stage II/III high-risk breast cancer patients enrolled on the I-SPY2 trial from 2021-2024, who received novel neoadjuvant therapies ± standard paclitaxel. pCR was assigned if tumor was absent in breast and nodes at surgery following neoadjuvant treatment. Patients (n = 288, pCR rate = 29%, 89% administered immunotherapy) were sent electronic PROs. 33 patient-reported AEs were measured using NCI's Patient Reported Outcomes - Common Terminology Criteria for Adverse Events (PRO-CTCAE). Each symptom was evaluated using severity, frequency, and interference on a Likert Scale. Presence of early PRO symptoms (cycles 1-3 of treatment) were binarized (at least one of moderate or greater), and odds ratios were computed with pCR as outcome. To assess whether higher grade AEs were enriched in patients that achieved a pCR, we also performed the Wilcoxan rank sum test using maximum (worst) symptom severity. **Results:** Of 288 patients included in our analysis (median age = 48 years, range = 20-78), 203 (70.5%) were White, 17 (5.9%) were Asian, 33 (11.5%) were Black or African American, and 35 (12.2%) were Hispanic. PRO analysis revealed that patients that had moderate to severe muscle pain (27% vs 10% OR = 3.15, $p < 0.05$), joint pain (22% vs 8% OR = 3.23, $p < 0.05$), headache (27% vs 12.5% OR = 2.59, $p < 0.05$), or mouth/throat sores (16% vs 5% OR = 3.56, $p < 0.05$) within weeks 1-3 had higher odds of achieving a pCR. When we looked at maximum severity between weeks 1-3, patients that achieved a PCR had higher grade muscle pain (p = 0.04), heart palpitations (p = 0.035), and significantly lower grade numbness and tingling (p = 0.002). Beyond 6 weeks, associations were weaker or insignificant. **Conclusions:** Our study utilizes an analysis framework that was able to determine sentinel symptoms such as muscle and joint pain, mouth/throat sores and palpitations as early as weeks 1-3 associated with increased efficacy. This may suggest an early immune reaction in patients that eventually respond favorably to treatment. Our work can help provide earlier proactive monitoring to mitigate toxicities, treatment redirection if needed, and a potential symptom-based early understanding to personalize treatment efficacy. A similar analysis is underway to predict immune related AEs. Clinical trial information: NCT01042379. Research Sponsor: National Cancer Institute.

611 **Poster Session**

Automated prediction of response to neoadjuvant chemotherapy from digitized H&E slides of pre-treatment core needle biopsies in INFORM (TBCRC 031) patients with low stromal TILs. First Author: Stuart J. Schnitt, Brigham and Women's Hospital, Boston, MA

Background: We previously performed anautomated analysis of whole slide images (WSI) of H&E-stained pre-treatment core needle biopsies (CNBs) from patients (pts) enrolled in the INFORM phase II trial of neoadjuvant cisplatin vs doxorubicin-cyclophosphamide in HER2-negative germline *BRCA* carriers. That analysis demonstrated that a digital biomarker of complex immune response (CmbI) which combines immune heterogeneity index (IHI), proliferative, and cell cycle G1/S deregulation signatures, was significantly predictive of response (RCB 0,1) to neoadjuvant chemotherapy (NAC) in all pts, in sub-cohorts including TNBC, and in both therapy arms. Further, a lower IHI, indicating less heterogeneity of stromal tumor infiltrating lymphocytes (sTIL), was predictive of a better response to NAC (RCB 0,1), whereas a higher IHI, indicating greater heterogeneity of sTIL was associated with a worse response (RCB 2,3). The predictive performance of IHI alone was modest compared to CmbI but superior to sTIL. High sTIL is associated with favorable prognosis for NAC, especially in TNBC. However, the impact of heterogeneity of immune cell distribution on NAC response, particularly in those with low sTIL is unknown. The current study evaluated if IHI could augment sTIL assessment by identifying NAC responders in patients with tumors demonstrating low sTIL. **Methods:** CNBs scanned at 40x on a Hamamatsu Nanozoomer scanner were evaluated using the 4D QPOR platform to generate IHI as a continuous index. Among 88 QPOR analyzable pts, 85 had sTIL scores available from prior visual pathologic review. Tumors with low sTIL ($<$ 30%, a previously documented clinically significant cut-off),were further stratified into low vs high IHI using median IHI for the population as the cut-off. We then determined the relationship between IHI and likelihood of response to NAC (RCB 0,1) in the overall cohort, and in the TNBC and ER low ($<$ 10%) sub cohorts. The analysis was also performed using the median sTIL cut-off $<$ 20% previously used in INFORM. **Results:** Low IHI was significantly predictive of NAC response (RCB 0,1) in low sTIL pts in the overall cohort (N = 64, OR = 4.75; 95% CI1.50, 16.21), p = 0.005, PPV = 70%) and in the ER low sub cohort (N = 46, OR = 4.04;95% CI 1.04-17.38, p = 0.04, PPV = 72%). IHI was modestly predictive in the low sTIL pts in TNBC sub cohort (N = 41, OR = 4.28 (0.99, 20.77), p = 0.03, PPV = 71%) but not predictive in high sTIL pts ($<$ 1/3 pts in each subgroup). For sTIL $<$ 20%, IHI had stronger predictive ability in all pts (N = 64, OR = 7.63 (1.83, 40.09), p = 0.0016, PPV = 80%). **Conclusions:** Heterogeneity of immune cell distribution determined by computational analysis of WSI of pre-treatment CNB of patients with germline BRCA mutations and HER2-negative cancers in the INFORM trial improves response prediction to NAC in patients with low baseline sTIL as determined by visual analysis. Research Sponsor: None.

612 **Poster Session**

I-SPY2 endocrine optimization pilot (EOP): Neoadjuvant lasofoxifene (Laso) in molecularly selected patients with hormone receptor positive (HR+)/HER2 negative (HER2-) stage 2/3 breast cancer (BC). First Author: Mei Wei, Huntsman Cancer Institute, University of Utah, Salt Lake City, UT

Background: EOP, an I-SPY2 sub-study, evaluates the tolerability and activity of novel endocrine strategies in stage 2/3 breast cancer (BC) patients (pts) predicted to have lower chemotherapy benefit. Laso, a selective estrogen receptor modulator (SERM), has shown favorable toxicity profile and activity in HR+/HER2- endocrine-resistant metastatic BC. **Methods:** Pts with Stage 2/3 HR+/HER2-, MammaPrint (MP) low risk BC were enrolled. Pts with MP High1 BC were included if clinically node-negative. Pts received oral laso 5 mg daily for six 28-day cycles. Laso was continued until the day prior to surgery. Premenopausal pts received ovarian function suppression (OFS) starting C2D1. The primary endpoint was feasibility ($>$75% of patients completing $>$75% study therapy). Baseline (T0), 3-wk (T1) biopsies, and the surgical specimen (T3) was assessed centrally for Ki-67. Breast MRI functional tumor volume (FTV) was performed at T0, T1, 12 weeks (T2), and pre-operatively (T3). Blood was collected for tumor informed ctDNA at T0, T1, T2, T3. Advance event (AE) was assessed using CTCAE V5. **Results:** From 3/2023 to 5/2024, 20 pts were enrolled. Median age 50.5 years, 50% premenopausal, and 1 male pt. 60% cN0, 80% MP low-risk signature. 18 (90%) pts completed $>$75% study therapy. Two pts discontinued treatment due to pt preference. Median Ki67 at T0 was 14.7%. At T1, 87.5% of pts remained or suppressed Ki67 to $<$10% and 37.5% suppressed to $<$2.7%. Ki67 at T1 was similar between pre-and postmenopausal pts despite OFS (Table). The median MRI FTV was 8.4 cc at T0, and 3.4 cc at T3. Median % FTV reduction from T0 to T3 was -47.5%. 2/20 pts (10%) achieved a modified PEPI score of 0. No patients achieved completed pathological response. Of the 16 pts with RCB results, 2 (12.5%) RCB-1, 6 (37.5%) RCB-2, 8 (50%) RCB-3 disease. 14 pts had ctDNA available at T0. 4/14 were ctDNA+ at T0, 2 of whom became ctDNA negative, and 2 remained ctDNA+. 10/14 pts were ctDNA negative at T0, 8 of whom remained negative, 2 became positive at T1 then cleared. All AEs were grade(G) 1 except 1 pt with G2 hot flashes. Most common AEs include hot flashes (85%), constipation (50%), fatigue (50%), and nausea (35%). One pt had G3 hypersensitivity and hypertension, both unrelated to therapy. **Conclusions:** Neoadjuvant laso demonstrates a favorable AE profile and promising anti-tumor activity in suppressing 3-wk Ki67 and MRI FTV change in pts with HR+ HER2-negative early BC. Ki67 suppression in premenopausal pts was seen in the absence of OFS. Clinical trial information: NCT01042379. Research Sponsor: NIH PO1-CA210961.

Ki67 expression at pre-treatment, and 3-wk time point.

	All Patients (n=20)	Premenopausal (n=10)	Postmenopausal (n=9)
Median Ki67 expression			
Baseline	10.0%	12.5%	10.0%
3-wk	5.1%	3.0%	6.0%
Number of pts with Ki67 expression <10% at 3-wk	87.5%[1]	87.5%	85.7%
Number of pts with Ki67 expression <2.7% at 3-wk	37.5%	50%	28.6%

[1]Include the one male pt.

613 **Poster Session**

Verification of the BREASTEST assay in an Australian population: A novel liquid biopsy assay measuring lipid biomarkers for early-stage breast cancer screening. First Author: David Speakman, BreastScreen Victoria, Melbourne, VIC, Australia

Background: Women with dense breasts are at higher risk of developing breast cancer however there is no agreement on how to screen these women, despite mandatory density reporting becoming more prevalent. Currently available image-based, population level breast screening modalities have poor sensitivity in these women. Likewise, the positive predictive value of imaging is reduced due to a higher false positive rate/recall rate compared to that of women with less dense breasts. Liquid biopsy approaches do not suffer from imaging-dependent challenges with density and provide a promising option in this population. We have discovered a novel liquid biopsy assay using a lipidomic discovery platform by combining liquid chromatography tandem mass spectrometry (LC-MS/MS) and machine learning. The BREASTEST assay is intended to complement standard of care screening and address gaps in the current screening paradigm. **Methods:** This study was conducted to verify the performance of the BREASTEST assay in an Australian population (n = 720). This verification study was an observational case-control study that prospectively recruited women with breast cancer (n = 275) or without (n = 446) across 10 clinical sites over a 34-month period. A primary imaging modality was identified for each subject and a binary classification was assigned to the outcome of this imaging (normal/suspicious) to enable comparison to, and combination with, the BREASTEST assay. An assay with a high sensitivity has utility as a rule-out test and would complement population-based imaging (high specificity). Therefore, the assay was designed to achieve a sensitivity of 0.90. The combined specificity of imaging with the assay was calculated to estimate the clinical benefit BREASTEST could bring in ruling-out women without breast cancer. A safe de-escalation rate was also calculated in this study to assess the potential reduction in unnecessary further assessment if this assay was added to standard imaging. **Results:** The utility of the BREASTEST assay was observed when results were combined with primary imaging data in the study cohort. Across all imaging modalities and breast densities, the assay improved the combined specificity in 45–75-year-old women by +6.1% (0.712, 0.773) and had a safe de-escalation rate of 21.0%. Highlighting the potential benefit to women with dense breasts, in women aged 30-49 years with breast density category D the combined specificity was +14.7% (0.585, 0.732) and safe de-escalation rate of 37.5%. The BREASTEST assay alone obtained a sensitivity of 0.90, specificity of 0.369 with an AUC of 0.743. **Conclusions:** The performance and utility of the BREASTEST assay was verified in this study in an Australian population. It has highlighted the potential of this assay in the workup of women with breast conditions, in particular women with dense breasts. Research Sponsor: BCAL Diagnostics.

TPS615 **Poster Session**

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

Background: The TAILORx and RxPONDER trials demonstrated that RS identifies many postmenopausal pts with node-neg and node-pos BC and RS $\leq$25, who do not benefit from addition of ACT to endocrine therapy (ET). Both trials also showed that certain subsets of premenopausal pts (node-neg/high clinical risk/RS 16-20, node-neg/RS 21-25, and node-pos/RS $\leq$25) benefited from adding ACT to ET. Most premenopausal pts in these trials did not receive ovarian function suppression (OFS) as part of their ET regimen. Given the observed benefit from OFS in high-risk premenopausal pts with HR+/HER2- BC in the SOFT/TEXT trials, many questioned whether all or part of the observed ACT benefit in the TAILORx/RxPONDER trials may have been the result of chemotherapy-induced OFS. To address this question, we developed OFSET, a phase III, multicenter clinical trial comparing OFS+ET *v* ACT+OFS+ET. **Methods:** We hypothesize that addition of ACT to OFS+ET is superior to OFS+ET in improving invasive breast cancer-free survival (IBCFS) among premenopausal, early-stage BC pts with HR+/HER2- tumors, and a 21-gene RS between 16-25 (for pN0 pts) and 0-25 (for pN1 pts). Secondary objectives include invasive disease-free survival, overall survival, distant recurrence-free interval, breast cancer-free interval, and health-related quality of life (HRQOL). Pts must be node-neg with RS 16-20 (plus high clinical risk), or RS 21-25, or have 1-3 positive nodes with RS $\leq$25. Stratification is by nodal status/RS status (pN0 RS 16-25 *v* pN1 RS 0-15 and pN1 RS 16-25), intent to receive CDK4/6 inhibitor (yes; no), and age (18-39 *v* $\geq$40). Pts are randomized after surgery to either OFS+ET or ACT+OFS+ET*v* ET is an aromatase inhibitor (AI). Choice is per investigator discretion; tamoxifen is allowed if AI is not tolerated or if OFS is incomplete. Radiotherapy will be administered per investigator discretion per protocol guidelines. The HRQOL sub-study will assess differences in severe menopausal symptoms, measured by the FACT ESS-19 score between arms, as well as increased pain severity (PROMIS). Blood and tumor specimens will be collected for future research. Accrual of 3,960 pts is anticipated to be completed in 7 yrs, 7 mos. Per NSABP B-28 and RxPONDER data, 5yr IBCFS of pN1 pts on the ACT+OFS+ET arm is estimated at 92.3%. Based on TAILORx data, 5yr IBCFS of pN0 pts on the ACT arm is ~95%. Assuming 56% of pts to be pN0 and 44% pN1, and a 0.5% annual loss-to-follow-up rate, the definitive analyses to detect a hazard ratio: 0.75 with ACT+OFS+ET *v* OFS+ET, with one-sided α of 0.025 and 80% power, will require 380 IBCFS events, expected to occur~11 yrs after study initiation. OFSETwas activated Aug 2023. As of 1-6-25, accrual is: 188/3,960. NCT #: NCT05879926. Support: U10CA180868, -80822, UG1CA189867, U24CA196067. Clinical trial information: NCT05879926. Research Sponsor: National Cancer Institute; U10CA180868; National Cancer Institute; U10CA180822; National Cancer Institute; UG1CA189867; National Cancer Institute; U24CA196067.

TPS616 **Poster Session**

A phase 3, randomized study of adjuvant sacituzumab tirumotecan plus pembrolizumab vs treatment of physician's choice in participants with triple-negative breast cancer who received neoadjuvant therapy and did not achieve a pathologic complete response at surgery. First Author: Heather L. McArthur, UT Southwestern Medical Center, Dallas, TX

Background: Trophoblast cell surface antigen 2 (TROP2) expression is higher in triple-negative breast cancer (TNBC) vs other breast cancer subtypes, and high expression is associated with poor prognosis. Sacituzumab tirumotecan (sac-TMT; also known as MK-2870/SKB264) is a novel antibody-drug conjugate composed of anti-TROP2 antibody coupled to a cytotoxic belotecan derivative via a novel linker (average drug/antibody ratio, 7.4). In a prior phase 3 study (OptiTROP-Breast01), sac-TMT alone improved PFS (HR, 0.31; 95% CI, 0.22-0.45; $P < 0.00001$) and OS (HR, 0.53; 95% CI, 0.36-0.78; $P = 0.0005$) vs chemotherapy in participants with heavily pretreated advanced TNBC. The current standard of care (SOC) for patients with newly diagnosed, high-risk, early-stage TNBC is neoadjuvant pembrolizumab + chemotherapy followed by adjuvant pembrolizumab after surgery. Patients who do not achieve a pathologic complete response (pCR) with the current SOC have higher rates of recurrence and mortality vs patients who achieve pCR. This study (NCT06393374) evaluates adjuvant sac-TMT + pembrolizumab vs treatment of physician's choice (TPC; pembrolizumab ± capecitabine) in participants with TNBC who received neoadjuvant therapy and did not achieve pCR at surgery. **Methods:** This phase 3, multicenter, open-label study is enrolling participants ≥18 years old with centrally confirmed TNBC per most recent American Society of Clinical Oncology/College of American Pathologists guidelines. Participants have non-pCR after ≥5 cycles of neoadjuvant pembrolizumab + chemotherapy, including ≥1 cycle of anthracycline-based neoadjuvant therapy. Participants must provide tissue from the surgical specimen for central TROP2 assessment and be able to continue on adjuvant pembrolizumab. Randomization must be conducted ≤12 weeks from surgical resection (window may be extended in consult with sponsor). Participants are randomized 1:1 to pembrolizumab 400 mg Q6W for 5 doses + sac-TMT 4 mg/kg Q2W for 12 doses or TPC with pembrolizumab 400 mg Q6W for 5 doses ± capecitabine 1000-1250 mg/m^2 BID on days 1-14 and days 22-35 every 42 days for 4 cycles until completion of therapy or disease recurrence, unacceptable toxicity, or withdrawal. Randomization is stratified by residual tumor and lymph node status, TROP2 expression, and intention to use capecitabine. Primary endpoint is invasive disease-free survival. Secondary endpoints are OS, distant recurrence-free survival, patient-reported outcomes, and safety. Enrollment began Q2 2024. Clinical trial information: NCT06393374. Research Sponsor: Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA.

TPS617 **Poster Session**

Adjuvant WIDER: A phase 3b trial of ribociclib (RIB) + endocrine therapy (ET) as adjuvant treatment (tx) in a close-to-clinical-practice patient (pt) population with HR+/HER2− early breast cancer (EBC). First Author: Stephanie L. Graff, Brown University Health Cancer Institute, The Warren Alpert Medical School of Brown University, Providence, RI

Background: The phase 3 NATALEE trial met its primary endpoint with significant invasive disease–free survival benefit with RIB + ET vs ET alone in a broad pt population with stage II/III HR+/HER2− EBC, sustained with additional follow-up at 44.2 months (hazard ratio, 0.715). The Adjuvant WIDER trial will evaluate RIB + ET in an HR+/HER2− EBC pt population that reflects pts seen in clinical practice as it has wider eligibility criteria, including an additional focus on enrolling minority pts underrepresented in NATALEE. Given the unmet need in pts with Stage II/III EBC, the results of this trial will complement existing data on benefits of RIB + ET. **Methods:** This phase 3b, multicenter, open-label, single-arm trial will evaluate, with early involvement of key pt advocacy groups, the efficacy and safety of adjuvant RIB + ET in a close-to-clinical-practice pt population with HR+/HER2− EBC. Eligible women and men aged ≥18 years with an ECOG PS of 0 to 2 and anatomic stage II/III disease (AJCC 8th ed), with additional criteria for stage IIA disease (N1 or N0 with grade 3, or grade 2 with Ki-67 ≥20% or high genomic risk), will be included. Pts will receive RIB (400 mg/d; 3 wk on/1 wk off) + ET (letrozole 2.5 mg/d, anastrozole 1 mg/d, or exemestane 25 mg/d) for 36 months, followed by ET alone as SOC per investigator's clinical judgment. Pre/perimenopausal women and men will receive goserelin 3.6 mg or leuprolide 3.75 mg/4 wk. Switching between ETs during study tx will be allowed in cases of unmanageable toxicity. Pts may have received (neo)adjuvant ET if initiated ≤36 months prior to enrollment. The number of pts with prior ET between 12 and 36 months will be capped at ≈30%; this cap will not be applicable to Black or African American pts. For pts with prior ET >12 months, restaging is recommended. Pts with prior CDK4/6i tx (except RIB) in the adjuvant setting for ≤6 months who discontinued due to toxicity can be included. Study tx may be held ≤28 days (or longer on agreement) to recover from RIB-related toxicity before restarting. If indicated, pts must have completed radiotherapy or chemotherapy before screening. Key exclusion criteria are distant metastases and/or recurrence and clinically significant, uncontrolled heart disease at screening. The primary endpoint is investigator-assessed invasive breast cancer–free survival rate at 3 years per STEEP v2.0 criteria. Secondary endpoints include invasive disease–free survival, distant disease–free survival, distant relapse–free survival, recurrence–free interval, overall survival, quality of life, and safety. Exploratory endpoints will assess subsequent antineoplastic tx, potential mechanisms of RIB benefit/resistance to RIB + ET, and RIB efficacy/safety in Black pts. Estimated enrollment is 1400 pts globally. Recruitment is ongoing. Clinical trial information: NCT05827081. Research Sponsor: Novartis Pharmaceuticals Corporation.

TPS618 **Poster Session**

Phase III study to evaluate the efficacy and safety of GLSI-100 (GP2 + GM-CSF) in breast cancer patients with residual disease or high-risk PCR after both neo-adjuvant and postoperative adjuvant anti-HER2 therapy: Flamingo-01. First Author: Snehal Patel, Greenwich LifeSciences, Stafford, TX

Background: GP2 is a biologic nine amino acid peptide of the HER2/*neu* protein delivered in combination with Granulocyte-Macrophage Colony Stimulating Factor (GM-CSF) that stimulates an immune response targeting HER2/neu expressing cancers, the combination known as GLSI-100. Of the 146 patients that have been treated with GLSI-100 over 4 clinical trials, GLSI-100 was well-tolerated and no serious adverse events observed were considered related to the immunotherapy. **Methods:** This Phase III trial is a prospective, randomized, double-blinded, multi-center study. After 1 year of trastuzumab-based therapy, 6 intradermal injections of GLSI-100 or placebo will be administered over the first 6 months and 5 subsequent boosters will be administered over the next 2.5 years. The participant duration of the trial will be 3 years treatment plus 1 additional year follow-up. Study Size – Interim Analysis: Approximately 498 patients will be enrolled. To detect a hazard ratio of 0.3 in invasive breast cancer free survival (IBCFS), 28 events will be required. An interim analysis for superiority and futility will be conducted when at least 14 events have occurred. This sample size provides 80% power if the annual rate of events in placebo patients is 2.4% or greater. Up to 250 non-HLA-A*02 subjects will be enrolled in an open-label arm. Eligibility Criteria: The patient population is defined by these key eligibility criteria: 1) HER2/neu positive and HLA-A*02, 2) Residual disease or High risk pCR (Stage III at presentation) post neo-adjuvant therapy, 3) Exclude Stage IV, and 4) Completed at least 90% of planned trastuzumab-based therapy. Trial Objectives: The trial objectives are to: 1) Determine if GP2 therapy increases IBCFS, 2) Assess the safety profile of GP2, and 3) Monitor immunologic responses to treatment and assess relationship to efficacy and safety. Study Status: The study is actively recruiting and enrolling patients in the US and Europe at up to 150 sites. Contact Information: Greenwich LifeSciences, Inc., Stafford, TX; Email: Flamingo-01@greenwichlifesciences.com; Website: greenwichlifesciences.com Funding: This trial is supported by Greenwich LifeSciences. Clinical trial information: NCT05232916. Research Sponsor: None.

TPS619 **Poster Session**

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

Background: Adjuvant ET is the standard of care (SOC) for treating ER+/HER2- eBC. Despite advances to optimize adjuvant treatment in high-risk ER+/HER2- eBC, there continues to be a risk of local and metastatic (incurable) recurrence that persists, and new therapies with desirable safety profiles are warranted. Elacestrant is a next-generation oral SERD that provides a novel mechanism of action that has shown both SERD (degradative) and SERM (partial agonist) activity that differs from currently available adjuvant ET (Wardell, ERC 2015). In the EMERALD trial, elacestrant significantly prolonged PFS vs SOC ET in the overall population (HR 0.70; 95% CI 0.55-0.88; P=0.0018) and in patients with *ESR1*-mut tumors (HR 0.55; 95% CI 0.39-0.77; P=0.0005) (Bidard, JCO 2022). In patients with *ESR1*-mut tumors who received prior ET+CDK4/6i ≥12 mo, mPFS with elacestrant was 8.6 vs 1.9 mo with SOC ET (Bardia, CCR 2024). In a preoperative, window of opportunity ER+/HER2- eBC trial (SOLTI-1905-ELIPSE), elacestrant was associated with complete cell cycle arrest (defined as Ki67<2.7%) rate of 27% and a statistically significant mean change from baseline, shifting tumor biology toward a more endocrine-sensitive and less proliferative tumor phenotype (Vidal, CCR 2025). Given that elacestrant demonstrated efficacy in mBC regardless of *ESR1*-mut status relative to SOC ET and has shown biologic activity in eBC, it is hypothesized that elacestrant can prolong invasive breast cancer-free survival (IBCFS) in patients with high-risk eBC who received prior adjuvant ET±CDK4/6i. **Methods:** ELEGANT (NCT06492616) is a global, multicenter, open-label phase 3 study designed to evaluate elacestrant vs SOC ET (AI or tamoxifen) in patients with eBC and a high risk of recurrence. Patients will be randomized 1:1 to continue SOC ET or to elacestrant for a duration of 5 yrs. Eligible patients are women or men with ER+/HER2− node-positive eBC who have completed 24-60 mo of adjuvant ET±CDK4/6i and have ECOG PS ≤1. Patients who received a prior CDK4/6i or a PARP inhibitor must have already completed or discontinued these treatments. Pre/perimenopausal women and men will be administered a LHRH agonist. Exclusion criteria include inflammatory breast cancer, history of prior invasive breast cancer, and >6 mo continuous interruption of prior SOC adjuvant ET or discontinuation of adjuvant ET >6 mo prior to randomization. The primary endpoint is IBCFS. Key secondary endpoints include distant relapse-free survival, overall survival, invasive disease-free survival, safety, patient-reported outcomes-quality of life, and pharmacokinetics. Status: Planned enrollment is 4,220 patients; recruitment is ongoing. Clinical trial information: NCT06492616. Research Sponsor: Menarini Group.

TPS620 **Poster Session**

EORTC-2129-BCG: Elacestrant for treating ER+/HER2- breast cancer patients with ctDNA relapse (TREAT ctDNA). First Author: Michail Ignatiadis, Breast Medical Oncology Clinic, Institut Jules Bordet, Université Libre de Bruxelles (ULB), Hôpital Universitaire de Bruxelles (HUB), Brussels, Belgium

Background: (Neo)adjuvant systemic treatment, with chemotherapy and/or endocrine therapy (ET), substantially reduces the recurrence rates of estrogen receptor positive (ER+) human epidermal growth factor receptor 2 negative (HER2-) early-stage breast cancer (BC). However, recurrences still occur up to 20 years after diagnosis. Circulating tumor DNA (ctDNA) has emerged as a useful biomarker for surveillance in several solid tumors. ctDNA-based detection of molecular recurrence could allow the start of effective therapies before the clinical evidence of metastases. Elacestrant, a selective ER degrader, approved in the advanced setting of ER+/HER2- ESR1-mutated BC following progression on a CDK4/6-inhibitor, could be used at the time of ctDNA-based molecular relapse to delay or prevent the clinical manifestation of distant metastasis. **Methods:** TREAT ctDNA is an European Organisation for Research and Treatment of Cancer (EORTC)-led intergroup international, multicentre, randomised, open label, superiority phase III trial to evaluate adjuvant elacestrant vs standard ET in patients with ER+/HER2- BC. The study comprises a screening and a randomised phase based on ctDNA status using a clinically-validated, tumor-informed molecular residual disease ctDNA assay (Signatera). Screening phase: 1960 patients with intermediate to high-risk stage II or III ER+/HER2- BC on medium to long duration ET will be screened for a ctDNA-based molecular relapse every 6 months. Randomised phase: 220 ctDNA-positive patients without imaging evidence of recurrence will be randomised 1:1 between continuing current ET versus switching to elacestrant for a duration of at least 7 years of ET in total. Participants will undergo intensive follow-up for 3 years with computed tomography and bone scans, in addition to the standard annual breast imaging. The primary endpoint of the study is distant metastasis free survival and secondary endpoints are invasive disease-free survival, relapse-free survival, overall survival, safety and quality of life. Recruitment started in December 2023 in Belgium, is open in 12 countries at 74 sites and anticipates up to 120 enrolling sites in 2025. Overall study status and databases status will be periodically reviewed by the IDMC. Clinical trial identification: EU trial number 2022-501453-36-00. NCT05512364. Study conducted under the Breast International Group (BIG) umbrella. Collaborative groups: GIM, CTI, SUCCESS, SOLTI, HeCOG, HORG, BOOG, SweBCG and ETOP-IBCSG. Clinical trial information: 2022-501453-36-00. Research Sponsor: BERLIN-CHEMIEAG MENARINI from Germany.

TPS621 **Poster Session**

The SURVIVE study: Standard surveillance vs. intensified liquid biopsy-based surveillance in early breast cancer survivors. First Author: Henning Schäffler, Department of Gynecology and Obstetrics, University Hospital Ulm, Ulm, Germany

Background: Current breast cancer (BC) follow-up relies on clinical examinations and breast imaging, as studies from the 1980s demonstrated no survival benefit from distant metastasis screening. However, with advancements in treatment strategies and the diagnostic potential of liquid biopsies, this approach warrants re-evaluation. To enable pre-symptomatic detection of distant relapse, we propose assessing a liquid biopsy-guided surveillance strategy incorporating tumor markers (CA 27.29, CA 125, CEA), circulating tumor cells (CTCs), and circulating tumor DNA (ctDNA). **Methods:** The SURVIVE study (NCT05658172) is the first large-scale, multicenter, partially double-blinded randomized controlled trial comparing intensified and standard surveillance in 3,500 survivors of medium- to high-risk early breast cancer (eBC). All subtypes are eligible. High risk includes (neo-)adjuvant chemotherapy, tumor size $>$50 mm, positive lymph nodes ($\geq$pN1mi), or high grade ($\geq$G3). Patients are randomized 1:1 to standard or liquid biopsy-guided intensified follow-up. Primary therapy (surgery, adjuvant chemo- or radiotherapy) completion is required, while adjuvant endocrine, antibody, or targeted therapy is permitted. Enrollment is allowed up to 24 months post-primary therapy for TNBC/HER2+ eBC and 60 months for HR+/HER2- eBC. In both arms, guideline-based follow-up is performed, with additional blood samples collected longitudinally (years 1–3 every 3 months; years 4–5 every 6 months). In the intervention arm, these samples are analyzed for tumor markers, CTCs, and ctDNA (RaDaR assay). Abnormal findings indicating minimal residual disease (MRD) trigger full staging. Recurrence is treated per national guidelines. In the case of M0 status, liquid biopsy testing and staging continue, with the option for inclusion in interventional trials, if applicable. The study is recruiting, with the first patient enrolled in December 2022. By January 2025, 812 patients were randomized across 78 centers. Final enrollment is scheduled for 2026 but may occur earlier due to accelerated recruitment. Statistics: The two primary objectives are to evaluate the lead time effect obtained by liquid biopsy marker testing in the intensified follow-up arm and to test whether intensified, liquid biopsy-guided surveillance improves overall survival (OS) compared to standard follow-up. OS will be analyzed in the ITT population using Kaplan-Meier and Cox regression, while the lead-time effect is assessed descriptively. Secondary endpoints include IDFS, DDFS, DRFS, BCSS, and QoL as well as biomarker sensitivities and specificities obtained in the intensified follow-up arm. Aims: We aim to determine whether liquid biopsy-guided follow-up enables earlier, sensitive, and specific detection of distant (oligo-)metastases, facilitating timely intervention and improving OS. Clinical trial information: NCT05658172. Research Sponsor: German Federal Ministry of Education and Research.

TPS622 **Poster Session**

The SURVIVE HERoes study: Targeting molecular relapse in breast cancer—A secondary adjuvant intervention study of trastuzumab deruxtecan versus SOC treatment in patients with HER2-positive or HER2-low early breast cancer and ctDNA positivity after primary therapy. First Author: Kerstin Pfister, Department of Gynecology and Obstetrics, University Hospital Ulm, Ulm, Germany

Background: Current research on circulating tumor DNA (ctDNA) in the adjuvant setting of early breast cancer (eBC) underscores its strong prognostic significance. Patients who are ctDNA-positive but show no radiological signs of relapse (i.e., molecular relapse) exhibit reduced disease-free and overall survival. Secondary adjuvant intervention studies represent an innovative and promising therapeutic approach. **Methods:** We introduce SURVIVE HERoes (NCT06643585), a phase III randomized clinical trial comparing the potent antibody-drug conjugate trastuzumab deruxtecan to standard of care (SoC) in patients with HER2-positive or HER2-low eBC and molecular residual or recurrent disease (ctDNA-positive, cM0) following primary therapy. Patients tested positive for ctDNA in a tumor-informed approach are eligible, if staging examinations do not show any residual or recurrent cancer. Participants are randomized in a 2:1 ratio to receive trastuzumab deruxtecan (+ endocrine therapy for HR+ patients) or SoC therapy. Stratification factors include hormonal receptor status (positive versus negative) and HER2 status (positive versus low). The primary endpoint is ctDNA clearance rate after 12 months of therapeutic intervention. Secondary endpoints include relapse-free survival, overall survival, safety, and quality of life (QoL). The trial will enroll a total of 180 participants across 50 centers in Germany. Staging examinations and ctDNA assessments will be performed at regular intervals. The study is accompanied by a comprehensive translational research program. Recruitment began in January 2025 and is anticipated to continue until 2030. Discussion: Treating ctDNA-positive patients without radiographic evidence of recurrence is a novel therapeutic strategy. If SURVIVE HERoes and similar studies targeting minimal residual disease (MRD) yield positive results, they could pave the way for a new molecularly driven individualized treatment approach aimed at achieving cure by liquid biopsy triggered early intervention in this new therapeutic window of pre-symptomatic MRD. Clinical trial information: NCT06643585. Research Sponsor: Astra Zeneca.

TPS623 **Poster Session**

Short-term pre-operative durvalumab (MEDI 4736) in early small triple-negative breast cancer patients (POP-Durva). First Author: Joana M. Ribeiro, Gustave Roussy, Department of Medical Oncology, IHU-National PRecISion Medicine Center in Oncology, France, Villejuif, France

Background: Pathological response to neoadjuvant immune checkpoint inhibitors (ICI) is associated with excellent survival in several tumor types. In Stage II-III triple negative breast cancer (TNBC), neoadjuvant anti-PD-(L)1 with chemotherapy improves pathological complete response (pCR) and reduces recurrence. In Stage I TNBC, (neo)adjuvant chemotherapy remains standard of care. Exceptional responses to ICI in TNBC have been observed, suggesting a subgroup of Stage I TNBC could be treated with ICI alone; however, biomarkers to select patients are lacking. **Methods:** Trial Design: POP-Durva (NCT05215106) is a prospective, single-arm phase II trial evaluating pCR after two doses of durvalumab in Stage I TNBC. Patients with untreated clinical stage I ($\leq$2cm, N0) TNBC (ER $<$ 10%, PR $<$ 10%, HER-2 non-amplified) with sTIL of $\geq$ 5% will be included. Study treatment consists of two doses of durvalumab 10mg/kg IV, on D1 and D15. On completion of study treatment, patients will undergo breast US and will proceed to surgery, or standard neoadjuvant treatment, per physician preference. Fresh tissue biopsy and Formalin-Fixed Paraffin-Embedded (FFPE) will be collected at screening, on D22 or at surgery; blood will be collected for PBMC and ctDNA at screening, D1, D15 and on D22; faecal specimen collection will occur at baseline and at end of treatment (for microbiota analysis). Trial Endpoints: The primary endpoint is pCR (ypT0/is ypN0). In patients who proceed directly to surgery following durvalumab, pCR will be assessed at surgery. Patients with residual invasive disease at the D22 biopsy who receive further neoadjuvant therapy will be considered non-pCR for the primary endpoint. With an expected pCR rate of 20%, a sample size of 195 patients provides a 95% confidence interval of a precision of 6.2%. The secondary objectives are ORR and safety. The key exploratory objective is to identify biomarkers of response to ICI. Spectral cytometry, single-cell RNA and TCR sequencing will be performed to describe on-treatment immune cell dynamics and to identify mechanisms of response to ICI monotherapy. Imaging-mass cytometry will characterise tumour-immune cell spatial interactions. Microbiome profiles will be correlated with response. 4 sites in France are actively recruiting; as of 27/01/2025, 35 patients have been treated. Clinical trial information: NCT05215106. Research Sponsor: None.

TPS624 **Poster Session**

RECAST (Re-Evaluating Conditions for Active Surveillance Suitability as Treatment) for DCIS: Clinical trial in progress. First Author: Ruolin Lorraine Jiang, University of California, San Francisco, San Francisco, CA

Background: Ductal Carcinoma In Situ (DCIS) is a condition where cancerous cells are confined to the breast ducts. The standard of care is surgery, either breast conservation and radiation or mastectomy. Data from the COMET study in hormone receptor-positive (HR+) DCIS demonstrates that active surveillance (AS) is a safe alternative for initial treatment. Starting with endocrine risk-reducing therapy first may assist in identifying candidates for risk reduction vs. focal surgical removal. The RECAST (Re-Evaluating Conditions for Active Surveillance Suitability as Treatment) study re-orders the treatment, starting with endocrine risk reduction, and uses serial imaging to assess treatment response to predict who can safely proceed with AS and endocrine therapy. Imaging response markers are tested to predict the success of endocrine therapy. Several novel endocrine treatments are tested. The trial gives patients a window of opportunity to evaluate the impact of endocrine therapy based on their imaging characteristics to explore alternatives to surgery. Rather than being randomly assigned to surgery or AS, all patients start with AS and serve as their own control. **Methods:** Women are screened for and randomized to 1 of 4 endocrine treatments, one of which is the standard of care endocrine therapy (choice of tamoxifen, baby tamoxifen, or an aromatase inhibitor is left to patient and physician discretion); MRIs are conducted at baseline, 3 and 6 months and semiquantitative imaging determines suitability for AS. Patients on AS are eligible to continue treatment for 3 years. Follow-up consists of an MRI alternating with a mammogram every 6 months. Quality of life (QOL) is measured using PROMIS and the FACT-ES composite scores. *Eligibility:* All patients with a diagnosis of HR+ DCIS (any grade), defined as $>$ 50% ER+ or PR+ on immunohistochemistry *Exclusion*: Presence of invasive disease, pregnancy or active breastfeeding, history of deep vein thrombosis. Patients with a solid mass on MRI must have a repeated biopsy *Primary objectives:* To determine whether novel endocrine therapy increases the fraction of patients who are suitable for long-term AS and how medications are tolerated compared to standard endocrine treatment *Primary endpoints:* QOL and fraction of patients who meet criteria for remaining on AS after 6 months based on MRI *Secondary endpoints:* Biomarkers of response and resistance *Progress to date:* RECAST activated on 01/22/2024. Currently,12 sites in the US are open to enrollment. 28 are in the process of activation. There are 22 patients accrued with 6 in screening. RECAST is an important next step in elucidating the factors that predict the success of AS and provide a framework for understanding endocrine resistance in the HR+ DCIS population. Clinical trial information: NCT06075953. Research Sponsor: Quantum Leap Healthcare Collaborative.

TPS625 **Poster Session**

NRG-BR007: A phase III trial evaluating de-escalation of breast radiation (DEBRA) following breast-conserving surgery of stage 1, HR+, HER2-, RS ≤18 breast cancer. First Author: Julia R. White, University of Kansas Medical Center Comprehensive Cancer Center, Kansas City, KS

Background: Approximately 50% of newly diagnosed invasive breast cancers are stage 1, with the majority being ER/PR-positive, HER2-negative. Genomic assays such as the Oncotype DX have identified patients (pts) with reduced risk of distant metastasis and without benefit from chemotherapy added to endocrine therapy (ET), freeing them from excess toxicity. Genomic assays are also recognized as prognostic for in-breast recurrence (IBR) after breast-conserving surgery (BCS) and could similarly allow de-escalation of adjuvant radiotherapy (RT). Reducing overtreatment is of interest to pts, providers, and payers. **Methods:** We hypothesize that BCS alone is non-inferior to BCS plus RT for IBR and breast preservation in women intending ET for stage 1 invasive breast cancer (ER and/or PR-positive, HER2-negative with an Oncotype DX Recurrence Score [RS] of $\leq$18). Stratification is by age ($<$60; $\geq$60), tumor size ($\leq$1 cm; $>$1-2cm), and RS ($\leq$11, $>$11-18/MammaPrint Low). Pts are randomized post-BCS to Arm 1 with breast RT using standard methods (moderate or ultra hypo- or conventional-fractionated whole breast RT with/without boost, or APBI) with $\geq$5 yrs of ET (tamoxifen or AI) or Arm 2 with $\geq$5 yrs of ET (tamoxifen or AI) alone. The specific regimen of ET in both arms is at the treating physician's discretion. Eligible pts are stage 1: pT1 ($\leq$2 cm), pN0, age $\geq$50 to $<$70 yrs, s/p BCS with negative margins (no ink on tumor), s/p axillary nodal staging (SNB or ALND), ER and/or PR-positive (ASCO/CAP), HER2-negative (ASCO/CAP), and Oncotype DX RS $\leq$18 (diagnostic core biopsy or resected specimen). A "low risk" MammaPrint is permissible if completed as part of usual care prior to screening. Primary endpoint is IBR (invasive breast cancer or DCIS). Secondary endpoints are breast conservation rate, invasive in-breast recurrence, relapse-free interval, distant disease-free survival, overall survival, patient-reported breast pain, patient-reported worry about recurrence, and adherence to ET. We assume a clinically acceptable difference in IBR of 4% at 10 yrs to judge omission of RT as non-inferior (10-yr event-free survival for RT group is 95.6% *v* 91.6% for the omission-of-RT group). BR007 is powered to detect non-inferiority with 80% power and a one-sided α=0.025, assuming that there would be a ramp-up in accrual in the first two years (leveling off in Yrs 3-5); 1,670 pts (835 per arm) are required for randomization. Conservative loss to follow-up is 1%/yr. Some T1a pts screened may have Oncotype DX scores $>$18, making them ineligible for the study. In the accrual process, 1,714 pts will be required to register to ensure that our final randomized cohort is 1,670 pts. As of 1-6-2025: 1,168/1,670 pts have been randomly assigned, and 1,294 screened. Support: U10 CA180868, -180822, UG1 CA189867. Clinical trial information: NCT04852887. Research Sponsor: National Cancer Institute; U10 CA180868; National Cancer Institute; UG1CA189867; National Cancer Institute; UG1 CA189867.

TPS627 **Poster Session**

MELODY: A prospective non-interventional multicenter cohort study to evaluate different imaging-guided methods for localization of malignant breast lesions (EUBREAST-4/iBRA-NET/AGO-B-062, NCT 05559411). First Author: Maggie Banys-Paluchowski, Department of Obstetrics and Gynecology, University Hospital of Schleswig Holstein, Campus Lübeck, Lübeck, Germany

Background: In the last decades, the proportion of breast cancer patients receiving breast-conserving surgery has increased, reaching 70-80% in developed countries. In case of non-palpable lesions, surgical excision requires some form of breast localization. While wire-guided localization has long been considered gold standard, it carries several limitations, including logistical difficulties, the potential for displacement and patient discomfort, and re-excision rates reaching 21% (in DCIS up to 30%). Other techniques (radioactive seed or radio-occult lesion localization, intraoperative ultrasound, magnetic, radiofrequency, and radar localization) have been developed with the aim of overcoming these disadvantages. However, comparative data on the rates of successful lesion removal, negative margins, and re-operations are limited. In most studies, the patient perspective, addressing e.g. discomfort and pain, has not been evaluated. The aim of MELODY (MEthods for LOcalization of Different types of breast lesions) is to evaluate different imaging-guided localization methods with regard to oncological safety, patient-reported outcomes, surgeon and radiologist satisfaction and economic impact. **Methods:** The EUBREAST and the iBRA-NET have initiated the MELODY study to assess breast localization techniques and devices from several perspectives (NCT05559411, http://eubreast.org/melody). MELODY is a prospective intergroup cohort study which enrolls female and male patients. planned for breast-conserving surgery with imaging-guided localization for invasive breast cancer or DCIS. Multiple or bilateral lesions and neoadjuvant chemotherapy are allowed. Primary outcomes are: 1) Intended target lesion and/or marker removal, independent of margin status on final histopathology, and 2) Negative resection margin rates at first surgery. Secondary outcomes are, among others: rates of second surgery and secondary mastectomy, Resection Ratio (defined as actual resection volume divided by the calculated optimum specimen volume), duration of surgery, marker dislocation rates, rates of marker placement or localization failure, patient-reported outcomes, rates of "lost markers", radiologist and surgeon satisfaction, and health economic evaluation of the different techniques. Target accrual is 7,416 patients. Enrollment started in January 2023. Until 24 January 2025, 3938 patients from 20 countries were enrolled in the study. The study is expected to complete patient enrollment in year 2026. The study will be conducted in 30 countries and is supported by the Oncoplastic Breast Consortium (OPBC), AWOgyn, AGO-B, SENATURK, the American Society of Breast Surgeons (ASBS) and the Korean Breast Cancer Study Group (KBCSG). Clinical trial information: NCT05559411. Research Sponsor: None.

TPS628 **Poster Session**

Radiation omission in patients with clinically node-negative breast cancer undergoing lumpectomy (ROSALIE). First Author: Elena Parvez, McMaster University, Hamilton, ON, Canada

Background: Currently, the standard of care for patients undergoing neoadjuvant chemotherapy (NAC) and breast conserving surgery (BCS) is adjuvant radiation (RT). However, high rates of pathologic complete response (pCR) after NAC have raised questions regarding the necessity of WBRT in these cases. A meta-analysis of 9 German NAC trials demonstrated a 5-year locoregional recurrence (LRR) of only 4% in patients with pCR who underwent BCS with radiation therapy. Data from two large National Surgical Adjuvant Breast and Bowel Project (NSABP) neoadjuvant trials (B.18 and B.27) demonstrated a local recurrence risk of 5.1% at 10 years (2.5% at 5 years) in patients $>$50 years with node negative breast cancer who had a pCR and were treated with BCS and RT. With such low rates of recurrence, we postulated that the absolute benefit that RT can offer is limited. Radiation therapy is not without side effects, which include both short-term and long-term toxicity. As such, a trial of de-escalation of RT is warranted. **Methods:** This study is a prospective, multi-center, single arm cohort study of omission of WBRT following BCS in patients with a pCR following NAC. Eligible and consenting female patients with newly diagnosed T1-3 node negative breast cancer age $>$50 years with no clinical evidence of distant metastatic disease, who have been treated with NAC, BCS and axillary staging surgery with final pathology demonstrating a pCR (ypT0N0) will be enrolled to the study and followed. Negative lymph node involvement at initial presentation must be documented by imaging (US or MRI), fine needle aspiration (FNA) or core needle biopsy. Marker clip must have been placed in the tumour bed prior to or during neoadjuvant chemotherapy when the tumour can still be identified. Study participants will not receive adjuvant RT, the current standard of care. Study participants will be followed and assessed for local recurrence, regional recurrence, distant recurrence, DFS and OS. Any additional breast cancer treatments received by the participant for the first recurrence event including repeat BCS, mastectomy, additional systemic therapy and radiation therapy (RT) will be documented. The primary outcome is ipsilateral breast tumour recurrence (IBTR) at median 5-year follow-up. A local recurrence of 5% without RT was felt to be acceptable. Based on a postulated 5-year IBTR risk of 3.0%, 4 years of accrual plus an additional 3 years of follow-up, a 90% two-sided CI for a postulated LR rate of 3.0% at 5 years would have an upper bound of $<$5% with 300 patients. To account for a 5% potential loss to follow-up and 10% receiving RT contrary to protocol, a sample size of 352 patients will be required. The trial opened in March 2024. Clinical trial information: NCT05866458. Research Sponsor: Canadian Institutes of Health Research (CIHR).

TPS629 **Poster Session**

HERTHENA-Breast03: A phase 2, randomized, open-label study evaluating neoadjuvant patritumab deruxtecan + pembrolizumab before or after pembrolizumab + chemotherapy for early-stage TNBC or HR-low+/HER2− breast cancer. First Author: Joyce O'Shaughnessy, Baylor University Medical Center, Texas Oncology, Dallas, TX and Sarah Cannon Research Institute, Dallas, TX

Background: The standard of care for patients with high-risk, early-stage TNBC is neoadjuvant pembrolizumab (pembro) + chemotherapy followed by adjuvant pembro. Patients with HR-low+/HER2− breast cancer may also be treated per recommendations for TNBC. There is a need for improved neoadjuvant therapy to increase the rate of pCR, as patients who do not achieve pCR have a high risk of recurrence, and to reduce risk of long-term toxicities associated with cyclophosphamide and anthracyclines. HER3 is frequently expressed in breast cancer and implicated in drug resistance. Patritumab deruxtecan (HER3-DXd) is an antibody-drug conjugate comprising a fully human anti-HER3 IgG1 monoclonal antibody linked to a topoisomerase I inhibitor (DXd) via a stable tetrapeptide-based linker that is selectively cleaved within tumor cells. This phase 2 study (NCT06797635) will evaluate neoadjuvant HER3-DXd + pembro before or after carboplatin + paclitaxel + pembro for early-stage TNBC or HR-low+/HER2− breast cancer. **Methods:** Eligible participants (pts) are adults (≥18 y) with untreated, locally advanced nonmetastatic (AJCC stage cT1c, N1–N2 or cT2–cT4, N0–N2) TNBC or HR-low+/HER2− breast cancer. Pts (N ≥10 and ≤30) in part 1 of the study (safety lead-in) will receive neoadjuvant HER3-DXd + pembro followed by carboplatin + paclitaxel + pembro (Table) then surgery. DLT evaluation and dose finding for HER3-DXd (three dose levels of 5.6 mg/kg Q3W, 4.8 mg/kg Q3W and 3.2 mg/kg Q3W) during cycle 1 of neoadjuvant HER3-DXd + pembro will be performed in part 1 to determine an acceptable dose of HER3-DXd for part 2. Pts (N ~342) in part 2 will be randomly assigned 1:1:1 to arm A, B or C (Table) for neoadjuvant treatment. Randomization will be stratified by cancer type (TNBC vs HR-low+/HER2−) and, in the TNBC subgroup, PD-L1 status (combined positive score ≥10 vs <10), overall stage (II vs III) and HER3 expression (low vs high). After neoadjuvant treatment, pts will undergo surgery (with postoperative radiotherapy if clinically indicated) and receive adjuvant pembro 400 mg Q6W for 5 cycles. Pts with residual disease may receive additional adjuvant treatment of physician's choice. Primary endpoints are safety (part 1 and 2) and pCR (ypT0/Tis ypN0) (part 2). Enrollment is ongoing. Clinical trial information: NCT06797635. Research Sponsor: Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA (MSD). This study is part of a collaboration between MSD and Daiichi Sankyo, Inc.

	Neoadjuvant cycles 1-4	Neoadjuvant cycles 5-8
Part 1 Arm A	HER3-DXd 5.6 or 4.8 or 3.2 mg/kg Q3W + pembro[a]	Carboplatin[b] + paclitaxel[c] + pembro[a]
Part 2 Arm A	HER3-DXd (selected dose from Part 1) + pembro[a]	Carboplatin[b]+ paclitaxel[c] + pembro[a]
Part 2 Arm B	Carboplatin[b] + paclitaxel[c] + pembro[a]	HER3-DXd (selected dose from Part 1) + pembro[a]
Part 2 Arm C	Carboplatin[b] + paclitaxel[c] + pembro[a]	Doxorubicin[d] OR epirubicin[e] + cyclophosphamide[f] + pembro[a]

[a]200 mg Q3W; [b]AUC 1.5 mg/mL/min QW; [c]80 mg/m^2 QW; [d]60 mg/m^2 Q3W; [e]90 mg/m^2 Q3W; [f]600 mg/m^2 Q3W.

TPS630 **Poster Session**

Eliminating breast surgery for triple negative or HR-/HER2+ breast cancer patients with clinical complete response to combined neoadjuvant chemotherapy and neoadjuvant radiotherapy: A multicenter, phase 2 trial (EBCS). First Author: Zhengjun Yang, Tianjin Medical University Cancer Institute and Hospital, Tianjin, China

Background: Recent advancements in immunotherapy and targeted therapies have significantly improved pathological complete response (pCR) rates in patients with triple-negative breast cancer (TNBC) and HER2-positive breast cancer undergoing neoadjuvant chemotherapy. The combination of neoadjuvant chemotherapy with radiotherapy may further enhance pCR rates through synergistic effects, prompting a reevaluation of traditional surgical approaches. The Sound trial demonstrated that omitting sentinel lymph node biopsy in node-negative patients is safe and feasible, supporting further de-escalation of surgical interventions. For patients achieving pCR, the necessity of breast and axillary surgery is increasingly questioned, given the potential to reduce surgical morbidity without compromising outcomes. Our study investigates whether omitting surgery in patients with pCR confirmed by vacuum-assisted core biopsy (VACB) yields non-inferior 5-year event-free survival (EFS) compared to standard surgery. **Methods:** This multicenter, phase 2 trial enrolls patients aged ≥18 years with untreated cT1-2 N0 M0 TNBC or HER2-positive breast cancer and ECOG 0-1. Patients receive four cycles of TCb (HP)* neoadjuvant chemotherapy, followed by neoadjuvantradiotherapy starting from the fifth cycle (50 Gy in 25 fractions + 14 Gy boost in 7 fractions). The TCb (HP)* regimen is tailored based on tumor subtype: triple-negative patients receive TCb (nab-paclitaxel + carboplatin) with or without immunotherapy (pembrolizumab), while HER2-positive patients receive TCbHP (nab-paclitaxel + carboplatin + trastuzumab and pertuzumab) regimens. After six cycles, patients undergo MRI. If MRI suggests complete clinical response (cCR), VACB of the primary lesion is performed under ultrasound/stereotactic guidance (6 cores, 7-10 G needle). If no residual tumor or atypical cells are found, breast and axillary surgery are omitted. Patients receive indicated immunotherapy/targeted therapy and are followed every 6 months for 5 years. The primary endpoint is 5-year EFS. Secondary endpoints include breast pCR rate (bpCR: ypT0), overall survival (OS), patient-reported outcomes (PROs), and safety. TheThis trial is designed to determine whether the 5-year EFS of patients who avoid breast surgery after pCR confirmed by VACB is non-inferior to that of patients who undergo standard breast surgery with confirmed pCR. Based on a 90.3% 5-year EFS in pCR patients (cT1-2N0 TNBC/HER2+), the trial uses a one-sided test (non-inferiority margin: 5%; power: 80%; α: 0.1) to determine if omitting surgery is non-inferior. 185 patients are needed to omit surgery. Assuming 80% pCR and 10% dropout, 256 participants will be enrolled. The trail is actively recruiting. Clinical trial information: NCT06498154. Research Sponsor: None.

TPS631 **Poster Session**

A randomized trial of trastuzumab deruxtecan and biology-driven selection of neoadjuvant treatment for HER2-positive breast cancer (ARIADNE). First Author: Alexios Matikas, Karolinska Institutet and Karolinska University Hospital, Stockholm, Sweden

Background: Neoadjuvant therapy is the standard of care for the treatment of non-metastatic HER2-positive breast cancer. Studies on first generation antibody-drug conjugates (ADC) such as trastuzumab emtansine (T-DM1) showed equal or slightly lesser efficacy than chemotherapy combined with dual HER2 blockade. Trastuzumab deruxtecan (T-DXd) is a next generation ADC approved for the treatment of metastatic HER2-positive breast cancer, with greatly improved efficacy compared with T-DM1. **Methods:** ARIADNE is an academic, international, open label, randomized, comparative phase IIB trial, actively enrolling in Sweden (ten sites) and in Norway (seven sites), with sites in Belgium (three), Netherlands (one) and Italy (three) activating during Q2 2025. A total of 370 patients with non-metastatic HER2-positive primary breast cancer and an indication for neoadjuvant therapy will be offered inclusion and randomized 1:1 to receive either i) a taxane, carboplatin, trastuzumab and pertuzumab for three cycles or ii) T-DXd for three cycles. Further treatment is based on the PAM50-defined intrinsic molecular subtype from a pretreatment biopsy: HER2-enriched (approximately 65%) patients continue with the same treatment for three more cycles. Estrogen receptor (ER) positive and luminal (approximately 25%) patients receive trastuzumab and pertuzumab for three cycles, combined with letrozole and ribociclib for two cycles. Finally, ER-negative and luminal or basal-like (approximately 10%) patients either continue with the same treatment for three additional cycles in case of radiologic complete response, or they receive four cycles of dose-dense epirubicin and cyclophosphamide in case of lack of complete response. The primary endpoint of ARIADNE is locally assessed rate of pathologic complete response (pCR) in patients with molecularly HER2-enriched tumors, defined as ypT0/Tis, ypN0, as determined by a pathologist blinded to treatment assignment (intention-to-treat analysis). Key secondary endpoints are rates of complete radiologic response at three cycles; rates of pCR in the other two molecular groups and in the two groups of the initial randomization; event-free survival, defined as the time from randomization to disease progression, locoregional or distant recurrence, contralateral breast cancer, other cancer, or death due to any cause. Tissue and plasma samples are collected at baseline, during treatment and surgery, as well as during follow-up. The first patient was randomized on 26th October 2023; 46 patients had been enrolled to the study until January 2025. Clinical trial information: NCT05900206. Research Sponsor: None.

TPS632 **Poster Session**

OPERETTA: A phase II study evaluating neoadjuvant and adjuvant olaparib plus pembrolizumab following platinum-based chemotherapy plus pembrolizumab for germline BRCA mutated triple negative breast cancer. First Author: Yuko Takahashi, Department of Breast and Endocrine Surgery, Okayama University Hospital, Okayama, Japan

Background: Triple negative breast cancer (TNBC) remains the most challenging phenotype of breast cancer. There is still an unmet clinical need for improving the fine-tuning of indications for targeted treatments in this population. In TNBC, the frequency of germline BRCA (gBRCA) 1/2 mutations was reported to be up to 19.5%. This has led to promising clinical strategies based on poly adenosine diphosphate (ADP)-ribose polymerase inhibitors that inhibit single-stranded DNA damage repair and/or modified chemotherapy approaches targeting the DNA damage response, using platinum-based regimens. Based on the results of the OlympiA and KEYNOTE522 study, the adjuvant treatment with olaparib for gBRCAm and neoadjuvant and adjuvant pembrolizumab for patients with a high risk of recurrence TNBC has been treatment options as the standard of care. We hypothesize that neoadjuvant and adjuvant combination treatment with olaparib and pembrolizumab following combination treatment with platinum-based chemotherapy and pembrolizumab would synergistically increase the anti-tumor effect through the enhancement of immunogenicity and DNA damage in patients with gBRCA mutated breast cancer. **Methods:** OPERETTA is a multicentered, prospective single-arm phase II feasibility study of patients treated with neoadjuvant olaparib plus pembrolizumab following platinum-based chemotherapy plus pembrolizumab in gBRCA 1/2 mutated TNBC. The patients with stage IIA-IIIB TNBC known as gBRCA 1/2 mutated will be registered. The primary objective is the pCR rate defined as the absence of residual invasive disease in the breast and axilla. The secondary objectives include additional efficacy measures (i.e., Residual Cancer Burden [RCB] 0/1rate, 3 years overall survival [3y-OS], 3 years event-free survivals [3y-EFS]), and safety. The estimated sample size using Simon's two-stage design, with a null hypothesis of a 45% pCR rate and an alternative hypothesis of 70%, was calculated. Given a significance level of 0.1 and 80% power, the design allows a maximum of 23 patients to be included. Eligible patients will be received combination treatment with paclitaxel (80 mg/m2 qw), carboplatin (AUC 1.5 qw or AUC 5 q3w), and pembrolizumab (200mg q3w) for first 12 weeks followed by olaparib (300mg BID) with pembrolizumab (200mg q3w) for another 12 weeks as neoadjuvant treatment. Breast/axillary surgery and radiotherapy are recommended per standard of care. After surgery, the combination of olaparib plus pembrolizumab will be continued for another 27 weeks as adjuvant treatment. This study is recruiting in Japan, and 2 patients are enrolled as of January 2025. This study is part of the West Japan Oncology Group (WJOG) breast cancer study group: WJOG14020B. Clinical trial information: NCT05485766. Research Sponsor: Merck; AMED.

LBA1000 **Oral Abstract Session**

Vepdegestrant, a PROTAC estrogen receptor (ER) degrader, vs fulvestrant in ER-positive/human epidermal growth factor receptor 2 (HER2)—negative advanced breast cancer: Results of the global, randomized, phase 3 VERITAC-2 study. First Author: Erika P. Hamilton, Breast Cancer Research Program, Sarah Cannon Research Institute, Nashville, TN

The full, final text of this abstract will be available at meetings.asco.org on the day of presentation and in the online supplement to the June 10, 2025, issue of the *Journal of Clinical Oncology*.

1001 **Oral Abstract Session**

Patient-reported outcomes (PROs) in patients with ER+, HER2- advanced breast cancer (ABC) treated with imlunestrant, investigator's choice standard endocrine therapy, or imlunestrant + abemaciclib: Results from the phase III EMBER-3 trial. First Author: Giuseppe Curigliano, Istituto Europeo di Oncologia, IRCCS, University of Milano, Milano, Italy

Background: Imlunestrant (imlu) is a next-generation, brain-penetrant, oral selective estrogen receptor degrader. The EMBER-3 trial, in patients (pts) with ER+, HER2- ABC who had disease progression on or after aromatase inhibitor-based therapy, showed significant progression free survival (PFS) improvement with imlu vs standard therapy (SOC, fulvestrant or exemestane) in pts with *ESR1* mutations (*ESR1*m), and with imlunestrant+abemaciclib (imlu+abema) vs imlu in all pts, regardless of *ESR1*m. Exploratory PRO analyses are presented here. **Methods:** EORTC QLQ-C30 was administered at baseline (BL) and every 8 weeks until treatment discontinuation. Prespecified QLQ-C30 analysis used a longitudinal mixed model for repeated measures to calculate mean change from BL in pts with BL and $\geq$1 post-BL score. PRO-CTCAE (diarrhea frequency) was administered weekly, reporting 0 (never) to 4 (almost constantly). PRO-CTCAE (injection site reaction [ISR]) was administered to fulvestrant recipients weekly for 2 weeks post-injection, reporting yes/no (pain, swelling, redness). Descriptive analysis was used for PRO-CTCAE. **Results:** In pts with *ESR1*m, imlu monotherapy was associated with many improved or maintained EORTC QLQ-C30 scores, whereas scores with SOC were declined or maintained. Specifically, pts with *ESR1*m on imlu had improved global health status (GHS)/quality of life (QOL) and physical function (PF) scores, while scores with SOC declined (mean change differences between treatments: 9.9 [0.1, 19.7] and 6.2 [-0.8, 13.1], respectively). These PRO findings mirror the PFS findings in this group. In the overall population, GHS/QOL scores declined similarly with imlu vs SOC (mean change differences: 0.5 [-4.7, 5.7]), while PF scores were maintained with imlu vs a slight decline with SOC (mean change difference: 2.5 [-1.1, 6.1]). Most fulvestrant recipients (72%) reported ISR at any time while on treatment, with a mean of 31% during the first week of the first 6 cycles. Imlu+abema vs imlu showed broadly similar declines in all pts, with minimal mean change differences in GHS/QOL and PF scores (0.8 [-7.4, 5.9]; -2.2 [-6.6, 2.2], respectively). Pts reported similarly low rates of "frequent" or "almost constant" diarrhea with imlu (3%) and SOC (2%) and higher rates with imlu+abema (22%). **Conclusions:** PROs from EMBER-3 demonstrated that patients with *ESR1*m had better GHS/QOL and PF with imlu vs SOC, mirroring efficacy results. While the frequency of CTCAE defined ISRs was low, the high rate of PRO-CTCAE ISR demonstrates that this clinically relevant adverse event is underappreciated by physicians. Additionally, all pts had generally comparable GHS/QOL and PF with imlu+abema vs imlu. Overall, these results support the efficacy and safety of imlu compared to existing SOC. Clinical trial information: NCT04975308. Research Sponsor: Eli Lilly and Company, Indianapolis, IN, USA.

1003 **Oral Abstract Session**

INAVO120: Phase III trial final overall survival (OS) analysis of first-line inavolisib (INAVO)/placebo (PBO) + palbociclib (PALBO) + fulvestrant (FULV) in patients (pts) with *PIK3CA*-mutated, hormone receptor-positive (HR+), HER2-negative (HER2−), endocrine-resistant advanced breast cancer (aBC). First Author: Nicholas C. Turner, Royal Marsden Hospital and Institute of Cancer, London, United Kingdom

Background: INAVO, a highly potent and selective PI3Kα inhibitor that also promotes mutated p110α degradation, is FDA-approved in combination with PALBO + FULV for *PIK3CA*-mutated, HR+, HER2−, endocrine-resistant aBC, based on the primary analysis of INAVO120 (NCT04191499), which showed a statistically significant and clinically meaningful investigator-assessed progression-free survival (INV-PFS) benefit in the INAVO arm vs. the PBO arm (hazard ratio 0.43; 95% confidence interval [CI] = 0.32–0.59; $p < 0.0001$). At that analysis, interim OS results were immature. Here we report the final OS analysis, including updated efficacy and safety. **Methods:** Pts received INAVO (9 mg orally once daily [PO QD]; Days 1–28 of each 28-day cycle)/PBO + PALBO (125 mg PO QD; Days 1–21 of each cycle) + FULV (500 mg intramuscularly; Cycle 1 Days 1 and 15 then every ~4 weeks). OS and objective response rate (ORR) were formally tested; updated INV-PFS and safety analyses are descriptive. **Results:** Data cut-off was Nov 15, 2024, at 34.2 months (mo) of median follow-up. Median OS was 34.0 mo (95% CI = 28.4–44.8) in the INAVO arm and 27.0 mo (95% CI = 22.8–38.7) in the PBO arm (stratified hazard ratio 0.67; 95% CI = 0.48–0.94; p = 0.0190 [boundary = 0.0469]). The OS benefit was consistent across key subgroups. The survival probability at 6, 12, 18, 24, and 30 mo was 96.8%, 87.0%, 74.3%, 65.8%, and 56.5% in the INAVO arm and 90.1%, 76.7%, 67.2%, 56.3%, and 46.3% in the PBO arm. ORR was 62.7% (95% CI = 54.8–70.2) and 28.0% (95% CI = 21.3–35.6), respectively ($p < 0.0001$). Median time to chemotherapy (TTC) was 35.6 mo (95% CI = 25.4–not reached) in the INAVO arm and 12.6 mo (95% CI = 10.4–16.1) in the PBO arm (stratified hazard ratio 0.43; 95% CI = 0.30–0.60). Updated median INV-PFS was 17.2 mo (95% CI = 11.6–22.2) in the INAVO arm and 7.3 mo (95% CI = 5.9–9.2) in the PBO arm (stratified hazard ratio 0.42; 95% CI = 0.32–0.55), with landmark analyses supporting durable benefit. 90.7% of pts in the INAVO arm and 84.7% in the PBO arm had grade 3/4 adverse events (AEs); there were no new grade 5 AEs; 63.4% and 13.5% experienced any-grade hyperglycemia (grouped term); and AEs led to INAVO and PBO discontinuation in 6.8% and 0.6% of pts, respectively. **Conclusions:** INAVO + PALBO + FULV demonstrated a statistically significant and clinically meaningful OS benefit compared with PBO + PALBO + FULV. Improvement in INV-PFS was maintained during longer follow-up, along with a substantial and statistically significant improvement in ORR. TTC was also substantially delayed (by ~2 years) by the addition of INAVO to PALBO + FULV. With longer exposure to INAVO, no new safety signals, nor changes in the safety profile, were noted, supporting good tolerability (reflected in low discontinuation due to AEs). Clinical trial information: NCT04191499. Research Sponsor: F. Hoffmann-La Roche Ltd; The authors acknowledge the Memorial Sloan Kettering Cancer Center support grant (P30 CA008748).

1004 **Oral Abstract Session**

Phase I/Ib study of inavolisib (INAVO) alone and in combination with endocrine therapy ± palbociclib (PALBO) in patients (pts) with *PIK3CA*-mutated, hormone receptor−positive, HER2-negative locally advanced/metastatic breast cancer (HR+, HER2− LA/mBC): Analysis of hyperglycemia (HG) in prediabetic/obese pts. First Author: Mafalda Oliveira, Vall d'Hebron University Hospital and Vall d'Hebron Institute of Oncology (VHIO), Barcelona, Spain

Background: INAVO, a highly potent and selective PI3Kα inhibitor that also promotes degradation of mutated p110α, is approved by the FDA in combination with PALBO + fulvestrant (FULV) for *PIK3CA*-mutated, HR+, HER2−, endocrine-resistant advanced BC. HG is a common on-target side effect of PI3K inhibitors. There are limited data for PI3K inhibitors in prediabetic/obese pts. Data from prediabetic/obese pts with HR+, HER2− LA/mBC treated with INAVO from a Phase I/Ib study (GO39374; NCT03006172) are reported here. **Methods:** Adults $\geq$ 18 years of age received INAVO alone (Arm A), + letrozole (LET) + PALBO (Arm B), + LET (Arm C), + FULV (Arm D), + FULV + PALBO (Arm E), or + FULV + PALBO + primary prophylactic metformin (Arm F). Data are reported across all arms unless indicated. Pts with baseline risk factors for HG were defined by HbA_{1c} $\geq$5.7%, fasting blood glucose $\geq$ 100 mg/dL, or body mass index $\geq$ 30 kg/m^2. Adverse events (AEs) were reported using NCI-CTCAE v4, which utilizes fasting laboratory glucose values for HG severity grading, rather than clinical interventions used in v5. **Results:** Clinical cut-off was Jan 1, 2024. From190 pts treated, 110 (57.9%) were prediabetic/obese; their median time on INAVO was 222 days (range, 7 to 2,152) and mean cumulative dose intensity was 91.8%. Most prediabetic/obese pts discontinued INAVO due to progressive disease (82 [74.5%]); six (5.5%) discontinued INAVO due to an AE (one due to HG). HG was reported in 80.9% of prediabetic/obese pts (grade 3–4: 34.5%). In pts with two risk factors, 87.9% reported HG (grade 3–4: 39.4%). Among pts with HG, median time to onset was 14 days (range, 1 to 1,674) and 86.0% of events resolved by clinical cut-off. Median time to improvement or resolution of first worst grade $\geq$ 2 event was 8 days (range, 1 to 64). INAVO dose interruptions, reductions, and discontinuations due to HG were reported in 41.8%, 13.6%, and 0.9% of pts, respectively. The most common anti-HG medications were metformin (52.7%; biguanide; concomitant use in Arm F excluded), empagliflozin (25.5%; SGLT-2 inhibitor), sitagliptin (22.7%; DPP-4 inhibitor), and pioglitazone (13.6%; thiazolidinedione); insulin was used in 8.2% of pts. Median time to metformin start (excluding Arm F) was 14 days (range, 1 to 1,710); the median start dose was 1,000 mg total daily; and the highest daily start dose was 2,000 mg. More than one anti-HG medication was often needed. **Conclusions:** A high proportion of prediabetic/obese pts were included in GO39374. In most of these pts, HG was manageable with dose interruptions and oral anti-HG medications, most commonly metformin. Data support the use of INAVO in prediabetic/obese pts; further investigation of INAVO in pts with diabetes is warranted. Clinical trial information: NCT03006172. Research Sponsor: Genentech, Inc.; The authors acknowledge the Memorial Sloan Kettering Cancer Center support grant (P30 CA008748).

LBA1005 **Oral Abstract Session**

A double-blind placebo controlled randomized phase III trial of fulvestrant and ipatasertib as treatment for advanced HER2-negative and estrogen receptor positive (ER+) breast cancer following progression on first line CDK 4/6 inhibitor and aromatase inhibitor: The CCTG/BCT MA.40/FINER study (NCT04650581). First Author: Stephen K. L. Chia, BC Cancer Agency, Vancouver, BC, Canada

The full, final text of this abstract will be available at meetings.asco.org on the day of presentation and in the online supplement to the June 10, 2025, issue of the *Journal of Clinical Oncology*.

1007 **Oral Abstract Session**

Phase III of oral paclitaxel (DHP107) vs intravenous paclitaxel in HER2-negative recurrent or metastatic breast cancer (mBC): Primary analysis of a multinational optimal trial (NCT03315364). First Author: Sung-Bae Kim, Asan Medical Center, University of Ulsan College of Medicine, Seoul, South Korea

Background: DHP107 is a novel oral formulation of paclitaxel that is approved in South Korea and China for the treatment of gastric cancer. DHP107 had encouraging monotherapy anti-tumor activity with objective response rate (ORR) of 55% and median progression free survival (PFS) of 8.9 months (Mo) as first-line therapy in 31 patients with HER2 negative metastatic breast cancer (mBC) in the OPTIMAL phase II study (Kim *Ther Adv Med Oncol* 2021). The first primary analysis is reported herein. **Methods:** This phase III, open-label, randomized, controlled trial evaluated the non-inferiority of DHP107 to intravenous (IV) paclitaxel in mBC, with non-inferiority margin of 1.33. Patients (Pts) had received one or more lines of endocrine-based therapy and no chemotherapy for mBC. Pts from Korea, China, and Europe were randomized 1:1 to receive either DHP107 (200 mg/m² orally, twice daily) or IV paclitaxel (80 mg/m² weekly). The primary endpoint was investigator-assessed PFS. Secondary endpoints included overall survival (OS), ORR, disease control rate (DCR), quality of life (QoL), and safety. **Results:** With the median follow-up of 38.8 Mo, the median age of the pts was 56 years. Of the 549 pts who underwent randomization, 481 pts had hormone receptor positive (HR+) disease and 68 pts had triple negative disease. Among all pts, DHP107 demonstrated non-inferiority to IV paclitaxel in PFS (mPFS: 10.02 vs. 8.54 Mo; HR 0.869, 95% CI 0.707–1.068). OS was comparable between groups (mOS: 32.95 vs. 32.46 Mo; HR 0.979, 95% CI 0.769–1.246). Among HR+HER2-pts, the mPFS was 10.74 Mo in the DHP107 arm, and 9.07 Mo in IV paclitaxel arm (HR 0.869, 95% CI 0.700-1.080). QoL outcomes showed no significant differences. ORR (45.8% vs. 39.7%) ad DCR (93.5% vs. 86.4%) were higher in the DHP107 group. DHP107 was associated with lower incidences of peripheral neuropathy (37.91% vs. 48.29%), hypersensitivity reactions, musculoskeletal and connective tissue disorders, and injection/infusion related reactions compared to IV paclitaxel. Neutropenia was the most common toxicity in both groups, occurring more frequently in the DHP107 group (81.6% vs. 59.3%) with higher rates of Gr≥3,4 neutropenia (67.15% vs. 29.66%), and febrile neutropenia (6.14% vs. 0.76%), but no grade 5 events were reported. Gastrointestinal toxicities were more frequent in the DHP107 group but were predominately Gr1. In this study, discontinuation rate due to AEs were comparable (12.27% vs. 8.75%, p=0.2081) and AEs leading to death occurred rarely in both groups (1.08% vs. 1.90%). **Conclusions:** DHP107 demonstrated comparable efficacy to IV paclitaxel with tolerable and manageable toxicity. These results establish DHP107 as an effective, convenient alternative to IV paclitaxel for patients with HER2-negative mBC, supporting its potential role in routine clinical practice. Clinical trial information: NCT03315364. Research Sponsor: DAEWHA PHARM. CO., LTD.

1009 **Clinical Science Symposium**

Circulating tumor DNA, pathologic response after neoadjuvant therapy, and survival: First results from TBCRC 040 (the PREDICT-DNA trial). First Author: Natasha Hunter, University of Washington, Seattle, WA

Background: Patients with Stage II/III breast cancer that overexpresses the human epidermal growth factor-2 (HER2+) or is triple-negative (TNBC) generally receive upfront neoadjuvant therapy (NAT) before definitive surgery. Pathologic complete response (pCR) after NAT is associated with improved survival but a small proportion of patients remain at risk for recurrence. Circulating tumor DNA (ctDNA) in patients whose primary tumors have detectable mutations could improve the identification of patients who remain at risk after NAT. **Methods:** The Pathologic Response Evaluation and Detection In Circulating Tumor-DNA (PREDICT-DNA) trial was a prospective, multi-center study aimed at validating ctDNA as a biomarker for treatment response in Stage II/III HER2+ or TNBC. The primary aim was to determine the negative predictive value (NPV) of ctDNA for residual disease following NAT; secondary aims included five-year invasive disease-free survival (IDFS), which were fit to a Cox proportional hazards model. Mutations were identified from tumor tissue; ctDNA was then analyzed in pre- and post-NAT blood and compared with surgical pathology. Proposed sample size was 229 patients based on simulation to control expected half-width of a confidence interval on NPV to be ≤15% when NPV=90%. The Personalis NeXT Personal ctDNA assay was centrally performed. **Results:** 228 participants were enrolled in 24 sites between 2016 and 2018. 53% had TNBC, and 47% had HER2+ disease. 92.2% (n=166/180) had detectable ctDNA at baseline, and 46% of patients had pCR (42% TNBC, 50% HER2+). 54% of all post-NAT ctDNA detections were in the ultrasensitive range below 100 PPM. Among 112 subjects with undetectable ctDNA prior to surgery, 45 were found to have residual disease resulting in an NPV of 60% (CI 0.51-0.69). Patients with TNBC and detectable ctDNA prior to surgery were approximately 12 times more likely to experience a recurrence regardless of pCR (HR 12.8 [95% CI: 2.3-71.5]). See Table describing landmark IDFS analyses after surgery. **Conclusions:** While lack of ctDNA detection after NAT and before surgery did not predict pCR, initial analysis of predefined secondary objectives suggest that ctDNA-negative patients before surgery have excellent prognosis regardless of pCR, particularly if TNBC. This suggests that ctDNA may be a better biomarker for long term clinical outcomes than pCR. Further correlations and interactions will be presented. Clinical trial information: NCT02743910. Research Sponsor: Susan B. Komen Breast Cancer Foundation; Breast Cancer Research Foundation; Johns Hopkins Clinical Research Network Research Accelerator and Mentorship Program (RAMP); Commonwealth Foundation; NIH/NCI grant; R01CA194024; NIH/NCI grant; R01CA214494; NIH/NCI grant; R01CA289528; NIH/NCI grant; P50CA098131; NIH/NCI grant; P30CA06485; The Helen Golde Fund; NIH/NCI grant; P30CA006973; The Translational Breast Cancer Research Consortium (TBCRC).

Invasive disease-free survival (IDFS) by breast cancer subtype, according to ctDNA after NAT and pathologic response.

TNBC (total n=64)	3y IDFS (n=40)	4y IDFS (n=32)	5y IDFS (n=18)
ctDNA- & pCR (n=20)	94.1%	94.1%	94.1%
ctDNA- & RD (n=25)	95.8%	89.8%	89.8%
ctDNA+ & RD (n=19)	48.9%	48.9%	48.9%
HER2+ (total n=58)	3y IDFS (n=41)	4y IDFS (n=31)	5y IDFS (n=17)
ctDNA- & pCR (n=19)	94.1%	94.1%	94.1%
ctDNA- & RD (n=31)	92.6%	87.5%	87.5%
ctDNA+ & RD (n=8)	60.0%	60.0%	60.0%

1010 **Clinical Science Symposium**

Circulating tumor (ct)DNA monitoring of ER+/HER2- high-risk breast cancer during adjuvant endocrine therapy. First Author: Lajos Pusztai, Yale Cancer Center, Yale School of Medicine, New Haven, CT

Background: ctDNA monitoring during adjuvant endocrine therapy is an opportunity to detect molecular relapse before clinically apparent recurrence. ctDNA positivity rates, dynamics and the frequency of asymptomatic imaging-detectable metastatic disease at the time of ctDNA detection remain unknown in high-risk ER+/HER2- BCs. We present ctDNA results from a prospective, multicenter, randomized ctDNA interventional trial, DARE (NCT04567420). **Methods:** Patients receiving adjuvant endocrine therapy for >6 months but <7 years, with either recurrence risk >15% (PREDICT, RSPC, CTS5), >4 positive axillary lymph nodes, (primary tumor >5 cm, or 1-3 positive nodes with grade 3 histology, or >3 cm tumor, or high molecular risk (Oncotype Dx RS >26, MammaPrint high risk, EndoPredict >4, Prosigna score >60) were eligible for ctDNA surveillance with the Signatera assay (Natera, Inc.) every 6 months. ctDNA+ patients had systemic staging with imaging and if there was no evidence of metastatic disease patients were randomized to switching to fulvestrant + palbociclib (Arm A) or to continuation of adjuvant therapy (Arm B). Negative predictive value (NPV) was calculated for recurrence in the screening group after each ctDNA- test. In randomized patients, early ctDNA dynamics were correlated with recurrence-free survival (RFS) and ctDNA clearance rates were calculated by trial arm. **Results:** 552 patients had tissue sent for assay design; 494 had ctDNA results; 52 failed WES and/or had incomplete tumor/normal/blood sets; 6 had pending reports. Among patients not randomized, 432 were ctDNA-, of these N=43 had one time point and 389 had >2 ctDNA- result, overall median screening time 27.4 months (0-45.5), 4 ctDNA- patients had recurrence (NPV 100% at 6 months and 99% at 12 months post-testing). Forty patients were randomized, 34 had post-randomization ctDNA result. Randomization rates were 53% and 76% for patients who tested ctDNA-positive on the first screening (N=19) versus those who turned positive in follow up testing (N=15). At any time post-randomization, ctDNA clearance rates were 63% (10/16) in Arm A and 22% (4/18) in Arm B. Among randomized patients, 6 of 9 patients with increased ctDNA levels from the pre-randomization to the 3-month on-treatment recurred (median time to recurrence 4.8 months, range: 3.3-24.3), among those with a decrease in ctDNA post-treatment only 1 of 6 experienced recurrence at 10.3 months (HR: 5.3, 95% CI: 1.1-53, p=0.04). **Conclusions:** This study demonstrates the ability of ctDNA to identify breast cancer patients at high risk of relapse for randomization in a prospective, multicenter, randomized clinical trial. Patients with serially ctDNA- results during surveillance had 99% RFS after a median f/u of 27.4 months. Interim analysis revealed higher clearance rates in Arm A compared to patients randomized to Arm B. Early on treatment ctDNA dynamics is prognostic of patient outcomes. Clinical trial information: NCT04567420. Research Sponsor: Pfizer; Natera Inc.

1011 Clinical Science Symposium

Circulating tumor DNA (ctDNA) dynamics as a predictor of treatment response in metastatic breast cancer (mBC). First Author: Pedram Razavi, Memorial Sloan Kettering Cancer Center, New York, NY

Background: ctDNA testing has emerged as a prognostic and predictive biomarker in the management of mBC. However, the relationship between ctDNA trends and real-world treatment outcomes has yet to be fully characterized. Here, we utilized a claims database to evaluate the association between ctDNA trends and the time to next treatment (TTNT) in patients with mBC. **Methods:** We utilized Natera's proprietary real-world database linked to commercially available claims data to identify patients who received treatment for mBC and had ctDNA testing performed commercially using a clinically validated, personalized, tumor-informed mPCR-NGS ctDNA assay (Signatera™, Natera, Inc.). Insurance claim codes for treatment regimens were used to determine BC receptor subtype and therapy dates. Treatment lines were included in the analysis if a ctDNA test result was available within 4 weeks before treatment initiation (T1) and a subsequent ctDNA test result was available 2-6 weeks after treatment initiation (T2). TTNT was calculated as the time from initiation of the first treatment to the subsequent treatment. T1 to T2 ctDNA dynamics were analyzed using the Student's t-test and were categorized as favorable (persistently negative, ctDNA-clearance, ctDNA-decrease) or unfavorable (ctDNA-negative to positive, ctDNA-increase). **Results:** A total of 7,222 treatment lines were assessed for duration of treatment and corresponding ctDNA dynamics, including3,117 lines (N=2,362 patients) for HR+/HER2- mBC, 3,717 lines (N=1,943 patients) for HER2+ mBC, and 888 lines (N=605 patients) for TNBC. Of these, 448 treatment lines met the inclusion criteria for ctDNA analysis. In HER2+ breast cancer, TTNT across 226 treatment lines was significantly longer in patients with favorable ctDNA dynamics (6.7 [3.18–10.3] months) relative to unfavorable dynamics (2.7 [1.4–5.1] months; $p<0.0001$). Among patients with HR+/HER2- mBC, TTNT across 156 treatment lines was longer in those with favorable ctDNA dynamics (median [Q1, Q3]: 7.51 [3.72–11.57] months) compared to unfavorable dynamics (5.02 [1.8–9.84] months; p=0.052). A similar trend was observed in TNBC, where TTNT across 66 treatment lines was longer with favorable ctDNA dynamics (6.03 [2.89–10.07] months) compared to unfavorable dynamics (2.7 [1.16–5.89] months; p=0.381), though this was not statistically significant. **Conclusions:** Early on-treatment ctDNA dynamics, assessed within the first 6 weeks of therapy, was associated with TTNT in a real-world ctDNA monitoring setting across different mBC subtypes and therapeutic regimens. An early rise in ctDNA levels correlated with the shortest TTNT, whereas ctDNA clearance was associated with the longest TTNT intervals. These findings highlight the potential of serial ctDNA testing in mBC for monitoring treatment response and informing clinical decisions. Research Sponsor: None.

1012 Clinical Science Symposium

Assessment of ctDNA somatic homologous recombination deficiency (HRD) in triple-negative breast cancer (TNBC) from SWOG S1416 trial. First Author: Shane R. Stecklein, University of Kansas Medical Center, Kansas City, KS

Background: HRD is observed in up to two-thirds of g*BRCA*-wildtype TNBC. S1416 (NCT02595905) showed that addition of a PARP inhibitor (veliparib) to cisplatin improved progression-free survival (PFS) in *gBRCA*-wildtype metastatic TNBC (mTNBC) with HRD phenotype ("*BRCA*-like"). In this study, we sought to evaluate concordance between circulating tumor DNA (ctDNA)-based detection of somatic homologous recombination repair (sHRR) alterations and tumor-based HRD and to assess if sHRR deficiency (sHRR+) was associated with benefit from veliparib in g*BRCA*-wild type mTNBC in SWOG S1416. **Methods:** S1416 enrolled patients with mTNBC who had received ≤ 1 line of prior therapy and randomized them to cisplatin plus veliparib or placebo. Central *gBRCA1/2* testing classified patients as *gBRCA*-mutated or -wildtype. An *a priori* defined biomarker panel classified *gBRCA*-wildtype patients into *BRCA*-like (HRD+) and non-*BRCA*-like (HRD-) groups. A third group with *gBRCA*-wildtype, but without tissue BRCA classification was also included. Pre-treatment and progression plasma samples were utilized for assessment of sHRR status. ctDNA was analyzed using the Guardant OMNI next-generation sequencing platform. sHRR+ was defined by detectable somatic alterations (SNVs, INDELs, fusions with a functional impact notation of deleterious, and/or CNVs with a functional characterization of homozygous deletion) in a 24 gene panel. **Results:** Among *N*=213 g*BRCA*-wildtype patients with evaluable pre-treatment blood samples, 25% were sHRR+. Among sHRR+ patients, alterations in *CHEK2* (18%), *BRCA1* (17%), *BARD1* (8%), *ATM* (7%), *BAP1* (7%), *CDK12* (7%), *NBN* (7%), *BRCA2* (5%), and *FANCA* (5%) accounted for 80% of sHRR alterations. Most sHRR+ patients (91%) had alterations in only one of 24 genes, suggesting mutual exclusivity of homologous recombination pathway alterations in ctDNA. sHRR+ status was numerically higher in *BRCA*-like compared to non-*BRCA*-like tumors or unclassified tumors (32% vs. 20% vs. 20%, respectively; *P*=0.12). Among *n*=98 patients with availability of evaluable pre-treatment and progression samples, 31% were sHRR+ at baseline and 28% were sHRR+ at progression. Numerically, conversion from sHRR+ to sHRR- was more common than conversion from sHRR- to sHRR+ (30% vs. 9%, respectively). sHRR was not prognostic for PFS (median 4.3 (sHRR+) vs. 4.1 (sHRR-) months, respectively; *P*=0.30) nor predictive of benefit from veliparib (*P*=0.40). **Conclusions:** One-fourth of *gBRCA*-wildtype mTNBC patients have ctDNA sHRR alterations, and there is incomplete overlap between tumor- and ctDNA-assessed HRD. ctDNA sHRR alterations were mostly mutually exclusive. Approximately one-third of patients with baseline sHRR+ converted to sHRR- at time of progression while receiving DNA damaging chemotherapy. sHRR was not prognostic and did not predict benefit from veliparib in S1416. Research Sponsor: NIH/NCI/NCTN; U10CA180888; NIH/NCI/NCTN; U10CA180819.

1013 Oral Abstract Session

Exploratory biomarker analysis of trastuzumab deruxtecan (T-DXd) vs physician's choice of chemotherapy (TPC) in HER2-low/ultralow, hormone receptor–positive (HR+) metastatic breast cancer (mBC) in DESTINY-Breast06 (DB-06). First Author: Rebecca Alexandra Dent, National Cancer Centre Singapore, Singapore, Singapore

Background: DB-06 (NCT04494425), a Phase 3, randomized, open-label study, demonstrated a clinically meaningful progression-free survival (PFS; 13.2 vs 8.1 months [hazard ratio: 0.64]) benefit with T-DXd vs TPC (capecitabine, nab-paclitaxel, or paclitaxel) in patients with HR+, HER2-low (immunohistochemistry [IHC] 1+ or IHC 2+ / in situ hybridization–negative) or -ultralow (IHC 0 with membrane staining) mBC after $\geq$1 endocrine-based therapy (primary data cutoff: March 18, 2024). Here, we report an exploratory circulating tumor DNA (ctDNA) analysis based on baseline genomic status. **Methods:** Baseline ctDNA profiling in blood samples was assessed via Guardant OMNI 500-gene liquid biopsy assay. In total, 625 patients had evaluable ctDNA samples and putative tumor content, and comprised the biomarker evaluable population (BEP) presented herein. Baseline characteristics and efficacy outcomes were evaluated in key genomic subgroups (PI3K pathway, *ESR1*m, *BRCA1/2*m), including confirmed objective response rate (cORR) and PFS, both by blinded independent central review. **Results:** Genomic alterations were observed in 45.0% (PI3K pathway, n=281), 51.5% (*ESR1*m, n=322), and 7.7% (*BRCA1/2*m, n=48) of patients. The median PFS (mPFS) for each mutational subgroup was 13.2 (T-DXd) and 7.1 (TPC) months (PI3K pathway), 11.3 (T-DXd) and 7.0 (TPC) months (*ESR1*m), and 21.4 (T-DXd) and 5.6 (TPC) months (*BRCA1/2*m). T-DXd improved PFS and cORR outcomes compared with TPC across all mutational subgroups reported (Table). **Conclusions:** In this exploratory ctDNA analysis, T-DXd demonstrated a greater clinical benefit vs TPC regardless of PI3K pathway, *ESR1*, or *BRCA1/2* mutation. Clinical trial information: NCT04494425. Research Sponsor: AstraZeneca; Daiichi Sankyo.

BEP (N=625) subgroup (n=T-DXd/TPC)	T-DXd cORR, %	TPC cORR, %	T-DXd mPFS, mo*	TPC mPFS, mo*	PFS hazard ratio
PI3K pathway†	57.6	41.5	13.2	7.1	0.65
(139/142)	[48.9, 65.9]	[33.3, 50.1]	[9.9, 15.5]	[6.0, 9.5]	[0.48, 0.87]
***ESR1*m**	60.2	32.1	11.3	7.0	0.64
(166/156)	[52.4, 67.7]	[24.8, 40.0]	[9.8, 13.5]	[5.6, 9.3]	[0.49, 0.83]
***BRCA1/2*m**	80.0	39.3	21.4	5.6	0.14
(20/28)	[56.3, 94.3]	[21.5, 59.4]	[15.2, NE]	[4.1, 6.9]	[0.05, 0.33]

Square brackets = 95% CIs (based on the Clopper-Pearson [cORR] or Brookmeyer-Crowley method [PFS]). PFS hazard ratios and CIs based on Cox proportional hazards model with no stratification factors, and ties handled by Efron approach. A hazard ratio <1 favors T-DXd vs TPC. No formal testing of significance was performed; *Number of PFS events: 89 (T-DXd) and 92 (TPC) in the PI3K pathway group, 115 (T-DXd) and 107 (TPC) in the *ESR1*m group, and 7 (T-DXd) and 23 (TPC) in the *BRCA1/2*m group; †includes *AKT*m, *PIK3CA*m, and *PTEN*m; CI, confidence interval; m, mutation; mo, months; NE, non-evaluable.

1014 Rapid Oral Abstract Session

Use of artificial intelligence–assistance software for HER2-low and HER2-ultralow IHC interpretation training to improve diagnostic accuracy of pathologists and expand patients' eligibility for HER2-targeted treatment. First Author: David Mulder, Mindpeak GmbH, Hamburg, Germany

Background: The advent of HER2-targeted antibody-drug conjugates and the introduction of HER2-low and HER2-ultralow diagnostic categories have made precise HER2 IHC assessment crucial for optimal breast cancer treatment. However, reproducible and accurate HER2 IHC scoring, particularly in cases with low level of HER2 expression, remains challenging. Many patients with HER2-low or HER2-ultralow expression risk being misclassified as HER2 null, potentially missing access to effective HER2 targeted therapies. Artificial intelligence (AI) assisted HER2 assessment may improve pathologists' diagnostic accuracy and concordance during interpretation training, especially in challenging cases with minimal membrane staining. **Methods:** A training platform for AI-supported digital HER2 IHC assessment of breast cancer samples was developed for pathologists. A total of 105 pathologists from 10 countries participated in masterclass sessions, assessing 20 digital HER2 IHC-stained breast cancer cases both without and with AI assistance. Cases assigned ground-truth IHC scores by a central reference center, were divided into three exams: A (n = 5), B (n = 7), and C (n = 8). The masterclasses consisted of: (1) Exam A, (2) a lecture on HER2 IHC scoring, (3) Exam B, (4) discussion of results from Exams A and B, and (5) AI-assisted Exam C. The AI software was used for decision support only for Exam C. The HER2 IHC scoring followed ASCO/CAP 2023 guidelines, adapted to include the HER2-ultralow (IHC 0 with membrane staining) and HER2 null (IHC 0 with no membrane staining), and provided individual tumor cell classifications for explainability. **Results:** Across 1,940 readings, pathologists achieved an average agreement of 76.3% with reference scores without AI (Exams A+B), compared to 89.6% with AI-assistance (Exam C). For HER2 clinical categories (null, ultralow, low, positive) accuracy improved from 66.7% without AI to 88.5% with AI. Misclassification of HER2-ultralow cases as HER2 null occurred in 29.5% of readings without AI but decreased to 4.0% with AI assistance. **Conclusions:** AI-assisted training improved pathologists' accuracy in HER2 IHC scoring by 13.3%, compared to central reference scores. Furthermore, AI reduced the misclassification of HER2-low and HER2-ultralow cases as HER2 null by 25.5%, potentially enabling more patients to access HER2-targeted therapies. These findings highlight the value of AI systems in biomarker interpretation training, providing pathologists with enhanced decision-making tools at the individual cell level and improving diagnostic precision in HER2 IHC interpretation. Research Sponsor: AstraZeneca.

1015 Rapid Oral Abstract Session

Treatment rechallenge after trastuzumab-deruxtecan–related interstitial lung disease: A multi-institution cohort study. First Author: Kelsey H. Natsuhara, University of California, San Francisco Helen Diller Family Comprehensive Cancer Center, San Francisco, CA

Background: T-DXd is an antibody-drug conjugate approved for advanced HER2+/low/ultra-low breast cancer and multiple other solid tumors. T-DXd carries a rare but serious risk of ILD (incidence 12-15%), requiring frequent imaging and symptom evaluation. For > grade (G) 2 ILD, guidelines recommend permanent drug discontinuation. For asymptomatic G1 ILD, drug is held with the option for rechallenge (RC) if imaging findings resolve. Limited data exist on outcomes of RC after ILD in diverse real-world patients (pts). **Methods:** In this multi-center retrospective study, we analyzed pts with T-DXd related ILD treated from 2017-2024. Pts with ILD were identified via chart/ICD code review. Adjudication of T-DXd related ILD was based on treating providers' assessment and graded via CTCAE v5. We collected pt demographics, T-DXd and steroid dosing, imaging results, and outcomes after RC. Statistical analysis was performed using Wilcoxon rank sum and Fisher's exact tests. **Results:** Four centers treated 712 pts with T-DXd, with a 9.1% rate of any grade ILD (n=65). One other center reported only RC data in 18 pts with ILD. In total, 47 pts were RC; 38 after G1 ILD (81%), 9 after G2. Median (med) time to initial ILD was 145 days (d) after 1st dose (interquartile range [IQR] 78-205). Demographics for pts RC are shown in the table. Among 50 pts with G1 ILD, including pts not RC, 28/50 (56%) received steroids for a med of 36d (IQR 27-79). Radiographic improvement was seen at a med of 24d (IQR 19-63) for pts treated with steroids vs 82d (IQR 48-94) without ($p<0.01$); and a med of 35d (IQR 22-82) for pts RC vs 81d (IQR 68-105) for pts not RC (p=0.01). Among pts with G1 ILD, 38/50 (76%) were RC at a med of 42d (IQR 36-57) from last dose; 23/38 (61%) were dose reduced. After RC, pts remained on T-DXd for a med of 215d (IQR 60-334); 10/38 (26%) developed recurrent ILD (7-G1, 2-G2, 1-G3) at a med of 211d (IQR 47-273) from RC. No statistically significant differences were seen between ILD onset, time to RC, or demographics for pts with recurrent ILD vs not. Of the 9 pts RC after G2 ILD, T-DXd was continued for a med of 129d (IQR 49-171); 2/9 (22%) developed recurrent ILD (1-G2, 1-G3). No G5 toxicity was seen with RC. **Conclusions:** In this multi-center study, high RC rates were seen after G1 ILD with long duration of clinical benefit. Pts treated with steroids had faster radiographic ILD improvement, highlighting the importance of early steroid use. Among pts RC after G1 ILD, recurrent ILD rates were low, with the majority G1 and no G5 events. Notably, 9 pts with G2 ILD were RC, with a similar rate of recurrent ILD; this must be interpreted cautiously. Our large cohort data further supports the safety of T-DXd RC in diverse real-world settings. Research Sponsor: None.

RC Pt Characteristics (n=47)	n (%) or Median (IQR)
Cancer type	
Breast	43 (91)
GI	3 (6)
Gyn	1 (2)
Age (yrs)	57 (52-68)
Prior # therapy lines in the advanced/metastatic setting	3 (1-5)
Renal impairment (CrCl < 60 mL/min)	8 (17)

1016 Rapid Oral Abstract Session

Phase IB and II study of ribociclib with trastuzumab plus endocrine therapy in HR+/HER2+ advanced breast cancer patients: Korean Cancer Study Group BR 18-2 MINI trial. First Author: Joohyuk Sohn, Division of Medical Oncology, Department of Internal Medicine, Yonsei Cancer Center, Yonsei University College of Medicine, Seoul, South Korea

Background: In HER2+ advanced breast cancer (ABC), standard treatment has been anti-HER2 therapy with chemotherapy, regardless of hormone receptor status. While prior studies support the use of CDK4/6 inhibitors with anti-HER2 and endocrine therapy in pretreated HR+/HER2+ ABC, data on their first line use without chemotherapy are limited. This study investigates ribociclib, trastuzumab, and letrozole as a first-line combination in HR+/HER2+ ABC. **Methods:** This multicenter, single-arm, prospective trial was conducted across 17 academic institutions in South Korea (NCT03913234). Eligible patients were HR+/HER2+ ABC with no prior systemic therapy for metastatic disease. The Phase IB study used a 3+3 design to determine the recommended Phase II dose (RPIID) of ribociclib with fixed doses of letrozole (2.5 mg QD) and trastuzumab (8 mg/kg loading, then 6 mg/kg every 3 weeks). The Phase II trial evaluated efficacy and safety at the RPIID. The primary endpoint was progression-free survival (PFS), targeting an improvement from 8 to 12 months. Secondary endpoints included overall survival (OS), objective response rate (ORR), duration of response (DOR), and safety. PAM50 testing assessed correlations between intrinsic subtype and treatment efficacy. **Results:** Phase IB (n = 13) identified the RPIID as ribociclib 600 mg QD, with one dose-limiting toxicity (Grade 3 ALT elevation) at 400 mg. In Phase II, 77 patients were enrolled, with a median age of 61 years (range 31–85), 18.2% (14/77) premenopausal, 66.2% (51/77) HER2 IHC 3+ and recurrent disease in 64.9% (50/77). 66.2% (51/77) had visceral metastases. At a median follow-up of 15.8 months (95% CI: 12.9-19.1) months, the median PFS was 30.4 months (95% CI: 19.6–NA), meeting the primary endpoint. The median OS was not reached. The ORR was 61.1%, including 3 complete and 41 partial responses, with a DOR of 11.8 months (95% CI: 7.6-13.4). Common adverse events included neutropenia (66.7%), pruritus (24.4%), and nausea (22.2%). There was a death reported due to aortic aneurysm. PAM50 analysis in 75 patients (phase IB/II) showed no significant correlation between intrinsic subtype and efficacy. **Conclusions:** Ribociclib, trastuzumab, and letrozole as first-line therapy in HR+/HER2+ ABC demonstrated a median PFS of 30.4 months with a manageable safety profile, supporting its potential as a chemotherapy-free option. Clinical trial information: NCT03913234. Research Sponsor: None.

1017 Rapid Oral Abstract Session

HER2-ADC trastuzumab rezetecan (SHR-A1811) in HER2-positive breast cancer with brain metastases: Update results from REIN trial. First Author: Min Yan, Department of Breast Disease, Henan Breast Cancer Center, The Affiliated Cancer Hospital of Zhengzhou University & Henan Cancer Hospital, Zhengzhou, China

Background: HER2-directed antibody-drug conjugates (ADCs) have been demonstrated to be of intracranial activity in patients with HER2+ breast cancer (BC) with brain metastases (BM). Our prospective, non-randomized phase 2 trial (NCT05769010) aimed to assess the feasibility of SHR-A1811, a novel HER2-target ADC, with or without other anti-tumor agents in HER2-expressing BCBM. Here we report the data of SHR-A1811 combined with bevacizumab in HER2+ BCBM, and update the results of SHR-A1811 in HER2+ BCBM (preliminary ORR data of the first 25 patients in Arm 1 has been published at 2024 ASCO), presenting the efficacy and safety of SHR-A1811 alone or in combination in the treatment of HER2+ BCBM. **Methods:** Patients with HER2-positive or -low BC with at least one radiotherapy-naïve measurable intracranial lesion were eligible for our trial. The patients with HER2+ disease enrolled in Arm 1 received SHR-A1811 6.4 mg/kg every 3 weeks, while those in Arm 3 were assigned to SHR-A1811 4.8 mg/kg and bevacizumab 15 mg/kg every 3 weeks until disease progression, unaccepted toxicity, or no further benefit. The primary endpoint was the intracranial overall response rate (ORR-IC) per RANO-BM. **Results:** Between March 30, 2023, and June 3, 2024, 58 patients were enrolled in Arm 1 (n = 33) and Arm 3 (n = 25). Among these, 56 patients (96.6%) had received anti-HER2 therapy previously, and the median number of prior systemic therapies in advanced setting was 2 (range: 0-9). 54 patients received at least one efficacy assessment and the confirmed ORR-IC in Arm 1 and Arm 3 were 84.4% (27/32) and 72.7% (16/22) respectively, which were numerically identical to the overall ORR in each arm, and all patients achieved intracranial disease control. As of December 31, 2024, the median PFS of Arm 1 was 13.2 (95% CI: 10.0-15.4) months, while the median PFS of Arm 3 was not mature. 78.8% (26/33) of patients in Arm 1 and 48.0% (12/25) in Arm 3 experienced treatment-related adverse events (TRAEs) of grade 3 or 4, and the frequencies of grade 4 TRAEs were 36.4% and 4% respectively. The grade 3/4 TRAEs that occurred in more than one patient included decreased neutrophil counts (Arm 1 / Arm 3: 69.7% / 36.0%), decreased leucocyte counts (51.5% / 16.0%), decreased platelet counts (30.3% / 0%), anemia (21.2% / 8.0%), decreased lymphocyte counts (21.2% / 0%), and nausea (6.1% / 0%). **Conclusions:** Our findings showed that SHR-A1811 6.4 mg/kg solely or SHR-A1811 4.8 mg/kg combined with bevacizumab both can attain high intracranial remission rates, while the lower-dose combination regimen might exhibit a better safety profile. The long-term outcomes will continue to be followed up. Clinical trial information: NCT05769010. Research Sponsor: None.

1018 Rapid Oral Abstract Session

A phase II clinical study of adebrelimab and bevacizumab combined with cisplatin/carboplatin in triple-negative breast cancer patients with brain metastases. First Author: Ting Li, Department of Breast and Urologic Medical Oncology, Fudan University Shanghai Cancer Center, Shanghai, China

Background: Brain metastases (BMs) of triple-negative breast cancer (TNBC) is a lethal disease often associated with a limited life span of approximately 6 months and local therapy is usually the first treatment choice due to lack of effective anti-tumor agents. Here reported a triplet, anti-PD-L1 (Adebrelimab, SHR-1316), bevacizumab plus cisplatin/carboplatin in BMs of triple negative breast cancer. **Methods:** This is a single center, single-arm, phase II clinical trial involving triple-negative breast cancer patients with active brain metastases. A total of 35 participants were administered a triplet treatment consisting of Adebrelimab, bevacizumab and cisplatin/carboplatin. Prior use of bevacizumab or anti-PD-1/PD-L1 was not allowed. Prior use of platinum was allowed only in cases with platinum-sensitive disease. The primary endpoint was the objective response rate in the central nervous system (CNS-ORR), and the secondary endpoints included the clinical benefit rate in CNS (CNS-CBR), progression-free survival (PFS), overall survival (OS), the first progression site and safety. **Results:** The data cutoff for this analysis was on December 20, 2024. A total of 35 patients enrolled in this study from August 2020 to October 2024. Among all patients, 42.9% (15/35) had neurological symptoms at baseline, and 80% (28/35) had not received any local treatment for their brain metastases. The median number of previous lines of therapy for metastatic disease was 2 (range 0-4), with 40% (14/35) patients having received a prior platinum agent. In the intention-to-treat population,which comprised patients who received at least one cycle of study treatment, the CNS-ORR was 77.1% (27/35), with 5 complete responses (CR), 22 partial responses (PR) and the confirmed CNS-ORR was 71.4%(25/35). Among the 23 patients who progressed, the brain was the site of first progression in 69.6% (16/23) of patients. The median PFS was 7.6 months (95%CI, 5.7-11.5), while CNS-PFS was 10 months (95%CI, 7.4-12.6), and median OS was 16 months (95%CI, 11.7 to not reached). Treatment-related adverse events (TRAEs) were reported in 100% (35/35) of patients, with the incidence of grade≥3 TRAEs being 48.6% (17/35), including neutropenia (8.6%, 3/35) and platelet count decreased (8.6%, 3/35). Adebrelimab related serious adverse events (SAEs) occurred in one patient (facial nerve disorder), no treatment-related deaths were reported. **Conclusions:** The triplet treatment of anti-PD-L1 Adebrelimab, bevacizumab and cisplatin/carboplatin, was the first regimen demonstrating a high intracranial anti-tumor activity, a prolonged CNS-PFS and OS with a good safety profile. Warranting further investigation in this highly aggressive disease. Clinical trial information: NCT04303988. Research Sponsor: None.

1019 Rapid Oral Abstract Session

Sacituzumab tirumotecan (sac-TMT) as first-line treatment for unresectable locally advanced/metastatic triple-negative breast cancer (a/mTNBC): Initial results from the phase II OptiTROP-Breast05 study. First Author: Yongmei Yin, Department of Oncology, the First Affiliated Hospital of Nanjing Medical University, Nanjing, China

Background: TROP2 (trophoblast cell surface antigen 2) is highly expressed in TNBC and associated with poor survival. Sac-TMT (MK-2870/SKB264) is a TROP2 ADC developed with a novel linker to conjugate the payload, a belotecan-derivative topoisomerase I inhibitor. It is approved in China for pts with a/mTNBC who have received at least two prior chemotherapies, including one for metastatic disease. The Phase II OptiTROP-Breast05 study (NCT05445908) evaluated sac-TMT as first-line treatment for pts with a/mTNBC. The study also explored the impact of PD-L1 combined positive score (CPS) status. Pts with CPS $<$ 10 (PD-L1-negative, IHC 22C3 pharmDx) have limited treatment options, representing a critical unmet need. **Methods:** Pts with a/mTNBC who had not received prior treatment for advanced disease were enrolled, regardless of PD-L1 or TROP2 status, to receive sac-TMT at 5 mg/kg Q2W until disease progression or unacceptable toxicity. For pts with recurrent TNBC, a disease-free interval (DFI) of at least 6 months was required for eligibility. Tumor assessment was performed every 6 weeks per RECIST v1.1 as assessed by investigator. **Results:** As of 18 Nov 2024, a total of 41 pts (median age 55 yrs; 43.9% ECOG PS 1; 78.0% PD-L1 CPS $<$ 10) were enrolled; 61.0% of pts had visceral metastases at baseline, 29.3% of pts had de novo metastasis, 19.5% of pts had a DFI of 6-12 months (mos), and 51.2% of pts had a DFI $>$ 12 mos. The median follow-up was 18.6 mo. The objective response rate (ORR) was 70.7% (29/41, 3 unconfirmed PR) and the disease control rate (DCR) was 92.7%. Median duration of response (mDoR) was 12.2 mo, while the median progression-free survival (mPFS) was 13.4 mo, and the 12-mo PFS rate was 64.6% (95% CI: 45.0%, 78.7%). Among the 32 pts with PD-L1 CPS $<$ 10, the ORR was 71.9% (23/32, 3 unconfirmed PR) and the DCR was 93.8%. The mPFS in this subgroup was 13.1 mo, with a 12-mo PFS rate 59.1% (95% CI: 37.1%, 75.7%). Treatment-related adverse events (TRAEs) of grade 3 or higher occurred in 63.4% of pts. The most common $\geq$ grade 3 TRAEs (occurred in $\geq$5% of pts) were neutrophil count decreased (46.3%), WBC count decreased (34.1%), anemia (12.2%), stomatitis (9.8%), lymphocyte count decreased (7.3%) and fatigue (7.3%). No treatment-related deaths occurred, and there were no reports of neuropathy or interstitial lung disease/pneumonitis. **Conclusions:** Sac-TMT demonstrated promising anti-tumor activity with a manageable safety profile as a first-line treatment for pts with a/mTNBC, independent of the PD-L1 status. A Phase 3 study comparing sac-TMT vs investigator's choice of chemotherapy in first-line PD-L1-negative (CPS $<$ 10) a/mTNBC is currently underway (NCT06279364). Clinical trial information: NCT05445908. Research Sponsor: Sichuan Kelun-Biotech Biopharmaceutical Co., Ltd.

1020 Rapid Oral Abstract Session

Dose optimization of PF-07248144, a first-in-class KAT6 inhibitor, in patients (pts) with ER+/HER2− metastatic breast cancer (mBC): Results from phase 1 study to support the recommended phase 3 dose (RP3D). First Author: Patricia LoRusso, Yale School of Medicine, New Haven, CT

Background: PF-07248144 is a selective catalytic inhibitor of KAT6, a histone lysine acetyltransferase. To inform the RP3D, we evaluated two pharmacokinetically distinguishable doses of PF-07248144 in combination with fulvestrant (FUL) from a phase 1 study in ER+/HER2− mBC in a dose expansion phase. **Methods:** Pts with ER+/HER2− mBC after prior CDK4/6i and endocrine therapy (ET) received PF-07248144 at recommended doses for expansion (RDEs) of 5 mg QD alone, 5 mg QD plus FUL, or 1 mg QD plus FUL (N = 107) and were followed up (at least 6 months across all cohorts) to assess for safety and efficacy. Primary objective wassafety/tolerability per CTCAE 5.0 and RDE selection. Other objectives included antitumor activity per RECIST 1.1, PK, PD, and predictive biomarkers. **Results:** 5 mg QD was identified as the RDE for both PF-07248144 monotherapy (35 pts treated) and FUL combination (43 pts treated) based on safety, PK, PD, and antitumor activity. 1 mg PF-07248144 plus FUL (29 pts treated) was selected as the lower RDE based on a distinguishable PK and safety profile while achieving maximal blood and tumor PD marker reduction and efficacious concentrations supported by preclinical models. As of Oct 11, 2024, a total of 107 pts were treated at RDEs. Baseline pt characteristics from the two RDEs plus FUL were comparable. All pts received prior CDK4/6i and ET in the metastatic setting. Positive dose-response relationships were identified for both safety (neutropenia) and efficacy (objective response rate [ORR]) endpoints. At 5 mg and 1 mg doses plus FUL, the most common treatment-related adverse event (TRAE) was dysgeusia (G1+G2: 83.7% vs 89.7%). The most common G$\geq$3 TRAE was neutropenia (G3: 39.5% vs 20.7%; G4: 7.0% vs 0.0%). The neutropenia was reversible and manageable with dose modifications. No febrile neutropenia was observed. The safety profile of 5 mg PF-07248144 monotherapy was consistent with 5 mg RDE plus FUL. No events of pneumonitis were reported in the 107 pts treated. For FUL plus 5 mg and 1 mg PF-07248144, ORR was 37.2% (95% CI: 23.0–53.3) vs 24.1% (10.3–43.5); median duration of response was 15.8 mos (9.2–not estimable [NE]) vs 4.6 mos (3.4–NE); clinical benefit rate was 55.8% (39.9−70.9) vs 37.9% (20.7–57.7). With median duration of follow-up 21.9 mos and 11.0 mos for pts receiving FUL plus 5 mg and 1 mg PF-07248144, the median progression-free survival was 10.7 mos (95% CI: 5.3−13.8) vs 3.6 mos (1.8–5.6), respectively. **Conclusions:** Based on a thorough benefit–risk assessment of two pharmacokinetically distinguishable doses with sufficient number of pts and follow up, 5 mg QD PF-07248144 was identified as the optimal dose in combination with FUL with acceptable safety and encouraging activity. A pivotal phase 3 trial is planned to address the high unmet medical need in ER+/HER2− mBC after progression on CDK4/6i plus ET. Clinical trial information: NCT04606446. Research Sponsor: Pfizer Inc.

1021 Rapid Oral Abstract Session

Phase II study of trastuzumab-pkrb plus gedatolisib in patients with HER2-positive metastatic breast cancer who progressed after 2 or more HER2-directed chemotherapies (KM-10A/KCSG BR18-13). First Author: Ju Won Kim, Korea University Anam Hospital, Seoul, South Korea

Background: The prognosis of patients with HER2 positive metastatic breast cancer (MBC) has dramatically improved with the advent of HER2-targeted therapy. However, resistance to anti-HER2 therapies remains inevitable. Aberrations in the PI3K-AKT-mTOR pathway are recognized as a key mechanism of resistance to HER2 directed therapies. This study is a multicenter, prospective, single-arm, phase II study to evaluate the antitumor activity and safety of trastuzumab-pkrb plus gedatolisib in patients with HER2 positive MBC who progressed after 2 or more HER2 directed chemotherapy. **Methods:** The primary endpoint was the overall response rate (ORR), assumed to be 25% with a type I error rate of 0.05 and a power of 0.9. Although the target enrollment was 62 patients, the study was prematurely terminated after 44 patients due to the drug supply issue of gedatolisib. Patients with HER2-positive MBC and PI3K pathway genomic aberrations, identified via tumor-targeted sequencing or cfDNA analysis, were enrolled after disease progression on at least two HER2-directed therapies. The treatment regimen included trastuzumab-pkrb and gedatolisib. Safety and efficacy outcomes were evaluated, with a data cutoff of December 31, 2024. **Results:** Primary efficacy and safety data were evaluable in 44 patients. The median age was 59 years (range: 28-72), and the median number of prior palliative treatment lines was 4 (range: 2-10). Genomic aberrations included mutations kinase domain (26 patients), helical domain (11), amplification (1) of *PIK3CA*, deletion of *PTEN* (2), and other mutations (4). Among the 44 evaluable patients, the best overall responses were complete response (CR) in 2 patients (4.5%), partial response (PR) in 17 (38.6%), stable disease (SD) in 19 (43.2%), progressive disease (PD) in 5 (11.4%), and non-evaluable (NE) in 1 (2.3%), resulting in an objective response rate (ORR) of 43.2% and a disease control rate (DCR) of 86.4%. The median progression-free survival (mPFS) was 5.8 months. After a median follow-up of 32.5 months, 22 deaths were recorded, and 19 patients were alive. The median overall survival (mOS) after study enrollment was 18.4 months. Common treatment-related adverse events (TRAEs) included oral mucositis (32.3%; 4.1% $\geq$ grade 3) and skin reactions (14.1%; 1.8% $\geq$ grade 3). Hyperglycemia was reported in 6.8% (0.5% $\geq$ grade 3). No fatal adverse event related to trial medications were reported. **Conclusions:** In this phase II study, the combination of trastuzumab-pkrb and gedatolisib demonstrated a 43.2% response rate with manageable toxicity in patients with HER2 positive MBC and *PIK3CA* mutations. A translational research study focused on the analysis of cfDNA and PBMC is currently being planned. Clinical trial information: NCT03698383. Research Sponsor: Korea Health Industry Development Institute; HI17C2206.

1022 Poster Session

Longitudinal tissue analysis and correlation of microenvironmental changes with combined immunotherapy and targeted therapy response in metastatic breast cancer. First Author: Jieqiong Liu, Yat-sen Memorial Hospital of Sun Yat-sen University, Guangzhou, China

Background: The ability to interrogate changes within the tumor microenvironment before, during and following therapeutic intervention could yield important understanding of treatment response and causes for disease progression.Here we conducted a multicenter phase II clinical trial (NCT04521179) examining the effect of a novel CTLA-4/PD-L1 bispecific (KN046) antibody in combination with a a novel anti-HER2 bispecific (KN026) antibody in treatment resistant metastatic breast cancer. Our on-going trial demonstrated that in advanced HER2-positive breast cancer (HER2+ BC) patients, who have progressed after prior anti-HER2 combinational therapies, the objective response rate (ORR) of this chemo-free therapy of KN026 in combination of KN046 was about 47.2% (95% CI: 30.4-64.5). To explore the underlying mechanism of this regimen, we collected tumor specimens from patients before and after receiving this combinational treatment for emerging multimodal molecular analyses ("Multi-omics") to provide an in-depth description of the tumor immune microenvironment and its correlation with treatment response. **Methods:** We performed matched pre- and on-treatment investigative biopsies on index tumors and performed single-cell RNA sequencing (scRNA-seq) and single-cell T cell receptor sequencing (scTCR-seq) analysis. **Results:** We performed comprehensive scRNA-seq on tumor biopsies obtained from a total of 17 patients that evaluable for overall response. Among them, 13 patients had two biopsies taken, and four patients had one biopsy collected either before or during treatment. Single-cell RNA and T cell receptor sequencing from 334,183 cells from site-matched tumors reveal significant temporal shift of various immune cell populations and phenotypes within the tumor microenvironment associated with treatment responses. In-depth analysis of subpopulations revealed that $CD8^+$ T cells are activated in responsive patients during treatment, and T_{REG} cells, one of $CD4^+$ T cell subtypes, are activated in non-responsive patients after therapy. Moreover, we also found that combined-therapy activates cDCs and induces an inflammation shift in Mϕs of responsive patients. **Conclusions:** We identified that regulatory T cells are activated while effector T cells, natural killer cells, and dendritic cells were significantly depleted in non-responding tumors. The immune response in responsive patients was effectively enhanced, whereas in nonresponsive patients, it was significantly diminished. And higher baseline levels of Mϕs were associated with therapeutic resistance. These results support that longitudinal analysis of tumor microenvironment to generate multi-omics data that can lead to rich insight disease process and to provide clinical value in evaluating treatment responses. Clinical trial information: NCT04521179. Research Sponsor: Guangdong Science and Technology Department (2023B1212060013, 2022B1515020100, 2022A1515012238); the Natural Science Foundation of China (82273033, 82072924, 82072906).

1023 Poster Session

Zongertinib in HER2-altered breast cancer: Preclinical activity and preliminary results from a phase Ia dose-escalation study. First Author: David Berz, Valkyrie Clinical Trials, Inc., Los Angeles, CA

Background: Preclinical studies have demonstrated that zongertinib, an irreversible TKI, selectively and potently inhibits oncogenic HER2 in a variety of cancer models. An ongoing Phase (Ph) Ia/Ib dose escalation/expansion trial (NCT04886804) has demonstrated preliminary clinical activity of zongertinib across a range of HER2-driven solid tumors. Here we present comparative preclinical data for zongertinib in breast cancer (BC) cell lines and cell line-derived xenograft (CDX) models, as well as clinical data from patients (pts) with HER2-driven BC who received zongertinib during Phase Ia dose escalation. **Methods:** Cell proliferation assays were undertaken in *HER2*-amplified BC cell lines (relative copy numbers ranging from 3.2–10.1) exposed to serial dilutions of zongertinib and tucatinib. Antitumor activity of zongertinib (5–40 mg/kg QD) *in vivo* was assessed in three *HER2*-amplified BC CDX models. Ph Ia of the trial enrolled pts with confirmed HER2 alterations (mutations, amplification or overexpression) who had exhausted all other treatment (Tx) options. In Ph Ia, zongertinib was administered at 15–150 mg BID or 60–360 mg QD in 21-day cycles. Primary endpoints were maximum tolerated dose (MTD) and dose-limiting toxicities (DLTs). Efficacy (objective response, OR) was evaluated as a secondary endpoint using RECIST v1.1. **Results:** Zongertinib inhibited tumor cell growth *in vitro* with greater potency (4.5–16.4-fold) than tucatinib (zongertinib IC_{50}: 2.6–40.6 nM; tucatinib IC_{50}: 13.2–664.0 nM). In mice, zongertinib was well tolerated and led to a dose-dependent inhibition of BC tumor growth, with tumor regressions at higher doses ($\geq$ 20 mg/kg QD). As of August 29, 2024, 121 pts had been treated in the Ph Ia trial. Two DLTs occurred during the MTD evaluation period; the MTD was not reached. Treatment-related adverse events (TRAEs; all/grade $\geq$3) occurred in 82.6%/12.4% of pts; the confirmed OR rate was 31.4% across all doses and tumor types. In total, 15 pts with Stage IV BC (HER2 overexpression/amplification: n = 10; *HER2* mutations: n = 4; both: n = 1) received zongertinib (100 mg BID: n = 1; 240–360 mg QD: n = 14). Most were white (60.0%) and had an ECOG PS of 1 (66.7%). Mean (standard deviation, SD) age was 58.1 (7.4) years. Mean (SD) Tx duration was 4.0 (3.4) months. TRAEs (any/grade $\geq$3) occurred in 93.3%/0.0% of pts. In pts with BC, the confirmed OR rate was 26.7% (4 partial responses). The confirmed disease control rate was 73.3%. Regardless of confirmation, the OR rate was 46.5%. At the time of data cut-off, 2 pts with responses were still on treatment, and an additional 3 patients had a response lasting longer than 4 months. **Conclusions:** Zongertinib potently inhibits HER2-driven BC growth in preclinical models *in vitro* and *in vivo*. Preliminary Ph Ia data indicate that zongertinib has encouraging clinical activity and manageable safety in pts with advanced, HER2-driven BC. Clinical trial information: NCT04886804. Research Sponsor: Boehringer Ingelheim.

1024 Poster Session

Transcriptomic analysis of HER2 expression in metastatic breast cancer: Insights from a UAE patient cohort. First Author: Rachel Su Jen Wong, Department of Haematology-Oncology, National University Cancer Institute, Singapore, Singapore

Background: HER2-low metastatic breast cancer (mBC) has emerged as a clinically significant subgroup since approval of trastuzumab deruxtecan. However, its relevance as a distinct subtype remains debated. We aimed to identify HER2-related gene signatures, examine the molecular characteristics of HER2-low mBC, and investigate the potential for classifying HER2-low mBC into subgroups with profiles resembling either HER2-positive (HER2+) or HER2-negative (HER2-) mBC. **Methods:** We performed differential gene expression (DGE) analysis using the TCGA-BRCA dataset, comparing HER2+ and HER2- samples to identify a 17-gene HER2 expression signature. The findings were validated on archival samples from a UAE clinical center, where DGE analysis was repeated to compare HER2+ and HER2-zero mBC. HER2-low samples were then classified into two subsets; positive-like and zero-like based on their HER2 signature gene expression level. Lastly, Gene Set Enrichment Analysis (GSEA) was conducted to evaluate the molecular characteristics of these subsets. **Results:** In the TCGA-BRCA dataset (n = 409; median age 59 years, range 26–90), 20.5% of samples were HER2+, and 79.5% were HER2-. DGE analysis identified a 17-gene HER2 signature that effectively separated HER2+ and HER2- mBC. These 17 genes including GSDMB, ERBB2, and MED1, are associated with HER2 expression. In the UAE cohort (n = 69; median age 52 years, range 24–84), comprising 7.25% HER2+, 60.87% HER2-low, and 31.88% HER2-zero mBC, 7 genes (GSDMB, GRB7, ERBB2, STARD3, PGAP3, MIEN1, TCAP) from the 17-gene HER2 signature were similarly upregulated in the HER2+ samples. We observed an increasing trend in HER2 signature expression across the groups, from HER2-zero to HER2-low and then HER2+ mBC showing the highest expression. This trend was supported by separation across HER2 status with gene-level expression, Gene Set Variation Analysis scores and Principal Component Analysis (PCA). Next, HER2-low mBC were classified into two distinct subgroups based on distance-to-centroid approach with PCA. Based on distance to HER2+ and HER2-zero centroids, HER2-low mBC were classified into positive-like and zero-like subgroups respectively. Separation of the positive-like and zero-like samples were observed with DGE analysis and expression of the HER2 signature genes. GSEA of HER2-low positive-like samples indicate increased activation of ERBB2 oncogenic pathway and suppression of gene sets involved in immune-mediated pathways compared to HER2-low zero-like mBC. **Conclusions:** This study reveals the potential utility of transcriptomic HER2 signature to characterize HER2-related molecular features in mBC, revealing a gradient of HER2 signature expression across HER2+, HER2-low, and HER2-zero. Identification of suppressed immune-mediated pathways in HER2-low positive-like mBC suggests combination with immune mediators as potential treatment strategy. Research Sponsor: None.

1025 Poster Session

Phase I summary of the C406 (CART) efficacy and safety for an HER-2–positive breast cancer population. First Author: Meili Sun, Department of Oncology, Jinan Central Hospital, Shandong University, Jinan, China

Background: C406 is a chimeric antigen receptor (CAR) modified autologous T cell, which is a CART targeting HER-2. Here we present the breast cancer results in Phase 1 study. **Methods:** This phase 1 trial to evaluate the safety and efficacy of chimeric antigen receptor (CAR) modified autologous T cells (C406) for pts with Her2-positive recurrent or refractory breast cancer. C406 is administered intravenously at a fixed dose. Response was evaluated by RECIST v.1.1 every 4 weeks. **Results:** As of Jan 18, 2025, 8 (F) breast cancer pts have received C406 at doses of $3*10^7$/kg (n = 6), $1*10^8$/kg (n = 2). Two patients in the $3*10^7$/kg -dose group received the second transfusion. Overall, the median age was 59 years, the median number of priortreatment lines was 3.125 and the median number of anti-HER-2 treatment lines was 2. The histological type was invasive breast cainoma, 7 cases of ductal carcinoma and 1 case of mucous carcinoma. These breast cancer hormone receptor types include ER+/PR+, ER-/PR-, and ER+/PR-. Cyclophosphamide combined with fludarabine was the regimen for lymphocyte clearance in all patients. Among them, 1 patient did not receive bridging therapy. Bridging treatment options for other patients were as follows, attillizumab bridging therapy (n = 1), albumin-bound paclitaxel combined with carboplatin and attillizumab (n = 1), albumin-bound paclitaxel combined with Attillizumab (n = 2), gemcitabine combined with attillizumab (n = 1), Albumin-bound paclitaxel + epirubicin + cyclophosphamide + Attilizumab + local radiotherapy (n = 1), docetaxel + Attilizumab + local radiotherapy (n = 1). Among the 8 pts having imaging tumor assessment, the DCR was 75%, which includes 0 partial responses (PR), 6 stable disease (SD), and 2 progressive disease (PD) according to RECIST v1.1. Among the 6 SD pts, 1 pt's progression-free survival (PFS) is 8 months. All the 8 pts experienced a treatment related adverse events (TRAEs). The most common TRAEs included white blood cell count decrease (100%, 8/8), neutrophil count decrease (100%, 8/8), lymphocyte count decrease (100%, 8/8) and cytokine release syndrome (25%, 2/8). No TRAE leading to discontinuation and death. **Conclusions:** C406 therapy showed an acceptable safety profile anti-tumor activity for advanced HER-2 positive breast cancer, but the antitumor activity needs to be further explored. Clinical trial information: ChiCTR2500096093. Research Sponsor: None.

1026 Poster Session

Decoding HER2 dynamics: Exploring HER2 expression across a real-world breast cancer cohort. First Author: Michelle Green, Labcorp, Durham, NC

Background: HER2 expression in breast cancer (BC) has evolved from a binary scoring system to a continuum-based approach, driven by the therapeutic benefits of trastuzumab deruxtecan (T-DXd) in patients with HER2-Low tumors. Our understanding of HER2 expression is complicated by several factors, including tumor heterogeneity, altered expression as tumors progress, and variations in assay technique and scoring. Here we describe HER2 expression patterns in a large cohort of patients with BC, including a subset with longitudinal results. **Methods:** HER2 expression levels were determined by IHC using the VENTANA 4B5 antibody. HER2 copy number and HER2/CEP17 ratios were determined using a validated dual-probe ISH assay. Tumors were retrospectively identified as HER2-Zero (IHC 0), HER2-Low (IHC 1+ or 2+ with negative ISH) or HER2-positive (IHC3+ or IHC2+ with positive ISH) based on the established IHC and ISH values scored at the time of reporting (Apr 2013 to Nov 2024). Estrogen and progesterone receptor (HR) levels were determined using validated IHC assays. All testing was performed in a CAP/CLIA accredited referral laboratory. Tumor histology, specimen collection site (CS), and patient demographics were abstracted from test requisition forms. Results are descriptive and presented in aggregate. **Results:** A total of 30,023 BC specimens from 27,055 patients were included in the analysis. Most patients were female (99%; 26,687) with a median age at testing of 63.5 years. Among HER2-Low specimens, 87% were HR-positive (HR+) and 13% were HR-negative/HR-Low (ER IHC $<$ 10%). Longitudinal specimens were available for 1,267 patients with a median of 77 days between collection dates. 69% (869) of longitudinal specimens demonstrated the same level of HER2 expression, including in 69% (597/868) of cases where both specimens were collected from breast and 69% (203/294) of cases where the first specimen was collected from breast and the second was collected from another site. Among 398 patients who had HER2 expression levels changes, 46% went from HER2-Low to HER2-Zero and 33% went from HER2-Zero to HER2-Low. **Conclusions:** HER2-Low status is common in BC, especially among HR-positive cases.HER2 expression status changed between longitudinal specimens in 31% of patients, which may inform therapeutic eligibility. This reaffirms current guidelines recommending a biopsy at first distant recurrence and suggests that serial biopsies might be helpful in detecting HER2 expression in an originally HER2-Zero tumor. Research Sponsor: None.

Longitudinal HER2 expression levels changes.

HER2 Expression Level Change	Both CSs Breast	Breast to Other CS	Other CS combinations	Total
Positive to Low	27	3	3	33
Positive to Zero	5	2	1	8
Low to Positive	23	6	3	32
Low to Zero	116	51	17	184
Zero to Positive	6	3		9
Zero to Low	94	26	12	132
No Change (Positive)	71	32	7	110
No Change (Low)	365	104	41	510
No Change (Zero)	161	67	21	249

1027 **Poster Session**

A phase Ib/IIa study of BAT8010+BAT1006, an anti-HER2 monoclonal antibody-exatecan conjugate combined with an ADCC-enhanced HER2 mAb in patients with advanced solid tumors. First Author: Shusen Wang, Sun Yat-sen University Cancer Center, Guangzhou, China

Background: BAT8010 is an ADC argeting HER2, while BAT1006 is a humanized monoclonal antibody targeting another epitope of HER2, with ADCC enhancement activity via completely devoid of fucose. This study investigates the combination of BAT8010 and BAT1006 in patients with advanced solid tumors. **Methods:** Patients in this open-label, multicenter clinical trial received BAT8010 +BAT1006 on day 1 of a 21-day cycle until intolerable or disease progression occurred. The study objectives included assessing tolerability, safety, pharmacokinetic characteristics, immunogenicity, and preliminary efficacy. **Results:** As of January 15, 2025, 20 patients with metastatic breast cancer (mBC, n=14) and gastric cancer (GC, n=6) were enrolled in three cohorts: BAT8010 (2.1mg/kg) + BAT1006, BAT8010 (2.4mg/kg) + BAT1006 and BAT8010 (2.7mg/kg) + BAT1006, with BAT1006 fixed at 15 mg/kg. HER2 positivity on tumor tissue was categorized as IHC2+/FISH+ or IHC3+. Two dose-limiting toxicity (grade 4 thrombocytopenia and neutropenia) were reported in the BAT8010 (2.7mg/kg) + BAT1006 group. The maximum tolerated dose was determined to be BAT8010 (2.4mg/kg) + BAT1006, and expansion studies have been proceeded at this dose. Safety: Among the 20 patients who received at least one dose of BAT8010 + BAT1006, 17/20 (85%) reported at least one treatment-emergent adverse events (TEAEs). The most common TEAEs (≥5%) included neutropenia, leukopenia, nausea, thrombocytopenia and anemia. Most TEAEs were Grade 1 or 2; however, 55% of the patients experienced Grade 3 or greater AEs, including neutropenia 7/20 (35%), thrombocytopenia 5/20 (20%), infusion-related reaction 1/20 (5%) and febrile neutropenia1/20 (5%). The infusion-related reaction was mild, and one subject discontinued the study treatment due to TEAEs. No cases of interstitial lung disease (ILD)/pneumonitis were reported. Efficacy: Fourteen mBC patients were recruited across the dose cohorts: BAT8010 (2.1 mg/kg)+BAT1006 (n=3), BAT8010 (2.4 mg/kg)+BAT1006 (n=7) and BAT8010 (2.7 mg/kg)+BAT1006 (n=4). Most had previously undergone 3-7 lines of systemic treatments, including trastuzumab and HER2 ADC regimens. Six GC patients were included in the BAT8010 2.4mg/kg + BAT1006 (n=4) and BAT8010 2.7mg/kg + BAT1006 (n=2) cohort. Sixteen patients had at least one tumor assessment, yielding an ORR of 43.7% (7/16) and a DCR of 87.5% (14/16). Among the 12 mBC patients, the ORR is 50% (6/12) with a DCR of 91.66% (11/12), including one CR. In the 4 GC patients, the ORR was 25% (1/4) with a DCR of 75% (3/4). **Conclusions:** The combination of BAT8010 and BAT1006 was well-tolerated, with manageable toxicity, and demonstrated promising preliminary antitumor activity in metastatic breast cancer and gastric cancer. Dose expansion studies are ongoing to further detect the safety and efficacy in these population. Clinical trial information: CTR20241120. Research Sponsor: None.

1028 **Poster Session**

JSKN003, a biparatopic HER2-targeting ADC, in heavily pretreated HER2-positive breast cancer: A pooled analysis of early-phase studies. First Author: Yiqun Du, Department of Medical Oncology, Fudan University Shanghai Cancer Center, Shanghai, China

Background: JSKN003 is a biparatopic HER2-targeting antibody-drug conjugate (ADC) conjugated to a topoisomerase I inhibitor (TOP1i) via a tetrapeptide linker, designed to enhance serum stability and anti-tumor activity. The efficacy and safety of JSKN003 in advanced ovarian cancer and other solid tumors have been highlighted in previous reports, and this analysis provides updated insights into its performance in HER2-positive breast cancer. **Methods:** JSKN003-101 is a dose-escalation and -expansion study in Australia, and JSKN003-102 is a phase I/II study in China, both involving patients with advanced solid tumors. A pooled analysis was performed to assess its efficacy and safety in HER2-positive advanced breast cancer. **Results:** As of November 29, 2024, the median follow-up duration was 3.52 months (range: 2.99-3.71). A total of 71 patients with HER2-positive breast cancer were enrolled, with the majority receiving 6.3 mg/kg or 8.4 mg/kg doses. The median age was 54 years (range: 32-79), with 78.9% ECOG 1. All patients had stage IV disease, with 76.1% having visceral metastases. All patients had prior anti-HER2 therapy, including 87.3% with prior ADCs or TKIs, and 56.3% having ≥3 prior lines. Among 62 evaluable patients, 56 were T-DXd naïve. In these 56 patients, the overall response rate (ORR) was 67.9% (95%CI: 54-79.7), and the disease control rate (DCR) was 94.6% (95%CI: 85.1-98.9). In the RP2D subgroup (6.3mg/kg, n = 30), the ORR was 70.0% (95%CI:50.6-85.3). Of 6 patients with prior T-DXd exposure, 1 achieved a partial response (PR), 3 had stable disease (SD), and tumor shrinkage was observed in 3. Both median progression-free survival (PFS) and median overall survival (OS) were immature. Treatment-related adverse events (TRAEs) ≥Grade 3 occurred in 11.3% of patients, and serious adverse events (SAEs) in 9.9%, with 2 drug-related. No TRAEs led to death or treatment discontinuation. The most common TRAEs (≥20%) included nausea, elevated liver enzymes, vomiting, decreased appetite, fatigue, diarrhea, and anemia. No≥Grade 3 neutropenia was observed. Grade ≥3 anemia and decreased platelet count were each reported in 1 patient (1.4%), both being Grade 3. Interstitial lung disease (ILD) occurred in three patients (4.2%), all Grade 1-2, with no Grade ≥3 events. **Conclusions:** JSKN003 demonstrated promising efficacy and manageable safety in heavily pretreated HER2-positive breast cancer, including T-DXd-experienced patients. The biparatopic HER2 antibody design likely enhanced its binding efficiency and contributed to the observed clinical benefit. These findings support the planned Phase 3 trial to further evaluate its therapeutic potential. Clinical trial information: NCT05494918; NCT05744427. Research Sponsor: Jiangsu Alphamab Biopharmaceuticals Co., Ltd.

1029 **Poster Session**

IBI354 (anti-HER2 antibody-drug conjugate [ADC]) in patients (pts) with HER2-positive breast cancer (BC) and other solid tumors: Updates from a phase 1 study. First Author: Charlotte Rose Lemech, Scientia Clinical Research, Randwick, Australia

Background: HER2 has been established as an important therapeutic target for BC. IBI354 consists of trastuzumab (anti-HER2 antibody) conjugated to a camptothecin derivative. In a global, multicenter, phase 1 study, IBI354 was well tolerated and showed promising efficacy in BC and other solid tumors (2024 ESMO 345MO/720MO/576P). Here, we report updated safety and efficacy of IBI354. **Methods:** Eligible pts with advanced solid tumors who had failed or were intolerant to standard treatment were enrolled. Positive HER2 was defined as immunohistochemistry (IHC) 2+/in situ hybridization (ISH)+ or IHC 3+. IBI354 was administered intravenously at 6-15 mg/kg Q3W or Q2W. Primary endpoint was safety. Secondary endpoints were objective response rate (ORR), disease control rate (DCR), duration of response (DoR) and progress-free survival (PFS) assessed by investigators per RECIST v1.1 and overall survival (OS). **Results:** As of Nov 12, 2024, a total of 368 pts with solid tumors were enrolled in China and Australia (females: 89.4%, median age: 56.0 years [range: 27-82], ECOG PS 1: 75.0%). Median follow-up time was 11.3 months (range: 5-19). Median treatment duration was 25.0 weeks (range: 3.1-63.3) and 124 (33.7%) pts remain on treatment. Treatment-related adverse events (TRAEs) occurred in 331 (89.9%) pts while ≥grade 3 (G3) TRAEs occurred in 93 (25.3%) pts. Most common TRAEs included white blood cell count decreased (48.6%, with 7.1% ≥G3), anemia (46.7%, with 4.9% ≥G3), nausea (46.2%, with 0.8% ≥G3) and neutrophil count decreased (38.3%, with 9.8% ≥G3). Interstitial lung disease occurred in 8 (2.2%) pts (5 treatment-related and 3 treatment-unrelated, all G1-2). TRAEs led to dose reduction in 5 (1.4%) pts and treatment discontinuation in 4 (1.1%) pts. No TRAE led to death. Efficacy was evaluable in 88 pts with HER2-positive BC (stage IV: 97.7%; prior systemic therapy regimens≥5: 65.9%; IHC 2+/ISH+: 19.3%, IHC 3+: 80.7%). The overall confirmed ORR was 58.0% (95% CI: 47.0-68.4) and DCR was 90.9% (95% CI: 82.9-96.0). Among 51 pts with confirmed responses, median DoR was not reached (events rate: 19.6%) and 12-month DoR rate of 71.8% (95% CI: 52.9-84.2). Median PFS was not reached with events rate of 37.5%. Median OS was not reached with events rate of 5.7% and 9-month OS rate of 96.2% (95% CI: 88.7-98.8). **Conclusions:** IBI354 continues to demonstrate favorable safety profiles with no new safety signals. Encouraging efficacy was observed in HER2-positive BC. Clinical trial information: NCT05636215. Research Sponsor: Innovent Biologics (Suzhou) Co., Ltd.

1030 **Poster Session**

Efficacy of tucatinib, trastuzumab, and capecitabine (TTC) following trastuzumab-deruxtecan (T-DXd) in HER2-positive metastatic breast cancer (MBC): Updated results and subgroup analyses from the UNICANCER multicenter retrospective cohort. First Author: Jean-Sebastien Frenel, Institut de Cancerologie de L'Ouest, Saint-Herblain, France

Background: T-DXd is the standard second-line treatment for HER2-positive MBC with TTC being the preferred third-line option. However, the efficacy of TTC following T-DXd remains unclear. Here, we provide an updated and subgroup analysis of a French cohort comprising 101 patients who received TTC after T-DXd. **Methods:** We conducted a retrospective study across 12 French comprehensive cancer centers, including patients with HER2-positive MBC treated with TTC after T-DXd exposure. The primary endpoint was progression-free survival (PFS), while secondary endpoints included overall survival (OS) and time to next treatment (TTNT). **Results:** A total of 101 patients who initiated TTC between August 2020 and December 2022 were included in the analysis. The median age was 56.4 years (range: 30.8–84.8). Patients had received a median of 4 prior MBC therapies (range: 2–15), which included pertuzumab (81%) and T-DM1 (93%). 82 patients (81%) experienced progression on T-DXd, while 19 discontinued due to toxicity or other reasons. The data cutoff date was December 1, 2024. For the whole population, with a median follow-up of 29.6 months (95% CI [26.0–34.0]), the median PFS was 4.7 months (95% CI [3.9–5.8]), the median TTNT was 5.2 months (95% CI [4.5–6.6]), and the median OS was 13.9 months (95% CI [12.4–19.0]). For the 86 patients who initiated TTC immediately after T-DXd, the median PFS and TTNT were 5.2 months (95% CI [4.4–6.4]) and 5.5 months (95% CI [4.7–7.2]), respectively. HR+ disease was identified in 71.3% (n=72) of the cohort, with 84.7% receiving TTC immediately post-T-DXd. With a median follow-up of 29.6 months (95% CI [25.1–NR]), the HR+ population had a median PFS of 4.1 months (95% CI [3.5–5.6]) and a median OS of 13.4 months (95% CI [12.3–19.0]). The median TTNT was 4.7 months (95% CI [4.0–6.3]). Among the 65 RECIST-evaluable HR+ patients, best response included progressive disease in 40%, stable disease in 29%, partial response in 29%, and complete response in 2%. With a median follow-up of 29.3 months (95% CI [26.0–NR]), the HR- population had a median PFS of 5.8 months (95% CI [4.4–10.5]) and a median OS of 17.5 months (95% CI [10.6–22.9]). The median TTNT was 6.0 months (95% CI [4.9–10.7]). Among the 24 RECIST-evaluable HR- patients, best response included progressive disease in 25%, stable disease in 38%, partial response in 33%, and complete response in 4%. **Conclusions:** This large retrospective cohort with extended follow-up highlights the efficacy of TTC in HER2-positive MBC patients previously treated with T-DXd. These findings support the role of TTC as a viable treatment option post-T-DXd and provide insights for optimizing therapeutic strategies in this setting. Research Sponsor: None.

1031 Poster Session

Eribulin plus pyrotinib In trastuzumab-resistant HER2-positive advanced breast cancer: A single-arm, multicenter phase II trial (EPIC trial). First Author: Zhenchuan Song, Fourth Hospital of Hebei Medical University, Shijiazhuang, China, Shijiazhuang, China

Background: This study (ChiCTR2000038832) aimed to evaluate the efficacy and safety of combining eribulin with pyrotinib in patients with advanced HER2-positive breast cancer who had developed resistance to trastuzumab. These patients typically face a poor clinical prognosis, and evidence-based guidance for treatment decisions remains limited. **Methods:** Eligible patients were those with pathologically confirmed HER2-positive metastatic breast cancer, an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1, and prior treatment with trastuzumab and taxanes. Participants received oral pyrotinib (400 mg once daily) and intravenous eribulin (1.4 mg/m² on days 1 and 8 of each 21-day cycle) for up to six cycles. Pyrotinib was continued until disease progression or intolerable toxicity. The primary endpoint was progression-free survival (PFS). The secondary endpoints include the objective response rate (ORR), disease control rate (DCR), duration of response (DoR), overall survival (OS), and safety. **Results:** Between February 2021 and September 2023, 30 patients were enrolled, with a median age of 57 years (range: 30–76). All had received prior trastuzumab and taxane therapies. As of November 30, 2024, the median follow-up was 20.1 months. Disease progression or death occurred in 15 patients, and the median PFS was 13.73 months (95% confidence interval [CI]: 11.1–14.8). The 12-month PFS rate was 61.7% (95% CI: 44.2%–86.0%). The 12-month OS rate was 75.3% (95% CI: 66.2%–84.4%). The objective response rate (ORR) was 53.3% (16/30), and the disease control rate (DCR) was 80.0% (24/30). Median overall survival was not reached. Common adverse events (AEs) of any grade occurring in > 15% of patients included diarrhea (40%), nausea (20%), anorexia (16%), and vomiting (16%), with grade 3 diarrhea reported in 3% of patients. No treatment-related deaths were observed. **Conclusions:** The combination of eribulin and pyrotinib shows promise as a therapeutic option for patients with HER2-positive advanced breast cancer resistant to trastuzumab. While advancements in anti-HER2 therapies continue, further studies are needed to address unresolved challenges in this clinical context. Clinical trial information: ChiCTR2000038832. Research Sponsor: None.

1032 Poster Session

Quantitative pre-treatment assessment of trastuzumab deruxtecan (T-DXd) antibody target (HER2) and payload target (topoisomerase 1, Topo1) to predict outcomes in metastatic breast cancer (MBC). First Author: Paolo Tarantino, Dana-Farber Cancer Institute, Boston, MA

Background: The antitumor activity of T-DXd for MBC is sub-optimally predicted by HER2 immunohistochemistry (IHC). We evaluated novel assays to quantify the expression of T-DXd antibody and payload targets and their association with outcomes. **Methods:** We retrieved pre-treatment FFPE tumor samples for patients (pts) with MBC receiving T-DXd at Dana-Farber Cancer Institute between 2017 and 2023. Patients were categorized by HER2 IHC status at start of T-DXd. The RPPA-based protein assessment of HER2 and Topo1 was performed in a CLIA lab after laser capture microdissection enrichment of tumor epithelium. The HER2DX standardized assay was performed after RNA extraction. We evaluated the association of each marker, continuously and by tertiles/quartiles, with time to next treatment (TTNT) with T-DXd. Cox proportional hazards models were utilized to estimate hazard ratios and log-rank test p-values were reported. The Kaplan-Meier method was used to calculate median estimates. **Results:** HER2DX and RPPA testing were conducted for 41 (25 with HER2+, 16 with HER2- MBC) and 38 pts (24 with HER2+, 14 with HER2- MBC), respectively.Both HER2DX and RPPA HER2 quantitative testing significantly predicted outcomes with T-DXd (Table). The HER2DX HER2 amplicon mRNA signature was significantly associated with TTNT with T-DXd (p=0.001), including when divided into tertiles, with a range of 4.7 months in the lowest vs 12.03 months in the highest tertile (p=0.02). Similarly, the RPPA-based HER2 protein expression was significantly associated with TTNT when divided into quartiles (p=0.02). Pre-treatment Topo1 protein expression was significantly associated with outcomes in pts with HER2-negative MBC (n=14), with higher expression of TOPO1 associated with worse TTNT with T-DXd (p=0.04). **Conclusions:** Higher pre-treatment HER2 mRNA signature (HER2DX) and protein (RPPA) expression predicted improved outcomes with T-DXd for MBC, whereas higher Topo1 expression was associated with worse outcomes with T-DXd among pts with HER2- MBC. Research Sponsor: Terri Brodeur Breast Cancer Foundation; Saverin Award; Susan G. Komen Breast Cancer Foundation; Breast Cancer Research Foundation.

Association of pre-treatment HER2 amplicon mRNA signature, HER2 RPPA and Topo1 RPPA expression with outcomes among patients receiving T-DXd.

	Group	Median TTNT (months)	95% CI	HR	95% CI	p-value
HER2 amplicon mRNA expression n=41	1 unit increase	-	-	0.70	0.56-0.87	**0.001**
HER2 amplicon tertiles n=41	Low (ref)	4.70	3.27-NA	0.71	0.33-1.55	Log-Rank
	Med	5.33	4.7-NA	0.23	0.08-0.69	p=**0.019**
	High	12.03	7.37-NA			
HER2 RPPA protein expression n=38	10 unit increase	-	-	0.95	0.90-1.01	0.083
HER2 RPPA quartiles n=38	≤ 25% (ref)	4.03	2.87-NA	0.64	0.25-1.61	Log-Rank
	>25%-50%	5.83	2.13-NA	0.28	0.10-0.74	p=**0.019**
	>50%-75%	8.00	5.33-NA	0.30	0.12-0.75	
	>75%	9.07	5.83-NA			
Topo1 RPPA expression (HER2- only) n=14	< median (ref)	5.87	4.90-NA	3.49	1.02-11.96	Log-Rank
	≥ median	2.70	2.47-NA			p=**0.036**

1033 Poster Session

Efficacy and safety results of TQB2930, a HER2-targeted bispecific antibody combined with chemotherapy in patients with HER2-positive breast cancer (BC) previously treated with ≥2 line treatments: Results from a phase 1b/2 study. First Author: Qingyuan Zhang, Breast Department, Harbin Medical University Cancer Hospital, Harbin, China

Background: TQB2930 is a HER2-targeted bispecific antibody designed to bind two distinct HER2 epitopes: the extracellular domain 4 (ECD4), and the extracellular domain 2 (ECD2). In an ongoing phase 1b/2 clinical trial, TQB2930 has demonstrated favorable tolerability alongside durable responses in patients with heavily pretreated metastatic HER2-positive BC. In this context, Cohort 4 of the trial was designed to evaluate the safety and efficacy of TQB2930 in combination with chemotherapy for patients with HER2-positive BC who had received at least two prior lines of treatment. **Methods:** Cohort 4 enrolled patients aged ≥18 years with recurrent or metastatic HER2-positive BC who had undergone at least two prior systemic therapies. Patients with stable brain metastases were permitted. All enrolled patients received TQB2930 intravenously at a dose of 30 mg/kg every three weeks (Q3W), administered in combination with one of four investigator-selected chemotherapies (capecitabine, eribulin, gemcitabine, or vinorelbine). The primary endpoint was the overall response rate (ORR), while secondary endpoints encompassed disease control rate (DCR), progression-free survival (PFS), overall survival (OS), safety, and immunogenicity. **Results:** As of December 15, 2024, 55 patients (pts) had been treated with TQB2930 combined with chemotherapy. The median follow-up duration was 4.14 months (95% CI: 3.55–4.31). Out of 52 patients evaluable for efficacy, the ORR was 48.1% (25/52), with 88.5% (46/52) experiencing a reduction in target lesion size. Among patients who had progressed on prior T-DM1 therapy, the ORR was 36.8% (7/19), whereas patients who had failed other HER2-ADC therapies exhibited an ORR of 50% (8/16), including RC48, DS-8201, and so on. Notably, the median PFS and OS had not yet been reached, while the 6-month PFS rate was estimated at 71%. Grade ≥3 TRAEs were primarily hematological, encompassing decreased white blood cell count, neutropenia, thrombocytopenia, and infusion-related reactions. Importantly, there were no grade ≥3 cardiac toxicities, and the incidence of sinus bradycardia or QT interval prolongation was < 3%. **Conclusions:** The combination of TQB2930 with chemotherapy demonstrates encouraging antitumor efficacy and an acceptable safety profile in patients with HER2-positive BC who have undergone at least two prior lines of treatment. These results support the potential of TQB2930 as a novel therapeutic strategy for HER2-positive BC and underscore the need for further clinical exploration. This study was funded by Chia Tai Tianqing Pharmaceutical Group Nanjing Shunxin Pharmaceutical Co., Ltd. Clinical trial information: NCT06202261. Research Sponsor: Chia Tai Tianqing Pharmaceutical Group Nanjing Shunxin Pharmaceutical Co., Ltd.

1034 Poster Session

Association of germline homologous recombination deficiency mutations with HER2 status conversion from negative to positive following neoadjuvant chemotherapy in breast cancer. First Author: Colin P. Bergstrom, Stanford University School of Medicine, Stanford, CA

Background: Neoadjuvant therapy (NT) is well established in breast cancer management, with subsequent adjuvant therapy guided by biomarker status and tumor response. While rare, biomarker status can change post-NT. The mechanisms driving conversion and optimal treatment strategies remain unclear. This study aimed to investigate clinicopathological characteristics, including germline mutations, in patients who underwent HER2 status conversion from negative to positive (N-P) after NT. **Methods:** Patients treated with NT for breast cancer between 2012 and 2023 were retrospectively identified from the Stanford STRIDE database. Clinicopathological features, including demographics, genetic data, treatment history, pathological characteristics, and recurrence, were collected through chart review. ER, PR, and HER2 status were assessed using immunohistochemistry (IHC) and fluorescence in-situ hybridization (FISH), with HER2 interpretation following ASCO/CAP guidelines relevant at the time of testing. Per institutional policy, both IHC and FISH were routinely performed for HER2 assessment. **Results:** A total of 28 patients with HER2 status change were identified; 26 (93%) were female and 2 (7%) male, with a median diagnosis age of 47 years (IQR 39–58). Most patients were ER-positive (N=24, 86%) at diagnosis. Among 25 patients who underwent germline testing, 56% harbored mutations in homologous recombination deficiency genes, including BRCA2 (5, 20%), BRIP1 (4, 16%), PALB2 (2, 8%), ATM (2, 8%), and BRCA1 (1, 4%). Post-NT, patients were classified into HER2 groups: 36% (10/28) in Group 1, 46% (13/28) in Group 1b (HER2 low amplified with HER2/cell <6 and ratio >2), 14% (4/28) in Group 3, and 4% (1/28) in Group 4. Adjuvant HER2-directed therapy was administered to 24 patients (89%): trastuzumab in 8 (29%), trastuzumab and pertuzumab in 12 (43%), and trastuzumab emtansine in 4 (14%); 4 patients (14%) did not receive adjuvant HER2 therapy. Recurrence occurred in 8 patients (29%), including 3 with germline mutations. One non-mutated case involved discordant HER2-positive recurrence with ipsilateral in-breast recurrence and liver metastases, testing HER2-positive by FISH despite IHC 0. **Conclusions:** This study highlights that a majority of patients who underwent HER2 status conversion after NT harbored homologous recombination deficiency mutations, suggesting a potential mechanistic basis. Furthermore, while 85.8% of patients received adjuvant HER2-directed therapy, the rarity of HER2-positive recurrences underscores the potential for overtreatment. Further studies are needed to elucidate the mechanisms of HER2 status conversion from negative to positive after NAT which will improve the efficacy of treatment strategies and patient outcomes. Research Sponsor: None.

1035 Poster Session

Recurrence risk prediction model in HER2-positive early breast cancer after HER2-targeted therapy. First Author: Qingyao Shang, National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China

Background: HER2-positive breast cancer patients treated with adjuvant targeted therapy, including trastuzumab or pertuzumab have demonstrated improved outcomes. However, a part of patients still experience recurrence despite targeted therapy. This study aims to develop a time-dependent model to predict recurrence risk in HER2-positive early breast cancer patients following targeted therapy, utilizing data from the APHINITY trial. **Methods:** The APHINITY trial included two arms: trastuzumab-only arm (n = 2,400) and trastuzumab + pertuzumab dual-target therapy arm (n = 2,404). Each group was randomly divided into training (70%) and validation (30%) cohorts, resulting in 3,363 patients in the training set and 1,441 patients in the validation set. The Cox proportional hazards model and two machine learning models, Random Survival Forest (RSF) and XGBoost (XGB), were used to predict invasive disease-free survival. Model performance was evaluated using Harrell`s C-index and area under the curve (AUC). **Results:** After selecting clinical variables provided by the APHINITY trial, 12 variables were included in the model training. The predictive performance of Cox model, RSF and XGB machine learning models was assessed. Among them, the RSF model demonstrated the best predictive effectiveness. In the training set, the RSF model achieved a C-index of 0.66, with AUCs of 0.78 for 1-year recurrence risk, 0.70 for 3-year recurrence risk, and 0.66 for 5-year recurrence risk. In the validation set, the RSF model achieved a C-index of 0.68, with AUCs of 0.79 for 1-year recurrence risk, 0.73 for 3-year recurrence risk, and 0.71 for 5-year recurrence risk. The XGB model performed slightly worse than RSF, and the machine learning methods significantly outperformed the Cox model. **Conclusions:** In this study, a time-dependent recurrence prediction model was established based on large-sample randomized controlled trial, demonstrating a favourable short-term recurrence prediction effect, which can serve as a clinical decision assistant for screening patients at high risk of recurrence for intensified adjuvant therapy or follow-up monitoring. Research Sponsor: None.

1036 Rapid Oral Abstract Session

Racial and ethnic disparities in clinical outcomes of HER2-positive metastatic breast cancer treated with antibody-drug conjugates: A TriNetX real-world evidence study. First Author: Zunairah Shah, Roswell Park Comprehensive Cancer Center, Buffalo, NY

Background: HER2-positive breast cancer (HER2+ BC) is an aggressive BC subtype driven by overexpression of the human epidermal growth factor receptor 2 (HER2). Antibody drug conjugates (ADCs), such as trastuzumab deruxtecan (T-DXd) and ado-trastuzumab emtansine (T-DM1), both approved for metastatic HER2+ BC, have significantly improved survival in this population. However, racial and ethnic disparities in outcomes with ADCs remain unclear. **Methods:** De-identified data from TriNetX, a global federated health research network, were analyzed for patients with metastatic HER2+ BC receiving HER2-directed ADCs. Kaplan-Meier analysis assessed overall survival. Statistical comparisons of survival rates between groups were made using log-rank tests. Propensity matching was used to adjust for age, comorbidities and lines of treatment. Two-sided P $\leq$0.05 was used to determine statistical significance. **Results:** A total 7,462 patients were included in this analysis. The median age was 56.2 years (range: 43-69), 68% were Non-Hispanic White (NHW), 17% Black, 5% Asian, and 10% Hispanic. 4,774 pts received TDM-1, 1,547 received T-DXd, and 1,141 received both. 37.6% patients treated with TDM-1 and 64.3% treated with T-DXd received $>$2 lines of prior therapy. Overall, the survival rate was 96% at 1 year, 89.3% at 3 years, and 83.7% at 5 years. At 3 years, the survival varied significantly by race: 90.3% in NHWs, 87.1% in Black, 92.9% in Asians, and 91.3% in Hispanics (p $<$ 0.001). Similar differences extended to 5 years: NHW 85.0%, Black 80.9%, Asian 89.5%, Hispanic 86.7% (p$<$0.001) (Table). Among patients receiving T-DM1, the 3-year survival rate was 71.9%, compared to 45.7% in the T-DXd cohort (p$<$0.05). After adjusting for age and comorbidities, there was no difference in survival between patients who received T-DXd and TDM1 (not including who received both) (HR 2.55 (95% CI: 2.20–2.96; p = 0.75). **Conclusions:** Our study shows better outcomes with use of ADCs in heavily pretreated metastatic HER2-BC, with 83.7% of patients surviving beyond 5 years. However, significant racial disparities were observed, with Asian patients showing the highest survival while Black patients had the poorest survival which could be due to multi-level factors. Future studies are needed to understand the underlying mechanisms behind this racial disparity in outcomes with HER2-directed ADCs to inform strategies to improve patient outcomes. Research Sponsor: None.

Survival rates and hazard ratios by race.

Race	3-year survival probability (%)	5-year survival probability (%)	Hazard Ratio
NHW	89.60	83.96	1.00
Black	86.90	80.30	1.33 (95% CI: 1.26–1.40)
Asian	92.26	88.92	0.69 (95% CI: 0.6–0.75)
Hispanic	91.20	86.27	0.89 (95% CI: 0.83–0.95)

NHW (Non-Hispanic White).

1037 Poster Session

Characterization of the immune microenvironment and spatial phenotypes across HER2 subtypes in advanced or metastatic breast cancer. First Author: Ayse A. Koksoy, The University of Texas MD Anderson Cancer Center, Houston, TX

Background: Breast cancer is defined by HER2 and hormone receptors (HR) status, which influence the clinical outcomes. HER2-positive has been traditionally defined as HER2 overexpression on immunohistochemistry (IHC score of 3+) or 2+ and *ERBB2* amplification on *in situ* hybridization (ISH). HER2^{low} (IHC 1+ or 2+ and non-amplified ISH) accounts for nearly half of tumors. There is a paucity of data regarding immune subpopulations and spatial phenotypes in HER2 subtypes. We have investigated the characteristics of tumor immune microenvironment contexture across HER2 groups (HER2$^+$ vs HER2^{low} vs HER2$^-$ (0 by IHC)) focusing tumor infiltrating lymphocytes (TIL) and on immune cell dynamics, including the distribution and spatial proximity to tumor cells to potentially inform treatment selection. **Methods:** Formalin-fixed paraffin-embedded (FFPE) samples of patients with metastatic breast cancer who had HER2 IHC/ISH testing according to ASCO-CAP guidelines were stained and analyzed using an 8-plex immunofluorescence (mIF) panel (CD3, CD8, CD69, FOXP3, Ki67, PD-L1, PD1, PanCK). For neighborhood analysis, samples with an area $>$ 2 mm^2 and a phenotypes density with $>$ 2 cells/mm² were considered. A novel spatial analysis method was used to quantify the Euclidian distance between tumor cells and surrounding immune cell populations. The clustering coefficient was used to determine the connectivity of immune cell node neighbors. These findings were analyzed in relation to the clinical characteristics. **Results:** Tumor and stromal compartment analysis was done on 44 FFPE samples (10 HER2$^-$, 19 HER2^{low}, and 15 HER2$^+$) with 84% collected from metastatic sites. HER2 status was not significantly associated HR status or overall TIL infiltration into the tumor compartment. The dominant TIL subset identified was non-regulatory CD3+ T cells as defined as CD3$^+$/FOXP3$^-$/CD8$^-$. HER2$^-$ samples were more associated with lack of PD-L1 expression on intratumoral myeloid cells and PD-L1 low expression on tumor cells as compared with HER2^{low} and HER2$^+$ (p = 0.06). For spatial analysis, 33 samples (6 HER2$^-$, 16 HER2^{low} and 11 HER2$^+$) were considered. Macrophages and proliferating tumor cells were more abundant in HER2$^-$ samples than HER2^{low} or HER2$^+$ (p = 0.006 and p-0.027, respectively). Median distances from tumor cells to macrophages and T_{regs} were shorter in HER2$^-$ cases compared to HER2I^{ow} (p $<$ 0.001). Although the clustering coefficient were similar between HER2 groups, HER2^{low} group clustered mostly around macrophages while HER2$^+$ group preferred cytotoxic T cells (CD8$^+$). **Conclusions:** The spatial organization and density of immune cells in the HER2^{low} and HER2$^+$ breast cancer microenvironment may provide insight into prognosis and guide therapeutic approaches for combination therapies and HER2-targeted immunotherapies. Research Sponsor: None.

1039 Poster Session

Risk of radiation necrosis with concurrent antibody-drug conjugates and radiotherapy in HER2-positive breast cancer with brain metastases: A meta-analysis. First Author: Zouina Sarfraz, Miami Cancer Institute, Baptist Health South Florida, Miami, FL

Background: Antibody-drug conjugates (ADCs) have transformed the outcomes of HER2-positive breast cancer (BC), particularly in patients with brain metastases (BM) due to the use of ADCs like trastuzumab emtansine (T-DM1) and trastuzumab deruxtecan (T-DXd), which have demonstrated intracranial efficacy. Radiotherapy (RT), especially stereotactic radiosurgery (SRS), remains a cornerstone for BM management. However, combining ADCs with RT may increase the risk of symptomatic radiation necrosis (SRN). This meta-analysis evaluates SRN outcomes in patients receiving concurrent (C-ADC) versus non-concurrent ADCs with RT (NC-ADC). **Methods:** A systematic search was performed in January 2025 across PubMed, Cochrane, and conference proceedings from ASCO, SNO, ESMO, and SABCS. Eligible studies included randomized controlled trials and cohort studies (CS) of C-ADC and NC-ADC in HER2-positive BC patients with BM. Studies reporting SRN rates or related outcomes were included. A random-effects model was used to calculate pooled proportions and risk ratios (RR) with 95% confidence intervals (CIs). Heterogeneity across studies was assessed using the I² statistic, with values of 0–25% considered low, 26–50% moderate, and greater than 50% high. **Results:** Out of 884 studies screened, 9 CS (N = 421) were included. The median age was 56.3 years (IQR: 49.8–57). Patients receiving prior intracranial RT was 41.28%, 19.28% underwent SRS, and 19.58% received prior whole brain radiotherapy (WBRT). The median time of C-ADC was 8.75 days (IQR: 8.0–18.0) and NC-ADC was 273.5 days (IQR: 225.75–327.75). The pooled proportion of SRN in the C-ADC group was 19.5% (95% CI: 9.2%–29.8%; I² = 39.19%, τ^2 = 0.0061, P = 0.1382) indicating moderate heterogeneity. NC-ADC group experienced a pooled SRN proportion of 6.9% (95% CI: 2.5%–11.2%; I² = 51.98%, τ^2 = 0.0014, P = 0.0089), signifying high heterogeneity. The pooled RR showed a significantly increased SRN risk in the C-ADC group (RR = 2.726, 95% CI: 1.454–5.109, P = 0.002). Heterogeneity for the pooled RR was negligible (I² = 0.0%, Q = 0.20, P = 0.977), indicating consistent findings across studies. **Conclusions:** C-ADC is associated with a significantly higher risk of SRN. This risk is concerning but must be balanced against potential improvements in local control and efficacy outcomes. Prospective studies are needed to optimize treatment schedule and sequences to minimize toxicity and optimize survival. Research Sponsor: None.

Meta-analytical findings.

Analysis/Measure	Effect Size	95% CI	I²	P-Value	Notes
Pooled Proportion (Overall)	0.110	0.050–0.169	76.53%	0.0003	High heterogeneity (τ^2=0.0047)
C-ADC Proportion	0.195	0.092–0.298	39.19%	0.0002	Moderate heterogeneity (τ^2=0.0061)
NC-ADC Proportion	0.069	0.025–0.112	51.98%	0.0021	High heterogeneity (τ^2=0.0014)
Risk Ratio (C-ADC vs. NC-ADC)	2.726	1.454–5.109	0.0%	0.002	No heterogeneity (τ^2=0.0000)

1040 Poster Session

Molecular and clinical insights of trastuzumab deruxtecan efficacy in advanced breast cancer (aBC). First Author: Elias Bou Farhat, Brigham and Women's Hospital, Boston, MA

Background: In aBC, trastuzumab deruxtecan (T-DXd) has demonstrated efficacy in HER2-positive, HER2-low, and HER2-ultralow disease subtypes. However, the impact of molecular markers on treatment outcomes requires further investigation, particularly in the context of HER2 status across biopsies, genetic alterations, and the tumor micro-environment (TME). **Methods:** We retrospectively analyzed 477 patients (pts) with aBC (DFCI = 369; Yale = 108) treated with T-DXd. HER2 immunohistochemistry (IHC) discordance was defined as a shift in HER2 status across the last two tumor samples prior to T-DXd (HER2 0 to 1, 2, or 3+ or vice versa). Concordance was defined as consistent HER2-0, HER2-low (1 or 2+) or HER2 3+ across samples. Outcomes included time-to-next treatment (TTNT) and overall survival (OS); multivariable Cox proportional hazards models were performed. Targeted tumor sequencing was conducted on 163 pts with aBC treated with T-DXd. TME analysis of 97 patients used machine learning on H&E slides to classify tumors as inflamed, desert, or altered. **Results:** Pts with discordant HER2 (n = 118, 25%) showed similar outcomes to those with concordant HER2-0 (n = 32) expression, both of which had significantly worse OS and TTNT compared to concordant HER2-low (both 1 or 2+) (n = 202) or HER2-3+ (n = 111) tumors (Table). *PTEN* mutations (mut; n=13) were associated with significantly shorter TTNT. *ERBB2* amplifications or gains (n= 31) correlated with improved outcomes. CDK12 deletions or loss (n = 14) were linked to poorer TTNT (Table). *PTEN* mut and *ERBB2* amplifications were predictive of outcomes with T-DXd, as neither alteration was associated with TTNT in pts receiving non-T-DXd first-line systemic therapy. Tumors with inflamed TME had the worst outcomes, followed by deserts and altered TMEs (Table). **Conclusions:** We identify favorable biomarkers of T-DXd efficacy in aBC, including concordant HER2-low or HER2-3+ status, absence of PTEN mut, and an altered or desert TME. These findings require validation to refine treatment strategies across HER2-driven malignancies. Research Sponsor: None.

	OS T-DXd: HR (95% CI)	p/q-value	TTNT T-DXd: HR (95% CI)	p/q-value	TTNT 1st Line: HR (95% CI)	p/q-value
Concordant HER2-0 (n = 32) vs discordant (n = 118)	1.07 (0.65-1.75)	0.789	1.17 (0.76-1.79)	0.474	-	-
Concordant HER2-low (n = 202) vs discordant	0.67 (0.49-0.92)	0.012	0.65 (0.50-0.85)	0.002	-	-
Concordant HER2-3+ (n = 111) vs discordant	0.23 (0.14-0.38)	< 0.001	0.27 (9.18-0.4)	< 0.001	-	-
PTEN mutations (n = 13) vs wild-type (WT) tumors (n =150)	-	-	2.20 (1.20-4.0)	0.068	0.99 (0.76-1.35)	0.93
ERBB2 amplifications/gains (n = 31) vs ERBB2 WT (n = 132)	0.43 (0.26-0.72)	0.045	-	-	1.1 (0.77 - 1.71)	0.51
CDK12 loss/deletions (n = 14) vs CDK12 WT (n = 116)	-	-	2.56 (1.39-4.76)	0.014	1.42 (1.04-1.86)	0.016
Altered (n = 28) vs Desert (n = 34)	0.58 (0.26-1.30)	0.18	0.97 (0.52-1.80	0.91	-	-
Inflamed (n = 35) vs Desert (n = 34)	2.21 (1.20-4.05)	0.011	2.13 (1.21-3.74)	0.0084	-	-

1041 Poster Session

Transcriptomic biomarkers of therapeutic response to antibody-drug conjugates in metastatic breast cancer: A comprehensive multi-center study. First Author: Samer Alkassis, UCLA Health Jonsson Comprehensive Cancer Center, Los Angeles, CA

Background: The three antibody-drug conjugates (ADCs) — sacituzumab govitecan (SG), trastuzumab deruxtecan (T-DXd), and trastuzumab emtansine (T-DM1) — that are FDA-approved for treatment of metastatic breast cancer (MBC) have markedly improved patient outcomes. However, most patients with MBC treated with ADCs ultimately have disease progression via either primary or acquired ADC resistance. Here, we characterized the transcriptomic profile of drug efflux genes in MBC prior to ADC treatment (tx) to elucidate biomarkers of response and resistance to SG, T-Dxd, and T-DM1. **Methods:** We analyzed the transcriptomic tumor profile of six drug efflux pump genes (*ABCB1*, *ABCC1-4*, *ABCG2*) generated from pre-tx biopsies collected from patients with MBC (N = 453; 36% TNBC, 26% HR+/HER2-, 20.5% HER2+, 19% NOS) 1 year prior to or up to 15 days post-tx with SG (n = 204), T-DXd (n = 178), or T-DM1 (n = 71). RNA-sequencing data were generated and processed with the Tempus xR assay. The correlation between duration of treatment (DoT) and gene expression was tested for all genes of interest using Pearson's correlation coefficient. Cox proportional hazards models with risk set adjustment were used to test for associations between pre-tx gene expression and overall survival (OS), where gene expression was modeled as a continuous linear predictor. The proportional hazards assumption for OS was tested, and Cox modeling results were omitted when evidence of non-proportional hazards was detected. Given the exploratory nature of the analyses, all p-values are uncorrected and nominal statistical significance was set at $p < 0.05$. **Results:** This diverse cohort had a median age of 52 and a range of races (55% White, 14% Black, 7.1% Other, 24% Unknown). Median DoT across all patients was 130 days. Higher expression of drug efflux pump genes was associated with shorter DoT for T-DXd (*ABCB1*: -0.290, p = 0.017; *ABCC1*: -0.274, p = 0.025). Additionally, higher expression of *ABCB1* was associated with worse OS for T-DXd (HR: 1.30, 95% CI: 1.10 - 1.53, p = 0.002). In the SG cohort, no significant associations between efflux pump expression and DoT were found, but higher pre-tx *ABCC1* and *ABCC4* gene expression was associated with worse OS (HR: 1.34, 95% CI: 1.02-1.75, p = 0.034; HR:1.19, 95%CI: 1.00-1.41, p = 0.042). In the T-DM1 cohort, no significant associations were found between efflux pump gene expression and DoT or OS. **Conclusions:** Multi-modal analysis identified drug efflux pump gene expression as a potential biomarker of resistance, primarily to T-DXd. These findings should be further validated, and combinatorial clinical trial strategies may be explored. Research Sponsor: Tempus AI, Inc.

1042 Poster Session

Integrating dynamic analysis of serial ctDNA testing to enhance diagnostic and prognostic assessments in patients with metastatic breast cancer. First Author: Qiang Zhang, Department of Medicine, Division of Hematology and Oncology, CTC Core Facility, Robert H. Lurie Comprehensive Cancer Center, Northwestern University, Chicago, IL

Background: The monitoring of circulating tumor DNA (ctDNA) in patient with metastatic breast cancer (MBC) plays a critical role in predicting therapy resistance, metastasis, and prognosis. Our previous studies have highlighted the importance of dynamic ctDNA analysis correlated with treatment resistance and prognosis in MBC (ASCO 2022 (#1057), AACR 2023 (#1031), and CCR Zhang Q., 2024). Here, we report that multivariable analysis of ctDNA mutations including P53, Myc, and BRAF, provides a significantly greater prognostic impact on survival. **Methods:** This study included 391 MBC patients who received systemic treatment between 2016 and 2022 (IRB-approved non-interventional trial, NU16B06) at the Robert H. Lurie Cancer Center, Northwestern University. Blood samples (15 ml each) were collected from patients at 3 time points: before treatment, and 3 and 6 months after treatment. Plasma ctDNA was analyzed by Guardant 360 using NGS for a 74-gene panel. The median follow-up was 26.6 months since enrollment. Causal Inference-Ensemble Learning was used for statistical analyses. **Results:** Among 391 patients (54.4% Luminal-like, 17.7% HER2-positive, 27.9% Triple-negative), the most common ctDNA mutations were $TP53^{Mut}$ (160 patients, 40.92%), $PIK3CA^{Mut}$ (39 patients, 29.4%), and Myc^{Mut} (53 patients, 13.55%) at any time point. Other notable mutations included $HER2^{Mut}$ (49 patients, 12.5%), $FGFR1^{Mut}$ (45 patients, 11.5%), $PTEN^{Mut}$ (39 patients, 9.9%), and $BRAF^{Mut}$ (35 patients, 8.95%). Less frequent mutations were $FGFR2^{Mut}$ (13 patients, 3.3%), $MAPK^{Mut}$ (8 patients, 2.0%), $BRCA1^{Mut}$ (20 patients, 5.1%), $BRCA2^{Mut}$ (17 patients, 4.3%), and $CDH1^{Mut}$ (21 patients, 5.37%). Patients in mutation groups showed significantly shorter median overall survival (OS) compared to wild-type groups: $TP53^{Mut}$ vs $TP53^{WT}$, Hazard Ratio (HR) = 1.91 (P = 0.0002); Myc^{Mut} vs Myc^{WT}, HR = 3.24 ($P < 0.0001$); and $BRAF^{Mut}$ vs $BRAF^{WT}$, HR = 2.45 (P = 0.007). No significant correlations were found between other gene mutations and OS. Analysis of multiple ctDNA mutations (TP53, Myc, and BRAF) revealed significant prognostic differences. Cohort 1 (no mutations, 231 patients) had a significantly longer median OS of 32.2 months compared to 20.5 months in cohort 2 (at least one mutation, 119 patients) and 15.3 months in cohort 3 (two or more mutations, 59 patients). Cohort 3 exhibited the worst prognosis compared to both cohort 1 and cohort 2 (Chi-square = 13.3, P = 0.0003). These findings suggest that combined analysis of ctDNA mutations enhances the ability to predict prognosis. **Conclusions:** In this study, we identified multiple ctDNA mutations during long-term follow-up, which are associated with prognosis. The synergy of multivariable analysis of ctDNA mutations during treatment enhances the role of single ctDNA alterations in monitoring metastatic prognosis, thereby supporting clinical decision-making. Research Sponsor: Robert H Lurie Cancer Center, Northwestern University.

1043 Poster Session

***TP53* genomic alterations including targetable *TP53* Y220C mutation in clinically advanced breast cancer.** First Author: Nicole Casasanta, Yale Cancer Center, Yale School of Medicine, New Haven, CT

Background: Recent studies demonstrating the ability of drugs such as Rezatapopt to target the *TP53* Y220C mutation motivated us to assess the *TP53* mutation landscape in clinically advanced breast cancer (CABC). **Methods:** FFPE blocks of 23,760 CABC were analyzed by hybrid capture-based comprehensive genomic profiling that evaluated broad types of genomic alterations (GA) including mutations, amplifications, deletions, and fusions. MSI-high (MSI-H) status, tumor mutational burden (TMB), genomic ancestry, mutational signature, and homologous recombination deficiency signature (HRDsig) were determined from sequencing data. PD-L1 expression was determined by IHC (Dako 22C3, TPS scoring system). GA were compared using Fisher's exact test with the Benjamini-Hochberg multiplicity adjustment. **Results:** Among analyzed cases of CABC, 12,653 (53%) had *TP53* GA and 254 (1.1%) were the Y220C mutation. When compared with *TP53* wild type (wt) cases, *TP53* GA group were younger (56 vs 60 years; $p < .0001$) and had a higher median GA (6 vs 5; $p < .0001$). Both *TP53* Y220C group (15.7% vs 11.2%; not significant [NS]) and *TP53* non-Y220C group (18.3% vs 11.2%; $p < .0001$) were more frequently of African genetic ancestry than *TP53*wt group. The *TP53* non-Y220C had significantly less European (*TP53* non-Y220C: 65.2% vs 74.7%; $p < .0001$) genetic ancestries. MSI-H was rare in all groups, but slightly higher in *TP53* Y220C than *TP53*wt cases (1.7% vs 0.3%; p = .036). Median TMB was low for all groups (range 2.41-2.61; NS). An APOBEC genomic signature was more common in *TP53* non-Y220C mutant than *TP53*wt (6.2% vs 5.0%; p = .0002) but not in *TP53* Y220C (4.3% vs 5.0%; NS). GA more frequent in *TP53* Y220C and non-Y220C groups versus *TP53*wt included *BRCA1*, *ERBB2*, *PTEN*, and *RB1*. GA more frequent in the *TP53*wt group included *BRCA2*, *CCND1*, *CDH1*, *ESR1*, and *PIK3CA*. More *TP53* Y220C than *TP53* non-Y220C mutant cancers had *CDH1* mutations (6.3% vs 2.8%; NS) suggesting the Y220C GA may be more frequent in lobular carcinomas. **Conclusions:** *TP53* Y220C is a relatively rare event in CABC. The *TP53* mutant group was associated with GA in tumor suppressor genes, including *BRCA1*, *PTEN*, and *RB1*, whereas the *TP53*wt group was associated with GA in pathways associated with endocrine resistance, including *PIK3CA* and *ESR1*. Research Sponsor: None.

	*TP53*wt (N=11107)	Y220Cmut (N=254)	P-value†	*TP53* wt (N=11107)	*TP53* non-Y220Cmut (N=12399)	P-value†	*TP53* Y220Cmut (N=254)	*TP53* non-Y220Cmut (N=12399)	P-value†
BRCA1	1.4%	7.5%	<.0001	1.4%	6.0%	<.0001	7.5%	6.0%	NS
BRCA2	5.2%	4.7%	NS	5.2%	3.6%	<.0001	4.7%	3.6%	NS
CCND1	24.3%	7.5%	<.0001	24.3%	11.3%	<.0001	7.5%	11.3%	NS
CDH1	23.8%	2.8%	<.0001	23.8%	6.3%	<.0001	2.8%	6.3%	NS
ERBB2	10.1%	16.5%	0.003	10.1%	13.5%	<.0001	16.5%	13.5%	NS
ESR1	11.5%	3.1%	<.0001	11.5%	4.2%	<.0001	3.1%	4.2%	NS
PIK3CA	44.3%	23.6%	<.0001	44.3%	28.2%	<.0001	23.6%	28.2%	NS
PTEN	9.4%	18.9%	<.0001	9.4%	15.4%	<.0001	18.9%	15.4%	NS
RB1	2.6%	10.6%	<.0001	2.6%	11.8%	<.0001	10.6%	11.8%	NS

†Benjamini/Hochberg adjustment.

1044 Poster Session

Comprehensive results of ESG401, a TROP2-targeting ADC: Updated phase 1 analysis in advanced solid tumors. First Author: Fei Ma, Cancer Hospital Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China

Background: ESG401 is a novel ADC comprising a humanized anti-TROP2 IgG1 monoclonal antibody conjugated to the Topoisomerase I inhibitor SN-38 via a stable cleavable linker. ESG401-101 is a phase 1, open-label, dose-escalation (1a) and dose-expansion(1b) study evaluating the safety and antitumor activity of ESG401 in advanced solid tumors. This report summarizes the comprehensive phase 1 results. **Methods:** Patients (pts) aged 18–75 years with locally advanced/metastatic solid tumors received ESG401 until unacceptable toxicity, progressive disease, or consent withdrawal. Phase 1a results (n = 40) have been reported previously. Phase Ib comprised three parallel cohorts: late-stage TNBC, late-stage HR+/HER2-, and first-line TNBC. **Results:** As of Oct 23, 2024, 156 pts were enrolled at 13 sites across China (40 in 1a; 116 in 1b). Most pts had metastatic HR+/HER2-BC (n = 65; median prior lines: 3; range: 1–10), followed by late-line TNBC (n = 47; median prior lines: 3; range: 1–12), first-line TNBC (n = 40), HER2+BC (n = 2), and one case each of endometrial cancer (EC) and adenoid cystic carcinoma (ACC). All pts had distant metastases at baseline; 13%, 57%, and 54% had brain, liver, and lung metastases, respectively. ESG401 demonstrated efficacy in pts with solid tumor(Table), including those with brain metastases. The safety profile remained consistent with no new or unexpected signals. The most common any-grade TEAEs were leukopenia, neutropenia, anemia, nausea, and vomiting. Grade ≥3 TRAEs were primarily neutropenia and leukopenia, none leading to permanent discontinuation. TRAEs led to delayed dosing, dose reduction, and discontinuation in 38.5%, 7.1%, and 2.6% of pts, respectively. **Conclusions:** ESG401 demonstrated favorable safety and efficacy benefits due to its enhanced linker, showing good safety and promising antitumor activity in advanced solid tumors across settings. These results warrant further clinical investigation. Clinical trial information: NCT04892342. Research Sponsor: Shanghai Escugen Biotechnology Co., Ltd.

	Late-line					First-line
	HR+/HER2−BC	TNBC	HER2+BC	EC	ACC	TNBC
n	58	37	2	1	1	35
ORR% (95% CI)	34.5 (22.5, 48.1)	35.1 (20.2, 52.5)	0	0	0	83.0 (66.4, 93.4)
DCR% (95% CI)	77.6 (64.7, 87.5)	62.2 (44.8, 77.5	100	100	100	100 (90.0, -)
mPFS Mons (95% CI)	7.4 (4.0, 9.2)	3.7 (2.1, 4.9)	3.8, 21.3[a]	8.3 [b]	3.7 [b]	NR
mDOR Mons (95% CI)	6.6 (4.6, 14.2)	4.5 (3.1, 13.6)	NA	NA	NA	NR

[a]The actual value for these two patients is listed.
[b]The actual value for one patient is listed.
NA, not applicable. NR, not reached.

1045 Poster Session

Effect of ERBB2 activating mutations on enhanced internalization and activity of trastuzumab deruxtecan in HER2-non-amplified metastatic breast cancer. First Author: Nicholas Mai, Memorial Sloan Kettering Cancer Center, New York, NY

Background: Trastuzumab Deruxtecan (T-DXd) is a HER2-targeting antibody drug conjugate approved for the treatment of HER2 low metastatic breast cancer (MBC). Whether HER2 activating mutations define a distinct clinical subset within HER2 low MBC is unknown. Here we present a single institution retrospective study of patients treated with T-DXd and report real world progression free survival (PFS), in patients with mutant vs. wild type (wt) HER2. We further modeled the impact of various HER2 mutations on T-DXd internalization and activity preclinically to characterize mechanistic and mutation-specific differences. **Methods:** All patients who had received T-DXd for HER2-low and HER2-null MBC at Memorial Sloan Kettering Cancer Center were eligible for inclusion. Clinicopathologic data were abstracted from patient records. PFS was determined clinically and calculated using the Kaplan-Meier method. Univariable and multivariable associations between PFS and patient characteristics were assessed using Cox-proportional hazards models. *ERBB2* mutations were modeled in breast cell lines and examined for kinetics of fluorescence-labeled T-DXd cell internalization and potency of T-DXd antitumor effects. **Results:** We found 278 patients who received T-DXd for HER2 non-amplified MBC. Thirty-one had triple negative breast cancer and 247 had estrogen receptor positive MBC. Median age was 59 and TDXd was the median 6th line of systemic treatment for MBC. Median PFS for all patients was 6.97 months (95%CI 5.73-8.4). *ERBB2* mutations were found in 23 (8.2%) patients on genomic sequencing via MSK-IMPACT. Among mutations, 20 were known oncogenic mutations per OncoKB (eg D769Y, L755S, S310F, V777L), while 3 were variants of unknown significance (L35R, P378L, R1169K). *ERBB2* activating mutations were significantly associated with prolonged T-DXd PFS; median 6.28 months in the wt population vs 10.58 months with an *ERBB2* mutation (HR 0.55, 95%CI 0.31-0.98, p = 0.04). After adjusting for age, treatment line, and ER status, *ERBB2* mutations were independently associated with longer PFS. Among patients with *ERBB2* activating mutations, 9 had HER2 IHC 0 disease, while the remaining 14 were at least HER2 IHC 1+. There was no statistically significant difference in PFS between patients with HER2 IHC 0 vs 1+ (HR 1.74, 95%CI 0.53-5.7, p = 0.35) among those with *ERBB2* mutations. Finally, expression of the most common *ERBB2* mutants in MCF10A cells lead to more rapid internalization of labeled TDX-d into cells and lower IC50 for inhibition of proliferation. **Conclusions:** *ERBB2* activating mutations are associated with longer T-DXd PFS in HER2-non-amplified MBC, even when HER2 IHC was 0, likely due to enhanced ADC internalization. The data imply that *ERBB2* mutant breast cancers may be uniquely sensitive to T-DXd, independent of HER2 expression levels. Research Sponsor: National Cancer Institute; CA009512-34A1; Brian Piccolo Cancer Research Fund; Sussman Family Fund.

1046 Poster Session

Differences in genomic profiles, targeted treatment use, and overall survival in patients with metastatic breast cancer by Area Deprivation Index. First Author: Emily L. Podany, Washington University in St. Louis, St. Louis, MO

Background: We previously showed racial differences in circulating tumor DNA (ctDNA) profiles and PI3K inhibitor (PI3Ki) use in patients (pts) with metastatic breast cancer (mBC); however, these findings may be influenced by socioeconomic disadvantage. A validated measure to explore this is the Neighborhood Atlas Area Deprivation Index (ADI, Kind et al NEJM 2018), which includes 17 measures of neighborhood disadvantage such as poverty, employment, and education. We sought to determine differences in genomic profiles, PI3Ki use, and overall survival (OS) in pts with mBC by ADI. **Methods:** This retrospective cohort study analyzed 1127 pts with mBC and ctDNA testing using the Guardant360 assay who were treated at Washington University in St. Louis (N = 634), Massachusetts General Hospital (N = 313), Weill Cornell (N = 109), and Northwestern University (N = 71). 9-digit zip codes were converted into national ADI ranks (0-100) divided into high deprivation (HDep, rank ≥60) and low deprivation (LDep, rank < 60) groups based on prior studies. Multivariate models were designed to determine genomic and prognostic differences by ADI. Pts with *PIK3CA* mutations were evaluated by ADI and use of PI3Ki in the second line or beyond, either through clinical trial enrollment or after FDA approval. OS from time of first ctDNA test was stratified by ADI and self-reported race. **Results:** The cohort included 165 Black pts (14.6%) and 335 pts (29.7%) from HDep zip codes. Black pts were more likely to be from HDep areas (Odds ratio [OR] 3.82, 95% confidence interval [CI] 2.62-5.57, P < 0.001). There were no differences in mBC subtype between ADI groups. Pts with HR+ HER2- mBC in the HDep group were significantly less likely to receive PI3Ki vs LDep (8/46, 17.4% vs 33/90, 36.7%, P = 0.02) despite equal incidence of *PIK3CA* mutations. Pts in the HDep group were more likely to have *TP53* single nucleotide variants (snv) (OR 1.58, 95% CI 1.18-2.10, P = 0.002) and less likely to have *AKT1* snv (OR 0.29, 95% CI 0.11-0.80, P = 0.017). Among pts in the HDep group, worse prognosis was seen in pts who self-identified as Black (hazard ratio [HR]1.51, 95% CI 1.02-2.25, P = 0.04), had *PIK3CA* snv (HR 1.73, 95% CI 1.23-2.44, P = 0.002), or *TP53* snv (HR 1.56, 95% CI 1.12-2.17, P = 0.009). Median OS was significantly shorter in the HDep vs LDep group (24 months [mos] vs 28 mos, P = 0.04) and significantly lower for Black pts in the HDep vs Black pts with LDep or White pts with HDep or LDep (15 mos vs 25-28 mos, P = 0.02). **Conclusions:** In this multi-institutional cohort, we identified significant disparities in the use of PI3Ki in HDep neighborhoods and higher rates of *TP53* snv, which are associated with aggressive tumor biology. Pts with mBC in HDep areas, especially Black pts, had shorter OS. Further research is needed to validate these findings, determine the root causes of these disparities, and implement change to achieve equity in precision medicine use. Research Sponsor: None.

1047 Poster Session

Dissecting primary endocrine resistance through ctDNA profiling of a hybrid real-world and clinical trial dataset in hormone receptor-positive, HER2-negative (HR+/HER2-) metastatic breast cancer (MBC). First Author: Lorenzo Gerratana, Department of Medical Oncology, Centro di Riferimento Oncologico di Aviano (CRO), IRCCS, Aviano, Italy

Background: New targeted therapies, including novel endocrine agents and antibody drug conjugates, are revolutionizing the treatment of HR+/HER2- metastatic breast cancer (MBC). However, questions surrounding primary and secondary endocrine resistance (R1 and R2, respectively) still hinder the development of personalized treatment strategies. This study aimed to investigate R1 by leveraging liquid biopsy in a hybrid real-world and clinical trial dataset. **Methods:** This study used the nationwide (US-based) deidentified Flatiron Health-Foundation Medicine MBC clinicogenomic database (FH-FMI CGDB), comprising data originated from ~280 US cancer clinics (~800 sites of care), and analyzed a cohort of 855 patients (pts) profiled through the FoundationOne Liquid CDx NGS panel, combining it with the first 65 pts enrolled in the GIM-24-PalboBP study (NCT04318223). R1 was defined as 1-line PFS of < 6 months. A 1:3 Propensity Score Matching was applied to balance key factors (i.e. age, ECOG performance status, visceral, lymph node, multiple metastasis, type of CDK6/4i). Pathogenic alterations with a > 10% prevalence were tested singularly and according to oncogenic pathways based on Sanchez-Vega F et al, Cell. 2018. Associations between ctDNA alterations, R1, and R2 were assessed using logistic regression, while prognosis was evaluated through Cox regression. **Results:** A set of 528 pts (respectively 132 and 396 for R1 and R2) was selected from the original cohort of 855 pts. Top detected alterations were PIK3CA SNV (46%), TP53 SNV (33%) and ESR1 SNV (24%). R1 was associated with TP53 SNV (OR = 2.30, P < 0.001), CCND1, FGF19, FGF3 and FGF4 CNVs (respectively OR = 1.75, P = 0.018; OR = 1.62, P = 0.044; OR = 1.80, P = 0.015; OR = 1.73, P = 0.024). On the other hand, ESR1 SNV was associated with R2 (OR = 0.47, P = 0.005). CCND1, FGF19, FGF3 and FGF4 CNVs were significantly co-occurring (P < 0.001) and located in the chromosome (chr) 11q13.3 region. In multivariable analysis, TP53 SNV, ESR1 SNV and chr11q13.3 CNV maintained their association with R1 (respectively OR = 2.22, P < 0.001; OR = 0.47, P = 0.006 and OR = 1.94, P = 0.006). Pathway analysis was consistent, showing a significant association between R1 and SNVs in the P53 and in the ER pathways (respectively OR = 1.92, P = 0.002; OR = 0.58, P = 0.024) and CNVs in the cell cycle pathway (OR = 2.18, P = 0.001). No differences were observed for 2-line (PFS2) across R1 and R2 (median PFS2 8.89 vs 8.03 months P = 0.589). Chemotherapy was prevalent in the R1 group (35% vs 15%). Within pts receiving 2-line endocrine therapy, TP53 SNV was the only prognostic factor in R1 (HR = 2.02, P = 0.008), while SNVs in TP53 and ESR1 had an impact on PFS2 in R2 (respectively HR = 1.50, P = 0.003 and HR = 1.45, P = 0.008). **Conclusions:** This study confirms TP53 and ESR1 as key factors for R1 and R2, respectively, with ESR1 showing a prognostic impact on PFS2 in R2 only. Additionally, chr11q13.3 emerges as a new candidate region for R1. These results provide critical data for both decision making and 2-line clinical trial design. Research Sponsor: None.

1048 **Poster Session**

Genomic alterations (GAs) associated with durability of benefit from trastuzumab deruxtecan (T-DXd), trastuzumab emtansine (T-DM1) and sacituzumab govitecan (SG) in metastatic breast cancer (MBC). First Author: Tess A. O'Meara, Dana-Farber Cancer Institute, Boston, MA

Background: Predictive biomarkers are needed to guide use of T-DXd, T-DM1 and SG in MBC. We used real-world comprehensive genomic profiling (CGP) of tumor tissue and circulating tumor DNA (ctDNA) to describe pre- and post-treatment somatic GAs in patients receiving these antibody-drug conjugates (ADCs) and evaluated the predictive value of *ERBB2* amplification (*ERBB2*amp) in MBC treated with T-DXd and T-DM1. **Methods:** MBC patients with FoundationOne CDx or FoundationOne Liquid CDx who received T-DXd, T-DM1 or SG monotherapy were included. Clinical data originated from 280 cancer clinics (~800 sites of care) between 1/2011-4/2024 included in the US-wide deidentified Flatiron Health-Foundation Medicine MBC clinicogenomic database. For each ADC and MBC subtype, we characterized the GA profile of pre-ADC samples. Pre- and post-treatment GAs were then compared by chi-square, adjusted for multiple comparisons. For patients who received T-DXd or T-DM1, time to next treatment (TTNT) was compared between patients with or without *ERBB2*amp by tissue CGP by Cox models, adjusted for age, ECOG status, HR status, and line of therapy. **Results:** We identified 1,177 pre-ADC samples (n = 972 tissue, n = 205 liquid biopsy; T-DXd n = 492, T-DM1 n = 167, SG n = 518). *TP53* (59.7%), *PIK3CA* (34.4%), and *ERBB2* (20.6%) were most commonly altered across all samples. Median TTNT for T-DXd in HER2+ MBC (n = 106) was 16.6 mo; *ERBB2* alterations were present in 84.6% of cases above the median vs 47.5% below. Median TTNT for cases with somatic *BRCA1/2* mutations (n = 6) was 8.48 mo vs 18 mo for *BRCA1/2* wildtype. Formal statistical analyses of baseline GAs and associations with TTNT on each ADC will be presented at the conference. GAs in *ATM* (24% vs 3.7%, $p < 0.0001$), *GNAS* (6% vs 2%, $p < 0.0001$), *EGFR* (4% vs 0.2%, $p < 0.01$) and *ERCC4* (2% vs 0, p = 0.02) were more prevalent in samples post-T-DXd (n = 50, 15 tissue/35 liquid) vs pre-T-DXd (n = 492, 378 tissue/114 liquid). GAs in *ERCC4* (3.3% vs. 0, p = 0.001) were more prevalent in samples post-SG (n = 60, 31 tissue/29 liquid) vs pre-SG (n = 518, 439 tissue/79 liquid). HER2+ MBC with *ERBB2*amp by CGP (n = 54) had more favorable TTNT on T-DXd vs non-amplified HER2+ (n = 30; 22.5 vs 6.4 mo, HR 0.10, 95% CI 0.04-0.24, $p < 0.0001$). HER2-low MBC with *ERBB2*amp by CGP (n = 6) had more favorable TTNT on T-DXd vs non-amplified HER2-low (n = 263; NR vs 7.4 mo, HR 0.22, 95% CI 0.05-0.90, p = 0.035). HER2+ MBC with *ERBB2*amp by CGP (n = 102) had more favorable TTNT on T-DM1 vs non-amplified HER2+ (n = 45; 8.3 vs 2.6 mo, HR 0.50, 95% CI 0.33-0.75, $p < 0.001$). **Conclusions:** This real-world analysis provides insight into baseline GAs and associations with TTNT on T-DXd, T-DM1 and SG in MBC as well as GAs that emerge on treatment. *ERBB2*amp by CGP carried additional predictive value to IHC/FISH HER2 status in both HER2+ and HER2-low MBC treated with T-DXd and HER2+ MBC treated with T-DM1. Research Sponsor: None.

1049 **Poster Session**

Macroscale genomic alterations in histomolecular invasive lobular carcinoma compared to other breast cancer subtypes. First Author: Jason A. Mouabbi, The University of Texas MD Anderson Cancer Center, Houston, TX

Background: Although invasive lobular carcinoma (ILC) is often classified as a separate breast cancer (BC) subtype with distinct molecular features, options for diagnosis and treatment remain similar to other BCs. Using an integrated histomolecular approach to classify 617 BC samples into either histomolecular ILC (hmILC) or histomolecular no special type (hmNST) subsets, we compared their macroscale genomic alterations to describe biological traits of the ILC BC subtype, which may lead to improved approaches in BC therapies. **Methods:** A total of 617 BC FFPE samples were subject to whole-exome and bulk RNA sequencing analysis. hmILC subset was defined based on CDH1 truncation/deletion or low CDH1 expression (z-score $< -2.5\times$MAD), while all other samples were classified as hmNST. Copy number variations (CNVs) were assessed using Sequenza to detect recurrent amplifications/gains and deletions; homologous recombination deficiency (HRD) scores were calculated based on large-scale state transitions and loss-of-heterozygosity events; tumor mutational burden (TMB) scores were evaluated as percent of mutations per megabase; and mutational signatures were deconvoluted using maftools R package. **Results:** Genome-wide CNV analysis revealed distinct patterns in hmILC compared to hmNST. hmILC showed hallmark deletions at regions harboring *CDH1* (16q), while gains were observed significantly more frequently at regions harboring *FCGR3A* (1q) compared to hmNST. Elevated APOBEC activation signature expression was found in 32% hmILC vs. 19% hmNST samples (p = 0.002, chi-squared test). HRD-positive cases were less frequent in the hmILC subset (25%) compared to hmNST (42%) (p = 0.001). In contrast, hmILC tumors more frequently demonstrated high TMB scores compared to hmNST (10% vs. 2%, p = 0.0003). Moreover, TMB-positive hmILC samples were mostly HRD-negative.Genetic alterations in genes like *FANCA*, *FANCD2* and *PALB2* were more frequently enriched in hmILC tumors compared to hmNST ($p < 0.1$). Furthermore, hmILC subset with high HRD scores frequently harbored additional DNA repair gene mutations (e.g., *BRCA2*) compared to the subset with low HRD scores (p = 0.02). **Conclusions:** This study revealed macroscale genomic alterations, such as unique CNV patterns, altered distributions of HRD- and TMB-positive cases and increased APOBEC-driven mutational processes, in the hmILC BC subset. These distinct genomic architectures highlight the need for innovative trials using inhibitors of DNA repair and related pathways for hmILC BC patients, particularly in those with high HRD-high tumors. Research Sponsor: None.

1050 **Poster Session**

Landscape analysis of proteins in the development of breast cancer brain metastasis. First Author: Dongyan Xu, The Second Affiliated Hospital, Zhejiang University School of Medicine, Hangzhou, China

Background: Breast cancer brain metastasis(BCBM) is a major cause of mortality in advanced breast cancer patients, and treatment options are limited. In this project, we investigated the proteomic landscape of primary breast cancer and brain metastasis. **Methods:** We conducted high-throughput proteomic analysis on primary and brain metastatic breast cancer tissues surgically resected from 21 patients. Following screening and sample processing using pressure cycle technology (PCT) for peptide extraction, we used the data-independent acquisition (DIA) mass spectrometry (MS) method to acquire the data. Additionally, we used biological function assays, co-culture experiments, and transcriptome sequencing analysis to further investigate the differentially expressed proteins. **Results:** Patients were mostly in clinical stage II, with two excluded from analysis due to no surgery. Breast cancer classifications included 47.6% HER2+/HR-, 28.6% HER2+/HR+, 9% HER2-/HR+, and 14.3% TNBC. All patients received chemotherapy, with 57% undergoing neoadjuvant therapy and 12 receiving targeted therapy (all with trastuzumab). A total of 9430 protein groups were identified, with 692 showing differential expression in BCBM. Notably upregulated proteins included CRYAB, GFAP, STXBP1 and significantly downregulated proteins included CACNA1A, AOC3, PMP2, OGN. Most differentially expressed proteins were involved in extracellular matrix (ECM) and cell-cell interactions, with collagen family proteins (e.g., COL14A1, COL22A1) playing key roles in BCBM. HER2+ BCBM was associated with ECM pathways, while TNBC impacted the immune microenvironment. Regardless of the subtype, we identified 11 proteins that collectively contribute to the development of BCBM, including CRYAB, ATP6V0A1, HLA-DQB1, TPM2, SERPINB9, NFATC2, GRAP, ALDH1L2, DHRS4L2, SEPTIN1 and SAMHD1. We found that high ACOX1 and low KRT9/KRT14 expression were linked to poor prognosis in BCBM. Analyzing whether patients had undergone targeted therapy, we found that resistance might be acquired through the oxidative phosphorylation pathway, promoting brain metastasis in HER2+ breast cancer. Interestingly, CRYAB expression was prominent across all subtypes of BCBM and targeted therapy groups, suggesting it may serve as an essential biomarker for BCBM. We have confirmed that CRYAB can promote the proliferation and migration of HER2+BCBM, and preliminarily verified that CRYAB is closely related to immune infiltration through CXCL5, CXCL8 and CCL3 in tumor microenvironment, which may promote the occurrence of HER2+BCBM by affecting the NF-κB pathway. **Conclusions:** Leveraging high-throughput proteomics, we present a detailed analysis that elucidates the biological processes involved in developing and progressing BCBM from multiple angles. This work offers new directions for early prediction, treatment, and prognosis of BCBM in clinical practice. Research Sponsor: National Natural Science Foundation of China; 81602716.

1051 **Poster Session**

Evaluation of tumor immune microenvironment in Hispanic and African American breast cancer. First Author: Robert Hsu, Norris Comprehensive Cancer Center, University of Southern California, Los Angeles, CA

Background: Hispanics or Latinos (HL) and African Americans or Black (AA) have a higher prevalence of advanced-stage breast cancer (BC) at diagnosis compared to Non-Hispanic Whites (NHW). To understand the role of immune system, we evaluated the tumor immune microenvironment (TIME) by race/ethnicity among HL, AA, and NHW BC patients. **Methods:** 15544BC samples were tested by NGS (592, NextSeq; WES, NovaSeq) and WTS (NovaSeq; Caris Life Sciences, Phoenix, AZ). Race/ethnicity data is self-reported. Immune cell were estimated using WTS deconvolution (Quantiseq). Gene expression profiles were analyzed for T-cell inflammation score (TIS) and interferon-gamma (IFN-gamma) score. Real-world overall survival (OS) was obtained from insurance claims and calculated from date of tumor biopsy to last contact using Kaplan-Meier estimates. Statistical significance was determined by chi-square and Mann-Whitney U test with *p*-values adjusted for multiple comparisons ($q < .05$). **Results:** 7170 NHW (35.3%, N = 2528) biopsied (bx) from primary breast cancer (pBC), 64.7% (N = 4642) metastatic bx (mBC), 1,508 AA (pBC 39.3% N = 592, mBC 60.7% N = 916), and 1,754 HL (pBC 44.1% N = 774, mBC 55.9% N = 980) cases were included. By subtype, there were 1,956 (60.4% NHW, 20.7% NHB, 18.9% HL) TNBC, 3425 HR+/HER2- (72.6% NHW, 11.9% NHB, 15.6% HL), and 694 HER2+ (64.6% NHW, 15.7% NHB, 19.7% HL). Across all cases, AA (20.5%) and HL (20.4%) had greater incidence (%) of PD-L1+ cases versus (vs) NHW (17.4%), all $q < .05$. TMB-High (³10 mut/Mb) was similar in NHW (11.5%), AA (10.8%), and HL (10.9%). AA tumors had lower median % cell infiltration of M2-like macrophages (M2 $M\varphi$), B cells, and neutrophils vs NHW (Table). HL had a lower fraction of M2 $M\varphi$ and higher CD8+ T cells (Table). AA had lower TIS (-8 vs 1, p = .02) while HL had lower IFN-gamma (-0.38 vs. -0.35, $q < .05$) vs NHW. By subtype, AA had lower neutrophils (4% vs 4.3%) and increased DC fractions (3.1% vs 2.8%) in TNBC vs NHW, all $q < .05$; no significant changes seen in HL vs NHW. AA had worse mOS than NHW overall (31.8 vs 36.8 months (mo)), HR 1.1, 95% CI 1 – 1.2, p = < .01), in pBC (40.3 vs 49.9 mo, HR 1.3, 95% CI 1.1 – 1.5, p = < .01), but not mBC (27.4 vs 29.1 mo, HR 1, p = 0.2). HL had similar mOS vs NHW overall (37.4 vs 36.8 mo, HR 0.9, p = 0.9) and in mBC (29.1 vs 31 mo, HR 0.96, p = 0.4), but worse mOS in pBC (44.7 vs 50.0 mo, HR 1.1, 95% CI 1 – 1.3, p = .01). **Conclusions:** Our study shows worse mOS in AA and HL pBC cases vs NHW, possibly from a less inflamed TIME in AA and HL and lower fraction of neutrophils and M2 $M\varphi$ despite higher % of PD-L1+. Targeting $M\varphi$ and CD8+ T cells and converting cold to hot TIME may lessen race/ethnic disparities, especially in early-stage BC. Research Sponsor: None.

Immune cell fraction of NHW, AA and HL BC.

	NHW (median %)	AA (median %)	HL (median %)	q-value NHW vs AA	q-value NHW vs HL
B cell	5.2	4.8	5.0	<.05	0.7
DC	2.6	2.7	2.6	0.08	0.4
M1 Mφ	2.5	2.4	2.4	0.4	0.9
M2 Mφ	4.6	3.7	4.2	<.05	<.05
Neutrophils	3.7	3.5	3.4	<.05	<.05
NK cell	2.9	2.9	2.9	0.7	0.6
CD8+ T cell	0.1	0.15	0.26	0.8	<.05
Treg	1.5	1.5	1.6	0.6	<.05

1052 Poster Session

Circulating tumor DNA (ctDNA)-based minimal residual disease (MRD) measured by Guardant Reveal in patients (pts) with HER2-positive (HER2+) metastatic breast cancer (mBC) with long-term disease control on first-line trastuzumab-pertuzumab. First Author: Antonio Llombart-Cussac, Hospital Arnau Vilanova - Lliria, FISABIO, Valencia, Spain

Background: The CLEOPATRA and PERUSE trials established the combination of a taxane with the antiHER2 monoclonal antibodies trastuzumab and pertuzumab (HP) as the gold standard first-line treatment for HER2+ mBC. In both studies, the progression events reached a plateau after 4 years and up to 30% of pts remained long-term progression-free, hypothesizing HP maintenance can be safely discontinued. We therefore evaluated whether epigenomic-based ctDNA MRD analysis can potentially identify pts with a higher chance of permanent remission. PRE-PHENIX is a multi-center observational study that explores the prevalence of MRD measured by Guardant Reveal in HER2+ mBC pts on long-term first-line HP maintenance. **Methods:** A total of 40 pts with HER2+ mBC on first-line treatment with HP maintenance for a minimum of 4 years were included. Confirmation of no progressive disease by CT or PET-scan in the last 3 months previous to study entry was mandatory. Plasma samples were analysed using Guardant Reveal powered by the Guardant Infinity platform, a tissue-free epigenomic assay interrogating differentially methylated regions of DNA optimized to detect breast cancer DNA from normal cell-free DNA. Two ctDNA tests were performed on each patient within a 6 – 12-week interval. Additionally, 11 pts with confirmed disease progression on antiHER2 therapy for mBC were included as case controls. The primary objective was to establish the prevalence of positive MRD in both populations and the agreement between the two tests for the Long-Term responders. **Results:** Median age was 63.2 years (range 30.8 – 84.4). The median duration of first-line HP treatment was 6.9 years (range 4.2 - 11.1). At diagnosis, 26 pts (65%) presented with "de novo" mBC and 20 (50%) had visceral disease. The last radiological evaluation categorized 6 pts (15%) as having stable disease (SD), 2 pts (5%) with partial response (PR), and 32 pts (80%) with complete response (CR). Among the 11 pts with confirmed progression, 2 presented exclusive Central Nervous System (CNS) disease. Guardant Reveal identified MRD in 4 long-term responders (10%), 3 out of 6 pts (50%) with SD, 1 of 2 pts (50%) with PR, and no MRD among the 32 pts with CR. A perfect agreement was observed between the two tests (Kappa-index of 1). Ten out of the 11 pts (91%) with disease progression had MRD, including the two with exclusive CNS involvement. **Conclusions:** Our study demonstrates clinically significant performance of a tissue-free MRD test, Guardant Reveal, as a potential non-invasive monitoring tool to guide de-escalation strategies in pts HER2+ mBC pts with long-term remissions on HP treatment. A prospective study (PHENIX) to guide HP interruption by ctDNA monitoring is planned. This study was funded by a Fundación Contigo full grant (Spain) and Guardant Health. Research Sponsor: None.

1053 Poster Session

Antibody drug conjugates treatment response score (ADC TRS) for sequencing trastuzuamb deruxtecan (T-DXd) and sacituzumab govitecan (SG) in advanced breast cancer (aBC). First Author: Andi Cani, University of Michigan Medical School, Rogel Cancer Center, Ann Arbor, MI

Background: T-DXd, targeting HER2, is approved in hormone receptor positive or negative (HR+/-) HER2-low (1-2+ by immunohistochemistry [IHC]) and HR+/HER2-ultralow (0+ with membrane staining) aBC. SG, targeting TROP2, is approved in HR+/HER2 negative [-; < 3+ by IHC] and triple negative BC (TNBC; HR-/HER2-). Given limitations in determining IHC 0-1+ status and lack of predictive biomarkers, biomarkers for sequencing these ADCs in those with HER2- aBC are needed. Recently, Thomas et al. reported the discovery of ADC TRS—a generalized model combining individual ADC target expression, proliferation, and adhesion to predict multi-ADC target/tumor type clinical benefit—as well as validation of SG and T-DXd TRS models (tuned by pan-tumor response rates) by a qRT-PCR based clinical trial assay (CTA; Strata Select ADC [SSA]) for predicting clinical benefit of first ADC (SG or T-DXd) in those with HER2- aBC (ASCO 2024 #3140; AACR 2025 #1014). Here, we evaluated ADC target expression and T-DXd/SG TRS status from SSA validation cohort HER2- BC patients stratified by clinical HR/HER2 IHC status. **Methods:** Adults with aBC from an observational trial (NCT03061305) with valid FFPE tumor tissue results from SSA validation cohort testing were included. aBC types were determined by HR/HER2 IHC results (by ASCO/CAP scoring), with those HER2 3+ or *HER2* amplified (by Strata Select testing) considered HER2+. ADC target component expression (*HER2* or *TROP2;* pan-tumor scaled absolute expression) and T-DXd and SG TRS statuses (+ associated with more clinical benefit) by SSA were compared by IHC defined aBC types. **Results:** 230 patients with aBC from SSA validation testing were included (median age 58 yrs, 40% self-reported non-European;180 with definitive aBC type [see Table for distribution]). *HER2* expression was significantly increased vs. *TROP2* in HER2+ and HR+/HER2 aBC, and did not significantly differ in those with TNBC (see Table). Across all patients, 42%, 30%, 27% and 0.4% were T-DXd/SG TRS +/+, -/-, +/- and -/+, respectively. Results were similar in those with HER2 IHC 0+ (n = 37, median *HER2* vs. *TROP2* = 2.2 vs. 2.3, p = 0.51; 8% and 3% T-DXd/SG TRS +/- and -/+, respectively. **Conclusions:** Pan-tumor optimized, validated ADC TRS models support sequencing T-DXd before SG in nearly all patients with advanced HER2- BC, including those with TNBC and HER2 0+ IHC. Prospective evaluation of the CTA is warranted. Research Sponsor: Strata Oncology.

ADC target expression (*HER2* or *TROP2*) and T-DXd | SG TRS status by SSA in BC patients.

					T-DXd/SG TRS Status			
BCa Type	(n)	HER2^	TROP2^	p-value^	+/+	-/-	+/-	-/-
HER2+	43	6.4	2.6	<0.0001	42%	7%	51%	0%
IHC NA*	50	2.6	2.7	0.31	44%	40%	16%	0%
HR+/HER2-	76	3.0	2.3	<0.0001	54%	20%	26%	0%
TNBC	61	2.3	2.3	0.7	25%	52%	21%	2%
Total	230	2.9	2.4	<0.0001	42%	30%	27%	0.4%

^Median, pan-tumor scaled *HER2* and *TROP2* target expression; Wilcoxon test.
*IHC not available; *HER2* not amplified.

1054 Poster Session

Estrogen receptor (ER) expression on circulating tumor cells (CTCs) and cell free DNA (cfDNA) mutational landscape in the PACE randomized phase II study. First Author: Carolina Reduzzi, Weill Cornell Medicine, New York, NY

Background: The PACE (NCT03147287) randomized phase II trial investigates CDK4/6 inhibition beyond progression in combination with endocrine treatment, with or without PD-L1 inhibition, in hormone receptor-positive (HR+)/HER2- metastatic breast cancer (MBC) (Mayer et al 2024). We previously reported that cfDNA alterations and CTC number correlated with survival and treatment response (Jeselsohn et al 2024; Gerratana et al ASCO 2023). Here we investigated ER expression on CTCs in relation to the cfDNA mutational landscape. **Methods:** Samples were collected at baseline. CTC enumeration and ER protein expression on CTCs (by immunofluorescence) was evaluated with the CellSearch and the ACCEPT software. Samples were classified as CTC^{high} or CTC^{low} (cutoff ≥5 CTC/sample). CTC^{high} samples were defined ER+ if >15% CTCs/sample expressed ER to ensure good inter-group stratification. Concurrently, cfDNA was analyzed with the Guardant360 assay. Only pathogenic single nucleotide (snv) and copy number variations (cnv) with ≥3% prevalence were included and categorized into oncogenic pathways (Sanchez-Vega et al 2018). Differences in distribution across CTC groups were tested through Chi-squared and Fisher's test. **Results:** From 220 enrolled patients, 167 were evaluable for ER on CTCs. Of these, 91 were CTC^{low}, 30 were CTC^{high}/ER-, and 46 CTC^{high}/ER+. *ESR1* mutations were more common in CTC^{high} /ER+ samples, while CTC^{high}/ER- samples had higher incidence of alterations in *SMAD4*, *PIK3CA*, *BRAF* and *CDK4* compared to the other 2 groups (Table 1). CTC^{high}/ER- had also higher mutant allele frequency compared to CTC^{high} /ER+ and CTC^{low} (MAF > 3% in 73% vs 54% and 31%, respectively, p < 0.001). CTC^{low} samples had overall lower cfDNA alteration incidence. Similarly, alterations in the ER pathway were more frequent in samples with CTC^{high} /ER+, whereas alterations in PI3K, cell cycle and P53 pathways were more common in CTC^{high}/ER- samples. Alterations in the RTK/RAS/RAF pathway were more common in CTC^{high} samples (23% and 28% for ER- and ER+ vs 9.9% for CTC^{low}, p = 0.017). Similar results were observed with a 10% threshold. **Conclusions:** Distinct cfDNA alterations were identified based on ER expression in CTCs in HR+/HER2- MBC. Integrating CTC enumeration and cfDNA profiling may help elucidate resistance mechanisms, identify actionable targets, and predict benefit from continued CDK4/6 inhibition beyond progression. Research Sponsor: Pfizer; Merck KGaA; CrossRef Funder ID: 10.13039/100009945.

Incidence of cfDNA alterations across the 3 CTC-based groups.

cfDNA alterations	CTC^{low}[1]	CTC^{high}/ER-[1]	CTC^{high}/ER+[1]	P value
ESR1[2]	36 (40)	15 (50)	31 (67)	0.009
SMAD4[2]	0 (0)	3 (10)	2 (4.3)	0.009
PIK3CA[3]	2 (2)	4 (13)	0 (0)	0.012
BRAF[3]	1 (1)	1 (3.3)	5 (11)	0.022
CDK4[3]	1 (1)	3 (10)	2 (4.3)	0.035
ER pathway[2]	40 (44)	15 (50)	32 (70)	0.017
PI3K pathway[3]	2 (2.2)	4 (13)	0 (0)	0.012
Cell cycle pathway[3]	8 (8.8)	9 (30)	8 (17)	0.019
P53 pathway[2]	27 (30)	16 (53)	13 (28)	0.040

[1]n (%); [2]snv; [3]cnv.

1055 Poster Session

Overall survival in patients with HR+/HER2- advanced or metastatic breast cancer treated with a cyclin-dependent kinase 4/6 inhibitor plus an aromatase inhibitor: A US Food and Drug Administration pooled analysis. First Author: Jennifer Gao, Oncology Center of Excellence, U.S. Food and Drug Administration, Silver Spring, MD

Background: Cyclin-dependent kinase 4/6 inhibitors (CDKI) are FDA-approved for use in combination with aromatase inhibitors (AI) for the treatment of patients with hormone receptor-positive (HR+), human epidermal growth factor receptor 2-negative (HER2-), advanced or metastatic breast cancer (MBC) as initial (1L) endocrine-based therapy. We have previously reported the pooled analyses of the benefit in progression-free survival of adding CDKI to AI, and here report the pooled overall survival (OS) results for adults treated with CDKI + AI for 1L HR+/HER2- MBC. **Methods:** We pooled individual patient data (N=2252) from 4 randomized trials (MONALEESA-2 & 7, MONARCH-3, PALOMA-2) of a CDKI (abemaciclib, palbociclib, ribociclib) or placebo + AI in adults with 1L HR+/HER2- MBC. OS was defined as time from randomization to death from any cause and was a key secondary endpoint in all 4 trials. Not all 4 trials reached OS statistical significance, but all OS hazard ratios of the individual trials were <1. The median OS was estimated using Kaplan-Meier methods, and hazard ratios with 95% confidence intervals (CI) were estimated using Cox regression models. Analyses were prespecified, with patients analyzed collectively and by various clinicopathological subgroups of interest. **Results:** Overall results in all patients and various clinicopathologic subgroups of interest are shown (Table). **Conclusions:** In this descriptive exploratory pooled analysis, the addition of a CDKI to AI suggested an association with an OS benefit for this class of drugs used as a component of 1L endocrine-based therapy for adults with HR+/HER2- MBC. Additional research is needed to determine which subgroup of patients may benefit more or less of the addition of a CDKI to AI. Research Sponsor: None.

	n	# Events CDKI/n (%)	# Events Placebo/n (%)	HR (95% CI)
All	2252	716/1320 (54)	550/932 (59)	0.81 (0.73, 0.91)
PR negative	273	84/155 (54)	89/118 (75)	0.51 (0.38, 0.70)
De Novo	752	233/450 (52)	173/302 (57)	0.82 (0.67, 1.00)
Lobular Histology	144	72/97 (74)	34/47 (72)	0.99 (0.66, 1.50)
Bone-Only	493	142/284 (50)	115/209 (55)	0.74 (0.58, 0.95)
Liver/Lung Mets	1111	365/639 (57)	291/472 (62)	0.81 (0.70, 0.95)
Age <40	193	40/106 (38)	44/87 (51)	0.78 (0.51, 1.21)
Age >70	403	159/247 (64)	106/156 (68)	0.86 (0.67, 1.09)
ECOG 1	851	305/499 (61)	239/352 (68)	0.78 (0.66, 0.93)
White	1594	529/919 (58)	407/675 (60)	0.88 (0.77, 1.00)
Asian	438	113/269 (42)	89/169 (53)	0.59 (0.45, 0.78)
Black or African American	43	14/25 (56)	11/18 (61)	0.80 (0.36, 1.76)

Additional clinicopathologic subgroup analyses conducted with results not shown.

1056 Poster Session

Prospective cohort study of palbociclib in HR+/HER2- metastatic breast cancer in Japan. First Author: Takashi Ishikawa, Department of Breast Surgical Oncology, Tokyo Medical University, Tokyo, Japan

Background: The combination of palbociclib (PAL) with an aromatase inhibitor or fulvestrant has been shown to improve progression-free survival (PFS) in hormone receptor (HR)-positive and human epidermal growth factor receptor (HER2)-negative metastatic breast cancer. However, the addition of PAL to endocrine therapy increases toxicity and cost compared to endocrine therapy alone. In addition, PAL treatment may affect the efficacy of subsequent treatments, as its benefit in terms of overall survival (OS) has not yet been demonstrated. Therefore, it is crucial to prospectively evaluate whether PAL can improve clinical outcomes and quality of life (QoL) for patients in a real-world setting. **Methods:** A prospective observational study of PAL is planned in three cohorts (A, B, and C) categorized by line of endocrine treatment (1st, 2nd, or 3rd or later line) for post-menopausal metastatic or unresectable breast cancer. The primary endpoint is PFS in each line of treatment. For cohort B, PFS2 is defined as time from initiation of first-line therapy for metastatic disease. Based on the results of the PALOMA-2 and -3 studies, the planned sample size was set at 700 cases with confidence intervals: 340 in cohort A, 200 in cohort B and 130 in cohort C. Secondary endpoints include OS, clinical benefit rate, time to chemotherapy, adverse events (AEs), patient-reported outcomes and health-related quality of life, which will also be evaluated during follow-up. This study aims to determine whether the efficacy, safety and QoL outcomes of PAL treatment in daily clinical practice are comparable to those observed in clinical trials, and whether PAL affects the efficacy and safety of subsequent treatments. This report presents PFS results from each cohort. An exploratory analysis of OS rates from the start of 1st-line therapy for metastatic disease is also reported. **Results:** A total of 700 patients were enrolled from April 2019 to January 2023. After excluding cases with contraindications, the final cohort distribution was as follows: 246 in cohort A, 282 in cohort B, and 65 in cohort C. The median PFS was 25.8 months (95% CI: 21.4) for cohort A, 18.0 months (95% CI: 14.0-22.7) for cohort B, and 12.0 months (95% CI: 7.7-17.4) for cohort C. The median PFS2 for cohort B was 57.9 months (95% CI: 45.2-65.1). The 3-year OS rates for cohorts A and B from the start of 1st-line metastatic therapy were 76.3% and 93.1%, respectively. **Conclusions:** The PFS result for the 1st-line cohort (Cohort A) was nearly equivalent to the 24.8 months observed in PALOMA-2, while the 2nd-line cohort (Cohort B) showed markedly better results than the 9.5 months reported in PALOMA-3. Although the background of each cohort needs to be further investigated, the PFS2 result of Cohort B was excellent and the subsequent 3-year OS of this cohort was satisfactory. Based on these results, the use of PAL in the 2nd line setting may be clinically acceptable. Clinical trial information: UMIN000035863. Research Sponsor: Pfizer Inc.

1057 Poster Session

Results of a phase 1 study of vosilasarm (EP0062), a first-in-class oral selective androgen receptor modulator (SARM) in patients with advanced or metastatic AR+/ER+/HER-2- breast cancer. First Author: Hyo S. Han, H. Lee Moffitt Cancer Center and Research Institute, Tampa, FL

Background: Vosilasarm (EP0062) is an oral, nonsteroidal, Selective Androgen Receptor Modulator (SARM). Initially developed under the code RAD140, EP0062 has been reformulated with markedly improved bioavailability and pharmacokinetics. Preclinically, vosilasarm has been shown to act as a potent tissue-selective AR agonist, suppressing growth and proliferation of multiple AR+/ER+/HER-2- breast cancer cell lines and patient-derived xenograft models, as monotherapy or in combination with standard of care (SoC) regimens (Clin Can Res 2017 23(24); SABCS 2019 P5-05-01). Here we report results from the dose finding and optimization cohorts of an ongoing phase 1/2 study (NCT05573126) in patients (pts) with advanced AR+/ER+/HER-2- breast cancer. **Methods:** The study recruited post-menopausal women with locally advanced or metastatic AR+/ ER+/HER-2- breast cancer, $\geq$ 18 years of age, with endocrine sensitive disease. AR+ defined as $\geq$ 10% AR nuclei staining by IHC. Primary objectives were to evaluate safety and determine the optimal dose for evaluation in future combination cohorts. Other endpoints included PK, ORR, DOR, CBR $\geq$6 months and genomic analysis (biopsy- or ctDNA-based NGS). **Results:** A total of 20 pts (Median age 59.5 y, PS 0/1 [70/30%]) were treated across 4 dose cohorts: 20mg QD (n = 2), 10mg BID (n = 10), 10mg QD (n = 5), 15mg BID (n = 3). The 10mg BID cohort was expanded for dose optimization. All pts received prior CDK4/6i and AI and/or SERD with a median of 4 prior lines (in any setting). CtDNA analysis showed genomic heterogeneity at baseline, with ESR1 mutations (8/19 pts) and TP53 mutations (9/19 pts) the most frequent. No DLTs were observed. 89% of all TEAEs were G1 or G2 with most common being increase in LFTs (55% of pts), nausea (40% of pts) and anemia (25% of pts). The LFT increases were transient, asymptomatic and generally occurred in cycle 1, with 2 pts requiring a dose interruption followed by reduction. Most common $\geq$ G3 TEAEs were ALT increase in 4 pts (20%). No treatment related deaths were observed. 19 pts were evaluable for efficacy. For 11/ 19 (58%) pts the best response was stable disease. 4/19 (21%) pts had clinical benefit with CBR $\geq$6 mo, corresponding with marked suppression of CA15-3 in 5/19 (26%) patients. Vosilasarm has a favorable PK profile with good bioavailability and no accumulation. Full data will be reported. 10 mg BID was selected as the optimal dose for Phase 2. **Conclusions:** Vosilasarm has promising clinical benefit, safety and tolerability in this heterogeneous, heavily pre-treated population. This confirms the potential of vosilasarm, a first in class SARM, as a new treatment strategy for AR+/ ER+/ HER-2- breast cancer. The study is continuing with evaluation of vosilasarm in combination with SoC therapies including oral SERD, mTOR inhibitor and CDK4/6 inhibitors. Clinical trial information: NCT05573126. Research Sponsor: Ellipses Pharma.

1058 Poster Session

Impact of BMI on CDK4/6 inhibitors efficacy and safety in advanced breast cancer: Results from a propensity score matched study—CAMELIA. First Author: Min Tian, Department of Oncology, the First Affiliated Hospital of Nanjing Medical University, Nanjing, China

Background: Body mass index (BMI) is strongly associated with the development and progression of breast cancer. Despite the widespread use of cyclin-dependent kinase (CDK) 4/6 inhibitors combined with endocrine therapy (ET) in hormone receptor (HR)-positive advanced breast cancer, the effect of BMI on therapeutic outcomes remains poorly understood. **Methods:** Patients aged ≥18 years with advanced HR-positive breast cancer who received CDK4/6 inhibitors at six hospitals in China were included. 588 patients admitted between December 2016 and December 2024 were evaluated. Patients were categorized into two groups based on BMI: Group 1 (BMI < 25.0 kg/m²) and Group 2 (BMI ≥ 25.0 kg/m²). Propensity score matching with a 3:1 ratio was performed, resulting in 452 patients included in the final analysis. The median follow-up duration was 21.53 months. Progression-free survival (PFS) and overall survival (OS) across BMI categories were compared using Kaplan-Meier (KM) curves and log-rank test. Univariate and multivariate cox regression analyses were performed to assess the impact of baseline clinical factors on PFS. **Results:** Of 452 patients, 339 (66.7%) were in Group 1, 113 (33.3%) were in Group 2 at baseline. The KM analysis revealed that patients with BMI ≥ 25 kg/m² had a significantly longer PFS compared to those with BMI < 25 kg/m². The median PFS was 16.77 months (95% CI: 12.86–20.67) in Group 1, versus 12.93 months (95% CI: 11.38–14.49) in Group 2 (p = 0.036, HR 0.737, 95% CI: 0.554–0.981). However, no significant difference in OS was observed between the two groups (Group 1: 55.6 months vs. Group 2: not reached, p = 0.949, HR 1.015, 95% CI: 0.637–1.618). Univariate and multivariate cox regression analyses identified BMI, lymph node, liver, bone, and brain metastasis are independent prognostic factors for the entire cohort. Subgroup analyses revealed that BMI ≥25 kg/m² was associated with improved survival in patients aged < 60 years, Eastern Cooperative Oncology Group (ECOG) performance status ≥ 1, with lung metastases, received ≥ 1 line of chemotherapy, and received ≥2 lines of CDK4/6 inhibitors. While Group 1 demonstrated a higher overall response rate (ORR) (30.4% vs. 26.5%, p = 0.476), Group 2 had a higher disease control rate (DCR) (87.0% vs. 91.2%, p = 0.314), though neither reached statistical significance. No significant differences were found in the incidence of grade 3/4 hematologic adverse events (AEs) (36.9% vs. 31.5%, p = 0.460) or non-hematologic AEs (17.1% vs. 14.4%, p = 0.605). **Conclusions:** In this study, overweight patients (BMI ≥ 25 kg/m²) with metastatic breast cancer may benefit more from CDK4/6 inhibitors. Moreover, similar adverse events were observed across BMI groups. These findings suggest that BMI could serve as a key predictor of CDK4/6 inhibitors treatment response, providing valuable insights for personalized therapeutic strategies in metastatic breast cancer. Research Sponsor: None.

Characteristics of patients before and after matching according to BMI categories.

	Unmatched cohort				Matched cohort			
Characteristics	BMI<25kg/m² (n=448)	BMI≥25kg/m² (n=140)	P	SMD	BMI<25kg/m² (n=339)	BMI≥25kg/m² (n=113)	P	SMD
Age grope at study entry, No. (%)			0.134	0.152			0.694	0.036
< 60years	286 (63.8)	79 (56.4)			204 (60.1)	70 (61.9)		
≥60years	162 (36.2)	61 (43.6)			135 (39.8)	43 (38.1)		
ECOG PS			0.064	0.189			0.350	0.078
0	248 (56.4)	52 (37.1)			140 (43.7)	45 (39.8)		
≥1	240 (53.6)	88 (62.9)			191 (56.3)	68 (60.2)		
Stage at diagnosis			0.217	0.124			0.406	0.072
I-III	368 (82.1)	108 (77.1)			279 (82.3)	96 (84.7)		
IV	80 (17.9)	32 (22.9)			60 (17.7)	17 (15.0)		
Estrogen receptor status, No. (%)			0.131	0.226			0.434	0.070
1–10%	9 (2.0)	0 (0.0)			0 (0.0)	0 (0.0)		
10–50%	37 (8.3)	16 (11.4)			29 (8.6)	12 (10.6)		
> 50%	402 (89.7)	124 (88.6)			310 (91.4)	101 (89.4)		
Progesterone receptor status, No. (%)			0.328	0.150			0.940	0.030
Negative	65 (14.5)	21 (15.0)			55 (16.2)	19 (16.8)		
1–20%	121 (27.0)	29 (20.7)			75 (22.1)	26 (23.0)		
> 20%	262 (58.5)	90 (64.3)			209 (61.7)	68 (60.2)		
HER-2 status, No. (%)			0.052	0.204			0.812	0.053
Negative	418 (93.3)	124 (88.6)			311 (91.7)	104 (92.0)		
Positive	23 (5.1)	9 (6.4)			21 (6.2)	6 (5.3)		
Unknown	7 (1.6)	7 (5.0)			7 (2.1)	3 (2.7)		
Ki-67 status, No. (%)			0.138	0.184			0.475	0.097
< 20	166 (37.1)	46 (32.9)			120 (35.4)	36 (31.9)		
≥20	246 (54.9)	75 (53.6)			188 (55.5)	64 (56.6)		
Unknown	36 (8.0)	19 (13.5)			31 (9.1)	13 (11.5)		
Resistance to previous endocrine treatment, No. (%)			0.085	0.234			0.924	0.031
Primary resistance	80 (17.9)	27 (19.3)			61 (18.0)	20 (17.7)		
Secondary resistance	325 (72.5)	90 (64.3)			239 (70.5)	81 (71.7)		
ET naïve	42 (9.4)	23 (16.4)			39 (11.5)	12 (10.6)		
non-sensitive	1 (0.2)	0 (0.0)			0 (0.0)	0 (0.0)		
Bone metastases			0.281	0.107			0.816	0.024
No	181 (40.4)	64 (45.7)			151 (44.5)	49 (44.1)		
Yes	267 (59.6)	76 (54.3)			188 (55.5)	64 (56.6)		
Visceral metastases			0.432	0.084			0.310	0.084
No	183 (40.8)	63 (45.0)			146 (43.1)	44 (40.5)		
Yes	265 (59.2)	77 (55.0)			193 (56.9)	69 (61.1)		
Previous endocrine therapy lines, No. (%)			0.136	0.198			0.673	0.068
0	206 (46.0)	77 (55.0)			170 (50.1)	59 (52.2)		
1	140 (31.2)	40 (28.6)			100 (29.5)	34 (30.1)		
≥2	102 (22.8)	23 (16.4)			69 (20.4)	20 (17.7)		
CDK4/6 inhibitors treatment lines, No. (%)			0.014	0.286			0.696	0.065
1	155 (34.6)	68 (48.6)			140 (41.3)	50 (44.2)		
2	90 (20.1)	22 (15.7)			60 (17.7)	20 (17.7)		
≥3	203 (45.3)	50 (35.7)			139 (41.0)	43 (38.1)		
Combination of CDK4/6 inhibitors therapy, No. (%)			0.644	0.070			0.943	0.028
Aromatase inhibitors	270 (60.3)	86 (61.4)			202 (59.6)	68 (60.2)		
Fulvestrant	172 (38.4)	53 (36.5)			132 (38.9)	43 (38.1)		
Others	6 (1.3)	3 (2.1)			5 (1.5)	2 (1.8)		
Disease-free survival, No. (%)			0.417	0.126			0.478	0.092
≤2years	75 (16.7)	23 (16.4)			54 (15.9)	21 (18.6)		
>2years	293 (65.4)	85 (60.7)			225 (66.4)	75 (66.4)		
De novo stage IV	80 (17.9)	32 (22.9)			60 (17.7)	17 (15.0)		

BMI: body mass index; ECOG: Eastern Cooperative Oncology Group; HER-2: human epidermal growth factor receptor 2; ET: endocrine treatment; CDK4/6: cyclin-dependent kinase 4/6.

1059 Poster Session

Clinical utility of [^{18}F]fluoroestradiol (FES) PET/CT to guide second-line treatment decision in patients with ER-positive HER2-negative metastatic breast cancer progressing on first-line endocrine therapy. First Author: Hannah M. Linden, University of Washington, Seattle, WA

Background: Second line treatment options for patients with ER+/HER2- metastatic breast cancer (MBC) after progression on 1st line endocrine therapy (ET) continue to expand with novel endocrine agents (oral SERDs) and combination therapies (PIK3CA/AKTi, CDKi). However, short median PFS reported in clinical trials show that many patients do not benefit from 2nd line ET. Identifying endocrine-resistant MBC at time of progression on 1st line ET can help place patients on potentially more effective non-ET options (e.g., chemotherapy / antibody-drug conjugates). FES PET/CT has been approved for clinical use in the U.S. and allows whole-body evaluation of ER expression in MBC. Difference in FES uptake across lesions may reflect ER loss/downregulation, a mechanism of endocrine resistance. Goal of this clinical trial was to evaluate the impact of FES PET/CT results on 2nd line therapeutic management decisions. **Methods:** In this multicenter trial in the U.S. [NCT05068726], patients with progression of ER+/HER2- MBC on 1st line ET were prospectively enrolled to undergo FES PET/CT in addition to standard of care (SOC) imaging (CT + bone scan / FDG PET/CT). Treating oncologists completed questionnaires before and after FES PET/CT, detailing therapeutic management plans plus their confidence in the plans. FES PET/CT scans were compared with SOC imaging to assess FES uptake in MBC lesions. An FES uptake score (number of FES-positive lesions divided by total number of lesions per patient) was calculated to evaluate ER expression heterogeneity by central blinded image evaluation. **Results:** 45 patients underwent FES PET/CT. FES PET/CT results led to a change in therapeutic management in 17/45 patients (37.8%; 95% CI 23.8% - 53.5%). Revised management plan was ET in 5/17 and non-ET in 12/17 patients. FES uptake score was 1 (all lesions FES-positive) in 14/45 patients and < 1 (with FES-negative lesions, indicating ER expression heterogeneity) in 31/45 patients. Of 14 patients with FES uptake score of 1, 11 received 2nd line ET. Of 31 patients with FES uptake score < 1, 15 were treated with ET and 16 with non-ET, based on guidelines suggesting that an FES-negative lesion is predictive of lack of endocrine response. FES PET/CT results led to 25/45 patients avoiding additional tests (20 biopsies, 5 scans) and 7/45 patients receiving further testing (4 biopsies, 1 scan, 2 other). Treating oncologist's confidence in 2nd line treatment decision (measured in n = 45 on 10-point scale with 10 being fully confident) increased on average with 2 points from 6.6 (SD = 1.7) pre-FES PET/CT to 8.6 (SD = 1.8) post-FES PET/CT. **Conclusions:** FES PET/CT is a clinically useful tool in the post-first line ER+/HER2- MBC setting. FES PET/CT results led to a change in management in 37.8% of patients and increased oncologist's confidence in 2nd line treatment decision. Clinical trial information: NCT05068726. Research Sponsor: Zionexa SAS, a GE HealthCare Company.

1060 Poster Session

Imlunestrant with or without abemaciclib in advanced breast cancer (ABC): Safety analyses from the phase III EMBER-3 trial. First Author: Joyce O'Shaughnessy, Baylor University Medical Center, Texas Oncology, Dallas, TX and Sarah Cannon Research Institute, Dallas, TX

Background: Imlunestrant is a next-generation, brain-penetrant, oral SERD. The EMBER-3 trial (NCT04975308) in patients with ER+, HER2- ABC and disease progression on/after aromatase inhibitor therapy showed significant progression-free survival improvement with imlunestrant (imlu; 400 mg once daily [QD]) over standard therapy (SOC, fulvestrant or exemestane) among patients with *ESR1* mutations, as well as with imlunestrant+abemaciclib (imlu [400 mg QD] + abema [150 mg twice daily]) over imlu in all patients regardless of *ESR1* mutation status. Detailed safety analyses are presented. **Methods:** The safety population included all patients who received at least one dose of study treatment. Analyses included incidence, severity (CTCAE v 5.0), management, and outcomes of common treatment-emergent adverse events (TEAEs). **Results:** Safety analyses included 859 patients: imlu (n=327), SOC (n=324), and imlu+abema (n=208). Incidence of any (imlu: 83%; SOC: 84%; imlu+abema: 98%), ≥ grade 3 TEAEs (imlu: 17%; SOC: 21%; imlu+abema: 49%), and serious AEs (SAEs; imlu: 10%; SOC 12%; imlu+abema: 17%) were similar between imlu and SOC arms and higher in the combination arm. Most common any-grade AEs with imlu were diarrhea (21%), nausea (17%), and fatigue (23%) and with imlu+abema were diarrhea (86%), nausea (49%), and neutropenia (48%); majority were grade 1 AEs. Incidence of elevated transaminases (any%/≥G3%: 16/1 and 20/5), VTE (1/0 and 3/1), ILD (1/0 and 2/0), bradycardia (2/0 and 1/0), and photopsia (0/0 and 0/0) were relatively low or not observed with imlu and imlu+abema, respectively. Dose reduction rates were 2% with imlu and 39% with imlu+abema, and discontinuation rates due to AEs were low (4% and 6%, respectively). The table characterizes the most commonly observed AEs. Further details will be presented. **Conclusions:** Imlunestrant had a favorable safety profile, similar to SOC, with mostly grade 1 AEs. Safety of imlunestrant + abemaciclib was consistent with the known abemaciclib profile, without additive toxicity. AEs were manageable with supportive medications and/or dose adjustments, resulting in few discontinuations in all arms. Imlunestrant, as monotherapy or in combination with abemaciclib, provides a safe, tolerable, all-oral targeted therapy option for patients with ER+, HER2- ABC. Clinical trial information: NCT04975308. Research Sponsor: Eli Lilly and Company.

Characterization of commonly observed AEs.

	Diarrhea			Nausea		
	Imlu N=327	SOC N=324	Imlu+abema N=208	Imlu N=327	SOC N=324	Imlu+abema N=208
Grade 1 AE, %	18	9	50	14	8	31
Grade 2 AE, %	3	3	28	3	5	15
Grade ≥3 AE, %	0.3	0	8	0.3	0	2
Median time to onset (Q1–Q3), days	30 (15–129)	52 (17–132)	5 (2–17)	20 (4–56)	57 (10–147)	15 (3–48)
Median duration of Grade 2 AE (range), days	3 (1–28)	5 (1–55)	13 (1–87)	16 (4–89)	10 (1–90)	19 (2–266)
Median duration of Grade ≥3 AE (range), days	8 (8–8)	0	9 (1–47)	24 (24–24)	0	7 (6–13)
Dose reduction/discontinuation, %	0/0	0/0	18/1	0.3/0	0/0	5/0
Antidiarrheal medication/ Antiemetic, %	10	7	68	10	10	21

1061 Poster Session

Giredestrant (G) with atezolizumab (ATEZO), and/or abemaciclib (ABEMA) in patients (pts) with ER+/HER2− locally advanced/metastatic breast cancer (LA/mBC): Interim analysis (IA) from the phase I/II MORPHEUS Breast Cancer study. First Author: Mafalda Oliveira, Vall d'Hebron University Hospital, Barcelona, Spain

Background: Endocrine therapy (ET) + a cyclin-dependent kinase 4/6 inhibitor (CDK4/6i) is a therapeutic mainstay for first-line treatment (tx) of ER+ mBC, but selection of effective ET combinations after progression remains a challenge. G is a highly potent, non-steroidal, oral (PO), selective ER antagonist and degrader shown to be well tolerated and to achieve robust ER occupancy. Immune checkpoint inhibition has shown a trend towards activity in a number of ER+ BC studies. Additionally, ABEMA (a CDK4/6i) has immunomodulatory activity, making its inclusion a compelling therapeutic approach. Here, we present a 24-week IA of the G + ATEZO ± ABEMA arms and a 22-week IA of the G + ABEMA arm from MORPHEUS BC (NCT04802759). **Methods:** Eligible pts had ER+, HER2− LA/mBC and had received prior tx with a CDK4/6i and 1–2 lines of ET. Pts were randomized to G (30 mg PO QD) alone (previously reported), G + ATEZO (840 mg IV Q2W), G + ATEZO + ABEMA (150 mg PO BID), or G + ABEMA until loss of clinical benefit/ unacceptable toxicity. Investigational drug doses were identical across all arms. Primary endpoints were safety and objective response rate (ORR). Exploratory analyses included evaluation of circulating tumor DNA alterations and tumor gene expression using RNAseq. **Results:** As of Apr 24, 2024, 15 pts in the G + ATEZO arm, 30 in the G + ATEZO + ABEMA arm and, as of Jan 9, 2023, 15 in the G + ABEMA arm, were efficacy/safety evaluable. Many pts had prior fulvestrant (60%, 43%, and 27%, respectively) and prior CDK4/6i duration ≥12 mo (73%, 77%, and 53%). Safety data are shown in the Table. In the triplet arm, the most common grade ≥3 adverse event (AE) was neutropenia/neutrophil count decreased (20%). No grade 5 AEs were reported. Confirmed ORR (all partial responses) were 20%, 33%, and 7% in the G + ATEZO, G + ATEZO + ABEMA, and the G + ABEMA arms, respectively. 7/9 confirmed responses (in *ESR1*-evaluable pts) in the G + ATEZO + ABEMA arm were in pts with *ESR1*-mutated disease. Data with longer follow-up, including progression-free survival, detailed safety, and exploratory biomarker analyses, will be presented. **Conclusions:** The combinations of G + ATEZO, G + ATEZO + ABEMA, and G + ABEMA were tolerable, with no unexpected safety signals including no high-grade interstitial lung disease/ pneumonitis and low rates of high-grade liver toxicity. Clinical activity was observed, with a trend towards improved ORR with G + ATEZO + ABEMA, particularly in tumors with *ESR1* mutations. Clinical trial information: NCT04802759. Research Sponsor: F. Hoffmann-La Roche Ltd.

n (%)	G + ATEZO (n = 15)	G + ATEZO + ABEMA (n = 30)	G + ABEMA (n = 15)
Any AE	14 (93)	30 (100)	15 (100)
AE: highest grade 3	8 (53)	15 (50)	8 (53)
AE: highest grade 4	0 (0)	0 (0)	1 (7)
Any-grade tx-related AE (TRAE)	12 (80)	30 (100)	13 (87)
TRAE leading to discontinuation of any tx	3 (20)	5 (17)	0 (0)

1062 Poster Session

Phase Ib study of inavolisib (INAVO) + weekly paclitaxel (wP) in patients (pts) with locally advanced/metastatic (LA/m) incurable solid tumors: Safety, pharmacokinetics (PK), and preliminary antitumor activity. First Author: Seock-Ah Im, Seoul National University College of Medicine, Cancer Research Institute, Seoul National University, Seoul, South Korea

Background: wP is commonly used for treating solid tumors as a single agent or in combination with targeted agents. However, it has an unfavorable benefit–risk profile when given with pan-PI3K inhibitors or alpelisib. INAVO, a potent and selective PI3Kα inhibitor that also promotes mutated p110α degradation, was FDA approved in combination with palbociclib + fulvestrant for hormone receptor-positive, HER2-negative (HR+, HER2−), endocrine-resistant advanced breast cancer (BC) following recurrence on/after completing adjuvant endocrine therapy. We report data from INAVO + wP in pts with LA/m solid tumors from a Phase Ib study (CO42800; ISRCTN45319897). **Methods:** Eligible pts had progressed after standard systemic therapy. In part 1 (dose-escalation phase; 3+3 design), pts with LA/m incurable solid tumors received INAVO 6 mg/9 mg orally daily (PO QD) + wP (80 mg/m^2). In part 2 (dose-expansion phase), pts with LA/m incurable *PIK3CA*-mutated solid tumors (triple-negative BC [TNBC]; HR+, HER2− BC; others) received INAVO 9 mg PO QD (recommended dose from part 1) + wP. Primary endpoint: Safety/tolerability in parts 1 and 2. Secondary endpoints: Preliminary antitumor activity in part 2 (only TNBC and HR+, HER2− BC data are available); PK in parts 1 and 2. **Results:** Of 66 pts enrolled (parts 1 and 2), four received no treatment and eight were still on treatment at clinical cutoff (Oct 11, 2024). Reasons for study discontinuation were per protocol study completion (56.1%), death (16.7%), pt withdrawal (9.1%), loss to follow-up (1.5%), and other (4.5%). There were no dose-limiting toxicities. In safety-evaluable pts (n = 62), grade 3, 4, and 5 adverse events (AEs) occurred in 59.7%, 3.2%, and 0% of pts, respectively. One pt discontinued INAVO due to AEs; INAVO dose modifications (reduction/interruption) due to AEs occurred in 61.3% of pts. The most common AEs (> 10% of pts) were diarrhea (61.3%), hyperglycemia (51.6%), and anemia (45.2%). Neutropenia (24.2%) and diarrhea (8.1%) were the most common grade 3–4 AEs. Serious AEs occurred in 30.6% of pts (mostly single AEs in individual pts, and unrelated to study treatment).In part 2, confirmed overall response rate in pts with TNBC (n = 20) was 50.0% and in pts with HR+, HER2− BC (n = 19) it was 36.8%. Median duration of confirmed response was 7.4 mo (95% confidence interval 5.2, 11.5) and 12.8 mo (3.7, not evaluable), respectively; median progression-free survival, 7.0 mo (3.5, 9.3) and 7.4 mo (6.2, 14.7). PK of INAVO and wP at Cycle 1, Day 15 were comparable to historic data. **Conclusions:** In CO42800, INAVO + wP was well tolerated in pts with LA/m solid tumors, including those with a *PIK3CA* mutation, with no new safety signals or drug–drug interactions observed. Encouraging preliminary antitumor activity shown in pts with HR+, HER2− BC or TNBC supports further investigation. Clinical trial information: ISRCTN45319897. Research Sponsor: Genentech, Inc.

1063 Poster Session

PARPi effectiveness after CDK4/6i in *BRCA1*- and *BRCA2*-associated HR+/ HER2- advanced breast cancer: Results from the multicenter real-world PAMBRACA study. First Author: Emma Zattarin, University of Modena, Modena, MO, Italy

Background: Poly(adenosine diphosphate–ribose) polymerase inhibitors (PARPi) are the paramount of personalized therapy for *BRCA1* and *BRCA2* pathogenic/likely pathogenic variant (P/LPV) carriers with hormone receptor-positive (HR+)/HER2-negative (HER2-) advanced breast cancer (aBC). Nevertheless, data on the efficacy of PARPi following cyclin-dependent kinase 4/6 inhibitors (CDK4/6i) combined with endocrine therapy (ET) are limited. **Methods:** The PAMBRACA study is a multicenter, hospital-based, retrospective-prospective cohort study enrolling *BRCA1* and *BRCA2*-P/LPV carriers with HR+/HER2- aBC treated with ET+CDK4/6i and/or PARPi. In this analysis, the real-world Progression-Free Survivals (rwPFS) of ET+CDK4/6i and subsequent lines were evaluated through Kaplan-Meier method and compared with the log-rank test. Median follow-up was calculated using the reverse Kaplan-Meier method. Multivariate Cox regression model was used to adjust the association between treatment regimens and rwPFS for clinically relevant variables. **Results:** We included12 *BRCA1* and 57 *BRCA2*-P/LPV carriers who were diagnosed with HR+/HER2- aBC between January 1998 and December 2023 in six Italian Institutions. All the patients (pt) received CDK4/6i+ET for aBC (85.5% as first line, 7.2% as second line, 7.3% as third or subsequent line). At CDK4/6i starting, median age was 45 years (range 28-80); 52.2% of pts had visceral metastases and 17.4% had *de novo* aBC. Median follow-up was 39.5 months (mo). Among pts treated with CDK4/6i as first or second line, median rwPFS was 15.1 mo (95%CI 11.8-18.5) and 3.1 mo (95%CI 2.1-NA), respectively. Among the 49 patients who progressed to first or second-line CDK4/6i, 17 (34.7%) received a PARPi as first line post-CDK4/6i, 12 (24.5%) a monochemotherapy (monoCT), 8 (16.3%) an ET (+/- everolimus), 8 (16.3%) a polychemotherapy (polyCT) and 4 (8.2%) died without receiving a subsequent line. No significant differences in clinicopathological characteristics were observed among the treatment groups, except for the number of metastatic sites (<3 vs >3), which was higher for pts receiving mono/polyCT (p = 0.053). PARPi treatment was associated with significantly higher median rwPFS (13 mo vs 4.5 mo for monoCT vs 3 mo for ET vs 6 mo for polyCT, $p < 0.001$), also after adjusting for the number of metastatic sites [for PARPi vs other lines, adjusted hazard ratio (aHR) 0.20, 95%CI 0.09-0.49, $p < 0.001$]. 17 pts received PARPi as later treatment lines, which were independently associated with lower median rwPFS vs PARPi as first post-CDK4/6i line (6 vs 13 mo, aHR 2.81, 95%CI 1.15-6.90, p = 0.024). **Conclusions:** AfterCDK4/6i+ET, PARPi were independently associated with longer rwPFS compared to other systemic therapies in *BRCA1* and *BRCA2*-P/LPV carriers with HR+/HER2- aBC. Earlier PARPi use after CDK4/6i was associated with greater clinical benefit. Research Sponsor: None.

1064 Poster Session

A phase I/IIa study to evaluate the tolerability, safety, pharmacokinetics and efficacy of ecuriclib (BPI-1178) alone in advanced solid tumors and in combination with endocrine therapy for advanced or recurrent HR+/HER2- breast cancer. First Author: Yiqun Du, Phase I Cinical Trial Center, Fudan University Shanghai Cancer Center, Shanghai, China

Background: Ecuriclib (BPI-1178) is a new cyclin-dependent kinases (CDKs) 2/4/6 inhibitor, which has shown strong inhibition on the expression of CDK2/4/6 in pre-clinical studies. This first-in-human phase I/IIa study aimed to assess the preliminary efficacy, safety and tolerability of ecuriclib monotherapy for advanced solid tumors or in combination with endocrine therapy (ET) for HR+/HER2- advanced breast cancer (ABC). **Methods:** Patients with advanced solid tumors included in phase I received ecuriclib alone at doses of 25~500 mg in a 3+3 dose-escalation or expansion manner. Phase IIa consisted of two cohorts, A and B. Cohort A included patients with HR+/HER2- ABC who had progressed after ET receiving ecuriclib in combination with fulvestrant, and treatment-naive patients with HR+/HER2- ABC in cohort B were treated with ecuriclib in combination with letrozole. All patients administered ecuriclib with either intermittent (21 days on, 7 days off) or continuous (28 days on) dosing schedule in a 28-day cycle until disease progression, unacceptable toxicity, etc. Safety was assessed as per CTCAE 5.0. Efficacy endpoints included confirmed objective response rate (ORR), disease control rate (DCR), progression-free survival (PFS), etc. assessed by investigators per RECIST 1.1. **Results:** As of August 9, 2024, a total of 129 patients have been enrolled. And 33 patients were enrolled in Phase I study. No DLT was observed. In Phase IIa Cohort A, 70 patients were enrolled and in which 64 patients were evaluable for efficacy. 26 patients were enrolled into cohort B with 25 efficacy-evaluable patients. In Cohort A, the top three treatment related adverse events (TRAEs) of grade $\geq$ 3 were neutrophil count decreased (35.7%), white blood cell count decreased (14.3%), and hypertriglyceridemia (14.3%) while in Cohort B those were neutrophil count decreased (23.3%), hypertriglyceridemia (16.7%), alanine aminotransferase increased (10.0%), and white blood cell count decreased (10.0%). No TRAE leading to permanent discontinuation or death occurred in this trial. **Conclusions:** Ecuriclib in combination with ET demonstrated promising efficacy and manageable safety profile in patients with HR+/HER2- ABC. Clinical trial information: NCT04282031. Research Sponsor: Beta Pharma (Suzhou) Co., Ltd.

	Cohort A (n = 64)				Cohort B (n = 25)	
	400 mg [a] (n = 20)	300 mg [a] (n = 16)	300 mg [b] (n = 20)	200 mg [b] (n = 8)	400 mg [a] (n = 19)	300 mg [a] (n = 6)
ORR, n (%)	9 (45.0)	7 (43.8)	11 (55.0)	0 15 (78.9)	5 (83.3)	
DCR, n (%)	17 (85.0)	13 (81.3)	20 (100.0)	8 (100.0)	18 (94.7)	6 (100.0)
Median PFS, months (95% CI)	18.3 (7.2, NR)	7.3 (2.4, NR)	NR (12.8, NR)	NR	NR (16.7, NR)	NR

[a]intermittent dosing schedule;
[b]continuous dosing schedule; NR, not reached.

1065 Poster Session

Quantifying the clinical impact of tissue reflex testing for liquid biopsy *ESR1* mutation–negative cases with low ctDNA tumor fraction (TF) in HR(+) HER2(-) breast cancer. First Author: Jing Du, Yale School of Medicine, New Haven, CT

Background: *ESR1* mutations (*ESR1*mut) commonly drive acquired resistance to estrogen deprivation by aromatase inhibitors, a first-line standard of care for HR(+)HER2(-) metastatic breast cancer (MBC). We previously published that approximately 63% of patients with HR(+)HER2(-) MBC at progression have a liquid biopsy (LBx) negative for *ESR1*mut. The absence of an *ESR1*mut may either accurately reflect the tumor genotype (true negative) or represent a false negative due to insufficient ctDNA shedding, with the risk of missing an actionable mutation. Among these patients, 40% exhibit a high ctDNA TF $\geq$1% (informative negative), while 60% have a low ctDNA TF $<$ 1% (indeterminate negative). This suggests that up to 38% of all patients with HR(+)HER2(-) MBC in this context could potentially benefit from reflex tissue biopsy (TBx) for *ESR1*mut in cases deemed indeterminate negative by LBx due to low ctDNA shedding. The goal of this study is to determine the rate of *ESR1*mut detection in a new TBx after an indeterminate negative result from FoundationOne Liquid CDx (F1LCDx). **Methods:** This study included a cohort of patients with BC who underwent tissue and liquid Foundation Medicine comprehensive genomic profiling (CGP) within an interval of up to 90 days during routine clinical care. Clinical data of a subset of patients with confirmed HR(+)HER2(-) MBC was obtained from the US-wide deidentified Flatiron Health-Foundation Medicine MBC clinicogenomic database (CGDB). The data originated from ~280 cancer clinics (~800 sites of care) between 01/2014-09/2024. False negative rate (FNR) and positive percent agreement (PPA) for *ESR1*mut detection were calculated with tissue CGP as reference. **Results:** A total of 522 BC patients underwent TBx and LBx. Among these, 229 (43.9%) had ctDNA TF $<$ 1%. Without accounting for TF, the overall FNR for *ESR1*mut was 6.3% and the PPA was 67.1%. In LBx with TF $\geq$1%, the FNR for *ESR1*mut was 0.9% and PPA was 96.0%. In contrast, for TF $<$ 1% samples, the FNR was 12.0% and the PPA 25.7%. 101 patients were included in the CGDB and had a confirmed HR(+)HER2(-) MBC, in which 56 (55.4%) had LBx with ctDNA TF $<$ 1%. The overall FNR for *ESR1*mut in this subset of patients was 9.5% and the PPA was 61.9%. In LBx with TF $\geq$1%, the FNR was 0% and PPA was 100%. And for TF $<$ 1%, the FNR was 15.1% and PPA 20.0%. **Conclusions:** BC patients with informative negative *ESR1*mut (defined as LBx *ESR1*mut negative with TF $\geq$1%) are unlikely to have *ESR1*mut detected on tissue CGP testing. However, patients with indeterminate negative *ESR1*mut (defined as LBx *ESR1*mut negative with TF $<$ 1%), 12-15% were found to be false negatives. This suggests that approximately 5% of all HR(+)HER2(-) MBC patients with *ESR1*mut could be missed without reflex testing with a TBx. ctDNA TF levels offer critical guidance in deciding when a reflex to tissue is warranted, ensuring accurate treatment. Research Sponsor: None.

1066 Poster Session

Thymidine kinase activity (TKa) as independent predictor of outcome in metastatic breast cancer (MBC) patients in the GEICAM/2013-02 PEARL trial. First Author: Angel Guerrero, Instituto Valenciano de Oncología (IVO). GEICAM Spanish Breast Cancer Group, Valencia, Spain

Background: TKa is a proliferation biomarker measurable in blood via the DiviTum™ TKa assay. Levels of TKa before and during treatment can provide prognostic, predictive and monitoring information in MBC. The PEARL trial (NCT02028507) was a phase III, multicenter, open-label, randomized study that compared endocrine therapy (ET) + CDK4/6 inhibitor Palbociclib (Palbo) vs. Capecitabine (Cape) in aromatase inhibitor-resistant HR+/HER2- MBC patients (pts). ET + Palbo did not improve median progression-free survival (mPFS 17.8 vs. 17.3 months (m.), p = 0.9) or overall survival (mOS 31.1 vs. 32.8 m., p = 0.5) over Cape. We explored whether TKa levels could predict better response to ET + Palbo vs Cape. **Methods:** Plasma from 555 pts (92%) was collected at baseline (BL) and on treatment (C1D15, C2D15). 1129 samples were analyzed using the DiviTum TKa assay (FDA approved/CE labelled, Biovica, Sweden). Cutoffs: 250/400 DiviTum units of Activity (DuA) for BL, 50 DuA or fold change (C1,C2/BL) $>$ 2 for on-treatment. The Kaplan-Meier method estimated median PFS and OS. Adjusted hazard ratio (HR) with 95% confidence interval (CI) were calculated using Cox proportional hazards regression model, considering relevant prognostic clinical variables. **Results:** BL TKa $\leq$ 250 DuA predicted better mPFS (11.4 vs. 4.04 m., aHR 2.1; 95% CI 1.7-2.6, p $<$ 0.0001) and mOS (38.47 vs. 17.31 m., aHR 3.2; 95% CI 2.45-4.19, p $<$ 0.0001) regardless of therapy. After starting therapy, Cape and ET + Palbo elicited distinct TKa responses due to their different mechanisms. At C1, C2, pts on Cape had higher mTKa vs ET + Palbo (448 vs. 28 DuA, p $<$ 0.0001). In the CT arm, an increase of TKa at C1 or C2 greater than 2-fold from BL predicted for better mPFS (13.04. vs. 6.34 m., aHR 0.59; 95% CI 0.43-0.81, p = 0.0013) and mOS (39.26 vs. 23.23 m., aHR 0.31; 95% CI 0.2-0.5, p $<$ 0.0001). In the ET + Palbo arm, a TKa at C1 or C2 $>$ 50 DuA predicted a shorter mPFS (3.68 v 11.27 m, aHR 2.81; 95% CI 2.08-3.8, p $<$ 0.0001) and mOS (18.73 vs. 45.11 m., aHR 3.44; 95%CI 2.34-5.06, p $<$ 0.0001). Similar results are observed regardless of BL TKa value. Exploring a BL TKa $>$ 400 DuA demonstrated a better response to Cape compared to ET+ Palbo, despite overall very poor outcomes: mPFS 4.04 m on Cape vs 2.01 on ET + Palbo, (aHR 1.72; 95% CI 1.14-2.59, p $<$ 0.0096), and showed a similar trend in mOS, 15.4 m on Cape vs 14.6m on ET+Palbo, (aHR 1.29 95% CI 0.84-1.99, p = 0.24). **Conclusions:** These data demonstrate that CT vs a CDK4/6 inhibitor influence TKa response differently, and the direction and magnitude of the TKa response can predict for benefit to a specific therapy. The original PEARL study analysis showed no outcome differences between Cape vs ET + Palbo in HR+/HER2- MBC pts, however assessment of TKa before and during therapy identified which patients had the highest probability of responding. Utilization of TKa as a predictive biomarker may allow for better personalized treatment selection. Clinical trial information: NCT02028507. Research Sponsor: None.

1067 Poster Session

Prognostic role of estrogen receptor (ER) expression in breast cancer (BC) metastases and its dynamics from primary to metastatic disease: Results from a large multicentric cohort of patients with phenotypically stable ER+(≥10%)/HER2- BC. First Author: Federica Miglietta, University of Padova Oncology 2 Unit, Istituto Oncologico Veneto IRCCS, Padova, Italy, Italy

Background: ER expression is one of the main determinants of prognosis in patients (pts) with BC. Phenotypic conversion from ER+ (ER$>$=10%)/HER2- primary BC towards ER$<$10%/HER2- advanced BC has a well-known negative impact on outcome. However, in the specific context of phenotypically stable ER+/HER2- BC, the prognostic impact of ER expression in metastases or ER dynamics during disease evolution, remains largely understudied. **Methods:** We enrolled pts with advanced BC undergoing biopsy of a metastatic site. ER+ was defined as ER$>$=10%. ER expression was evaluated both as continuous and categorical variable (categories: 10-30%, 30-50%, 50-100%). Overall survival (OS) was the primary study endpoint. Cox multivariable models included covariates associated with OS in univariate analysis. **Results:** Among 1114 pts, 410 had ER+/HER2- phenotype in both primary and metastatic tumor specimens. In this subgroup, ER expression (both continuous and categoric) in metastases had significant prognostic value: for each 10% lower ER expression, the risk of death increased by 6.7% (p=0.011). Pts with ER 10-30% had significantly worse OS than those with ER 50-100% (HR 0.62, p=0.023), and numerically shorter than ER 30-50% (HR 0.51, p=0.063). The table shows the evolution of ER categories from primary BC to metastases. ER expression dynamics also had prognostic impact. Regarding continuous ER expression changes in paired primary vs. metastatic BC, each 10% ER increase corresponded to 5.9% decrease in the risk of death (p=0.008). Pts whose tumors showed an increased ER expression from 10-30% to 50-100% had the most favorable outcome overall, with better OS compared to pts with persistently low ER levels (HR 6.73, p=0.002), or to pts with decreased ER expression in metastases - particularly pts whose ER levels dropped from 50-100% to 10-30% (HR 2.89, p=014). These pts also had superior OS when compared to pts with persistently high ER levels (HR 2.08, p=0.043). The prognostic impact was preserved at the multivariate analysis (including age, grade, visceral/non-visceral disease, biopsy site). **Conclusions:** Intratumor ER expression and dynamics may in part explain the prognostic heterogeneity of pts with ER+/HER2- stable phenotype from primary to advanced BC. Pts with lower ER levels in metastases are prognostically disadvantaged. Dynamic changes in ER expression provide additional insights beyond those captured by single-point assessment. Interestingly, pts whose tumors shifted from ER 10–30% to ER 50–100% showed the most favorable prognosis, even outperforming those with consistently high ER levels. Research Sponsor: None.

	Metastases, ER							
	10-30%		30-50%		50-100%		Total	
Primary BC, ER	n	%	n	%	n	%	n	%
10-30%	5	1.2	0	0	18	4.4	23	5.6
30-50%	7	1.7	4	1.0	11	2.7	22	5.4
50-100%	24	5.9	21	5.1	320	78.0	364	89
Total	36	8.8	25	6.1	349	85.1	410	100

1068 Poster Session

SIM0270 in combination with palbociclib in patients with ER+/ HER2- advanced breast cancer: The phase Ib study. First Author: Jiong Wu, Fudan University Shanghai Cancer Center, Shanghai, China

Background: SIM0270 is a highly potent oral selective estrogen receptor degrader (SERD) which has shown ER degradation and robust antitumor activity across variety of preclinical models. Here, we present results of SIM0270 combined with palbociclib cohort(dose escalation and dose expansion) from Phase I study in patients with ER+/ HER2- advanced breast cancer (NCT05293964). **Methods:** Patients with ER+/HER2- advanced breast cancer were enrolled. The key inclusion criteria for dose escalation and dose expansion were the same as follows: ≥ 1 prior endocrine therapy (ET) with disease recurrence/ progression while being treated with adjuvant ET for ≥ 24 months and/or first line ET for ≥ 6 months in advanced setting; ≤2 prior chemotherapies in advanced setting; and prior fulvestrant was allowed. A Bayesian Optimal Interval design (BOIN) was adopted for dose escalation. The key endpoint of dose escalation was dose limiting toxicities (DLT), and the key endpoints of dose expansion included safety and tolerability, pharmacokinetics (PK) and efficacy. **Results:** As of December 26, 2024, 44 patients were enrolled including 12 from dose escalation and 32 from dose expansion, with a median follow up of 11.8 months. No DLT was reported in dose escalation. In total, 38 patients (86.4%) had visceral disease, and 8 patients (18.2%) had ESR1 mutation at baseline. 22 patients (50%) received prior endocrine therapy in the advanced setting, of which, 15 patients (34.1%) had aromatase inhibitor (AI), 12 patients (27.3%) had fulvestrant. 13 patients (29.5%) received prior chemotherapy in the advanced setting.The most common treatment emerged adverse events (TEAEs) were white blood cell count decreased (95.5%) and neutropenia (95.5%). Sinus bradycardia was reported in 77.3% (34/44) of the patients, 85.3% (29/34) were grade 1 (asymptomatic) requiring no dose modification. Grade 3/4 treatment-related AEs (TRAEs) occurred in 77.3% of the patients with most commonly reported events including neutropenia (70.5%) and white blood cell count decreased (40.9%). No fatal AEs were reported. TRAEs led to dose reduction were reported in 38.6% for palbociclib and 9.1% for SIM0270. No TRAEs led to treatment discontinuation. And 24 patients remain on study treatment. In the response evaluable patients, confirmed overall response rate (ORR) was 41.5% (17/41) and clinical benefit rate (CBR, defined as complete response, partial response or stable disease ≥ 24 weeks) was 82.5% (33/40). Median progression free survival (PFS) was not reached (NR). In patients with ESR1 mutation at baseline, ORR and CBR were 87.5% (7/8) and 100% (8/8), respectively. **Conclusions:** SIM0270 in combination with palbociclib showed acceptable safety and tolerability, promising clinical activity in patients with ER+/HER2- advanced breast cancer. Clinical trial information: NCT05293964. Research Sponsor: Simcere Zaiming Pharmaceutical Co., Ltd.

1069 Poster Session

First-line (1L) ribociclib (RIB) + endocrine therapy (ET) vs combination chemotherapy (combo CT) in clinically aggressive hormone receptor (HR)+/HER2− advanced breast cancer (ABC): A subgroup analysis of patients (pts) with or without liver metastases (mets) from RIGHT Choice. First Author: Nagi S. El Saghir, American University of Beirut Medical Center, Beirut, Lebanon

Background: The phase II RIGHT Choice trial reported a statistically significant progression-free survival (PFS) benefit at the primary prespecified analysis and a 9-month (mo) benefit at the final analysis with 1L RIB + ET over combo CT in pts with clinically aggressive HR+/HER2− ABC. As liver mets in ABC indicate a worse prognosis, an analysis by liver mets status was performed (data cutoff: May 10th, 2023). **Methods:** Pre- and perimenopausal women (N = 222) with no prior systemic therapy for clinically aggressive HR+/HER2− ABC were randomized 1:1 to receive RIB + letrozole or anastrozole + goserelin or physician's choice of combo CT. Enrolled pts had ABC for which combo CT was clinically indicated by physician's judgment. **Results:** In total, 107 (RIB + ET, n = 54; combo CT, n = 53) and 115 (RIB + ET, n = 58; combo CT, n = 57) pts presented with or without liver mets, respectively. Pts with liver mets had PFS of 18.3 vs 12.7 mo and median time to treatment failure (mTTF) of 13.2 vs 8.3 mo with RIB + ET vs combo CT, respectively (Table). A clinical benefit rate (CBR) of 77.8% vs 67.9%, overall response rate (ORR) of 64.8% vs 60.4%, and median time to response (mTTR) of 6.4 vs 3.0 mo were seen in the RIB vs CT arm, respectively. Pts without liver mets had PFS of 25.2 vs 15.4 mo and mTTF of 24.0 vs 10.1 mo in the RIB vs CT arm, respectively, and similar CBR, ORR, and TTR regardless of treatment (tx). No new safety signals were observed in pts with liver mets. A numerically longer median time to deterioration (mTTD) in FACT-B total score was seen with RIB + ET vs combo CT in pts with and without liver mets. **Conclusions:** This analysis from RIGHT Choice showed similar clinically meaningful efficacy and quality-of-life benefits and no new safety signals for RIB + ET vs combo CT between pts with and without liver mets. These results support the 1L use of RIB + ET in pts with clinically aggressive HR+/HER2− ABC even in the presence of liver mets. Clinical trial information: NCT03839823. Research Sponsor: Novartis Pharmaceuticals Corporation.

Liver mets	Tx arm	n	mPFS, mo (95% CI)	HR (95% CI)	mTTF, mo (95% CI)	HR (95% CI)	CBR[a], % (95% CI)	ORR[a], % (95% CI)	mTTR[a], mo (95% CI)	HR (95% CI)	mTTD (FACT-B total score)[b], mo	HR (95% CI)
Yes	RIB + ET	54	18.3 (10.3-24.0)	0.68 (0.42-1.11)	13.2 (10.2-21.2)	0.60 (0.39-0.92)	77.8 (64.4-88.0)	64.8 (50.6-77.3)	6.4 (4.6-23.9)	0.68 (0.42-1.10)	37.7	0.68 (0.34-1.34)
	Combo CT[c]	53	12.7 (7.5-21.0)		8.3 (5.3-12.8)		67.9 (53.7-80.1)	60.4 (46.0-73.5)	3.0 (2.6-6.7)		18.4	
No	RIB + ET	58	25.2 (18.6-NE)	0.57 (0.34-0.93)	24.0 (16.4-32.2)	0.44 (0.29-0.69)	84.5 (72.6-92.7)	67.2 (53.7-79.0)	4.6 (2.8-10.2)	0.81 (0.52-1.28)	NE	0.59 (0.29-1.21)
	Combo CT[c]	57	15.4 (8.8-20.0)		10.1 (7.8-13.6)		80.7 (68.1-90.0)	63.2 (49.3-75.6)	4.5 (1.4-8.2)		37.1	

NE, not evaluable.
[a]Without confirmation;
[b]≥7 point decrease;
[c]docetaxel + capecitabine, paclitaxel + gemcitabine, or capecitabine + vinorelbine.

1070 Poster Session

Elacestrant (Ela) combinations with ribociclib (Ribo) and everolimus (Eve) in patients (pts) with ER+/HER2- locally advanced or metastatic breast cancer (mBC): Update from ELEVATE, a phase (Ph) 1b/2, open-label, umbrella study. First Author: Hope S. Rugo, University of California, San Francisco Helen Diller Family Comprehensive Cancer Center, San Francisco, CA

Background: Progression of ER+/HER2- mBC on 1L endocrine therapy (ET) + CDK4/6i is associated with several mechanisms of resistance that impact efficacy and subsequent therapy. Treatment options include endocrine monotherapy, continuing ET+CDK4/6i, or PI3K/AKT/mTOR pathway–ET combination regimens. Acquired *ESR1* mutations emerge in up to 50% of patients and continuing SOC ET is limited by resistance to ET due to these mutations. Several trials have shown improved mPFS with the addition of Eve: 3.6-6.8 mo (Cook 2021, Vasseur 2024) or switch in CDK4/6i: 5.3 mo (Kalinsky 2023). In the Ph 3 EMERALD trial, single-agent Ela significantly improved PFS vs SOC ET (*ESR1*-mut tumors HR 0.55; 95% CI 0.39-0.77; P=0.0005; all pts HR 0.70; 95% CI 0.55-0.88; P=0.0018) with manageable safety in pts with ER+/HER2- mBC who had prior ET+CDK4/6i (Bidard 2022). This analysis reports updated safety and preliminary efficacy for Ela in combination with Ribo or Eve. **Methods:** ELEVATE evaluates Ela in combination with everolimus (Eve), alpelisib (Alp), capivasertib (Capi), ribociclib (Ribo), palbociclib (Palbo), or abemaciclib (Abema) to address different resistance mechanisms. Pts with ER+/HER2- mBC and 1-2L of prior ET are eligible regardless of *ESR1*-mut status. Objectives are to identify the RP2D (Ph 1b) and evaluate PFS (Ph 2) with each combination. **Results:** Elacestrant combinations with Ribo or Eve showed safety consistent with the known profiles of each drug + SOC ET. The most common AEs (≥30%) with Ela + Ribo (n=32) from Ph 1b were neutropenia (38%; 25% ≥Gr3) and nausea (31%; 0 ≥Gr3). The most common AEs for Ela + Eve (n=72) from Ph 1b + Ph 2 were nausea (54%; 6% ≥Gr3), diarrhea (43%; 7% ≥Gr3), stomatitis (38%; 3% ≥Gr3), and fatigue (32%; 6% ≥Gr3). Median PFS for Ela + Ribo was 7.2 months, while for Ela + Eve was 8.5 months. Table 1 summarizes mPFS from Ph 1b in efficacy-evaluable pts who received prior ET+CDK4/6i, as of Dec 2024. Updated data will be presented. **Conclusions:** Elacestrant plus Ribo or Eve demonstrates promising Ph 1b efficacy in pts with ER+/HER2- mBC with progressive disease after ET+CDK4/6i in all patients. Ela 345 mg + Ribo 400 mg QD was determined as the RP2D. Previously, Ela 345 mg + Eve 7.5 mg was identified as the RP2D. Elacestrant has the potential to become an ET backbone for various targeted agents, offering an all-oral treatment regimen in pts with ER+/HER2- mBC, delaying chemo or ADC-based regimens. Clinical trial information: NCT05563220. Research Sponsor: None.

Ph 1b mPFS in prior ET+CDK4/6i, efficacy-evaluable population.

	N	Ela (86-345 mg) + Ribo (400-600 mg)	N	Ela (258-345 mg) + Eve (5-10 mg)
mPFS, mo (95% CI)	32	7.2 (3.52 - 12.78)	22	8.5 (7.23 - 16.07)

1071 Poster Session

Differential genomic landscape of estrogen receptor (ER)-low versus ER-positive (ER+) and ER-negative (ER-) metastatic breast cancer (MBC). First Author: Chiara Corti, Dana-Farber Cancer Institute, Boston, MA

Background: Guidelines define ER+ breast cancer (BC) as ≥1% tumor nuclei staining positive by IHC. Data on managing ER-low tumors (1–10% ER staining) is limited, with mixed evidence suggesting outcomes similar to ER- but a higher risk of death with adjuvant endocrine therapy (ET) omission. We aimed to examine the genomic landscape of ER-low MBC compared to ER+ and ER-. **Methods:** This retrospective study included consecutive patients (pts) with MBC who consented to clinicopathologic data collection and genomic profiling (OncoPanel) on tumor samples with matched ER IHC through the EMBRACE (Ending Metastatic Breast Cancer for Everyone) program. For multiple sequencing timepoints, the first was analyzed. SNVs, CNVs and TMB were compared among ER groups. Genes altered in > 3% of pts were analyzed for ER status association, with Benjamini-Hochberg adjusted p < 0.2 subjected to Holm-corrected pairwise testing. **Results:** Between 10/2000-12/2020, 1199 pts were identified:48 ER-low, 797 ER+, and 354 ER-. Median age at diagnosis was 63.8 (34.8-86.8), 64.4 (30.8-96.3), and 62.6 (30.3-92.7) years for ER-low, ER+, and ER- groups, respectively. De novo stage IV disease was observed in 8.3% (4/48) of ER-low, 27.0% (215/797) of ER+, and 17.2% (61/354) of ER- cases. Overall, 801/1199 (66.8%) had metastatic and 398/1199 (33.2%) had primary samples sequenced. 27/48 ER-low (56.3%), 451/797 ER+ (56.6%), and 73/354 ER- (20.6%) pts received ET before sequencing. CDK4/6i were administered in 8/48 ER-low (16.7%), 107/797 ER+ (13.4%), and 5/354 ER- (1.4%) pts prior to sequencing. The most clinically relevant genomic alterations are shown in the Table. *TP53* mutations (mts) were more frequent in ER-low vs ER+ BC, and not significantly different between ER-low and ER- tumors. *PIK3CA* and *CDH1* alterations were more frequent in ER-low than ER- BC, with no significant difference compared to ER+. *AKT1* and *RB1* alterations were significantly higher in ER-low vs ER+ BC. *ESR1* mts were not significantly different between ER+ and ER-low BC. Median TMB was higher in ER-low vs ER+ cases, without significant differences between ER-low and ER- cases. **Conclusions:** ER-low BC has a distinct genomic profile, with high *TP53* mts (similar to ER-) and frequent PI3K pathway alterations (typical of ER+). Ongoing analyses of clinicopathologic features and survival across ER-low, ER+, and ER- cohorts will be presented. Research Sponsor: Terri Brodeur Breast Cancer Foundation; The Benderson Family Fund; NIH/NCI grant; 1P50CA168504.

Characteristic	ER+ (N = 797)	ER-low (N = 48)	ER- (N = 354)	ER-low vs ER+ (p value)	ER-low vs ER- (p value)	ER+ vs ER- (p value)
TP53	24%	79%	83%	**1.45 x 10^-14**	0.689	**1.85 x 10^-79**
PIK3CA	39%	31%	13%	0.291	**0.00292**	**1.96 x 10^-21**
CDH1	19%	17%	3%	0.85	**0.00193**	**6.66x10^-14**
AKT1	2%	15%	4%	**0.0155**	**0.0155**	0.635
RB1	1%	12%	9%	**0.00354**	0.35	**0.000116**
PTEN	9%	10%	14%	0.828	0.828	0.828
ESR1	11%	6%	0%	0.612	**0.00322**	**3.06x10^12**
***CCND1* (CNV)**	17%	12%	3%	0.551	**0.0258**	**2.83 x 10^-11**
TMB, median (IQR)	6.844 (4.562)	8.365 (6.917)	7.604 (4.562)	**0.018**	0.212	**0.001**

1072 Poster Session

Molecular and prognostic convergence of HR+/HER2− metastatic breast cancer (MBC) to a TNBC-like profile: Insights from circulating tumor DNA (ctDNA)-based genomic analysis across treatment lines. First Author: Lorenzo Foffano, Universita degli Studi di Udine, Udine, Italy

Background: While the transition to a triple negative (TNBC)-like profile represents a recognized mechanism of treatment resistance for hormone receptor-positive, HER2-negative (HR+/HER2-) MBC, the molecular mechanisms of this phenomenon remain largely unknown. This analysis investigated the genomic and prognostic differences between HR+/HER2− and TNBC across treatment lines through ctDNA profiling analysis **Methods:** This retrospective study analyzed a multi-institutional cohort of 1071 patients (pts) with HER2 negative MBC and ctDNA testing with the Guardant360 NGS panel within a large academic consortium (PMAC). HR and HER2 status were defined based on the most recent biopsy, pts with ER-low profile (ER $<$ 10% regardless of PR status) were excluded. Associations across single nucleotide and copy number variations (SNVs and CNVs), HR+/HER2− and TNBC subtypes across treatment lines were tested by multinomial logistic regression (MLR) in terms of Relative Risk Ratio (RRR). The impact of prognosis was evaluated through Cox regression for overall survival (OS), defined from time of baseline ctDNA collection. **Results:** There were 827 pts with HR+/HER2- MBC (77.2%) and 244 pts with TNBC (22.8%). Multivariable MLR, designed with first line HR+/HER2- as the reference, investigated genomic alterations across treatment lines. In second line, *ESR1* SNVs (RRR 7.34, p $<$ 0.001) and *EGFR* CNVs (RRR 0.15, p = 0.01) were significantly associated with HR+/HER2-, while *TP53* SNVs had a higher prevalence in TNBC (RRR 2.71, p = 0.009). In third line, *ESR1* SNVs were significantly enriched in HR+/HER2- (RRR 5.44, p $<$ 0.001), while *TP53* SNVs emerged for TNBC (RRR 5.26, p $<$ 0.001). From fourth line onward ($\geq$ 4L), *ESR1* SNVs (RRR 8.09, p $<$ 0.001), *TP53* SNVs (RRR 1.81, p = 0.022) and *PIK3CA* CNVs (RRR 5.93, p = 0.003) showed higher prevalence in HR+/HER2- relative to first line HR+/HER2-, while *TP53* SNVs were also associated with TNBC (RRR 10.43, p $<$ 0.001). Compared to TNBC, HR+/HER2− had a favorable prognostic impact in terms of OS in first (HR 0.32, p $<$ 0.001), second (HR 0.35, p $<$ 0.001) and third line (HR 0.37, p $<$ 0.001). However, in $\geq$ 4L, no significant differences emerged (HR 0.79, p = 0.282), with similar results observed with respect to TNBC across all lines (HR 1.01, p = 0.929). *MYC* CNVs had an unfavorable prognostic role for both HR+/HER2− $\geq$4L (HR 2.41, p = 0.004) and TNBC in all lines (HR 2.14, p = 0.014). **Conclusions:** Our study suggests a dynamic molecular evolution of HR+/HER2− MBC, with a progressive acquisition of molecular and prognostic features compatible with a TNBC-like profile and loss of endocrine sensitivity. These findings highlight the need for comprehensive biological characterization of this subtype across treatment lines to better understand its evolution under therapeutic pressure and consequently adapt treatments. Research Sponsor: None.

1073 Poster Session

Ultrasensitive ctDNA monitoring during CDK4/6 inhibitor therapy for metastatic breast cancer. First Author: Julia Ah-Reum An, Memorial Sloan Kettering Cancer Center, New York, NY

Background: The combination of CDK4/6 inhibitor (CDK4/6i) and endocrine therapy (ET) is the standard first-line treatment for patients with hormone receptor-positive/HER2-negative (HR+/HER2-) metastatic breast cancer (MBC). However, it exhibits highly variable efficacy, with some cancers progressing within 3–6 months while many others achieve durable and potentially indefinite complete responses (CRs). While pharmacologic strategies to escalate or deescalate this therapy exist, diagnostic tools to identify the patients who would benefit from each approach are needed. Ultrasenstive ctDNA offers the potential to assess disease burden dynamically and with more precision. In this study, we evaluate the validity of an ultrasensitive assay capable of detecting ctDNA levels in the parts per million range for monitoring patients with HR+/HER2- MBC. **Methods:** Patients from the MSK-LINC prospective ctDNA monitoring study, who received CDK4/6i+ET for HR+/HER2- MBC were included in the study. MRD monitoring was performed using personalized tumor-informed panels designed from whole genome sequencing (WGS) of matched tumor and normal specimens to identify up to 2,000 somatic alterations for each patient using the Precise MRD assay (Myriad Genetics). Results were reported as an overall ctDNA detection status and a quantitative tumor fraction. **Results:** 29 patients with HR+/HER2- MBC (8 *de novo*, 21 recurrent) were included in this ongoing study. The median progression-free survival (PFS) was 48.8 months (range 2.6 – 78.5) with 17/29 of patients experiencing disease progression. ctDNA panels were successfully designed for all cases, and 140/146 (95.9%) plasma samples passed QC. All pre-treatment samples had detectable ctDNA with a median tumor fraction of 1.4% (range 0.00093%, 14.0%). An early decrease in ctDNA levels, $>$ 50% reduction from baseline or levels $<$ 0.01% in the second sample collected within 3 months, was significantly associated with longer PFS (p $<$ 0.001). We focused on 7 patients who achieved radiographic CR all with PFS $>$ 3y. Notably, 3 patients had continued to have ultra low levels of ctDNA (median: 0.0086%, range 0.00032%, 0.11%), indicating stable viable micrometastatic disease below the threshold of imaging, effectively controlled by treatment. In contrast, 4 patients also achieved molecular CR (mCR) defined as sustained undetectable ctDNA suggesting that metastatic disease was either eradicated or rendered dormant without significant cell turnover. **Conclusions:** Ultrasensitive ctDNA monitoring is a promising tool for monitoring disease burden and treatment response. Our results highlight the ability of ctDNA to distinguish between stable molecular disease vs. mCR, highlighting the potential of ctDNA as a biomarker for tailoring treatment strategies in patients who achieve outstanding clinical responses. Research Sponsor: Myriad Genetics, Inc.; Susan G. Komen.

1074 Poster Session

Effectiveness comparison of palbociclib, ribociclib and abemaciclib in patients with HR+/HER2- aBC: Updated results from the real-world, Italian study PALMARES-2. First Author: Claudio Vernieri, Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy

Background: The Cyclin Dependent Kinase 4/6 inhibitors (CDK4/6i) Palbociclib (P), Ribociclib (R) and Abemaciclib (A) combined with Endocrine Therapy (ET) are the standard 1st line therapy for patients (pts) with Hormone Receptor positive, Human Epidermal growth factor Receptor 2-negative, advanced Breast Cancer (HR+/HER2- aBC). However, based on conflicting results of large real-world (RW) studies (Vernieri C et al. Abstr 1014, ASCO 2024; Rugo H et al. PS2-03, SABCS 2024), it remains unclear whether P, R and A are similarly effective. **Methods:** PALMARES-2 is a multicenter, observational Italian RW study comparing the effectiveness of 1st line P, R or A in female pts with HR+/HER2- aBC. The primary endpoint is overall survival (OS); RW progression-free survival (rwPFS) and time to chemotherapy (TTC) are secondary endpoints. rwPFS, TTC and OS were defined as the time between 1st line ET+CDK4/6i initiation and disease progression/death, initiation of 1st chemotherapy line/death, or patient death, respectively. We used Inverse Probability of Treatment Weighting (IPTW) to balance 14 prognostic covariates related to patients (age, ECOG PS, menopausal status), tumor biology (ER, PgR, HER2, Ki67, grading, histology, endocrine sensitivity/resistance/*de novo* metastatic) and metastatic sites (liver, bone, lung, serosal) in P, R and A cohorts. Effectiveness comparisons were reported as adjusted Hazard Ratio (aHR) and 95% confidence interval (CI). **Results:** With a cutoff date of Jan 10th, 2025, we enrolled 3598 pts, of whom 1392 (38.7%), 1408 (39.1%) or 798 (22.2%) received P, R or A, respectively. Pts receiving A were more likely to have endocrine-resistant disease, liver metastases and lower PgR expression, and less likely to have *de novo* metastatic disease (p $<$ 0.001). Median follow-up was shorter in R/A cohorts (31.8/29.6 months) than in the P cohort (52.4 months). Median rwPFS, TTC and OS in the whole population were 26.1, 39.4 and 67.1 months, respectively. After IPTW adjustment, R and A were associated with better rwPFS and TTC when compared to P, while only R was associated with better OS (Table). R and A did not show significant rwPTS, TTC or OS differences (Table). **Conclusions:** The three CDK4/6i have different effectiveness in HR+/HER2- aBC pts. Longer follow-up of PALMARES-2 study and more pts/events in the A cohort are needed to perform definitive OS comparisons between P, R and A. Research Sponsor: None.

	P (N = 1392) N° events (%)	R (N = 1408) N° events (%)	A (N = 798) N° events (%)
rwPFS	992 (71.2%)	711 (50.5%)	418 (52.4%)
TTC	845 (60.7%)	516 (36.6%)	332 (41.6%)
OS	586 (42.1%)	270 (19.2%)	189 (23.7%)
	R vs P: aHR (95% CI; *P*)	**A vs P: aHR (95% CI; *P*)**	**A vs R: aHR (95% CI; *P*)**
rwPFS	0.88 (0.80-0.97; 0.02)	0.88 (0.77-0.99; 0.04)	0.99 (0.87-1.13; 0.91)
TTC	0.83 (0.74-0.94; $<$0.01)	0.86 (0.75-0.99; 0.04)	1.04 (0.89-1.20; 0.65)
OS	0.75 (0.64-0.87; $<$0.01)	0.91 (0.76-1.09; 0.3)	1.21 (0.99-1.49; 0.06)

1075 Poster Session

Use of baseline plasma circulating tumor DNA (ctDNA) to predict duration of endocrine therapy (ET) and CDK4/6 inhibitor (CDK4/6i) therapy (tx) and to analyze intrinsic vs acquired endocrine resistance. First Author: Pietro De Placido, Dana-Farber Cancer Institute, Boston, MA

Background: ET + CDK4/6i is standard-of-care for patients (pts) with hormone receptor-positive/HER2-negative (HR+/HER2-) metastatic breast cancer (MBC). We aimed to identify predictors ET + CDK4/6i tx duration and to compare genomic profiles in pts with intrinsic vs acquired resistance. **Methods:** Plasma samples were collected from pts with HR+/HER2- MBC enrolled in the EMBRACE cohort study who had plasma collection within 3 months (mo) prior to CDK4/6i initiation to 14 days after initiation. The primary outcome was duration of ET+CDK4/6i tx, defined as time from tx initiation to end of tx. Intrinsic resistance was defined as pts with tx duration $<$ 180 days. Plasma samples were analyzed using the Guardant360 assay, which includes genotyping of $>$ 700 genes and tumor fraction (TF) score. TF was estimated by normalizing cancer-specific differentially methylated regions with matched control regions in each sample. The predictive value of baseline TF (0 vs $>$ 0) was tested using a Cox regression model including age, line of tx, and liver metastases. For comparison of pts with intrinsic vs acquired resistance, analysis was limited to samples with TF $>$1% to minimize the impact of variation in tumor shed. Gene frequency between intrinsic and acquired resistance samples were compared using q-tests(q $<$ 0.25). **Results:** A total of 188 pts were included. Median age at MBC diagnosis was 57.5 yrs. ET+CDK4/6i was given in the first-line (1L) in 115 pts, second-line (2L) in 37 pts, and $>$ 2L in 36 pts. Of 167 pts, TF was undetectable (TF = 0) in 19 (11%) and detectable (TF $>$ 0) in 148 (89%). In Cox regression, baseline TF (p = 0.001), line of tx (n = 0.002), and presence of liver metastasis (p = 0.014), but not age, were predictors of duration of tx. Median duration of tx was 44.6 mo in pts with baseline TF = 0 vs. 5.8 mo in pts with baseline TF $>$ 0 (HR 0.28, 95% CI 0.14-0.56). Similar results were found when restricting the analysis to those receiving tx in the 1L or 2L. There were notable differences in the frequency of ESR1 (63% vs 48%), CDH1 (38% vs 18%), PTEN (21% vs 9%), RB1 (32% vs 20%), and CDKN2A (20% vs 5%) alterations in pts with intrinsic vs acquired resistance, though these did not reach statistical significance in the setting of small sample size. ESR1 fusions were seen in 14% (8/56) pts with intrinsic resistance vs 7% (3/44) pts with acquired resistance. Among pts with intrinsic resistance, ERBB2 copy number loss was present in 7(13%) (6 het loss, 1 homozygous deletion), RB1 copy number loss in 10 (18%) (all het loss), and CDKN2A copy number loss in 9(16%) (7 het loss, 2 homozygous deletions). **Conclusions:** Baseline TF in ctDNA is highly predictive of time on ET+CDK4/6i tx in pts with HR+/HER2- MBC. Baseline genomic profiles differ qualitatively between pts with intrinsic vs acquired resistance. If validated, baseline plasma may provide a valuable tool in tx selection. Research Sponsor: Guardant Health; Breast Cancer Research Foundation; Saverin Breast Cancer Research Fund; Pan Mass Challenge; NCCN-Pfizer Collaborative Grant.

1076 Poster Session

Comparing clinical benefit of trastuzumab deruxtecan (T-DXd) and sacituzumab govitecan (SG) in a large cohort of HER2-negative metastatic breast cancer (MBC). First Author: George W. Sledge Jr., Caris Life Sciences, Phoenix, AZ

Background: T-DXd and SG are antibody-drug conjugates (ADCs) increasingly used in HER2-negative BC, however, there are insufficient data to guide ADC sequencing and use in tumors of various HER2 expression levels. **Methods:** A total of 4033 HER2 negative MBC treated with SG or T-DXd that underwent tumor profiling at Caris Life Sciences (Phoenix, AZ) were studied. HER2 low (Her2-L), ultra low (Her2-UL) and null (Her2-N) were tested by IHC and CISH. Hormone receptor status (HR+/-) was tested by ER and PR IHC. Real-world clinical data were obtained from insurance claims. Time on treatment (TOT) was determined as the interval from start to end of the ADCs. Cox proportional hazards model was used for hazard ratio (HR) and log-rank for p values. **Results:** Overall, 1444 (36%) were treated with T-DXd but not SG (T-only) while 1808 (45%) with SG but not T-DXd (S-only). HR+ cases comprise 64% of T-only and 24% of S-only cohorts; 75% and 68% of T-only and S-only tumors were taken from metastatic sites. As expected, HER2-L, HER2-UL and HER2-N cohorts treated with T-DXd had decreased TOT (4.8 months (m), 4.1m and 3.5m, p< .001) while HER2 status had no impact on SG TOT (3.0m, 2.8m and 3.4m). Interestingly, even in HER2-N group, T-only showed a borderline better TOT than S-only (Table, p=.053); this effect was significant in HR+ HER2-N subset but not significant in HR- HER2-N. Similarly, in HER2-UL and L, T-DXd TOT was significantly longer than SG TOT; when further stratified by HR status, the effect was highly significant in HR+ and not seen in HR- cohorts. In cohorts crossed over from one ADC to another, patients treated with T-DXd first (N=420) or SG first (N=361) showed no TOT difference (10.4m vs. 10.8m, p= .4); although the HER2-N subset had moderate preference of SG first (11.5m vs. 8.5m, HR=0.66 [0.52-0.84], p< .001, while TOT were similar in HER2-UL (HR=0.93, p=.7) and HER2-L (HR=1.04, p=.7) groups. **Conclusions:** We report outcome from a large real world dataset and demonstrate that T-DXd shows statically significant improved outcome in HR+ tumors across HER2 subgroups while in TNBC, both agents exhibit comparable benefit. In patients treated with both ADC's, SG first showed preferred outcome in HER2-N group but not in HER2-UL or L. We provide important insight on clinical benefit of the two widely used ADCs in breast cancer and warrants further validation in independent cohorts. Research Sponsor: None.

T-DXd (T-only) TOT and SG TOT (S-only) in cohorts stratified by HER2 and HR status.

	All				HR+				HR-			
	TOT (T;S, months)	N (T;S)	HR [95% CI]	p	TOT	N	HR	p	TOT	N	HR	p
HER2-N	4.7; 3.4	262; 1116	1.1 [1-1.3]	0.053	4.8; 3.0	209; 277	1.5 [1.2-1.8]	**<0.001***	4.6; 3.5	48; 822	1.1 [0.8-1.4]	0.6
HER2-UL	4.8; 3.0	295; 289	1.4 [1.2-1.7]	**<0.001***	5.1; 2.5	245; 99	1.8 [1.4-2.2]	**<0.001***	3.2; 3.0	46; 188	1.1 [0.8-1.6]	0.4
HER2-L	4.9; 3.5	707; 244	1.2 [1-1.4]	**0.011***	5.1; 3.1	595; 77	1.5 [1.2-1.9]	**<0.001***	4.2; 3.9	100, 164	1.1 [0.8-1.3]	0.7

*: Significant

1077 Poster Session

Steroid receptor expression and overall survival in breast cancer patients with ER+ bone metastasis: A retrospective review. First Author: Anthony Michael Rossi, University of Arizona College of Medicine, Tucson, AZ

Background: Endocrine therapy (ET) resistance is common in estrogen receptor-positive (ER+) metastatic breast cancer (BC), where bone metastases (BMET) are usually the first sign of spread. ER signaling and ET effects can depend on other steroid hormones receptors (SHRs), such as progesterone receptors (PR) and androgen receptors (AR). However, the roles of these receptors in ER+ BC BMET are underexplored. To address this gap, PR and AR protein expression in HER2-/ER+ BMET and associations with overall survival (OS) were examined. **Methods:** In a retrospective analysis on BC BMET samples analyzed at Caris Life Sciences, n = 2038 HER2- BMETS were identified by immunohistochemistry (IHC) (≤1+intensity or ≤10% staining, or 2+ & > 10% with CISH-null reflex test). HER2- ER+ (by IHC, ≥1+ & ≥1%) BMETs ("ER+ BMET" n = 1700; 84.5% of total) were then examined for prevalence of IHC+ SHR expression (PR: ≥1+ & ≥1%; AR: ≥1+ & ≥10%) and associated pathogenic/likely pathogenic *ESR1* or *PIK3CA*gene mutations (mut). Associations of SHR status with clinical outcomes were tested by inferring OS from biopsy collection or start of therapy to last contact. **Results:** Most ER+ BMET expressed PR (59.3%) or AR (87.1%). Only 9.4% of PR+/ER+ BMET were AR-null, while 38.2% of AR+/ER+ BMET were PR-null. Overall, "triple positive" (AR+/PR+/ER+) BMET comprised the largest group (53.7%), followed by PR-null AR+/ER+ BMET (33.2%). AR-null ER+ BMET with (5.6%) or without PR (7.3%) were less common. AR+ status was associated with better outcomes for ER+ BMET patients (pts) with longest OS for "triple positive", while "loss" of PR was associated with shorter OS (Cox proportional hazards ratio (HR) = 1.37, p < 0.0001). AR-null status was associated with worse OS compared to "triple positive" regardless of PR status (AR-/PR- HR = 1.66, p < 0.001; AR-/PR+ HR = 1.85, p < 0.0001). In ER+ BMET with *ESR1mut* (16.3%), OS for triple positive tumors, which were more prevalent (74.0%) due to increased PR expression, was reduced (HR = 1.92, p < 0.0001 vs *ESR1wt*). For *PIK3CA*, "loss" of PR abrogates benefits associated with AR+ status only in *PIK3CAmut* pts (48.7%) with patterns between SHR groups otherwise maintained. Among ER+ BMET pts who received aromatase inhibitors or fulvestrant, AR+ status was associated with the best OS, regardless of PR status, where treatment was associated with significantly longer OS (vs no treatment) across SHR groups, except in PR+/AR-null. For ER+ BMET pts treated with CDK4/6 inhibitors, OS was highest in the "triple positive" cohort, with onlyAR+ SHR groups demonstrating improved OS with treatment. **Conclusions:** Based on this analysis, AR expression is more prognostic of OS than PR, regardless of treatment, in pts with ER+ BC BMETs, with "triple positive" BMETs generally associated with the best OS. Research on SHRs as mediators vs biomarkers of risk in ER+ BC BMETs is needed to provide direction for possible therapeutic targeting. Research Sponsor: None.

1078 Poster Session

Evaluating accuracy and concordance of pathologists and the utility of AI assistance software for digital HER2 IHC assessment in breast cancer including HER2-ultralow scoring: An international multicenter observational study. First Author: Gabriela Acosta Haab, Pathology Department, Maria Curie Hospital, Buenos Aires, Argentina

Background: The emergence of novel therapeutic agents demonstrating improved progression-free survival (PFS) and overall survival (OS) in breast cancer patients with low HER2 expression underscores the need for accurate and reproducible HER2 status assessment. However, challenges such as subjective interpretation of immunohistochemistry (IHC) staining and variability in assay quality hinder diagnostic consistency. AI-based decision support software could enhance diagnostic accuracy and reproducibility. To date, systematic evaluation of pathologist performance in scoring low HER2 expression, as well as the role of AI assistance, remains limited in real-world, multicenter settings. **Methods:** Six academic centers from different countries provided digital HER2 IHC-stained breast cancer images (n = 728) generated with five whole-slide scanner models and one microscope camera. In a two-arm observational study, consensus ground truth (GT) scores were established by two expert pathologists per center without AI assistance. Subsequently, two additional pathologists (scorers) evaluated each case both without and with AI support. Scoring followed ASCO/CAP 2023 HER2 interpretation guidelines, with an additional subclassification of IHC 0 cases into "null" (IHC 0 with no staining) and "ultralow" (IHC 0 with membrane staining). **Results:** For the HER2-low decision range, AI software alone achieved 91.0% accuracy in distinguishing HER2 0 from 1+/2+/3+ scores against GT. Across the four categories, AI achieved 80.3% accuracy compared to 77.6% for scorers alone and 81.4% with AI assistance. AI support improved inter-reader agreement from 73.5% to 86.4%. When the HER2 ultralow category was included, AI assistance increased scorers' average accuracy across all classes from 70.4% to 74.7% and boosted inter-reader agreement from 65.6% to 80.6%. For differentiating HER2 null from HER2 ultralow, AI improved scorers' accuracy from 68.6% to 77.9%, resulting in 40% more cases being classified as HER2 ultralow and 65% reduction in the number of incorrectly scored HER2 null cases. **Conclusions:** This first international multicenter study on HER2 IHC diagnosis, including HER2 ultralow scoring highlights the challenges faced by pathologists and the significant benefits of AI decision-support systems in real-world settings. AI assistance improved pathologist concordance and accuracy, particularly at the HER2 null vs. ultralow boundary, reducing diagnostic errors. Incorporating AI into routine clinical diagnostics has the potential to optimize treatment selection for breast cancer patients. Research Sponsor: AstraZeneca.

1079 Poster Session

Elacestrant combinations in patients (pts) with ER+/HER2- locally advanced or metastatic breast cancer (mBC): Safety update from ELEVATE, a phase (Ph) 1b/2, open-label, umbrella study. First Author: Nancy Chan, NYU Langone Health, New York, NY

Background: Tumors develop resistance following 1L endocrine therapy (ET) + CDK4/6i in ER+/HER2- mBC. Elacestrant (Ela) significantly improved PFS vs standard-of-care (SOC) ET (*ESR1*-mut tumors HR 0.55; 95% CI 0.39-0.77; P=0.0005; all pts HR 0.70; 95% CI 0.55-0.88; P=0.0018) with a manageable safety profile for pts with ER+/HER2- mBC and prior ET+CDK4/6i (Bidard 2022). ELEVATE (NCT05563220) evaluates Ela in combination with everolimus (Eve), alpelisib (Alp), capivasertib (Capi), ribociclib (Ribo), palbociclib (Palbo), or abemaciclib (Abema) to address different resistance mechanisms. Prior analyses have demonstrated safety consistent with the known profiles of each agent in combination with SOC ET. Ph 1b safety and efficacy evaluations reported the RP2D and antitumor activity with the following combinations: Ela + Eve (RP2D: Ela 345 mg QD + Eve 7.5 mg QD) and Ela + Abema (RP2D: Ela 345 mg QD + Abema 150 mg BID)(Ciruelos ESMO 2024, Rugo ESMO 2024). Ela 345 mg + Palbo 125 mg was determined as the RP2D (Rugo SABCS 2024). Herein, we report updated safety that includes additional pts/dose levels, and longer observation time for Ela in different combinations. **Methods:** Eligible pts have ER+/HER2- mBC and 1-2L of prior ET regardless of *ESR1*-mut status. Objectives are to determine the RP2D (Ph 1b) and evaluate PFS (Ph 2) with each combination. **Results:** Table 1 reports the most common all-grade AEs from Ph 1b (Ribo, Alp, Capi combinations) and Ph 1b + Ph 2 (Eve combination) as of Dec 2024. Ela 345 mg + Ribo 400 mg QD was identified as the RP2D. Updated data will be presented. **Conclusions:** Elacestrant combinations continue to demonstrate safety consistent with the known profiles of each drug + SOC ET without increased risk of associated AEs. Elacestrant has the potential to become an ET backbone for multiple targeted agents, providing an all-oral treatment option in pts with ER+/HER2- mBC, delaying chemo or ADC-based regimens. Clinical trial information: NCT05563220. Research Sponsor: None.

Treatment-emergent AEs (≥30%).

	Ph 1B Ela (86-345 mg) + Ribo (400-600 mg) (n=32)	Ph 1B + Ph 2 Ela (258-345 mg) + Eve (5-10 mg) (n=72)	Ph 1B Ela (258 mg) + Alp (150-250 mg) (n=11)	Ph 1B Ela (258-345 mg) + Capi (320 mg) (n=9)
All grades, n (%)	Neutropenia* 12 (38) Nausea 10 (31)	Nausea 39 (54) Diarrhea 31 (43) Stomatitis 27 (38) Fatigue 23 (32)	Nausea 8 (73) Vomiting 6 (55) Rash† 4 (36)	Nausea 6 (67) Fatigue 5 (56) Diarrhea 5 (56) Vomiting 3 (33)
Grade ≥3, n (%)	Neutropenia* 8 (25)	Diarrhea 5 (7) Nausea 4 (6) Fatigue 4 (6) Stomatitis 2 (3)	Rash† 2 (18) Nausea 1 (9)	0

*Combined terms;
†Maculopapular rash.

1080 **Poster Session**

Enhancing precision oncology for Haitian breast cancer patients through deep learning-enabled computational pathology tools. First Author: Rebecca Henderson, University of Alabama at Birmingham, Birmingham, FL

Background: While early-stage breast cancer is often curable in high-resource settings, mortality-to-incidence ratios remain unacceptably high for women in lower- and middle-income countries (LMIC). This disparity is due to an inability within LMICs for patients to access basic cancer diagnostics (e.g., IHC). Consequently, there is a major need to develop innovative approaches for the cancer diagnostic-therapeutic pipeline to deliver high-quality care for LMIC patients. To this end, deep learning (DL) has shown considerable promise in identifying clinically relevant biology within histopathology (H&E). Therefore, we have curated an unprecedented dataset of H&E whole slide images (WSIs) and tissue-matched estrogen receptor (ER) status for 5500 breast cancer slides from Zanmi Lasante (Haiti). **Methods:** Using The Cancer Genome Atlas (TCGA) breast cancer and Haitian datasets, we trained a DL-enabled tool, using H&E WSIs, to predict ER status for each patient. As the TCGA dataset predominantly comprises patients of European ancestry, we assessed whether a TCGA-trained model would generalize to Haitian patients. After WSI processing and feature extraction, attention-based weakly supervised multiple instance learning was used to train a classification model. To assess performance, both the TCGA and Zanmi Lasante datasets were split into training (70%), validation (15%), and testing (15%) sets, and the results were compared across both patient populations. **Results:** Using the TCGA dataset (2100 H&E WSIs), we trained an ER classification model. This model demonstrated a performance of an area under receiver operating characteristic (AUROC) of 0.92 on the "held-out" TCGA test set, but only an AUROC of 0.71 on the Haitian "held-out" test set for ER status prediction. This drop in model performance, or domain shift, is consistent with known biological differences between breast cancers enriched in Black women compared to those in Caucasian women. Notably, pre-training our model on the TCGA dataset and then fine-tuning on a portion of the Haitian training set (2800 WSIs) substantially improved predictive performance to an AUROC of 0.85 on the Haiti test set. **Conclusions:** This study illustrates the potential of DL to advance precision oncology in low-resource settings and highlights the need for adequate training data from LMIC patients. We anticipate tools from this work will be deployed for use in Haitian breast cancer patients to inform precision-based use of endocrine therapies. Research Sponsor: None.

1081 **Poster Session**

Cell-free circulating chromatin profiling for epigenomic characterization of mechanisms of response and resistance to sacituzumab govitecan in breast cancer. First Author: Ana Christina Garrido-Castro, Dana-Farber Cancer Institute, Boston, MA

Background: The efficacy of sacituzumab govitecan (SG), a TROP2-directed antibody-drug conjugate (ADC), in hormone receptor-positive/HER2-negative (HR+/HER2-) metastatic breast cancer (mBC) has been demonstrated, yet biomarkers predicting response and resistance remain an unmet clinical need. We applied a novel multimodal epigenomic liquid biopsy assay to characterize tumor-specific transcriptional activation of relevant genes of interest and resistance mechanisms in the phase 2 SACI-IO HR+ trial (NCT04448886). **Methods:** Baseline plasma samples were collected from patients (pts) with HR+/HER2- mBC enrolled in SACI-IO HR+, which compared SG alone to SG combined with pembrolizumab (SG-pembro). Genome-wide signals from promoters, enhancers and DNA methylation were profiled from 1 mL of plasma from 95 pts, of which 80 met the assay quality control thresholds and ctDNA metrics required for downstream analysis (ctDNA $\geq$ 0.5%, N_{SG}= 42, $N_{SG\text{-}pembro}$= 38). We used epigenomic and RNA-seq datasets from 23 breast cancer cell lines to train a model to predict *TROP2* expression ($r = 0.66$, $P < 0.01$) and tested for association with progression free survival (PFS). We used Gene Set Variation Analysis to score samples for HALLMARK gene set activities using gene-proximal epigenomic signals and tested for independent association of those activities with PFS via CoxPH models, with baseline ctDNA fraction included as a known prognostic covariate. Statistical significance was determined based on improved model fit compared to ctDNA alone. **Results:** Compared to healthy donors, plasma from trial pts was enriched for breast cancer specific signatures such as estrogen response and hedgehog signaling (FDR $<$ 0.05), highlighting the ability of the liquid biopsy platform to extract tumor specific signal. Baseline ctDNA fraction was prognostic in both treatment arms (Hazard Ratio $[HR]_{SG}$= 0.38, $P < 0.01$; $HR_{SG\text{-}pembro}$= 0.28, $P < 0.01$). Conversely, predicted *TROP2* expression was not associated with PFS in either treatment arm. In the SG arm, higher activity of pathways such as epithelial to mesenchymal transition and Wnt signaling were associated with shorter PFS (FDR $<$ 0.1), highlighting potential mechanisms of resistance. Gene signatures related to cell cycle such as mitotic spindle and E2F targets were associated with longer PFS (FDR $<$ 0.1). The above pathway associations with PFS were not statistically significant in the SG-pembro arm. **Conclusions:** This study demonstrates the feasibility of a multimodal epigenomic liquid biopsy platform for non-invasive characterization of therapeutic response and resistance to SG with or without pembrolizumab in HR+/HER2- mBC. By providing real-time insight into transcriptional regulation, this approach may improve patient stratification and guide ADC treatment strategies. Clinical trial information: NCT04448886. Research Sponsor: Gilead Sciences; Merck; Komen; METAvivor; Gateway for Cancer Research; Mehlman Family Fund.

1082 **Poster Session**

Treatment patterns in HR+/HER2- metastatic breast cancer (MBC) with co-occurring *PIK3CA* and *ESR1* mutations. First Author: Jimmitti Teysir, Memorial Sloan Kettering Cancer Center, New York, NY

Background: *PIK3CA* and *ESR1* mutations co-occur in 12-15% of patients with HR+/HER2- MBC. While FDA-approved PI3K inhibitors (PI3Ki) and selective estrogen receptor degraders (SERDs) have advanced care for patients with biomarkers, treatment outcomes and optimal sequencing in those with co-occurring mutations remain unclear. **Methods:** We conducted a retrospective analysis of patients with HR+/HER2- MBC and co-occurring *PIK3CA* and *ESR1* mutations treated at Memorial Sloan Kettering (MSK) between 2010 and 2024. Mutations were identified via MSK-IMPACT (tumor tissue) and MSK-ACCESS (ctDNA), with additional genomic data integrated from Guardant and Foundation One. Clinical and treatment data, including PI3Ki (alpelisib, inavolisib or investigational agents) and/or SERDs (fulvestrant or oral agents) were abstracted. Median progression-free survival (mPFS) was assessed in patients with mutations identified prior to therapy initiation. **Results:** 3,166 patients with HR+/HER2- MBC were identified, including 1,444 (46%) with *PIK3CA* mutations, 664 (21%) with *ESR1* mutations and 243 (8%) with co-occurring mutations. After excluding 26 patients with incomplete records or concurrent malignancies, the final cohort included 217 patients (7%), with 206 having MSK-IMPACT, 58 MSK-ACCESS, 49 Guardant, and 3 FoundationOne data. Of 217 patients, 77 (36%) received a PI3Ki after a median of 4 prior lines (range: 1–16), with 68 (88%) having prior CDK 4/6i. Single-agent SERD was administered to 46 patients (21%) after a median of 3 prior lines (range: 2–18), including 34 (74%) with prior CDK 4/6i. 8 patients received PI3Ki followed by SERD, and 7 received SERD followed by PI3Ki, either consecutively or with intervening treatments. The mPFS was 7.1 m with PI3Ki (95% CI: 4.6–9.3) and 4.0 m with single-agent SERD (95% CI: 3.4–9.8). In the SERD cohort, earlier line of treatment (1–2 vs. 3+; HR 0.29, 95% CI 0.09–0.90) and liver metastasis (HR 3.42, 95% CI 1.10–10.6) were independently associated with PFS. CDK 4/6i duration $\geq$12 m in the SERD cohort was associated with improved mPFS in stratified analysis (9.8 vs. 2.7 m; log-rank p = 0.002). For patients treated with PI3Ki followed by SERD (n = 8), mPFS1 was 8.9 m (95% CI: 5.6, NE) and mPFS2 was 6.0 m (95% CI: 2.3, NE). SERD to PI3Ki (n = 7) yielded a mPFS1 of 3.4 m (95% CI: 1.8, NE) and mPFS2 of 10.0 m (95% CI: 1.6, NE). **Conclusions:** Prior CDK4/6i $\geq$ 12 m in patients with co-occurring mutations treated with a SERD was associated with significantly improved PFS, potentially reflecting a conditioning effect of prior therapy. The total PFS (PFS1 + PFS2) in patients treated with sequential targeted therapies was similar; however, small sample sizes and potential confounders in this retrospective cohort limit definitive interpretations. Larger prospective studies are needed to determine optimal sequencing strategies. Research Sponsor: None.

1083 **Poster Session**

Targeting PARP-1 in ER-positive endocrine-resistant breast cancer. First Author: Azzurra Zicarelli, University of Chicago, Chicago, IL

Background: Resistance to endocrine therapy (ET) in breast cancer (BC) patients is frequently associated with acquired ESR1 gene mutations like the Y537S, which triggers a constitutive estrogen receptor (ERα) activation. Therefore, the identification of novel therapeutic strategies is crucial for the management of ER-positive, ET-resistant BC. In this context, PARP1 poly(ADP-ribose) polymerase 1 (PARP-1) has emerged as a promising therapeutic target, based on its involvement in the regulation of oxidative DNA damage in BC cells. **Methods:** Data from the METABRIC dataset were used to assess the clinical relevance of PARP-1 in ER-positive BC patients. As experimental models, MCF7 and T47D BC cell lines expressing ERα wild type (wt) or Y537S mutation were used. PARP-1 regulation was investigated by western blotting, immunofluorescence, and chromatin immunoprecipitation (ChIP) assays. Gene expression, promoter assays, and chromatin immunoprecipitation sequencing (ChIP-seq) studies allowed us to analyze the transcriptional activity mediated by ERα. Cell cycle, proliferation and colony formation experiments as well as *in vivo* studies were performed to evaluate the biological effects of the PARP-1 inhibitor niraparib. **Results:** We observed that the up-regulation of PARP-1 upon exposure to 17β-estradiol (E_2) occurs through ERα in BC cells expressing either ERα wt or Y537S mutation. Moreover, we assessed that the transcriptional activity of ERα relies on PARP-1, as demonstrated by the ability of nirabarib to prevent the transactivation of ERα and the regulation of ERα target genes. In addition, niraparib halted the proliferation and cycle progression of BC cells expressing either ERα wt or Y537S mutation. Of note, niraparib suppressed primary tumor growth in xenograft tumors derived from ERα Y537S mutated MCF7 cells. **Conclusions:** Our data suggest that crosstalk between PARP-1 and ERα is involved in the proliferative responses of ERα wt or Y537S mutated BC cells. Therefore, targeting PARP-1 could provide a promising strategy to overcome the ET resistance of BC cells. Research Sponsor: None.

1084 **Poster Session**

Racial and ethnic differences in biomarker testing for targetable alterations among patients with HR+ HER2- metastatic breast cancer (mBC). First Author: Catherine Keane, Flatiron Health, New York, NY

Background: In recent years novel therapies have been approved for patients (pts) with mBC and *ESR1*, *AKT1*, *PTEN*, *PIK3CA*, and *gBRCA* alterations. Given limited evidence on which patients are receiving standard of care, this study assessed racial and ethnic inequities in biomarker testing and the role of social determinants of health (SDOH) in explaining potential inequities. **Methods:** This study leveraged the US nationwide Flatiron Health electronic health record (EHR)-derived, deidentified database of > 750 000 pts with BC. Adult female pts diagnosed (dx) with HR+ HER2- mBC between 1/1/2011, and 4/30/2024, with a geocodeable address were included. Testing rates for alterations in *ESR1*, *PIK3CA*, *AKT1*, *PTEN*, and *gBRCA* were measured over time from mBC dx using variables extracted from unstructured clinician documentation in the EHR using machine learning. Fine and Grey models accounting for competing risks were used to estimate subdistribution hazard ratios (HR) and 95% confidence intervals (CI) for biomarker access. Models were adjusted for covariates including age, stage, ECOG status, and dx year, followed by practice setting and area-level SDOH factors (ie, English language proficiency, residential segregation, vehicle ownership, urbanicity, and residence in medically underserved areas). **Results:** The cohort included 36 316 pts (61.5% non-Latinx [NL]-White, 6.1% Latinx, 9.7% NL-Black, 1.9% NL-Asian, and 20.8% NL-Other/Unknown). Overall, Asian, Black, and Latinx pts were less likely than White pts to undergo biomarker testing (adjusted HR [95% CI]: Latinx, 0.88 [0.82-0.95]; NL-Black, 0.87 [0.82-0.93]; NL-Asian, 0.87 [0.76-0.98]). Racial/ethnic inequities in overall biomarker testing were partially explained by SDOH factors. Specifically, the White-Latinx inequity in testing was mediated by residential segregation ie, association attenuated towards the null (mediated HR [95% CI], 0.94 [0.87-1.02]), limited English proficiency (0.92 [0.85-1.00]), and lack of vehicle ownership (0.91 [0.84-0.98]). Compared with White pts, NL-Black pts were less likely to be tested for *ESR1* (HR [95% CI], 0.86 [0.77-0.95]) and *PIK3CA* (0.86 [0.80-0.92]). Latinx pts were less likely to be tested for *PIK3CA* (0.87 [0.80-0.95]) and this inequity was mediated by residential segregation (0.96 [0.87-1.05]) and limited English proficiency (0.92 [0.84-1.00]). **Conclusions:** Asian, Black, and Latinx pts were generally less likely than their White counterparts to receive biomarker testing after a mBC dx, especially for *PIK3CA* and *ESR1*. SDOH factors explained some of these biomarker testing inequities. Equitable access to biomarker testing should be prioritized to ensure patients have access to the most effective therapies. Future research should examine whether racial/ethnic inequities in biomarker testing are associated with inequities in treatment and outcomes. Research Sponsor: Flatiron Health.

1085 **Poster Session**

Therapeutic impact of novel agents in patients with stage IV de novo HR+ve/Her2-ve breast cancer: Results from a real world dataset. First Author: Shaheenah S. Dawood, Mediclinic City Hospital, Dubai, United Arab Emirates

Background: The objective of this retrospective analysis was to look at the therapeutic impact of CDK4/6i and novel agents among pts with stage IV Denovo HR+ve/HER2-ve breast cancer (BC). **Methods:** We utilized a federated network of de-identified health data representing approximately 165 million pt lives available through the TriNetX Research Network. We identified 41,843 pts with HR+ve/HER2-ve stage IV Denovo BC treated diagnosed between Jan 2005 - Jan 2025. Propensity score matching analysis by age and site of metastases was carried out. OS was computed using the Kaplan Meier product limit method. The index event is the date of diagnosis. **Results:** 8,541(20.4%) received a CDK4/6i. Among pts treated with CDK4/6i 1,396(16.3%), 6,169 (72.2%) and 2,157 (25.2%) pts received Ribo, Palbo and Abema respectively. Over time there has been a significant decrease in use of palbocilcib with significant increase in use of abema and ribo. Median OS was similar between Ribo and Abema(HR 0.88; 95%CI (0.75,1.04) p=0.14). Compared to pts receiving palbo median OS was signficantly better among pts receiving abema (HR 0.77; 95%CI (0.69,0.85) p<0.0001) or ribociclib (HR 0.69; 95%CI (0.60,0.81) p<0.0001).628 pts received more than one CDK4/6i. (152 palbo + ribo, 118 ribo + abema, 368 abema+ palbo). 5-year OS was 63.9% and 70.4%(HR 1.37; 95%CI 1.06,1.77) respectively among pts who received 1 vs >1 CDK4/6i. Among patients treated with CDK4/6i, OS was significantly longer among pts who received elacestrant vs those who did not (HR 0.401; 95%CI (0.215,0.745). 228 pts treated with a CDK4/6i received an antibody drug conjugate (ADC). Median time to use of an ADC was 45m. 5yr OS was 75.8% vs 58.7% among those who did and did not receive an ADC respectively (HR 0.45, 95%0.30,0.67). 5yr OS was 76.2% vs 52.7% among those who did and did not receive Trastuzumab deruxtecan respectively (HR 0.37, 95%0.19,0.70). 5yr OS was 76.2% vs 60.4% among those who did and did not receive Sacituzumab govetican respectively (HR 0.40, 95%0.25,0.65). **Conclusions:** Among pts with stage IV Denovo HR+ve/HER2-ve BC treated with a CDK4/6i using a CDK4/6i beyond progression is an option. Novel agents such as oral SERDS and ADCs are also associated with improved prognostic outcome in the real world setting. Research Sponsor: None.

1086 **Poster Session**

Updated efficacy of mutant-selective PI3Kα inhibitor RLY-2608 in combination with fulvestrant in patients with *PIK3CA*-mutant HR+HER2- advanced breast cancer: ReDiscover trial. First Author: Sarah L. Sammons, Dana-Farber Cancer Institute, Boston, MA

Background: Oncogenic *PIK3CA* mutations constitutively activate PI3Kα and drive approximately 40% of HR+HER2- breast cancer (BC); however, the toxicity (hyperglycemia, rash, diarrhea, stomatitis) of non-selective inhibitors (i) limits their tolerability and efficacy. RLY-2608 is the first oral, pan-mutant-selective, allosteric PI3Kαi designed to overcome these limitations. We report efficacy and safety of RLY-2608 + standard-dose fulvestrant (F) in pts with *PIK3CA*-mutant, HR+HER2- BC treated in the FIH study, ReDiscover (NCT05216432). **Methods:** Previously treated adult pts with advanced HR+HER2- BC and *PIK3CA* mutation per local assessment were eligible. Pts were eligible to enroll with measurable or non-measurable disease. Key objectives were investigator-assessed efficacy per RECIST 1.1 and adverse events (AEs) per CTCAE v5.0. **Results:** As of 4NOV24, safety was assessed in 118 pts treated across RLY-2608 doses 100-1000 mg BID, and efficacy in the 52 pts without detectable *PTEN/AKT* co-alterations treated at the RP2D (600 mg BID). All pts received prior endocrine therapy and CDK4/6i with 48% having ≥ 2 prior systemic therapies for advanced disease including 56% with prior F/SERD and 25% with prior chemotherapy or antibody-drug conjugate. Median follow-up was approximately 9.5 months. The RP2D provided exposure in the target therapeutic range and rapid clearance of mutant *PIK3CA* ctDNA. 31/52 pts had measurable disease with 26/31 (83.9%) achieving disease control, 23/31 (74.2%) experiencing radiographic tumor reduction and 12/31 achieving an objective response (38.7%, 95% CI 21.8-57.8) with median time-to-response 8 weeks. mPFS was 9.2 months (95% CI 5.8,18.4) across all 52 RP2D pts, and 11.4 months (95% CI 7.2-NR) in 32 pts receiving RLY-2608 at the RP2D as 2L treatment. Treatment-related AEs (TRAEs) were generally low-grade, manageable and reversible, most commonly hyperglycemia (42.4% any grade; 2.5% Gr 3), nausea (41.5%; 0.8% Gr 3), fatigue (40.7%; 8.5% Gr 3), creatinine increased (34.7%; 0.8% Gr 3), and diarrhea (30.5%; 1.7% Gr 3). There were no grade 4/5 TRAE; and severe, off-target stomatitis and rash were absent or rare. **Conclusions:** RLY-2608 demonstrates favorable safety/tolerability along with highly encouraging PFS observed across *PIK3CA* genotypes in pts with advanced *PIK3CA*-mutant HR+HER2- BC previously exposed to CDK4/6i. These data validate RLY-2608 as the first allosteric pan-mutant selective PI3Kαi and support advancing RLY-2608 + F to pivotal testing, which is planned for later this year. Clinical trial information: NCT05216432. Research Sponsor: Relay Therapeutics.

1087 **Poster Session**

Impact of body weight and body composition on survival and toxicities in patients receiving CDK4/6 inhibitors for ER+/HER2- metastatic breast cancer. First Author: Jorge Avila, Montefiore Medical Center, Bronx, NY

Background: Body composition influences treatment outcomes and adverse events in many oncologic conditions including metastatic breast cancer (mBC). The objective of our study was to evaluate the impact of body composition measures on progression-free survival (PFS) and adverse events in patients treated with cyclin-dependent kinase 4/6 (CDK4/6) inhibitors for estrogen receptor-positive (ER+)/HER2- mBC. **Methods:** A single institution retrospective analysis of 207 patients treated with CDK4/6 inhibitors was conducted. Baseline body weight and body composition measures (total fat, visceral fat, subcutaneous fat, skeletal muscle area, skeletal muscle density and muscular adiposity) were analyzed. PFS was evaluated using Cox proportional hazard models, and logistic regression was used to evaluate the relationship between these variables and adverse events. Early changes in body composition were defined as variations in muscle or fat compartments within 3 months. Low muscle quality was defined as muscle power index value of 1 to 2 Standard Deviations below the normal range. **Results:** The median age of our cohort was 61 years, with 77% of patients being postmenopausal and 46% identifying themselves as Black. Most patients received palbociclib (76%), followed by abemaciclib (14%) and ribociclib (10%) as part of their treatment. Median BMI was 27.97 kg/m2, with 36% being classified as obese. Sarcopenia was present in 18% of our patients, and 71% had low muscle quality. Higher BMI (HR, 0.96; 95% CI, 0.93-0.99; p 0.01), obesity (HR, 0.60; 95% CI, 0.42-0.86; p = 0.01) and weight (HR, 0.99; 95% CI, 0.98-0.99; p = 0.01) were significantly associated with improved PFS. Modest but statistically significant associations with PFS were observed for total fat (HR 0.99; 95% CI 0.98-0.99; p = 0.01) and subcutaneous fat (HR, 0.99; 95% CI, 0.98-0.99; p = 0.01); however, this was not the case for visceral fat and muscle adiposity. There was no significant association between body muscle compartment distribution (including sarcopenia) and PFS. Early changes in skeletal muscle density were associated with improved PFS (HR, 0.95; 95% CI, 0.91-0.99; p = 0.01), while sarcopenia and low muscle quality were not significant predictors. Grade 3/4 hematologic toxicities were associated with lower muscle area (p = 0.02), but no significant association between fat compartments and adverse events was found. **Conclusions:** Obesity is associated with improved survival outcomes in patients receiving CKD4/6 inhibitors for ER+/HER2- mBC; furthermore, this effect is driven by subcutaneous fat. Early changes in skeletal density during CDK4/6 inhibitors treatment is a potential predictor of improved outcomes. Muscle area is a potential predictor of treatment toxicities. Our findings suggest that body composition plays an important role in outcomes and adverse events in this group of patients. Research Sponsor: None.

1088 Poster Session

Phase 1 trial of exercise as first-line therapy for hormone receptor (HR)–positive advanced breast cancer (TBCRC 054). First Author: Neil M. Iyengar, Memorial Sloan Kettering Cancer Center, New York, NY

Background: Observational studies show post-diagnosis exercise is associated with reduced risk of cancer death in patients with HR-positive breast cancer. We conducted a phase 1a dose-finding trial of exercise therapy as first-line treatment for HR-positive advanced breast cancer (TBCRC 054). **Methods:** This multicenter trial was conducted using a patient-centric, decentralized platform (NCT03988595). Non-exercising patients receiving first line endocrine plus CDK4/6 inhibitor therapy were allocated using an adaptive continual reassessment design to one of four escalated exercise therapy dose levels (range: 90 to 300 min/week) of individualized, moderate-intensity treadmill walking for 6 consecutive months. The trial was later amended to add a fifth dose level of 375 min/week and to allow dose cohort backfilling. Exercise therapy sessions were conducted remotely in patient's homes with real-time monitoring. The primary objective was to identify the recommended phase 2 dose (RP2D) as determined by feasibility and preliminary clinical efficacy. Feasibility was evaluated by relative exercise dose intensity (REDI). A dose level was considered feasible if ≥70% of patients achieved a REDI ≥75%. One-year progression free survival (PFS) rates were assessed by the Kaplan-Meier method. **Results:** Fifty-four women (median age 53 [46 to 63] years) were enrolled between August 2019 and April 2024; 23 (43%) had visceral metastases, 43 (80%) received an aromatase inhibitor, 11 (20%) received fulvestrant, and 53 (98%) received a CDK4/6 inhibitor. The proportion of patients with REDI ≥75% in each dose level was: 90 min/week (n = 10): 80%, 150 min/week (n = 10): 60%, 225 min/week (n = 11): 82%, 300 min/week (n = 13): 62%, and 375 min/week (n = 10): 40%. Among the two feasible dose levels (90, 225 min/week), 1-year PFS rate was 70% (95% CI, 47% to 100%) in the 90 min/week dose level and 91% (95% CI 75% to 100%) in the 225 min/week dose level. No serious adverse events were observed. Overall, 225 min/week (~ 45 minutes per treatment at 5 times weekly) was selected as the RP2D. **Conclusions:** This multicenter phase 1 trial showed that exercise therapy doses of 90 and 225 min/week are feasible and safe in patients receiving first line endocrine-based therapy. These data also support the rationale for a phase 2 trial testing the preliminary clinical efficacy of exercise at the RP2D of 225 min/week in HR-positive advanced breast cancer. Clinical trial information: NCT03988595. Research Sponsor: National Cancer Institute; R01CA235711.

1089 Poster Session

Pulmonary toxicities in patients (pts) with metastatic breast cancer (mBC) treated with trastuzumab deruxtecan (T-DXd): The Mayo Clinic Enterprise Experience, updated. First Author: Jenna Elizabeth Hoppenworth, Mayo Clinic, Rochester, MN

Background: T-DXd has become an important treatment option in mBC and other malignancies. Interstitial lung disease/pneumonitis (ILD) occurred in 10-14% of pts in the DESTINY-Breast trials (0-2% G5 ILD), and with potential lower incidence/severity in earlier line settings (Krop et al, ASCO 2023). We previously reported the Mayo Clinic Rochester, MN experience with T-DXd related ILD in mBC (Hoppenworth et al, ASCO 2024). Here, we expand the data to include patients treated at all locations of the Mayo Clinic Enterprise. **Methods:** We retrospectively identified pts with mBC who received ≥1 dose of T-DXd across the Mayo Clinic enterprise (Rochester, MN; Mayo Clinic Health System locations in MN/WI; Scottsdale, AZ; and Jacksonville, FL) between July 2022-December 2023. Demographic, mBC characteristics, and pulmonary clinical variables were abstracted from the clinical records. Data were summarized using descriptive statistics. Diagnosis of ILD was determined by treating clinicians, and severity was approximated to CTCAE V5 based on clinical documentation. **Results:** 252 pts with mBC received T-DXd during the study period. The majority were Caucasian (86%) and female (99%) with a median age of 63. 91 pts (36%) were current/formers smokers and 97 (39%) had prior pulmonary comorbidities. The majority had HER2 low (155, 62%) and HR positive (164, 65%) mBC. 35 (14%) developed any grade ILD [G1: 6 (17%), G2: 13 (37%), G3: 3 (8.6%), G4: 3 (8.6%), G5: 10 (29%)], with 15 (43%) presenting with ≥G3. 29 (83%) presented with at least 1 symptom (cough or SOB). Among those with previous pulmonary toxicity, 4 (33%) had previous pneumonitis in the ILD cohort. The median prior lines of all therapies (including endocrine therapy) were 5, with a median of 3 prior lines of chemotherapy in both the ILD (range 1-13) and non-ILD cohorts (range 1-13). Median onset to any grade ILD was 7 cycles. 20 pts (57%) received steroids for ILD. 14 (40%) had a bronchoscopy, all had a CT chest, 16 (46%) were hospitalized, 7 (20%) were intubated and 1 (3%) had a lung biopsy. Pts with G5 ILD had a median of 3 lines of chemo and a median of 8 cycles prior to onset of ILD, compared to 3 lines of chemo and a median of 7 cycles for those with G1-4 ILD. G5 pts were all Caucasian females, 5 were former smokers, 5 were non-smokers, 1 had a history of pneumonitis. T-DXd was rechallenged in 4 pts (G1-2 ILD) without ILD recurrence. **Conclusions:** In this retrospective case series,14% of pts treated with T-DXd experienced any grade ILD (4% G5) which is in alignment with the rate observed in the pivotal DESTINY-Breast trials, though with higher rates of G5 toxicity. Among those with ILD, increased lines of therapy were not associated with increased risk. Further research is needed to correlate risk. Research Sponsor: None.

1090 Poster Session

Preliminary efficacy and safety of TQB2102 in patients with HER2 low-expressing recurrent/metastatic breast cancer: Results from a phase 1b study. First Author: Shusen Wang, Department of Medical Oncology, Sun Yat-Sen University Cancer Center; State Key Laboratory of Oncology in South China; Collaborative Innovation Center for Cancer Medicine, Guangzhou, China

Background: TQB2102 is a novel antibody-drug conjugate (ADC) comprised of a recombinant humanized anti-HER2 bispecific antibody that simultaneously binds to two distinct HER2 epitopes (ECD4 and ECD2), an enzyme-cleavable linker, and a DNA topoisomerase I inhibitor payload. This study aims to evaluate the efficacy and safety of TQB2102 for patients (pts) with HER2-expressing relapsed/metastatic breast cancer. **Methods:** This 1b phase, open-label, multicenter, randomized trial was divided into two cohorts: Pts in cohort 1 were HER2 low-expressing breast cancer and in cohort 2 were HER2 positive BC, all pts were refractory or intolerant to standard therapy. In cohort 1, HER2 low-expressing pts were randomly assigned to receive TQB2102 monotherapy at a dose of 6.0 mg/kg (Q3W, IV) or 7.5 mg/kg (Q3W, IV). The primary endpoint was ORR per RECIST v1.1, and the secondary endpoints were PFS, DCR and safety etc. **Results:** 73 HER2 low-expressing female pts were randomized to receive at least one dose of TQB2102 6mg/kg (n = 37) or 7.5mg/kg (n = 36), the median age was 53. All pts had received chemotherapy in the metastatic setting, and hormone receptor positive pts (n = 50) also had received prior CDK4/6 inhibitors. In cohort 1, pts had undergone a median of 4 prior treatment lines (range: 1-10) in the metastatic setting, the median prior lines of chemotherapy therapies were 2 (range: 1-5), and 12.3% (n = 9) pts had received prior ADCs. As of data cutoff on Nov 1, 2024, median follow-up time was 7.16 months. ORR was 53.4% (39/73) in cohort 1, and the ORR of 7.5mg/kg (58.3%) was better relative to 6.0mg/kg (48.7%). Objective responses were observed in subgroups with HR positive pts (27/50, ORR 54.0%), HR negative pts (12/23, ORR 52.2%); of which the ORR of 7.5mg/kg with HR+ and HR- was 66.7% (14/21) and 46.7% (7/15), respectively. For HER2 low-expressing pts who received prior ADC therapies, the ORR was 44.4% (4/9). In cohort 1, DCR was 86.3% (63/73, among 6 pts was not available), and median PFS was not yet mature. TRAEs were reported in 71 (97.3%) HER2 low-expressing pts. Grade≥3 TRAEs and serious TRAEs were reported in 30 (41.1%), 13 (17.8%) pts, respectively. The main TRAEs were neutropenia, leukopenia, anemia, nausea, vomiting. The common TRAEs and grade ≥3 TRAEs occurred similarly at both doses, with hematologic toxicities such as anemia were slightly higher at 7.5mg/kg than at 6.0mgkg, but all were tolerable. No Interstitial lung disease was reported in cohort 1 pts. **Conclusions:** TQB2102 was well-tolerated and showed promising antitumor activity in heavily pretreated HER2 low-expressing recurrent/metastatic breast cancer pts. The recommended phase 3 dose of TQB2102 in HER2 low-expressing r/m BC was 7.5 mg/kg Q3W. A phase III trial to evaluate the efficacy and safety of TQB2102 versus investigator-selected chemotherapy in HER2 low-expressing r/m BC is currently ongoing (NCT06561607). Clinical trial information: NCT06115902. Research Sponsor: None.

1091 Poster Session

Standard-dose vs fixed-dose capecitabine in patients with advanced gastrointestinal and metastatic breast cancer. First Author: Nanuli Gvazava, The University of Kansas Cancer Center, Westwood, KS

Background: Capecitabine at the FDA-approved standard dose (SD) of 1250 mg/m² twice daily for 14 days with a 7-day break, has significant toxicities. We conducted a randomized trial comparing SD and fixed dose (FD) Capecitabine 1500 mg twice daily, 7 days on, 7 days off in patients with metastatic breast cancer (MBC) and advanced gastrointestinal (GI) cancers. We previously reported that in MBC cohort progression-free survival and overall survival were similar, and FD had significantly lower toxicities. We now present time to treatment failure (TTF) and toxicity in MBC and GI cohorts. **Methods:** Patients with MBC or advanced GI cancers (colorectal, small bowel, gastroesophageal, pancreatic and bile duct) with any prior lines of therapy were randomized 1:1 to either FD-7/7 or SD-14/7. Post hoc analysis was performed to determine TTF, and landmark analysis was performed for Freedom from Treatment Failure (FFTF). Capecitabine-related toxicities [diarrhea, hand foot syndrome (HFS) and stomatitis] were solicited and graded at each visit. **Results:** 182 patients were enrolled (N=93 FD, N=89 SD) of which 153 had MBC and 29 had an advanced GI cancer. Median TTF was 4.92 months (3.02, 5.93) in FD arm, and 3.11 months (2.49, 3.90) in SD arm (log rank p=0.0111). Landmark analysis of FFTF is shown in Table 1. At 24 months, the FFTF in the FD arm was 15.6%, while in the SD arm it was 2.5% (p=0.0054). Grade 2 and higher toxicities were more common in SD compared to FD, including HFS, diarrhea, and stomatitis (Table 1) **Conclusions:** Fixed-dose capecitabine at 1500 mg twice daily for 7 days on and 7 days off demonstrates a longer time to treatment failure compared to the standard FDA-approved dosing in patients with MBC and advanced GI cancers and is associated with significantly lower toxicities. Clinical trial information: NCT02595320. Research Sponsor: None.

Landmark freedom from treatment failure at 12, 24 and 36 months; solicited adverse events.

Time	FD-7/7, N=93 Survival Probability Estimate	SD-14/7, N=89 Survival Probability Estimate	P-value
3-month	61.3%	51.4%	0.1917
6-month	39.6%	30.6%	0.2224
12-month	23.8%	14.1%	0.1188
24-month	15.6%	2.5%	0.0054
Adverse Event		Number (proportion)	
Diarrhea			
Any Grade	51 (54.8%)	59 (66.3%)	0.1142
Grade 2-4	8 (8.6%)	35 (39.3%)	<0.0001
Grade ≥ 3	3 (3.2%)	20 (22.5%)	<0.0001
HFS			
Any Grade	46 (49.5%)	61 (68.5%)	0.0090
Grade 2-4	13 (14.0%)	40 (44.9%)	<0.0001
Grade ≥ 3	1 (1.08%)	15 (16.9%)	0.0002
Stomatitis			
Any Grade	24 (25.8%)	48 (53.4%)	0.0001
Grade 2-4	2 (2.2%)	13 (14.6%)	0.0023
Grade ≥ 3	0 (0.0%)	6 (6.7%)	0.0125*

*Fisher's exact test.

1092 **Poster Session**

Limited changes in the CNS immune microenvironment in patients with breast cancer metastasis and capturing these changes using machine learning. First Author: Andrew Ip, John Theurer Cancer Center, Hackensack University Medical Center, Hackensack, NJ

Background: Metastasis of breast cancer to the central nervous system (CNS) is common, especially in triple negative and HER2-positive tumors. The CNS is considered immune specialized and likely the brain and brain-border immune microenvironment creates a sanctuary site for breast cancer CNS metastasis. A better understanding of the immune microenvironment may allow for better utilization of immunotherapy to treat CNS metastasis. Toward this goal, we evaluated the cellular transcriptomic profile of cerebrospinal fluid (CSF) cells and compared between patients with documented metastatic tumor by cell-free DNA (cfDNA) testing of the CSF fluid (cfCSF-Pos) and patients without evidence of cfDNA metastasis (cfCSF-Neg) (Charifa et al., https://doi.org/10.1016/j.jlb.2024.100281). **Methods:** RNA was extracted from the CSF cells of 63 cfCSF-Pos patients and 93 cfCSF-Neg patients. The RNA was sequenced and quantified using a targeted RNA panel of 1600 genes by next generation sequencing (NGS). We used two thirds of the samples for training a machine learning (ML) system and one third for testing. The ML system uses Bayesian statistics with k-fold cross-validation (with k = 12) to first rank the top biomarkers distinguishing CSF-Pos from CSF-Neg samples. Then Random Forest was used to distinguish between the two classes using the top ranked biomarkers. **Results:** cfCSF-Neg contains mainly T-cells with median CD2:CD22 RNA ratio of 70.07 (range 0.01-14820). This was not significantly different (p = 0.19) from cfCSF-Pos cases (median: 41.31, range: 0.4-10172). The ratio of CD4:CD8A in cfCSF-Neg (median: 4.89, range: 0.47-2522) was also not significantly different (p = 0.31) from that in cfCSF-Pos cases (median: 5.0, range: 0.29-48). While significant variation in the levels of T- and B-cells is noted within each group, there was no significant difference in the individual cell population (T-cells, B-cells, plasma cells, natural killer cells, neutrophils, monocytes, or dendritic cells) overall after adjusting for multiple testing. Despite this lack of difference in cell populations, the testing set showed that cfCSF-Pos patients can be readily distinguished from cfCSF-Neg patients with AUC of 0.886 (CI: 0.797-0.976) using 30 top genes selected by ML. Except for KRT8 and KRT19, the majority of the top genes selected by the ML algorithm suggests modulation of T-cell activation including but not limited to TBX21, CD3D, CD5, IKZF3, NFATC2, and INPP5D. **Conclusions:** The data suggest the CNS remains immunologically specialized with modulating the adaptive immune response in the setting of breast cancer metastasis. Significant modulation in the CSF T-cells suggests selective targeting with immunotherapy may prove beneficial with the potential for active monitoring using this combination CSF cellular and cfDNA approach. Research Sponsor: None.

1093 **Poster Session**

A phase II study to evaluate the safety and efficacy of BB-1701 in subjects with HER2 expression locally advanced/metastatic breast cancer previously treated with HER2-ADC containing TOP-I inhibitor. First Author: Xiaoxiang Guan, The First Affiliated Hospital of Nanjing Medical University, Nanjing, China

Background: BB-1701 is an HER2-targeting antibody-drug conjugate (ADC) containing eribulin. In phase I study, BB-1701 had shown promising antitumor activity in breast cancer (BC) patients with HER2 high/low expression and manageable safety profile. Currently, there are no approved treatment options for metastatic BC patients with high/low expression who have received HER2-ADC containing TOP-I inhibitor, especially for trastuzumab deruxtecan. We report the preliminary efficacy and safety results from the ongoing phase 2 study of BB-1701 in advanced or metastatic breast cancer patients with HER2 expression previously treated with HER2-ADC containing TOP-I inhibitor. **Methods:** Patients enrolled were $\geq$18 years of age; had confirmed locally advanced/metastatic HER2 expressing breast cancer; disease progression after previous HER2-targeting ADC (containing TOP-I inhibitor) therapy; an ECOG PS $<$ 2; and measurable lesion(s) (per RECIST v1.1). HER2 expression was confirmed by IHC before patient enrollment. BB-1701 is administered at 1.6 mg/kg Q3W. **Results:** As of 28 January 2025, 23 patients with HER2 high/low-expressing breast cancer have been enrolled and treated. Median age is 51 years, all patients are female, and 26.1%/73.9% patients have ECOG PS 0/1. The median number of prior systemic therapy lines was 4.0, 21.7%/78.3% HER2 status are high expression/low expression. All patients experienced at least one treatment-emergent adverse events (TEAEs). The most common ($\geq$10%) all grade TEAES are neutrophil count decreased, platelet count decreased, Aspartate aminotransferase increased, and white blood cell count decreased. One grade 3 TEAEs is peripheral neuropathy, and another grade 3 TEAE is neutrophil count decreased. There has been no grade 4 or grade 5 events as of data cut-off date. One treatment emergent serious adverse event is peripheral neuropathy. Of the 23 patients, 14 were evaluable for efficacy. Among 14 evaluated patients, 4 patients achieved partial response (PR) and 9 patients had stable disease (SD), with disease control rate (DCR) of 92.8%. Among 3 HER2 high-expressing patients who were previously treated with trastuzumab deruxtecan, 1 patient achieved PR and 2 patients had SD with DCR of 100.0%. Among 8 HER2 low-expressioning (IHC 1+) patients, 3 patients achieved PR (2 patients received prior trastuzumab deruxtecan and 1 patient received prior SHR-A1811) and 4 patients had SD with DCR of 87.5%. More data will be presented at the ASCO meeting. **Conclusions:** BB-1701 shows promising antitumor activity and a manageable safety profile in HER2 expressing breast cancer patients who had previously been treated with HER2-ADC (containing TOP-I inhibitor). Clinical trial information: CTR20241422. Clinical trial information: CTR20241422. Research Sponsor: None.

1094 **Poster Session**

Results of a phase I study of alpelisib and sacituzumab govitecan (SG) in patients with HER2-negative metastatic breast cancer (MBC). First Author: Priyanka Sharma, University of Kansas Medical Center, Westwood, KS

Background: Sacituzumab govitecan (TROP2-directed antibody drug conjugate, ADC) is effective in treatment of pretreated HER2-negative MBC. PI3K is the most frequently altered pathway in breast cancer. This phase I trial investigated the combination of SG plus alpelisib (oral α-specific PI3K inhibitor) in HER2-negative MBC. **Methods:** Eligible patients had HER2-negative MBC and had received $\geq$1 prior line of chemotherapy in the advanced or neo/adjuvant setting and had not received prior PI3K/AKT inhibitor. The study was 3+3 dose escalation design: dose level 1: alpelisib 250 mg+SG 8 mg/kg; dose level 2: alpelisib 250 mg+SG 10 mg/kg; dose level 3: alpelisib 300 mg+SG 10 mg/kg. Alpelisib was dosed PO daily and SG IV, D1 and 8 every 21 days. Antidiarrheal prophylaxis was utilized for the first two cycles. Primary endpoint was recommended phase 2 dose (RP2D). Additional endpoints included adverse events (AEs), objective response rate (ORR), progression-free survival (PFS), and pharmacokinetics. **Results:** 12 patients were enrolled between 2022-2024 (dose level 1: N = 3, dose level 2: N = 6, dose level 3: N = 3). 7/12 (58%) had triple-negative breast cancer (TNBC), and 5/12 (42%) had hormone receptor (HR)-positive disease. All patients had visceral disease. 8/12 (67%) had $\geq$1 prior metastatic chemotherapy; 4/12 (33%) had prior immunotherapy; 3/12 (25%) had prior ADC. One dose-limiting toxicity (hyperbilirubinemia) was observed at dose level 2. RP2D was alpelisib 300 mg + SG 10 mg/kg. The most frequent grade $\geq$3 treatment-related AEs were electrolyte imbalance (G3 17%, G4 17%), neutropenia (G3 33%, G4 0%), diarrhea (G3 17%, G4 0%), and hyperglycemia (G3 8%, G4 8%). There were no G5 AEs. Pharmacokinetics of SG and its metabolites were consistent with previous reports. Among 11 patients evaluable for response, ORR was 36% (4/11) (complete response [CR] = 1, partial response [PR] = 3) and clinical benefit rate (CR + PR + stable disease $>$ 24 weeks) was 64% (7/11). ORR in TNBC was 50% and in HR-positive disease was 20%. Among patients with prior ADC, ORR was 33% and clinical benefit rate was 67%. Three of four patients with ORR had response lasting $>$ 6 months, with median duration of response of 14.9 (range 3.2 to 28.1) months. Median PFS was 5.7 months. Tumor and serial ctDNA analysis are ongoing. **Conclusions:** Combination of SG + alpelisib was feasible, with manageable side effects. The toxicity profile of the combination was consistent with the known safety profiles of the two agents. This combination demonstrated encouraging efficacy in HER2-negative MBC, with prolonged duration of responses, and warrants further evaluation in larger studies. Clinical trial information: NCT05143229. Research Sponsor: Novartis; Gilead Sciences.

1095 **Poster Session**

Assessing the impact of scalp cooling in patients receiving trastuzumab deruxtecan for metastatic breast cancer. First Author: Elahe Salehi, Dana-Farber Cancer Institute, Boston, MA

Background: Outcomes for patients (pts) with metastatic breast cancer (MBC) have improved with novel antibody drug conjugates like trastuzumab deruxtecan (T-DXd). While T-DXd has been associated with increased risk of alopecia, there are limited data describing the efficacy of scalp cooling in preventing alopecia and improving quality of life among pts receiving T-DXd. **Methods:** This prospective, phase II study enrolled pts with MBC without alopecia at baseline who were initiating treatment with T-DXd; pts elected to participate in a scalp cooling (SC) arm with the Paxman scalp cooling system or a non-SC arm. The primary endpoint was hair loss, defined as locally assessed CTCAE v5.0 grade $\geq$1 alopecia occurring at C3D1, C5D1, or end of treatment (EOT), whichever occurred first. The impact of SC on quality of life (QOL) was assessed using the Chemotherapy-Induced Alopecia Distress Scale (CADS) and body image scale (BIS) at baseline, C3D1, C5D1, and EOT. The study aimed to enroll 20 pts per arm to provide at least 80% power to detect a 28% decrease in hair loss rate between the SC vs non-SC arms (8% vs 36%) using a difference in proportions test (one-sided type I error 10%). **Results:** A total of 40 evaluable pts were enrolled: 20 in SC arm and 20 in non-SC arm. Median age was 61 (33-77); 2 (5%) were Black, 2 (5%) were Hispanic. Twenty-eight (70%) pts had hormone receptor positive disease, 11 (27.5%) HER2+, 2 (5.0%) triple-negative. Thirty-five (87.5%) had prior chemotherapy for MBC; median prior lines was 1 [range: 0-5]. 27 (67.5%) had prior endocrine therapy, 28 (70.0%) had prior CDK4/6 inhibition; 7 (17.5%) had prior use of SC. Thirty-three (82.5%) pts (18 [90%] in SC arm, 15 [75%] in non-SC arm) experienced $>$grade 1 alopecia, with similar rates observed in both arms (p = 0.41). Grade 2 alopecia was the main reason (45%) for SC discontinuation. Median time to G2 alopecia was 2.76 months (95% CI: 1.64-NA) in SC arm and 4.60 months (95% CI: 2.53, NA) in non-SC arm (p = 0.8). Median CADS scores trended upward from baseline to EOT (Baseline: 3.50; C3: 7.22; C5: 9.00; EOT: 11.5) in the SC arm and were more variable in the non-SC arm (baseline: 3.00; C3: 5.00; C5: 2.56; EOT: 6.50); median BIS scores trended upward in both the SC (baseline: 3.00; C3: 8.00; C5: 9.00; EOT: 11.5) and non-SC arms (baseline: 3.00; C3: 5.00; C5: 5.00; EOT: 9.00), with no statistically significant difference. **Conclusions:** In this prospective phase II trial, the use of SC with T-DXd did not show a benefit in hair preservation vs no SC. QOL analysis was not significantly different for those receiving SC vs no SC. Small sample size and lack of randomization may limit interpretation of results. Further work is planned to investigate strategies to improve efficacy of SC with ADCs. Clinical trial information: NCT04986579. Research Sponsor: AstraZeneca and Daiichi Sankyo; Paxman Scalp Cooling; Friends of Dana-Farber.

CTCAE v5 alopecia.

CTCAE v5 Alopecia	All N=40	SC Arm N=20	Non-SC Arm N=20	P-value
No alopecia	7(17.5%)	2(10.0%)	5(25.0%)	0.41
Grade 1	11(27.5%)	7(35.0%)	4(20.0%)	
Grade 2	22(55.0%)	11(55.0%)	11(55.0%)	

1096 Poster Session

Bria-IMT + checkpoint inhibitor: Phase I/II survival results compared to benchmark trials in metastatic breast cancer. First Author: Saranya Chumsri, Mayo Clinic Florida, Jacksonville, FL

Background: Bria-IMT is a combination immunotherapy consisting of allogeneic whole cell cancer vaccine (SV-BR-1-GM) administered w/ immune checkpoint inhibitor (CPI). SV-BR-1-GM breast cancer cells are engineered to directly stimulate anti tumor immunity via expression of tumor associated antigens and secretion of GM-CSF to enhance dendritic cell activation. Addition of CPI potentiates SV-BR-1-GM to overcome the immune suppressive tumor microenvironment. **Methods:** This Ph I/randomized Ph II study evaluated the Bria-IMT regimen in pts w/ metastatic breast cancer; CTX (300 mg/m²) on day -2/-3, SV-BR-1-GM and CPI on Day 0, w/ low dose peg interferon α at inoculation sites on day 2 ($\pm$1) . Phase II pts were randomized 1:1 to receive CPI at cycle 1 or cycle 2. Two SV-BR-1-GM formulations (w/ vs w/o IFNγ incubation) were evaluated. Biomarkers included cancer-associated macrophage-like cells, circulating tumor cells, PD-L1 scores, and delayed-type hypersensitivity skin tests. **Results:** 54 pts (22 Ph I, 32 Ph II) enrolled; 11 received pembrolizumab, 44 retifanlimab (1 crossover). 33 (61%) pts were ER+/PR+/HER2-, 18 (33%) TNBC, 3 (6%) HER2+. Median OS, PFS, ORR, and CBR were evaluated against two pivotal Ph 3 trials, ASCENT[1] (SG in TNBC) and TROPiCS-02[2] (SG in HR+/HER2- MBC) (see Table 1). In randomized pts, C1 vs C2 CPI had PFS (3.7 vs 3.2 mos, P=0.09) and OS (11.4 vs 7.4 mos, P=0.19). Pts receiving Ph 3 formulation (w/o IFNγ; N=37) had greater PFS (3.6 vs 2.6 mos, P=0.01) and OS (13.4 vs 6.9 mos, P=0.01). Bria-IMT was well tolerated w/ no Tx related D/Cs. **Conclusions:** The Bria-IMT Ph 3 formulation cohort OS was comparable to ASCENT and TROPiCS-02 (13.43 vs 11.8, 14.4 mos), exceeding TPC arms (6.9, 11.2 mos). CBR (61%) compared favorably to ASCENT (40%) and TROPiCS-02 (34%); ORR (14%) matched or exceeded TPC arms (4%, 14%). These outcomes were observed in a more heavily pretreated population, demonstrating Bria-IMT's clinical activity. Randomized Ph 2 results suggest efficacy and safety in heavily pretreated MBC, w/ no significant OS difference between C1 and C2 CPI initiation and 22% of pts still in active survival follow up. Superior outcomes w/ the Ph 3 formulation support its continued evaluation. A randomized Ph 3 trial is ongoing, comparing Bria-IMT vs treatment of physician's choice (NCT06072612). Clinical trial information: NCT03328026. Research Sponsor: BriaCell Therapeutics Corp.

Trial (Cohort)	Age (Median, Range)	Prior Therapies (Median)	OS (Median, mos)	PFS (Median, mos)	ORR (%)	CBR (%)
Bria-IMT (Overall Cohort)	61 (38-81)	6 (2-13)	9.9 (1.8-30.3)	3.6	10%	55%
Bria-IMT (Ph 3 Formulation)	62 (44-80)	6 (2-13)	13.43 (1.8-30.3)	3.6 (1.8-16.5)	14%	61%
ASCENT (SG)	54 (27-82)	4 (2-17)	11.8	4.8	31%	40%
ASCENT (TPC)	53 (27-81)	4 (2-14)	6.9	1.7	4%	8%
TROPiCS-02 (SG)	57 (49-65)	3	14.4	5.5	21%	34%
TROPiCS-02 (TPC)	55 (48-63)	3	11.2	4	14%	22%

References:
Bardia A et al. J Clin Oncol. 2024 May 20;42(15):1738-1744Rugo, Hope S et al. The Lancet, Volume 402, Issue 10411, 1423 – 1433.

1097 Poster Session

First-line durvalumab plus chemotherapy with or without oleclumab for locally advanced or metastatic triple-negative breast cancer: SYNERGY overall survival and circulating tumor DNA analysis. First Author: Elisa Agostinetto, Université Libre de Bruxelles (ULB), Hôpital Universitaire de Bruxelles (HUB), Institut Jules Bordet,, Brussels, Belgium

Background: SYNERGY (NCT03616886) is a randomized, investigator-initiated, phase I/II trial testing if targeting the immunosuppressive adenosine pathway with the anti-CD73 antibody oleclumab, plus the anti-PD-L1 durvalumab and chemotherapy, enhances antitumor activity in untreated locally advanced or metastatic triple-negative breast cancer (TNBC). Here, we report the overall survival (OS) and circulating tumor DNA (ctDNA) analysis. **Methods:** 133 patients received weekly carboplatin and paclitaxel x12 plus durvalumab, with (arm A) or without (arm B) oleclumab (6 in phase I, 63 in arm A, 64 in arm B). Maintenance with durvalumab +/- oleclumab was continued until disease progression or unacceptable toxicity. The primary endpoint was clinical benefit rate at week 24 (previously reported, Nat Commun. 2023;14(1):7018). Secondary endpoints included OS and progression-free survival (PFS). Exploratory endpoint included ctDNA analysis. Circulating cell free DNA (cfDNA) was extracted from 343 plasma samples collected at baseline (n = 128), week 3 (n = 122), and week 13 (n = 93). For ctDNA detection, we performed low-coverage genome-wide sequencing of cfDNA from the above-mentioned samples and from 55 plasma samples from healthy donors to correct a possible batch effect. **Results:** Data cut-off was September 13, 2024, with a median follow-up of 21.7 months. Median OS was not significantly different between arms: 25.1 vs. 20.9 months in arm A vs. B, respectively; HR 0.97 (95%CI 0.63-1.50, p = 0.90). The updated median PFS showed similar PFS: 4.8 vs. 5.4 months in arm A vs. B, respectively; HR 1.22, (95%CI 0.84-1.78, p = 0.29). Among the 343 plasma samples analyzed, ctDNA detection declined from 77% at baseline to 46% at week 3, to 18% at week 13. At any timepoint, CtDNA detection was significantly associated with worse PFS and OS (Table). Twelve patients across both arms exhibited exceptional long responses, without progressive disease and still receiving the study treatment at data cutoff; all exceptional responders evaluable for ctDNA analysis had ctDNA clearance. **Conclusions:** Theaddition of oleclumab to chemo-immunotherapy did not improve PFS or OS in advanced TNBC. However, a subgroup of patients experienced exceptional long-lasting response, indicating potential benefit in selected cases. CtDNA detection was strongly associated with poorer outcomes at all timepoints, underscoring its potential as a biomarker in this disease/setting. Clinical trial information: NCT03616886. Research Sponsor: AstraZeneca.

Timepoint	ctDNA detection	mPFS (95% CI)*	P value	mOS (95% CI)*	P value
Baseline	Yes	4.6 (4.2-5.4)	0.002	19.3 (16.6-25.9)	0.007
	No	9.2 (5.7-16.4)		37.5 (22.5-NE)	
Week 3	Yes	3.9 (2.7-4.7)	<.001	18.1 (12.8-26.5)	0.003
	No	5.7 (4.6-9.3)		25.7 (19.0-NE)	
Week 13	Yes	0.7 (0.4-2.4)	<.001	8.4 (7.3-24.2)	<.001
	No	3.7 (3.4-6.2)		25.6 (22.1-34.5)	

*PFS and OS for Week 3 and 13 estimated from this time point.

1098 Poster Session

Multiomic profiling of LRRC15 in triple negative breast cancer (TNBC). First Author: Dan Morgenstern Kaplan, University of Miami/Jackson Memorial Hospital, Miami, FL

Background: Leucine-rich repeat-containing protein 15 (*LRRC15)* has emerged as a potential biomarker and therapeutic target for various cancers due to its high expression in cancer-associated fibroblasts (CAFs) and role in tumor progression. High LRRC15 expression is associated with poor prognosis in TNBC. This study aims to define the multiomic profile of *LRRC15* in TNBC. **Methods:** 3,038 TNBC samples were analyzed via Next-Generation Sequencing (592, NextSeq; Whole Exome Sequencing, NovaSeq) and Whole Transcriptome Sequencing (NovaSeq; Caris Life Sciences, AZ). Immune cell fractions were estimated using WTS deconvolution (Quantiseq). Stromal cell abundance in the tumor microenvironment (TME) was estimated from RNA expression profiles using MCP Counter. *LRRC15*-high (H) and -low (L) tumors were classified by RNA expression above or below the 25th percentile. Real-world overall survival (OS) and treatment-related survival were derived from insurance claims and calculated from tissue collection or treatment initiation to last contact using Kaplan-Meier. Statistical significance was assessed using chi-square and Mann-Whitney U tests with multiple comparison adjustments ($q < .05$). **Results:** *LRRC15*-H TNBC tumors had higher frequency of *PIK3CA* (25.9% vs 16.8), PIK3R1 (6.2% vs 1.6%), PTEN (11.3% vs 5.8%), but lower frequency of *RB1* (7.8% vs 12.1%) and *KMT2D* (2% vs 4.4%) compared to *LRRC15*-L, all $q < 0.05$. *LRRC15*-H had higher PD-L1 positivity (32.3% vs 24.5%, $q < 0.05$). Analysis of immune cells showed *LRRC15*-H TNBC had higher infiltration of B cells (4.2% vs 3.5%), M1 macrophages (4.3% vs 2%), M2 macrophages (4% vs 2.5%), Tregs (1.9% vs 1.1%), neutrophils (4.9% vs 3.9%), $CD8^+$ T cells (0.4% vs 0.1%), but lower dendritic cells (2.5% vs 3%), all $q < 0.05$. *LRRC15*-H tumors had greater abundance of CAFs (575.6 vs 93.78, 6.14 fold change (FC)) and endothelial cells (7.3 vs 3.7, 1.97 FC), all $q < 0.05$. *LRRC15*-H had higher T-cell inflamed score (71.5 vs -77) and *IFNg* score (-0.14 vs -1.72), all $q < 0.05$. *LRRC15*-H tumors had higher expression of immune checkpoint genes (*CD274, PDCD1, PDCD1LG2, CTLA4, LAG3, HAVCR2, FOXP3, IDO1, TNFSF14, TIGIT, BTLA, CEACAM1, CD47, CD80, CD86, CD160, CD274*; FC 1.2-2.5, $q < 0.05$). *LRRC15*-H was associated with better OS (mOS: 24.7 vs 13.6 months; HR 0.61, 95% CI 0.53-0.7, $p < 0.001$). Post-pembrolizumab survival was longer for *LRRC15*-H patients (mOS: 27.2 vs 19.4 months; HR 0.61, 95% CI 0.42-0.89, p = 0.01). **Conclusions:** *LRRC15*-H TNBC exhibited better outcomes with pembrolizumab, likely due to higher immune cell fractions and increased CAFs. These findings highlight TNBC heterogeneity and position *LRRC15* as a potential biomarker for tumor stratification, a possible adverse prognostic biomarker and a positive predictive biomarker. Ongoing phase I trials targeting LRRC15 show promise. Combining *LRRC15*-targeted therapies with immunotherapy may improve TNBC outcomes, warranting further validation in breast cancer models. Research Sponsor: None.

1099 Poster Session

Acute circulating tumor DNA dynamics during and after infusional therapy initiation. First Author: Briana To, The Ohio State University Comprehensive Cancer Center, Columbus, OH

Background: For patients with advanced breast cancer, the proportion of tumor-derived DNA in circulation ('tumor fraction'/TF) has been shown to be prognostic. There is evidence that early change in TF may correlate with response to therapy, potentially providing a rapid, minimally-invasive predictive biomarker. However, there is little known regarding TF dynamics during and in the hours immediately after infusion of targeted or cytotoxic therapies, including whether there is a 'surge' in ctDNA corresponding to acute cell death. We hypothesized that tracking TF change peri-infusion would provide insight regarding acute ctDNA dynamics. **Methods:** Banked plasma samples were derived from a phase 1b trial of HSP90 inhibitor onalespib with paclitaxel in patients with advanced triple negative breast cancer. Plasma was collected during the first cycle of therapy on study pre-infusion, end-of-infusion (EOI), then 0.5/1/2/4/6/8/24 hours post-infusion for 1) onalespib alone (day -7); 2) paclitaxel alone 7 days later (day 1); 3) onalespib+paclitaxel 7 days later (day 8) for a total of maximum 26 time points per patient. 317 samples from 14 patients underwent shallow whole genome sequencing (sWGS) and TF determination. The objective was to evaluate change in TF from pre-infusion to 6-hours and 24-hours post-infusion. Exploratory objectives included association of TF dynamics with progression-free survival (PFS) and overall survival (OS). **Results:** 313/317 (98.7%) of available plasma samples completed sWGS. Of these, 104/313 (33.2%) were collected on onalespib alone, 114/313 on paclitaxel alone (36.4%), and 95/313 (30.4%) on onalespib+paclitaxel. For the co-primary objectives, there was a significant decline in TF from pre-infusion to 6 hours for paclitaxel alone (Wilcoxon signed rank p = 0.03) but no significant change for onalespib alone/onalespib+paclitaxel or from pre-infusion to 24 hours for any treatment group (all Wilcoxon signed rank $p > 0.05$). There was a significant decline in TF from pre-infusion day -7 (median TF 16%) to 24 hours after C1D8 (median TF 6.5%, Wilcoxon signed rank p = 0.004). Baseline TF≥20% was associated with significantly worse PFS (log-rank p = 0.002) with a trend toward worse OS (log-rank p = 0.067) but categorization of TF change using ctDNA-RECIST was not associated with significant differences in PFS or OS. **Conclusions:** In this study of > 300 plasma timepoints during the first cycle of treatment on a phase Ib clinical trial, there was no significant 'surge' in ctDNA TF within minutes to 24 hours of infusion of onalespib, paclitaxel or both in combination. However, there was a significant decline in TF over the first full cycle of therapy. This suggests that despite ctDNA half-life of minutes-to-hours, consistent change in TF may not be detectable for days or weeks, providing important insight in the design of studies evaluating ctDNA change as a minimally-invasive biomarker. Research Sponsor: None.

1100 Poster Session

A phase 1b study of Plk1 inhibitor onvansertib in combination with paclitaxel in metastatic triple-negative breast cancer (mTNBC) patients. First Author: Antonio Giordano, Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA

Background: TNBC represents 15-20% of all breast cancer and is characterized by a more aggressive clinical course compared to other subtypes with response rate < 10% after 2-3 lines of chemotherapy. Onvansertib is an oral polo-like kinase 1 (PLK1) ATP-competitive inhibitor with preclinical data showing synergy when combined with paclitaxel (P) in TNBC models. Here, we report safety and outcome data for subjects enrolled in a phase 1b clinical trial of onvansertib and P for patients (pts) with mTNBC. **Methods:** Eligible pts received escalating doses of onvansertib, studied using a Bayesian Optimal Interval (BOIN) design, with a fixed dose of P to determine the maximum tolerated dose and recommended phase 2 dose (RP2D) of onvansertib. The primary objective was the characterization of dose-limiting toxicity (DLT). Onvansertib was tested at 9, 12, and 18 mg/m² dose levels (DL). Onvansertib was administered orally, once daily for 21 consecutive days, followed by 7 days off; P was administered intravenously at 80 mg/m^2 once on days 1, 8, and 15 of every 28-day cycle. Exploratory objectives included pharmacokinetic (PK) and circulating tumor DNA analyses. **Results:** 17 pts enrolled from September 2022 to August 2024. Median line of chemotherapy for mTNBC was 3 (range 1-11), 14/17 pts received prior taxane, 7/17 immunotherapy (IO), and 13/17 a prior antibody drug conjugate (ADC). There were 3 pts enrolled at DL0 (9 mg/m²), 4 at DL1 (12 mg/m²), and 10 at DL2 (18 mg/m²). One pt in DL2 remains on treatment, and 16 are off study (11 pts discontinued due to disease progression (PD) per RECIST 1.1; 3 due to clinical PD; 1 due to unacceptable toxicity; 1 death unrelated to the study drug). DLTs were observed in 0/3 pts at DL0, 1/4 (25%) at DL1, and 3/10 (30%) at DL2. Common adverse events were anemia (47% ≥ Grade 2, 12% Grade 3), decreased neutrophil count (47% ≥ Grade 2, 24% Grade 3-4), and fatigue (24% ≥ Grade 2, 6% Grade 3). Best responses included 24% partial response (PR, 2/4 confirmed) and 24% stable disease (2/4 SD ≥ 12 weeks) (Table 1). All 4 responders were treated in DL2 (18mg/m^2), 3/4 pts received prior P (2/4 in mTNBC setting) and IO (all in mTNBC), 2/4 received an ADC. The RP2D of onvansertib in combination with P is 18 mg/m². PKs and other biomarkers will be presented. **Conclusions:** The combination of onvansertib and P demonstrated a safe toxicity profile and promising clinical activity in pretreated mTNBC pts and warrant further exploration of the combination at the RP2D. Clinical trial information: NCT05383196. Research Sponsor: METAVIVOR; Cardiff Oncology.

Best response per RECIST 1.1 among different DL.

Response	All Pts (N=17)	DL0 (N=3)	DL1 (N=4)	DL2 (N=10)
PR	4 (23.5%)	0 (0.0%)	0 (0.0%)	4 (40.0%)
Confirmed PR	2 (11.8%)	0 (0.0%)	0 (0.0%)	2 (20.0%)
Unconfirmed PR	2 (11.8%)	0 (0.0%)	0 (0.0%)	2 (20.0%)
SD	4 (23.5%)	2 (66.7%)	2 (50.0%)	0 (0.0%)
SD > 12 wks	2 (11.8%)	2 (66.7%)	0 (0.0%)	0 (0.0%)
SD < 12 wks	2 (11.8%)	0 (0.0%)	2 (50.0%)	0 (0.0%)
PD	9 (52.9%)	1 (33.3%)	2 (50.0%)	6 (60.0%)
By RECIST 1.1	8 (47.1%)	1 (33.3%)	1 (25.0%)	6 (60.0%)
Clinical PD	1 (5.9%)	0 (0.0%)	1 (25.0%)	0 (0.0%)

1101 Poster Session

Camrelizumab plus nab-paclitaxel and cisplatin as first-line treatment for metastatic triple-negative breast cancer: A prospective, single-arm, open-label phase II trial. First Author: Biyun Wang, Department of Medical Oncology, Fudan University Shanghai Cancer Center, Shanghai, China

Background: Platinum-based chemotherapy plays an important role in the treatment of TNBC. Our previous research has demonstrated the superiority of nab-paclitaxel/cisplatin (AP) regimen as the initial treatment for metastatic TNBC(mTNBC; *Xichun Hu, 2020ESMO)*. Camrelizumab is a humanized monoclonal antibody against PD-1. Herein, we conducted this prospective, single arm, open-label phase II study to evaluate the efficacy and safety of camrelizumab in combination with AP regimen as the first-line treatment of mTNBC (NCT04537286). **Methods:** Patients with untreated mTNBC received camrelizumab (200 mg D1), nab-paclitaxel (125 mg/m^2 D1,D8) and cisplatin (75 mg/m^2 D1) intravenously every 3 weeks until disease progression or intolerable toxicity. The primary endpoint was progression-free survival (PFS). Secondary endpoints included objective response rate (ORR), disease control rate (DCR),overall survival (OS) and safety. Exploratory analyses included immunohistochemistry and RNA sequencing of archival tumour samples. **Results:** A total of 90 patients were enrolled. Overall, median age was 51 years; 46.7% of patients had three or more metastatic sites; 78.9% of patients had visceral involvement; 82.2% of patients had taxanes exposure. As of data cutoff (July 10th 2024), median duration of follow-up was 18.1 months. Median PFS was 11.8 (95%CI 10.1-13.6) months and median OS was 27.1 (95%CI 22.1-33.6) months. ORR was 71.1% and DCR was 86.7%. Median time to response was 1.5 months. TRAEs were reported in all patients while grade 3-4 TRAE occurred in 55.6% patients, including neutropenia (34.4%), leukemia (24.4%), and anemia (10.0%). irAEs were reported in 57.8% patients, including RCCEP (45.5%), rash (11.1%), pneumonitis (10.0%), while grade 3-4 irAEs only occurred in 4.4% patients. Three-months landmark analyses showed that patients with irAE have significantly longer OS than those without (29.3 vs. 22.1 months, *P* = 0.018). Exploratory analyses demonstrated that patients with PDL1 CPS ≥10 had significantly longer PFS (13.7 vs 11.4 months, *P* = 0.039). Patients with high TILs had significantly longer OS (23.1 vs.10.3 months, *P* = 0.003). The proportion of PDL1 positive (CPS ≥1) patients was 81.8% in basal compared to 0% in non-basal subtype (*P* = 0.023). Hallmark pathway analysis showed that the activation of DNA repair pathway (HR,11.6, 95%CI 2.4-55.7, *P* = 0.002) and MYC target pathway (HR,7.4,95%CI 1.9-28.2, *P* = 0.004) was significantly associated with shorter PFS, while the activation of KRAS signaling (HR,3.2, 95%CI 1.1-9.7, *P* = 0.035) was significantly associated with worse OS. **Conclusions:** Camrelizumab plus AP as first-line treatment in patients with mTNBC demonstrated satisfying efficacy with manageable toxicity. Randomized controlled trial is warranted in the future. Clinical trial information: NCT04537286. Research Sponsor: None.

1102 Poster Session

Safety and efficacy of the anti-TROP2 antibody-drug conjugate (ADC) IBI130 in patients (pts) with advanced triple-negative breast cancer (TNBC) and other solid tumors: Results from the phase 1 study. First Author: Fan Wu, Fujian Cancer Hospital, Fuzhou, China

Background: TROP2 is a promising therapeutic target in various solid tumors. IBI130 is composed of an anti-TROP2 antibody conjugated to the camptothecin derivative NT1. Herein, we report the multi-regional, first-in-human, phase 1 study of IBI130. **Methods:** Eligible pts with unresectable locally advanced or metastatic solid tumors who failed or intolerant to standard treatment were enrolled. The study included dose escalation and dose expansion. IBI130 was intravenously administered at 1/2/4/6/8/10/12 mg/kg Q3W during dose escalation, which was guided by modified continuous reassessment method (mCRM) according to Bayesian logistic regression model (BLRM) and escalation with overdose control (EWOC) principle. Primary endpoint was safety. Secondary endpoint was efficacy assessed by investigator per RECIST v1.1 including objective response rate (ORR), disease control rate (DCR), duration of response (DoR) and progression-free survival (PFS). **Results:** As of Dec 15, 2024, 71 pts were enrolled from China and Australia (median age: 60 years [range: 30-81], female: 85.9%, Caucasian: 16.9%, ECOG PS 1: 48.6%; prior lines of anticancer treatment≥2: 63.8%). Median follow-up of the study was 4.6 months (range: 0.8-9.7). No dose-limiting toxicity (DLT) was observed across all dose levels during dose escalation (n = 18). Median treatment duration was 18 weeks (range: 3-45) with 40 (56.3%) pts still on treatment. Treatment-emergent adverse events (TEAEs) occurred in 68 (95.8%, with 90.1% treatment-related adverse events [TRAEs]) pts including grade 3 (G3) events in 17 (23.9%, with 15.5% TRAEs) pts. No grade 4-5 events occurred. Common TEAEs (≥30%) were stomatitis (52.1%, with 9.9% G3), nausea (31.0%, with 2.8% G3) and rash (31.0%, with 1.4% G3). Interstitial lung disease occurred in 1 pt (1.4%, G1). Only 1 pt (1.4%) had G3 lymphocyte count decreased. Other ≥G3 hematological toxicities were not observed. TRAEs led to dose reduction in 5 (7.0%) pts and treatment discontinuation in 1 (1.4%) pts. Efficacy of IBI130 was evaluable in 30 pts with TNBC treated at 4/6/8/10 mg/kg (all stage IV, and 96.7% had failed or were intolerant to taxanes). The overall ORR was 50.0% (95% CI: 31.3-68.7) and DCR was 83.3% (95% CI: 65.3-94.4). As for different dose levels, ORR and DCR were 40.0% (95% CI: 5.3-85.3) and 60.0% (95% CI: 14.7-94.7) for 4 mg/kg (n = 5), 40.0% (95% CI: 5.3-85.3) and 80.0% (95% CI: 28.4-99.5) for 6 mg/kg (n = 5), 50.0% (95% CI: 18.7-81.3) and 100% (95% CI: 69.2-100.0) for 8 mg/kg (n = 10), 60.0% (95% CI: 26.2-87.8) and 80.0% (95% CI: 44.4-97.5) for 10 mg/kg (n = 10). DoR and PFS data were not mature as of the cutoff date. **Conclusions:** IBI130 was well tolerated featured by superiority of hematological safety, and encouraging efficacy of IBI130 was observed in advanced TNBC, supporting its potential as a best-in-class TROP2 ADC. Clinical trial information: NCT05923008. Research Sponsor: Innovent Biologics (Suzhou) Co., Ltd.

1103 Poster Session

SHR-A1811 plus adebrelimab in unresectable or metastatic triple-negative breast cancer: Results from a phase 1b/2 expansion cohort. First Author: Yan Liang, The First Affiliated Hospital of Nanjing Medical University, Nanjing, China

Background: SHR-A1811 is a novel HER2-directed antibody-drug conjugate with promising antitumor activity in breast cancer (BC), yielding a confirmed objective response rate (ORR) of 79.4% in HER2 positive BC, 60.9% in HER2 low-expressing BC, and 52.0% in triple-negative BC (TNBC) as monotherapy. We evaluated SHR-A1811 in combination with adebrelimab (anti-PD-L1 antibody), pyrotinib (irreversible, pan-HER receptor tyrosine kinase inhibitor), pertuzumab, or albumin-bound paclitaxel in unresectable or metastatic breast cancer in an open-label, dose-finding and efficacy expansion phase 1b/2 study. Here, we report the safety and efficacy results of the SHR-A1811 plus adebrelimab cohort. **Methods:** Patients (pts) with unresectable or metastatic TNBC and ≥1 line of prior treatment received intravenous SHR-A1811 at an escalating dose of 4.8 mg/kg and 5.6 mg/kg Q3W, in combination with adebrelimab (1200 mg Q3W) in phase 1b part. In phase 2 part, TNBC pts with no systematic antitumor therapy in the recurrent or metastatic setting were treated with SHR-A1811 at 4.8 mg/kg Q3W plus adebrelimab. Primary endpoints were safety and ORR. The data cutoff date was Nov 30, 2024. **Results:** Fifty TNBC pts were enrolled in total. In phase 1b, 8 pts were enrolled and treated. No DLT was observed. The confirmed ORR was 66.7% (2/3) and 60.0% (3/5) in the 4.8 mg/kg and 5.6 mg/kg dose group, respectively. In phase 2, 42 treatment naive TNBC pts were enrolled. 13 (31.0%) pts had ≥3 metastases sites, 22 (52.4%) pts were HER2-low (IHC 2+/ISH- or IHC 1+)/ultra-low (IHC 0-1), 20 (47.6%) pts were HER2-nul (IHC 0), and 30 (71.4%) pts were PD-L1-positive (CPS ≥1). At the time of data cutoff, the median follow-up time was 4.6 mo (range, 0.2-10.4). Among efficacy evaluable TNBC pts, the overall ORR was 66.7% (26/39) (Table). ORR was 77.8% (21/27) in the PD-L1-positive subgroup. The 6-month PFS rate was 86.2%. SHR-A1811 plus adebrelimab was well tolerated with no new safety concerns identified. Treatment-emergent adverse events of grade ≥3 occurred in 26 (61.9%) out of 42 pts in phase 2, with decreased neutrophil count (45.2%), decreased white blood cell count (33.3%), and decreased lymphocyte count (9.5%) being the most common. **Conclusions:** SHR-A1811 plus adebrelimab had a good safety and tolerability profile. The combination showed encouraging antitumor activity in unresectable or metastatic TNBC, irrespective of HER2 or PD-L1 expression status. Clinical trial information: NCT05353361. Research Sponsor: Jiangsu Hengrui Pharmaceuticals.

Phase 2 preliminary efficacy summary[1].

	SHR-A1811 4.8 mg/kg + adebrelimab		
	CPS ≥1 (N = 30)	CPS <1 (N = 12)	Total (N = 42)
ORR, Overall[2]	21/27 (77.8)	5/12 (41.7)	26/39 (66.7)
HER2-low/-ultralow	11/13 (84.6)	4/9 (44.4)	15/22 (68.2)
HER2-nul	10/14 (71.4)	1/3 (33.3)	11/17 (64.7)
6-mo PFS rate, % (95% CI)	88.9 (43.3, 98.4)	78.8 (38.1, 94.3)	86.2 (60.7, 95.7)

[1]HER2 and PD-L1 results were based on central lab assessment.
[2]Data are n/N1(%) with N1 = the number of efficacy evaluable patients.

1104 Poster Session

ETER901: A randomized, open-label, phase III trial of anlotinib in combination with anti-PD-L1 antibody benmelstobart (TQB2450) versus nab-paclitaxel in first-line treatment of recurrent or metastatic triple-negative breast cancer. First Author: Jiayu Wang, National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China

Background: Recurrent or metastatic triple-negative breast cancer (TNBC) represents an aggressive malignancy with unfavorable prognoses. Benmelstobart (TQB2450) is a humanized monoclonal antibody targeting PD-L1, and anlotinib (ALTN) is an anti-angiogenic oral multi-target tyrosine kinase inhibitor. Herein, we present the findings of a randomized, open-label, phase 3 study comparing the combination of benmelstobart plus ALTN with nab-paclitaxel as first-line treatments for patients (pts) with recurrent or metastatic TNBC. **Methods:** In this phase 3 trial, patients with previously untreated stage IV or recurrent/metastatic TNBC were randomly allocated in a 1:1 ratio. One group received 1200 mg of intravenous benmelstobart on day 1, along with 12 mg of oral ALTN from days 1 to 14, following a 3-week cycle. The other group was administered 100 mg/m² of intravenous nab-paclitaxel on days 1, 8, and 15 within a 4-week cycle. Randomization was stratified based on whether patients had received neoadjuvant or adjuvant taxane therapy and the presence or absence of liver or brain metastases at baseline. The primary endpoint was progression-free survival (PFS), evaluated by the blinded independent central review by RECIST version 1.1. **Results:** The initial plan was to enroll 332 pts in this trial. However, due to the COVID-19 pandemic, the enrollment process was delayed, and recruitment was terminated in January 2023. Eventually, 147 pts were randomized (with a median follow-up of 14 months), among whom 75 were assigned to the benmelstobart plus ALTN group and 72 to the nab-paclitaxel group. In the intention-to-treat analysis, as assessed by the investigators, the median PFS was 7.85 months for the benmelstobart plus ALTN combination, in contrast to 5.55 months for nab-paclitaxel (hazard ratio, 0.70; 95% confidence interval, 0.46 to 1.06; P = 0.1687). The median overall survival was 35.81 months for study group and 21.03 months for control group (hazard ratio, 0.78; 95% confidence interval, 0.49 to 1.24; P = 0.2625). Grade ≥3 drug-related adverse events occurred in 56.5% of the patients in the study group and 36.6% in the control group. The most prevalent grade ≥3 adverse events in the study group were hypertension (28.0%) and hypertriglyceridemia (13.3%). **Conclusions:** The combination of benmelstobart plus ALNT might extend both progression-free survival and overall survival in the first-line treatment of patients with recurrent or metastatic TNBC. The adverse events were in line with the previously established safety profiles of each individual agent. (Funded by Chia Tai Tianqing Pharmaceutical Group Co., Ltd. ClinicalTrials.gov number, NCT04405505). Clinical trial information: NCT04405505. Research Sponsor: Chia Tai Tianqing Pharmaceutical Group Co., Ltd.

1105 Poster Session

Clinical, sociodemographic, and facility-related determinants of immunotherapy use in metastatic triple-negative breast cancer. First Author: Ismail Ajjawi, Yale School of Medicine, New Haven, CT

Background: Immunotherapy has emerged as a promising treatment option for metastatic triple-negative breast cancer (mTNBC), yet the factors influencing its adoption remain poorly understood. This study investigates the clinical, sociodemographic, and facility-related determinants of immunotherapy use in patients with mTNBC from 2015 to 2020, utilizing data from the National Cancer Database (NCDB). **Methods:** We conducted a retrospective cohort study of mTNBC patients from the NCDB between 2015 and 2020, categorizing them into two groups: those who received immunotherapy and those who did not. Patients were excluded if they had missing data on key variables such as immunotherapy receipt and clinical characteristics (e.g., tumor stage, subtype). Univariable and multivariable logistic regression analyses were performed to identify factors influencing immunotherapy adoption. The impact of immunotherapy on overall survival was assessed using Cox proportional hazards regression analysis. Overall survival between the two groups was compared using the log-rank test. **Results:** A total of 1,887 mTNBC patients were included in the study: 1,656 (87.8%) did not receive immunotherapy, and 232 (12.2%) received immunotherapy. Multivariable logistic regression identified several factors associated with immunotherapy use. Later year of diagnosis (2018-2020: OR 5.35, $p < 0.001$) and academic facilities (OR 1.43, p = 0.044) were positively associated with immunotherapy use. In contrast, older age (71+: OR 0.49, p = 0.019), facilities in rural areas (OR 0.43, p = 0.042), Black race (OR 0.73, p = 0.039), Hispanic ethnicity (OR 0.53, p = 0.026), and higher Charlson comorbidity scores (OR 0.31, p = 0.035 for scores ≥2) were associated with a lower likelihood of receiving immunotherapy. Insurance status did not significantly influence immunotherapy use. Log-rank test showed that patients receiving immunotherapy had significantly improved survival compared to those who did not (Figure 1). The median survival for patients receiving immunotherapy was 2.21 years (95% CI: 1.80–2.96), compared to 1.01 years (95% CI: 0.93–1.11) for those not receiving immunotherapy (log-rank $p < 0.001$). Cox regression analysis showed that immunotherapy use was associated with a significantly reduced risk of death (HR 0.59, 95% CI: 0.46–0.77, $p < 0.001$). **Conclusions:** Immunotherapy use in mTNBC has increased in recent years, with clinical, sociodemographic, and facility-related factors influencing its adoption. Patients receiving immunotherapy had significantly better survival outcomes. Our findings highlight the importance of addressing disparities in access to immunotherapy, particularly related to race, age, ethnicity, and comorbidity burden, to ensure equitable treatment and outcomes for all mTNBC patients. Research Sponsor: None.

1106 Poster Session

Chemokines as predictive biomarkers for immune checkpoint inhibitor (ICI) efficacy in triple negative breast cancer (TNBC). First Author: Shipra Gandhi, Roswell Park Comprehensive Cancer Center, Buffalo, NY

Background: TNBC, although an aggressive breast cancer (BC) subtype, is highly immunogenic and the only BC subtype where the ICI pembrolizumab is approved. However, predictive biomarkers for pembrolizumab benefit are limited. The chemokines *CXCL9* and *CXCL10* attract $CD8^+$ T cells into the tumor microenvironment (TME) and are associated with chemotherapy benefit, but little is known about their role in prediciting pembrolizumab benefit in TNBC. We investigated the association of *CXCL9*, *CXCL10* and their cognate receptor *CXCR3* with TME and ICI efficacy. **Methods:** 3,038 TNBC samples were analyzed via NGS (592-gene panel, NextSeq; WES/WTS, NovaSeq; Caris Life Sciences, Phoenix, AZ). Tumor mutational burden (TMB) totaled somatic mutations per tumor (high > 10 mt/MB). Immune cell fractions were estimated using WTS deconvolution (Quantiseq). *CXCL9*/*CXCL10*/*CXCR3*-high (H) and -low (L) tumors were classified by RNA expression above or below the 50th percentile. Real-world overall survival (OS) was derived from insurance claims and calculated from start of pembrolizumab to last contact using Kaplan-Meier. Statistical significance was assessed using chi-square and Mann-Whitney U with multiple comparison adjustments ($q < .05$). **Results:** TNBC expressed higher levels of *CXCL9* and *CXCL10* (median (TPM): 5.3 and 14.7) compared to N = 1,082 HER2+ (4.8 and 10.3, $p < 0.05$) and N = 4,918 HR+HER2- (2.7 and 7, $q < .05$) BC. *CXCR3* expression was higher in TNBC compared to HR+HER2- (1.9 vs 1.7, $q < .05$), but no difference when compared to HER2+ (1.9 vs 2, q = 0.97) BC. *CXCL9*/*CXCL10*/*CXCR3*-H TNBC had higher median OS post pembrolizumab [*CXCL9*-H vs -L: 26.5 vs 15.7 months (mo), HR: 0.65 (95% CI 0.5-0.84); *CXCL10*-H vs -L: 26.0 vs 20.6 mo, HR 0.74 (0.57-0.95); *CXCR3*-H vs -L: 32.6 vs 18.3 mo, HR 0.68 (0.52-0.88), all $p < 0.05$]. *CXCL9*-H, *CXCL10*-H and *CXCR3*-H had higher PD-L1 positivity (22C3), TMB high, higher T cell inflamed score, *TP53* mutations, elevated B and $CD8^+$T cells infiltration, but not neutrophils, and higher expression of immune checkpoint genes (Table). **Conclusions:** High *CXCL9*/*CXCL10*/*CXCR3* expression is associated with longer survival in patients with TNBC post pembrolizumab, and characterized by an immune-enriched TME. Further investigation is needed to evaluate this chemokine axis in TNBC and its potential as a therapeutic target to enhance ICI efficacy. Research Sponsor: NIH (NCATS, NCI); K08CA279766-01A1.

TME characteristics by *CXCL9, CXCL10* and *CXCR3* expression.

	CXCL9			*CXCL10*			*CXCR3*		
	High	Low	q-value	High	Low	q-value	High	Low	q-value
PD-L1 %	54	14	<.05	54	14.7	<.05	49	19	<.05
TMB high %	14.3	8	<.05	12.6	9.7	<.05	12.4	9.8	<.05
B cell (median %)	4.4	3.5	<.05	4.3	3.6	<.05	5	3.4	<.05
CD8+T cell (median %)	1.2	0	<.05	1	0	<.05	1.3	0	<.05
Neutrophil (median %)	4.2	4.5	<.05	4.2	4.4	<.05	4.2	4.3	0.2
T cell inflamed score	100	-84	<.05	98	-84	<.05	108	-100	<.05
***CTLA4* (median TPM)**	3.2	0.7	<.05	3	0.8	<.05	3.4	0.7	<.05
***LAG3* (median TPM)**	6.6	2.1	<.05	6.9	2	<.05	6.8	2	<.05
***TP53* mutation %**	88	81	<.05	90.5	78.6	<.05	86	83	0.08

1107 Poster Session

Comprehensive molecular and immune characterization of adrenergic stress-signaling receptor *ADRB2* in triple negative breast cancer (TNBC). First Author: Sachin Kumar Deshmukh, Caris Life Sciences, Phoenix, AZ

Background: Chronic stress-mediated β2-adrenergic receptor (β2-AR) signaling promotes tumor growth via immunosuppression in the tumor microenvironment (TME) in preclinical models. Blockade of β2-AR has shown higher survival benefit in patients with TNBC in observational studies compared to other breast cancer (BC) subtypes. However, the molecular and immunological features associated with *ADRB2* (gene for β2-AR) gene expression in TNBC are unknown, prompting this investigation. **Methods:** 3,038 TNBC samples were analyzed via NGS (592-gene panel, NextSeq; WES/WTS, NovaSeq; Caris Life Sciences, Phoenix, AZ). Immune cell fractions were calculated by deconvolution of WTS: Quantiseq. TNBC *ADRB2*-high(H) and *ADRB2*-low(L) RNA expression were classified as above or below the 50^{th} percentile, respectively. Real-world overall survival (OS) was obtained from insurance claims and calculated from tissue collection to last contact using Kaplan-Meier estimates. Statistical significance was assessed using chi-square and Mann-Whitney U tests with multiple comparison adjustments ($q < 0.05$). **Results:** *ADRB2* gene expression was lowest in TNBC (median (TPM: 1.6) compared to N = 453 HR-HER2+ (1.9), N = 629 HR+HER2+ (2.0) and N = 4,918 HR+HER2- (2.2) BC (all $q < 0.05$). African American or Black patients (N = 670) had lower expression of *ADRB2* compared to European American or White (N = 1,412) TNBC patients (1.3 vs 1.7, $q < 0.05$). *ADRB2*-H TNBC had higher mutation frequency of *PIK3CA* (21% vs 15.4%), *CDH1* (7% vs 3.5%), *NF1* (8% vs 4%), *AKT1* (3.5% vs 2.1%), but lower frequency of *TP53* (81.6% vs 87.5%), *NOTCH1* (2.5% vs 4.5%) and *NOTCH3* (4.4% vs 11.7%) compared to *ADRB2*-L, all $q < 0.05$. *ADRB2*-H had greater PD-L1 (22C3) positivity (39.1% vs 30.2%, $q < 0.05$), higher % of B cells (4.5 vs 3.4), M1 Mφ (3.4 vs 2.8), M2 Mφ (3.9 vs 2.2), Tregs (2.2 vs 1.3), NK cells (3.1 vs 2.6), DC (3.1 vs 2.9), $CD8^+$ T cells (0.9 vs 0.2), all $q < 0.05$. *ADRB2*-H TNBC had higher T-cell inflamed score (95 vs -80), *IFNγ* score (-0.23 vs -0.37), MAPK activation score (-0.46 vs -1.7), all $q < 0.05$; and higher expression of immune checkpoint genes (*CD274, PDCD1, PDCD1LG2, CTLA4, LAG3, HAVCR2, FOXP3, IDO1, TNFSF14, TIGIT, BTLA, CEACAM1, CD47, CD274*; fold change: 1.6-3.7, all $q < 0.05$). *ADRB2*-H tumors had higher expression of genes related to inflammatory response, IFNγ response, IL6-JAK-STAT3 signaling (normalized enrichment score (NES): 1.9 – 2.1), while *ADRB2*-L had enrichment of MYC targets V1, MYC targets V2, E2F targets and G2M checkpoint (NES: 2.5 – 4.2), all FDR < 0.01. *ADRB2*-H TNBC had better OS (mOS: 23.6 vs 18.6 months; HR 0.81, 95% CI 0.73-0.89, $p < 0.0001$) compared to *ADRB2*-L. **Conclusions:** High *ADRB2* expression in TNBC is associated with better survival and an immune enriched TME, elevated immune checkpoints and other targetable vulnerabilities. Future studies are needed to investigate *ADRB2* as a potential stress biomarker and therapeutic target. Research Sponsor: NIH (NCATS and NCI); K08CA279766-01A1.

1108 Poster Session

Enhanced efficacy of inavolisib combined with anti-PD-1 or anti-HER2 antibody in treating brain metastases from breast cancer. First Author: Jian-Li Zhao, Sun Yat-sen Memorial Hospital, Sun Yat-Sen University, Guangzhou, China

Background: The PI3K/AKT/mTOR signaling pathway is a crucial regulatory pathway involved in cell proliferation, survival, migration, and metabolism. This dysregulation can occur through various mechanisms, such as PIK3CA gene mutations and PTEN gene loss. The research of PI3K inhibitors has made significant progress in the treatment of ER-positive and HER2-negative breast cancer. Alpelisib is the only approved PI3K inhibitor for treating PIK3CA mutation-positive breast cancer. The SOLAR-1 trial demonstrated that Alpelisib combined with endocrine therapy significantly prolongs progression-free survival in these patients. However, despite improving PFS, the side effects of PI3K inhibitors pose limitations on their widespread application. Consequently, researchers are exploring next-generation PI3K inhibitors with improved safety and efficacy. Inavolisib is a novel, highly selective PI3Kα inhibitor that shows better tolerability and safety compared to existing PI3K inhibitors and has demonstrated promising antitumor effects in clinical trials. Building on this, our study aims to identify the optimal treatment regimen combining Inavolisib with various breast cancer therapies to effectively target brain metastases. **Methods:** We established a brain metastasis model in C57BL/6 mice by intracardiac injection of control (triple-negative) and hHER2+ Py8119 breast cancer cells. In addition to the Inavolisib monotherapy and vehicle control groups, Inavolisib was combined with a PD-1 antibody or albumin-bound paclitaxel in the triple-negative model. In the HER2+ model, Inavolisib was combined with Tucatinib, trastuzumab, or SHR-A1811 (an ADC drug targeting HER2). We monitored changes in body weight and survival rates in each group and assessed brain metastasis using IVIS small animal in vivo imaging. **Results:** In the triple-negative model, Inavolisib monotherapy or its combination with albumin-bound paclitaxel reduced intracranial tumor size but did not significantly extend mouse survival. Conversely, the combination of Inavolisib and PD-1 antibody significantly prolonged overall survival in triple-negative breast cancer mice. In the HER2+ breast cancer model, all three combination therapies reduced tumor burden and extended survival compared to monotherapy. However, overall, the combination with trastuzumab achieved unexpectedly good results, which were comparable to SHR-A1811 and superior to Tucatinib. **Conclusions:** Our findings suggest that the combination of the PI3K inhibitor Inavolisib with anti-PD-1 or anti-HER2 antibody therapy may offer an effective strategy for treating brain metastases in breast cancer. This discovery provides new insights and possibilities for improving treatment options in breast cancer brain metastasis. Further research is needed to validate the efficacy and safety of this combination therapy. Research Sponsor: None.

1109 Poster Session

Efficacy and safety of RC48-ADC in triple-negative breast cancer subtypes: FUSCC-TNBC-umbrella trial results. First Author: Yin Liu, Fudan University Shanghai Cancer Center, Shanghai, China

Background: RC48-ADC is a novel HER2-targeting antibody-drug conjugate. This study evaluated RC48-ADC in pretreated triple-negative breast cancer (TNBC) patients with low HER2 expression, stratified by AR status. **Methods:** In this phase Ib/II trial, pretreated metastatic TNBC patients with low HER2 expression were enrolled: RL group (LAR subtype, n=20) and RO group (non-LAR subtype, n=20). All received RC48-ADC 2.0 mg/kg intravenously every 2 weeks. Primary endpoint: objective response rate (ORR). Secondary endpoints: progression-free survival (PFS), overall survival (OS), disease control rate (DCR), and safety. **Results:** 40 heavily pretreated patients were enrolled (median 2 previous lines, range 1-7). In the overall population, best ORR was 35.0% (confirmed ORR: 32.5%), DCR 47.5%, median PFS 4.0 months. RL group showed better outcomes: best ORR 45.0% vs 25.0%, confirmed ORR 40.0% vs 25.0%, DCR 50.0% vs 45.0%, median PFS 4.9 vs 3.1 months. Median OS was not reached in RL group vs 16.6 months in RO group. Most common treatment-related adverse events (TRAEs) were AST increased (70% vs 40%) and ALT increased (65% vs 20%), mostly grade 1-2. Peripheral neuropathy occurred in 15% (RL) and 10% (RO) patients. Hematologic toxicities were mild. No treatment-related deaths occurred. **Conclusions:** RC48-ADC showed promising antitumor activity with manageable safety in pretreated TNBC patients with low HER2 expression, particularly in LAR subtype. The 35.0% ORR in heavily pretreated TNBC warrants further investigation in biomarker-selected populations. Clinical trial information: NCT03805399. Research Sponsor: None.

Efficacy and key safety outcomes of RC48-ADC in overall population and by subgroups.

Outcomes	Overall (n=40)	RL Group (n=20)	RO Group (n=20)
Efficacy			
Confirmed ORR, n (%)	13 (32.5)	8 (40.0)	5 (25.0)
Best ORR, n (%)	14 (35.0)	9 (45.0)	5 (25.0)
DCR, n (%)	19 (47.5)	10 (50.0)	9 (45.0)
Median PFS, months	4	4.9	3.1
Median OS, months	NR	NR	16.6
Best Response, n (%)			
CR	1 (2.5)	1 (5.0)	0 (0.0)
PR	13 (32.5)	8 (40.0)	5 (25.0)
SD	5 (12.5)	1 (5.0)	4 (20.0)
PD	21 (52.5)	10 (50.0)	11 (55.0)
Selected TRAEs, n (%)			
AST increased			
- Grade 1-2	22 (55.0)	14 (70.0)	8 (40.0)
- Grade ≥3	0 (0.0)	0 (0.0)	0 (0.0)
ALT increased			
- Grade 1-2	17 (42.5)	13 (65.0)	4 (20.0)
- Grade ≥3	0 (0.0)	0 (0.0)	0 (0.0)
Peripheral neuropathy			
- Grade 1-2	3 (7.5)	2 (10.0)	1 (5.0)
- Grade ≥3	2 (5.0)	1 (5.0)	1 (5.0)

1110 Poster Session

Artificial Intelligence-based tumor microenvironment and PD-L1 analysis using digital pathology to predict pembrolizumab response in metastatic triple-negative breast cancer. First Author: Jee Hung Kim, Division of Medical Oncology, Department of Internal Medicine, Gangnam Severance Hospital, Yonsei University College of Medicine, Seoul, NA, South Korea

Background: The combination of pembrolizumab and chemotherapy improves survival in programmed death ligand 1 (PD-L1) positive metastatic triple-negative breast cancer (mTNBC). However, responses vary even among PD-L1 positive, and predictive biomarkers remain undefined. This study investigates the predictive biomarkers to pembrolizumab through digital pathology and artificial intelligence (AI)-based tumor microenvironment (TME) and PD-L1 analysis. **Methods:** We retrospectively analyzed 53 PD-L1 positive, mTNBC patients treated with pembrolizumab at Gangnam Severance Hospital (2017–2024). PD-L1 positivity was defined as a combined positive score (CPS) $\geq$ 10. Immune phenotypes and immune cell density in both tumor and stroma were analyzed in 67 H&E images using Lunit SCOPE IO, an AI-powered whole slide image analyzer. PD-L1 CPS was analyzed in paired PD-L1 staining images by both Lunit uIHCv2 analyzer and pathologists. Samples were categorized as pre-(pre) or post-treatment (post). Pre-samples were collected before any therapy exposure, while post-samples were obtained after recurrence following neo/adjuvant therapy. These features were analyzed for their association with pembrolizumab response and clinical outcome. **Results:** With a median follow-up of 13.2 months, the median age was 53 years, and 16 patients (22.5%) were *de novo* stage IV TNBC. AI-assessed PD-L1 positivity was seen in 52.2% (35/67) of cases, compared to 74.6% (50/67) by pathologist. Overall, AI-based PD-L1 positive cases had a median progression-free survival (mPFS) of 8.8 months (mo) vs 6.7 mo in PD-L1 negative (p = 0.028), while pathologist-reported cases showed 7.9 mo vs 6.3 mo, respectively (p = 0.17). AI-based PD-L1 positivity in pre-samples was associated with better PFS with pembrolizumab (mPFS 7.7 mo vs 4.4mo, HR 0.32, p = 0.014), while post-samples showed no significant association (mPFS 7.3 mo vs 6.4mo, HR 0.69, p = 0.4). Notably, post-samples (50.0%) had a higher proportion of cases with AI-based CPS $\geq$ 10 compared to pre-samples (36.4%), primarily driven by increased PD-L1-expressing macrophages, as revealed by AI-based cell composition analysis (22.7% vs 7.7%, p = 0.0007). When categorized by AI-based immune phenotype, notable differences were seen between pre/post-samples despite PD-L1 positivity. Post-samples showed a higher prevalence of the immune-desert phenotype, reflecting significant changes in the TME following prior therapy exposure (40.0% vs 20.0%, p = 0.06). **Conclusions:** This study highlights the role of the TME and PD-L1 assessed by AI in predicting pembrolizumab response in mTNBC. While PD-L1 positivity in pre-samples was associated with outcome, PD-L1 positivity in post-samples showed limited association with PFS, potentially influenced by immune desert phenotype and increased PD-L1-expressing macrophages. Research Sponsor: None.

1111 Poster Session

Geographic access to triple negative breast cancer (TNBC) clinical trials: Are trials located near Black women? First Author: Laura Burns Amin, The University of Texas MD Anderson Cancer Center, Houston, TX

Background: Despite recent treatment advances, TNBC has a poor prognosis relative to other breast cancer subtypes. Black women in the U.S. are more likely to be diagnosed with TNBC, are diagnosed at more advanced stages, and have higher mortality even after controlling for socioeconomic variables than women of other races. Although clinical trials are essential to improving TNBC treatment, Black women are underrepresented. We investigated the geographic availability of TNBC clinical trials for Black women in the U.S. to elucidate potential trial access limitations. **Methods:** All trials registered on ClinicalTrials.gov as of 9/30/2024 were queried (N= 510,397). Phase II and III interventional treatment trials in active status in the U.S. including "breast" in the title or disease variable (n =449) were considered. We narrowed results to TNBC trials through keyword searches of title and disease variables (e.g., TNBC, HER2 negative and hormone receptor negative). We tabulated the number of trials per county and supplemented with 5-year population estimates (2018-2022) and county adjacency data from the U.S. Census Bureau to evaluate for geographic and demographic differences in TNBC trial availability. **Results:** We identified 108 active TNBC trials (58 metastatic [54%], 50 nonmetastatic [46%]), including 87 Phase II (81%) and 21 Phase III (19%). There were 1,230 U.S. study sites, of which 217 had one active TNBC trial (18%), 529 had 2-4 trials (43%), and 484 had $\geq$5 trials (39%). Most sites had metastatic and nonmetastatic offerings (700, 57%) while 450 sites had only non-metastatic trials (37%) and 80 had only metastatic trials (7%). State-level differences in trial availability were observed (see Table). For example, 37% of Black and 34% of non-Black women 18+ in Alabama had no TNBC trials in their or neighboring counties while all women 18+ in nine states had a trial available in at least a neighboring county. **Conclusions:** A geographical analysis of active Phase II and III therapeutic TNBC clinical trials found uneven trial availability across the country. Most study sites had $<$ 5 TNBC trials available; a third of sites had no metastatic trials, suggesting that many women may have difficulty finding an applicable trial even when near to a site. On a national scale, distance does not appear to be a primary reason for disparities in TNBC trial participation for Black and non-Black women. Nevertheless, millions of women live in areas without any trials, therefore expanding geographic reach is a necessary but insufficient approach to improve access. Research Sponsor: None.

Category (Number of Counties)	Black women 18+ in millions (%)	Non-Black women 18+ in millions (%)	Total in millions (%)
Counties with trial (748)	14 (82%)	88 (77%)	102 (78%)
Trials only in adjacent county (1452)	2 (12%)	21 (18%)	22 (17%)
No trials in county nor adjacently (944)	1 (6%)	6 (5%)	7 (5%)
Total (3144)	17 (100%)	115 (100%)	131 (100%)

1112 Poster Session

Immunotherapy vs. chemotherapy run-in followed by pembrolizumab plus nab-paclitaxel in metastatic triple negative breast cancer (mTNBC): Results from a phase II study. First Author: Alessandro Leal, Perlmutter Cancer Center, NYU Langone Health, New York, NY

Background: Pembrolizumab (pembro) with chemotherapy has shown survival benefit in PD-L1+ (CPS10+) mTNBC, but many responses are not durable, and patients with PD-L1 negative/low tumors do not benefit from the combination. Data from GeparNuevo and TONIC suggest that induction therapy can remodel the tumor immune environment and improve responses. We have conducted a trial with two run-in cohorts and mandatory serial tissue and blood collections in 50 mTNBC patients, comparing pembro vs. nab-paclitaxel (nab-P). **Methods:** Single-arm, single institution phase II study (NCT02752685) to evaluate safety and clinical activity of nab-P+pembro in PD-L1 unselected mTNBC, 0-2 prior lines of chemotherapy allowed. Patients (n = 50) were enrolled sequentially into two cohorts: chemotherapy run-in (cTNBC, nab-P before nab-P+pembro) and immunotherapy run-in (iTNBC, pembro before nab-P+pembro). Serial tumor biopsies assessed by IHC (Dako 22C3), quantitative multiplex immunofluorescence (qMIF), and gene expression (NanoString). Overall response rates assessed using irRECIST. Tumoral T- and myeloid-cell phenotypes, peripheral lymphocyte-to-neutrophil ratio (LNR), and monocyte-to-lymphocyte ratio (MLR) were correlated with overall response rate (ORR) and survival outcomes. **Results:** 50 patients enrolled and completed treatment, for 80% of patients: treatment was 1L for metastatic disease. Median follow-up is 19.9 months, clinical results for cTNBC and iTNBC cohorts shown in table. Across both cohorts higher LNR was associated with improved OS (R= 0.37, p= 0.0075), conversely, higher MLR was associated with poorer OS (R= -0.46, p= 0.00087). Tumor immune cell subpopulations showed no significant differences between iTNBC and cTNBC at baseline. Analyses of on-treatment samples will be presented at the meeting. PD-L1 expression, while not different at baseline, remained unchanged in cTNBC but increased significantly in iTNBC ($p < 0.02$), possibly reflecting pembrolizumab-driven immune modulation. With the caveat of comparing sequential cohorts, the iTNBC cohort showed a trend for higher ORR (47% vs. 23%, p= 0.08) and longer median PFS (8.4 vs. 5.5 months, HR = 0.68, 95%CI: 0.37-1.24), with significantly longer OS (25.8 vs. 18 months, HR = 0.50, 95%CI: 0.26-0.98, p = 0.043) compared to cTNBC. **Conclusions:** Timing of pembro administration may influence PD-L1 expression and clinical outcomes in mTNBC. We show that the immunotherapy run-in strategy converts more PD-L1-negative/low into PD-L1-positive tumors, possibly rendering more patients eligible for chemoimmunotherapy and improving outcomes. Clinical trial information: NCT02752685. Research Sponsor: Merck & Co., Inc.

	cTNBC (n=30)	iTNBC (n=20)
PD-L1 CPS >/=10	5/23 (22%)	2/16 (12%)
PD-L1 CPS conversion (CPS<10 to CPS>/=10)	2/14 (14%)	4/13 (31%)
Confirmed ORR (CR+PR)	7/30 (23%)	9/19 (47%)
mPFS (months)	5.5	8.4
mOS (months)	18.0	25.8

1113 Poster Session

Trop2-targeted PET/CT with ^{68}Ga-MY6349 for the diagnosis of primary and metastatic breast cancer and evaluation towards patient stratification in Trop2-targeted ADCs. First Author: Liang Zhao, The First Affiliated Hospital of Xiamen University, Xiamen, China

Background: Trop2-targeted ADCs have demonstrated promising efficacy and have been approved in patients with HR+HER2- and triple-negative breast cancer (TNBC). However, not all patients within these subtypes benefit equally from such treatment, highlighting the urgent need for developing tools for patient selection and stratification. We have previously developed a novel PET/CT imaging agent (^{68}Ga-MY6349) that specifically targets Trop2, which has shown high specificity for Trop2 in preclinical and clinical studies (DOI: 10.1172/JCI185408). **Methods:** This study enrolled patients with newly diagnosed or previously treated breast cancer at the First Affiliated Hospital of Xiamen University between January 2024 and December 2024. All patients underwent paired ^{18}F-FDG PET/CT and ^{68}Ga-MY6349 PET/CT imaging. SUVmax derived from the two PET/CT modalities and pathological results were recorded to evaluate the tumor uptake pattern and lesion detectability of the two imaging modalities. **Results:** A total of 61 patients were prospectively enrolled, including 7 true-negative and 54 true-positive cases. Among the 562 true-positive lesions, ^{68}Ga-MY6349 uptake (SUVmax) was significantly associated with breast cancer subtypes ($P<0.001$, Kruskal-Wallis H=34.9). SUVmax values were highest in HR+/HER2- [7.2 (4.4–9.4)], followed by TNBC [5.2 (3.8–6.4)], HER2+ [4.8 (1.7–7.4)], and HR+/HER2+ [3.3 (2.1–8.1)]. In HR+/HER2- subtypes, ^{68}Ga-MY6349 demonstrated significantly higher uptake compared to ^{18}F-FDG [7.2 (4.4–9.4) vs. 3.6 (2.3–5.5), $P<0.001$]. However, no significant difference regarding tumor uptake was observed in other subtypes. In 27 patients with HR+/HER2- subtypes, ^{18}F-FDG PET/CT detected 139/208 lesions (missing 2 primary, 40 visceral and bone metastases, and 27 lymph node metastases), while ^{68}Ga-MY6349 PET/CT detected 202/208 lesions (missing 1 visceral and bone metastasis and 5 lymph node metastases). Interestingly, among 215 lesions in 16 TNBC patients, ^{18}F-FDG PET/CT detected 206 metastatic lesions (missing 9 lymph node metastases), whereas ^{68}Ga-MY6349 PET/CT detected all lesions. For HER2+ (7 patients with 74 lesions) and HR+/HER2+ (4 patients with 65 lesions) subtypes, the two tracers exhibited comparable lesion detectability. **Conclusions:** ^{68}Ga-MY6349 PET/CT demonstrated superior uptake and greater lesion detectability compared to ^{18}F-FDG PET/CT in patients with HR+/HER2- breast cancer. The high uptake of ^{68}Ga-MY6349 in HR+/HER2- and TNBC lesions may partially explain the favorable clinical outcomes observed with Trop2-targeted ADCs in these subtypes, suggesting its potential role for patient selection and stratification for Trop2-targeted therapies. However, the observed heterogeneity in uptake warrants further investigation to clarify its applications across different patient populations. Clinical trial information: NCT06188468. Research Sponsor: None.

1114 Poster Session

Comprehensive characterization of interleukin-enhanced factor 2 (ILF2) in triple-negative breast cancer (TNBC). First Author: Matias Alberto Bustos, Saint John's Cancer Institute at Providence Saint John's Health Center, Santa Monica, CA

Background: While treatment and management of TNBC has improved, there is a need for novel prognostic biomarkers to better inform outcomes and guide therapeutic options. *ILF2* is a poorly characterized protein with pleiotropic functions that is highly expressed in TNBC. Here we evaluated the associations of *ILF2* with 1) genomic and transcriptomic data, 2) tumor microenvironment (TME), and 3) clinical outcomes in TNBC. **Methods:** 15,544 breast cancer (BC) samples, including 3,038 TNBC, were tested by NGS (592, NextSeq; WES, NovaSeq) and WTS (NovaSeq; Caris Life Sciences, Phoenix, AZ). *ILF2*-high (H) and *ILF2*-low(L) TNBC were defined by respective quartiles. Immune cell fractions were estimated by WTS deconvolution (Quantiseq). Real world overall survival (OS) was obtained from insurance claims and calculated from tissue collection to last contact using Kaplan-Meier estimates. Statistical significance was determined by chi-square, Fisher's exact, and Mann-Whitney U test with p-values adjustments ($q < .05$). **Results:** *ILF2* expression (median Log2(TPM+1) was higher (all $q < .05$) in key subgroups: ductal compared to lobular carcinoma (6.4 vs 6.0); primary compared to metastatic BC (6.4 vs 6.3); African American compared to White (6.4 vs 6.3); basal compared to luminal A, luminal B, HER2 PAM50 subtypes (6.9 vs 5.8, 6.3, 6.3); and TNBC compared to HR+HER2+, HR-HER2+, HR+HER2- subtypes (6.7 vs 6.3, 6.4, 6.2). Biopsied tissues from primary TNBC (pTNBC) and metastatic TNBC (mTNBC) patients were stratified into *ILF2*-H and *ILF2*-L groups. In both mTNBC and pTNBC, *ILF2*-H groups had 1) higher percentage of young patients (age < 50) (pTNBC: 35.5% vs 19.8%; mTNBC: 28.1% vs 17.3%; all $q < .05$); 2) higher mutation frequency of *TP53* (pTNBC: 94.5% vs 79.6%; mTNBC: 92.4% vs 74.4%), but lower frequencies for *PIK3CA* (pTNBC: 5.1% vs 23.4%, mTNBC: 8.8% vs 27.4%), *CDH1* (pTNBC: *0.8% vs 6.1%;* mTNBC: 2.8% vs 12.2%; all $q < .05$); 3) higher infiltration of NK cells (pTNBC: 3% vs 2.6%; mTNBC: 2.8% vs 2.6%), but lower infiltration of M2 Mφ (pTNBC: 2.5% vs 3.3%; mTNBC: 2.6% vs 3.2%) and Tregs (pTNBC: 1.5% vs 1.9%; mTNBC: 1.4% vs 1.7%; all $q < .05$); 4) higher expression levels of immune checkpoint (*CD274, PDCD1LG2, CTLA4, LAG3, HAVCR2, FOXP3, IDO1, CD276*, FC: 1.2-3.1; all $q < .05$), stem cell genes (*CD44, NANOG, POU5F1, KLF4, ALDH1A1*, FC: 1.4-2.4; all $q < .05$), and drug efflux genes (*ABCC3, ABCC11, ABCC2, ABCB1, ABCG2, ABCC1*, FC: 1.1-4.5; all $q < .05$) compared to *ILF2*-L group. In pTNBC, *ILF2*-H had significantly shorter OS vs *ILF2*-L group (22.3 vs 28.9 months, HR 1.2 [95% CI 1-1.5], p = .03), but no significant differences were observed between mTNBC *ILF2* groups (HR 1.1 [95% CI 0.93-1.3], p = .2). **Conclusions:** *ILF2*-H TNBC patients showed differential genomic and transcriptomic alterations that relate to therapy resistance, immune suppressive TME, and shorter OS. Further studies are warranted to validate the effects of *ILF2* upregulation on therapeutic efficacy. Research Sponsor: The Fashion Footwear Association of New York (FFANY) Foundation; None.

1115 Poster Session

Concurrent GLP1R-agonist use with chemoimmunotherapy for early-stage triple-negative breast cancer. First Author: Bethania Santos, UT Southwestern Medical Center, Dallas, TX

Background: Glucagon-like peptide-1 receptor agonists (GLP-1RAs) have emerged as a key class of drugs for treating type 2 diabetes mellitus (DM2) and obesity. GLP-1 is rapidly degraded by DPP4, which led to the development of DPP4 inhibitors (DPP4i). Prior work has shown GLP-1R in tumor cells activates key growth signaling and GLP-1RA likely dampen inflammation. This suggests that GLP-1R activation may influence response rates to chemoimmunotherapy. This study aims to investigate the impact of GLP-1RAs and DPP4i (GLP1 drugs) exposure on pathological complete response (pCR) rates for patients with early-stage triple negative breast cancer (TNBC) receiving neoadjuvant chemoimmunotherapy. **Methods:** Patients with early-stage TNBC diagnosed between July 1, 2021, and December 31, 2023, who received the KEYNOTE-522 regimen were identified at three institutions. Patients using GLP-1RAs and DPP4i at breast cancer diagnosis and throughout the neoadjuvant period, alone or with other diabetes medications, were included. Those who started or discontinued GLP-1 drugs during chemoimmunotherapy were excluded. Group comparisons were made using Chi-square and two-sample t-tests. Human TNBCs were analyzed by IHC and CosMx 6000-plex spatial transcriptomics. **Results:** Among 343 patients, 7.5% were using GLP-1 drugs. The pCR rate among patients exposed to GLP-1 drugs was 30.8% compared to 64.4% in those not exposed (p = 0.001). For patients using other classes of DM2 medications (n = 46), the pCR rate was 65.2%, while for those not taking any DM2 medications (n = 271), the pCR rate was 64.2%. In univariate analysis, patients exposed to GLP-1 drugs were significantly older than non-exposed (median age: 60 vs. 51 years; p = 0.009), had a higher BMI (35.0 vs. 28.9 kg/m²; p = 0.002), and had higher rates of DM2, hypertension, and hyperlipidemia. In multivariate analysis, only age was associated with pCR (OR: 0.97, 95% CI: 0.96-0.99, p = 0.007). When comparing patients taking GLP-1 drugs with those using other DM2 medications, no significant differences were observed regarding age, BMI, or clinical T or N stage. To evaluate tumor-intrinsic factors that may influence treatment response, we examined TNBC specimens (n = 84) and identified GLP-1 receptor expression in tumor cells in 35.7% of cases and in the tumor microenvironment in 60.7% of cases. A spatial transcriptomics atlas of GLP-1 drug-exposed tumors (469,029 cells) provides evidence of GLP-1 pathway activity in both malignant and non-malignant cells of the tumor microenvironment. **Conclusions:** We observed significantly lower pCR rate among patients taking GLP1 drugs during neoadjuvant chemotherapy for TNBC. These effects were not observed with other diabetic medications. Detection of GLP1R expression in TNBC specimens indicates there may be direct and indirect effects of agonists to the GLP1 pathway on chemoimmunotherapy response rates. Research Sponsor: None.

1116 Poster Session

HAI-score, an objective HER2 artificial intelligence method for accurate H-score estimation from IHC-stained breast cancer samples. First Author: Sahar Almahfouz Nasser, Emory University, Atlanta, GA

Background: Accurate HER2 assessment is essential for breast cancer (BC) treatment, as it directs targeted therapy decisions and predicts patient prognosis. While immunohistochemistry (IHC) is widely used, its manual scoring is susceptible to inter-observer variability. RNAscope, an RNA in situ hybridization (ISH)-based technique, has shown to have a strong correlation with HER2 protein levels and has outperformed AQUA, a high-throughput quantitative immunofluorescence imaging system, in detecting HER2-low cases. However, RNAscope is constrained by its higher cost and technical complexity compared to IHC staining assays. To address this, we propose the HAI-Score, an objective, robust, accessible, non-tissue disruptive, and fast Artificial Intelligence method for evaluating the H-score from IHC images, validated using RNAscope values. **Methods:** The dataset comprises 526 tissue microarray (TMA) cores for RNAscope and IHC evaluations. The dataset includes 100 commercially available BC cores (from TissueArray.Com) and 426 cores from 243 patients at MD Anderson Cancer Center. We digitized TMA cores stained with HercepTest (Dako) (S1 dataset, n=566) and Ventana Pathway 4B5 (Roche) (S2 dataset, n=580) assays. Half of the images were randomly allocated for training and the remaining half were used for validation. A computer vision algorithm detects cell membranes using a specially designed image filter based on domain knowledge. Different visual features were then extracted from these detected cell membranes, including perimeter, normalized area, Feret diameter, fractal dimension, porosity, and staining intensities. These features were used to train a neural network to predict the HAI-Score. The ground truth was defined as HER2 RNA levels measured by RNAscope. We evaluated the HAI-Score accuracy by correlating it (Pearson, R^2) with RNA values and compared it to correlations from AHSQ (a state-of-the-art deep learning model), an expert pathologist, and FDA-approved HER2 IHC assays (HercepTest, Ventana PATHWAY). **Results:** HAI-Score yielded a correlation of 0.85 and an R^2 value of 0.711 on the testing dataset, which includes images from both the S1 and S2. This performance surpassed AHSQ, the H-score by a breast pathologist, and the scores of two FDA assays with RNA values (Table 1). **Conclusions:** HAI-Score provides an objective alternative to evaluate HER2 expression. It is strongly correlated with HER2 RNA levels and was superior to evaluations by an experienced breast pathologist. Following additional independent multi-site validation, HAI-Score could enable treatment personalization, optimize better surgical planning, and reduce overtreatment. Research Sponsor: National Cancer Institute; the National Heart, Lung and Blood Institute; the National Institute of Allergy and Infectious Diseases; the National Institute of Dental and Craniofacial Research; the National Library of Medicine; the National Instutute on Aging; the VA Research and Development Office through the Lung Precicision Oncology Program; the Office of the Assistant Secretary of Defense for Health Affairs through the Prostate Cancer Research Program; the Kidney Mapping and Atlas Project (KMAP); sponsored research agreements from Astrazeneca, Bristol Myers Squibb, the Prevent Cancer Foundation, Innovation in Cancer Informatics, and the Scott Mackenzie Foundatio; the National Institute of Diabetes and Digestive and Kidney Diseases; the Kidney Mapping and Atlas Project (KMAP); the VA Biomedical Laboratory Research and Development Service.

Comparison of methods with RNAscope using Pearson correlation and R^2.

Method	Pearson Correlation	R^2
Roche	0.58	0.33
Dako	0.76	0.57
Pathologist	0.76	0.58
AHSQ	0.83	0.69
HAI-Score	**0.85**	**0.71**

1117 Poster Session

Impact of HER2-ultralow heterogeneity and optimal threshold on trastuzumab deruxtecan (T-DXd) efficacy in metastatic breast cancer: A national multicenter cohort study (HEROIC). First Author: Yutian Zou, Sun Yat-sen University Cancer Center, Guangzhou, China

Background: Trastuzumab deruxtecan (T-DXd) has been approved for patients (pts) with HER2-ultralow metastatic breast cancer (MBC). HER2 discordance commonly occurs between primary and metastatic lesions within the same patient; however, its incidence remains unknown in the HER2-ultralow era. Additionally, there is still controversy about which specimen to use to determine HER2-ultralow status and optimal threshold to guide T-DXd therapy. **Methods:** This national, multicenter cohort study included MBC pts treated with T-DXd (5.4 mg/kg) with HER2 status available for both primary tumors and matched metastases between January 2020 and October 2024 (NCT06551220). HER2 status was determined according to the DB-06 protocol. Pts were divided into three cohorts based on HER2 discordance patterns: cohort 1 (HER2-positive/low/ultralow in both primary and metastases), cohort 2 (HER2-positive/low/ultralow in primary and HER2-null in metastases), and cohort 3 (HER2-null in primary and HER2-positive/low/ultralow in metastases). Endpoints included progression-free survival (PFS), overall survival (OS), objective response rate (ORR), disease control rate, and clinical benefit rate. **Results:** From 24 centers nationwide, 3546 pts met the criteria and were included. The incidence of HER2 discordance between primary and matched metastases has changed across eras of HER2-positivity definitions: HER2-positive era (9.8%, K = 0.78), HER2-low era (25.0%, K = 0.39), and HER2-ultralow era (20.2%, K = 0.16). Among T-DXd-treated pts (n = 1052), a higher response rate was observed in cohort 1 (ORR = 55.7%) and cohort 3 (ORR = 53.1%) compared to cohort 2 (ORR = 13.0%). ORR is positively correlated with HER2 expression if metastatic lesions are used as the examined tissue (positive 62.9%, low 49.8%, ultralow 47.0%, null 13.0%). However, the correlation between ORR and HER2 expression is not significant when primary lesions were examined (positive 57.8%, low 41.5%, ultralow 54.4%, null 53.1%). Additionally, cohort 1 (mPFS = 11.6 mo, mOS = 30.7 mo) and cohort 3 (mPFS = 10.9 mo, mOS = 18.4 mo) exhibited significantly superior PFS and OS compared to cohort 2 (mPFS = 6.1 mo, mOS = 12.3 mo). Faint incomplete membrane staining percentage $\geq$5% in metastatic lesion was the best threshold to distinguish PFS (HR = 0.54, P= 0.02; mPFS, 11.4 vs 8.6 mo) and ORR (OR = 4.00, P= 0.01; 60% vs 27%) among HER2-ultralow MBC treated with T-DXd. **Conclusions:** A high HER2-ultralow discordance rate was observed between primary tumors and matched metastases. HER2 status in metastatic specimens more accurately predicts T-DXd efficacy compared to primary specimens. A staining threshold of $\geq$5% tumor cells in metastatic lesions may optimize T-DXd treatment in HER2-ultralow MBC. Therefore, re-evaluating HER2 status in metastatic lesions is recommended for T-DXd treatment decision. Research Sponsor: None.

1118 Poster Session

Opioid use disorder among females with breast cancer: A comprehensive analysis of prevalence in the United States and associated factors. First Author: Aneri Sanepara, Pandit Deendayal Upadhyay Medical College, Rajkot, Gujarat, India

Background: Patients with breast cancer (BC) are frequently prescribed opioids for pain management, placing them at risk of opioid use disorder (OUD). This study analyzes the prevalence of OUD and identifies factors contributing to its risk among BC patients in the United States. **Methods:** We conducted a retrospective analysis using the National Inpatient Sample (NIS) database, a Healthcare Cost and Utilization Project (HCUP) component. Females with BC were identified through ICD-10 codes. The Cochran-Armitage trend test assessed OUD prevalence trends from 2016 to 2022. Multivariable regression models estimated the impact of multiple patient demographics and comorbidities on the presence of OUD. **Results:** Among 1,189,884 females aged$\geq$18 with BC, 2.3% (27,500) had OUD. The mean age of OUD patients was 58.38 years, compared to 64.46 years in the non-OUD cohort. OUD prevalence was highest in those aged 18–50 years (3.8%), followed by 51–60 years (3.0%), and lowest in those $>$ 60 years (1.7%). Between 2016 and 2020, OUD prevalence increased from 1.9% to 2.8%, followed by a decline to 2.4% in 2022 (p-trend $<$ 0.01). Factors that were linked with higher OUD involved patients with neoplasm-related pain(NRP)(aOR 5.718, 95% CI 5.549-5.893, $p < 0.01$), on palliative care (aOR 1.397, 95% CI 1.353-1.443, $p < 0.001$), with metastasis (aOR 1.573, 95% CI 1.526-1.621, $p < 0.01$), depression (aOR 1.447, 95% CI 1.400-1.495, $p < 0.01$), bipolar disorder (aOR 2.173, 95% CI 2.038-2.317, $p < 0.01$), suicidality (aOR 3.228, 95% CI 2.938-3.546, $p < 0.01$), and anxiety (aOR 1.617, 95% CI 1.572-1.664, $p < 0.01$). Moreover, substance use such as cocaine (aOR 5.252, 95% CI 4.708-5.859, $p < 0.01$) and amphetamine (aOR 3.948, 95% CI 3.443-4.527, $p < 0.01$) was also associated with higher odds, while cannabis users (aOR 0.876, 95% CI 0.793-0.968, $p < 0.01$) had lower odds of OUD. Our study further found racial disparities, with reduced odds among Blacks (vs Whites, aOR 0.933, 95% CI 0.901-0.967, $p < 0.01$) and Hispanics (vs.Whites, aOR 0.866, 95% CI 0.827-0.906, $p < 0.01$). Socio-economic differences were also noted, with lower odds among those of the 26th-50th (vs. 0-25th, aOR 0.932, 95% CI 0.9-0.966, $p < 0.01$), 51st-75th (vs. 0-25th, aOR 0.951, 95% CI 0.918-0.986, $p < 0.01$), and 76th-100th (vs. 0-25th, aOR 0.916, 95% CI 0.882-0.951, $p < 0.01$) household income quartiles. **Conclusions:** This study showcases the significant prevalence and impact of OUD among BC patients, identifying socioeconomic and racial disparities, and key risk factors such as NRP, psychiatric comorbidities, and concurrent substance use, like cocaine and amphetamines. Interestingly, cannabis use was associated with a lower risk of OUD, which may reflect its role as an alternative pain management strategy. Overall, this study suggests the need to adopt crucial preventative measures against OUD in patients exhibiting these characteristics. Research Sponsor: None.

1119 Poster Session

Treatment patterns, genomic characteristics, and outcomes among patients with metastatic lobular breast cancer. First Author: Sherry Shen, Memorial Sloan Kettering Cancer Center, New York, NY

Background: Invasive lobular carcinoma (ILC) is characterized by loss of E-cadherin expression and accounts for 10-15% of breast cancer diagnoses. ILC differs from the more common invasive carcinoma of no special type in the pattern of metastatic spread and genomic characteristics; however, clinicopathologic characteristics among patients with metastatic ILC are not well described. Here, we present comprehensive treatment, genomic, and outcome data in a large single-center cohort of patients with metastatic ILC. **Methods:** Patients were identified for inclusion in this retrospective study if they had ILC histology on early-stage breast biopsy/surgical pathology and/or *CDH1* mutation on metastatic site biopsy; all patients were required to have MSK-IMPACT somatic next generation sequencing (NGS) data available. Clinicopathologic characteristics were abstracted from the EMR. The Kaplan-Meier method was used to estimate overall survival (OS). The log-rank test was used to compare OS by ILC subtype and by genetic mutations. Wilcoxon rank sum test and Kruskal-Wallis test were used to compare number of treatment lines by receptor status. **Results:** 654 patients were included, of whom 99.8% were female, 89% were white, and 96% non-Hispanic. 438 (67%) had recurrent disease whereas 212 (33%) had *de novo* metastatic disease. Among 307 with ILC histologic subtype data available, 139 (45%) had classic type, 65 (21%) had pleomorphic, 45 (15%) had mixed, and 58 (19%) had other ILC subtypes. 454 (87%) had hormone receptor-positive (HR+) disease, 45 (9.1%) had HER2+ disease, and 50 (9.5%) had triple negative disease at metastatic diagnosis. In the total cohort, median number of treatment lines for metastatic disease was 4 (IQR 2-7) and median number of chemotherapies was 2 (IQR 1-3). In the HR+ cohort, median number of endocrine therapies was 2 (IQR 1-3). Among patients with genomic data from a biopsy obtained within 2 months of metastatic diagnosis, 79% had a *CDH1* mutation, 48% had a *PIK3CA* mutation, 5.6% had an *AKT1* mutation, 11% had a *PTEN* mutation, 9.3% had an *ESR1* mutation, 17% had a *HER2* mutation, and median tumor mutation burden (TMB) was 4 (IQR 3-7); 17% had TMB ^{3}10. Median OS in the total cohort was 4.4 years (95%CI 4.1-4.8). OS did not differ significantly by ILC subtype (p= 0.8). OS differed significantly by *CDH1* mutation status (wt 5.3 years, 95%CI 4.1-6.6; mut 3.7 years, 95%CI 3.5-4.2, p= 0.01), *PIK3CA* status (wt 4.6 years, 95%CI 4.0-5.8; mut 3.4 years, 95%CI 3.1-3.9, $p<$ 0.001), and *PTEN* status (wt 4.2 years, 95%CI 3.7-4.5; mut 3.4 years, 95%CI 2.2-4.3, p= 0.008). OS did not differ significantly by *HER2*, *AKT1*, or *ESR1* mutation status. **Conclusions:** In a large single-center cohort of patients with metastatic ILC, OS did not vary by ILC subtype, but did differ significantly by *CDH1, PIK3CA,* and *PTEN* mutation status. This underscores the prognostic importance of NGS in metastatic ILC. Research Sponsor: None.

TPS1120 **Poster Session**

A phase III randomized trial of radiotherapy optimization for low-risk HER2-positive breast cancer (HERO): NRG-BR008. First Author: Lior Zvi Braunstein, Memorial Sloan Kettering Cancer Center, New York, NY

Background: Breast radiotherapy (RT) is the standard of care for patients with early-stage breast cancer (BC) who undergo breast-conserving surgery (BCS). However, the magnitude of benefit of RT is less clear in BCS patients with low-risk disease who receive effective systemic therapy. Among patients with early-stage HER2-positive (HER2+) BC, 10-year locoregional recurrence has been reported as low as 1.5% following BCS, adjuvant chemotherapy and HER2-targeted therapy, and RT. Given these exceedingly favorable outcomes, with the addition of HER2-directed therapy, we seek to evaluate the feasibility of omitting RT among patients with early-stage HER2+ BC following BCS and appropriate systemic therapy. **Methods:** This is a phase III randomized trial for patients ≥18 years with early-stage, node-negative, HER2+ (IHC/FISH) BC treated with BCS with negative margins and sentinel lymph node biopsy or axillary dissection. Patients undergoing primary surgery must have pathologic T1-2 (≤3 cm) N0 disease, whereas patients receiving neoadjuvant therapy must have clinical T1-2 (with radiographically T≤5 cm) N0 disease and exhibit a pathologic complete response (ypT0N0) at surgery (residual DCIS [ypTis] spanning ≤1 cm is permitted, and surgical margins are negative for DCIS). All patients must receive cytotoxic chemotherapy and HER2-targeted therapy, either in the adjuvant or neoadjuvant setting. Stratification is by age (<60; ≥60), tumor size (≤1 cm; >1 cm), estrogen-receptor status (positive; negative), and systemic therapy sequencing (adjuvant *v* neoadjuvant). Patients will be randomized to standard breast RT in addition to continuation of trastuzumab to complete one year of treatment (Arm 1), or trastuzumab alone (Arm 2). Endocrine therapy will be recommended for patients with hormone-receptor-positive tumors. The primary endpoint is the recurrence-free interval (RFI). Secondary endpoints include time to ipsilateral breast recurrence, locoregional recurrence, disease-free survival, and overall survival, in addition to the 7-year ipsilateral breast recurrence rate among those not receiving RT. A health-related quality of life sub-study will assess differences in patient-reported breast pain and worry. We estimate a 7-year RFI of 97.5% with RT and allow for a clinically acceptable decrement of 3.63% without RT (7-year RFI of 93.87%; HR 2.5) to establish omission of RT as non-inferior. NRG-BR008 aims to enroll 1,300 patients over 7.25 years, yielding 80% power to detect the non-inferiority of RT omission with a one-sided α=0.05. We expect to observe the required 38 RFI events within 4.5 years of additional follow-up. The NRG-BR008/HERO trial opened to accrual in March 2023. Accrual is 64/1,300 as of 1/23/24. NCT #: NCT05705401. Support: U10 CA180868, -180822, UG1 CA189867, U24 CA196067. Clinical trial information: NCT05705401. Research Sponsor: National Cancer Institute; U10CA180868; National Cancer Institute; U10CA180822; National Cancer Institute; UG1CA189867; National Cancer Institute; U24CA196067.

TPS1121 **Poster Session**

IND.241: A Canadian Cancer Trials Group liquid-biopsy informed platform trial to evaluate treatment in CDK4/6-inhibitor resistant ER+/HER2- metastatic breast. First Author: David W. Cescon, Princess Margaret Cancer Centre/UHN, Toronto, ON, Canada

Background: The combination of a CDK4/6 inhibitor + endocrine therapy (CDK4/6i+ET) is standard first-line systemic treatment for patients with ER+/HER2-negative metastatic breast cancer (MBC). Beyond this initial therapy, there are numerous therapeutic agents available/ in development for subsequent lines of treatment. Circulating tumor DNA (ctDNA) via liquid biopsy is a promising, non-invasive approach for blood-based tumor genotyping, patient stratification and response assessment with the potential to enhance biomarker-driven strategies and aid in development of new therapeutics. **Methods:** IND.241 is a master protocol platform design consisting of independent substudies monitoring patients with ER+/HER2- MBC prior to progression (PD) on CDK4/6i+ET and investigating novel agents or drug combinations in 2nd/3rd lines after progression on CDK4/6i+ET. The primary objective of the novel drug/combination substudies is to centrally interrogate ctDNA (Tempus xF+, a 523-gene liquid biopsy panel) and evaluate whether biomarker selection improves ORR or CBR as assessed by RECIST 1.1. Secondary objectives include safety and toxicity profile for each drug/combination, PFS, and OS. The monitoring substudy (Substudy A) enrolls patients currently on CDK4/6i+ET treatment and aims to characterize the molecular profile, clinical features, and ctDNA dynamics of acquired resistance. This platform trial enables creation and maintenance of a tissue and data bank including clinical data, genomics, and radiomics from all substudies to evaluate surrogates of treatment outcomes and potential biomarkers of response, resistance, and disease progression. Patients with specific biomarkers detected in ctDNA will be enrolled into corresponding biomarker positive cohorts of substudies. Patients with no substudy-specific biomarkers are randomized to biomarker negative cohorts of available substudies. Treatment substudies follow a 2-stage design. Currently, the monitoring substudy A is actively accruing. Substudy B is evaluating lunresertib (PKMYT1 inhibitor) + gemcitabine in patients +/-CCNE1 overexpression / amplification. Substudy C is evaluating niraparib (PARP inhibitor) + fulvestrant (ET) in patients +/- alterations in BRCA1/2 (germline/somatic) or PALB2 (germline). These latter two substudies have now closed to accrual, with efficacy and safety evaluation ongoing. Substudy D, which has recently been added, is evaluating lunresertib + camonsertib (ATR inhibitor) in patients +/- CCNE1 overexpression/amplification, FBXW7 or PPP2R1A alterations. Additional substudies are in development for inclusion in this platform trial. Clinical trial information: NCT05601440. Research Sponsor: Repare Therapeutics; GSK.

TPS1122 **Poster Session**

Phase II study evaluating 68Ga-FAPI PET uptake heterogeneity as a predictor of T-DXd treatment response in HER2-positive breast cancer brain metastases. First Author: Biyun Wang, Department of Medical Oncology, Fudan University Shanghai Cancer Center, Shanghai, China

Background: Breast cancer is a leading cause of metastasis to the central nervous system (CNS). Approximately 30% of patients with HER2-positive breast cancer develop brain metastases, which are associated with a poor prognosis and limited treatment options. T-DXd has shown promise in treating brain metastases from HER2-positive breast cancer. However, up to 10% patients showed brain metastasis progression at the initial evaluation of treatment and may require radiotherapy or neurosurgery immediately. Identifying predictors of treatment response and determining the timing for local therapy intervention is crucial for personalized medicine. Heterogeneity in tumor metabolism, as assessed by (68Ga)–labeled fibroblast-activation protein inhibitor (68Ga-FAPI) PET-CT which displays the activity of cancer-associated fibroblasts (CAFs) in the tumor microenvironment, with good sensitivity and specificity in brain metastasis imaging, may serve as a biomarker for treatment response. This study aims to investigate the predictive value of 68Ga-FAPI PET uptake heterogeneity for T-DXd treatment response in HER2-positive breast cancer brain metastases. **Methods:** This open-label, single-center, phase II clinical trial will investigate the heterogeneity of brain metastasis and analyze the difference between stable and active brain metastasis evaluated by 68Ga-FAPI uptake in HER2-positive MBC. Patients with HER2-positive metastatic breast cancer and confirmed brain metastases by MRI were enrolled; at least one measurable intracranial lesion (≥ 1.0 cm) that has not previously been treated with radiation. Radiotherapy or neurosurgery is allowed with an interval ≥ 4 weeks. Patients will receive T-DXd treatment and undergo 68Ga-FAPI PET-CT scans before and after two cycles of treatment. The primary endpoint is the difference in baseline heterogeneity index by 68Ga-FAPI PET-CT between cerebral lesions achieving ORR and those that do not. Secondary endpoints include 68Ga-FAPI PET-CT value changes (SUVmax, SUVmean) at baseline and after treatment; difference in baseline heterogeneity index for PFS, CBR and OS; difference of baseline heterogeneity index, SUVmax and SUVmean between active or stable brain metastasis; 68Ga-FAPI PET-CT value changes (heterogeneity index, SUVmax, SUVmean) at baseline and 2 cycles after T-DXd treatment of whole body metastasis lesions. The study plans to enroll 50 patients and is actively enrolling. Clinical trial information: NCT06797622. Research Sponsor: CSCO-LingHang Oncology Research Foundation (Y-2022HER2AZQN-0378).

TPS1123 **Poster Session**

SOLTI-2201 ACROSS-TROP2 trial: A phase II study to identify predictive biomarkers of sacituzumab govitecan benefit and to understand resistance mechanisms in HR+/HER2- advanced or metastatic breast cancer. First Author: Eva Maria Ciruelos, University Hospital 12 de Octubre/ SOLTI Cancer Research Group, Madrid, Spain

Background: Sacituzumab Govitecan (SG) is a TROP2-directed antibody-drug conjugate (ADC) linked to a topoisomerase I inhibitor via a hydrolysable CL2A linker. It is approved for the treatment of metastatic triple-negative breast cancer (mTNBC) patients who have undergone at least two prior systemic therapies, including one for advanced disease, and of hormone receptor-positive (HR+)/HER2-negative metastatic breast cancer (mBC) patients after endocrine therapy (ET) and two systemic treatments. Currently, no biomarkers, including TROP2 protein expression, have been identified to predict SG response, highlighting the need to explore biomarkers of efficacy and to identify key resistance mechanisms to the drug. The ACROSS-TROP2 study aims to address this unmet medical need. **Methods:** ACROSS-TROP2 (NCT06236269) is a phase II, open-label, single-arm trial investigating SG in HR+/HER2-negative mBC patients. The study initially planned to enroll 50 pre- or post-menopausal female or male participants who progressed during or after treatment with CDK4/6 inhibitors and received up to one prior chemotherapy or ADC regimen for metastatic disease. Due to high recruitment rates and promising findings demonstrating ADC benefits in earlier treatment lines (Bardia et al., NEJM 2024), a protocol amendment was introduced to expand the sample size to 100 patients. Participants will receive SG at 10 mg/kg via IV infusion on Days 1 and 8 of each 21-day cycle until disease progression (PD). Fresh tumor biopsies will be obtained at baseline, after 2–3 weeks of treatment (C2D1), and at PD. The primary endpoint is to measure changes in the CelTIL score—a composite of tumor cellularity and tumor-infiltrating lymphocytes—between baseline and C2D1 biopsies, as CelTIL is associated with long-term efficacy. Secondary endpoints include overall response rate, progression-free survival, duration of response, time to response, safety, and tolerability. Correlative analyses of molecular markers in tissue and blood will be conducted to correlate biological findings (e.g., CelTIL, Ki67, TROP2, PD-1/PD-L1, PAM50) with clinicopathological data, evaluate the predictive value of early dynamic changes in ctDNA, identify genomic alterations linked to treatment response and resistance, and explore changes from baseline to PD to identify mechanisms of resistance. A paired t-test will assess whether the mean change in CelTIL score is statistically different from zero. The study has been approved in Spain and is actively enrolling participants at 10 sites within the SOLTI network. Previously presented at ESMO Breast 2024, FPN: 265TiP, Eva Ciruelos et al. - Reused with permission. Clinical trial information: NCT06236269. Research Sponsor: None.

TPS1124 **Poster Session**

LITESPARK-029: A phase 2, randomized, open-label study of belzutifan plus fulvestrant in participants with estrogen receptor–positive, HER2-negative unresectable locally advanced or metastatic breast cancer after progression on previous endocrine therapy. First Author: Bora Lim, Department of Breast Medical Oncology, The University of Texas MD Anderson Cancer Center, Houston, TX

Background: Endocrine-based therapy (ET), with or without cyclin-dependent kinase 4/6 inhibitors (CDK4/6i), prolongs PFS and OS in participants (pts) with metastatic hormone receptor–positive (HR+) and human epidermal growth factor receptor 2–negative (HER2–) breast cancer. After PD on first-line therapy, next-line therapy options provide limited PFS gains, in part due to resistance mechanisms (eg, hyperactive FOXA1). The transcription factor hypoxia-inducible factor 2α (HIF-2α), a major target of FOXA1, regulates key components of angiogenesis and subsequent development of metastasis. Preclinical studies show suppression of tumor growth with an HIF-2α antagonist, particularly when combined with fulvestrant. Belzutifan, an HIF-2α inhibitor, is approved for the treatment of pts with advanced renal cell carcinoma following a PD-(L)1 inhibitor and vascular endothelial growth factor tyrosine kinase inhibitor. LITESPARK-029 (NCT06428396) evaluates belzutifan + fulvestrant vs everolimus + fulvestrant or exemestane in pts with estrogen receptor–positive (ER+)/HER2– unresectable locally advanced or metastatic breast cancer. **Methods:** This phase 2, randomized, active-controlled, open-label, multicenter study is enrolling pts ($\geq$18 y) with locally confirmed ER+/HER2– unresectable, locally advanced or metastatic disease who have had radiographic PD on $\geq$12 mo of ET + CDK4/6i therapy in the noncurative setting or received $\geq$2 lines of ET in the noncurative setting including CDK4/6i where the CDK4/6i was discontinued due to intolerance (not due to progression). Pts must also be eligible for additional ET with everolimus plus either fulvestrant or exemestane per local investigator assessment, have an ECOG PS of 0 or 1, and provide a new or recent core biopsy for central determination of ER and HER2 status. Prior treatment with chemotherapy, antibody-drug conjugates, or PARP inhibitors in the noncurative setting is prohibited. Pts are randomized 1:1 to receive oral belzutifan 120 mg once daily + fulvestrant 500 mg on days 1 and 15 of cycle 1 and on day 1 of all subsequent 28-day cycles or oral everolimus 10 mg once daily + fulvestrant (as above) or oral exemestane 25 mg once daily until PD or unacceptable toxicity. Randomization is stratified by treatment with prior ET + CDK4/6i therapy ($<$ 18 mo duration before PD vs $\geq$18 mo duration before PD or no PD). Tumor imaging is performed at screening, Q8W from randomization through week 56, and Q12W thereafter. The primary endpoint is PFS per RECIST v1.1 by blinded independent central review (BICR). Secondary endpoints include PFS rate per RECIST v1.1 by BICR at 6 and 12 mo, OS, ORR per RECIST v1.1 by BICR, clinical benefit (CR, PR, or stable disease for $\geq$24 weeks), and safety. The study start date was July 2024. Clinical trial information: NCT06428396. Research Sponsor: Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA.

TPS1125 **Poster Session**

ALISertib in combination with endocrine therapy in patients with hormone receptor-positive (HR+), HER2-negative (HER2–) recurrent or metastatic breast cancer: The phase 2 ALISCA-Breast1 study. First Author: Pooja Prem Advani, Mayo Clinic, Jacksonville, FL

Background: Despite the many available treatments for patients (pts) with HR+, HER2– recurrent/metastatic breast cancer (MBC), optimal treatment after progression on CDK4/6 inhibitors (CDK4/6i) is unclear. One possible CDK4/6i resistance mechanism is increased expression of Aurora kinase A (AURKA), a key mitosis regulator associated with poor prognosis. Further implicated in CDK 4/6i resistance, high c-Myc or RB1 loss of function (LOF) are associated with transcriptional co-regulation or synthetic lethality, respectively, with AURKA. Alisertib is a highly selective, reversible, ATP-competitive, orally administered, small-molecule AURKA inhibitor with antiproliferative activity in HR+ BC-derived cell lines and BC xenograft models. Models with elevated AURKA or c-Myc expression, or RB1 LOF show greater alisertib sensitivity. Alisertib had activity in phase 1 and 2 trials, including objective response rates (ORRs) of 19.6–20% and median progression-free survival (PFS) of 5.4–5.6 months alone or with fulvestrant in pts with HR+/HER2–, endocrine-resistant MBC. The most common treatment-related grade $\geq$3 adverse events (AEs) were neutropenia, anemia, and leukopenia. **Methods:** ALISCA-Breast1 (NCT06369285) is a randomized phase 2 study. Primary objective: to determine the optimal alisertib dose administered with endocrine therapy (ET) based on AEs and serious AEs per CTCAE v5.0 and efficacy (ORR, duration of response, disease-control rate, PFS, overall survival). Secondary objectives: to identify biomarkers of efficacy and alisertib pharmacokinetics (PK). Key inclusion criteria: $\geq$18 years; ECOG performance status 0 or 1; confirmed HR+, HER2–, recurrent/metastatic breast adenocarcinoma not amenable to curative therapy; available tumor tissue for biomarker analyses; progression on or after $\geq$2 prior ET lines in recurrent/metastatic setting; prior CDK4/6i with ET in recurrent/metastatic setting. Key exclusion criteria: prior chemotherapy in recurrent/metastatic setting; prior AURKA-specific or pan-Aurora-targeted agents; unstable brain metastases. Eligible pts will be randomized 1:1:1 to alisertib 30 mg, 40 mg, or 50 mg orally twice daily on days 1—3, 8–10, and 15–17 every 28 days, plus physician's choice of anastrozole, letrozole, exemestane, fulvestrant, or tamoxifen not previously used in recurrent/metastatic setting or progressed upon in adjuvant setting; $\leq$50 pts will be enrolled per arm in the USA and Europe. All pts will undergo sparse PK sampling. Tumor tissue will be centrally assessed for biomarkers, including *RB1, MYC, TP53, ESR1,* PI3K/AKT pathway, *HER2* and *AURKA* genomic alterations/expression levels. The study will determine the optimal alisertib dose to combine with ET and may identify biomarker(s) defining pts with the greatest benefit from alisertib-based therapy. Clinical trial information: NCT06369285. Research Sponsor: Puma Biotechnology Inc.

TPS1126 **Poster Session**

Integrating gene signatures to guide HR+/HER2- MBC therapy in a diverse cohort (INSIGHT). First Author: Sonya A. Reid, Vanderbilt-Ingram Cancer Center, Vanderbilt University Medical Center, Nashville, TN

Background: Black women with breast cancer (BC) have a 40% higher mortality rate compared to Non-Hispanic White (NHW) women. Worse outcomes have been observed among Black women with hormone receptor positive (HR+), human epidermal growth factor receptor 2 negative (HER2-) BC despite comparable systemic therapies. Gene expression profiling has been used in early-stage BC to provide prognostic and predictive information beyond standard immunohistochemical classifications. BluePrint, an 80-gene molecular subtype signature, and MammaPrint (Agendia), a 70-gene risk of distant recurrence signature, further classify HR+/HER2- BC into luminal A, luminal B, HER2-enriched, and basal-type tumors. Non-Luminal A (Luminal B, HER2-enriched, and Basal-type) tumors are more aggressive and are associated with worse survival compared to Luminal A tumors. Our preliminary data demonstrate that non-Luminal A tumors are overrepresented in Black women (11% Black vs. 5% White). The role of molecular subtyping in guiding therapy for patients with HR+/HER- MBC is not defined. Retrospective studies have shown that non-Luminal A HR+/HER2- tumors derive less benefit from endocrine therapy (ET). We hypothesize that patients with non-Luminal A, HR+/HER2- MBC progressing on ET +/- CDK4/6 inhibition derive more benefit from chemotherapy than ET in the second line. Furthermore, the impact of the intervention will be more pronounced in Black women compared to NHW women. INSIGHT is a randomized phase II study evaluating the anti-tumor effect of capecitabine versus physician's choice ET as second line for patients with non-Luminal A HR+/HER2- MBC (NCT05693766). **Methods:** In this study, patients progressing on 1st line ET +/- a CDK4/6i are enrolled. Archival primary or metastatic tumor samples are analyzed using MammaPrint and BluePrint. Patients with non-Luminal A tumors are randomized (1:1) to receive physician's choice ET versus capecitabine, stratified by molecular subtype and race. Disease assessments are performed every three months. The primary endpoint is progression free survival (PFS). Secondary endpoints include overall response rate, clinical benefit rate, overall survival, and patient reported outcomes. The study has 80% power to detect a minimal hazard ratio of 0.5 in 5-year PFS with one-sided α = 0.05. Exploratory correlative studies are planned. This trial enriches for racial/ethnic minority patients through collaborations with the University of Texas Southwestern and the University of Alabama at Birmingham, health systems that serve large minority populations. Seven of the 64 planned patients have been enrolled. Clinical trial information: NCT05693766. Research Sponsor: Susan G. Komen.

TPS1127 **Poster Session**

ELCIN: Elacestrant in women and men with CDK4/6 inhibitor (CDK4/6i)-naïve estrogen receptor-positive (ER+), HER2-negative (HER2-) metastatic breast cancer (mBC)—An open-label multicenter phase 2 study. First Author: Virginia G. Kaklamani, University of Texas Health Science Center at San Antonio, San Antonio, TX

Background: Endocrine therapy (ET) plus a CDK4/6i is the mainstay treatment in first-line ER+/HER2- mBC; however, a subset of patients are unable to tolerate CDK4/6i, and resistance to ET emerges. Intrinsic resistance mechanisms include alterations in the PI3K/AKT/mTOR or cell cycle pathways; acquired resistance mechanisms include estrogen receptor gene 1 mutations (*ESR1*-mut), which emerge in up to 50% of patients during prolonged aromatase inhibitor therapy in mBC. In the phase 3 EMERALD trial, elacestrant significantly prolonged PFS vs standard-of-care (SOC) ET and was associated with a manageable safety profile in patients with ER+/HER2- mBC previously treated with ET+CDK4/6i, leading to its approval as the first clinically available oral SERD. Elacestrant significantly reduced the risk of progression or death vs SOC ET by 30% in the overall population (HR 0.70; 95% CI 0.55-0.88; P=0.002) and by 45% in patients with *ESR1*-mut tumors (HR 0.55; 95% CI 0.39-0.77; P=0.0005) [Bidard, 2022]. Preclinical studies demonstrated that elacestrant is equally active in both in vitro and in vivo models of ER+/HER2- breast cancer, regardless of prior exposure to CDK4/6i. Based on preclinical models and clinical efficacy data, elacestrant may improve clinical outcomes in CDK4/6i-naïve patients and provide a convenient all-oral treatment option if combined with CDK4/6i. The ELCIN trial will evaluate efficacy and safety of elacestrant in patients with ER+/HER2- mBC who received prior ET and no prior CDK4/6i in the metastatic setting. **Methods:** ELCIN (NCT05596409) is an open-label, multicenter, single-arm phase 2 trial. Eligible patients are women or men with ER+/HER2— mBC who received 1-2 lines of prior ET and no prior CDK4/6i or chemo in the metastatic setting. Patients must have measurable disease per RECIST v1.1 or a mainly lytic bone lesion (for bone disease only), ECOG PS $\leq$1, adequate bone marrow and organ function, and no active or newly diagnosed CNS metastases or visceral crisis. Patients will receive elacestrant 345 mg once daily. The primary objective is investigator-assessed PFS. Secondary objectives are ORR, DoR, CBR, OS, PROs-QoL, and safety. Exploratory objectives include elacestrant efficacy according to *ESR1*-mut status, changes in biomarkers, including allele mutation frequencies (cfNAs), and relationship between efficacy endpoints. Status: ELCIN has a planned sample size of 60 patients; recruitment is ongoing worldwide. Clinical trial information: NCT05596409. Research Sponsor: Menarini Group.

TPS1128 **Poster Session**

SIMRISE: A randomized phase III trial evaluating SIM0270 in combination with everolimus versus treatment of physician's choice in patients with ER+/HER2- advanced breast cancer, previously treated with CDK4/6 inhibitors. First Author: Jiong Wu, Fudan University Shanghai Cancer Center, Shanghai, China

Background: CDK4/6 inhibitors (CDK4/6i) in combination with endocrine therapy (ET) have demonstrated sustained benefits in the first-line treatment of HR+/HER2- advanced breast cancer(aBC). However, effective ET options are limited for patients who progressed after the treatment of ET in combination with CDK4/6i. SIM0270 in combination with everolimus exhibited promising anti-tumor activities in a Phase I study. **Methods:** SIMRISE is an ongoing randomized, open label, Phase III trial designed to evaluate SIM0270 in combination with everolimus versus the treatment of physician's choice (TPC) for patients with ER+/HER2- aBC progressed on previous ET and CDK4/6i. A total of 460 patients will be enrolled across approximately 50 sites in China. Patients are randomized in a 1:1 ratio to receive either SIM0270 + everolimus or TPC (exemestane + everolimus or fulvestrant). Stratification factors include: visceral metastasis (yes or no); prior fulvestrant (yes or no); baseline ESR1 status (mutation detected or not detected). Key eligibility criteria include: ER+/HER2- aBC patients having measurable disease per RECIST 1.1 or bone only disease with at least one predominant lytic bone lesion or mixed lytic-blastic lesion; postmenopausal women and pre-/perimenopausal women or men receiving luteotropic hormone releasing hormone agonist(LHRHa) therapy per local prescribing information; patients must have received at least one line and no more than two lines of ET; recurrence while on or within 12 months of completion of adjuvant ET for $\geq$24 months is considered as first-line ET, or first line ET in advanced setting for $\geq$6 months. Patients must have previously received CDK4/6i combined with ET for $\geq$6 months; one line chemotherapy for aBC is allowed. The Primary endpoint is progression-free survival (PFS) as assessed by blinded independent review committee (BIRC). The secondary endpoints include PFS (assessed by investigators), overall survival (OS), objective response rate (ORR), duration of response (DoR), clinical benefit rate (CBR), time to progression (TTP), safety, pharmacokinetics (PK) and patients-reported outcomes (PRO). The analysis of primary endpoint will use a stratified log-rank test at an overall of 0.05 significance level (two-sided). Futility analyses are planned, and an independent data monitoring committee will be in place. Clinical trial information: NCT06680921. Research Sponsor: Simcere Zaiming Pharmaceutical Co., Ltd.

TPS1129 **Poster Session**

ADELA: A double-blind, placebo-controlled, randomized phase 3 trial of elacestrant (ELA) + everolimus (EVE) versus ELA + placebo (PBO) in ER+/HER2- advanced breast cancer (aBC) patients with *ESR1*-mutated tumors progressing on endocrine therapy (ET) + CDK4/6i. First Author: Antonio Llombart-Cussac, Medica Scientia Innovation Research (MEDSIR), Hospital Arnau de Vilanova, FISABIO, Translational Oncology Group, Universidad Cardenal Herrera-CEU, Alfara Del Patriarca, Spain

Background: ET+CDK4/6i is standard-of-care (SOC) in 1L ER+/HER2- aBC; however, tumors eventually develop resistance. Constitutive activation in the PI3K/AKT/mTOR pathway can contribute to endocrine resistance in breast cancer. *ESR1* mutations are a common type of acquired resistance that emerges in 40-50% of patients in the metastatic setting after prolonged aromatase inhibitor exposure. There is an unmet need for novel therapeutic approaches to overcome resistance mechanisms and improve outcomes in patients with ER+/HER2- aBC with *ESR1*-mutated tumors progressing after ET+CDK4/6i. ELA is a next-generation oral SERD that binds to ER-alpha, inducing its degradation. In EMERALD, ELA improved PFS vs SOC ET in patients with *ESR1*-mutated tumors (HR 0.55; 95% CI 0.39-0.77; P=0.0005) [Bidard 2022]. Differences were notable among patients who received prior ET+CDK4/6i $\geq$12 mo; median PFS with ELA was 8.6 mo vs 1.9 mo with SOC ET (HR 0.41; 95% CI 0.26-0.63) [Bardia 2024]. Crosstalk between ER and PI3K/AKT/mTOR pathways provides a rationale for evaluating ELA+EVE (a mTORC1 inhibitor). In ELEVATE phase 1b (NCT05563220), ELA+EVE demonstrated ORR 22% and CBR at 24 weeks 72% in patients with ER+/HER2- aBC progressing after ET+CDK4/6i; ELA 345 mg + EVE 7.5 mg was identified as the RP2D [Rugo ESMO 2024]. Safety was consistent with the known profile of EVE+SOC ET. ADELA compares ELA+EVE vs ELA+PBO in ER+/HER2- aBC patients with *ESR1*-mutated tumors progressing on ET+CDK4/6i. **Methods:** ADELA (NCT06382948) is an international, multicenter, double-blind, placebo-controlled phase 3 trial. Eligible patients are adults ($\geq$18 yrs) with ER+/HER2- aBC and *ESR1*-mutated tumors, previously treated with 1-2 lines of ET for aBC, and evidence of disease progression on prior ET+CDK4/6i for aBC after $\geq$6 mo. Patients receiving CDK4/6i-based adjuvant therapy are eligible (disease progression must be confirmed after $\geq$12 mo of treatment but $<$12 mo following CDK4/6i completion). Other criteria include adequate organ function and ECOG PS 0-1. Exclusion criteria include prior chemotherapy for aBC and active uncontrolled/symptomatic brain metastasis. Patients will be randomized 1:1 to 28-d cycles of ELA 345 mg + EVE 7.5 mg QD or ELA 345 mg + PBO QD until disease progression or unacceptable toxicity. Patients will receive dexamethasone mouthwash during the first 8 wks. Stratification factors are presence of visceral metastases (yes vs no) and duration of prior CDK4/6i ($\geq$12 mo vs $<$12 mo). The primary objective will be to evaluate PFS based on blinded independent review committee. Secondary endpoints include investigator-assessed PFS, OS, ORR, CBR, DoR, TTR, best percentage change in tumor burden, safety, and HRQoL. Status: Planned enrollment is 240 patients; recruitment is ongoing. Clinical trial information: NCT06382948. Research Sponsor: Menarini Group.

TPS1130 **Poster Session**

Dauntless-1, a phase 2 clinical trial to evaluate PMD-026, a first-in-class pan-RSK inhibitor, combined with fulvestrant to overcome resistance to CDK4/6 inhibitors in advanced or metastatic HR+/HER2- breast cancer. First Author: Sandra Elaine Dunn, Phoenix Molecular Designs, Vancouver, BC, Canada

Background: Resistance to CDK4/6 inhibitors (CDK4/6i) is common for many patients with HR+/HER2- advanced or metastatic breast cancer, therefore new strategies are urgently needed to overcome this challenge. Ribosomal S6 kinases (RSK1-4) are implicated in breast cancer growth and resistance, and they are activated by the PI3K and MAPK pathways, which are linked to CDK4/6i resistance. As a convergence point of these pathways, RSK drives resistance by promoting the G2/M phase of the cell cycle and bypassing G1/S control. Inhibiting RSK with PMD-026, a first-in-class oral small molecule inhibitor, halts G2/M progression and blocks growth in CDK4/6i-resistant models, including those cross-resistant to abemaciclib and palbociclib. RSK also complexes with estrogen receptor alpha (ERα), enhancing transcription and tumor growth. PMD-026 disrupts this interaction, showing activity in both ESR1 wild-type and mutant HR+/HER2- models, making it a promising partner for endocrine therapies. It synergizes with fulvestrant and oral SERDs, achieving significant growth inhibition in preclinical models, including a 7000-fold improvement with fulvestrant in soft agar assays. Nuclear translocation of RSK is a key driver of breast cancer in mice and serves as a biomarker for RSK signalling activity. In the Phase 1/1b monotherapy study, PMD-026 was generally well-tolerated, and it reduced the risk of progression or death in patients by 93% in a subset of RSK2 high metastatic breast cancer patients. **Methods:** Dauntless-1 is a Phase 2a study for locally advanced or metastatic HR+/HER2- breast cancer patients previously treated with a CDK4/6i in combination with endocrine therapy (NCT04115306). It is designed to prospectively enroll RSK2+ ($\geq$50% nuclear staining with $\geq$2+ staining intensity) patients to evaluate PMD-026 in combination fulvestrant. Fulvestrant will be dosed per the package insert (500 mg IM, Day 1 and 15 of the first 28-day cycle, then Day 1 of every cycle thereafter) in combination with PMD-026 at the RP2D (200 mg, PO, Q12h), determined in the dose-finding portion of the study. The combination regimen will have a safety lead-in cohort of 6 patients. The SRC will review the safety data after the sixth patient has been treated for at least 28 days. If determined to be safe, up to 14 additional patients will receive the combination for a total of 20 patients. A Bayesian safety monitoring rule will be used to evaluate the rate of DLTs during expansion. Primary objectives will be safety, pharmacokinetics, and progression free survival. Secondary objectives include duration of response, overall response and overall survival. Exploratory objectives will evaluate PMD-026 in the context of mutations (ESR1, PIK3CA, AKT1, p53, KRAS) at baseline using ctDNA. Clinical trial information: NCT04115306. Research Sponsor: None.

TPS1131 **Poster Session**

OPERA-01: A randomized, open-label, phase 3 study of palazestrant (OP-1250) monotherapy vs standard-of-care for ER+, HER2- advanced or metastatic breast cancer patients after endocrine therapy and CDK4/6 inhibitors. First Author: Barbara Pistilli, Breast Cancer Unit, Gustave Roussy, Villejuif, France

Background: Endocrine therapy(ET) resistance is a major challenge in treating estrogen receptor-positive (ER+), human epidermal growth factor receptor 2-negative (HER2–) metastatic breast cancer (MBC); estrogen receptor (ESR1) mutations are an important mechanism of resistance. The standard of care (SOC) first-line treatment for ER+, HER2– MBC is ET plus a cyclin-dependent kinase 4/6 inhibitor (CDK4/6i). Despite the benefit of ET and CDK4/6i, disease progression and acquired resistance to the combination remain a challenge. Novel, more effective ETs that can overcome resistance are needed to improve outcomes and delay time to chemotherapy. Palazestrant (OP-1250) is a novel oral, complete estrogen receptor antagonist (CERAN) and selective ER degrader (SERD) that acts by blocking both transcriptional activation function domains, AF1 and AF2, regardless of ESR1 mutation status. As monotherapy, palazestrant showed a tolerable safety profile, favorable pharmacokinetics and encouraging antitumor efficacy in heavily-pretreated patients during phase 1/2 studies, regardless of *ESR1* mutation status (NCT04505826; Lin et al. ESMO 2023 MO382). **Methods:** OPERA-01 (NCT06016738) is a multicenter, randomized, open-label, phase 3 clinical trial comparing the efficacy and safety of palazestrant as a single agent to SOC ET (fulvestrant, anastrozole, letrozole, or exemestane) in patients with ER+, HER2– MBC that relapsed or progressed on 1-2 prior lines of ET, including a CDK4/6i. Adult patients are eligible with a diagnosis of evaluable ER+, HER2– inoperable locally advanced or MBC and an Eastern Cooperative Oncology Group performance status of 0 or 1. Prior treatments must include 1 or 2 prior lines of ET with the last ET duration of $\geq$6 months; must have received and have disease progression on CDK4/6i with ET for MBC. Prior chemotherapy for MBC is not allowed. The study included a dose selection phase, where participants were randomized to 90 mg qd or 120 mg qd palazestrant or SOC; enrollment in this phase is complete. After the dose selection of palazestrant, the study will continue with the selected dose compared to SOC ET at a 1:1 randomization. Overall, 510 patients will be randomized to palazestrant or SOC ET during the study. The primary endpoint of progression-free survival will be assessed by blinded independent central review in patients with and without *ESR1* mutations (dual primary endpoint). Secondary endpoints include overall survival, antitumor activity (objective response rate, clinical benefit rate, and duration of response), safety, exposure and patient-reported outcomes in patients with and without *ESR1* mutations. Study recruitment began in November 2023. Clinical trial information: NCT06016738. Research Sponsor: Olema Oncology.

TPS1132 **Poster Session**

Immunologic targeting of native and mutated ESR1 receptor for treatment of hormone receptor expressing metastatic breast cancer. First Author: Aixa Elena Soyano Muller, H. Lee Moffitt Cancer Center and Research Institute, Tampa, FL

Background: Hormone receptor positive (HR+) HER2 negative metastatic breast cancer (MBC) remains a difficult clinical problem. Endocrine therapies have remained the mainstay of therapy for decades and despite combination with targeted agents and development of novel targeted therapies, the 5-year survival rate of MBC remains low. Resistance to ET can occur due to the development of point mutations in the estrogen receptor alpha type I (ESR1), which constitutively activates the receptor, making it resistant to anti-estrogen. We produced a peptide library of the entire wild type (WT) ESR1 and identified four promiscuous peptide epitopes that routinely drive a CD4 Th1 response in healthy donors and breast cancer patients. Additionally, we created overlapping peptides around each known ESR1 mutation site and pulsed them on type I polarized dendritic cells (DC1) also resulting in an increased CD4 Th1 response. We hypothesize that ER alpha receptor can serve as a target for the immune response and ESR1 mutations that develop in HR+ breast cancer patients can be utilized as a neoantigen that will drive CD4 Th1 responses and antibodies that can be developed as an immune based therapy for patients with HR+ MBC. Combining DC1 vaccination with novel endocrine therapies such as Elacestrant, we expect an increase in ESR1 degradation and enhanced antigen presentation leading to an expanded immune and clinical response. **Methods:** In this open pilot study, up to 18 patients with HR+ HER2 negative, ESR1 mutated MBC with measurable or evaluable disease will be enrolled to determine the feasibility and safety of the combination of DC1 vaccines and Elacestrant. Prior use of elacestrant is exclusionary. Eligible patients will undergo apheresis of peripheral blood to collect and create DC1 vaccines. DC1 will be pulsed with ESR1 WT and mutated peptides. Patients will be injected in their groin nodes (or accessible tumor if available) weekly with these pulsed DC1 (20-50 million) for eight consecutive weeks. They will alternate between WT ESR1 DC1s and mutated ESR1 DC1s. Patients will receive combination of DC1 vaccinations and Elacestrant at 345 mg orally daily concurrently during vaccination and continued after. After the initial vaccination series, patients will undergo radiological assessment of their disease, and if no evidence of progression they will receive booster DC1s every four weeks x 3 doses. The primary objective of this pilot study is safety and feasibility. Secondary objectives include preliminary efficacy, biomarkers assessment, safety and patient reported outcomes. Tumor tissue and blood samples will be collected for correlative analyses including ctDNA and changes in variant allele frequency of ESR1 during treatment. The study is open at H. Lee Moffitt Cancer Center. Clinical trial information: NCT06691035. Research Sponsor: V Foundation.

TPS1133 **Poster Session**

Adaptive designed eniluracil + capecitabine phase 2 trial in advanced or metastatic breast cancer patients. First Author: David Young, Processa Pharmaceuticals, Inc., Hanover, MD

Background: Ethynyl-uracil (eniluracil or 6422), an irreversible inhibitor of the dihydropyrimidine dehydrogenase enzyme that metabolizes 5-FU to catabolites, eliminates the formation of 5-FU catabolites and catabolite side effects while exposing cancer cells to more 5-FU and more cancer killing 5-FU anabolites. The combination of a single 40 mg day 1 dose of 6422 followed by Day 2 Capecitabine (6422+Cap) on a 7 day on + 7 day off schedule (7+7) of Capecitabine (Cap) is being evaluated. The dose of Cap used in 6422+Cap will be approximately 15% of the therapeutic dose of Cap used in clinical practice for breast cancer. A Phase 1B study in patients with refractory gastrointestinal (GI) cancer has been completed. The Maximum Tolerated Dose of Cap in 6422+Cap was determined to be 225 mg BID. The Recommended Phase 2 Dose Range of Cap in 6422+Cap was determined to be from 75 mg BID to 225 mg BID. based on the FDA's Optimal Design Guidance and Project Optimus initiative to define the dose-response relationship for both safety and efficacy. Since FDA believed that determining the optimal dosage regimen following the Principles of Project Optimus would be extremely difficult for 6422+Cap in GI cancer given the standard combination chemotherapeutic treatments, the target population was changed to breast cancer patients. FDA also determined that a Phase 1B study in breast cancer would not be required given the GI cancer Phase 1B data. **Methods:** Several Project Optimus focused Phase 2 designs were evaluated. Based on guidance from the FDA, an adaptive, 3 arm, 30 patients/arm, phase 2, open-labelled, randomized trial was selected which would compare 2 regimens of 6422+Cap vs. standard dose of Cap alone. The study would initially enroll patients into 2 treatment arms. The 2 arms are: a 1000 mg/m2 BID monotherapy Cap control group and a 6422+Cap regimen of 40 mg on day 1 followed by day 2 Cap dose of 150 mg BID on 7+7 schedule. Upon completing the enrollment and evaluation of 9-10 patients in each of the first 2 arms, an interim analysis will be conducted to determine the Cap dose to be used in the 6422+Cap 3rd arm. Depending on the interim results, Cap dose in the 3rd arm will either be increased to 225 mg BID or decreased to 75 mg BID. Patients with triple-negative or HR positive/HER2 negative, advanced or metastatic breast cancer are eligible for the study. Patients should have measurable disease in accordance with RECIST 1.1. Patients with stable brain metastases are eligible. The primary endpoint of the study is Objective Response Rate. This will be assessed based on the null hypothesis that the endpoint in each 6422+Cap arm is less than or equal to the monotherapy arm. Additionally, safety will be assessed by the incidence and severity of adverse events across treatment groups. The pharmacokinetics of Cap, 5-FU, and the FBAL catabolite will be evaluated using population PK analysis. Currently 3 patients have been enrolled in the study. Clinical trial information: NCT06568692. Research Sponsor: Processa Pharmaceuticals Inc.

TPS1134 **Poster Session**

DATO-Base: A phase II study of DATOpotamab deruxtecan for patients with breast cancer brain metastases or leptomeningeal disease. First Author: Paolo Tarantino, Dana-Farber Cancer Institute, Boston, MA

Background: Approximately half of patients with metastatic TNBC and one fifth of those with estrogen receptor (ER)+/HER2-negative metastatic breast cancer (MBC) eventually develop breast cancer brain metastases (BCBM), with an adverse prognostic effect. Intracranially penetrant systemic therapies in HER2-negative MBC are very limited. In this setting, antibody-drug conjugates (ADCs) have shown promise, with impressive intracranial activity observed with trastuzumab deruxtecan. Datopotamab deruxtecan (Dato-DXd) is a novel anti-Trop2 ADC with robust antitumor activity in HER2-negative MBC. In the TROPION-Breast01 phase 3 trial, Dato-DXd outperformed chemotherapy for ER+/HER2-negative MBC, and promising early-phase data was also reported in triple-negative MBC. Preclinical data in tumor models found favorable intracranial penetration for Dato-DXd, and encouraging clinical data were reported in patients with lung cancer brain metastases. Based on the relevant unmet need and the promising preclinical and clinical data seen with Dato-DXd, there is a strong rationale in testing Dato-DXd for patients with HER2-negative MBC and BCBM or leptomeningeal disease (LMD). **Methods:** DATO-Base is an ongoing, open label, multicenter, investigator-initiated phase II trial for patients with HER2-negative MBC with active BCBM and/or LMD. Eligible participants are women and men with HER2-negative active (newly diagnosed/untreated or treated/progressive) brain metastases or LMD. Patients are enrolled in one of three cohorts: Cohort A (n = 24) for HR+/HER2-negative BCBM; Cohort B (n = 24) for triple-negative BCBM; Cohort C (n = 10) for HER2-negative LMD (any ER status). Patients in Cohort A require prior treatment with at least one line of endocrine treatment in the metastatic setting; no prior treatment is required for Cohorts B and C. Prior treatment with approved or investigational ADCs is allowed. Participants receive Dato-DXd 6 mg/kg IV on day 1 of each 21-day cycle until progression, unacceptable toxicity, withdrawn consent, noncompliance, or death. The primary endpoint for Cohorts A and B is intracranial objective response rate per RANO-BM criteria. Patients in each cohort will be enrolled based upon Simon two-stage designs: if $\geq$1/9 patients respond, a total of 24 patients will be enrolled. Cohort C is exploratory, with description of overall survival and exploratory endpoints. Blood and cerebrospinal fluid is being collected at baseline, C2D2, and at progression for translational studies. The trial was activated in December 2023, with enrollment ongoing. Clinical trial information: NCT06176261. Research Sponsor: None.

TPS1135 **Poster Session**

The efficacy and safety of eutideron, etoposide, and bevacizumab in patients with brain metastases from breast cancer. First Author: Bishal Tiwari, Nassau University Medical Center, East Meadow, NY

Background: Brain metastases (BM) from breast cancer (BC) are a significant therapeutic challenge, with limited systemic treatment options capable of crossing the blood-brain barrier (BBB). Median overall survival (OS) ranges from 4 to 16 months, influenced by molecular subtype and treatment modality. Triple-negative and HER2-positive subtypes are associated with higher BM incidence. There is a crucial need to explore systemic therapies that address both intracranial and extracranial disease. Eutideron, a novel small-molecule inhibitor with robust CNS penetration, has demonstrated activity against metastatic BC models involving the brain. Early clinical studies suggest its efficacy in advanced BC, with intracranial activity and manageable toxicity. Combining eutideron with etoposide, a cytotoxic agent, and bevacizumab, an anti-VEGF monoclonal antibody, may enhance therapeutic outcomes. Bevacizumab, known for reducing BM-associated edema and improving quality of life, has shown promise in combination regimens but has not been evaluated alongside eutideron and etoposide. This Phase II trial investigates this novel three-drug regimen in patients with recurrent BC and measurable BM. **Methods:** This open-label, single-arm Phase II trial evaluates the efficacy and safety of eutideron, etoposide, and bevacizumab in female patients aged $\geq$18 years with recurrent metastatic BC and measurable BM. Eligible patients had an ECOG performance status of 0–2, life expectancy $\geq$12 weeks, and progressed untreated or previously treated BM not requiring immediate local treatment. Baseline brain MRIs confirmed at least one measurable CNS lesion per RANO-BM criteria. The treatment regimen includes eutideron (30 mg/m²/day, IV, Days 1–5 of a 21-day cycle), etoposide (30 mg/m²/day, IV, Days 1–3 of a 21-day cycle), and bevacizumab (10 mg/kg, IV, Days 1 and 21 of each cycle). After 4–6 cycles, responders continued bevacizumab maintenance until progression or intolerable toxicity.Primary endpoint: CNS Objective Response Rate (CNS-ORR) per RANO-BM. Secondary endpoints: CNS Clinical Benefit Rate, CNS Progression-Free Survival, Overall Survival, and systemic ORR by RECIST 1.1. Safety was monitored using CTCAE v5.0. The trial, targeting 43 patients across Chinese centers, aims to inform future strategies for BC patients with BM. Clinical trial information: NCT05781633. Research Sponsor: None.

TPS1136 **Poster Session**

Trial in progress: A study of Bria-OTS cellular immunotherapy in metastatic recurrent breast cancer. First Author: Neal Shiv Chawla, Sarcoma Oncology Center, Santa Monica, CA

Background: Metastatic breast cancer is almost always fatal. Objectives: Primary: To evaluate the safety of BC1 cell line immunotherapy in patients with advanced late-stage metastatic breast cancer; Secondary: To evaluate the tumor response to BC1 cellular immunotherapy; Exploratory: To evaluate progression-free (PFS) and overall survival (OS); To evaluate the immune responses elicited by BC1 cellular immunotherapy; To evaluate patient and tumor characteristics that may be predictive of responses to HLA-matched cellular immunotherapy; To evaluate time to subsequent therapy; and To evaluate PFS 2 on subsequent therapy. **Methods:** Study Population: Patients with metastatic recurrent breast cancer after progression on prior therapies. Key Inclusion Criteria: Histologically-confirmed metastatic breast cancer after failure of standard therapies; $\geq$18 years old; Expected survival of $>$4 months; Adequate performance status (ECOG $\leq$2); Adequate hematologic and organ function; Clinically stable with resolution of toxicities from previous treatment to baseline with the exception of alopecia. Key Exclusion Criteria: Concurrent anti-cancer treatment or concurrent cancer; Anti-cancer treatment within 3 weeks of first treatment; History of hypersensitivity to study therapies; New York Heart Association stage 3-4 cardiac disease; Moderate-severe pleural or pericardial effusion; Pregnant or nursing; HIV+; Known immunodeficiency or ongoing treatment with immunosuppressive therapy $>$10 mg/day prednisone equivalent; Severe psychiatric or other clinically progressive major medical problems. Study Design: This is an open-label study. Phase 1: BC1 cell line alone; Phase 2, Bria-OTS regimen with check point inhibitor (CPI). Phase 1: Patient 1: 20 million cells BC1 intradermally q2 wks x 8 wks (4 doses); Patient 2: 40 million cells of BC1; Patient 3: 60 million cells BC1. If no DLT with BC1 monotherapy, the combinational phase of the study will begin with BC1 and the Bria-OTS regimen q3 wks + CPI. During the Phase 1 combination and Phase 2 expansion phases, all patients will be treated with BC1 cells as part of the Bria-OTS regimen, which includes cyclophosphamide 300 mg/m^2 2-3 days prior to BC1 cell inoculation, and concurrent peg-interferon 0.6 mcg s.c. on the day of BC1 cell inoculation. Imaging studies: At screening, after monotherapy phase, before combination phase, and q9 weeks thereafter for 6 months, then q12 weeks. Patients who had PD but with clinical benefit may continue treatment. Subjects will continue to be followed for time on subsequent therapy (PFS2) and survival q3 mos. for 2 years. The phase 1 monotherapy part of the study has enrolled and treated 3 patients. Clinical trial information: NCT06471673. Research Sponsor: BriaCell Therapeutics Corp.

TPS1137 **Poster Session**

Trial in progress: ENCORE—Multicenter prospective registry of sequential antibody drug conjugates (ADCs) in HER2 negative metastatic breast cancer (MBC) (TBCRC-067). First Author: Laura Ann Huppert, University of California San Francisco, San Francisco, CA

Background: Antibody-drug conjugates (ADCs) have demonstrated substantial improvement in progression free survival (PFS) and overall survival (OS) in phase III clinical trials in patients with metastatic triple negative breast cancer (mTNBC) and hormone receptor positive/HER2-negative (HR+/HER2-) metastatic breast cancer (MBC), offering an effective new treatment strategy. Several outstanding questions impact the use of these drugs clinically, and prospective real-world data is needed. First, it is important to understand the safety and efficacy of these agents in a real-world population with diverse patient characteristics. Second, it is critical to understand the safety and efficacy of these ADCs in sequence. Third, it is essential to identify biomarkers that can help clarify mechanisms of response and resistance to ADCs, which may inform future sequencing and treatment strategies. **Methods:** This is a multicenter prospective registry study of patients with HER2-negative MBC who are treated with sequential ADCs per standard of care (SOC) with the goal to understand the safety and efficacy of sequential ADCs in a real-world setting (NCT06774027). A total of 100 participants with HER2-negative MBC will be enrolled in this study, either prior to starting their first ADC per SOC (cohort 1 = HR+/HER2-; cohort 2 = mTNBC) or prior to starting their second ADC per SOC (cohort 3 = HR+/HER2-; cohort 4 = mTNBC). The dual primary endpoints are real-world progression free survival (rwPFS) of ADC1 and rwPFS of ADC2. Secondary endpoints include overall response rate (ORR), duration of response (DOR), best overall response (BOR), disease control rate (DCR), and real-world overall survival (rwOS), and safety for each ADC. Exploratory endpoints include translational correlates of response/resistance to ADCs (e.g., circulating tumor DNA, circulating tumor cells, and tissue spatial correlates) and patient-reported outcomes (PROs). rwPFS and rwOS will be estimated by the Kaplan-Meier method. Statistics will be descriptive. Enrollment to start in the first quarter of 2025. Clinical trial information: NCT06774027. Research Sponsor: Gilead.

TPS1138 **Poster Session**

Update on phase III pivotal trial of Bria-IMT + CPI vs physician's choice in advanced metastatic breast cancer (BRIA-ABC). First Author: Saranya Chumsri, Mayo Clinic Florida, Jacksonville, FL

Background: The SV-BR-1-GM breast cancer cell line activates anti-tumor immunity by expressing tumor associated antigens and secreting GM-CSF which enhances dendritic cell activation and promotes adaptive (T-cell mediated) and innate (dendritic and NK cell) immune responses. The cells are also engineered to optimize immune recognition through pt specific HLA antigen matching. SV-BR-1-GM acts through direct antigen presentation and CD4+ T-cell activation and, when combined w/ checkpoint inhibitors (CPIs), has demonstrated clinical benefit in 54 heavily pretreated metastatic breast cancer (MBC) pts. In pts w/ disease progression following CPI therapy, similar or improved progression free survival (PFS) compared to their prior treatment regimen. Disease control following antibody drug conjugates was observed in 40%of pts. Clinical benefit was seen in 5 out of 8 pts w/ untreated intracranial metastases. CD8+ Immuno-PET imaging suggests systemic activation, w/ increased CD8+ tumor infiltrating lymphocytes at both primary and metastatic tumor sites, as well as lymphoid organs. Optimized sequencing of CPI w/ SV-BR-1-GM and its latest phase 3 formulation have shown enhanced clinical outcomes, including improved overall survival (OS) (median 13.4 mos), PFS (3.6 mos), and clinical benefit rate (CBR; 61%).These findings have informed refinements to the ongoing pivotal, registration enabling Phase 3 trial, designed to optimize pt selection and treatment sequencing strategies. **Methods:** This ongoing multicenter, randomized, open label Phase 3 trial evaluates Bria-IMT + CPI vs. Treatment of Physician's Choice (TPC) in MBC pts lacking approved curative therapies. Pts are randomized 1:1:1 to Bria-IMT + CPI, TPC, or Bria-IMT monotherapy (discontinued after 150 enrollments to prioritize combination arms). The Bria-IMT regimen consists of: Day -2: Cyclophosphamide 300 mg/m², Day 0: 20M irradiated SV-BR-1-GM cells, Day 2/3: 0.1 mcg pegylated α interferon at each inoculation site. CPI infusion is administered Day -3 to 3. Cycles q3w. TPC regimens follow site specific SOC. Imaging q6w (first 2 cycles), then q8w. Eligibility includes all MBC subtypes, including CNS mets, and permits prior CPI therapy ($>$21 days pre-treatment). There will be 100 sites across the U.S., Canada, and ex-North America w/ an enrollment target of 404. The trial is currently active at 59 sites with 217 sub investigators. To date, 67 pts screened: 46 randomized (median age 56 yrs [34–83], median 6 [2–13] prior lines of therapy. The primary endpoint is OS, with an interim analysis at 144 events targeting a hazard ratio of 0.6. Secondary endpoints: PFS, overall response rate, CBR, CNS event free survival, and TWiST. Safety analyses ongoing; pt reported outcomes assess subjective treatment impact. Clinical trial information: NCT03328026. Research Sponsor: BriaCell Therapeutics Corp.

TPS1139 **Poster Session**

Efficacy and safety of disitamab vedotin in combination with RC148 versus albumin-bound paclitaxel ± toripalimab for patients with HR-negative HER2-low-expressing unresectable locally advanced or metastatic breast cancer: An open-label, randomized, controlled phase II study. First Author: Jiayu Wang, Cancer Hospital, Chinese Academy of Medical Sciences, Beijing, China

Background: Patients (pts) with hormone receptor (HR)-negative and HER2-low-expressing (defined as IHC 1+, or IHC 2+/ISH-) advanced breast cancer have poor prognosis and more effective treatment options are needed. Disitamab vedotin (DV) is a novel humanized anti-HER2 antibody conjugated with monomethyl auristatin E (MMAE) via a cleavable linker. DV alone or in combination with a PD-1 inhibitor showed encouraging antitumor activities with manageable safety in pts with HER2-low-expressing (IHC 1+, or IHC 2+/ISH-) advanced or metastatic breast cancer, gastric cancer and other solid tumors (Wang J., et al., *Cancer Commun*, 2024; Wang Y., et al., *eClinicalMedicine*, 2024). RC148 is a bispecific monoclonal antibody directed against programmed death receptor-1 and vascular endothelial growth factor receptor. DV+RC148 combination is expected to exert a synergistic antitumor effect by improving the tumor immune microenvironment. We aim to evaluate the efficacy and safety of DV plus RC148 versus albumin-bound paclitaxel $\pm$ toripalimab in pts with HR-negative HER2-low-expressing advanced breast cancer in this randomized phase II trial (NCT06642545). **Methods:** The key eligibility criteria are pts aged 18 years or older with unresectable stage III or stage IV breast cancer, negative HR status, low HER2 expression (defined as IHC1+, or IHC2+/ISH-), no previous chemotherapy for locally recurrent or metastatic disease, and no disease recurrence within 6 months after treatment completion (within 12 months if using taxanes) if with radical treatment. Pts who previously received anti-HER2 therapy or immunotherapy are excluded (except pts receiving neoadjuvant/adjuvant PD-[L]1 inhibitors 12 months prior to recurrence or progression). Pts will be randomized (stratified by PD-L1 expression status: positive or negative) in a ratio of 1:1 to receive DV (2.0 mg/kg) plus RC148 (20 mg/kg) intravenously once every two weeks or to receive albumin-bound paclitaxel (125 mg/m^2 day 1 and day 8) $\pm$ toripalimab (240 mg day 1) intravenously every three weeks until occurrence of disease progression or intolerable toxicity. The primary endpoint is objective response rate (ORR) in all pts per investigator's assessment according to RECIST v1.1. The secondary endpoints are ORR in the PD-L1-positive pts; investigator-assessed progression-free survival, disease control rate, duration of response, and overall survival in all pts and the PD-L1-positive pts. This study was initiated in August 2024. Clinical trial information: NCT06642545. Research Sponsor: RemeGen Co., Ltd.

TPS1140 **Poster Session**

A phase II trial to assess the impact of β2 adrenergic receptor (β2-AR) blockade in metastatic triple negative breast cancer (mTNBC). First Author: Shipra Gandhi, Roswell Park Comprehensive Cancer Center, Buffalo, NY

Background: In PD-L1+ mTNBC patients (pts), the standard of care treatment is chemotherapy and pembrolizumab (P) in the first-line setting. Our group and others have demonstrated that chronic β2-AR signaling suppresses $CD8^+$ cytotoxic T lymphocytes (CTL) function, drives their exhaustion, and increases the number of immunosuppressive myeloid-derived suppressor cells (MDSCs) and regulatory T cells (Tregs) in the tumor microenvironment (TME), thus supporting tumor proliferation. Consequently, abrogation of β-AR signaling using the pan β-blocker propranolol or $\beta\text{-AR}^{-/-}$ knockout mice increased the intratumoral frequency of CTLs and elevated the CTL:Treg ratio (Bucsek et al. Cancer Res. 2017; PMID: 28819022). Similarly, mouse tumor models also demonstrated decreased exhaustion markers (PD1, TIM3, LAG3) on CTLs when β-AR was blocked, via propranolol (Qiao G et al. Cancer Immunol Res. 2021, PMID: 33762351). Confirming this phenomenon, we have shown, in a prospective clinical trial in metastatic melanoma, that β-AR blockade with propranolol significantly increased response to P with an objective response rate (ORR) of 78%, as opposed to 30-40% with P alone (Gandhi et al. Clin Cancer Res 2021, PMID: 33127652). Moreover, clinical β-AR blockade was associated with higher immune infiltration in the TME (Hiller JG, Clin Cancer Res 2020, PMID: 31754048). Therefore, we hypothesize that using propranolol with chemotherapy and P should improve response for pts with newly metastatic PD-L1+ TNBC. **Methods:** This is a phase II single-arm, non-randomized multi-center study. Pts are women ≥18 yrs with PD-L1+ mTNBC, who will receive propranolol, chemotherapy (paclitaxel, nab-paclitaxel, gemcitabine-carboplatin) and P in the upfront setting: chemotherapy on days 1, 8 and P on day 1 every 3 weeks in addition to propranolol 30 mg BID, with intra-pt propranolol dose-escalation by 10 mg BID weekly to a total of 80 mg BID as tolerated by blood pressure and heart rate as natural biomarkers for dose. Treatment will continue until disease progression per RECIST. The primary endpoint is ORR, defined as complete or partial response. The secondary endpoint is safety, 6-month progression-free and overall survival. As an exploratory endpoint, changes in TME and blood immune markers will be assessed. In stage 1, n1=23 evaluable pts will be enrolled. If ≥ 13/23 responses are observed, then the study will continue to enroll another n2=14 pts for a total of n=37, otherwise will be suspended for futility. If ≥ 24/37 responses are observed, then the proposed therapy will be considered promising. Pre- and 6-week post-treatment tumor biopsies and blood samples will be analyzed for changes in stress-induced biomarkers (epinephrine, norepinephrine, and frequency of CTL, MDSC, Treg) and exhaustion markers (PD1, TIM3, LAG3). The study is currently open and has accrued one patient. Clinical trial information: NCT05741164. Research Sponsor: NIH (NCI).

TPS1141 **Poster Session**

Emiltatug ledadotin (Emi-Le): A B7-H4-directed dolasynthen antibody-drug conjugate (ADC) being investigated in phase 1 dose expansion in patients with triple negative breast cancer who received at least one prior topoisomarase-1 inhibitor ADC. First Author: Hyo S. Han, H. Lee Moffitt Cancer Center and Research Institute, Tampa, FL

Background: Breast cancer is the leading cause of cancer death for women worldwide, with triple-negative breast cancer (TNBC) considered one of the more aggressive breast cancers, accounting for ~15% of all cases. Unfortunately, there remains an unmet medical need for effective and well-tolerated treatments for advanced/metastatic TNBC; in heavily pretreated patients, standard-of-care single-agent chemotherapy has limited efficacy, with response rates of ~5%, PFS ~7 weeks. Emiltatug ledadotin (Emi-Le; XMT-1660) is a B7-H4-directed Dolasynthen ADC designed with a precise, target-optimized drug-to-antibody ratio (DAR 6) and a proprietary auristatin F-HPA microtubule inhibitor payload with controlled bystander effect. The FDA has granted Emi-Le two Fast Track designations for the treatment of adult patients with breast cancer, including patients with TNBC who have previously been treated with topoisomerase-1 inhibitor (topo-1) ADCs. Initial dose escalation clinical data from the ongoing Phase 1 trial at doses ranging from 38.1-67.4 mg/m2 per cycle demonstrated a 23% confirmed response rate in patients with B7-H4 high TNBC who were heavily pretreated all of whom received at least one prior topo-1 ADC. **Methods:** Based on encouraging clinical activity and tolerability data in the initial dose escalation data, the expansion portion (EXP) of the Phase 1 trial has been initiated and is actively enrolling patients. EXP has a Simon 2-stage design and will evaluate two doses in patients with advanced/metastatic TNBC who have received 1-4 prior lines of systemic therapy, including at least one topo-1 ADC. Patients will be evaluated for B7-H4 expression prospectively by IHC and will be stratified into B7-H4 TPS “high” and B7-H4 TPS “low” cohorts. The first EXP dose is 67.4 mg/m2 Q4W. Dose exploration is ongoing to identify a potential second higher EXP dose. The protocol includes the option for multiple additional indications, including HR+/HER2- breast cancer, endometrial cancer, ovarian cancer, and ACC-1. Clinical trial information: NCT05377996. Research Sponsor: Mersana Therapeutics.

TPS1142 **Poster Session**

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

Background: Triple-negative breast cancer (TNBC) refers to a heterogenous group of breast cancers (BC) that lack expression of ER, PR, and HER2. Despite recent advances with immunotherapy (IO) and antibody-drug conjugates (ADCs), TNBC remains the most aggressive subtype, characterized by a high risk of recurrence and a short overall survival in the metastatic setting. BCs with low levels of ER and PR expression (1-10%) clinically behave like TNBC, and clinical management follows the TNBC treatment (tx) paradigm. We and others have identified a subset of ER/PR/HER2 negative breast cancers (BC) that express the androgen receptor (AR). Enzalutamide (enza), an AR-antagonist, has demonstrated activity in AR+ metastatic TNBC (Traina et al, JCO 2018). Activation of the glucocorticoid receptor (GR) has been implicated as a mechanism of resistance to AR inhibition in prostate and BC (Kach et al, Sci Transl Med 2015). Advanced TNBC remains an area of unmet need, particularly in patients who are ineligible for or progress following a checkpoint inhibitor. This randomized study will evaluate the efficacy of enza or enza plus the GR antagonist mifepristone (mif) as compared to physician’s choice chemotherapy (TPC). **Methods:** This is a randomized phase II trial; 201 patients (pts) will be randomized 1:1:1 to enza, enza with mif, or TPC (carboplatin, paclitaxel, eribulin, or capecitabine). The primary endpoint (endpt) is progression free survival (PFS), and the trial is designed to test the hypothesis that PFS in the pooled enzalutamide arms is superior to TPC; there is 80% power to detect a hazard ratio (HR) of 0.70, corresponding to increase in PFS from 3.5 months (mos) with TPC to 5.0 mos with enza-based tx. Secondary endpts include pairwise comparisons of PFS among the 3 arms and evaluation of response rate, clinical benefit rate, duration of response, overall survival, safety/toxicity, and patient-reported outcomes by arm. Exploratory endpts include correlation of tumor and circulating markers (constitutively active AR variants in circulating tumor cells and circulating tumor cell DNA) with tx response. Eligible pts must have: ECOG 0-2, metastatic ER/PR low or negative, HER2 0-2+ (FISH not amplified) (BC), measurable or evaluable disease (dz) per RECIST v1.1, < 3 prior lines of chemotx, any # prior endocrine txs, no prior anti-AR tx or CYP17 inhibition, no prior mif. Pts with PD-L1+ BC must have received prior IO if not contraindicated. Tumors must have AR >10%, normal organ function, no history of brain mets. As of 1/23/25, 11 of 201 pts have begun protocol-specified tx. Clinical trial information: NCT06099769. Research Sponsor: Breast Cancer Research Foundation; TBCRC; Astellas; Corcept; The TaTa Sisterhood Foundation; Pfizer.

TPS1143 **Poster Session**

AXALAP: Phase Ib study of axatilimab in combination with olaparib in *BRCA1/2* and *PALB2*-associated metastatic HER2-negative breast cancer (BC). First Author: Filipa Lynce, Dana-Farber Cancer Institute, Boston, MA

Background: Poly(ADP-ribose) polymerase (PARP) inhibitors (PARPi) have revolutionized the treatment of patients (pts) with germline *BRCA1/2* (gBRCA)-associated HER2-negative BC. However, resistance eventually occurs in almost all pts. Tumor-associated macrophages (TAMs), a key component of the BC tumor microenvironment, are highly immunosuppressive and associated with poor clinical outcomes. In preclinical immunocompetent models of BRCA-associated BC, PARP inhibition induces suppressive CSF-1R+ TAMs, contributing to resistance, so that combining anti-CSF-1R therapy with PARPi significantly enhances progression free survival (PFS) compared to PARPi monotherapy (190d vs 92d). Axatilimab (SNDX-6352; Ab969.g2), a humanized IgG4 monoclonal antibody targeting CSF-1R, reduces TAMs, potentially slowing tumor growth and enhancing anti-tumor immunity. In the Phase I SNDX-6352-0502 study for advanced solid tumors, axatilimab showed tolerability at the highest dose (6 mg/kg), with biomarker modulation observed at doses as low as 1 mg/kg. Axatilimab is FDA-approved for chronic graft-versus-host disease (cGVHD). **Methods:** AXALAP (NCT06488378) is a non-randomized open-label, proof-of-concept phase 1 study designed to evaluate axatilimab 1mg/kg or 3mg/kg every 2 weeks in combination with olaparib 300 mg twice daily in pts with somatic or germline *BRCA1/2*- and *PALB2*-associated HER2-negative metastatic BC. Patients must be PARPi naïve, or have not progressed on prior PARPi, and have received up to 2 prior lines of chemotherapy for metastatic disease. Pts will receive a two-week lead-in of olaparib monotherapy, followed by combined olaparib and axatilimab. Pts will undergo mandatory tumor biopsies pre-treatment, after the 2-week olaparib lead-in, and after 2 cycles of olaparib/axatilimab, with an optional biopsy at time-of-progression. Primary objectives are to establish the maximum tolerated dose (MTD) and recommended phase 2 dose and to assess the safety and tolerability of axatilimab and olaparib. Secondary objectives include assessment of changes in CSF-1R+ CD163+ macrophage levels after olaparib monotherapy and after 2 cycles of combination treatment at the MTD; to determine the objective response rate and the median PFS of the combination per RECIST 1.1 criteria. The MTD will be determined by Bayesian Optimal Interval (BOIN) design. Pts will be treated in cohorts of 3 with a maximum of 10 at each dose. If the MTD is identified as 3mg/kg, we will complete enrollment of 10 pts at 1 mg/kg to assess biological effectiveness and clinical efficacy of the lower dose. We expect to treat up to 20 pts, who will receive study treatment until development of unacceptable toxicity or disease progression. Enrollment began on 5/2024 at Dana-Farber Cancer Institute and the trial will also open at Beth Israel Deaconess Medical Center and Mayo Clinic-Rochester. Clinical trial information: NCT03604692. Research Sponsor: Incyte; U.S. National Institutes of Health; U.S. National Institutes of Health.

1500 Oral Abstract Session

Pharmacist-led medication reconciliation televisit (MRT) for phase 1 oncology clinical trials: A telemedicine model. First Author: Sarah O'Neill, Massachusetts General Hospital Cancer Center, Boston, MA

Background: Accurate medication reconciliation is critical in oncology trials to mitigate drug-drug interactions (DDIs), address eligibility and enhance patient safety. Cancer patients often experience polypharmacy (≥5 medications), increasing the risk of additive toxicities when investigational agents are introduced. Medication lists in Electronic Medical Records (EMRs) are often incomplete or outdated, complicating eligibility evaluations. To streamline screening for Phase 1 trials, a pharmacist-led medication reconciliation televisit (MRT) model was implemented to improve baseline medication list accuracy and reduce in-clinic time. **Methods:** From December 2022 to January 2025, one MRT was scheduled for each patient screening for Phase 1 trials (≥18 years, English-speaking or with interpreter support), after trial consent but before registration. Pharmacists reviewed EMRs and dispense histories, then conducted structured phone interviews with patients to review prescription (RX), over-the-counter (OTC), herbal and cannabis product usage, including name, strength, dose, frequency, start dates, indications and ingredients. Inactive medications were discontinued, allergies were updated, patient concerns and medication details were documented in the EMR. **Results:** A total of 525 MRTs across 82 trials had a median turnaround time of 2 days. Patients (median age 61 years) reported a median of 12 medications (range 2–41) and a median total time spent of 45 minutes (range 5–330) including documentation. 4.8% of patients required interpreter support. Primary cancer types (12 total) included gastrointestinal (32%), breast (20%) and head and neck (11%). Table 1 summarizes MRTs April 2024 and later which captured additional data: 64% required an EMR-prompted outside source reconciliation, 32% modified allergies, a median of 3 medications were added (range 0–37), 2 were changed (range 0-13), 3 were discontinued (range 0-18) and the median call time was 18 minutes. **Conclusions:** Pharmacist-led MRTs provided substantial value for investigators and research nurses, enabling them to focus on patient care. Flexible scheduling of remote MRTs supported presence of caregivers and medications, reducing list omissions and hospital chair time for patients. Sponsors and study teams gained more accurate baseline records, lowering the risk of unknown prohibited medications. This scalable telemedicine model offers potential for broader use in oncology trials, improving efficiency and patient safety. Research Sponsor: None.

MRT identification of previously undocumented medications with DDI potential (n=235).

> 1 medication on EMR categorized as:	Before MRT n (%)	After MRT n (%)	Absolute Change	% Increase
RX	208 (98%)	232 (99%)	+24	+12%
OTC Non-herbal	179 (84%)	224 (95%)	+45	+25%
OTC Herbal	26 (12%)	46 (20%)	+20	+77%
Antacid/H2 Blocker/PPI	81 (38%)	107 (46%)	+26	+32%
Cannabis	11 (5%)	66 (28%)	+55	+500%

1501 Oral Abstract Session

Remote clinical pharmacist impact on reducing total cost of care in Enhancing Oncology Model—enrolled oncology practices. First Author: Daniel Kendzierski, McKesson Specialty Health, The US Oncology Network, The Woodlands, TX

Background: The national cost of cancer care is estimated to exceed $245 billion by 2030, primarily due to the high cost of cancer drugs. The Enhancing Oncology Model (EOM) is a voluntary 6-month, 2-sided, risk-based payment model implemented by the Centers for Medicare and Medicaid Services (CMS) to improve cancer care while simultaneously reducing the total cost of care (TCOC). The US Oncology Network (The Network) comprises approximately 50% of all providers participating in EOM nationwide across twelve practice sites. In The Network, drug costs represented an average of 63% of a patient's TCOC. This study aims to demonstrate the impact of a pharmacist in reducing TCOC in the EOM model. **Methods:** Medication initiatives were clinically evaluated and adopted at an individual practice level and included: monoclonal antibody (moAB) dose rounding, pembrolizumab dose banding, biosimilar therapeutic interchange (TIC) to preferred products, use of a preferred PD-1 agent in metastatic NSCLC, decreased upfront usage of long-acting growth factor (GF) in metastatic cancer, and preferred use of zoledronic acid over alternatives. ClinReview pharmacists (CRP) remotely reviewed oncology treatment orders for cost-savings opportunities. CRPs updated eligible treatments per practice protocols or reviewed with the treating oncologist. Interventions were submitted by the CRP into a tracking system and marked as an EOM-related intervention. TCOC reduction was calculated using the difference between the CMS allowable for the original treatment ordered and the new order. **Results:** From July 1, 2023, to December 31, 2024, seven CRPs within five of The Network's EOM participating practices evaluated over 5,600 patients for medication initiatives. A total of 1,271 interventions were identified, with 1,180 accepted. The sum of TCOC reduction amounted to 8,982,235. Further breakdown of each initiative and average TCOC reduction per intervention are shown in Table 1. In addition to the six initiatives, the CRP contributed an additional 1,201,326 in medication savings associated with drug selection. **Conclusions:** CRP's medication initiatives within The Network's EOM participation reduced TCOC by nearly $9 million across five practices. Key initiatives such as pembrolizumab dose banding and preferred use of zoledronic acid were the largest contributors. These findings demonstrate the potential for pharmacist-driven interventions to lower costs and drive the success of value-based care models in oncology practices. Research Sponsor: None.

EOM Initiative	n (%)	TCOC Reduction, $	Average TCOC Reduction per intervention, $
moAB dose rounding	443 (35)	1,537,273	3,470
Pembrolizumab dose banding	106 (8)	1,962,105	18,510
TIC	356 (28)	1,510,945	4,244
Preferred PD-1 agent for NSCLC	26 (2)	153,117	5,889
Decrease GF use	37 (3)	109,822	2,968
Zoledronic acid use	181 (14)	2,157,895	11,992

1502 Oral Abstract Session

Video-based genetic counseling to reduce physician workload and enhance consulter understanding: A prospective randomized clinical trial. First Author: Georg Pfeiler, Department of Obstetrics and Gynecology and Center for Breast Health, Comprehensive Cancer Center, Medical University of Vienna and Austrian Breast and Colorectal Cancer Study Group, Vienna, Austria

Background: Genetic counseling is an essential part of germline genetic testing, which is reccomended for use of PARP inhibitors in breast cancer treatment. Despite its importance, only about 40-60% of breast cancer patients receive genetic counseling. A video tool has been developed to provide genetic counseling, aiming to reduce the physician's workload and improve the patient's understanding. **Methods:** Advice seekers at increased risk for hereditary breast and ovarian cancer as well as breast and ovarian cancer patients were included in the trial. They were randomly assigned 1:1 to either standard of care (physician only, PO) or video based followed by physician genetic counseling (VPO). A 15-minute video tool was created for VPO participants, who watched it on an iPad and answered 6 comprehension questions online. The physician then clarified any misunderstood topics. In both groups, counseling time was measured from conversation start to blood donation. Afterwards, participants completed a questionnaire with 9 comprehension questions (16 points total). Data analysis included Bernard's and Pearson's tests for categorical data, Kendall's test for correlations, and ordinal logistic regression for multivariable analysis. **Results:** A total of 110 participants with a median age of 47 years were randomized into two groups: PO counseling (55 participants, 50%) and VPO counseling (55 participants, 50%). Among them, 29% (32 participants) received therapeutic counseling for breast/ovarian cancer, while 71% (78 participants) received predictive counseling with no cancer diagnosis. Participant characteristics were well balanced between groups, with no significant differences in age, indication for counseling, sex (90% female), level of education, or German-speaking proficiency. Participants reported their sources of genetics knowledge as previous knowledge (30%) and physician counseling (70%) in the PO group, and as previous knowledge (20%), physician counseling (30%), and the video tool (45%) in the VPO group. The video significantly improved comprehension scores from 62.5% (10 points, PO group) to 81.3% (13 points,VPO group) ($p < 0.0001$). Additionally, the video tool significantly reduced the time physicians spent on counseling from 6.6 minutes to 2.4 minutes ($p < 0.0001$). According to the logistic regression model, both the level of education (estimate -1.34, $p = 0.002$) and German language comprehension level (estimate 1.62, $p = 0.001$) significantly influenced the genetic counseling comprehension score. **Conclusions:** In this prospective randomized trial, video genetic counseling improved comprehension and reduced physician counseling time. The genetic video tool, which can be translated into various languages, facilitates genetic counseling by decreasing the workload for physicians, which may increase the genetic counseling rate in the clinic. Research Sponsor: None.

1503 Oral Abstract Session

Electronic patient-reported outcome-based weight management versus usual care during induction chemotherapy followed by concurrent chemoradiotherapy in nasopharyngeal carcinoma: A phase II randomized controlled trial. First Author: Qiu-Yan Chen, Department of Nasopharyngeal Carcinoma, Sun Yat-Sen University Cancer Centre, Guangzhou, China

Background: Nearly almost patients with nasopharyngeal carcinoma (NPC) experience weight loss (WL) and malnutrition during treatment. However, effective patients' weight management remains a challenge, as no standardized approach currently exists. This study aimed to evaluate the feasibility and efficacy of an electronic patient-reported outcome (ePRO) based weight management in mitigating WL and malnutrition in patients with locally advanced NPC (LA-NPC) receiving induction chemotherapy (IC) followed by concurrent chemoradiotherapy (CCRT). **Methods:** In this phase II randomized controlled trial, eligible patients aged 18 to 70 years with stage III-IVa (AJCC ^{8}th) NPC were randomly assigned in a 1:1 ratio to either ePRO-based weight management (ePRO group) or usual care (UC group). Body weight, NRS2002, PG-SGA, EORTC QLQ-C30 and hematological indicators were collected at six timepoints during treatment. Patients in ePRO group used the ePRO weight management system (ePRO-WMS). When predefined e-alert were triggered (e.g., WL $>$ 5%), the MDT promptly communicated and responded with patients. Patients in UC group did not use the ePRO-WMS and had no e-alerts. The primary outcome was the proportion of patients experiencing WL $>$ 10% at one month after completing CCRT (Post-1m). The secondary outcomes included WL $>$ 10% and WL $>$ 20% at the end of CCRT (W7-CCRT), as well as comparisons of NRS2002, PG-SGA, EORTC QLQ-C30, and hematological indicators. WL was compared using the χ^2 test, while other secondary outcomes were analyzed with linear mixed-effects models (ClinicalTrials.gov, NCT05834712). **Results:** From May 2022 to August 2023, 112 patients were enrolled in each group (76.8% male, 86.6% with ≥ junior high school education). 110 patients (UC group) and 109 patients (ePRO group) completed IC+CCRT. Among ePRO group, 107 patients successfully completed the ePRO-WMS, generating 561 e-alerts. Compared to UC group, ePRO group had significantly fewer patients with WL $>$ 10% at Post-1m (37.5% *vs.* 57.1%, $P = 0.003$) and W7-CCRT (22.3% *vs.* 38.4%, $P < 0.001$). Additionally, ePRO group showed improved nutritional status (Retinol Binding Protein, 38.3 *vs.* 34.8, $P = 0.011$) and quality of life. Notably, reductions in inflammation (C-reactive protein, 10.4 *vs.* 15.9, $P = 0.027$) and immune suppression ($CD4^+CD25^+$ regulatory T cells, 20.1 *vs.* 22.2, $P = 0.034$) were also observed. No significant differences were found between groups for acute adverse and progression-free survival (median follow-up time: 16 months). However, 2 cases of nasopharyngeal necrosis were observed in the UC group during follow-up. **Conclusions:** Compared to usual care, ePRO-based weight management in LA-NPC patients mitigated weight loss, alleviated inflammation, and significantly improved nutritional status and quality of life. Clinical trial information: NCT05834712. Research Sponsor: None.

1504 Oral Abstract Session

A novel virtual reality supportive care intervention (BMT-VR) for patients undergoing hematopoietic stem cell transplantation (HSCT): A pilot randomized clinical trial. First Author: Hermioni L. Amonoo, Department of Supportive Oncology, Dana-Farber Cancer Institute; Department of Psychiatry, Mass General Brigham; Harvard Medical School, Boston, MA

Background: Patients with hematologic malignancies undergoing HSCT experience immense physical and psychological symptom burden during their extended transplant hospitalization. Interventions that help manage patients' psychological distress and improve their quality of life (QOL) during this inpatient stay are limited. Virtual reality (VR), with its three-dimension capabilities for user engagement, offers a novel delivery modality for scalable, targeted, and patient-centered supportive care interventions aiming to address the persistent unmet psychosocial needs of these patients. **Methods:** We conducted a pilot randomized clinical trial (RCT) of a VR supportive care intervention (BMT-VR). Patients undergoing HSCT were randomly assigned to BMT-VR or usual care during their 3-4-week hospitalization. BMT-VR consisted of five self-directed modules addressing 1) supportive psychoeducation and managing expectations during HSCT; 2) effective coping; and 3) acceptance and gratitude while dealing with uncertainty. The primary endpoint was feasibility ($\geq$60% of eligible patients enrolling, and $\geq$60% of BMT-VR participants completing $\geq$3/5 modules). To assess BMT-VR's acceptability, we used the System Usability Scale ($>$ 80 = excellent acceptability). We assessed psychological distress (Hospital Anxiety and Depression Scale), QOL (Functional Assessment of Cancer Therapy-BMT), post-traumatic stress symptoms (PTSD-Checklist), coping (Measure of Current Status-A), and self-efficacy (Cancer Self-Efficacy Scale) at baseline (i.e., 3 days post-HSCT) and 4-, 12-, and 24-weeks post-HSCT. We used analysis of covariance (ANCOVA) to explore the preliminary effects of BMT-VR on outcomes. **Results:** We enrolled 58.3% (81/139) of eligible patients (BMT-VR (n = 40); usual care (n = 41)) with a mean age of 57.9 (SD = 14.7) and 51.9% women. 74.4% of BMT-VR participants completed $\geq$3/5 modules and 65.1% completed 5/5 modules, with median acceptability score = 81.2. At 4-weeks, BMT-VR vs. usual care participants reported improved anxiety (5.3 vs. 3.6, P = 0.016), QOL (108.2 vs. 96.8, P = 0.014), coping (36.6 vs. 32.4, P = 0.023), and self-efficacy (144.6 vs. 131.9, P = 0.019). Although BMT-VR vs. usual care participants reported sustained improvements in QOL (B = 3.8, P = 0.002), coping (B = 1.8, P = 0.011), and self-efficacy (B = 4.5, P = 0.017), BMT-VR effects became more pronounced for depression (B = -0.5, P $<$ 0.001), and PTSD (B = -1.7, P $<$ 0.001) symptoms longitudinally across all time points. **Conclusions:** A novel VR-delivered supportive care intervention tailored to the psychosocial needs of HSCT recipients is feasible and acceptable and demonstrated preliminary efficacy for improving psychological distress and QOL. A subsequent multi-site RCT will evaluate BMT-VR's efficacy for improving outcomes in diverse HSCT settings. Clinical trial information: NCT05629676. Research Sponsor: Doris Duke Charitable Foundation; Clinician Scientist Development Award; National Cancer Institute; K08CA251654.

1505 Oral Abstract Session

Geriatric assessment and management with a question prompt list using a web-based application to reduce treatment toxicity in older patients with cancer: A randomized controlled trial (J-SUPPORT 2101 study). First Author: Ayumu Matsuoka, Division of Survivorship Research, National Cancer Center Institute for Cancer Control, National Cancer Center, Tokyo, Japan

Background: Older adults with cancer experience aging-related physical, psychosocial and cognitive challenges that require comprehensive communication with their oncologists. Geriatric assessment (GA) can assess these aging-related problems and guide management. Communication support may further facilitate the implementation of GA-guided management (GAM). We report secondary outcomes of a single-blind, parallel-group, multicenter, randomized controlled trial evaluating the efficacy of a program combining GAM recommendations and communication support to facilitate aging-related communication between older Japanese patients with cancer and their oncologists. **Methods:** This study included patients aged $\geq$70 years with advanced or recurrent gastrointestinal cancers who were scheduled to receive first- or second-line systemic therapy and had impairment in at least one GA domain as assessed with a web-based application at baseline. In the intervention group, GAM recommendations and a question prompt list were given to patients by trained intervention providers to be shared with their oncologists at the first outpatient visit after randomization. During 5 months after the initial intervention, the implementation of the GAM recommendations was reviewed monthly by the intervention providers with the patients and their oncologists. The control group received usual care. Secondary outcomes included the incidence of grade 3-5 adverse events (National Cancer Institute Common Terminology Criteria for Adverse Events, ver. 5.0), dose modifications, early treatment discontinuation, unplanned hospital utilization during 3 months, overall survival rate at 6 months, and health-related quality of life and patient satisfaction at 3 and 6 months. **Results:** Between September 2021 and September 2023, 215 patients (99 women, 116 men; median age 75 [range 70-88] years) were randomized (n=108/107 in the intervention/control group). No differences were found between the groups in patient background characteristics. The incidence of any grade 3-5 adverse event was significantly lower in the intervention group than in the control group (50.9% vs. 66.4%, P$<$0.05); the incidence of hematologic toxicities was significantly reduced (37.0% vs 55.1%, P$<$0.01), while that of non-hematologic toxicities remained similar (29.6% vs 36.4%, P=0.31). Early treatment discontinuation was also significantly lower in the intervention group than in the control group (26.9% vs. 43.0%, P$<$0.05). No significances were found in other secondary outcomes including overall survival rate at 6 months (77.7% vs 78.7%, P=0.88) **Conclusions:** Our program combining GAM recommendations with communication support significantly reduced severe treatment toxicity without compromising survival in older patients with cancer. Clinical trial information: UMIN000045428. Research Sponsor: Japan Agency for Medical Research and Development.

1506 Oral Abstract Session

A technology-enabled clinical trial program's impact on patient screening and trial enrollment in 2024. First Author: Samantha Mallahan, Tempus AI, Inc., Chicago, IL

Background: Typical workflows for clinical trial start-up and screening are time- and resource-intensive. The Tempus AI TIME program offers a novel clinical trial solution, collaborating with clinical sites to increase trial access and alleviate site burden by streamlining study activation and screening methods. **Methods:** The TIME program consists of an algorithmic trial screening platform (TApp), team of oncology nurses, diverse trial portfolio, and rapid study activation processes. Patient-level clinical information is centralized within the TIME database and includes structured and unstructured data generated from Electronic Medical Record integration, next generation sequencing results, and natural language processing models. The TApp used this data combined with trial eligibility criteria to algorithmically match patients to TIME trials. TApp searches were triggered by changes to study criteria and/or updates to clinical data. Algorithmic matches were filtered based on site capabilities, site interest in the trial, and trial lookback criteria, which defined the required recency of a patient's latest clinical document or encounter. Qualifying matches were then reviewed by a Tempus nurse and sent to sites if confirmed eligible. Trial activations followed TIME's streamlined operational methods using a pre-negotiated rate card for site reimbursement of all clinical trial activities, standardized clinical trial agreement, and central IRB. Trials could be activated prospectively before the first eligible patient was identified, or in a "just-in-time" (JIT) manner if a patient was ready to consent. Data collected included TIME network information, TApp and nurse screening results, activation timelines, and enrollments across all active TIME sites and trials from 01/01/2024 - 12/31/2024. **Results:** During 2024, the TIME network consisted of 87 sites (79 Community, 8 Academic) and 98 trials. The TApp completed 1,323,259,353 searches across 1,281,676 patients resulting in 2,251,505 potential TApp trial matches. After applying site capability and trial lookback filters, TIME nurses screened 35,912 of these matches with 5,034 confirmed. These matches led to 186 activations (82 JIT, 104 prospective) and 573 consents. **Conclusions:** The Tempus AI TIME program facilitated the screening of 1.28M+ patients for over 95 clinical trials, averaging 1.57 consents per day over 1 year. Future trial matching strategies should utilize algorithmic screening and rapid activation processes to improve patient access and trial success. Research Sponsor: Tempus AI, Inc.

2024 patient screening and consents.

Patient Population	1,281,676
TIME Trials	98
TApp Searches	1,323,259,353
Algorithmic Matches	2,251,505
Matches Screened	35,912
Matches Confirmed	5,034
Interventional Consents	225
Observational Consents	348
Total Activations	JIT: 82, Prospective: 104
Avg Activation Time (business days)	JIT: 16.1, Prospective: 39.6

ABSTRACT WITHDRAWN

1508 Oral Abstract Session

Effect of human-AI teams on oncology prescreening: Final analysis of a randomized trial. First Author: Ravi Bharat Parikh, Emory University, Atlanta, GA

Background: Eligibility assessment for oncology clinical trials – "prescreening" – relies on manual review of unstructured clinical notes, which is error-prone and time-consuming. Artificial intelligence (AI) language models that merge deep learning with oncologist-derived rules (neurosymbolic AI) can enhance prescreening by automating eligibility extraction from longitudinal electronic health records (EHRs), yet real-world evaluations are limited. We compared the accuracy and efficiency of traditional vs. AI-augmented (Human+AI) prescreening. **Methods:** In this randomized non-inferiority trial, two research coordinators (RCs) abstracted 12 common trial eligibility criteria from complete EHRs from patients with advanced non-small cell lung cancer (NSCLC) or colorectal cancer (CrC) treated in a community oncology practice. Before the trial, gold-standard abstraction was performed by 3 independent oncologist reviewers. Charts were randomized in blocks of 20 to be viewed alone (Human-alone) or augmented by a pretrained neurosymbolic model (Human+AI) in a paired design, such that each RC reviewed each patient chart. The primary aim was to evaluate noninferiority (margin ±5%) and subsequent superiority of chart-level accuracy (proportion of correctly abstracted elements per chart relative to gold standard) between Human+AI vs. Human-alone. Secondary outcomes were criterion-level accuracy (proportion of correctly abstracted elements across charts for each eligibility criterion), and efficiency (median abstraction time per chart). Paired t-tests and Wilcoxon rank-sum tests assessed differences between Human+AI vs. Human-alone. We descriptively compared accuracy of both arms vs. the AI algorithm (AI-alone). **Results:** Among 356 charts (196 NSCLC, 160 CrC), Human+AI had noninferior and superior accuracy than Human-alone (76.1% vs. 71.5%, $p < 0.001$); both Human arms were superior to AI-alone (59.9%). Human+AI had greatest criterion-level accuracy for 7 of 12 criteria. Efficiency was similar between Human arms (32.1 vs. 31.8 min, p = 0.51). **Conclusions:** AI-augmented prescreening was more accurate than RC or AI prescreening alone. Human+AI teaming most improved accuracy for biomarker, staging, and response criteria. While Human+AI did not save time, efficiency gains may be realized as RCs become more familiar with AI eligibility models. AI language models can enhance CRC prescreening and identification of trial-eligible patients. Clinical trial information: NCT06561217. Research Sponsor: Mendel AI.

Accuracy across arms.

		Accuracy (%)			
	Criteria	Human- Alone	Human+AI	AI-Alone	p-value
	Overall	71.5	**76.1**	59.9	<0.001
Neoplasm	Cancer Type	**86.9**	86.4	73.3	0.80
	Stage Group	71.7	**73.4**	57.0	0.57
	M Stage	43.9	57.0*	**60.2**	<0.001
	N Stage	50.5	**66.3***	52.6	<0.001
	T Stage	56.3	**71.6***	54.3	<0.001
Biomarker	Biomarker Tested?	84.6	**93.2****	88.1	<0.001
	Biomarker Result	67.9	**79.0***	32.5	<0.001
	Biomarker Result Interpretation	80.8	**91.3***	35.7	<0.001
Other	Outcome	23.7	35.9*	**55.2**	0.004
	Response	47.1	51.7	**60.4**	0.20
	ECOG	**84.7****	78.1	34.4	0.10
	Medications	89.0	**89.1**	59.4	0.92

Bold indicates arm with greatest accuracy for a given criterion. *>10% accuracy difference between Human+AI vs Human-alone. **5-10% accuracy difference between Human+AI vs Human-alone.

1509 Clinical Science Symposium

Disparities in pediatric oncology outcomes in the occupied Palestinian territories: A retrospective study from Augusta Victoria Hospital. First Author: Ru'a Rimawi, Dana-Farber Cancer Institute, Boston, MA

Background: Childhood cancer survival rates exceed 80% in high-income countries, but over 80% of the global burden occurs in low- and middle-income countries, where survival rates are significantly lower. The occupied Palestinian territories (OPT)—comprising the West Bank, Gaza, and East Jerusalem—face additional and location-specific challenges, including political instability, movement restrictions, and fragmented healthcare, that would be expected to further negatively impact care. The aim of our study is to report on outcomes of children treated at the only specialized pediatric oncology cancer center, Augusta Victoria Hospital (AVH), located in East Jerusalem. **Methods:** This was a retrospective IRB approved study conducted by Dana-Farber Cancer Institute and AVH. Chart review was performed to obtain diagnoses, treatments and outcomes of all pediatric oncology patients with histologically confirmed cancer admitted at AVH from January 2018 to June 2024. **Results:** A total of 424 patients were included, with a median age at diagnosis of 6.95 years (IQR, 3.35–11.2). Of these, 51.2% were male. Patients resided in the West Bank (51.2%), Gaza (43.4%), and East Jerusalem (3.8%). The median diagnostic delay, defined as date of symptom onset to date of diagnosis, was 24.5 days (IQR, 10-45), with significant variation by gender (males: 30 days; females: 20 days, p = 0.018), age group (<5 years: 14 days; ≥5 years: 30 days, p = 0.003), and oncology diagnosis (leukemia: 14 days, lymphoma and solid tumors: 30 days, p = 0.014). Treatment delays, defined as the time form diagnosis to treatment initiation, was 14 days (IQR, 4-30), with the shortest duration for leukemia (2 days) and the longest for solid tumors (30 days, p = 0.008). There were no significant differences in time to treatment by region. The majority of patients lost to follow-up were living in Gaza (15/21, 71%). Among the 13% deaths, 15.4% were treatment-related, primarily due to infection, and most of these treatment-related deaths (65%) occurred in patients living in Gaza. The 3-year overall survival (OS) rate was 76.31%, and event-free survival (EFS) rate was 62.36%. Gaza patients had the lowest 3-year EFS rate (37.12%) compared to the West Bank (70.37%) and East Jerusalem (77.78%; $p < 0.0001$). **Conclusions:** This study is the first to report on outcomes of pediatric oncology patients treated at the only specialized center in the OPT. Males and patients older than 5 years experienced longer diagnostic delays, while patients with solid tumors faced treatment delays 15 times longer than those with leukemia. Gaza patients had higher lost to follow-up rates and treatment-related deaths with significantly inferior EFS. Research Sponsor: None.

1510 Clinical Science Symposium

Analysis of evidence in NCCN harmonized guidelines for sub-Saharan Africa. First Author: Scott Swartz, Department of Medicine, University of California, San Francisco, San Francisco, CA

Background: The National Comprehensive Cancer Network (NCCN) Harmonized Guidelines for Sub-Saharan Africa (SSA) have emerged as leading cancer treatment guidelines in SSA. The NCCN-SSA guidelines, derived by adapting NCCN guidelines for the SSA context, offer standardized recommendations to guide cancer care and shape policy in SSA. This study examines the evidence cited in support of the NCCN-SSA guidelines, with a focus on population characteristics and generalizability to SSA. **Methods:** Two reviewers independently examined the NCCN-SSA guidelines for the eight most common cancers in SSA to identify all studies cited in support of treatment/management recommendations. Study selection discrepancies were resolved by discussion. Full-text articles were reviewed and data on age, sex, race, and recruitment geography were abstracted. Descriptive analyses were performed using R statistical software. **Results:** Overall, 4,589 citations were reviewed, and 2,938 (64.0%) studies with individual-level data were included, representing >10.4 million study participants. Of the 2,061 studies reporting geographic information (70%), 50 (2.4%) recruited in SSA; of these, 39 (83.0%) recruited from South Africa. Three studies (0.2%) recruited exclusively in SSA. Most studies (95.3%) recruited exclusively from high or upper-middle income countries. Only 29.2% of studies with race data included >10% Black study participants. **Conclusions:** Most studies cited in the NCCN-SSA guidelines were conducted in high-income countries outside SSA. A small minority of all study participants were Black. Our findings underscore potential limitations in the generalizability of the NCCN-SSA guidelines to SSA and highlight a pressing need to generate and incorporate context-specific data to guide care and inform policy. Research Sponsor: UCSF Helen Diller Family Comprehensive Cancer Center.

WHO region of recruitment, race, and country-level income of studies included in NCCN-SSA guidelines.

Cancer type	# (%) studies reporting geography	# (%) studies by recruitment region*: Americas	# (%) studies by recruitment region*: Europe	# (%) studies by recruitment region*: Sub-Sah. Africa	% participants, White	% participants, Black	% participants, Other race	# (%) studies representing only HMIC (per World Bank)
Overall	2061 (70%)	1177 (57%)	921 (45%)	50 (2%)	79%	9%	11%	1964 (95%)
B-cell	325 (57%)	173 (53%)	178 (55%)	5 (2%)	82%	7%	10%	307 (94%)
Breast	206 (44%)	123 (60%)	124 (60%)	12 (6%)	80%	9%	11%	179 (87%)
Cervical	163 (90%)	100 (61 %)	44 (27%)	3 (2%)	64%	14%	22%	158 (97%)
Colorectal	584 (82%)	278 (48%)	292 (50%)	11 (2%)	80%	10%	10%	571 (98%)
Hepato-cellular	183 (74%)	80 (44%)	68 (37%)	0 (0%)	69%	9%	22%	169 (92 %)
Kaposi sarcoma	51 (80%)	25 (49%)	19 (37%)	5 (10%)	38%	51%	10%	44 (86%)
Ovarian	115 (56%)	76 (66%)	35 (30%)	0 (0%)	83%	4%	13%	115 (100%)
Prostate	434 (88 %)	322 (74 %)	161 (37%)	14 (3%)	79%	9%	12%	421 (97%)

HMIC = high and upper-middle income countries.
*Percent of studies includes as the denominator only the number of studies with reported geographies.

1511 Clinical Science Symposium

Integrated health system for resolving breast cancer screening actions: Multicenter randomized clinical study—Itaberaí randomized trial, ReBEC, RBR-39vm2nd. First Author: Ruffo Freitas-Junior, CORA – Advanced Center for Diagnosis of Breast Diseases Federal University of Goias, Goiania, Goias, Brazil

Background: The ITABERAÍ Project involves an intervention through training of Community Health Workers (CHW), based on evidence from clinical breast examinations (CBE) screening. It is a randomized, prospective, phase III, multicenter clinical study. The target population is divided into a Control Group (CG) and an Intervention Group (IG), where the CG receives the Brazilian Ministry of Health's (MS) recommendations for breast cancer screening, The IG, in addition to the MS recommendations, receives the CBE. Among the stages of the project are the training of CHW and the development of tools for data collection. Objective: This study aims to evaluate the functioning of the integrated system as a tool for the resolution of breast cancer screening actions, according to the ITABERAÍ Project. **Methods:** Information stored in the integrated system database developed for the project, from 2022 to 2024, was analyzed. The system comprises a set of services and applications that integrates actions from the registration of participants to the diagnosis and treatment of altered cases. It involves the integration of the App Rosa with the Web System (RosaWatch). The App Rosa was created for exclusive use by the CHW to collect data from participants who agree to participate in the study, while RosaWatch is for use by the Family Health Team (FHT), specialist doctors, nurse navigators, and researchers, and was created to collect information on the follow-up of altered cases. To evaluate the functioning of the system, data on the completeness of the information stored according to the Study Group and the follow-up of cancer cases were checked. **Results:** At the end of 3 years of project implementation, data from 3,670 randomized women were reported, of which 92% (3,359) were active in the project, out of this 1,780 (53%) in the CG and 1,579 (47%) in the IG ($p < 0.05$). Regarding the completeness of the information, by the end of 2024, it was found that 2,984 (88.8%) had consistent data. Stratifying by year of data collection, a significant increase in completeness was observed: in 2022, of the 425 records, 278 (65%) were compliant; in 2023, of the 2,255 records, 2,117 (94%) were compliant; and in 2024, of the 679 records, 654 (96%) were compliant. During the study period, 3,143 breast exams were performed by the CHW of the IG, with 594 (19%) altered cases. Of these, after screening at the Family Health Units (ESF), 90 (15%) participants received care from a specialist doctor (mastologist), and 10 had a confirmed breast cancer. In the CG, ESF doctors referred 33 women for specialist consultations, and six diagnoses were confirmed. **Conclusion:** The integrated system proved to be effective in monitoring the actions of the ITABERAÍ Project. Additionally, it contributed to the adherence of the CHW and the quality standard of the information, facilitating better data monitoring. Clinical trial information: RBR-39vm2nd. Research Sponsor: None.

LBA1512 **Rapid Oral Abstract Session**

Anesthesia type during surgery for treatment of biologically aggressive cancers: Results of the GA-CARES randomized, multicenter trial. First Author: Elliott Bennett Guerrero, Stony Brook University School of Medicine, Stony Brook, NY

The full, final text of this abstract will be available at meetings.asco.org on the day of presentation and in the online supplement to the June 10, 2025, issue of the *Journal of Clinical Oncology*.

1513 **Rapid Oral Abstract Session**

General practitioner-led vs surgeon-led colon cancer survivorship care: A randomized clinical trial. First Author: Julien Vos, Amsterdam UMC, Amsterdam, Netherlands

Background: The role of general practitioners (GPs) in providing survivorship care for cancer patients remains debated. In 2015, the randomized I CARE trial was initiated to evaluate the impact of GP-led vs. surgeon-led survivorship care on quality of life (QoL) and assess the effect of the eHealth application Oncokompas. An interim analysis after 12 months revealed no clinically relevant differences in QoL changes. However, patients continued to have follow-up consultations for up to 60 months after treatment. This study addressed the long-term QoL outcomes of the trial. **Methods:** The I CARE trial was a pragmatic, 2x2 factorial, open-label, randomized controlled trial. The trial was conducted in 8 hospitals and 225 general practices across the Netherlands. The trial included patients who underwent primary surgical treatment for stage I-III colon cancer or rectosigmoid carcinoma, and who were eligible for routine follow-up according to national guidelines. Inclusion lasted from March 26, 2015, to Nov 21, 2018. Patients were randomized using variable block randomization, stratified by age and tumor stage, into four groups (1:1:1:1): usual surgeon-led care, surgeon-led care with Oncokompas, GP-led care, and GP-led care with Oncokompas. The primary outcome was QoL at 5 years, as measured by the change from baseline in the EORTC QLQ-C30 summary score (range 0-100). Generic and disease-specific QoL were measured at baseline, 3, 6, and 12 months, and annually up to 60 months post-treatment. Differences in QoL changes were analyzed using piecewise linear mixed-effects models with a knot at 24 months to capture potential deviations in QoL recovery. A 10-point difference was considered clinically relevant (superiority design with α = 0.05, power of 80%, and 15% dropout). The trial is registered with the Netherlands Trial Register (NTR4860). **Results:** In total 303 patients were enrolled; 79 were randomized to surgeon-led care, 83 to surgeon-led care with Oncokompas, 73 to GP-led care, and 68 to GP-led care with Oncokompas. Patients were male (67%) with a mean age of 68.0 years (SD 8.4). Of the 151 patients assigned to Oncokompas, 51 (36%) reported using the app at least once in the first year. Baseline QoL was high in all groups. No clinically meaningful differences in QoL were observed between GP-led and surgeon-led groups at 24 months (difference of -0.5 [95% CI -1.6 to 0.5]) and 60 months (-0.01 [-0.8 to 0.8]). Oncokompas also had no meaningful effect (difference of 0.8 [0.0 to 1.6] at 60 months). **Conclusions:** In this pragmatic, randomized controlled trial conducted in the Netherlands, GP-led survivorship care did not improve long-term QoL compared to traditional surgeon-led care among non-metastatic colorectal cancer survivors. Due to low usage rates, the impact of Oncokompas is inconclusive. Survivorship care models can be tailored to fit individual preferences. Clinical trial information: NTR4860. Research Sponsor: Dutch Cancer Society; grant BMA 5954.

1514 **Rapid Oral Abstract Session**

Effect of post-discharge symptom monitoring on hospital readmissions: A randomized trial. First Author: Robert Michael Daly, Memorial Sloan Kettering Cancer Center, New York, NY

Background: There is growing interest to improve patient care transitions from hospital to home and to prevent readmissions but effective interventions are lacking. **Methods:** We conducted a randomized clinical trial among patients with cancer discharged after an unplanned hospital admission at a specialty cancer center. Hospitalized patients on medical oncology services were randomized at discharge to receive either a digital symptom monitoring and management intervention or to usual care. Patients randomized to the intervention received a daily electronic symptom assessment for 10 days post-discharge, consisting of 9 common symptoms from the National Cancer Institute Patient Reported Outcomes version of the Common Terminology Criteria for Adverse Events and an open-ended question to allow for patients to provide further symptom context and for two-way engagement with their clinical team. Patients also received customized self-management education delivered through the patient portal based on their reported symptoms. Primary oncologists received alerts through the portal for moderate and severe symptoms. Usual care consisted of symptom monitoring at the discretion of the primary clinical team, generally comprising an oncologist and an office practice nurse. The primary outcome was the 30-day readmission rate, analyzed using cumulative incidence functions and Gray's test with death as a competing risk. Secondary endpoints included 90-day readmission rate and 30-day emergency room visit without admission rate. **Results:** Between 04/19 and 09/19/2024, 1,713 patients were randomized with median age 66 years (range: 19 – 99), 66% white, 12% African American, 11% Asian, and 11% Hispanic with 53% female. The most common cancer diagnoses were gastrointestinal (26%), thoracic (11%), genitourinary (10%), gynecologic (10%), leukemia (9%), and lymphoma (9%). In the intervention group, the most frequently reported moderate and severe symptoms were fatigue and pain. The two arms had roughly similar proportions of patients who died before a hospital readmission. The 30-day readmission rate was 30% in the intervention group compared to 37% in the usual care group (p = 0.001). The decrease in readmission rate was maintained at 90 days (45% vs. 52%, p = 0.002). Emergency room visits without admission at 30 days were also lower in the intervention group (12% vs. 17%, p = 0.007). **Conclusions:** Digital post-discharge symptom monitoring and customized patient self-management education for 10 days post discharge reduced hospital readmissions in patients with cancer. Further research is necessary to identify the precise mechanisms that contribute to the success of this intervention. Research Sponsor: National Cancer Institute; Emerson Collective Digital Oncology Care.

1515 **Rapid Oral Abstract Session**

SNF-CLIMEDIN: A HECOG prospective randomized trial of digital support and intervention in patients with advanced non-small cell lung cancer (NSCLC)—Final results. First Author: Paris A. Kosmidis, Department of Medical Oncology, Hygeia Hospital, Athens, Greece

Background: This trial aims to investigate the feasibility and effectiveness of online digital intervention to NSCLC patients in terms of adverse events (AEs), quality of life (QoL), cost, and the interrelation with clinical and molecular characteristics. **Methods:** This prospective randomized trial recruited 200 advanced NSCLC patients (3/22-10/23). Final analysis was undertaken in 12/24. All had NGS tissue analysis for 161 genes, and received standard treatment (predominantly immuno-chemotherapy). Through the CareAcross online platform, they received information about their disease and treatment, and periodically reported any of the 22 preplanned AEs. Patients were randomized 1:1 in the Intervention (A) and Control (B) arm; patients in arm A received digitally, additionally, evidence-based guidance for the reported AEs. The study was designed to assess AE improvement (measured per patient as reduction of AEs reported at last contact, compared to those previously reported) and QoL. EQ5D-5L scores were collected. Patient-case level hospitalization data were collected and costs were estimated based on reimbursed cost as defined by the Ministry of Health. Results were correlated with patients' clinical and molecular characteristics. **Results:** Clinical and molecular characteristics will be presented during ASCO Congress. Comparing arms A vs B: ORR: 42.1% vs 41.7%; Median PFS: 11m (8.0-15) vs 10m (7.0-13), 1-year PFS: 43% (31%-54%) vs 42% (31%-53%) (p = 0.4). Median OS: 15m (12-20) vs 16m (12-21), 1-year OS: 59% (48%-68%) for both arms (p = 0.9). PFS and OS were improved for those with best responses ($p < 0.001$). Patients with EGFR mutations had better OS (p = 0.05). The most common AEs reported in both arms were fatigue, cough, anorexia, nausea. More AEs were reported online vs to clinicians (89% vs 68% of patients; $p < 0.01$). Baseline EQ5D-5L was similar for both arms; when compared with data at best response, Anxiety/Depression showed the biggest difference in improvement for arm A vs B. Among the 22 AEs, 17 improved more in arm A, 1 improved equally, and 4 improved more in Arm B. The comparative improvements of rash and stomatitis in arm A vs B were statistically significant (p = 0.0073 & p = 0.0447). The mean hospitalization cost (arm A vs B, in Euros) was 455.4 (95%CI: 91.9-941.5) vs 779.5 (346.6-1328.5) ($p < 0.001$); the mean diagnostics cost was 20.3 (0.5-50.8) vs 73.3 (1.3-186.1) ($p < 0.001$). **Conclusions:** Digital oncology is feasible, cost-effective by reducing hospitalizations and tends to improve QoL (especially anxiety and depression) and most AEs of NSCLC patients regardless of clinical and molecular status. Patients report, digitally, more informative AEs for clinical and research analysis. Through the digital transformation of healthcare, digital oncology can be a complementary tool to the Oncology team and warrants further exploration. Clinical trial information: NCT05372081. Research Sponsor: Stavros Niarchos Foundation.

1516 Rapid Oral Abstract Session

Breast cancer diagnosis, management, and outcomes in transgender, nonbinary, and gender-diverse individuals: A multicenter cohort. First Author: Chandler Scott Cortina, Division of Surgical Oncology, Department of Surgery, Medical College of Wisconsin & MCW Cancer Center, Milwaukee, WI

Background: Paucity of data on breast cancer (BC) in transgender, nonbinary, and gender-diverse (TGD) individuals leads to suboptimal screening and treatment algorithms. We developed a national multicenter retrospective cohort to describe demographic, clinicopathologic, and treatment characteristics of TGD individuals with BC and report outcomes. **Methods:** The cohort included TGD persons age ≥18yrs with stage 0–IV BC treated at 22 US centers from 1990–2023. Demographic and clinicopathologic characteristics were evaluated and compared to BC patients in the SEER 2016–21 dataset. Wilcoxon rank sum tests, χ^2 tests, and KM analysis were used to compare variables and estimate 5-yr BC-specific survival (BCSS). **Results:** 112 TGD persons with 113 BCs were included. Median age at diagnosis was 42.5yrs (IQR 36.5–51), 92.9% were female sex at birth (FSAB), 73.2% were NH-White, and 38.4% used gender-affirming hormones pre-BC. Of those FSAB (n=104), 61.5% were premenopausal and 11.5% had undergone gender-affirming top surgery (GATS) pre-BC. Most BCs (51.8%) were self-detected, 27.7% were screen-detected (48.2% underwent screening pre-BC), 13.4% were incidentally found on GATS pathology, 3.6% were provider-detected, and 2.7% were incidentally found on other imaging. Of 84 (75%) tested patients, 16/84 (19%) had a pathogenic germline variant, with *BRCA2* (25%) and *BRCA1* (18.8%) being most common. Most tumors were HR+ (85.7%) and early stage (25.7% DCIS and 45.1% stage I). Regarding local treatment, most (61.6%) underwent mastectomy, with 63.8% omitting reconstruction; after lumpectomy, 29% omitted radiation (RT). 41.1% received systemic chemotherapy and while endocrine therapy (ET) was recommended for 79, only 81% (64/79) received ET. There was no difference in surgery type (p = 0.22) or ET receipt (p = 0.32) by SAB. Compared to patients in SEER (N = 401,311), the TGD cohort was younger (median age 42.5 *vs* 62yrs), more frequently NH-White (75.2% *vs* 65.1%), more often had PR+ disease (79.5% *vs* 70.7%), and had a higher proportion of males (MSAB) (7.1% *vs* 0.8%) (p <0.01 for all); but there was no difference in disease stage (p = 0.39). At 38 months median follow-up: 12 (10.7%) had a locoregional recurrence (LRR), and 2 died of metastatic BC. 5-yr BCSS probability was 96.2% (95% CI 85.3–99.0%). **Conclusions:** The first multicenter cohort study of TGD individuals with BC identified they were younger and had a higher proportion MSAB compared to BC patients in SEER. Most tumors were self-detected, and the pathogenic germline variant rate was high – suggesting a possible role for earlier screening in high-risk TGD persons regardless of SAB. The elevated LRR rate along with low ET and RT uptake indicates opportunities to improve adherence to guideline concordant care. Findings underscore the necessity for prospective research to inform gender-inclusive evidence-based BC screening and treatment guidelines. Research Sponsor: National Cancer Institute.

1517 Rapid Oral Abstract Session

Inclusion of people living with HIV in Food and Drug Administration (FDA) oncology pivotal registration trials from 2020 to 2024. First Author: Alberto Giovanni Leone, Department of Oncology and National Centre for HIV Malignancy, Chelsea and Westminster Hospital, London, United Kingdom

Background: People living with HIV (PLWH) have an increased risk of developing cancers compared to the population without HIV, with cancer being the leading cause of death for this population in high-income countries. Previous research by the ASCO-led HIV working group found only 11% of clinical trials supporting FDA cancer therapy approvals from 2010-2014 allowed for inclusion of PLWH, leading to clinical uncertainty in the efficacy-safety profile of new cancer treatments in this group. To address this gap, ASCO (2017) and FDA (2020) issued guidelines encouraging inclusion of PLWH in cancer clinical trials. To explore their impact, we examined inclusion of PLWH in pivotal cancer trials post-guidelines release. **Methods:** We reviewed all new FDA-approved indications of the past five years (Jan/2020-Nov/2024). For each new approval, two authors independently assessed the inclusion/exclusion criteria outlined in the primary protocol of each pivotal trial. We analyzed data on the FDA label, cancer type, therapeutic modality, inclusion/exclusion criteria, sponsor, and the protocol (version 1) publication date. **Results:** We identified 244 new therapy indications, based on supporting data from 259 pivotal clinical trials. 27% of trials permitted inclusion of PLWH. Pivotal trials for hematological cancers, compared to solid cancers, were significantly more likely to exclude PLWH [unadjusted Odds Ratio (OR) 3.15, 95% confidence interval (CI): 1.51-6.56; p=0.0012]. Pivotal trials of immunomodulatory agents were significantly more likely (OR 3.87, 95% CI: 1.91–7.83; p<0.0001) to exclude PLWH compared to other cancer therapies. The inclusion rate was 10.3% for AIDS-defining cancers and 29.8% for non-AIDS-defining cancers. Trials funded only by industry were significantly more likely (OR 2.80, 95% CI: 1.36-5.77; p=0.0078) to exclude PLWH, compared to non-industry funded trials. Inclusion rate of PLWH was higher in protocols published after 2020 (39.1%) compared to those before (26.3%). **Conclusions:** Our analysis indicates an improvement in the inclusion of PLWH in oncology pivotal trials following ASCO and FDA guidance. However, nearly three out of four pivotal cancer trials continue to exclude PLWH. This highlights an unmet need, resulting in uncertainty for healthcare professionals regarding the safety and clinical utility of new cancer treatments in PLWH. Additional strategies must be considered to address this disparity. Research Sponsor: None.

Rates of PLWH inclusion in oncology pivotal trials.

	Include PLWH (%)
Total (n=259)	27.4
Solid Cancers (185)	33
Haematological malignancies (74)	13.5
Immunomodulatory agents (89)	12.4
Other agents*(170)	35.3
Industry-funded (223)	24.2
Non-industry funded (36)	47.2
AIDS-Defining Cancers (30)	10
Non-AIDS Defining Cancers (45)	29.8

*Chemotherapy, targeted therapy, drug-antibody conjugates, hormone therapy, radionuclide therapy.

1518 Rapid Oral Abstract Session

Economic modelling to inform pricing for LMICs of immune checkpoint inhibitors in advanced PD-L1-high non-small cell lung cancer. First Author: Giulia Segafredo, Medicines Patent Pool, Genève, Switzerland

Background: Lung cancer is the most common cancer and cause of cancer death, encompassing for 16.8% of all cancer-related deaths worldwide. Anti-PD(L)1 Immune Checkpoint Inhibitors (ICIs) as monotherapy currently represent the standard of care (SoC) for advanced Non-Small Cell Lung Cancer with high (≥50%) PD-L1 expression in high-income countries. Despite their efficacy, ICIs remain largely inaccessible in low- and middle-income countries (LMICs), with affordability being a significant barrier. Providing evidence on cost-effective (CE) price ranges for ICIs in LMICs is critical for global health policymakers to devise strategies to enhance access. **Methods:** A partitioned-survival model was used to estimate CE price targets for three ICIs (atezolizumab, cemiplimab, and pembrolizumab) as single agents compared to platinum-based combination chemotherapy (current SoC in several LMICs). Treatment duration was assumed of up to 35 cycles or until disease progression. Cost-effectiveness thresholds were set at 1, 2, and 3 times the gross domestic product (GDP) per capita per quality-adjusted life year (QALY) gained. Case studies were modelled in two LMICs (India and South Africa – not all ICIs were registered in both countries) to determine the maximum price at which ICIs would be CE from the perspective of publicly-funded health systems. Primary efficacy data were sourced from phase III clinical trials (KEYNOTE-024, IMpower110, and EMPOWER-Lung 1), and country-specific data were collected through interviews with key technical stakeholders. Values were reported in USD for 2023. **Results:** The analysis determined that the maximum acquisition costs for ICIs to be cost-effective at 1-, 2-, and 3-times GDP per capita in India and South Africa, range from $14.20 to $648.00 per cycle per patient. Current reference prices would require discounts of up to 93.3% to meet the 3 GDP threshold. Dose-optimization strategies such as low-dose and vial sharing were identified as feasible and evidence-based approaches to achieve partial price reduction (sensitivity analysis will be provided). **Conclusions:** To make ICIs cost-effective in LMICs, significant discounts from current reference prices are needed. Similar price reductions (up 93%) have been achieved for other monoclonal antibodies, such as trastuzumab, in India and South Africa, also driven by the availability and uptake of quality-assured biosimilars. A comprehensive approach, combining accelerated biosimilar availability, also leveraging voluntary licensing and technology transfer, with dose and treatment-duration optimization strategies could help achieve target price levels and improve accessibility. Research Sponsor: Medicines Patent Pool.

Country	WTP threshold (xGDP)	Pembrolizumab	Atezolizumab	Cemiplimab
India	1	$72.6	$74.2	$66.5
	2	$199.7	$166.9	$181.5
	3	$308.6	$259.6	$300.0
South Africa	1	$51.5	$53.1	$14.2
	2	$349.9	$289.0	$314.7
	3	$648.2	$525.0	$615.2

1519 Rapid Oral Abstract Session

Association of court-documented major adverse financial events before cancer diagnosis and mortality risk in the US. First Author: Robin Yabroff, Surveillance and Health Equity Science, American Cancer Society, Atlanta, GA

Background: Cancer diagnosis is associated with increased risk of financial hardship in the US. This study examined the associations of court-documented major adverse financial events (AFEs) of bankruptcies, liens, and evictions prior to cancer diagnosis and risks of all-cause and cancer-specific mortality. **Methods:** Individuals aged 21 to 69 years diagnosed with common cancer types, including bladder, female breast, colorectal, kidney, lung and bronchus, oral cavity/pharynx, or prostate cancers or melanoma during 2014-2015 were identified from the SEER population-based registries for Seattle, Louisiana, and Georgia. Registry data were linked with LexisNexis consumer data to identify history of court-documented AFEs of bankruptcies, liens, and evictions. Vital status and cause of death were examined through December 31, 2021. The association of pre-diagnosis AFEs and risk all-cause and cancer-specific mortality was assessed with separate multivariable Cox proportional hazards models for each survival outcome, stratified by cancer site. Models were adjusted for stage, age, race and ethnicity, marital status, registry, registry-specific income categories, and the interaction between income and registry. **Results:** Of 58,796 individuals diagnosed with one of the 8 selected cancers, 21,694 (36.9%) had a pre-diagnosis AFE and there were 16,714 deaths (28.4%) during the study period between 2014 and 2021. Pre-diagnosis AFEs were associated with higher risk of all-cause mortality for individuals diagnosed with female breast (hazard ratio (HR): 1.18; 95% confidence interval (CI): 1.09-1.28), colorectal (HR: 1.14; 95% CI: 1.06-1.23), oral cavity/pharynx (HR: 1.14; 95% CI: 1.06-1.23) and prostate (HR: 1.33; 95%CI: 1.20-1.47) cancer and early- and late-stage melanoma (HR: 2.23; 95% CI: 1.89-2.99 and HR:1.34; 95% CI:1.01-1.80, respectively), in adjusted models. Pre-diagnosis AFEs were also associated with significantly higher risk of cancer-specific mortality for these five cancers. **Conclusions:** Court-documented AFEs of pre-diagnosis bankruptcy, lien, or eviction was associated with increased risk of all-cause and cancer-specific mortality for multiple cancer types in this study using a novel SEER cancer registry-LexisNexis consumer data linkage. The association of pre-diagnosis AFEs and mortality risk underscores lasting adverse consequences of patient financial vulnerability prior to incurring high out-of-pocket costs of cancer treatment. Our findings are especially timely, with growing efforts by health care providers to screen and address patient health-related social needs as part of comprehensive oncology care. Research Sponsor: None.

1520 Rapid Oral Abstract Session

Effect of broad-based genomic sequencing on survival outcomes in advanced non-small cell lung cancer: A national cohort study, 2011-2023. First Author: Patricia Mae Garcia Santos, Division of Health Services, Outcomes, and Policy, Department of Radiation Oncology, Winship Cancer Institute, Emory University, Atlanta, GA

Background: Use of broad-based genomic sequencing (BGS) for advanced non-small cell lung cancer (aNSCLC) is rising. While older studies have found no survival benefit with BGS, its impact on survival outcomes in the era of modern targeted therapy is unknown. **Methods:** In this retrospective cohort study, the 2011-2023 Flatiron Health Database—a nationally representative database of electronic health records from > 280 US cancer clinics—was queried for patients with Stage IIIB-IV NSCLC who received at least one line of systemic therapy with ≥12 months follow-up. Primary exposure was receipt of BGS vs. "Focused" biomarker testing (i.e., *ALK* FISH, *EGFR* PCR) within 90 days of first- and second-line therapy start. To address baseline confounding, we used 1:1 nearest-neighbor propensity score matching based on age at initial diagnosis, sex, self-reported race/ethnicity, histology (squamous vs. non-squamous), insurance status, smoking status, ECOG performance status, practice type (academic vs. community), stage at diagnosis, advanced diagnosis year, and practice rate of BGS. Adjusted Cox proportional hazards models compared median progression-free survival (mPFS) and median overall survival (mOS) between groups. Sensitivity analyses adjusted for biomarker status and used an instrumental variable approach. **Results:** Our initial unmatched cohort consisted of 35,060 patients (BGS, *n* = 14,192; Focused, *n* = 20,868; 52% female, 3.5% Asian, 9.3% Black, 3.8% Hispanic, 79% community practice). In the propensity-matched first-line therapy cohort (BGS vs. Focused, *n* = 10,008 in each group; all standardized mean differences < 0.1), BGS was associated with greater mPFS (6.4 vs. 6.0 months; adjusted HR [95%CI], 0.96 [0.92-1.0], $p = 0.046$) and mOS (16 vs. 14 months; 0.91 [0.86-0.95], $p < 0.001$). Sensitivity analyses were consistent with primary results. Patients receiving BGS had higher rates of *ALK/EGFR* positivity (18% vs. 13%) and receipt of targeted therapy (20% vs. 17%). Upon adjustment for biomarker status, however, BGS remained associated with improved OS (1.01 [0.88-0.98], $p = 0.004$) but not PFS (0.98 [0.94-1.03], $p = 0.4$). In the propensity-matched second-line therapy cohort, no associations between BGS and survival outcomes were observed. **Conclusions:** This is the first national analysis of survival outcomes in aNSCLC to demonstrate a survival benefit with BGS. These findings support guideline endorsement and payer coverage of BGS prior to 1st line therapy. Research Sponsor: None.

			Median (95%CI)	Univariate HR (95%CI)	Adjusted HR (95%CI)
First Line	PFS, *months*	Focused	6.0 (5.8-6.1)	–	–
		BGS	6.4 (6.2-6.5)	0.95 (0.91-0.99)	0.96 (0.92-1.00)
	OS	Focused	14 (14-15)	–	–
		BGS	16 (16-17)	0.90 (0.86-0.95)	0.91 (0.86-0.95)
Second Line	PFS	Focused	3.8 (3.5-4.1)	–	–
		BGS	4.2 (4.0-4.5)	0.91 (0.82-1.01)	0.92 (0.83-1.02)
	OS	Focused	13 (12-14)	–	–
		BGS	12 (12-14)	1.02 (0.91-1.15)	1.01 (0.89-1.14)

1521 Poster Session

Financial toxicity and drivers of delayed care among cancer survivors across the lifespan. First Author: Justine Po, Keck School of Medicine of University of Southern California, Los Angeles, CA

Background: Financial toxicity has been increasingly recognized as a cause of poor outcomes among cancer survivors. Cancer survivors have been shown to face greater healthcare access and affordability issues than the general population, and available evidence suggests that adolescent/young adult (AYA) cancer survivors may face especially high financial toxicity. However, existing research is limited by small sample sizes and methodological constraints. Understanding age-specific healthcare barriers could inform targeted interventions to improve outcomes for cancer survivors across the lifespan. **Methods:** Participants aged 18 and older were enrolled with informed consent in the All of Us Research Program, an NIH database integrating multiple health information sources. Included participants were cancer survivors who had available data for age, sex and other demographics. Cancer diagnoses were identified using ICD and SNOMED codes. Survey data were used to assess outcomes of financial toxicity and drivers of delayed care, as well as covariates of race, ethnicity, income, education, marital and insurance status. As all participants were insured, insurance status was dropped from the final models. Age groups were coded as 18-39, 40-49, 50-64, 65-74 and 75+. Statistical analysis was conducted using logistic regression by age group, adjusted for covariates. **Results:** 15,637 cancer survivors were included for analysis, including 1,090 participants aged 18-39 and 2,104 participants over age 75. Compared to 18-39 year olds, odds of being unable to afford specialist care decreased with age: [40-49] OR = 0.57 ($p = 0.01$), [50-64] OR = 0.18 ($p < 0.0001$), [65-74] OR = 0.07 ($p < 0.0001$), [75+] OR = 0.006 ($p < 0.0001$). Results were similar for primary care, with more extreme effect sizes. Causes of delayed care differed by age group. 18-39 year olds were more likely to report elderly caregiving responsibilities and inability to get time off work as drivers of delayed care, while 40-49 year olds were more likely to report difficulties accessing child care as a driver (OR = 5.25, $p < 0.0001$). Older cancer patients were also more likely than AYAs to report lack of transportation access as a cause of delayed care ([65-74] OR = 2.33, $p < 0.0001$). **Conclusions:** To date, this study represents the largest and most comprehensive analysis of healthcare barriers among cancer survivors across the lifespan. Targeted interventions based on the most significant barriers by age group may more effectively improve healthcare access and outcomes for all ages. Our results support that AYA cancer survivors may benefit most from financial support, elderly care resources and medical notes to facilitate time off work. By comparison, expanding childcare support may be most important for increasing access among those aged 40-49. Among older cancer survivors, ensuring reliable transportation presents the greatest opportunity for improving healthcare access. Research Sponsor: National Institutes of Health, Office of the Director.

1522 Poster Session

Spillover effects of Medicaid expansion on insurance coverage, diagnosis, and survival among low-income elderly patients with cancer. First Author: Kewei Sylvia Shi, American Cancer Society, Atlanta, GA

Background: Medicaid expansion under the Affordable Care Act is associated with increased health insurance coverage and improved outcomes among patients with cancer < 65 years. Although not the target population, individuals ≥65 years may also benefit from Medicaid expansion through "welcome mat" effects, referring to the indirect increase in Medicaid enrollment from increased public awareness and streamlined enrollment procedures. This study examines the associations of Medicaid expansion with Medicaid coverage, stage at diagnosis, and survival among cancer patients ≥65 years. **Methods:** Using the National Cancer Database, we identified patients ≥65 years newly diagnosed with cancer between 2010-2022 residing in areas with median household income below 200% of the federal poverty level. We applied a quasi-experimental difference-in-differences design, with multivariable linear probability models to compare the changes in the percentage of dual-eligible or Medicaid-only coverage, stage at diagnosis, and two-year survival post (vs. pre) Medicaid expansion in expansion states compared with non-expansion states. **Results:** A total of 1,468,116 patients with cancer were identified, with 885,671 patients from expansion states and 582,445 patients from non-expansion states. After adjusting for sociodemographic characteristics, the percentage of patients with dual or Medicaid-only coverage increased from 10.27% to 11.33% in expansion states and decreased from 9.4% to 8.11% in non-expansion states, resulting in a net increase of 1.34 percentage points (ppt, 95% confidence interval [CI]: 1.12, 1.56) associated with Medicaid expansion. Differences were more pronounced among patients with stage III-IV cancers, females, non-Hispanic Black, metropolitan residents, and those with ≥2 comorbidities. The percentage of early-stage (I/II) cancer diagnoses decreased more in non-expansion states (49.82% to 47.19%) than in expansion states (47.63% to 46.06%), resulting in a net increase of 0.96 ppt (95% CI: 0.58, 1.34). The protective effects of Medicaid expansion were stronger for late-stage (III/IV) non-small cell lung and uterine cancers, as well as early-stage thyroid and bladder cancers. Two-year overall survival rates increased from 58.86% to 62.39% in expansion states and from 59.18% to 62.55% in non-expansion states, leading to a net increase of 0.95 ppt (95% CI: 0.61, 1.29). Improvements were most notable for prostate, lung, kidney, and bladder cancers. **Conclusions:** Medicaid expansion was associated with an increase in Medicaid coverage, early-stage cancer diagnoses, and improved two-year survival among patients diagnosed with cancer ≥65 years. Findings underscore the spillover benefits of Medicaid expansion in supporting low-income elderly populations and the importance of indirect benefits when evaluating Medicaid expansion's broader impact. Research Sponsor: None.

1523 Poster Session

Bolstering access to clinical trials: Sociodemographic characteristics of patients enrolled in interventional clinical trials within a large, NCORP-designated community oncology practice setting. First Author: Meera Vimala Ragavan, Kaiser Permanente San Francisco Medical Center, San Francisco, CA

Background: Access to clinical trials is an important aspect of cancer care given rapidly changing treatment paradigms.Most patients with cancer including those belonging to racial/ethnic minoritized groups are treated in community oncology settings, but only a minority (< 5%) of these patients are enrolled on clinical trials. Barriers to trial enrollment in community oncology settings have been well described at the patient, provider, and system levels. The National Cancer Institute Community Oncology Program (NCORP) aims to address these barriers- and improve equity in trial enrollment- by providing support and infrastructure for community oncology practices to conduct clinical trials. Kaiser Permanente Northern California (KPNC) is a large integrated health system comprising thirty cancer trial sites and is part of the Kaiser Permanente NCORP, one of the largest NCORP-designated sites. In this study, we compared sociodemographic characteristics of patients enrolled in interventional trials with the overall cancer population within KPNC. **Methods:** We evaluated all patients enrolled on interventional cancer clinical trials within KPNC between 1/1/2015-12/31/2022. We abstracted demographic and clinical characteristics from the KPNC cancer registry. We compared characteristics to the incident cancer population diagnosed over the study period across KPNC. We used Pearson chi squared tests (categorical), binomial tests (binary) and one-sample t tests (continuous) to compare sociodemographic characteristics. **Results:** We identified 1,341 patients who were enrolled onto interventional clinical trials and compared them to 97,764 patients diagnosed with cancer over the study period. Patients enrolled on interventional trials were younger (mean age 60.2 vs 62.9 years, $p < 0.001$), more likely to have Stage IV disease (22.7% vs 11.2%, $p < 0.001$), more likely to reside in high-socioeconomic status neighborhoods (27.7 vs 23.8%, $p < 0.001$), and less likely to speak a language other than English (4.7 vs 7.1%, $p < 0.001$). There were no differences in race, ethnicity or sex distributions between the trial population and overall population. **Conclusions:** Across a large NCORP-designated community oncology trials program, the racial and ethnic makeup of patients enrolled on trials was similar to the broader cancer population within KPNC. These findings suggest that the trial infrastructure provided by NCORP may surmount the structural barriers that drive low access to trials among racial/ethnic minorities. Small differences in enrollment based on age, language and socioeconomic factors persisted. Efforts to bolster clinical trial portfolios in community oncology settings may address existing barriers to enrollment. Research Sponsor: KPNC Community Benefit Program- Cancer Section Pilot Funding.

1524 Poster Session

Integrating collaborative care in oncology: Improving quality of life and mental health for patients with cancer. First Author: Kyle N. Lavin, University of North Carolina at Chapel Hill, Chapel Hill, NC

Background: In the U.S., 22 million patients with cancer face unmet behavioral health needs, contributing to up to $245B in preventable healthcare costs. These unique challenges stem from physical, emotional, practical, and relational stressors associated with their cancer journey. Collaborative care, an evidenced based model that integrates behavioral health into medical settings, has been shown to improve access, outcomes, and reduce overall healthcare costs in primary care. Cerula Care offers a virtual collaborative care model that seamlessly integrates with oncology practices to improve quality of life and behavioral health outcomes. The team includes a Consulting Psychiatrist, Behavioral Health Care Manager, and Behavioral Health Coach working in coordination with oncology teams. **Methods:** This study analyzed data from 127 patients with cancer enrolled in Cerula Care's 12-week virtual care program between 1/31/24 and 8/31/24. Behavioral health outcomes, including anxiety (GAD-7), depressive symptoms (PHQ-9), and quality of life (FACT), were assessed monthly. Analyses focused on baseline to two-month outcomes due to limited sample sizes beyond two months (many patients were still in earlier stages of the program). Correlations and paired t-tests were conducted to evaluate changes in outcomes. **Results:** Of the 127 patients enrolled, mean age was 57.1 years (range: 28–78), 83.5% were female, 52.8% identified as White, 33.9% Black or African American, 0.8% Asian, and 3.1% other races. Breast cancer was the most common diagnosis (52.8%), followed by lung, colorectal, pancreatic, and ovarian cancers. Behavioral health outcomes from baseline to month 2 are shown in the table. **Conclusions:** Within just two months of care, Cerula Care significantly improved depressive symptoms and anxiety, as well as quality of life for cancer patients. Notably, improvements in quality of life were correlated with minority status, highlighting the program's potential to reduce disparities in cancer care. By integrating behavioral health into oncology treatment, this model demonstrates a scalable, impactful solution to enhance patient outcomes. Future research should focus on long-term sustainability, cost-effectiveness, and broader implementation across diverse oncology settings. Research Sponsor: None.

Behavioral health outcomes from baseline to month 2.

Outcome	Measure	Sample Size (n)	Change	Statistical Significance (p-value)
Depressive Symptoms	PHQ-9 Score	50	↓ 4.47 points	**p < .001**
Anxiety Levels	GAD-7 Score	52	↓ 2.06 points	**p = .007**
Quality of Life	FACT Score	N/A	**Improved,** especially in racial minority patients	**r = .439, p = .017**

1525 Poster Session

From food deserts to clinical trial deserts: Challenges in access to breast cancer trials. First Author: Rachel Ann Sachs, Robert Wood Johnson Medical School, New Brunswick, NJ

Background: Patients who live in food deserts have high mortality rates from breast cancer and stand to benefit from participating in research studies, yet they may face complex barriers to doing so. This study explores the relationship between living in a food desert and breast cancer clinical trial enrollment and assesses the contribution of transportation barriers and distance. **Methods:** The national Vizient Clinical Database (which includes 98% of academic and 1,000 community hospitals) was queried for women treated for breast cancer between January 2022 and June 2024. Patients who traveled $>$ 4 hours to get to treatment were excluded ("destination care"). The outcome of interest was participation in a clinical trial. A "clinical trial desert" was defined as $>$ 2 hour driving time to the nearest hospital enrolling patients in clinical trials. Multivariable analysis evaluated the association between living in a level 1 (most severe) USDA food desert census tract, a clinical trial desert, a census tract with high transportation vulnerability (households with limited access to a car or public transit), and breast cancer clinical trial participation. Interaction analysis was performed between food desert and clinical trial desert status. **Results:** Of 1,317,269 patients, 103,790 (7.9%) lived in a food desert, and 22,779 (1.7%) participated in a clinical trial. Patients living in a food desert comprised 6.2% of patients enrolled in a trial vs 7.9% of patients not enrolled, $p < .0001$. 41.0% of patients living in a food desert also resided in a clinical trial desert. On multivariable analysis, living in a food desert was associated with decreased odds of trial participation (aOR 0.87, 95% CI 0.82-0.92, $p < .0001$), as was living in a clinical trial desert (aOR 0.89, 95% CI 0.84-0.94, $p < .0001$), and living in the most vulnerable quartile for neighborhood transportation (aOR 0.89, 95% CI 0.85-0.93, $p < .0001$; ref: least vulnerable). Medicaid insurance also decreased the odds of enrollment (aOR 0.84, 95% CI 0.80-0.89, $p < .0001$; ref: private). Conversely, receiving care at an academic hospital increased the odds of enrollment (aOR 2.98, 95% CI 2.62-3.15, $p < .0001$; ref community hospital). Living in both a food desert and a clinical trial desert decreased the odds of clinical trial participation by 27% (aOR 0.73, 95% CI 0.70-0.76, $p < .0001$) compared to 19% if living in a food desert alone (aOR 0.81, 95% CI 0.78-0.84, $p < .0001$); $p < .0001$ for interaction. **Conclusions:** Neighborhood transportation barriers, clinical trial deserts, and food deserts all independently confer a similar lower likelihood of participation in a clinical trial. Living in a clinical trial desert compounds the negative impact of living in a food desert alone, further taxing already disadvantaged populations. Interventions such as patient navigation, food banks, and opening clinical trials near communities experiencing food insecurity may mitigate these challenges. Research Sponsor: None.

1526 Poster Session

Low-dose anti-PD-(L)1 inhibitor strategies: A systematic review. First Author: Pablo Jiménez Labaig, Head and Neck Unit, The Royal Marsden NHS Foundation Trust, London, United Kingdom

Background: Immune checkpoint inhibitors (ICIs) targeting the PD-(L)1 pathway have revolutionized cancer therapy, but their high costs significantly limit accessibility, particularly in low- and middle-income countries (LMICs). Low-dose regimens may offer a viable solution to this challenge. This systematic review analysed study designs, dosing strategies, clinical outcomes, and potential cost savings of low-dose ICIs. **Methods:** A PRISMA/EQUATOR compliant systematic search of WebOfScience, Cochrane Central Register of Clinical Trials, ASCO and ESMO conference databases was conducted until October 10th, 2024. Studies investigating reduced-dose anti-PD(L)1 from those FDA/EMA-approved regimens were included. Data were categorized by dose and country income level. **Results:** From 1,751 records, 25 studies (4 clinical trials, 21 observational studies) involving 1,793 participants met inclusion criteria, with 1,202 receiving low-dose ICIs. Two studies used non-inferiority designs, and 21 evaluated participants across multiple treatment lines. The population had a median age of 53.1 years (range 19–84), 26% female, 88% with advanced disease, and 9% ECOG $\geq$2. Most studies were conducted in Asia (81.4%, n = 1,459), with head and neck (22.8%, n = 409) and non-small cell lung cancers (17.3%, n = 311) being most studied. 48% studies were from LMICs, 44% from high-income countries (HIC), and 8% from upper middle-income countries (UMIC). India contributed the most (studies, *k*= 12, 839 participants). Nivo (*k*= 21), pembro (*k*= 6) and atezo (*k*= 1) were assessed. The most common regimens were Nivo40mg Q2W (*k*= 7), Nivo20mg Q3W (*k*= 6) and Nivo20mg Q2W (*k*= 5) [Table 1]. A radiological response rate between 5-75% was noted when low-dose ICI was used as monotherapy (*k*= 10). High variability in participant selection and interventions restricts further conclusions about efficacy and safety. The median projected savings were 83.3% (25–99.40%), with $\geq$70% savings in half of the studies. **Conclusions:** This review described the use of low-dose anti-PD(L)1 drugs, especially in healthcare settings with limited resources, highlighting radiological responses observed with monotherapy. Non-inferiority or near-equivalence randomized clinical trials will be helpful in establishing their clinical validity. Research Sponsor: None.

Tumor type (origin from participants assessed)	HNSCC n=409	NSCLC n=311	HCC n=93	RCC n=73	HL n=70	Multiple n=57	Melanoma n=56	Gastric/GEJ n=42	Gyne n=35	CCR n=30	Cervical n=20	Thymic n=6
LMIC	409			57		57		42		30	20	
UMIC					23							6
HIC		311	93	16	47		56		35			
Number of studies (k) assessing each dose per tumor	k: 6	k: 4	k: 2	k: 2	k: 3	k: 2	k: 1	k: 1	n: 1	n: 1	n: 1	n: 1
Nivo 0.3 mg/Kg Q2W											1	
Nivo 10 mg Q2W							2			1		
Nivo 10 mg Q8W							1					
Nivo 20 mg Q2W	1		2	1				1				
Nivo 20 mg Q3W	3	1		1								
Nivo 40 mg Q2W	1				3	2						1
Nivo 40 mg Q3W	3					1		1		1		
Nivo 40 mg Q4W				1								
Nivo 80 mg Q4W						1						
Nivo 100 mg Q2W			1	1	1							
Nivo 100 mg Q3W		1										
Nivo 100 mg Q4W	1											
Nivo 140 mg Q2W				1	1							
Pembro 1 mg/Kg Q3W		1										
Pembro 1 mg/Kg Q6W						1						
Pembro 50 mg Q3W									1			
Pembro 100 mg Q3W		3			1				1			
Pembro 300 mg Q6W		1										
Atezo 1 mg/Kg Q3W						1						

1527 Poster Session

Characterizing transportation need and missed visits among patients receiving radiotherapy. First Author: Kathleen Cui, University of California, San Francisco, San Francisco, CA

Background: Patients with cancer receiving radiotherapy (RT) are vulnerable to treatment interruptions, which affect oncologic outcomes. To prioritize program development for improved RT access, we aimed to characterize transportation need via standardized department screening and its association with missed RT visits. **Methods:** We prospectively identified a cohort of 552 consecutive patients with cancer who received RT at a single academic institution between September 2023 and March 2024, during which a quality improvement program for standardized transportation needs screening was implemented. Missed RT visits were determined computationally and counted if a patient did not arrive for a scheduled RT visit; these missed visits may have been due to pre-planned reasons, unplanned hospital admissions, or other logistical causes. Clinical data were extracted from the electronic medical record system. Univariable and multivariable logistic regression analyses were used to determine associations between demographic variables and transportation need. Fisher's exact test was used to compare missed RT visits between patients with varying social needs. **Results:** Median age was 66 years (IQR: 53.75-74). Most patients were English-speaking (85.1%), male (54%), and white (51.8%). Common planned transportation modes were driving (76.2%) and public transit (8%), as well as Veterans Affairs transportation, rideshare, and taxi. Of all patients, 26.4% missed $\geq$1 RT visit and 19.9% reported transportation need. Overall, 39.1% versus 23.3% of patients with versus without transportation need missed $\geq$1 RT visit ($p = 0.001$). Other social needs were found among 17.6% of patients, the most common being housing (80.3%). Of those with transportation need, 45.5% had additional social needs. Frequency of missed RT visits were similar between patients with sole transportation need (41.7%) and those with additional social needs (39.1%) ($p = 0.563$). On univariable analysis, there was increased transportation need among patients identifying as Asian (OR = 1.87, 95% CI 1.05-3.27, $p = 0.030$), Latinx (OR = 3.14, 95% CI 1.74-5.63, $p < 0.001$), unknown/declined race/ethnicity (OR = 2.84, 95% CI 1.29-5.99, $p = 0.007$), non-English speaking (OR = 3.01, 95% CI 1.80-4.98, $p < 0.001$), with Medicaid insurance (OR = 3.61, 95% CI 1.94-6.71, $p < 0.001$), and with Medicare insurance (OR = 1.81, 95% CI 1.11-2.97, $p = 0.019$). On multivariable analysis, Latinx (OR = 2.18, 95% CI 1.02-4.52, $p = 0.040$) and Medicaid versus private insurance (OR = 2.28, 95% CI 1.12-4.61, $p = 0.022$) were independent predictors of transportation need. **Conclusions:** Our findings support the utility of transportation screening as a tool for anticipating and providing resources to minimize missed RT treatments. Future initiatives toward improving RT access may benefit from proactive assessment and support of social needs, including but not limited to transportation. Research Sponsor: None.

1528 **Poster Session**

Disparities in breast cancer screening for the Brazilian Unified Health System (SUS): A warning of the need to change public policies. First Author: Ruffo Freitas-Junior, CORA – Advanced Center for Diagnosis of Breast Diseases Federal University of Goias, Goiania, Goias, Brazil

Background: Breast cancer is the most prevalent form of cancer in Brazilian women, contributing significantly to cancer-related mortality, particularly when diagnosed at advanced stages. Public policies of the Ministry of Health have been not changed for the last 2 decades. **Methods:** This ecological, temporal series study evaluated breast cancer screening coverage, clinical staging, and the time from diagnosis to treatment initiation in women of 40-49, 50-69 and 70 years of age in Brazil as a whole, its geographical regions, and states between 2013 and 2022. The data were extracted from databases of the Unified Health System (DATASUS). **Results:** There was a decreasing trend in screening coverage for the 40-49-year age group between 2013 and 2020 (APC = -10.79; $p < 0.001$), followed by stability in 2020-2022. Rates for the 50-69-year group remained stable, while coverage fell for women 70 years of age (APC = -6.27; $p < 0.001$) between 2013 and 2022. Cases of advanced stages at diagnosis tended to increase in all age groups: 40-49 (APC = 1.71; $p < 0.001$), 50-69 (APC = 1.43; $p < 0.001$) and 70 years (APC = 1.82; p = 0.001). Breast cancer screening coverage was low for all the age groups and all geographical regions, with lower rates found for the 40-49 and 70-year age groups. The poorest coverage was in the north, northeast and Midwestof the country, revealing regional disparities. The proportion of cases diagnosed at advanced stages (III/IV) increased,particularly in younger women (40-49 years) and the elderly (70 years). Time from diagnosis to treatment initiationexceeded 60 days in > 50% of cases in all age groups, with an increasing trend in women of 50-69 (APC = 1.27; $p < 0.001$) and 70 years of age (APC = 1.83; $p < 0.001$). **Conclusions:** This study highlightsthe urgent need for public policies to increase breast cancer screening coverage beyond the 50-69-year age group, and to guarantee equitable access to early diagnosis and timely treatment, particularly in less affluent areas. Dealing with these disparities is crucial to improving breast cancer outcomes in Brazil. Research Sponsor: None.

1529 **Poster Session**

Differences in insurance status among Asian Americans with cancer: A disaggregated analysis by ethnic subgroup. First Author: Lilac Nguyen, Memorial Sloan Kettering Cancer Center, New York, NY

Background: Asian Americans, the fastest-growing racial/ethnic group in the U.S., experience significant variation in barriers to cancer care access, yet most research treats them as a monolithic group. Insurance is crucial for accessing cancer care, but limited data exist on non-insurance rates among Asian Americans. This study investigates the heterogeneity in insurance status across Asian American subgroups in the context of common cancers. **Methods:** We analyzed data from the National Cancer Database (NCDB), and focused on breast, prostate, and non-small-cell lung cancers among patients under 65. Insurance status was dichotomized as non-insured/Medicaid versus private/government/Medicare/other, and binary logistic regression was used to calculate odds ratios (ORs) for insurance status by Asian American subgroups. **Results:** There were 2,161,947 patients with breast cancer, 603,172 with lung cancer, and 964,423 with prostate cancer. We found significant heterogeneity in insurance status among Asian American subgroups; such heterogeneity was mirrored across the three most common cancer types. Consistently, Japanese Americans were less likely to be uninsured or have Medicaid than White Americans (4.5%, 2.5%, and 12.2%, for patients with breast, prostate, and lung cancer, respectively, among Japanese-Americans vs. 10.2%, 5.5%, and 20.7% among White Americans, (odds ratio 0.54(95% CI: 0.47-0.61) for breast, 0.55(0.37-0.83) for prostate, 0.72(0.56-0.91) for lung), while every other Asian subgroup was significantly more likely to be uninsured or have Medicaid than White Americans (OR range 1.24 to 7.23 for breast, 1.25 to 10.42 for prostate, 1.12 to 6.39 for lung, all p-values <0.05 except for Laotians, Hmongs, and Thai with prostate cancer). Pakistani Americans were the group most likely to be uninsured or on Medicaid among patients with breast cancer (OR 7.22 (6.17-8.46) and prostate cancer (OR 10.41 (7.08-15.33) and were the second-most likely subgroup among patients with lung cancer (OR 4.82 (3.21-7.23). Hmong and Kampuchean were among the top three groups with breast or lung cancer who were uninsured or on Medicaid. **Conclusions:** Significant heterogeneity exists in insurance coverage among Asian American subgroups, which highlights the diversity of disparities Asian American patients face; these findings call into question the model minority myth, as every other Asian American subgroup besides Japanese-American was significantly less likely to be insured than White Americans. Asian American patients have broad differences in histories, social determinants of health, and barriers to accessing care, which may merit differentially targeted health interventions among certain subgroups. Research Sponsor: None.

1530 **Poster Session**

Breast cancer screening mammography among transgender and gender diverse (TGD) individuals: A nationwide study of >10,000 TGD individuals. First Author: Elizabeth Jane Cathcart-Rake, Mayo Clinic, Rochester, MN

Background: Regular breast cancer screening reduces mortality. The American College of Radiology (ACR) recommends annual screening mammography for asymptomatic, average risk 1) transgender and gender diverse (TGD) men (individuals assigned female sex at birth but identify as men) age 40+ and with residual breast tissue and 2) TGD women (individuals assigned male sex at birth but identify as women) age 40+ and on gender-affirming hormone therapy for 5+ years. This nationwide study investigated screening mammography in TGD individuals. **Methods:** Four cohorts were identified with complex algorithms of medical and pharmacy data in the OptumLabs Data Warehouse, a longitudinal, administrative insurance claims database that includes patients with commercial insurance and Medicare Advantage: 1) TGD men, 2) TGD women, 3) individuals with gender dysphoria not meeting other TGD criteria (NMOT), and 4) cisgender women – all of whom met ACR screening criteria. The primary endpoint was the percentage of individuals with high adherence, defined as completing >75% of recommended screenings; comparisons were made across the cohorts (Chi-square test). Multivariable logistic regression was used to compare adherence between TGD men and cisgender women with adjustment for demographics and with 1:4 matching (on race/ethnicity, age group, year of healthcare plan enrollment, and duration of follow-up). **Results:** 10,478 TGD individuals (3,778 TGD men; 1,294 TGD women; and 5,406 with gender dysphoria NMOT) and 6,218,369 cisgender women were identified. For TGD men, TGD women, individuals with gender dysphoria NMOT, and cisgender women, high adherence was observed in 41.1% (95% confidence interval (CI): 39.5, 42.6%); 7.4% (95% CI: 6.0, 8.8%); 11.9% (95% CI: 11.0, 12.7%); and 38.3% (95% CI: 38.3, 38.4%), respectively, $p < 0.0001$. No screening ever in these same populations was observed in 23.6% (95% CI: 22.2, 24.9%); 81.3% (95% CI: 79.2, 83.4%), 72.8% (95% CI: 71.6, 74%), and 35.9% (95% CI: 35.8, 35.9%), respectively, $p < 0.0001$. When TGD men were matched and compared to 15,112 cisgender women, a differential association was observed between gender and high adherence by age group ($p < 0.0001$); compared to cisgender women, the likelihood of high adherence in TGD men ages 40-49 (n = 2,472), 50-59 (n = 852), 60-69 (n = 320), and 70+ (n = 134) were as follows: odds ratios (OR's): 1.38 (95% CI: 1.28, 1.50), $p < 0.0001$; 1.57 (95% CI: 1.35, 1.81), $p < 0.0001$; 0.812 (95% CI: 0.619, 1.065), p = 0.1316; and 1.277 (95% CI 0.835, 1.951), p = 0.2595, respectively. **Conclusions:** This study found that TGD men manifest relatively high adherence to screening mammography, whereas TGD women and individuals with gender dysphoria NMOT manifest low adherence. Future research should focus on improving breast cancer screening in these underserved populations. Research Sponsor: National Institutes of Health, National Institute of Aging; K23 MD019644; National Institutes of Health, NCI; K07 AG076401.

1531 **Poster Session**

Implementation of an academic precision oncology service in a community setting. First Author: Junlone Moy, Eshelman School of Pharmacy, The University of North Carolina at Chapel Hill, Chapel Hill, NC

Background: Implementation of precision oncology (PO) in community practice remains challenging due to insufficient resources to order and interpret genomic test results. In 2023, our PO program (located at an academic hub) partnered with a community site to optimize clinical workflows around molecular testing and to provide documented expert review of testing results. To date, the service has reviewed over 150 cases. We undertook a retrospective review to determine the impact of our intervention on the rates of next generation sequencing (NGS) ordered at this site. **Methods:** Patients with visits to the community cancer center between 1/2022 and 7/2024 were screened for inclusion (n = 900). Eligible patients had an advanced/metastatic solid tumor and were managed at the community site. Patients were placed in the historical or interventional cohort based on the date that their cancer became advanced/metastatic relative to the service implementation (1/1/2023). Due to a historical lack of genomic data integration within the EHR, evaluation of NGS results and subsequent treatment required manual chart review. The study was approved by the IRB of the University of North Carolina. **Results:** We identified 109 historical patients and 76 interventional patients who met eligibility. NSCLC patients comprised the majority of the population (27%), followed by prostate (12%), breast (10%), and colon (7%) cancers. We observed a significantly increased rate of NGS testing in solid tumors after implementation of the service (40.4% versus 57.9% before and after, p = 0.0192). The rate of NGS testing within 30 days of diagnosis of advanced/metastatic disease also improved in the interventional cohort (21.1% versus 36.8%, p = 0.0187). The median time from first clinic visit to results was 20.5 days in those who were testing in the historical cohort versus 10.5 days in the interventional cohort. RNA transcriptome sequencing was used more frequently in the interventional cohort (40.9% versus 6.8%, p = 0.0003). **Conclusions:** Utilization of a PO program at an academic hub to support NGS testing at a community site resulted in increased testing rates and more timely access to results in advanced cancer patients. Although limited by sample size, the data emphasizes a continued need for infrastructure to support the application of PO in community settings. Research Sponsor: None.

	Historical *(Prior to 1/1/2023)*	Interventional *(After 1/1/2023)*	P-value
Rate of NGS testing in all patients	44/109 (40.4%)	44/76 (57.9%)	**0.0192**
Rate of NGS testing within 30 days of diagnosis	23/109 (21.1%)	28/76 (36.8%)	**0.0187**
Rate of NGS testing in NSCLC	15/24 (62.5%)	22/26 (84.6%)	0.109
Rate of blood-only NGS testing in those with results	27/44 (61.4%)	19/44 (43.2%)	0.0896
Rate of genome-informed therapy (all patients)	5/109 (4.6%)	8/76 (10.5%)	0.121
Rate of genome-informed therapy (NSCLC)	1/24 (4.2%)	4/26 (15.4%)	0.3508
Median time from clinic visit to NGS testing results	20.5 days	10.5 days	–––

1532 Poster Session

Development and fairness assessment of machine learning models for predicting 30-day readmission after lung cancer surgery. First Author: Atulya Aman Khosla, Department of Internal Medicine, William Beaumont University Hospital, Royal Oak, MI

Background: Predicting post-surgical readmissions is essential for improving patient outcomes and reducing healthcare costs. While machine learning (ML) models offer high predictive accuracy, they may perpetuate healthcare disparities if not rigorously evaluated for algorithmic bias. In this study, we examine the limitations of ML-based readmission prediction models, highlighting how bias can persist despite strong performance metrics. We also explore the impact of integrating fairness constraints to mitigate these disparities, ensuring equitable clinical decision-making across racial and ethnic groups. **Methods:** We analyzed National Surgical Quality Improvement Program (NSQIP) data (2016–2020) for 23,843 lung cancer surgery patients. Multiple ML models were developed using demographic, clinical, and laboratory variables. Model performance was assessed using standard accuracy metrics alongside fairness evaluations, including Demographic Parity and Equalized Odds, to measure disparities across racial groups. **Results:** The cohort had 56.5% females; 66.4% of cases belonged to the White race, 6.3% were Black, and 2.9% belonged to the Hispanic ethnicity. The median [Q1, Q3] was 69.0 [62.0, 74.0] years, and the overall readmission rate was 7.5%. The median operation time was higher among readmitted cases (171 minutes vs. 157.0; $p < 0.001$). However, there was no clinically significant difference between median [Q1, Q3] LOS between the two groups (4.0 [2.0, 6.0] vs. 4.0 [3.0, 7.0]; $p < 0.001$). The best-performing model (CatBoost) achieved high accuracy but showed disparities in prediction rates across racial groups (Demographic Parity Difference: 0.030, Equalized Odds Difference: 0.333) since the model disproportionately flagged Hispanic patients for readmission risk while potentially under-identifying risk in other groups. Significant predictors included operative time, preoperative sodium (139 vs. 140 mmol/L, $p < 0.001$), and COPD status (33.8% vs. 25.3%, $p < 0.001$). After implementing fairness constraints, the model maintained strong predictive performance while reducing demographic disparities, with selection rates balancing across racial groups (range: 0.51%-3.50%). **Conclusions:** Despite their high accuracy, ML models for predicting post-surgical readmissions can reinforce existing healthcare disparities. Our findings underscore the importance of fairness-aware modeling to mitigate bias, ensuring equitable clinical decision support. While fairness constraints improved demographic balance, residual disparities persisted, highlighting the need for ongoing scrutiny when deploying AI in clinical settings. This study emphasizes the critical need for continuous fairness evaluation in medical AI applications to prevent unintentional harm to vulnerable patient populations. Research Sponsor: None.

1533 Poster Session

Fall risk assessment by QTUG device in geriatric cancer patients on chemotherapy at a tertiary care hospital. First Author: Tilak Tvsvgk, Command Hospital (AF), Bengaluru, India

Background: Age-related changes, such as declines in muscle strength, balance, and coordination, are exacerbated by cancer and its treatments elevating the risk of falls. Cancer chemotherapy often lead to adverse effects which can increase fall risk. The consequences of falls in older cancer patients can be severe impacting the recovery process. The aim of the study was to estimate the baseline fall risk and frailty in geriatric patients and comparing the same after 03 cycles of chemotherapy and correlate the factors contributing to the increased risk. **Methods:** A prospective observational study enrolling elderly cancer patients, who are not bed-bound or using a limb prosthesis were enrolled. Patients with brain/spinal cord tumours were excluded. Fall risk assessment was done using the Kinesis Q-TUG device. Based on the scores the patients were classified into low-risk, moderate-risk and high-risk of falls. The fall risk assessment was repeated after three cycles of chemotherapy. **Results:** A total of 94 males and 122 females (n = 216) patients, 25% of whom were more than 70 yrs of age were enrolled. Overall the females were associated with higher fall risk and frailty compared to males. The combined fall risk estimates at baseline and post 3 cycles did not reveal a significant fall risk increase, however the timed-up-and-go (TUG) times were significantly lower post 3 cycles [Table-1]. The average stride length, stride velocity did not show any significant difference but the number of steps to turn increased post 3 cycles. Though the frailty did not show a significant difference, the correlation between fall risk and frailty showed a significant positive correlation (r = -0.91). **Conclusions:** While there was a slight increase in fall risk and frailty among geriatric cancer patients undergoing chemotherapy, these changes were not statistically significant. However, the decline in mobility underscores the adverse effects of chemotherapy on functional performance. The strong correlation between fall risk and frailty emphasizes the need for assessments and targeted interventions to mitigate fall risks. With increasing number of older adults with cancer, the findings advocate for enhanced monitoring and early management strategies to improve safety and outcomes for elderly cancer patients. Research Sponsor: None.

Characteristics of QTUG device in elderly cancer patients.

Parameter	Category	Median	IQR	Min	Max	P value
Combined Fall Risk (%)	**Pre**	49.18	73.44 - 31.53	11.78	79.46	0.098
	Post	47.75	60.28 – 36.15	13.96	84.64	
Combined Frailty Risk (%)	**Pre**	63.48	74.98 – 47.27	12.33	93.15	0.743
	Post	60.25	75.29 – 39.98	11.31	94.41	
TUG (s)	**Pre**	12	17 – 9.69	6.5	28.29	**0.002**
	Post	13.44	15.8 – 11.19	7.19	274.29	
Average Stride Velocity (cm/s)	**Pre**	93.73	105.67 – 73.37	48.31	135.67	0.062
	Post	95.73	115.23 – 77.29	54.22	132.66	
Time taken to turn (s)	**Pre**	2.78	3.4-2.24	1.10	36.32	**<0.001**
	Post	6.18	7.2-5.3	3.66	56.48	
Number of steps to turn	**Pre**	2.5	3-2	1	9	**<0.001**
	Post	3.5	4-3	2	10	

1534 Poster Session

APP-first as a strategy to increase new patient access and treatment of patients with gastrointestinal malignancies within a cancer center. First Author: Amalia Stefanou, H. Lee Moffitt Cancer Center and Research Institute, Tampa, FL

Background: Quality cancer care depends on timely and efficient evaluation of patients to determine next steps in treatment. To support this goal, we implemented a care delivery model where advanced practice providers (APP) were tasked with seeing new patients as an entry into the system, with a goal of completing testing and referrals prior to a subsequent visit with a surgical oncologist. **Methods:** A retrospective review was performed focusing on four hepatobiliary and pancreatic surgeons and their corresponding APP teams. The *APP-First* program was deployed in 2021. The purpose was to increase capacity and best prepare the patient's work-up prior to an appointment with the surgeon to facilitate treatment initiation. We compared NPs during two distinct time periods, before (7/2018-6/2020) and after (7/2022-6/2024) implementation of *APP First*. The primary outcome, impact on access, was determined by change in the number of NP seen by the group, and the secondary outcomes were number and proportion of patients receiving treatment at our institution. Patients were excluded if time to care was > 180 days or they received non-GI related care. Changes in outcomes of interest before and after implementation of the program were compared by Chi-square with significance set at p = 0.05. **Results:** A total of 2585 NPs were seen during the study period with 1797 beginning treatment at our facility (69.5%). During the pre-intervention period 1091 NPs were seen by the group, including 277 (25.5%) initially evaluated by an APP. Following the model implementation, 1494 NPs were seen, 915 (61.2%) by an APP and 579 (38.8%) by an MD ($p < 0.001$). There was no change in percent of NPs choosing to pursue care at our institution (68.7% vs 68.7%, p = 0.970), however after implementation, patients were more likely to be scheduled for operations after their initial visit (11.4% vs 14.3%, p = 0.031). **Conclusions:** Implementation *APP-first* led to increased NPs capacity translating into a 36.9% higher volume of NPs seen, without change in patient satisfaction as demonstrated by an unchanged percentage of patients choosing treatment at our institution. The established workflow within this model facilitated expedited care, resulting in higher proportion of patients treated and an increase in the number and proportion of patients receiving surgery. These data support the implementation of delivery of care models leveraging the role of APPs in a well-integrated system, with overall improved capacity, access, and treatment for patients with cancer. Research Sponsor: None.

Outcomes of APP-First program.

	FY 19-20 (n,%)	FY 23-24 (n,%)	*p* value
Total # NP	1,091	1,494	–
NP Distribution			
APP	277 (25.4)	915 (61.2)	**<0.001**
MD	814 (74.6)	579 (38.8)	
Treated			
Yes	750 (68.7)	1026 (68.7)	0.970
No	341 (31.3)	468 (31.3)	
Surgery	124 (11.4)	213 (14.3)	**0.031**
Chemotherapy	143 (13.1)	194 (13.0)	0.928
Endoscopy	376 (34.5)	466 (31.2)	0.080
Radiation	112 (10.3)	154 (10.3)	0.972

1535 Poster Session

Gender, place of death, and racial disparities in the reporting odds ratio of cardiovascular disease burden in leukemia across age groups (15–85) in the U.S.: A CDC WONDER disproportionality analysis. First Author: Tehmasp Mirza, Shalamar Medical and Dental College, Lahore, Pakistan

Background: Leukemia, a hematologic malignancy, often coexists with cardiovascular disease (CVD), worsening outcomes due to shared risk factors like diabetes, hypertension, and smoking. Despite CVD's known impact on leukemia mortality, research on demographic and geographic disparities remains limited. This study examines disparities in the Reporting Odds Ratio (ROR) of CVD burden among leukemia deaths across age, gender, place of death, and race/ethnicity using CDC WONDER data (1999–2020). **Methods:** A disproportionality analysis of CDC WONDER death certificate data for U.S. adults (15–85) was conducted. Records were grouped into four variables: leukemia deaths with CVD (A), leukemia deaths (B), CVD deaths (C), and all deaths (D). RORs were calculated as (A/B) / (C/D) and stratified by gender, race/ethnicity, urbanization, and place of death. Age groups were categorized into 15–24, 25–64, and 65+ years. Joinpoint regression was used to compute annual percentage change (APC) and average annual percentage change (AAPC) to identify trends. **Results:** Analysis of 22 years of data revealed disparities in RORs across demographics. The 15–24 age group had the highest ROR for males (2.51) and females (1.59), indicating a greater CVD burden in leukemia deaths than all-cause mortality. Middle-aged (25–64) and older adults (65+) had lower RORs (<1), suggesting a reduced CVD-leukemia burden in these groups. Trends: The young female cohort showed a sharp ROR decline (2018–2020, APC: -22.02%; 95% CI -36.00 to -1.23; p=0.039), while the elderly male cohort (85+) had a steady rise (APC: 6.93%; 95% CI 1.74–9.24; p<0.0001). Place of Death: Medical facilities had the highest CVD burden in leukemia deaths, especially in younger cohorts (15–24; ROR: 1.47). Hospice facilities had the lowest RORs across age groups. The "Other/Unknown" category had an outlier ROR of 4.81 in the youngest cohort, suggesting data limitations. Race/Ethnicity: Hispanics had the highest ROR (2.64) in the 15–24 age group, followed by Asians (2.21). In middle and older age groups, RORs declined for all races. Hispanics (65–74) showed an increasing ROR trend (AAPC: 0.92%; 95% CI 0.45–1.36; p=0.002). **Conclusions:** Significant disparities exist in CVD burden among leukemia deaths, with younger cohorts, males, Hispanics, and patients in medical facilities showing the highest RORs. These findings highlight the need for targeted cardio-oncology strategies to address CVD risk in leukemia patients. Further research on chemotherapy-related cardiotoxicity and healthcare disparities is crucial to reducing inequities and improving outcomes. Research Sponsor: None.

1536 **Poster Session**

Oncofertility practice patterns in NCCN cancer centers after the overturn of *Roe v. Wade*. First Author: Nikita V. Baclig, University of California Los Angeles, Los Angeles, CA

Background: The Supreme Court decision of *Dobbs v. Jackson* to overturn *Roe v. Wade* gave states authority to regulate reproductive health. This has led to concerns about access to assisted reproductive technologies used in oncofertility. The impact of this legal climate on oncofertility practices remains unknown. This study aims to understand how academic cancer centers across the United States have experienced changes in oncofertility care in a post-*Roe* world. **Methods:** In collaboration with the National Comprehensive Cancer Network (NCCN) Best Practices Committee, a survey was developed to evaluate changes in oncofertility access and utilization in the 2 years since the *Dobbs* decision. In July 2024, the survey was sent to NCCN Member Institutions, which represent 23 states with varied post-*Roe* protections for reproductive care. The survey responses were de-identified for analysis. Questions were both multiple choice and free response. **Results:** The survey was sent to 33 NCCN Member Institutions and yielded 24 responses (72.7%). A majority (83.3%) indicated that reproductive care was a moderate-high priority for their cancer center. Most (62.5%) reported an increase in the number of cancer patients receiving fertility preservation. According to the Center for Reproductive Rights, 13 institutions are in states that have restricted reproductive rights since the *Dobbs* decision. However, only 4 (16.7%) survey respondents reported that reproductive health laws had become more restrictive. The remaining reported that laws had not changed, were less restrictive, or abstained (83.3%). All 4 respondents who indicated more restrictive laws reported moderate-high priority placed on reproductive care and half reported an increase in cancer patients receiving fertility care. In the states that reported no or neutral change (n=14, 58.3%) or less restrictive laws (n=5, 20.8%), most (68.4%) reported an increase in patients receiving fertility care. One respondent who indicated more restrictive laws reported a decrease in resources for fertility care. Many centers have prioritized oncofertility by developing oncofertility programs, assigning fertility navigators, and creating electronic health record-assisted referral alerts and clinical pathways. **Conclusions:** Large academic NCCN Member Institutions, most in states with no change or less restrictive reproductive laws since the *Dobbs* decision, reported an increase in number of patients who accessed fertility care. Additional studies will clarify whether this reflects underlying trends or increased fertility care due to a fear of limited future access. Only a minority of the institutions in restrictive states responded to the survey and most who did reported similar or improved access to oncofertility care. The lack of response from restrictive states needs to be examined further as it may reflect concerns about oncofertility care in the new political landscape. Research Sponsor: None.

1537 **Poster Session**

Trade-off preferences in older adults with newly diagnosed acute myeloid leukemia. First Author: Kah Poh Loh, University of Rochester Medical Center, Rochester, NY

Background: Treatment decisions for older adults with acute myeloid leukemia (AML) are highly preference-sensitive, requiring a balance between survival and other important outcomes such as toxicities and quality of life (QoL). Understanding patients' trade-off preferences is critical for guiding personalized treatment planning. We examined the trade-off preferences of older adults newly diagnosed with AML and factors influencing these preferences. **Methods:** We collected data from two clinical trials evaluating an AML communication tool. Older adults completed questionnaires at diagnosis assessing trade-offs between survival and two key outcomes: a) maintaining QoL and b) treatment-related toxicities (nausea/vomiting, bedbound status, assistance with daily activities, worsening memory, and confusion). The survival-QoL trade-off was categorized as agree vs. disagree. Trade-offs for treatment-related toxicities were scored from 0 to 5, with higher scores indicating a greater willingness to endure toxicities for survival. We used binary logistic regression to identify factors associated with survival-QoL trade-off, while ordinal logistic regression was used for survival-toxicity trade-off. **Results:** We included 95 older patients with newly diagnosed AML; mean age was 73.7 (SD 7.6), 38% female, and 94% White. Approximately 37% received intensive and 54% received lower-intensity treatment. Only 15% prioritized survival over maintaining QoL, 39% neutral, and 46% prioritize maintaining QoL over survival (Table). Over 60% would decline treatments leading to confusion, and 45% would avoid treatments causing bedbound status. On multivariable analyses, patients enrolled with a caregiver had a significantly higher odds of prioritizing survival over QoL [Odds Ratio (OR): 5.92, p=0.04]. Employed patients were more likely to endure treatment-related toxicities for survival compared to those who were unemployed, retired or homemaker (OR: 7.76, $p<0.01$). **Conclusions:** Trade-off preferences among older adults with AML vary widely and are influenced by caregiving support and employment status. Actively eliciting these preferences is essential to align treatment decisions with individual patient values. Research Sponsor: Conquer Cancer Foundation Walther Cancer Foundation; American Cancer Society.

Preferences of older adults with AML.

I would like to try treatments for my cancer if they could help me live longer, even if it is very likely they would	Agree/ Strongly agree	Neutral	Disagree/ Strongly disagree
Have high level of side effects (e.g., nausea/vomiting)	60%	24%	16%
Make me require more assistance from family and friends with completing daily activities (e.g., shopping, managing money)	53%	22%	25%
Make me bedbound and unable to use the bathroom without assistance	35%	20%	45%
Make my memory worse	29%	29%	40%
Cause me to become confused often so that I am not aware of my surroundings	15%	23%	61%
Living longer is more important to me than maintaining my quality of life	15%	39%	46%

1538 **Poster Session**

OP-35: Does a tool designed to measure potentially preventable chemotherapy toxicities do so effectively? First Author: Ryan W. Huey, The University of Texas MD Anderson Cancer Center, Houston, TX

Background: OP-35 is a measure developed by the National Quality Foundation that the Center for Medicare and Medicaid Services (CMS) uses to evaluate the quality of care for patients undergoing outpatient chemotherapy treatment. Launched in 2021, it was intended to measure rates of potentially preventable complications of chemotherapy treatment. The tool assesses the rate of emergency department visits and admissions (EDV/A) visits for patients receiving outpatient intravenous (IV) systemic anti-cancer therapy (SACT) and defines potentially preventable by the presence of $\geq$1 of 10 diagnoses: anemia, dehydration, diarrhea, emesis, fever, nausea, neutropenia, pain, pneumonia, or sepsis. However, it is unknown if these diagnoses track truly preventable visits and therefore if it is a valid measure of quality. **Methods:** We conducted a retrospective review of patients who received outpatient IV SACT (the denominator for OP-35) at the University of Texas MD Anderson Cancer Center between January 2023 and December 2023. All patients who had an EDV/A were assessed to understand the primary and secondary diagnoses associated with their encounters. **Results:** The total number of patients included in the population who received outpatient IV SACT was 10,353. Of these, 2,401 (23.2%) had an EDV/A within 30 days of receiving outpatient IV SACT. Of patients with an EDV/A, 67% of patients had one EDV/A, 21% had 2, and 12% had $\geq$3. The most common diagnosis groups were pain (83%), anemia (69%), nausea (44%), and fever (35%). 82% of patients had more than one qualifying diagnosis. For 68%, the qualifying diagnosis was a secondary diagnosis. Of patients with a qualifying EDV/A, only 15% did not have a qualifying OP-35 diagnosis. **Conclusions:** While OP-35 was designed to measure potentially preventable chemotherapy-related complications, the exclusion of relatively few patients among those with an EDV/A suggests that a significant proportion of qualifying events may not truly be preventable. The qualifying diagnosis list may need to be tailored to exclude non-preventable admissions. This would improve the metric's specificity and validity as measure of care-quality. Future work should clarify which diagnoses lead to misclassification of non-preventable EDV/As. Research Sponsor: None.

Patients with qualifying EDV/A		N = 2,401
Type of Cancer	Solid Malignancy	2,020 (84%)*
	Heme Malignancy	383 (16%)*
Qualifying OP-35 Diagnosis	Pain	1,998 (83%)
	Anemia	1,652 (69%)
	Nausea	1,065(44%)
	Fever	833 (35%)
	Dehydration	679 (28%)
	Pneumonia	552 (23%)
	Neutropenia	509 (21%)
	Diarrhea	534 (22%)
	Sepsis	364 (15%)
	Emesis	148 (6%)
Number of EDV/A Per Patient	1	1,614 (67%)
	2	502 (21%)
	$\geq$3	285 (12%)

**Two patients categorized with both solid and heme malignancies.*

1539 **Poster Session**

Qualitative findings from providers and patients for planning implementation of screening clinical breast examination in Soweto, South Africa. First Author: Daniel O'Neil, Yale Cancer Center, Yale University, New Haven, CT

Background: Over 50% of South African women with breast cancer (BC) are diagnosed at stages III & IV. To inform an Implementation Mapping process to design strategies for implementing screening clinical breast exam (CBE) in primary care facilities in Soweto, South Africa, we gathered qualitative data from local primary care providers and patients on barriers to CBE and possible implementation approaches. **Methods:** We conducted semi-structured interviews with administrators, nurses, doctors, and community health workers (CHWs) and focus groups with women potentially eligible for screening CBE at four Soweto primary care facilities that do not offer BC screening. Our discussion guide explored BC screening perceptions among both groups. We also asked providers for recommendations about how to best implement a future CBE screening program, and we asked patients about factors that would motivate them to participate in such a program. We analyzed transcripts deductively in parallel with data collection. We organized themes using the Consolidated Framework for Implementation Research (CFIR). To support Implementation Mapping's emphasis on addressing the needs of individual stakeholders, our analysis focused on the CFIR Individuals domain and Characteristics subdomain taken from the COM-B system. **Results:** We analyzed 27 interviews with 8 administrators, 1 medical officer, 14 nurses, 3 CHWs, and 1 clerk, and 4 focus groups with 23 total women. Providers (*i.e.,* deliverers) and patients (*i.e.,* recipients) alike expressed enthusiasm for CBE's potential to decrease BC mortality and morbidity. Both groups also cited CBE's potential to overcome and counteract patients' limited knowledge of breast health and BC symptoms. The primary barrier to CBE, according to both groups, is the high patient volume at public facilities. Providers described staff shortages limiting opportunity to perform CBE and patients cited long wait times as a barrier to pursuing "extra" services. Providers often recommended hiring new personnel designated for CBE screening. Patients suggested various approaches to expanding access, such as screening in both the clinic and community, opportunistic screening while patients wait for other clinic services, and walk-in access for "screening only" visits. Patients also emphasized the need to improve trust in the clinics and their staff. Regarding educational outreach, providers focused on expert-delivered teaching in both the clinic and community. Patients valued experts but also recommended engaging BC survivors and other community members to promote screening through word-of-mouth. **Conclusions:** Soweto's primary-care clinicians and patients expressed enthusiasm for the health benefits of BC screening, but successful implementation must address barriers faced by both groups, including long clinic wait times and personnel shortages. Research Sponsor: National Cancer Institute.

1540 Poster Session

Development of an early sepsis treatment-decision algorithm in children and adolescents with cancer in a middle-income country: Results from a multinational modified Delphi consensus. First Author: Paula Aristizabal, Division of Hematology/Oncology, Department of Pediatrics, University of California San Diego and Rady Children's Hospital-San Diego and University of California San Diego Moores Cancer Center, San Diego, CA

Background: Despite global efforts, striking childhood cancer survival gaps between low- and middle-income countries (LMIC) and high-income countries persist. Based on data from the Colombian childhood cancer clinical outcomes surveillance system, VIGICANCER, sepsis accounts for approximately 90% of all preventable deaths. In response, we developed a consensus-based Treatment-Decision Algorithm (TDA) for early sepsis detection and treatment, adapted to the local context and balancing optimal clinical management and resource utilization. **Methods:** We used RAND/UCLA Delphi method (preparatory phase, literature review, rating) to consult experts on the appropriateness of the proposed risk/alert definitions, critical steps, evidence-based interventions, and decision-making trees in the adapted TDA. Consensus involved: a) Pilot anonymous voting on a 22-statement online survey (5-point Likert scale, open-ended questions); b) Reading/rating in a hybrid meeting (in-person/virtual); and c) Voting on statements where consensus was not reached. Consensus was defined as: ≥70%, strong; 51%-69%, moderate; ≤50%, no consensus. **Results:** Preparatory phase and literature review: A multinational (Colombia, Mexico, US), interprofessional panel of 19 members, including from pediatric cancer centers and academic societies (oncology, emergency medicine, hospital medicine, critical care, infectious diseases, nursing) ensured geographic and resource representation. A Colombian internal expert taskforce (n = 6) completed a comprehensive literature review, met biweekly, and developed the *Colombian Protocol for Early Sepsis Detection in Children with Cancer* and accompanying TDA with 3 domains: sepsis screening, sepsis huddle, and early treatment. Consensus results: a)Pilot(n = 19 members), strong agreement was obtained for 81% of statements in one round; b) Reading/rating (n = 8 members), strong agreement was reached in 90% of statements after two rounds; and c) Voting on statements without consensus (n = 11 members, online), moderate agreement was reached in 100% of statements (2) in one round. **Conclusions:** Through collaborative consensus, we successfully developed an evidence-based, user-friendly TDA for early sepsis detection and treatment, tailored to resource-constrained settings. The diverse, interprofessional panel facilitated contextual adaptations of the TDA. The proposed TDA provides clinicians serving children with cancer in Colombia with an easy-to-follow TDA that is clear, exhaustive, and suitable for adaptation to individual local settings. Next steps involve applying improvement science methodology to implement the TDA in Colombia and Mexico and evaluating its predictive value for prompt sepsis detection in children with cancer, contributing to reduction of survival gaps in LMIC. Research Sponsor: None.

1541 Poster Session

Impact of the eSyM symptom monitoring program on nurse telephone encounters across six cancer centers. First Author: Michael J. Hassett, Dana-Farber Cancer Institute, Boston, MA

Background: After developing an ePRO-based, EHR-integrated symptom monitoring program (eSyM) and implementing it across 6 health systems, we found lower odds of acute care utilization among those who used eSyM to report symptoms. Facilitating communication between patients and clinicians is a potentially important mechanism by which symptom monitoring programs may improve outcomes. We measured the association between eSyM deployment, symptom reporting and severe symptom reporting on the frequency and number of nurse telephone encounters (TELs). **Methods:** eSyM was deployed in a stepped wedge RCT from 2018-2023 for adults who started chemotherapy (CHEM) or were discharged following surgery (SURG) for a suspected or confirmed GI, GYN or thoracic cancer. We analyzed three cohorts: 1) for all patients, we compared those treated before vs. after eSyM deployment; 2) for post-deployment patients (eSyM eligible), we compared those who did vs. did not report symptoms within 30 days of first eSyM prompt; and 3) for symptom reporters (eSyM users), we compared those who did vs. did not report severe symptoms. Outcomes of interest were the proportion of patients with at least one TEL and total number of TELs within 30 days of first eSyM prompt. Poisson regression was used to estimate the number of TELs within 30 days accounting for cancer and treatment type, as well as age, gender, and other factors. **Results:** In total, 18,830 patients were and 21,112 were not exposed to eSyM (median age 64, 66% female). Among eligible patients, 8,298 (44%) reported symptoms within 30 days. Among eSyM users, 3,666 (44%) reported one or more severe symptoms within 30 days. The proportion of patients with TELs and the number of TELs per patient are below (Table). In regression analyses, there were more TELs within 30 days after eSyM deployment (SURG 0.09 [95%CI 0.07-0.11; P < .0001], CHEM 0.26 [95% CI 0.23-0.28; P < .0001]) and among severe symptom reporters (SURG 0.42 [95%CI 0.38-0.45; P < .0001], CHEM 0.43 [95% CI 0.38-0.48; P < .0001]). **Conclusions:** eSyM exposure and reporting severe symptoms were associated with a greater likelihood and larger number of TELs, supporting nurse intervention as a mediator of the association between ePRO monitoring and clinical outcomes. Future studies should explore the impacts of ePRO systems on nursing workload and health system costs. Clinical trial information: NCT03850912. Research Sponsor: National Cancer Instiute; 1UM1CA233080-01.

Cohort	Treatment	% patients reporting within 30 days, P value			Mean number of TELs among those with at least one TEL (SD), P value		
All patients		Control	Intervention		Control	Intervention	
	Surg	63%	69%	<.0001	2.6 (2.5)	2.9 (2.5)	<.0001
	Chemo	60%	79%	<.0001	3.9 (3.6)	4.0 (3.5)	0.08
eSyM eligible		Non-reporter	Reporter		Non-Reporter	Reporter	
	Surg	66%	71%	<.0001	3.0 (2.6)	2.9 (2.4)	0.23
	Chemo	77%	81%	<.0001	4.1 (3.6)	3.9 (3.4)	0.04
eSyM users		No severe symptoms	Severe symptoms		No severe symptoms	Severe symptoms	
	Surg	67%	77%	<.0001	2.6 (2.1)	3.3 (2.7)	<.0001
	Chemo	76%	89%	<.0001	3.4 (3.0)	4.5 (3.5)	<.0001

1542 Poster Session

Cost and resource utilisation for liquid biopsy vs tissue biopsy genotyping in advanced NSCLC: A micro-costing model. First Author: David O'Reilly, Beaumont RCSI Cancer Centre, Dublin, Ireland

Background: For patients with advanced non-small cell lung cancer, tumour genotyping identifies actionable variants that inform targeted therapeutic choices, that improve outcomes. Liquid biopsy genotyping (LBG) is a non-invasive approach to tissue biopsy genotyping (TBG) that reduces turnaround, avoids repeat tissue biopsy, and can identify additional actionable variants. However, despite these benefits, patient access to LBG is not universal in a range of healthcare systems. While others have developed models evaluating the cost-effectiveness of LBG, these have are limited by assumptions regarding frequency of oncogenic variants and treatment utilisation. We utilised a micro-costing model (MCM) to quantify the cost/resources of LBG and TBG in a prospective trial (*PLAN;* ClinicalTrials.gov Identifier: NCT05542485) aimed at investigating the feasibility of LBG in a tertiary cancer centre. **Methods:** A deterministic MCM was developed to enumerate the cost to generate a genomics report for both LBG and TBG in NSCLC. Capital costs were calculated based on up-front investment and annual depreciation/maintenance. Costs of consumables and staff time associated with each procedure was sourced from relevant hospital departments (e.g. Medical Physics) and evaluated for accuracy by a health economist and medical oncologist. We calculated the cost of sample acquisition (endobronchial ultrasound-guided biopsy or phlebotomy), processing, and genotyping for both LBG and TBG, from patients enrolled on the *PLAN* study (n = 100) between 08/2023-07/2024. Finally, we performed an exploratory analysis investigating potential reduction in staff time associated with automated library preparation, using currently available technology. **Results:** We identified that TBG requires more staff time (€534 vs €330), capital investment (€326 vs €16), and consumables (€1544 vs €788), resulting in an overall increased cost, compared with LBG (€2404 vs €1135). Automation of library preparation would reduce staff time required for LBG (Reduced to €191; 33% reduction) with less of an impact on TBG (Reduced to €485; 10% reduction). This difference was due to the increased wet-lab time with LBG and greater staff time for sample acquisition in TBG vs LBG (€298 vs €8). Finally, in the *PLAN* study, LBG resulted in cancellation of 12 repeat tissue biopsies, resulting in further savings. **Conclusions:** LBG is a cheaper alternative to TBG. Our data indicates LBG saves cost in the areas of healthcare staffing and capital infrastructure with further savings made through avoidance of repeat tissue biopsies. Thus, the resources required for LBG and TBG are different and should be considered in service planning for tumour types such as NSCLC in which genotyping is standard-of-care. Clinical trial information: NCT05542485. Research Sponsor: AstraZeneca; Amgen; Novartis; Irish Cancer Society; Charitable Infirmary Charitable Trust.

1543 Poster Session

Impact of a collaborative care-based symptom intervention model on chemotherapy adherence in patients with breast cancer. First Author: Michael H. Storandt, Mayo Clinic, Rochester, MN

Background: Treatment toxicity may limit the ability of cancer patients to receive all recommended cycles of therapy. Four to six cycles of docetaxel plus cyclophosphamide (TC) is a common adjuvant chemotherapy regimen for early-stage breast cancer. We assessed the impact of routine collection of patient-reported outcomes (PROs), coupled with a collaborative care model-based symptom management intervention, on the number of cycles of TC received by patients with breast cancer. **Methods:** The Enhanced, EHR-facilitated Cancer Symptom Control (E2C2) trial was a cluster-randomized, pragmatic clinical trial, conducted between March 2019 and January 2023 at Mayo Clinic Rochester and within the Mayo Clinic Health System in Minnesota and Wisconsin. Patients regularly reported the severity of 6 SPPADE symptoms (Sleep deficit, Pain, Physical function impairment, Anxiety, Depression, and Energy deficit/fatigue) on 11-point numerical rating scales. Each symptom score was interpreted as none to mild (0-3), moderate (4-6), or severe (7-10). The E2C2 intervention included symptom management education modules, clinician decision support aids, and the option to discuss severe symptoms with a nurse, physical therapist, or social worker. Patients with breast cancer who received at least one cycle of TC were included in this analysis. We compared the number of cycles of docetaxel and cyclophosphamide completed by patients in the control condition versus those in the intervention condition. **Results:** We identified 198 patients with breast cancer who received TC during the control condition and 128 who received TC during the intervention condition. Median age was 61.3 years in the control group and 60.3 years in the intervention group, and 94% and 95% were white, respectively. Those receiving treatment during the control condition, on average, completed 3.53 cycles of docetaxel, while those receiving TC during the intervention condition completed 3.77 cycles (p = 0.014). Seventy-eight percent in the control group completed at least 4 cycles of docetaxel, compared to 84% in the intervention group. Those receiving TC during the control condition completed an average of 3.71 cycles of cyclophosphamide, compared to 3.78 cycles in the intervention condition (p = 0.231). Eighty-four percent of patients in the control group and 86% in the intervention group completed at least 4 cycles of cyclophosphamide. **Conclusions:** Routine PRO surveillance, coupled with guideline-based collaborative care interventions, was associated with completion of a greater number of cycles of docetaxel. These findings suggest that routine symptom surveillance and management may enhance the docetaxel tolerance profile and improve treatment adherence in patients with early-stage breast cancer, allowing for delivery of an optimized treatment course. Research Sponsor: NCI of the National Institutes of Health; UM1CA233033 (PI Cheville, Mayo Clinic, Rochester, MN).

1544 Poster Session

Successful accrual of a cluster randomized controlled trial (RCT) comparing an educationally enhanced genomic tumor board (EGTB) intervention to usual practice (S2108CD, NCT# 05455606). First Author: Meghna S. Trivedi, Herbert Irving Comprehensive Cancer Center, Columbia University Medical Center, New York, NY

Background: Observational studies show genomic tumor boards (GTBs) can enhance clinician knowledge and application of genomic tumor test (GTT) results. An RCT is needed to evaluate the impact of GTBs on treatment and outcomes. Conducting such a trial requires physician engagement and recruitment of an unbiased study population over a short period of time due to rapid changes in cancer genomics. S2108CD prospectively evaluates the impact of an educationally enhanced GTB (EGTB) intervention through a cluster RCT design across rural and community oncology practices in the United States. **Methods:** Recruitment Centers (RCs) were selected from the NCI Community Oncology Research Program (NCORP) with a focus on rural and minority/underserved (RMU) sites and cluster randomized 1:1 to EGTB intervention (virtual GTB and physician educational materials) versus usual practice (UP). Oncologists and their patients with advanced solid tumors who had GTT ordered were enrolled. The primary aim is to compare the proportion of patients receiving evidence-based genome informed therapy by arm. Here, we describe accrual and baseline characteristics of the RCs and the enrolled physicians and patients. **Results:** Between 8/2022 and 11/2024, 18 RCs were randomized to UP versus EGTB intervention. A median of 5 clinics (range, 1-13) comprised each RC. Six RCs were classified as RMU in each arm (n = 12). Overall, 121 physicians registered to the study and they registered 1284 patients (median 47.5 patients/month), of which 983 (77%) were registered at RMU RCs. In the UP arm, 614 patients and 61 physicians registered, and in the EGTB arm, 670 patients and 60 physicians registered (demographics of registered patients in table; unknown race/ethnicity [3%] not shown), meeting accrual goal within target timeframe. The 3 most common patient neoplasms were lung, mediastinal and pleural (n = 352, 27.4%), gastrointestinal (n = 344, 26.8%), and breast (n = 152, 11.8%). **Conclusions:** Timely accrual to S2108CD demonstrates the feasibility of conducting a cluster RCT to evaluate an EGTB intervention. There was high participation of RMU sites with a study population reflecting cancer types relevant for GTT; however, there were fewer than anticipated non-White and Hispanic patients registered. Study endpoint data are currently maturing. The final analysis of S2108CD will be conducted and reported in 2026. Clinical trial information: NCT05455606. Research Sponsor: NIH/NCI/NCORP; UG1CA189974; The Hope Foundation for Cancer Research.

Patient characteristic		Overall (N=1284, %)	UP (N=614, %)	EGTB (N=670, %)
Age, median (range)		67.7 (20.3, 96.7)	67.6 (20.3, 96.7)	67.7 (22.4, 94.2)
Sex	Female	646 (50)	325 (53)	321 (48)
Race	American Indian or Alaska Native	10 (1)	4 (1)	6 (1)
	Asian	56 (4)	51 (8)	5 (1)
	Black or African American	88 (7)	26 (4)	62 (9)
	Native Hawaiian or other Pacific Islander	23 (2)	23 (4)	0(0)
	White	1047 (82)	490 (80)	557 (83)
	Multiracial	25 (2)	8 (1)	17 (3)
Ethnicity	Hispanic	106 (8)	25 (4)	81 (12)

1545 Poster Session

Electronic patient-reported outcomes with vital sign monitoring versus usual care during trastuzumab deruxtecan treatment for metastatic breast cancer: Updated results from the PRO-DUCE study. First Author: Yuichiro Kikawa, Department of Breast Surgery, Kansai Medical University Hospital, Hirakata, Japan

Background: The PRO-DUCE study (jRCTs031200387), a multicenter, randomized controlled study, evaluated the impact of ePRO plus body temperature (BT)/SpO_2 monitoring (ePROm) vs.usual care (UC) on the quality of life (QoL) for patients (pts) with HER2-positive metastatic breast cancer (MBC) treated with T-DXd. The primary results presented at ASCO 2024 showed that at week 24, ePROm demonstrated better results for global health status (GHS) vs. UC. Based on recent studies showing that symptom monitoring and alert notifications via ePROs could improve pt QoL and overall survival (OS), we consider the effects of long-term QoL scores and OS. **Methods:** The pts population was observed from March 1, 2021, to February 29, 2024 (data cutoff date: May 20, 2024). We randomized pts with HER2-positive MBC eligible for T-DXd to the ePROm or UC group. ePROm involved weekly reporting of symptoms based on PRO-CTCAE and daily monitoring of BT and SpO_2 reports via a smartphone at home. If any reported symptoms exceeded the predetermined thresholds, an email alert was sent to the medical staff; the ePRO data were then reviewed, and, if necessary, a phone consultation was provided. Endpoints in this updated analysis included QoL scores and cancer-related fatigue beyond week 24 using the EORTC QLQ-C30 (C30) and EORTC QLQ-FA12 (FA12), OS, and safety. **Results:** Between March 2021 and January 2023, 111 pts were enrolled (ePROm: 56; UC: 55). Throughout the observation period, 1045 alert notifications were generated, of which 279 were considered necessary to contact pts and 231 telephone counseling was conducted by healthcare providers (response rate: 82.8%). Throughout 48 weeks, the PRO-CTCAE response rate was $>$ 89% in the ePROm group. The number of evaluable pts at 48 weeks was 37 in the ePROm and 41 in the UC group. At week 48, changes in GHS from baseline in the ePROm and UC groups were -3.7$\pm$18.6 and -12.7$\pm$23.8, and those in FA12 total score were -4.9$\pm$14.3 and 8.1$\pm$16.4, respectively. The median OS was 24.5 months (95% CI: 21.8, not reached) in the ePROm group with a median follow-up duration of 18.3 months, whereas in the UC group, the median OS was not reached (95% CI: 20.7, not reached) with a median follow-up duration of 18.1 months [HR = 1.39; 95% CI: 0.75, 2.59]. The majority of any-grade treatment-emergent adverse event using CTCAE were reported in a higher proportion of pts in the ePROm group than in the UC group during the observation period. Interstitial lung disease incidence was similar in both groups (7.4% in ePROm group vs. 9.3% in UC group), with all cases being grade 1. **Conclusions:** Long-term findings from the PRO-DUCE study demonstrated that QoL observed at week 24 in the ePROm group was maintained over time. While there was no difference in OS, these findings might support the integration of ePROm in clinical practice to optimize QoL for pts receiving T-DXd. Clinical trial information: jRCTs031200387. Research Sponsor: Daiichi Sankyo.

1546 Poster Session

Advancing equity and collaboration in a dedicated young onset cancer clinic: A prospective study. First Author: Ilit Turgeman, Lin Medical Center, Haifa, Israel

Background: Coordinated young onset cancer (YOC) clinics improve patient experience and access to supportive services. However, geographic and ethnic disparities hinder equitable representation and outcomes. This study describes the design and impact of a YOC clinic serving a socioeconomically diverse population. **Methods:** A YOC clinic was established at a peripheral cancer center for patients aged 18-49, staffed with an oncologist, nurse, and social worker. Tailored referrals were facilitated to designated psychosocial and integrative services. Monthly team meetings and biweekly patient support activities were implemented. Data on demographics, cancer characteristics, coping styles (BASIC-Ph model), anxiety and depression (HADS-A/D), referral patterns and satisfaction were prospectively collected and analyzed across ethnic and clinical subgroups. **Results:** From 6/2022 - 4/2023, 104 patients enrolled (mean age 38; 76% female; 62.4% Jewish, 34.7% Arab). Most were married (63.5%), had children (81.4%), unemployed (72.3%), with up to high school education (50.7%). Most (76%) were on active treatment and 38% had metastatic disease. Breast cancer was most common (46.2%), followed by gastrointestinal and thoracic malignancies. Family cancer history (61.5%) actionable somatic (25%) and germline (6.7%) alterations were noted. Referrals were most frequent for integrative medicine (50%), genetics (41.3%), psychology, occupational therapy, with adherence rates of 88%. Ethnic and cancer-type variations in referral patterns were observed, but high uptake was consistent. HADS-A correlated with lack of exercise and HADS-D with unemployment and non-metastatic disease ($p < 0.05$). Females tended more to belief-based coping, males favored imagination, academics employed cognitive strategies, alcohol use to affect and cannabis to imagination ($p < 0.05$), while those with advanced cancer preferred physical coping (p = 0.82). HADS-A correlated with psychology referrals (M = 9.78 vs. 6.86, p = 0.013), belief-based coping to spirituality, social coping to physiotherapy and nutrition ($p < 0.05$). Social coping and sexuality services were less utilized in ethnic minorities and those on active treatment. Nearly all (94.2%) had no prior support group yet satisfaction was high (mean 5/5) with patients citing community, supportive services and side effect management as key benefits. **Conclusions:** A structured, multidisciplinary YOC clinic leverages existing services to enhance collaboration, equity, and access to tailored resources, meeting the unique needs of diverse young cancer patients. Beyond addressing disparities, this model fosters a sense of community among patients, promoting engagement with supportive services that may enhance treatment outcomes. Sharing this approach globally may inspire broader adoption of YOC clinics to benefit underserved populations and advance cancer care equity. Research Sponsor: None.

1547 Poster Session

Automated conversational artificial intelligence (AI) for outpatient malignant bowel obstruction (MBO) symptom monitoring. First Author: Ainhoa Madariaga, Hospital Universitario 12 de Octubre, Madrid, Spain

Background: MBO is a severe complication of advanced cancer. A Canadian ambulatory MBO program with nurse-led proactive call management demonstrated reduced hospitalization rates and improved survival. To overcome resource limitations, a smartphone app was developed, achieving 65% adherence. Building on this foundation, automated phone calls offer a promising approach to enhance adherence and improve symptom monitoring. **Methods:** We conducted a prospective pilot study at a tertiary Spanish hospital to remotely monitor MBO signs and symptoms using a conversational AI-based platform (Lola-Tucuvi). Patients (pts) with cancer with an active MBO or at risk of developing it (per PMMBO criteria) were enrolled. Automated, interactive phone calls were performed by the platform (Lola) weekly or biweekly. Lola performed structured MBO symptom assessments utilizing advanced natural language processing and AI algorithms, to analyze responses in real time. Alerts were generated for moderate or severe symptoms, which were flagged on a dashboard. Nurses contacted pts based on alerts. The primary objective was feasibility measured by adherence (% of answered calls), with a hypothesized adherence of $\geq$65% considered optimal. **Results:** From January 2024 to January 2025, 54 pts were enrolled, with 25 still active at the time of analysis. Median age was 60 years (range 29-86), and 96% of pts are female. Type of tumors included gynecologic (87%) and gastrointestinal (13%). All pts were on systemic therapy: chemotherapy (50%), immunotherapy (24%), ADC (15%), targeted (11%). Median prior lines of therapy were 2 (1-6), and 41% (22/54) of pts had an active MBO prior to enrollment. Lola performed 716 phone calls and 645 were answered, with an adherence of 90%. This resulted in an estimated 183.2 hours of nursing call time saved. Median time on the program was 117 days (7-356), and pts received a median of 14 calls. Of answered calls, the 36% (234/645) generated alerts, with 44% classified as severe. Most frequent severe and moderate alerts were constipation and abdominal pain, respectively. Nurses acted on 73% (171/234) of the alerts, providing interventions such as dietary modifications, medication adjustments, clinical or emergency assessments. During follow-up in the program 31.5% (17/54) of pts had $\geq$1 active MBO and 18.5% (10/54) required admissions for MBO. Feedback was received from 26 pts, indicating a high satisfaction (4.6/5), and 96% would recommend the use of Lola. **Conclusions:** This conversational AI platform demonstrated excellent feasibility with 90% adherence, higher than prior app-based solutions. It effectively monitored MBO symptoms, enabling timely clinical interventions and enhancing patient engagement. These results highlight the potential of AI-driven remote monitoring system to improve outcomes in cancer care. Further validation through randomized studies is warranted. Research Sponsor: Spanish Society of Medical Oncology (SEOM).

1548 **Poster Session**

Oncologists' perspectives on challenges using chemotherapy, immune checkpoint inhibitors, and targeted kinase inhibitors for metastatic cancer. First Author: Christine M. Veenstra, University of Michigan, Ann Arbor, MI

Background: Compared to cytotoxic chemotherapies, the standard of care for metastatic cancers for decades, use of immune checkpoint inhibitors (ICI) and targeted kinase inhibitors (TKI) has rapidly expanded with evolving indications for patients with advanced disease. We evaluated oncologists' report of challenges to using each type of therapy and associations between challenges and oncology practice resources. **Methods:** From 2023-24 we surveyed 824 medical oncologists, identified using SEER registry data, in Georgia and Los Angeles. We asked oncologists about challenges to using chemotherapy, ICIs and TKIs for the treatment of metastatic cancer. We also asked about resources available at their practice, including administrative and clinical support staff, financial counselors, dedicated pharmacists, social workers, genetic counselors, and interpreters. We generated descriptive statistics of challenges and assessed bivariate associations between challenges and practice resources. **Results:** We present results for a preliminary sample (N = 370). The Table shows the proportion of oncologists who endorsed each challenge. Compared to cytotoxic chemotherapy, oncologists were more likely to endorse moderate to big challenges using ICIs and TKIs related to insurance approval/prior authorization, co-pay assistance and out-of-pocket costs, as well as keeping up with clinical guidelines and familiarity with dosing and side effects; symptom management was more likely to be a moderate to big problem for chemotherapy and TKIs than for ICIs (all $p < 0.01$). Challenges with insurance approval/prior authorization, co-pay assistance, and out-of-pocket costs were associated with the availability of administrative and clinical support staff, dedicated pharmacists, and social workers (all $p < 0.05$). Challenges with symptom management were associated with the availability of clinical support staff and dedicated pharmacists (all $p < 0.05$). **Conclusions:** Oncologists endorsed more challenges using ICIs and TKIs compared to cytotoxic chemotherapy in the treatment of metastatic cancer. TKIs were associated with the most challenges, including problems keeping up with clinical guidelines and familiarity with dosing and side effects for nearly 20% of respondents. It is reassuring that many practice resources exist to help address these challenges. Oncologists may benefit from more educational resources—particularly related to TKIs—in their practices. Research Sponsor: National Cancer Institute; CA251464.

Oncologist-reported challenges.

	% reporting moderate to big challenge			
	Cytotoxic chemotherapy	ICI	TKI	P
Obtaining insurance approval/prior authorization	13	26	35	<0.01
Obtaining co-pay assistance for patients	19	27	43	<0.01
Out-of-pocket costs to patients	25	42	66	<0.01
Symptom management	50	17	43	<0.01
Keeping up with clinical guidelines	7	14	19	<0.01
Familiarity with dosing and side effects	6	7	17	<0.01

1549 **Poster Session**

Improving access to cancer screening through national telehealth-based lung and colorectal cancer screening programs. First Author: Deanna Brockman, Color Health, Burlingame, CA

Background: Access to routine cancer screening remains a significant barrier to early detection, especially among historically underserved populations. However, little is known about how virtual care can improve access to cancer services. Color and the American Cancer Society (ACS) collaborated to develop two community-based, telemedicine programs for national colorectal and lung cancer screening. Here we evaluate the impact of these programs in expanding access. **Methods:** The Colorectal Cancer (CRC) Screening Program (launched in June 2025) provides at-home fecal immunochemical tests (FIT) to eligible individuals aged 45-75 years. Kits are distributed through federally qualified health centers and other community locations. The Lung Cancer Screening Program (launched in November 2023) offers eligible individuals access to scheduling support for low-dose screening CTs based on ACS guidelines. Both programs leverage a virtual-first approach: patients provide health history information for a cancer risk assessment through an online platform where they can also access educational resources and schedule appointments with physicians to discuss cancer risk (note: screening eligibility is determined based on self-report). Care advocates provide personalized support, including step-by-step guidance on completing tests, navigating screening guidelines, and coordinating follow-up care. **Results:** Across both cancer screening programs (n = 548), participants were predominantly female (CRC: 62.0%; lung: 62.9%) and had similar average ages (CRC: 50.3 years, range 18-90; lung: 53.9 years, range 18-81). In the CRC screening program, 397 participants picked up or requested kits, with the highest demand in California (10.1%), Texas (9.1%), and Florida (7.1%). In total, 126 participants were eligible and activated a kit; participant ineligibility was largely due to already being up-to-date with screening (29.1%) or age (28.5%). Of the 94 completed tests, 4 (4.3%) were abnormal results. In the lung cancer screening program, 71 participants (47%) across 28 states met ACS eligibility criteria; the remaining participants were ineligible due to age (21.1%), less than 20-pack year smoking history (25.4%), no smoking history (25.4%), or a combination of age and smoking history (28.2%). A total of 17 participants (23.9%) subsequently completed a lung CT. Average time to appointment was 29 days (range 9-93), and all appointments were located within 11 miles of the participant's preferred location. Clinically significant findings included Lung-RADS 3 or 4 nodules (29.4%, n = 5) and other incidental findings requiring follow-up care. **Conclusions:** These results illustrate how targeted, community-based approaches can bridge critical gaps in cancer screening by simplifying logistics, reducing costs, and providing tailored support through virtual and community-based solutions. Research Sponsor: None.

1550 **Poster Session**

Current treatment patterns for early breast cancer among healthcare professionals and concordance with expert recommendations: Analysis of an online interactive decision support tool. First Author: Timothy Quill, Clinical Care Options, Reston, VA

Background: The treatment paradigm for HER2-negative early breast cancer (EBC) now includes pembrolizumab and targeted therapies such as olaparib, abemaciclib, and most recently, ribociclib in the adjuvant setting for eligible patients. Here, we assess current intended treatment patterns among healthcare professionals (HCPs) for EBC and compare them with those of experts using an online Interactive Decision Support Tool (IDST). **Methods:** We developed an online IDST in July 2024 with input from 5 breast cancer experts providing therapy recommendations for 12 unique patient case scenarios based on presentation characteristics including disease subtype, disease burden, treatment history, *BRCA* mutation status, and risk of recurrence. HCPs entered specific patient characteristics to define a case along with their intended management for that case. The IDST then showed each expert's recommendation for that case scenario and asked the HCPs if the recommendations affected their intended approach. Here, we report a comparison of the expert recommendations and HCP-selected therapy for different EBC case scenarios. **Results:** Between August 2024 and January 2025, 140 HCPs entered 182 cases. Among the 138 HCPs who indicated their treatment plan, plans were concordant with experts for 59% of the cases. Of note, the 5 experts showed complete concordance in their treatment recommendations for all 12 unique case scenarios. Concordance with the experts was higher among HCP treatment plans for cases of hormone receptor–positive (HR+)/HER2-negative (HER2-) cases compared with triple-negative cases (65% vs 49%). High concordance was seen for HR+/HER2- cases receiving adjuvant AI with *BRCA* WT and high risk of recurrence per the monarchE trial criteria (86%; n = 37) with lower concordance for this setting without a high risk of recurrence (65%, n = 26) with HCPs often choosing endocrine therapy plus a CDK4/6 inhibitor. In the setting of TNBC, HCPs entered cases predominantly related to adjuvant therapy after neoadjuvant chemotherapy plus pembrolizumab (n = 44). Among cases without a pathologic CR in this setting (n = 29), concordance was 50% with or 54% without a pathologic germline *BRCA* variant, respectively. Among TNBC cases with a pathologic CR in this setting (n = 15), concordance was 40% with overtreatment by HCPs evident in 33% of cases. HCPs indicated that expert recommendations changed their intended treatment in 28 of 84 (33%) cases and confirmed their choice in 45 of 84 cases (53%). **Conclusions:** These data suggest ongoing challenges with incorporating pembrolizumab and the newest targeted therapies into adjuvant treatment plans for high-risk EBC, particularly TNBC. Continued education and development of resources for HCPs, including online IDSTs, may be increasingly important as the treatment of high-risk EBC continues to evolve. Research Sponsor: None.

LBA1551 **Poster Session**

Cancer Care Beyond Walls (CCBW): A randomized pragmatic trial of home-based versus in-clinic cancer therapy administration. First Author: Roxana Stefania Dronca, Mayo Clinic, Rochester, MN

The full, final text of this abstract will be available at meetings.asco.org on the day of presentation and in the online supplement to the June 10, 2025, issue of the *Journal of Clinical Oncology*.

1552 Poster Session

Evaluation of longitudinal image-derived AI prognostication as a predictor of overall survival (OS) in a phase 3 advanced non-small cell lung cancer (aNSCLC) trial. First Author: Javier Montalt-Tordera, Bayer, Sant Joan Despi, Spain

Background: Confidently anticipating an overall survival (OS) benefit in cancer care and therapeutic research is a defining challenge. AI tools may offer longitudinal measurements that predict OS differences objectively from existing data. Longitudinal imaging-based prognostication (IPRO-Δ), a fully automated deep learning system, was independently trained on real-world imaging data to predict survival from pairs of longitudinal computed tomography (CT) scans. **Methods:** We retrospectively assessed and compared how IPRO-Δ and percent change in RECIST sum of longest diameters (ΔSLD) predicted OS from 165 pairs of baseline and week 13 CT scans acquired in NExUS (NCT00449033), a phase 3 randomized controlled trial evaluating chemotherapy in combination with either sorafenib or placebo for first-line treatment of subjects with aNSCLC. The two study arms did not show a difference in OS and were combined for this analysis. To examine the association of IPRO-Δ and ΔSLD with OS, we measured the concordance index (c-index) and the standardized hazard ratios (HRs, change in risk for a one-standard-deviation increase in the marker). We also report median OS (mOS) for patients with partial response (PR, *n* = 60), stable disease (SD, *n* = 83) and progressive disease (PD, *n* = 22) at week 13, as defined by RECIST 1.1 guidelines (zero patients had a complete response). To explore the stratification potential of IPRO-Δ, we also define equivalent strata by ordering patients by their IPRO-Δ score and maintaining the same proportions (e.g., the top 60 patients by IPRO-Δ would be IPRO-PR, while the bottom 22 patients would be IPRO-PD), and report the mOS for these strata. **Results:** For the combined trial arms, median OS was 10.9 months (95% CI: 8.6 – 13.6), 108 (65.4%) were male, and 145 (87.9%) were diagnosed as stage IV. Table 1 reports the c-index, HR and stratified mOS values for both survival markers. **Conclusions:** At week 13 in NExUS, IPRO-Δ predicted OS differences significantly better than ΔSLD. Future work will explore how IPRO-Δ could serve as the basis for a surrogate endpoint in aNSCLC trials. Research Sponsor: None.

Summary of association of IPRO-Δ and ΔSLD with OS.

	IPRO-Δ @ Week 13 (95% CI)	ΔSLD @ Week 13 (95% CI)	*p*-value
C-Index	0.654 (0.604 – 0.713)	0.543 (0.495 – 0.599)	<0.01
HR (1SD)	1.72 (1.38 – 2.15)	1.14 (0.94 – 1.38)	<0.01
OS (months, PR / SD / PD or IPRO equivalent)	16.5 / 10.9 / 5.7	12.5 / 12.3 / 4.6	-

1553 Poster Session

Real-world side effects of targeted therapies: High-throughput association studies leveraging the CancerLinq Discovery lung cancer database. First Author: Joseph Vento, Department of Internal Medicine, Division of Hematology and Oncology, UT Southwestern, Dallas, TX

Background: Targeted therapies have unique side effect profiles distinct from other cancer drugs. Challenges of collecting generalizable toxicity data on these medications include the self-reporting infrastructure of existing post-market surveillance databases, as well as the infrequent use of many of these drugs by single cancer centers. The CancerLinQ Discovery (CLQD) database synthesizes deidentified electronic health record (EHR) data from millions of U.S. cancer patients. Diagnosis codes in this database can be used to study treatment side effects. **Methods:** We developed high-precision phenotyping algorithms to identify non-small cell lung cancer (NSCLC) patients receiving targeted therapies in the CLQD database. We then performed phenome-wide association studies (PheWAS) comparing new diagnosis codes in patients receiving each targeted therapy to new codes in patients receiving chemotherapy or immunotherapy. Codes with significant associations were compared to toxicity data reported in clinical trials and the FDA Adverse Event Reporting System (FAERS) database. **Results:** We identified 5,278 NSCLC patients who received targeted therapies with the latest CLQD data pull in 2022. For each of the 18 targeted therapies with five or more patients in the database, descriptive statistics and two PheWAS analyses are reported: one for diagnosis codes relative to chemotherapy, and one relative to immunotherapy. These analyses identified significant associations corresponding to known toxicity profiles as well as potentially underreported side effects. **Conclusions:** This high-throughput framework augments the characterization of side effect profiles for existing targeted therapies and can proactively monitor for toxicity signals as novel therapies and treatment indications emerge. The importance of collecting real-world data across institutions is highlighted in the ability to find clinically relevant associations even in targeted therapies directed against rare mutations. Research Sponsor: National Library of Medicine.

PheWAS analysis sample for side effects of osimertinib and capmatinib.

Drug	Control	Side Effect Code	p-value	OR
Osimertinib	IO	Abnormal EKG	3.68E-14*	2.91
		Dermatitis	1.91E-09*	1.98
		Disorders of muscle	8.18E-06*	2.13
		Other CNS disorders	2.41E-05*	2.17
		Thrombosis	2.90E-05*	1.49
	Chemo	Dermatitis	1.42E-62*	7.90
		Skin symptoms	5.00E-45*	3.70
		Abnormal EKG	3.95E-33*	4.93
		Other musculoskeletal symptoms	5.61E-27*	6.14
		Joint pains	1.09E-22*	2.43
Capmatinib	IO	Edema	2.34E-08*	4.19
		Other soft tissue disorders	9.93E-05*	3.81
		Hypocalcemia	1.06E-02	3.82
		Pleural effusion	1.96E-02	2.22
		Abnormal LFT results	4.97E-02	3.24
	Chemo	Edema	2.05E-14*	7.03
		Other soft tissue disorders	1.75E-11*	10.10
		Respiratory failure	4.20E-08*	7.12
		Abnormal LFT results	3.12E-04*	8.70
		Stroke	1.48E-03	6.68

IO-immunotherapy, OR- odds ratio.
*Statistically significant after Bonferroni correction.

1554 Poster Session

Transforming oncology clinical trial matching through multi-agent AI and an oncology-specific knowledge graph: A prospective evaluation in 3,800 patients. First Author: Arturo Loaiza-Bonilla, St. Luke's University Health Network, Easton, PA

Background: Clinical trial enrollment in oncology is often hampered by the manual, time-intensive process of matching patients to trials with highly specific eligibility criteria. Advances in artificial intelligence (AI)—particularly multi-agent large language models (LLMs) and oncology-specific knowledge networks—hold promise for streamlining this workflow and minimizing human labor. This abstract presents a prospective evaluation of an AI platform that automates medical data extraction, leverages an oncology-specific knowledge graph, and provides real-time trial recommendations, demonstrating a significant reduction in staff effort while maintaining high clinical accuracy. **Methods:** Multi-Agent AI & Oncology Knowledge Graph 1. OncoAgents: Specialized LLMs (data extraction, eligibility, trial matching), collaborating to outperform generic or zero-shot AI. 2. OncoGraph: Domain-specific knowledge graph uniting patient data, molecular profiles, and clinical guidelines for context-aware matching. 3. OncoRecommend: Real-time engine processing new data, trials, and guidelines, delivering rapid, relevant suggestions. 4. OncoSet: Expert-curated dataset (>2,000 patient records, 14,000+ trials, 50+ tumor subtypes) ensuring robust AI performance. Prospective Analysis (Jan–Dec 2024): Cohort: 3,804 patients (ECOG 0–2) with metastatic/progressing malignancies seeking trial options. Data Extraction: 157,367 pages (~86.5M tokens) processed for tumor type, stage, treatment lines, and biomarkers. Trial Matching: Automated application of inclusion/exclusion criteria; oncologists validated AI-generated matches. Efficiency: Manual matching for large cohorts can require thousands of hours; this AI approach condensed it to ~1 hour of expert review. **Results:** 1. Screening & Identification: 3,804 patients screened; 23,912 trials identified; 17,912 confirmed after expert review. 2. Time-to-Recommendation: Under one week from screening to final recommendations via real-time AI prioritization. 3. Performance Metrics: Sensitivity (Recall): 0.8375, Specificity: 0.8359, Precision: 0.8121, F1 Score: 0.8246. Demonstrates advantages over zero-shot or frontier GPT-based models. 4. GPT Comparison: Extraction Accuracy: 80.29% vs up to 63.15% (GPT-4o); Trial Matching Accuracy: 82.06% vs 47.00% (GPT-4o). **Conclusions:** This multi-agent AI platform, underpinned by an oncology-specific knowledge graph, significantly boosts efficiency and accuracy in oncological trial matching. By cutting manual workloads from thousands of hours to near-automated speeds, recommendations allow for just-in-time, decentralized and patient-centric trial activation. Ongoing enhancements—such as deeper biomarker integration, expanded knowledge graph coverage, and seamless EHR interoperability—promise further gains in personalized oncology care. Research Sponsor: None.

1555 Poster Session

Breath-based VOC analysis leveraging canine olfaction for multi-cancer detection: Insights from a 1000-sample study. First Author: Akash Kulgod, Dognosis, Inc., Bangalore, India

Background: Volatile organic compound (VOC) analysis is a validated approach for identifying disease-specific metabolic alterations through exhaled breath. The non-invasive and low-cost nature of breath sample collection makes it particularly suitable for large-scale cancer screening in resource-limited settings, such as those commonly found in the Global South. Canine olfaction has been demonstrated in prior controlled studies to detect VOCs with high accuracy across a range of pathologies, including malignancies. This study evaluates the performance of trained biomedical detection dogs in identifying multiple cancer types using VOC analysis and examines the integration of neurobehavioral data to support real-world diagnostic applications. **Methods:** A retrospective case-control study was conducted involving 1000 participants across three clinical sites in Hubli, India. Exhaled breath samples (n = 105 cancer-positive, n = 895 healthy controls) were collected using standardized protocols designed to maintain VOC integrity. Trained biomedical detection dogs analyzed these samples, with their behavioral responses recorded via motion sensors, video data, and electroencephalography (EEG) systems. A consensus-based decision framework was implemented to account for variability among individual dogs. Preliminary machine learning models were trained using the recorded neurobehavioral data to evaluate their potential for augmenting detection accuracy; however, these models remain in the validation phase. **Results:** The detection system demonstrated a sensitivity of 96% and a specificity of 100% across multiple cancer types in the test set, including oral, breast, esophageal, and cervical cancers. Sensitivity for early-stage cancers was 85%. The consensus-based approach among dogs enhanced reliability and minimized individual variability. Preliminary analysis of neurobehavioral data indicates potential for machine learning applications to refine diagnostic interpretation. **Conclusions:** Breath-based VOC analysis combined with canine olfaction demonstrates high accuracy in multi-cancer detection, including early-stage cancers. Its suitability for non-invasive and low-cost implementation, particularly in resource-constrained settings like the Global South, highlights its potential for addressing disparities in cancer screening access. Future research will focus on validating machine learning models and comparing the system's performance with existing diagnostic standards to further support global scalability and clinical adoption. Research Sponsor: None.

1556 **Poster Session**

PRESCIENTai, an AI-based digital histopathological image signature for risk of late distant recurrence and extended endocrine therapy (EET) benefit in hormone receptor–positive breast cancer. First Author: Eleftherios P. Mamounas, NSABP and AdventHealth Cancer Institute, Orlando, FL

Background: A subset of patients (pts) with hormone receptor-positive (HR+) breast cancer (BC) experiences late distant recurrence (DR) and is more likely to benefit from EET. Clinical practice guidelines recommend use of genomic assays such as Breast Cancer Index (BCI) to identify these pts. We developed an updated AI-based digital histopathological risk score model to predict risk of late DR and extended letrozole therapy (ELT) benefit in this population. **Methods:** The AI model, PRESCIENTai, was trained on eligible samples (N = 2,271) from the National Surgical Adjuvant Breast and Bowel Project (NSABP) B-42 cohort, which randomized postmenopausal women with HR+ BC who were disease-free after 5 yrs of endocrine therapy (aromatase inhibitor (AI) or tamoxifen followed by AI) to either 5 yrs of letrozole or placebo. A transformer-based end-to-end deep learning model predicted risk score from H&E whole-slide images (WSI) in conjunction with clinical information (age at randomization, surgery type, node status, prior use of tamoxifen, race, lowest bone mineral density T-score, HER2 status). CTransPath was used for feature extraction from WSI tiles. 5-fold cross validation was performed with data split into training, validation, and test sets (60:20:20). The risk score threshold was defined by the 50% quantile of the training set for each fold. Cox regression and Kaplan-Meier analysis evaluated late DR and ELT benefit in high- and low-risk pts. **Results:** Hazard ratio (HR) was computed for DR in low- vs. high-risk pts [HR = 0.198 (95% CI: 0.124, 0.317); $p < 0.001$], with absolute difference of 7.61% in 10-yr DR (1.84% vs. 9.46%). High-risk pts experienced greater ELT benefit over placebo (HR = 0.622; 95% CI: 0.416–0.929; $p = 0.02$) than low-risk pts (HR = 0.727; 95% CI: 0.305–1.733; $p = 0.471$), with 10-yr absolute benefit of 3.74% vs. 0.66%. Even among node(+) pts, PRESCIENTai identified greater ELT benefit for high-risk pts (HR = 0.521; 95% CI: 0.329–0.827; $p = 0.006$) than low-risk pts (HR = 0.53; 95% CI: 0.048-5.905, $p = 0.606$), with 10-yr absolute benefit of 6.66% vs. 1.89%. ELT benefit was also observed for high-risk pts in other clinical subgroups such as age ≤60 years and prior tamoxifen. However, p-interaction for ELT benefit in high- vs. low-risk groups was not significant for all pts ($p = 0.791$) or node(+) pts ($p = 0.889$). **Conclusions:** This novel digital signature predicts risk of late DR in pts with HR+ BC. Although absolute ELT benefit was greater in high- vs. low-risk pts, the treatment by risk score interaction was not statistically significant. This is, to our knowledge, the first AI model to predict long-term outcomes in pts with HR+, early BC using a single slide image and clinical information. Successful validation in additional pt cohorts will confirm the clinical utility of PRESCIENTai for prediction of late DR risk and EET benefit. Research Sponsor: U.S. National Institutes of Health; U10CA180868; U.S. National Institutes of Health; UG1CA189867; U.S. National Institutes of Health; U24CA196067; U.S. National Institutes of Health; U10CA180822.

1557 **Poster Session**

Computational pathology to predict docetaxel benefit for high-risk localized prostate cancer in NRG/RTOG 0521 (NCT00288080). First Author: Sebastian R. Medina, Wallace H. Coulter Department of Biomedical Engineering at Georgia Tech and Emory University, Atlanta, GA

Background: The benefit of adding docetaxel (DTX) to standard of care (SOC) for high-risk localized prostate cancer remains debated. The NRG/RTOG 0521 randomized phase III trial demonstrated that docetaxel, when added to SOC—comprising radiotherapy (RT) and long-term androgen deprivation therapy (ADT)—improved overall survival (OS). However, while RTOG 0521 demonstrated improved OS with DTX, the observed improvement did not meet the predetermined threshold for clinical significance, leaving the role of DTX intensification uncertain. Enhanced stratification methods are needed to identify aggressive disease phenotypes and guide patient selection for adjuvant chemotherapy. This study aims to develop and validate a computational AI derived pathology image classifier (APIC) to quantify the tumor-immune microenvironment from diagnostic biopsy specimens and predict DTX benefit in patients from the NRG/RTOG 0521 trial. **Methods:** The study included patients with available high-quality biopsy images from the NRG/RTOG 0521 trial. Primary outcome was OS, median follow-up was 5.7 years. After segmenting nuclei and identifying lymphocytes, we derived features that captured immune-tumor spatial patterns and nuclear diversity in the tumor microenvironment to construct APIC. DTX benefit was evaluated using Cox proportional hazards models with interaction terms, log-rank tests and Kaplan-Meier analyses by comparing OS between treatment arms within APIC-stratified groups. **Results:** Among NRG/RTOG 0521 trial participants, 350 patients had evaluable quality biopsy slide images. Half of the SOC (RT+ADT) arm was used for training (84 patients), and 266 patients were used for validation (SOC: 85 patients, and SOC+DTX arm: 181 patients). DTX significantly improved OS in APIC-positive (n = 119, 45%) patients (HR = 0.49, 95% CI: 0.26-0.92, p = 0.023) but not in APIC-negative (n = 147, 55%) patients (HR = 1.17, 95% CI: 0.59-2.3, p = 0.66). APIC-positive patients derived 22% 10-year OS benefit (95% CI: 1.7%-41.6%) from DTX. The 10-year OS was 74% in the DTX arm compared to 52% with RT and ADT alone in the APIC-positive group. A significant interaction (p = 0.024) was observed between APIC status and treatment. **Conclusions:** We validated APIC as a predictive biomarker for DTX benefit in high-risk localized prostate cancer patients from NRG/RTOG 0521, identifying a subset who achieved significant survival improvement from treatment intensification – a benefit not reached in the unselected trial population. Further investigation is warranted to evaluate APIC's predictive potential of DTX intensification in metastatic disease settings. Research Sponsor: NCORP; UG1CA189867; NCI/NIH; R01CA202752-01A1; NCI/NIH; R01CA208236-01A1; NCI/NIH; R01CA216579-01A1; NCI/NIH; R01CA220581-01A1; NCI/NIH; R01CA257612-01A1; NCI/NIH; 1U01CA239055-01; NCI/NIH; 1U01CA248226-01; NCI/NIH; 1U54CA254566-01; National Heart, Lung and Blood Institute; 1R01HL15127701A1; National Heart, Lung and Blood Institute; R01HL15807101A1; NRG Oncology Operations; U10CA180868; National Institute of Biomedical Imaging and Bioengineering; 1R43EB028736-01; VA Merit Review Award; IBX004121A; Breast Cancer Research Program; W81XWH-19-1-0668; Prostate Cancer Research Program; W81XWH-20-1-0851; Lung Cancer Research Program; W81XWH-18-1-0440; Peer Reviewed Cancer Research Program; W81XWH-20-1-0595; Peer Reviewed Cancer Research Program; W81XWH-18-1-0404; Peer Reviewed Cancer Research Program; W81XWH-21-1-0345; Peer Reviewed Cancer Research Program; W81XWH-21-1-0160; NRG Oncology SDMC; U10CA180822; NRG Specimen Bank; U24CA196067; National Cancer Institute (NCI) and Sanofi; NCI/NIH; R01CA268287A1; NCI/NIH; U01CA269181; NCI/NIH; R01CA26820701A1; NCI/NIH; R01CA249992-01A1.

1558 **Poster Session**

Use of a large language model (LLM) for pan-cancer automated detection of anti-cancer therapy toxicities and translational toxicity research. First Author: Ziad Bakouny, Memorial Sloan Kettering Cancer Center, New York, NY

Background: Understanding why patients develop adverse events to anti-cancer therapies and predicting the occurrence of these toxicities has lagged behind tumor response biomarker development. This critical gap is primarily due to limited availability of large-scale curated toxicity data. Here, we leverage advances in natural language processing (*Jee J et al., Nature, 2024*), pooled clinical trial data, and associated germline sequencing to detect adverse event data and determine clinical and genomic correlates. **Methods:** We utilized the Llama 3.1 LLM to automatically annotate patient adverse event data for 5 of the most common anti-cancer therapy related adverse events (adrenal insufficiency, hyperthyroidism, hypothyroidism, colitis, and pneumonitis). To validate LLM predictions at the patient-level, we used a pooled institutional dataset with gold standard prospectively collected adverse event data from 1,754 patients with solid tumors across 675 individual clinical trials. We further validated the LLM predictions at the clinical note-level using a subset of 100 manually curated notes. We evaluated note-level and patient-level predictions using sensitivity and specificity. Patient-level time-to-adverse event development predictions were evaluated using Pearson R^2 coefficients. Common Terminology Criteria for Adverse Events v 5.0 was used for toxicity definitions. **Results:** The patients' average age (standard deviation) was 61.6 (14.5) years and 836 (47.7%) were female. The most common cancers were non-small cell lung cancer (N= 194, 11.1%), soft tissue sarcoma (N=171, 9.7%), breast cancer (N= 155, 8.8%), and melanoma (N=129, 7.4%). 44 (2.5%) patients had adrenal insufficiency, 88 colitis (5.0%), 253 hypothyroidism (14.4%), 66 hyperthyroidism (4.4%), and 146 pneumonitis (8.3%). Among 1258 patients with complete systemic therapy information available, 422 (33.5%) were treated with immunotherapy and 563 (44.8%) with chemotherapy. The performance metrics for LLM predictions at the note and patient levels are summarized in the table. **Conclusions:** We demonstrate the ability of an LLM to accurately annotate anti-cancer therapy toxicity data across a large number of patients. This approach is scalable to other toxicities and promises to spur adverse event research. Clinical and genomic correlates of anti-cancer therapy adverse events, using data from all patients with solid tumors with MSK-IMPACT data, will also be presented at the meeting. Research Sponsor: National Cancer Institute; T32CA009512-35; National Cancer Institute; P30-CA008748.

Performance metrics for LLM model.

Toxicity	Note-level (N= 100 notes)		Patient-level (N= 1,754 patients)		
	Sensitivity	Specificity	Sensitivity	Specificity	R^2
Adrenal insufficiency	100.0%	97.8%	97.7%	94.7%	98.2%
Colitis	66.7%	99.0%	94.3%	80.4%	89.2%
Hyperthyroidism	57.1%	100.0%	74.0%	91.4%	98.7%
Hypothyroidism	100.0%	88.9%	88.1%	74.0%	96.1%
Pneumonitis	76.9%	97.7%	98.6%	70.1%	83.9%

1559 **Poster Session**

Association of deep learning CT response assessment and interpretable components with overall survival in advanced NSCLC: Validation in a trial of sasanlimab and a real-world dataset. First Author: Chiharu Sako, Onc.AI, San Carlos, CA

Background: Identifying advanced non–small cell lung cancer (aNSCLC) patients who derive long-term benefit from immune checkpoint inhibitors (ICIs) remains a significant challenge. Radiomic analyses, particularly leveraging deep learning, hold promise for improving prognostic accuracy beyond tumor size metrics. We developed serialCTRS, a novel biomarker using deep learning to quantify thoracic CT changes from baseline to 3 months post-treatment, predicting overall survival (OS) in patients receiving PD-(L)1 inhibitors. **Methods:** SerialCTRS was previously trained and validated on a multi-institutional Real-World Dataset (RWD) (training: 1,171 aNSCLC patients, 14,424 CT scans; validation: 612 patients; Sako et al. SITC, 2024). For this study, we retrospectively validated serialCTRS in two distinct cohorts of aNSCLC patients: (1) a clinical trial (N = 52) treated with the PD-1 inhibitor sasanlimab in the second or later line and (2) a fully blinded RWD from Baylor Scott & White Health system (N = 147), an institution not used for training. The pipeline—spanning image quality control, preprocessing, feature extraction, and survival modeling—operated without manual annotations. To enhance interpretability, we developed 3D submodels for prognostic signals related to (i) tumor burden, (ii) body composition, and (iii) lung vasculature. Predictive performance was compared to RECIST 1.1 using concordance index (c-index) and ROC-AUC for 24-month OS (OS24 AUC). **Results:** SerialCTRS outperformed RECIST in OS prediction and remained a significant predictor after multivariate adjustments with other known predictors including age, sex, PD-L1 TPS, and NLR across both validation cohorts. In the sasanlimab cohort, serialCTRS achieved a c-index of 0.77, surpassing RECIST (0.72), with an OS24 AUC of 0.86 (95% CI: 0.74–0.98). In the Baylor cohort, serialCTRS demonstrated a c-index of 0.68 vs. RECIST (0.62) and an OS24 AUC of 0.76 (0.67–0.86). Submodels targeting individual components achieved c-indices of 0.65 (tumor burden), 0.61 (body composition), and 0.61 (vasculature) in the sasanlimab cohort, and 0.63, 0.61, and 0.59, respectively, in the Baylor cohort. Combining the submodels improved c-indices to 0.69 (sasanlimab) and 0.66 (Baylor), demonstrating complementary signal among radiographic features. **Conclusions:** SerialCTRS outperformed RECIST 1.1 in predicting OS in independent clinical trial and RWD datasets. Interpretable submodels highlighted the prognostic value of tumor burden, body composition, and vasculature changes. SerialCTRS offers a promising tool for personalizing therapy and accelerating drug development in aNSCLC, with a fully automated pipeline for robust and scalable clinical use. Future work will focus on larger, more diverse cohorts to validate utility in guiding precision oncology. Research Sponsor: None.

1560 **Poster Session**

Computational pathology to predict docetaxel benefit in patients with metastatic hormone-sensitive prostate cancer from the CHAARTED trial (ECOG-ACRIN E3805). First Author: Sebastian R. Medina, Wallace H. Coulter Department of Biomedical Engineering at Georgia Tech and Emory University, Atlanta, GA

Background: The CHAARTED trial demonstrated the efficacy of early docetaxel (DTX) in combination with androgen deprivation therapy (ADT) for metastatic hormone-sensitive prostate cancer (mHSPC), particularly in patients (pts) with high volume (HV) disease. Volume of metastases has been shown to assist pts selection, however more precise biomarkers are needed to select pts that might benefit from early DTX, especially in low volume (LV) metastasis. We aim to validate a computational AI pathology image classifier (APIC), that quantifies the tumor-immune microenvironment from biopsy images to predict DTX benefit in pts from the CHAARTED trial. **Methods:** The study included a subset of pts from CHAARTED for whom high-quality biopsy images were available. Outcomes were defined as overall survival (OS) and time to castration resistance (CRPC). After segmenting nuclei and identifying lymphocytes, we derived features that captured immune-tumor spatial patterns and nuclear diversity to construct APIC and stratify patients into positive or negative groups. DTX benefit was evaluated using Cox proportional hazards with interaction terms, log-rank tests and Kaplan-Meier analyses by comparing endpoint estimates between treatment arms within APIC-stratified groups. **Results:** Among CHAARTED trial pts, we analyzed H&E images that met quality control and excluded prostatectomies (N = 286/790, 36.2%). Half of the ADT arm was used for training (78 pts), and 208 pts were used for validation (ADT = 77, DTX = 131). Among these, 118 pts (56%) were classified as APIC-positive and 90 pts (44%) as APIC-negative. In APIC-positive, DTX significantly improved OS (HR = 0.52 [95% CI: 0.31–0.85], p = 0.0075, interaction $p < 0.05$) and delayed time to CRPC (HR = 0.48 [95% CI: 0.33–0.71], p = 0.00019, interaction $p < 0.05$). APIC-positive pts who received DTX derived a 24.3% higher 5-year OS and remained castration-sensitive 21.8% longer than those who received ADT alone. In APIC-negative pts, no prolongation effects of OS or time to CRPC were observed from the addition of DTX. APIC was able to identify pts benefiting from DTX in the HV group for OS (HR = 0.43 [95%CI: 0.24-0.77], p = 0.0035), and in both HV (HR = 0.50 [95%CI: 0.31-0.79], p = 0.0027) and LV (HR = 0.42 [95%CI: 0.20-0.91], p = 0.023) groups for time to CRPC. While CHAARTED showed modest CRPC delay in LV pts and no clear OS benefit, APIC identified a subset of LV pts who derived substantial CRPC delay from DTX. **Conclusions:** We validated APIC as a predictive biomarker for DTX benefit in mHSPC pts from CHAARTED. Notably, in unselected pts with LV disease where the benefit of DTX is less, APIC identified an LV subset who derived significant delayed progression to CRPC from adding DTX to ADT. This work, validated in the context of ADT alone, warrants investigation alongside androgen receptor axis-targeted agents. Research Sponsor: NCI/NIH; R01CA268287A1, U01CA269181, R01CA26820701A1, R01CA249992-01A1,R01CA202752-01A1,R01CA208236-01A1,R01CA216579-01A1,R01CA220581-01A1,R01CA257612-01A1, 1U01CA239055-01, 1U01CA248226-01, 1U54CA254566-01; National Heart, Lung and Blood Institute; 1R01HL15127701A1, R01HL15807101A1; National Institute of Biomedical Imaging and Bioengineering; 1R43EB028736-01; United States Department of Veterans Affairs; IBX004121A; Biomedical Laboratory Research and Development Service the Office of the Assistant Secretary of Defense for Health Affairs, through the Breast Cancer Research Program; W81XWH-19-1-0668; Biomedical Laboratory Research and Development Service the Office of the Assistant Secretary of Defense for Health Affairs, through the Prostate Cancer Research Program; W81XWH-20-1-0851; Lung Cancer Research Program; W81XWH-18-1-0440, W81XWH-20-1-0595; Peer Reviewed Cancer Research Program; W81XWH-18-1-0404,W81XWH-21-1-0345, W81XWH-21-1-0160; Kidney Precision Medicine Project; Sanofi.

1561 **Poster Session**

Frailty in motion: How Fitbit data reflects patients with cancers' functional status in the All-of-Us database. First Author: Kenan Najjar, Carle Illinois College of Medicine, Champaign, IL

Background: Frailty is a vital determinant of outcomes in adults with cancer, leading to heightened toxicity, morbidity, and reduced survival. Despite its significance, comprehensive frailty assessment remains constrained by time, resources, and knowledge. Deficit-based frailty indices (FIs) require extensive surveys, limiting real-world use. Wearable devices (e.g., Fitbit) that track daily steps offer a straightforward measure of physical function, yet their associations with FIs are uncertain in oncology. Leveraging the All of Us Research Program (Controlled Tier Dataset Version 7), one of the most diverse NIH resources, we examined the association between steps and the validated All of Us Frailty Index (AoU-FI) [Wong et al. *J Gerontol A Biol Sci Med Sci.* 2023]. We hypothesized that higher step counts would correspond to lower (fitter) AoU-FI scores. **Methods:** We identified adults $\geq$50 years old with cancer and 3–7 days of Fitbit data between 2017–2025. The AoU-FI comprises 33 deficits encompassing lifestyle, comorbidities, overall health, and healthcare access. Frailty was categorized as Fit (< 0.15), Pre-Frail (0.15–0.25), or Frail (> 0.25). Scores were matched with wearable data $\pm$ 30 days; outliers (< 300 or $> 20{,}000$ steps/day) and records missing $\geq$20% of FI items were excluded. Demographics (age, sex, race/ethnicity) and cancer diagnoses were documented. Mean step counts were compared via t-tests. A linear regression assessed the step–frailty link, and a multivariable logistic model for discerning Fit vs Pre-Frail or Frail (age$\geq$65, male, $>$ one cancer) employed normalized step counts (per 1,000). **Results:** Among 361 participants (mean age 65.7$\pm$7.8; 66.8% female; 92.5% White; 97.5% non-Hispanic/Latino), 86.2% had one cancer (skin 55.7%, breast 24.8%, prostate 9.9%). Frailty categories were 44.0% Fit, 40.4% Pre-Frail, and 15.5% Frail. Mean steps declined with increasing frailty (Fit vs. Pre-Frail 8,136$\pm$3,251 vs. 7,067$\pm$3,598; p = 0.007; vs. Frail 5,486$\pm$3,623; $p < 0.0001$). A linear regression confirmed an inverse link between frailty and steps. (slope = -7.38×10^{-6}; $p < 0.0001$). Adjusted analysis showed steps remained highly significant (OR = 1.14, 95% CI: 1.07–1.21, $p < 0.0001$), whereas gender, $>$ one cancer, and age$\geq$65 were not. **Conclusions:** All-of-Us is designed to represent many populations, and our sample showed older adults adopting wearable technologies, highlighting their potential for clinical use. However, the sample was primarily White individuals with skin cancer, reflecting coverage gaps in wearable data across the cancer population. Step counts strongly correlated with fitness, supporting wearable-based functional assessment in oncology. Chronological age did not correlate with frailty, aligning with guidelines prioritizing holistic assessments. Future efforts should integrate broader populations, minute-level metrics, and cancer and treatment information to refine frailty classification as recruitment grows. Research Sponsor: "The All of Us Research Program is supported by the National Institutes of Health, Office of the Director. The program would not be possible without the partnership of its participants."

1562 **Poster Session**

DeepSeal: Empowering clinical researchers to analyze clinicogenomic data with an intuitive chat-based interface. First Author: Gaurav Sharma, Ocean Genomics, Pittsburgh, PA

Background: Traditional clinicogenomic analysis workflows in oncology require substantial bioinformatics expertise and custom coding, creating a bottleneck where clinical researchers must rely on analysts for data interpretation. This dependency hinders hypothesis development, exploration and discovery, as researchers cannot directly interact with their data in real-time. DeepSeal addresses these challenges by providing a user-friendly, chat-based interface that enables immediate analysis of clinicogenomic data and seamless generation of results, empowering clinical researchers to independently explore and validate hypotheses. **Methods:** DeepSeal, an integration of a large language model with clinical and molecular databases and bioinformatics tools, was evaluated by replicating the findings of Riaz et al. (Cell, 2017), in advanced melanoma patients treated with nivolumab. Through natural language prompts, DeepSeal performed multiple analyses including differential gene expression analysis and Gene Set Enrichment Analysis (GSEA) to generate comprehensive molecular profiles of responders versus non-responders and to identify molecular signatures associated with treatment response. **Results:** DeepSeal successfully replicated the key findings of Riaz et al., identifying significant differential expression of immune-related genes in treatment responders. GSEA executed through DeepSeal's chat interface further revealed enrichment of immune-related pathways critical for response, including B cell activation (GO:0042113), T cell activation (GO:0042110), and regulation of adaptive immune response (GO:0002819). The chat interface enabled rapid hypothesis testing and visualization generation, with analyses completed in minutes without the need for programming expertise. **Conclusions:** DeepSeal demonstrates the feasibility of enabling clinical researchers to independently analyze complex clinicogenomic data through natural language interaction. By successfully replicating and validating findings from Riaz et al., it generates reliable insights without programming expertise, offering a transformative approach to accelerate translational research. This removal of technical barriers between researchers and their data has the potential to substantially speed hypothesis testing and discovery in oncology, ultimately enhancing the pathway from molecular insights to improved patient care. Research Sponsor: None.

1563 **Poster Session**

Virtual oncology collaborative tumor board using multiple artificial intelligence agents. First Author: Jiasheng Wang, Comprehensive Cancer Center & James Solove Research Inst., The Ohio State University Medical Center, Columbus, OH

Background: Clinical guidelines are complex documents with tables and figures. Finding specific answers to questions within these guidelines can be challenging and time-consuming. Current AI tools often struggle to extract information from these PDF guidelines. To address this, we developed a novel system that uses a group of artificial intelligence (AI) agents, where each agent is designed to perform a distinct job, like finding information, reading documents, or summarizing findings. These agents communicate with each other to analyze complex clinical guidelines, working as a team to answer physician questions like trained oncologists discussing cases in a tumor board environment. **Methods:** Publicly available PDF guidelines published by the ASCO from Jan 2021 to Dec 2024 were acquired. A three-agent framework was constructed using the AutoGen platform, comprising a Coordinator Agent, a PDF Viewer Agent, and a Reviewer Agent. The Coordinator Agent selects the appropriate guideline based on a user's question; the PDF Viewer Agent extracts information from the selected guideline file, and the Reviewer Agent generates a summary of the findings answering the original question. The agents were powered by Anthropic's Claude 3.5 Sonnet. The primary objective of the study was to evaluate the platform's accuracy in selecting the relevant guideline based on user questions and in subsequently answering those questions accurately. **Results:** A total of 34 ASCO guidelines were obtained, covering a range of cancer types: breast (15), GI (4), head and neck (4), thoracic (4), neuro-oncology (3), GU (2), melanoma (1), and gynecologic (1). One hundred question-answer pairs were created by board-certified oncologists based on these guidelines to evaluate the system's performance. It's important to note that these answers were based directly on the information in the guidelines and may not always reflect the most current clinical knowledge, thus serving as a rigorous test of the framework's ability to adhere to the provided documents. Our multi-agent framework achieved a 93% accuracy rate in matching user questions with the correct guideline and answered 88% of the questions accurately. Comparatively, when the same questions were evaluated using OpenAI's GPT-4o (ChatGPT) and Claude 3.5 Sonnet without the multi-agent framework, the accuracy was significantly lower at 48% and 49%, respectively. The total computational cost of processing all questions using the multi-agent framework was 13.44 USD. The complete code, dataset, and detailed results are publicly accessible at https://github.com/jwang-580/ASCO_guideline_agents. **Conclusions:** This study demonstrates that a collaborative AI agent system can accurately provide answers from clinical guidelines that is more accurate than ChatGPT and similar software. Our results suggest a promising way to develop more effective AI tools for clinicians to use in their practice. Research Sponsor: None.

1564 **Poster Session**

Comparison of artificial intelligence to expert physician assessments of real-world oncology cases. First Author: Olivia Main, NYU Perlmutter Cancer Center, NYU Grossman Long Island School of Medicine, Mineola, NY

Background: Artificial intelligence (AI) is increasingly being incorporated into the oncology field as a tool to support clinical decisions. AI tools such as ChatgGPT or OpenEvidence provide responses to user-generated queries, whereas some institutions or companies such as Primum, Inc, offer consultations with actual experts who provide personalized responses to clinician-submitted real-world cases. However, the value of AI tools to augment expert consultations continues to evolve. We report results of a study comparing AI versus expert oncologists' responses to 107 real-world hematology/oncology cases. **Methods:** Among 107 cases, inquiries included lymphomas (30), myeloma (24), leukemias (11), myeloid disorders (10), as well as classical hematology (32), assessed among 20 experts. Responses to de-identified cases submitted by practicing clinicians to Primum (www.primum.co) between June 2022-July 2023 were compared to GPT-4 responses (openai.com/chatgpt). The instructional prompt to GPT-4 was, "You are an expert oncologist conversing with another oncologist as a peer. You prefer to rely on guidelines and data published in reputable medical journals when responding." Five expert faculty at our institution adjudicated the blinded comparative responses, including their preference, quality and practical value scores, and prediction of which response was AI generated. Comparison of scores was by t-test to generate P-values between expert and AI groups, and Pearson correlation was used for comparisons between adjudication scores. **Results:** Expert responses were preferred by $>$ 50% of adjudicators in 75% of cases (deviation $\pm$25%). Randomized AI responses were correctly identified 90% of the time. Mean expert vs AI scores (Likert scale 0-4) for quality (2.0 vs 2.1, P = 0.9) and practical value (2.1 vs 2.1, P = 0.9) were equivalent. Interestingly, AI responses were preferred in 46% (n = 15) of classical hematology and 31% (n = 9) of lymphoma cases, largely due to being more concise. However there was no concordance between high practical value scores and disease subtype for either group. **Conclusions:** : Expert physician responses were preferred over AI responses for most of the cases based on the level of detail presented, suggesting an implicit value of personalized responses compared to AI. Results showed no significant differences in quality or practical utility between AI generated responses and those from experts, reflecting a similarity in the information extracted from standardized guidelines, and potentially adding value of AI in supporting clinical decision making. Our findings are limited by the broad coverage of hematologic conditions for which experts and guidelines vary. Overall, these data suggest that while AI can supplement knowledge of management paradigms by providing basic management strategies, at present it cannot replace personalized expert consultation in clinical practice. Research Sponsor: None.

1565 **Poster Session**

Evaluating fairness and mitigating bias in models predicting financial toxicity among patients with genitourinary cancers. First Author: Atulya Aman Khosla, Department of Internal Medicine, William Beaumont University Hospital, Royal Oak, MI

Background: Financial toxicity, the economic burden patients face from healthcare expenses, is a growing concern in cancer care. Recognizing the high costs of diagnosis and treatment of genitourinary (GU) cancers, this study aims to (1) comprehensively characterize the socioeconomic, demographic, and care-related factors associated with financial toxicity in patients with GU cancers, and (2) evaluate bias in the predictive model developed using these patient factors. **Methods:** The 2019–2022 Medical Expenditure Panel Survey (MEPS) data was used to identify patients with GU cancers. MEPS captures utilization, frequency, cost, and payment sources of U.S. health services alongside health insurance coverage characteristics and accessibility in the workforce. Financial toxicity was defined as patient-reported difficulties paying medical bills, high out-of-pocket expenses ($>$ 10% of total income), and high self-pay ratios ($>$ 20% of total healthcare expenditure). Predictive modeling was performed using logistic regression using age, sex, race/ethnicity, income, insurance status, and expenditure-related predictors. To address potential algorithmic bias, Fairlearn's *ThresholdOptimizer, a postprocessing algorithm,* was applied to this predictive model, adjusting predictions to ensure equalized odds across racial groups. Performance metrics, including accuracy, precision, and recall, were evaluated overall and by racial group. **Results:** Overall, we identified 1131 patients with GU cancers (weighted *n* = 11,723,024) in the MEPS data; median age 72 yrs; sex 93.4% male; 71.6% White, 18.3% Black, 6.5% Hispanic, and 3.5% Other. 22.2% of patients reported financial toxicity with a median [Q1, Q3] total healthcare expenditure of $2,645.0 [$898.5, $5328.0] vs. $503.5 [$171.0, $1286.8]. Logistic regression achieved an overall accuracy of 95%, with a precision of 97% and recall of 77% for financial toxicity cases. Fairness metrics of the unadjusted predictions revealed bias to specific communities with lower recall for Black (46.2%) and Other Races (33.3%) compared to Hispanic (75.0%) and White (90.4%) patients. After threshold optimization, recall improved to 61.5% for Black and 50% for Other Races, while Hispanic (84.6%) and White (100%) patients maintained high performance. However, disparities persisted, as evidenced by an equalized odds difference of 0.21. **Conclusions:** This study underscores the critical need for responsible development of predictive models impacting cancer care. Our findings show that a bias-correcting postprocessing algorithm can be an essential tool since it can be applied to existing models without requiring retraining; however, these algorithms do not represent a definitive solution since this model's underlying bias persists, highlighting the need to ensure models learn from fair data sets that are representative of the US population. Research Sponsor: None.

1566 **Poster Session**

Machine learning model to forecast patient availability for oncology clinical trials. First Author: Rajeev Kulkarni, ConcertAI, Cambridge, MA

Background: Automating eligibility criteria assessment for oncology clinical trials is an emerging application of machine learning (ML). However, machine learning applications to predict patient availability – the likelihood of a patient beginning a new treatment (time to next treatment) in a prespecified time window – are not well described. We used a large clinicogenomic database of patients diagnosed with solid cancer indications to train ML model to predict patient availability for clinical trials. **Methods:** This was a retrospective study based on data drawn from the ConcertAI Oncology Research database, enriched by key variables derived from unstructured data. Line of therapy was derived from expert rules applied to structured medications data. Our cohort consisted of patients with confirmed diagnosis of solid cancers without a second malignancy. Patient follow-up period started on the date of diagnosis of metastasis and ended on the earlier of last date of activity / date of death. Random observation date was set between start and end dates to label patients. Patients administered a new treatment after the random observation date were labelled evet, else censored (no new treatment began). Label date is start of new treatment and end dates for event & censored cases respectively. The time to event (TTE) was defined as the duration between the random observation and the label dates. In the event cases, this duration is the time to next treatment (TTNT). Over 2000 features based on variables broadly grouped as tumor-specific biomarkers (PTEN, KRAS, etc.), ECOG, staging, disease status, medications, and imaging (evidence of image, not report) were employed to build multiple ML models. Temporal validation of the models was performed by setting up a simulated index date and predicting the probability of patient beginning a new treatment within 60 days of the simulated index date. Patients receiving new treatment within the 60 days were true positives. **Results:** TTE models were trained on a cohort comprised of 90K patients across 12 cancer indications with 54% patients starting a new treatment. Median age and overall survival (OS) of the cohort was 73 years and 703 days respectively. Temporal validation was performed on 25K patients with similar demographics/OS and 58% patients starting new treatment. Multiple ML methods were used to train models, with boosted gradient model demonstrating highest c-index of 0.73 based on 87 features. Temporal validation demonstrated AUC and weighted F1 of 87% and 67% respectively. True positive cases were assigned high predicted probability in 75% of the cases. **Conclusions:** AI models supporting 12 solid cancer indications accurately predicted patient availability. These models can be integrated into real-time clinical workflows alongside patient eligibility models to provide clinicians and patients visibility in ascertaining a patient's likelihood of being eligible for a clinical trial. Research Sponsor: None.

1567 **Poster Session**

Magnetic resonance imaging (MRI) radiomics as predictor of clinical outcomes to neoadjuvant immunotherapy in patients with muscle invasive bladder cancer undergoing radical cystectomy. First Author: Andrea Necchi, IRCCS San Raffaele Hospital, Vita-Salute San Raffaele University, Milan, Italy

Background: Muscle-invasive bladder carcinoma (MIBC) is a deadly disease, for which we pioneered the use of neoadjuvant immune-checkpoint inhibitors (ICI) in a clinical trial (PURE-01, NCT02736266) testing 3 cycles of neoadjuvant pembrolizumab before radical cystectomy (RC). The objective of this study is to assess the ability of radiomic features extracted from a robust MRI processing pipeline to predict the pathological response to neoadjuvant pembrolizumab. **Methods:** A total of 120 patients (pts) with MIBC (102M/18 F), with median age of 68 years, a clinical stage T2N0 (n = 53; 44%) or T3-4N0 (n = 67; 56%), who were enrolled in PURE-01 study were analyzed. Patients had matched pre- and post-ICI MRIs, and tumors were segmented on both T2w images by GU radiologists. The MRI signal intensities were standardized by N4-bias field correction and robust z-scores. IBSI-compatible pyCERR software was used to extract radiomics features. A total of 289 radiomic features, including shape, first-order statistics, and higher-order textures, were analyzed for associations with pathological complete response (pCR at RC). An additional association was also investigated for major response groups, i.e., CR and partial response (PR, i.e. downstaging to ypT$\leq$1N0) versus no response (NR). We employed Elastic Net, a machine learning technique that blends the strengths of Lasso and Ridge regression and is particularly effective for datasets with many correlated features such as in our study. The endpoint was modeled by training Elastic Net logistic regression models separately for pre- and post-ICI MRI features, as well as clinical T-stage. Models were evaluated on a 30% held-out test set using ROC curves (AUC). **Results:** For pCR, the best-performing model included four post-ICI MRI features: shape (flatness) and texture features from Gray Level Co-occurrence Matrix (GLCM: homogeneity, sum average, and sum entropy), and had a test AUC of 0.83 (95%CI: 0.66 - 0.99). Separate models fit on pre-ICI MRI features selected two important pre-ICI MRI features: shape (surface-to-volume ratio) and first order (robust mean absolute deviation), but the overall performance was lower than post-ICI models (test AUC 0.66; 95%CI: 0.42 - 0.89). For major response assessment, the best-performing model included two post-ICI MRI features: shape (flatness) and texture (GLCM sum average) and had a test AUC of 0.92 (95%CI: 0.8-1.0). **Conclusions:** This is one of the first machine learning models using MRI radiomics to predict neoadjuvant immunotherapy response in pts with MIBC. These results could be instrumental for improving the way we can predict the pathological response in these pts. Clinical trial information: NCT02736266. Research Sponsor: Associazione Italiana per la Ricerca sul Cancro (AIRC); IG 27746.

1568 **Poster Session**

Acoustic biomarkers and AI: Transforming NSCLC detection and personalized care. First Author: Chiara Giangregorio, Department of Electronics, Information and Bioengineering, Politecnico di Milano, Milan, Italy

Background: Implementing a mass screening program for lung cancer using low-dose chest CT presents significant challenges, including financial constraints and concerns about radiation exposure. Nonetheless, recent evidence reveals that lung cancer is not limited to smokers, as it also affects non-smoker populations who are currently excluded from existing screening programs. As part of the I3LUNG study (NCT05537922), we investigated the use of AI-based forced cough analysis as a non-invasive approach to distinguish NSCLC patients undergoing immunotherapy (IO) from healthy individuals. Additionally, we examined whether cough features could differentiate patients based on their baseline clinical features. **Methods:** Machine Learning-based preprocessing isolated meaningful cough events and extracted 39 acoustic features from the time and frequency domains. To reduce redundancy and improve model performance, highly correlated features ($>$ 85%) were eliminated. Support Vector Machines (SVM) and Deep Learning (DL) models were then employed to distinguish NSCLC patients from healthy controls. Additional statistical analyses of acoustic features were conducted on cough recordings from patients to evaluate differences based on smoking status (current, former, or never smokers) using the Kruskal-Wallis test with Benjamini-Hochberg post-hoc correction. Similarly, differences based on the presence or absence of lung metastases were assessed using the Mann-Whitney test. **Results:** A total of 200 individuals were enrolled in the study, including 91 stage IIIB-IV NSCLC patients undergoing IO and 109 healthy controls. Cough recordings were analyzed, with the SVM model achieving an accuracy of 82% and a specificity of 92% on the test set. The DL model demonstrated superior performance, with an accuracy of 95% and a specificity of 100%. Significant differences were observed in the peak-to-root-mean-square value ratio and cough duration among smokers (current, former, or never), with P-values of 0.026 and 0.042, respectively. Furthermore, spectral features - including centroid, rolloff, spread, kurtosis, bandwidth, and flatness - differed significantly between patients with and without lung metastases ($P < 0.01$). **Conclusions:** These findings highlight the potential of cough as a valuable digital biomarker for NSCLC diagnosis. The tool's high sensitivity facilitates the effective identification of individuals at risk for lung cancer, while its exceptional specificity makes it a promising initial screening method, efficiently triaging positive cases for follow-up chest CT scans. Future studies should validate these results on larger cohorts. Moreover, the correlation of specific cough features with smoking status and the presence of lung metastases suggests that this tool could extend beyond screening to monitoring disease progression over time. Research Sponsor: HorizonEurope; Grant agreement ID: 101057695.

1569 **Poster Session**

Real-time AI-based computer-aided detection/diagnosis (AI-CAD) for breast ultrasound: A prospective, multicenter, multinational study. First Author: Jeeyeon Elizabeth Lee, Department of Surgery, Kyungpook National University Chilgok Hospital, School of Medicine, Kyungpook National University, Daegu, South Korea

Background: To evaluate the effectiveness of a real-time AI-based computer-aided detection/diagnosis (AI-CAD) system as a diagnostic decision support tool for breast ultrasound in a real-world clinical setting, conducted as a prospective, multicenter, and multinational study. **Methods:** From May to December 2024, a total of 75 patients undergoing breast ultrasound were enrolled in a prospective study conducted in Korea (n = 38) and Hong Kong (n = 37). In this study, six experts operated a real-time AI-CAD system (CadAI-B, BeamWorks Inc., Korea) on a tablet PC connected to a handheld ultrasound device during breast ultrasound examinations. Image and clinical data were collected from patients with established ground truth through follow-up, biopsy, or surgery. The AI-CAD system highlights suspicious areas during scanning to assist physicians in detecting breast cancer and supports big data-driven differential diagnosis by providing BI-RADS categories and malignancy scores (0–100%) when the user freezes the image. The diagnostic performance of experts and the real-time AI-CAD system was evaluated using the area under the receiver operating characteristic curve (AUC), along with sensitivity and specificity. **Results:** The analysis included 75 patients (mean age 55 years, IQR 46–66) with 24 malignancies (32.0%), 45 benign lesions (60.0%), and 6 normal cases (8.0%). The mean breast mass size was 1.2 cm ($\pm$1.0 cm): benign 0.8 cm ($\pm$0.7 cm), malignant 1.8 cm ($\pm$1.3 cm). The BI-RADS category distribution was as follows: for experts—category 1 (4.0%), 2 (21.3%), 3 (24.0%), 4a (16.0%), 4b (18.7%), 4c (4.0%), 5 (12.0%); and for AI-CAD—category 1 (32.0%), 2 (5.3%), 3 (9.3%), 4a (17.3%), 4b (21.3%), 4c (13.3%), 5 (1.3%). The overall diagnostic performance of experts and AI-CAD, as AUCs calculated by BI-RADS, were 0.801 and 0.751, respectively (P = .679). The sensitivity and specificity were 91.7% (22/24) and 68.6% (35/51) in experts and 87.5% (21/24) and 57.8% (32/51) in AI-CAD, respectively (P = .481). **Conclusions:** In this real-world clinical study conducted across multiple centers and countries, CadAI-B demonstrated performance comparable to that of experts and showed its potential as a valuable diagnostic tool. Clinical trial information: NCT06622967. Research Sponsor: None.

1570 **Poster Session**

Cancer patients' messages about radiology/pathology reports: Insights for AI. First Author: Susan Chimonas, Memorial Sloan Kettering Cancer Center, New York, NY

Background: Cancer patients often use portals to view results prior to discussing with physicians, leading to messages with questions or concerns.[1] These messages vary widely in content and urgency, creating challenges for healthcare providers to respond effectively.[2] Categorizing and triaging these messages through AI-enhanced tools could streamline communication and improve patient care and satisfaction. **Methods:** This study assessed common themes in 1 week (April 1-8, 2023) of patients' portal messages about "rapidly read" pathology and radiology reports (viewed by patients within 6 hours of posting to the portal, as a proxy for viewing before discussing with physicians) at Memorial Sloan Kettering Cancer Center in New York City. **Results:** Five notable themes emerged across a total of 48 messages about rapidly read radiology and pathology results: Interpretation (24/48, 50%): Half of the messages contained questions like, *"What does this mean?"* Patients sought explanations of pathology and radiology findings, reflecting a need for clear, accessible interpretations. Implications (14/48, 29%): With questions like, *"What are the next steps?"* patients often asked how findings might alter treatment plans, highlighting a need for guidance on the care implications of their reports. Concern (5/48, 10%): Some patients expressed worry or pessimism about pathology and radiology reports: *"I am very worried"* and *"Maybe it's time to give up."* Such statements indicated a need for supportive communication. Relief (3/48, 6%): In other messages, patients shared positive emotions regarding favorable results – *"It is a huge weight off my mind."* These responses offer clinicians opportunities to reinforce patient satisfaction. Errors/Omissions (3/48, 6%): Occasionally, patients perceived errors or omissions in their reports – *"The radiologist totally misread the size of the lesion"* – which impacted their trust in the information. Addressing these concerns promptly can help strengthen the patient-provider relationship. **Conclusions:** This novel study highlights opportunities for AI-enhanced tools to triage messages and facilitate timely, effective responses. This study found common themes in patients' diverse questions about rapidly read pathology and radiology reports. By implementing AI to categorize and triage message patterns, providers could support patients more efficiently. Methods in development could be used to classify the message content.[3] For instance, AI-driven natural language processing tools could recognize queries related to "What does this mean?" and offer clear, accessible explanations of medical terms. Similarly, AI could be trained to flag high-priority messages based on distress signals, ensuring that these messages are addressed swiftly. Implementing such AI-based solutions could help meet patients' immediate needs while they await conversations with their providers. Research Sponsor: None.

1571 **Poster Session**

Analysis of a large language model-based system versus manual review in clinical data abstraction and deduction from real-world medical records of patients with melanoma for clinical trial eligibility assessment. First Author: Christine Vecchio, Cleveland Clinic Taussig Cancer Institute, Cleveland, OH

Background: Manual chart review (MCR) is the gold standard for assessment of information from electronic medical records (EMRs) for clinical trial eligibility. However, this method is labor-intensive, prone to error, and limited in scalability with high volumes of unstructured EMR data. Large language models (LLMs), have shown promise in natural language understanding, and automating chart review and abstraction would significantly improve efficiency and accuracy in data review for clinical research. In this evaluation project, we compared the performance of Synapsis LLM, a medically-specialized LLM, with medical professionals at answering questions tied to eligibility criteria of relevant clinical trials, by reading clinical notes of patients with melanoma. **Methods:** We conducted a comparative analysis using records of randomly selected patients with melanoma from the Cleveland Clinic. Two parallel processes were assessed: (1) MCR conducted by a melanoma and an oncology specialized research nurse (2) Automated chart review using the Synapsis LLM. Both processes ran on two cohorts: Cohort (A) consisting of 25 EMRs that were posed 23 eligibility questions each, and Cohort (B) consisting of 25 different EMRs, posed 22 eligibility questions each. In total, there were 1,125 questions answered by each of the research nurses as well as Synapsis AI. The questions addressed focused on melanoma-specific clinical characteristics, including but not limited to treatment approaches, related surgical procedures, imaging findings, and genetic testing. Performance metrics included accuracy of answers to the questions, and time required to complete the abstraction process. Discrepancies between the responses of the two research nurses and the LLM were analyzed in comparison to the established ground truth, which was determined through a consensus review by physicians to ensure the validity and reliability of the results. **Results:** Synapsis LLM performed the task with 95.73% accuracy in 2.5 minutes while the melanoma specialized nurse responded with 95.11% accuracy in 427 minutes. The oncology specialized research nurse's accuracy was 88.09%, and the tasks was completed in 540 min. The comparison demonstrated significant time savings and medical-grade accuracy for the application of this LLM-based technology compared to manual methods. **Conclusions:** This is the first project that compares an LLM-based system vs research nurses in deducing clinical characteristics from patients' EMRs for clinical trial eligibility. Synapsis LLM accurately completed the abstraction process, outperforming in accuracy and time the clinical personnel. This study highlights the potential of LLMs like Synapsis AI in scalable clinical research applications that currently rely solely on MCR. Research Sponsor: None.

1572 **Poster Session**

Leveraging AI to enhance symptom capture and reduced hospitalizations. First Author: Arman Koul, Cancer Center, Stanford Healthcare, Stanford, CA

Background: Unplanned hospitalizations and ED visits for cancer patients impose significant morbidity, financial costs, and reduced quality-of-life. Efficient resource allocation in oncology care requires proactive strategies to identify patients at high risk for preventable admissions, optimizing bed availability and outpatient management. CMS classifies acute care utilization (ACU), hospital stays or ED visits, within 30 days of chemotherapy for certain conditions, as "preventable" under OP-35, emphasizing the need for better risk stratification. By leveraging artificial intelligence (AI) including machine learning and large language models (LLM), predictive models can analyze the electronic health record (EHR) to identify patients who may benefit from early outpatient interventions. This study leverages AI to assess preventable admissions and quantify the benefits of proactive management, enhancing patient outcomes and care efficiency in oncology. **Methods:** This study analyzed data from 18,187 patients across a multisite cancer center to develop predictive models for ACU within 30 days of any systemic therapy following OP-35 criteria. Models incorporated structured data and clinical notes using LLMs. Using 2010–2019 data for training and 2020–2024 for validation, XGBoost and Random Forest models were developed to maximize sensitivity while maintaining acceptable specificity. Estimates of preventable hospital bed days were modeled to evaluate the impact of AI-driven risk stratification and targeted interventions on hospital resource utilization. **Results:** The 30-day hospital visit prediction model demonstrated strong performance, with the XGBoost algorithm achieving an AUROC of 0.84 (95% CI: 0.83–0.86). Incorporating later therapy lines improved accuracy by accounting for the complexity of advanced disease. A threshold was set to prioritize sensitivity for identifying high-risk patients while maintaining specificity to minimize unnecessary interventions. Model implementation was estimated to prevent 22% of hospital visits when paired with timely intervention, saving 1,160 of the 5,370 bed days observed in the 2021–2024 cohort. **Conclusions:** This study underscores the potential of AI-driven prediction models to enhance precision oncology by identifying patients at risk for unplanned hospital visits following systemic cancer therapy—a critical quality indicator impacting patient outcomes, healthcare costs, and operational efficiency. By incorporating multi-line therapy data and leveraging advanced modeling techniques, the approach effectively captures disease progression and personalized treatment histories. Utilizing LLMs to structure fragmented data across care systems addresses a prevalent challenge in oncology. Accurate risk prediction of hospitalization facilitates proactive interventions, improves care coordination, reduces bed occupancy, and supports informed decision-making, ensuring timely and targeted support for high-risk patients. Research Sponsor: None.

1574 **Poster Session**

The role of healthcare system distrust in shaping patients' attitudes and beliefs of artificial intelligence (AI) use in oncology. First Author: Marco Santos Teles, Memorial Sloan Kettering Cancer Center, New York, NY

Background: AI offers significant potential to improve cancer care, yet little is known about patients' attitudes and beliefs around its use and which factors influence acceptance of this new technology. Distrust in healthcare is increasingly prevalent and may hinder patient perceptions of innovations such as AI. This study aimed to evaluate the relationship between healthcare system distrust and acceptance of AI in oncology. **Methods:** We conducted a cross-sectional survey study with patients at an urban academic cancer center. We developed an 8-item AI Patient Acceptance scale, where patients rated their comfort with AI in different aspects of oncologic care (e.g. diagnosis, treatment planning) on a 5-point Likert scale (range 8-40, higher scores indicate greater comfort; Cronbach's α = 0.94). The survey also included a 10-item Health Care System Distrust (HCSD) scale (range of 10-50, higher scores indicate greater distrust). Multiple linear regression was performed to evaluate the association between HCSD and AI Patient Acceptance scores, adjusted for demographic and clinical factors. **Results:** Of 383 patients approached, 330 (86%) participated. Among these, 49.4% were age 65 or older, 55.9% male, 68.1% non-Hispanic white, 77.4% had a college degree or more. The most common tumor types reported were prostate (34.5%) and breast (26.4%) cancer, with 70.6% currently receiving treatment. Patients were most comfortable with AI use in cancer screening (80.2% somewhat or very comfortable), and supportive care applications, such as exercise (78.2%) and diet (74.8%). They were least comfortable with AI use to assist with diagnosis (70.4%) and other clinical decision-making applications, including treatment planning (64.8%) and prognosis (61.5%). Higher levels of distrust measured by the HCSD scale were negatively associated with the AI Patient Acceptance scale scores after adjusting for co-variates (B = -0.263, p = 0.002). Younger patients (age $<$ 65) were more likely to report lower scores on the AI acceptance scale (B = -1.996, p = 0.021), while sex, race/ethnicity, and education level were not associated with AI acceptance. **Conclusions:** Higher distrust in the healthcare system is associated with lower acceptance of AI in cancer care. As we integrate new technologies like AI into oncology, mitigating distrust in the medical community will be essential to ensure patient-centered implementation. Research Sponsor: None.

1575 **Poster Session**

Cross-sectional study on the impact of receiving potentially sensitive test results online on the emotional health of patients with breast cancer. First Author: Anezka Carvalho Rubin de Celis Ferrari, Hospital Sirio Libanês, São Paulo, Brazil

Background: Internet has changed the way people communicate. In healthcare, patients have now easy access to their test results online; however, this has been particularly challenging in oncology because of potentially sensitive results present in imaging and pathology reports and tumor markers. In breast cancer, survival rates have improved significantly and more people are getting screened regularly. Providing online access to test results to patients may have ambiguous outcomes, such as increasing their engagement, but also their anxiety levels. This study aims to investigate associations between online access to potentially sensitive test results and effects on the emotional health of patients with breast cancer, particularly for symptoms of anxiety and depression. **Methods:** We conducted a cross-sectional study with 385 patients who had been diagnosed with breast cancer in the past 5 years. Participants completed a printed questionnaire on their approach to receiving test results (whether or not they accessed the results online), their feelings of anxiety about the results, and validated questionnaires assessing symptoms of anxiety (GAD-7) and depression (PHQ-9). Descriptive data analysis was performed using simple and cross tabulations for qualitative variables and measures such as mean, median, mode and standard deviation for quantitative variables. The normality of the data was checked using the Shapiro-Wilk test, while associations between qualitative variables were assessed using the Pearson chi-square test or Fisher's exact test. The significance level was set at 5%, using SPSS software version 22.0. **Results:** Partial results presented here include 329 patients, representing 85.45% of the total sample. A statistically significant association was found between the habit of accessing test results online and higher levels of anxiety ($p < 0.05$). Patients with positive screening for anxiety on GAD-7 reported greater anxiety while waiting for results ($p < 0.05$), while no such association was found for depression. In addition, online access to results showed a significant association with education level ($p < 0.05$) and patient age ($p < 0.05$), with younger patients and those with a higher level of education showing a greater propensity for this practice. However, no significant associations were found between tumor stage (early vs. metastatic) or time from diagnosis and the perception of anxiety ($p > 0.05$). **Conclusions:** There is an apparent association between the habit of receiving test results online and anxiety levels in patients with breast cancer. The recruitment is now complete, and results of the entire cohort will be available for presentation. Research Sponsor: None.

1576 **Poster Session**

Utilization and impact of a digital care platform on cancer patients in India. First Author: Vamshi Krishna Muddu, AIG Hospitals, Hyderabad, India

Background: Cancer patients experience complex symptoms and treatment-related side effects that impair quality of life (QoL) and increase healthcare utilization. Digital health tools have the potential to improve symptom management and patient outcomes by facilitating real-time communication and support, especially for patients with limited access to immediate care. This study aimed to assess the usability and impact of a digital cancer care platform (Alivius) among Indian cancer patients, their primary caregivers, and care teams. **Methods:** We conducted a prospective, interventional, real-world study at a single tertiary cancer center in India from Jan 30, 2024, to Jun 11, 2024. We enrolled 100 cancer patients aged 18–80 years who had access to a smart phone, can read English, had a confirmed cancer diagnosis and had undergone at least one cycle of chemotherapy or radiotherapy. Patients were asked to communicate their symptoms and concerns to the care team and got health education materials for their disease. Primary endpoints included the Monthly Active Users (MAU) and Net Promoter Score (NPS) a metric used to measure customer loyalty and satisfaction by asking customers how likely they are to recommend a company or product. Secondary endpoints included the number of chat interactions, patient-logged symptoms, and use of educational content. Data were collected through in-app user activity and user feedback surveys. Descriptive statistics summarized the data with chi-square test for categorical variables and t-tests or non-parametric tests for continuous variables. **Results:** Out of 100 registered patients (mean age 58.7 $\pm$ 12.5 years; 61% male), the majority had gastrointestinal (55%) and genitourinary (18%) cancers. 66 caregivers participated in survey, with 84.8% being immediate family members. Average MAU during the study period was 58. The NPS for recommending the hospital and the digital application was 30.9 and 32.4 respectively, indicating positive user perception. User engagement was high during the study period: 85% accessed educational content, 82% updated health status, and 78% tracked mood. A total of 2,825 app activities were recorded, including 888 health status updates and 436 chat interactions. 507 side effects alerts generated, 29.5% were high severity, primarily related to tiredness and fatigue (29.2%), gastrointestinal issues (27.2%), and pain (17.5%). Customer Satisfaction Score (CSAT) was 50 and 48.5 among care teams (Doctors & Nurses) and patients, respectively. The app facilitated real-time communication between patients, caregivers, and care teams. **Conclusions:** Digital platform demonstrated high user engagement and positive perceptions among both the patients and their caregivers. The app effectively facilitated communication, symptom tracking, and management of treatment side effects. Patient centered digital platforms hold promise for improving cancer care support. Research Sponsor: Dr reddys Laboratories.

1577 **Poster Session**

Biologically interpretable pathomics-driven transformer model with self-supervised training for outcome prediction of immunotherapy in non-small cell lung cancer. First Author: Butuo Li, Shandong Cancer Hospital and Institute, Shandong First Medical University and Shandong Academy of Medical Science, China Institution or Organization, Jinan, China

Background: Only a subset of non-small cell lung cancer (NSCLC) patients experiences durable benefit from immune checkpoint inhibitors (ICIs), and precise biomarkers remain scarce. Meanwhile, computational pathology, based on digital pathology, has led to significant advancements in NSCLC prognosis prediction. Yet limited generalization and interpretation remain critical challenges in current clinical practice. Self-supervised learning, pretrained on unlabeled data to comprehensively capture underlying biological information in pathological images, may enable expandable, interpretable pathomics models for outcome prediction of ICIs. **Methods:** H&E-stained slides from pan-cancer patients were digitized as whole slide images (WSIs), then segmented for preprocessing. A self-supervised foundation model (patho-GPT) were performed to extract WSI features, and further fine-tuned for outcome prediction of immunotherapy in NSCLC with progression-free survival (PFS) labels. Its performance was evaluated by accuracy, sensitivity, specificity, and AUC in internal and external validation. Patients were classified as immunotherapy-resistant (R) or immunotherapy-sensitive (S), and ROC/survival curves were generated. The model was also tested in an operable cohort on neoadjuvant immunotherapy. Finally, single-cell RNA (scRNA) sequencing analyses were performed to provide biological insights. **Results:** A total of 13770 whole slide images (WSIs) from 6589 patients were included to construct the self-supervised patho-GPT model, which utilizes a context encoder, target encoder, and predictor based on the Vision Transformer architecture. There were 771 WSIs from 511 NSCLC patients receiving immunotherapy, labeled using 5.23 months as the cut-off value. All patients were divided into training and validation sets at a 7:3 ratio. For downstream outcome prediction of immunotherapy, the weight of patho-GPT was fine-tuned in the training set, and performance was evaluated in internal and independent external validation sets. The accuracy was 0.828 (AUC 0.774) in the internal set and 0.758 (AUC 0.752) externally. Survival analyses showed the model's risk group was significantly associated with survival after immunotherapy. In contrast, the ViT-ViT model using initial weights achieved 0.677 accuracy (AUC 0.547) in the external set, which was significantly inferior. ScRNA sequencing and differential analysis between R and S groups were performed, and a high level of H1.2hi Teffs was found in R, linked to dysfunction of cytotoxicity-related genes and immune pathways. **Conclusions:** The self-supervised patho-GPT can be used for the accurate prediction of immunotherapy outcome, with well generalization and biological interpretation. Research Sponsor: None.

1578 **Poster Session**

Artificial intelligence based music therapy intervention in cancer patients undergoing chemotherapy in oncology day care (MUSICC). First Author: Sujith Kumar Mullapally, Apollo Proton Cancer Centre, Chennai, India

Background: Studies on the role of music therapy for improving the quality of life of cancer patients are scarce. Artificial intelligence (AI) is being increasingly utilised in healthcare universally. Echo Care ©DigiNxtHlt Solutions leverages AI technology multi-class neural networks to make personalised recommendations by learning continuously from patients' usage and interactions. We aim to study impact of this AI based music therapy in health-related quality of life (HR-QOL) in cancer patients undergoing chemotherapy. **Methods:** A pilot interventional study for 50 consecutive cancer patients being administered chemotherapy at daycare facility was conducted. After informed consent, each patient underwent assessments during chemotherapy on week 1, week 3 and week 6. Vitals assessment, FACT G7 and HADS assessment was done at baseline, 3rd week and 6th week.30 minutes experience of sounds rendered by "echo Care" AI based application ©DigiNxtHlt Solutions was provided at each session of chemotherapy at 1st week, 3rd week and 6th week. Vitals were checked on admission to daycare unit followed by HR-QOL assessments which were done on digital platform by patients using unique ID and password. After completing the FACT G7 and HADS assessment, option was given to select from multiple music modules generated by AI based on data entered by patients. Once they completed the 30min session, post session vitals were measured. Qualitative feedback also was collected. The primary objective was quality of life as defined by FACT G7/ HADS scores and secondary endpoint was change in physiological vital parameters at baseline, 3 weeks, 6 weeks. Statistical analysis done by SPSS version 22.0. **Results:** A total of 50 patients were enrolled for the study during study period from March 2023 to Dec 2024. Mean HADS score for depression was 10.2 +/-4 and for anxiety was 7.5 +/- 3. 40% patients had high HADS score for anxiety. 18% had high HADS score for depression.50% of patients had improvement in HADS score for anxiety and depression whereas 50% did not have much change in their scores. Mean FACT-G7 score is 13.5+/-2 with majority having value less than 16 (70%). From qualitative feedback, 25% reported "very satisfied", whereas 75% reported to be "satisfied" with music intervention. 54% patients felt less anxious, 50% had calming effect and masking of pain, 37.5% felt mood elevation, positivity and closer to their family. 30% patients felt muscle relaxing effect. 37.5% felt sleepy during music session with 25% not feeling any change in them during the sessions. **Conclusions:** Artificial intelligence-based music therapy intervention in cancer patient undergoing chemotherapy shows promising results in terms of health-related quality of life, satisfaction and experience and can be offered to cancer patients as a non-pharmacological intervention to improve their quality of life during their treatment. Clinical trial information: CTRI/2023/03/050509. Research Sponsor: None.

1579 **Poster Session**

A randomized, controlled pilot trial of a neuromodulatory digital therapeutic for individuals with breast cancer. First Author: Samantha Adler, Click Therapeutics, Inc, New York City, NY

Background: Fatigue, pain, and mood symptoms are common side effects of cancer therapy and cancer patients. Frontoparietal circuitry has been implicated in chemotherapy-induced cognitive impairment as well as post-treatment fatigue. We hypothesized that a smartphone-based multimodal multistable bias modification (MMBM) intervention could improve fatigue, mood, and pain-related attentional biases in breast cancer patients by correcting the neurocircuitry alterations caused by uncertainty stress induced by cancer diagnosis, as well as alterations resulting from chemotherapy, correcting frontoparietal circuitry changes resulting from cancer or its treatment. **Methods:** A randomized, single-blinded exploratory study in patients with breast cancer (n = 81) was conducted. Participants were randomized 1:1 to an active MMBM app or a control app and instructed to use it for 7 minutes daily over 4 weeks. Clinical endpoints included PROMIS-29+2, Brief Pain Inventory (BPI), and Pain Catastrophizing Scale (PCS). Feasibility and acceptability of app usage were also evaluated. **Results:** The MMBM app group showed significant improvements over control in PROMIS-29 fatigue (-3.4, $p < 0.05$), depressive symptoms (-2.8, $p < 0.05$), and symptoms of anxiety (-3.0, $p < 0.05$) domains. There were also several pain measures that showed significant improvement over time in the MMBM group, but not the control group, such as the PROMIS-29 pain intensity measure (-0.9, $p < 0.001$), the BPI average pain intensity (-0.7, $p < 0.001$) and current pain intensity (-0.7, $p < 0.01$), and the PCS total score (-3.3, $p < 0.01$). **Conclusions:** This study provides preliminary evidence that the MMBM intervention may alleviate fatigue and mood-related symptoms in breast cancer patients, with potential for improving pain-related symptoms as well. These findings underscore the potential of digital neuromodulation as an innovative approach to enhance the quality of life of patients with complex conditions, specifically breast cancer. Clinical trial information: NCT06136923. Research Sponsor: None.

1580 **Poster Session**

Exploring social determinants of health and immunotherapy utilization in patients with stage III non-small cell lung cancer following definitive chemoradiation. First Author: Chaewon Hwang, Beth Israel Deaconess Medical Center, Boston, MA

Background: Since the approval of immunotherapy (IO) for maintenance therapy in stage III non-small cell lung cancer (NSCLC) in 2018, its use has expanded rapidly. This study aimed to evaluate patterns of IO use among diverse patient populations who received definitive chemoradiation (CRT) followed by adjuvant IO for stage III NSCLC. **Methods:** A retrospective analysis was performed using the National Cancer Database for patients $\geq$ 18 years old with stage III NSCLC diagnosed between 2018 to 2021. Patients receiving $\geq$ 60 Gy of radiation in $\geq$ 30 fractions and IO delivered 50-150 days from starting CRT were included. Patients who underwent surgery were excluded. Social determinants of health included race, ethnicity, insurance, treatment site, Charlson-Deyo comorbidity index (CCI), high school graduation rate (HSGR; lowest, low, mid, high per US Census data), income (categorized similarly to HSGR), sex, and age. Odds ratios (OR) were calculated for IO use. Logistic regression analyses were performed for each variable followed by multivariable analysis with statistically significant factors ($P < 0.05$). IRB exemption was granted. **Results:** 25,746 patients were included: 21,848 White, 3,236 Black, 558 Asian, and 104 Native American. 620 were Hispanic. On univariate analysis, the following were predictive of IO receipt: Black vs White race (OR 0.86, $P < 0.001$), Hispanic vs non-Hispanic ethnicity (0.72, $P < 0.001$), Medicare or other governmental insurance vs private (OR 0.94, P = 0.037 and 0.85, P = 0.034), CCI 1 or 2 vs 0 (1.11, $P < 0.001$ and 1.13, P = 0.005), community site vs academic/research center (0.88, P = 0.007), lowest and low vs high HSGR (0.78, $P < 0.001$ and 0.87, $P < 0.001$), lowest vs high income (0.90, P = 0.005), female vs male sex (1.06, P = 0.028), and age (-0.88%/year, $P < 0.001$). On multivariate analyses, Black patients were 3.3% less likely to receive IO than White patients (0.88, $P < 0.001$). Hispanic patients were 8.2% less likely to receive IO than non-Hispanic patients (0.72, $P < 0.001$). Medicare insurance (0.93, P = 0.012) and treatment at community sites (0.86, P = 0.002) were associated with reduced IO use. Patients from areas with lower HSGR were less likely to receive IO than those with the highest HSGR (lowest: 0.75, $P < 0.001$; low: 0.83, $P < 0.001$; mid 0.91, P = 0.039). Higher CCI (CCI 1: 1.12, $P < 0.001$; CCI 2: 1.13, P = 0.004; CCI 3: 1.10, P = 0.046), lower income (lowest: 1.11, P = 0.048; low: 1.10, P = 0.041; mid: 1.10, P = 0.025), and female sex (1.05, P = 0.048) were associated with increased IO use. **Conclusions:** This study highlights disparities in IO use following CRT for stage III NSCLC patients. Black race, Hispanic ethnicity, Medicare or governmental insurance, treatment at community sites, and lower education were associated with decreased IO use. These findings emphasize the need for strategies to ensure equitable access to advanced cancer therapies. Research Sponsor: None.

1581 Poster Session

Food insecurity and disparities in mental health symptoms and severity among breast cancer survivors. First Author: Kent Schechter, Ben May Department for Cancer Research, The University of Chicago, Chicago, IL

Background: Breast cancer survivors (BCS) often experience mental health challenges during survivorship. Food insecurity is a growing public health concern in the US, which may exacerbate the challenges faced by BCS. However, little is known about the associations between food insecurity and mental health symptoms and severity among BCS. **Methods:** We conducted a secondary analysis of the 2022 National Health Interview Survey that used stratified clustering sampling to interview US adults aged ≥18. This study was limited to women with a breast cancer history. Food insecurity (secure/insecure) was measured using a 10-item questionnaire assessing past 30-day household food situations. Ever having anxiety was self-reported (yes/no), and the severity level in the past 2 weeks was examined using the 7-item Generalized Anxiety Disorder scale. Women reported ever having a depressive symptom (yes/no), and the 8-item Patient Health Questionnaire depression scale was used to evaluate the severity level in the past 2 weeks. We compared weighted percentages using Rao-Scott Chi-squared tests and computed *P*-trends using the Cochran-Armitage test. We performed weighted logistic regression to estimate adjusted odds ratios (AOR). All analyses accounted for survey weights. **Results:** We obtained an unweighted sample of 644 BCS (weighted sample 4,234,520). Overall, 7.6% experienced food insecurity. BCS who were food insecure were younger than those secure (mean age 61 vs 69 years; $P<.002$). Black (20.4%) or Hispanic (24.3%) BCS were more likely than White BCS (4.7%) to experience food insecurity ($P<.001$). BCS who were food insecure reported a higher percentage of depression than those secure (52.9% [95% CI: 35.5-70.3%] vs 24.4% [95% CI: 20.2-28.6%]; $P<.001$). The proportion of anxiety was higher among BCS who were food insecure than those secure (45.4% [95% CI: 27.7-63.1%] vs 19.8% [95% CI: 16.0-23.6%]; $P<.001$). After controlling for demographic and socioeconomic factors, BCS who were food insecure had greater odds of depression (AOR 3.19, 95% CI: 1.42-7.17) or anxiety (AOR 3.14, 95% CI: 1.34-7.34) than those secure. Compared with BCS who were food secure, those insecure were more likely to experience moderate (26.0% vs 6.0%) or severe (7.5% vs 0.6%) depression (*P*-trend$<.001$), as well as moderate (6.4% vs 4.4%) or severe (14.5% vs 1.3%) anxiety (*P*-trend$<.001$). BCS who were food insecure also reported a higher proportion of forgoing mental health counseling due to cost than those secure (6.8% vs 1.5%; $P=.02$). **Conclusions:** Our findings highlight food insecurity prevalence and associated disparities in mental health symptoms and severity among BCS. Interventions and policies, e.g., food pantries/meals programs and nutrition assistance, are needed to address food insecurity. Cancer centers should also consider routine mental health screening and offer proper services to reduce racial disparities among BCS. Research Sponsor: National Institute on Aging; T32AG000243; Susan G. Komen Breast Cancer Foundation; TREND21675016.

1582 Poster Session

Real world treatment patterns and outcomes in metastatic EGFR mutation–positive NSCLC patients: A retrospective study from a tertiary care cancer center in India. First Author: Jyothis P. Jose, MVR Cancer Centre & Research Institute, Calicut, India

Background: Lung cancer is the leading cause of cancer related mortality worldwide with Non small lung cancer (NSCLC) constituting the majority of cases. EGFR mutations, predominantly exon 19 and Exon 21 L858R are actionable targets in approximately 25-30% Indian patients. Third generation EGFR tyrosine kinase inhibitors have set new benchmarks in the treatment of metastatic EGFR mutation positive NSCLC. However real world adoption in India faces significant barriers including financial constraints and healthcare disparities. **Methods:** Our objective was to evaluate whether patients with EGFR mutation positive metastatic NSCLC receiving the standard of care treatment and analyze demographic, clinical and molecular characteristics of EGFR mutation positive lung cancer patients treated at our center and compare treatment patterns and survival outcomes with national and global data. This retrospective study analyzed 894 stage 4 NSCLC patients treated between 2018-2023 of these 252 (28.1%) were EGFR mutation positive. Data on EGFR types, treatment modalities and survival outcomes were collected and analyzed. Kaplan Meir survival analysis was performed to estimate progression free survival (PFS) and overall survival (OS). **Results:** First line Osimertinib was median OS was 30 months and PFS was 20 months. The standard of care at that time received by 13.5% only. Other TKI alone (Gefitinib, Erlotinib and Afatinib) median OS was 21 months while PFS was 12 months. Other TKI with chemotherapy median OS 27 months and PFS was 18 months. Mutation specific outcomes showed exon 19 deletions had better overall survival 27 months PFS 16 months compared to Exon 21 L858R (OS 16; PFS 11 months). T790M were identified in 71% patients progressing after first line treatment. Second line osimertinib achieved a median PFS of 9.5 months. **Conclusions:** Despite the efficacy of osimertinib demonstrated in global trials, its adoption was limited to 13.5% of eligible patients in this cohort due to economic barriers. These findings emphasize the urgent need for systemic interventions to improve access to advanced therapies in India. Policymakers and healthcare systems must address these gaps through measures like government subsidies, expanded insurance coverage and cost effective diagnostic platforms to ensure equitable access to precision oncology in resource limited settings. Research Sponsor: None.

1583 Poster Session

Racial disparities in oncology clinical trials by absolute neutrophil count eligibility criteria: A single center retrospective analysis. First Author: Arvind Suresh, Department of Medicine, University of California San Francisco, San Francisco, CA

Background: Black individuals have been historically underrepresented in clinical trials. The Duffy-null phenotype leads to clinically insignificant lower absolute neutrophil counts (ANC) and is found in 66% of non-Hispanic Blacks (NHB) and < 1% non-Hispanic Whites (NHW) in the United States. Although the ANC lower limit of normal for Duffy-null individuals is estimated to be 1,210/μL, little is known about the impact of ANC criteria on racial underrepresentation in clinical trial eligibility and enrollment. **Methods:** We conducted a single-center retrospective study of patients newly diagnosed with five cancers (lung, breast, prostate, colorectal, non-Hodgkin lymphoma) between 1988-2024. Baseline organ function data (Hgb, ANC, platelets, AST, ALT, creatinine, and bilirubin) were compared between NHB and NHW. We also identified ANC thresholds above which eligibility proportions differ between NHB and NHW. **Results:** We identified 23,854 patients. 14,585 had available baseline lab data within one year prior to starting anti-cancer therapy. The table lists the percentage of NHW and NHB who meet ANC eligibility criteria at thresholds of 1,000, 1,500, and 2,000/μL. Among patients with breast cancer, the median ANC was 3,500 for NHB and 3,890 for NHW (p = 0.63) and fewer NHB were eligible at all ANC thresholds of 1,500/μL or greater (94.5% NHB vs 97.2% NHW, p = 0.03). For those with prostate cancer, the median ANC was 3,780 for NHB and 4,450 for NHW (p = 0.03) and significantly fewer NHB were eligible at all ANC thresholds of 1,400/μL or greater (97.6% NHB vs 99.6% NHW, p = 0.04). For those with non-Hodgkin lymphoma (NHL), the median ANC was 4,260 for NHB and 4,020 for NHW (p = 0.34) and significantly fewer NHB were eligible at all ANC thresholds of 1,600/μL or greater (90.4% NHB vs 97.1% NHW, p = 0.008). Patients with lung cancer (ANC NHB 4,820 vs NHW 4,920; p = 0.85) and colorectal cancer (ANC NHB 3,930 vs NHW 4,150; p = 0.27) did not have significant ANC eligibility differences between NHB and NHW. No significant differences were found for other baseline labs. **Conclusions:** Our findings provide further evidence that ANC criteria may contribute to differences in clinical trial eligibility between NHB and NHW for breast cancer, prostate cancer, and NHL. Further work is needed to identify optimal cutoffs for each disease group. Limitations include lack of Duffy status for most patients and race is an imperfect approximation. Future clinical trials should proactively address these differences by using ANC eligibility criteria based on Duffy phenotyping. Research Sponsor: UCSF Department of Epidemiology and Biostatistics.

Cancer (n=NHB; NHW)	NHB ANC >2000	NHW ANC >2000	p value*	NHB ANC >1500	NHW ANC >1500	p value*	NHB ANC >1000	NHW ANC >1000	p value*
Lung (n=73; 726)	90.4%	94.4%	0.27	93.2%	97.4%	0.10	95.9%	99%	0.08
Breast (n=237; 2,905)	86.1%	92.7%	**<0.001**	94.5%	97.2%	**0.03**	98.7%	99%	0.99
Prostate (n=124; 961)	88.6%	97.8%	**<0.001**	96.8%	99.4%	**0.02**	100%	99.9%	-
Colorectal (n=80; 800)	87.5%	93.5%	0.08	100%	98.6%	-	100%	99.9%	-
NHL (n=103; 1,414)	76.7%	85.6%	**0.02**	87.4%	90.2%	0.39	94.2%	93.6%	1.0

*Calculated by Chi-squared tests.

1584 Poster Session

Factors associated with receipt of surveillance breast MRI among racially/ethnically diverse women with a personal history of breast cancer. First Author: Preeti Kakani, Columbia University Irving Medical Center, New York, NY

Background: Surveillance breast imaging among breast cancer (BC) survivors is recommended for early detection of local recurrence or contralateral BC. Breast MRI is increasingly used as a screening modality given its heightened sensitivity compared to mammography, and in 2018, the American College of Radiology released guidelines recommending supplemental breast MRI among women diagnosed with BC under age 50 or with dense breasts. We investigated demographic and clinical factors associated with receipt of surveillance breast MRI among women with a personal history of BC. **Methods:** We conducted a retrospective cohort study of women with stage 0-III BC between January 2018-June 2023 at Columbia University Irving Medical Center in New York, NY. We excluded women with bilateral mastectomies. The primary outcome was receipt of at least one breast MRI > 1 year after initial diagnosis. Data from the electronic health record included age at diagnosis, race/ethnicity, primary language, health insurance, first degree family history of BC, germline genetic testing results, stage at diagnosis, mammographic density (MD), and BC treatments (surgery, radiation, chemotherapy, and hormonal therapy). We performed multivariable logistic regression to assess factors associated with receipt of surveillance breast MRI. **Results:** Among 1,990 evaluable patients, mean age was 59.7 years (SD 12.2), and the cohort included 14% non-Hispanic Black, 33% Hispanic, and 6% Asian women. About 22% of women were diagnosed before age 50, 53% had dense breasts (BIRADS C-D), and 18% received at least one surveillance breast MRI > 1 year after diagnosis. On adjusted analysis, younger age at diagnosis, higher MD, first-degree family history of BC, receipt of germline genetic testing, and having a germline pathogenic variant were associated with receipt of breast MRI. Compared to non-Hispanic White women, Hispanic and non-Hispanic Black women had lower odds of receiving breast MRI (odds ratio [OR] = 0.44, 95% confidence interval [CI] = 0.31-0.63 and OR = 0.57, 95% CI = 0.38-0.86, respectively). However, compared to patients with commercial insurance, those with Medicaid were more likely to undergo breast MRI (OR = 1.57, 95% CI = 1.10-2.25). Results were similar when restricting the analysis to those diagnosed before age 50 or with dense breasts. **Conclusions:** Hispanic and non-Hispanic Black women with BC were less likely to receive surveillance breast MRI than their non-Hispanic White counterparts. Also, as patients with Medicaid were more likely to undergo breast MRI than those with commercial insurance, there may be varying health insurance coverage for breast MRI. These results highlight the need for more standardized guidelines surrounding surveillance breast MRI among BC survivors, which may inform public health initiatives aimed at promoting equitable breast imaging practices in this population. Research Sponsor: None.

1585 Poster Session

Meeting enrollment targets in IMbrave152/SKYSCRAPER-14, a global phase 3 study in patients with unresectable hepatocellular carcinoma (HCC). First Author: Christopher Cotter, Genentech, Inc., South San Francisco, CA

Background: The FDA has released guidance that the patient population in clinical studies should be representative of the intended-use population and the epidemiology of the disease, particularly in terms of race and ethnicity. IMbrave152/SKYSCRAPER-14 (NCT05904886) is a global phase 3 trial in patients with HCC, a disease with a globally high Asian and African prevalence, and which significantly impacts underrepresented (including Black and Hispanic) patients in the USA. Enrollment goals (by race/ethnicity), as well as operational and protocol-driven tactics to meet those goals, were implemented for IMbrave152. As of January 2, 2025, the targets for Black and Hispanic patients were met. **Methods:** Global recruitment began on September 14, 2023. Operational tactics included: feasibility questions about the ability to recruit underrepresented populations; utilization of internal and external databases to identify sites that could enroll underrepresented patients; incorporation of patient input; and enhanced patient-support services to facilitate recruitment and retention. Protocol-driven tactics included: modifying inclusion and exclusion criteria (considering race/ethnicity); streamlining study assessments; flexibility to use decentralized processes; and inclusion of an Africa Extension Cohort, which allowed for the recruitment of patients in Africa beyond the intent-to-treat population. **Results:** As of January 2, 2025, the randomized, global population included 8% Black and 14% Hispanic patients (US recruitment included 16% Black and 19% Hispanic patients), exceeding other global HCC studies, which recruited 2% or fewer Black patients and 11% or fewer Hispanic patients. Only two out of seven phase 3 studies in recent years have reported on Hispanic patient recruitment. **Conclusions:** IMbrave152 recruited the highest percentage of Black and Hispanic patients to date in a global phase 3 HCC study. These results demonstrate that recruitment of an underrepresented population is feasible if operational and protocol-driven tactics are utilized. Clinical trial information: NCT05904886. Research Sponsor: F. Hoffmann-La Roche Ltd.

Study	White, %	Asian, %	Black, %	Hispanic, %	Global enrollment from Asia (excl. Japan), %
IMbrave152	32.7	54.7	8.0	13.6	46.7
IMbrave150[1]	34.9	56.7	2.0	NR	40.1
REFLECT[2]	28.9	69.2	NR	NR	67.1*
HIMALAYA[3]	44.5	50.9	1.6	4.7	40.9
LEAP-002[4]	43.5	43.5	1.6†	11.2	30.7
CheckMate-459[5]	53.2	44.7	0.7	NR	25.3
RATIONALE-301[6]	NR	NR	NR	NR	63.1
COSMIC-312[7]	50.9	31.4	1.7	NR	28.8

[1]Finn et al. NEJM 2020;
[2]Kudo et al. Lancet 2018;
[3]Abou-Alfa et al. NEJM Evid 2022;
[4]Llovet et al. Lancet 2023;
[5]Yau et al. Lancet Oncol 2022;
[6]Qin et al. JAMA Oncol 2023;
[7]Kelley et al. Lancet Oncol 2022.
NR, not reported.
*Asia-Pacific region.
†Multiple races, including 9 additional patients who were Black plus either Asian or White, were also reported.

1586 Poster Session

Intervention adherence, engagement and tool utilization in the breast cancer weight loss (BWEL) trial by race and ethnicity (Alliance A011401). First Author: Ashley Odai-Afotey, Dana-Farber Cancer Institute, Boston, MA

Background: Black and Hispanic breast cancer (BC) survivors have a higher prevalence of obesity and experience less success with weight loss interventions (WLI) than White BC survivors. The BWEL trial (Alliance A011401; NCT02750826) is a phase III randomized trial evaluating the impact of a 2-year telephone-based WLI on invasive disease-free survival in participants (pts) with stage II-III HER2-negative BC and a BMI $\geq$ 27 kg/m^2. At 12-months, the WLI induced significant weight loss across demographic factors, including race and ethnicity. However, Black and Hispanic pts lost less weight and completed fewer calls than White pts. Here, we evaluate intervention adherence, engagement and tool utilization in BWEL pts by race and ethnicity. **Methods:** BWEL randomized pts to a WLI plus health education (HE) or HE alone. WLI pts received semi-structured telephone-based health coaching, delivered in English or Spanish, and received an activity monitor and wireless scale. Pts self-reported race and ethnicity. Mean values for call duration, call density (time to complete the initial 12-week intensive intervention phase), intervention attrition, and frequency of Fitbit use and weight tracking over 12-months were compared by race and ethnicity, comparing least squares means with Tukey-Kramer adjustment for multiple comparisons with adjusted p-values. **Results:** Of 3181 pts randomized to the study between 08/2016 and 02/2021, 1591 pts were allocated to the WLI arm. 80.5% of pts were White, 12.8% Black, and 7.1% Hispanic. Average BMI was 34.5 ($\pm$5.7) kg/m2. Compared to White pts, Black pts had fewer days of Fitbit usage (113.6 vs. 159.8, p$<$0.0001) and weight tracking (77.9 vs. 135.6 days, p$<$ 0.0001). Hispanic pts had fewer days of Fitbit usage (108.8 vs. 154.9, p= 0.001) and weight tracking (87 vs. 129.5 days, p=0.0002) compared to non-Hispanic pts. There were no differences in attrition rate, average call duration, or call density by race or ethnicity. **Conclusions:** In a phase III WLI trial, engagement with tools designed to support weight loss was significantly lower in Black and Hispanic pts. Future work is needed to explore ways to enhance engagement and improve weight loss outcomes for racial and ethnic minority pts. Support: U10CA180821, U10CA180882, UG1CA189823; https://acknowledgments.alliancefound.org. Clinical trial information: NCT02750826. Research Sponsor: National Cancer Institute/U.S. National Institutes of Health.

	Race			Ethnicity		
Measure of engagement	White N=1281	Black N=204	p-value	Non-Hispanic N=1459	Hispanic N=113	p-value
Withdrew from intervention n (%)	58 (4.5%)	13 (6.4%)	0.56	70 (4.8%)	6 (5.3%)	0.51
Call Duration (min) Mean (SD)	34.5 (7.6)	34.6 (9.1)	0.99	34.6 (7.8)	33.3 (7.9)	0.25
Call density (weeks) Mean (SD)	14.2 (7.2)	14.2 (8.8)	0.99	14.2 (7.3)	14.2 (9.7)	0.99
Days of Fitbit Use Mean (SD)	159.8 (132.2)	113.6 (124.7)	$<$ 0.0001	154.9 (131.8)	108.8 (125.7)	0.001
Days of weight tracking Mean (SD)	135.6 (109.5)	77.9 (87.5)	$<$ 0.0001	129.5 (108.8)	87 (96.5)	0.0002

1587 Poster Session

Breast cancer optimal care timeframes for culturally and linguistically diverse populations and First Nations People: A regional centre experience in Australia. First Author: Matthew Hon, Townsville University Hospital, Douglas, QLD, Australia

Background: Culturally and linguistically diverse (CALD) populations and First Nations People are at-risk communities who face unique challenges in cancer diagnosis and management resulting in inequities. Optimal Care Pathways (OCP) established by Cancer Council Australia aim to address these disparities. The Breast cancer OCP outlines an integrated model of care with optimal timeframes such as time from general practitioner (GP) referral to specialist surgical review, time from decision to treat to surgery or neoadjuvant chemotherapy (NAC), and time from completion of NAC to surgery. **Methods:** Retrospective data was collected for all CALD (migrant from non-English speaking country and/or primary language identified as not English) and First Nations patients diagnosed with breast cancer treated at a regional centre in Australia (Townsville University Hospital) from 2018 – 2022. A comparison cohort (control) of consecutive non-CALD, non-First Nations patients was included. Data collected included patient demographics, tumour characteristics, stage, and identified timeframes which were compared with OCP. **Results:** 133 patients were included with 43 CALD (32%), 41 First Nations (31%) and 50 control (37%). CALD and First Nations cohorts had higher rates of stage IV disease at diagnosis (12 v 15%) compared to control cohort (0%). They were also more likely to be diagnosed via emergency department admission (CALD 16 v First Nations 7%) compared to control cohort (0%) suggesting later presentation. Of those referred through OCP defined GP pathway, a similar percentage were reviewed by specialist surgeon within optimal 2-week timeframe in all groups (CALD 47%; First Nations 39%; control 44%). Median time from decision to treat to surgery were longer in CALD versus control groups (19 v 13 days; p = 0.03), and in First Nations versus control groups (22 v 13 days; p = 0.02). Less CALD (89%, n = 24) and First Nations (82%, n = 18) patients underwent surgery within optimal 5-week timeframe compared to control (98%, n = 40). Similarly, median time from decision to treat to NAC were longer in CALD versus control groups (19 v 14 days; p = 0.05), and First Nations versus control groups (20 v 14 days; p = 0.03). Most patients (91%, n = 29) commenced NAC within optimal 4-week timeframe; 2 CALD and 1 First Nations patients did not. Median time from completion of NAC to surgery was longer in CALD versus control groups (29 v 24 days; p = 0.15), and in First Nations versus control groups (35 v 24 days; p = 0.04). Of those who recieved NAC, 100% CALD (n = 9), 69% First Nations (n = 9), and 89% control (n = 8) patients underwent surgery within optimal 4-week timeframe. **Conclusions:** Achievement of key OCP timeframes was lower in both CALD populations and First Nations People. Strategies need to be further developed to address the delays and health outcome disparities in these vulnerable cohorts. Research Sponsor: None.

1588 Poster Session

Continuous financial toxicity screening in community oncology. First Author: Thomas Gregory Knight, Atrium Health Levine Cancer Institute, Wake Forest University School of Medicine, Charlotte, NC

Background: Financial Toxicity (FT) has been repeatedly linked with adverse cancer clinical outcomes. However, screening practices vary widely, especially in community settings where $<$ 50% routinely proactively engage patients to discuss care costs. This quality improvement pilot examined the feasibility and impact of continuous FT screening in a community-based clinical practice. **Methods:** Using PDSA methodology, an electronic distress screening (EDS) tool was implemented at each visit at two rural oncology practices. Evidence of FT was defined as answering "yes" to the question "Do you have insurance/financial problems or concerns?" The EDS tool would automatically email the financial navigation (FN) team on "yes" response and patients were contacted by FN within 48 hours. Contact was attempted at least 3 additional times if unable to be reached. Four successive monthly PDSA cycles ran from April to July 2024. In addition to demographic trends, success metrics were: % of screened patients with FT; % of FT patients new to the FN team; number and types of resolutions of FT concerns; and satisfaction and feasibility survey of clinical teams and patients. **Results:** In the 4-month study,1071 patients were screened using the EDS tool: 169 (16%) affirmed FT. Of those with FT concerns, 140 (83%) were new to FN. The FN team provided a primary resolution to 85 patients of 169 (50%) who alerted. Of the remainder, 45 (27%) could not be contacted after multiple attempts and 39 (23%) reported clicking in error. Primary resolutions included: Charity Care Program Referral (36%), Financial Teaching (29%), Billing Changes (11%), Social Work Referral (9%), Medication Assistance (6%), and Marketplace Insurance Obtained (5%). The patients receiving FN services were majority female (75%) and between 35 and 64 yo (57%). The most prevalent cancer types were Blood/Marrow (35%) and Breast (31%). 66% were white, 24% African American, and 14% Hispanic. Payors included 40% commercial insurance, 31% Medicare, 19% Medicaid, and 9% other. Geographically, 62% of patients resided in rural areas, 24% suburban, and 4% urban. Patient satisfaction with FN was high across all categories; 55% agreed or strongly agreed that FN services helped lower stress about bills. Scores were highest for "FN cared about my concerns and needs" (69%); "would recommend it to others in need" (63%); and "information from FN was clear and easy to understand" (61%). The clinic teams survey in participating locations felt the EDS screening tool was feasible in their practice environment (67%) and reported they felt routine FT screening was useful for patients (67%) (n=9). **Conclusions:** Structured implementation of routine FT screening with an EDS tool in a rural, oncology community practice is feasible with high patient and clinical team satisfaction and may allow for earlier identification of at-risk patients. Future directions include screening questionnaire refinements and expansion to other clinical sites. Research Sponsor: None.

1589 **Poster Session**

Socioeconomic- and insurance-based inequities in Oncotype DX testing and score-guided treatment. First Author: Courtney Williams, University of Alabama at Birmingham, Birmingham, AL

Background: Personalized approaches to breast cancer treatment are increasingly guided by expensive, lab-based genomic testing like Oncotype DX (ODX) Breast Recurrence Score Test.Little is known about how socioeconomic and insurance status may affect utilization of ODX testing and subsequent ODX score-guided treatment. **Methods:** This retrospective cohort study included women diagnosed with an early-stage, HR+/HER2- breast cancer from 2011-2023 within the nationwide Flatiron Health electronic health record-derived deidentified database. Socioeconomic status was measured by the Yost index, a census block-level measure of neighborhood deprivation. Insurance status was captured at time of diagnosis. Utilization of ODX testing was compared descriptively. Likelihood of receiving adjuvant chemotherapy by neighborhood deprivation or insurance status was estimated using relative risk, predicted probabilities, and 95% confidence intervals from adjusted Poisson models with robust variance estimates. Analyses were stratified by age due to differing recurrence risk score categorizations. ODX scores indicating low or low/medium recurrence risk suggests chemotherapeutic benefit will likely not outweigh risk of side effects, while scores indicating medium or high recurrence risk suggests chemotherapeutic benefit will likely outweigh risk of side effects. **Results:** Of 4,367 patients eligible for ODX testing, mean diagnosis age was 62 years (SD 12), 77% were white, 69% had stage I cancer, 8% had ≥1 comorbidity, 48% were commercially insured, and 30% lived in a highly deprived neighborhood. Compared to those without, patients with an ODX test (46%, n = 2,026) were more often white (81% vs. 74%), commercially insured (51% vs. 45%), or lived in a neighborhood of low deprivation (73% vs. 67%). For patients aged ≤50 with ODX testing (n = 370), 51%, 25%, 12%, and 12% had low, low/medium, medium, and high recurrence risk. Of those with low recurrence risk, patients who resided in neighborhoods of low vs. high deprivation had 9% higher probability of receiving potentially inappropriate overtreatment with adjuvant chemotherapy (15%, 95% CI 10-25% vs. 6%, 95% CI 2-24%). Of those with low/medium recurrence risk, publicly vs. commercially insured patients were 2.7x more likely to receive adjuvant chemotherapy (RR 2.71, 95% CI 1.00-7.39). For patients aged > 50 with ODX testing (n = 1,656), 83% and 17% had low and high recurrence risk. Of those with high recurrence risk, patients who resided in neighborhoods of high vs. low deprivation were 18% less likely to receive recommended adjuvant chemotherapy, suggesting undertreatment (RR 0.82, 95% CI 0.67-1.00). **Conclusions:** Socioeconomic- and insurance-based inequities, including both overtreatment and undertreatment, were observed in this national cohort of women with early stage breast cancer eligible for ODX testing, indicating opportunities to increase care quality. Research Sponsor: Flatiron Health.

1590 **Poster Session**

Empowering minority patients: A tailored education initiative for clinical trial awareness in thoracic oncology. First Author: Tadana Angelica Vazquez Rothschuh, Ponce Health Sciences University, Ponce, PR, Puerto Rico

Background: Minority populations are underrepresented in clinical trials. Underrepresentation stems from multiple barriers that include restrictive eligibility criteria, systemic inequities, and patient-related factors. Effective educational interventions are needed to address barriers toward increasing minority patient understanding and participation in clinical trials. Despite their potential, video-based, culturally tailored interventions for minority patient education on clinical trials remain understudied and underutilized. **Methods:** We developed 3 brief (<5 min) culturally tailored educational videos about clinical trials in thoracic oncology for Black (English) and Hispanic/Latino patients (English and Spanish). Patients completed pre- and immediate post-video surveys to assess knowledge about, attitudes toward, and willingness to participate in clinical trials. Inclusion criteria included age ≥18 years, diagnosis of stage I-IV lung cancer, ECOG performance status 0-2, self-identification as Black or Hispanic/Latino, proficiency in English or Spanish, and access to an electronic device. Feasibility was measured by participant recruitment rates, completion of pre-and post-video surveys, and video acceptability via self-reported satisfaction. **Results:** Between April and September 2024, 54 patients were approached, and 30 (56%) were successfully enrolled (Table). Among those approached, 4 were ineligible, and 20 declined participation. All enrolled patients completed the pre- and post-video surveys. Over 90% reported high satisfaction with the videos. The total knowledge score increased significantly following the intervention ($p < .001$). For specific items, significant improvements were observed in understanding pre-clinical studies (p = .012), placebo use (p = .001), and clinical trial registration (p = .012). After the videos, over 90% of patients believed that clinical trials are useful and play an important role in developing new drugs and improving lung cancer outcomes. Potential barriers were observed in ~50% of patients, including concerns with informed-consent language, randomization, costs, and healthcare team communication style. There was a significant increase in willingness to participate in a clinical trial after watching the educational videos (p=.04). **Conclusions:** Our culturally tailored, patient-centered educational videos on clinical trials in thoracic oncology were both feasible and well-accepted. Future studies should explore whether such interventions can increase minority patient enrollment in therapeutic clinical trials. Research Sponsor: Moffitt Cancer Center Foundation; Bristol Myers Squibb Foundation; Fundacion Intellectus; National Cancer Institute/U.S. National Institutes of Health; U54 CA163068.

Patient demographics.

Variable	Level	N = 30	%
Preferred Language	English	23	76.7
	Spanish	7	23.3
Age Group	30-49	5	16.7
	50-69	12	40.0
	70-89	13	43.3
Sex at Birth	Female	19	63.3
	Male	11	36.7
Race	White	10	33.3
	Black/AA	16	53.3
	Other	4	13.3
Ethnicity	Not Hispanic	15	50.0
	Hispanic	15	50.0

1591 **Poster Session**

Development of a culturally tailored educational tool designed to increase access to somatic testing among Black men with metastatic prostate cancer (mPCa). First Author: Christopher Johns, University of California, San Francisco, San Francisco, CA

Background: Somatic testing (ST), also known as molecular profiling, has become increasingly important for therapy selection in men with mPCa. Interventions targeting known racial inequities in the use of ST are lacking. Our objective was to design a culturally tailored educational tool to augment patient education with the ultimate goal of increasing equitable access to ST for Black patients with mPCa. **Methods:** We used principles of human-centered design to develop a ST educational tool. We first designed a prototype with key stakeholders, then conducted a qualitative study of Black patients with mPCa at three sites – a tertiary care academic center, a VA medical center, and a safety net oncology clinic. Trained interviewers conducted semi-structured interviews to explore patients' perceptions of ST and elicit feedback about the educational tool until data saturation was met. Based on this feedback, we iteratively revised the tool. Interviews were transcribed, and two coders qualitatively analyzed transcripts using the COM-B framework to identify barriers/facilitators of tool use. **Results:** For the initial prototype, four physicians, one genetic counselor, and two patients contributed to the design of a 7-min video of a Black oncologist with informative animations followed by a text-based decision aid. We approached 18 patients, of whom 11 (61%) consented to review the tool then complete the interview. All participants expressed a positive perception of the tool and comprehension of the information. Tool facilitators included 1) trust in the tool, 2) actionability of the tool's content, and 3) appreciation for a Black physician featured in the video. Barriers included 1) difficulty navigating the electronic interface, 2) negative emotions from reflection on their cancer diagnosis or racial inequities, 3) too much information in the decision aid, particularly about biopsy risks and testing costs, and 4) content concerns on risks associated with ST/biopsy. For participants' perceptions of ST, facilitators included 1) desire to learn more about mPCa and 2) motivation to improve their health, their family's health, or the health of the Black community. Barriers included 1) misinformation about ST and mPCa, 2) difficulty accessing affordable healthcare, 3) mistrust of the healthcare system due to prior negative experiences, and 4) belief that mPCa and its treatments are emasculating. Overall, 10/11 patients reported planning to either discuss ST with their oncologist (7/11) or obtain ST (5/11). **Conclusions:** We successfully designed an educational tool for pre-test education about ST for Black men with mPCa. This educational tool was well received and may have contributed to PCa patients further pursuing somatic testing. Further evaluation of the feasibility, acceptability, and efficacy of this educational tool is warranted. Research Sponsor: Prostate Cancer Foundation.

1592 **Poster Session**

Comparative analysis of demographics and outcomes in young versus average onset hospitalized gastrointestinal cancer patients in New York State. First Author: Mrinalini Ramesh, University at Buffalo, Buffalo, NY

Background: Recent studies have shown an increasing incidence of gastrointestinal (GI) cancers among young patients. This study investigates clinical outcomes and healthcare utilization among young (< 50) versus average onset (≥50) GI cancer patients admitted to hospitals in New York State (NYS). **Methods:** We performed a retrospective analysis using the Statewide Planning and Research Cooperative System (SPARCS) database from 2009 to 2022. Patients were divided into two groups: young-onset GI cancer patients (YOGIC, < 50 years) and average-onset GI cancer patients (AOGIC, ≥50 years). GI cancers included anal, biliary tract, colorectal, esophageal, gallbladder, liver, pancreatic, peritoneal, small intestine, and stomach cancers. The study population was further stratified by demographic and clinical characteristics. All variables were compared using the Kruskal-Wallis test or Fisher's exact test, along with multivariate linear and logistic regression in RStudio version 4.4.2, with a significance level of $p \leq 0.05$. Clinical characteristics, including severity of illness and risk of mortality, were defined using the All Patient Refined (APR) grading system. **Results:** A total of 256,924 patients were identified (26,071 YOGIC and 230,853 AOGIC) with a primary admitting diagnosis of a GI cancer from 2009 to 2022. The AOGIC group had a higher proportion of white and female patients, whereas the YOGIC group included a higher proportion of black and male patients ($p < 0.001$). Anal, peritoneal, and stomach cancers were more prevalent in YOGIC, while pancreatic and esophageal cancers were more common among AOGIC ($p < 0.001$). AOGIC patients were more likely to have extreme (13% vs. 9.7%) or major (39% vs. 32%) severity of illness compared to YOGIC ($p < 0.001$). However, the median total cost of stay for YOGIC was significantly higher than that for AOGIC ($21,421 vs. $19,658 respectively, $p < 0.001$). YOGIC patients were more likely to undergo procedures during hospitalization (95%) compared to AOGIC (93%) ($p < 0.001$). YOGIC patients were more likely to be discharged home (66%) vs. AOGIC (48%) ($p < 0.001$). Longer hospital stays were associated with patients diagnosed with esophageal, peritoneal, and stomach cancers ($p < 0.001$) versus the reference group (anal cancer), and in AOGIC [log fold-change 0.029 (95% CI: 0.021-0.038), $p < 0.001$]. Despite a higher mortality risk in AOGIC, mortality rates decreased faster over the study period [OR 0.97 (95% CI: 0.96-0.98), $p < 0.001$]. **Conclusions:** AOGIC patients experience a higher risk for mortality and longer hospital stays. However, YOGIC patients undergo further procedural interventions and have been found to have higher inpatient admission costs. Policies focused on earlier outpatient interventions may alleviate the burden on inpatient care. Research Sponsor: This work was supported by funding from the National Cancer Institute. The study's design and decision to publish were independent of any involvement from the funding sources.

1593 **Poster Session**

Assessing the effects of financial toxicity on quality of life among hematopoietic stem cell transplantation recipients. First Author: Grace Ann Hanvey, Mayo Clinic, Rochester, MN

Background: "Financial toxicity" refers to the financial burden imposed by treatment costs on individuals with cancer, constituting a major barrier to achieving equitable cancer outcomes. Recent literature increasingly demonstrates the detrimental impacts of financial toxicity on quality of life (QOL) among individuals with cancer, including individuals who have undergone hematopoietic stem cell transplantation (HSCT). This study evaluates associations among treatment cost burden and various aspects of QOL following HSCT. **Methods:** Seven hundred one HSCT recipients completed a survey examining their biopsychosocial health one year following transplant. The survey included the Functional Assessment of Cancer Therapy – Bone Marrow Transplantation (FACT-BMT), a multifactorial measure of QOL specific to this population. Treatment cost burden endorsement was measured on a 5-item Likert scale. Hierarchical regression models were developed to assess the incremental effects of demographic characteristics (i.e., Block 1), clinical predictors (Block 2), and cost burden (Block 3) on physical, emotional, social, functional, BMT-specific, general, and composite QOL outcomes. **Results:** Significant model improvement was observed with the addition of clinical factors ($\Delta F(2,650) = 20.28$, $p < .001$), and subsequently, treatment cost burden ($\Delta F(1,649) = 110.29$, $p < .001$). In the final model, higher cost burden was associated with poorer physical ($\beta = -0.323$, $p < .001$), emotional ($\beta = -0.301$, $p < .001$), social ($\beta = -0.250$, $p < .001$), functional ($\beta = -0.317$, $p < .001$), BMT-specific ($\beta = -0.341$, $p < .001$), general ($\beta = -0.377$, $p < .001$), and composite QOL ($\beta = -0.381$, $p < .001$). Poorer performance score was associated with each QOL indicator ($p < .001$), with allogeneic transplant type associated with poorer functional ($\beta = -0.001$, $p = .002$), but higher emotional ($\beta = 0.118$, $p = .002$), wellbeing. Older age ($\beta = 0.113$, $p = .003$) and female sex predicted higher ($\beta = 0.183$, $p < .001$), while Hispanic ethnicity predicted poorer ($\beta = -0.095$, $p = .010$), social wellbeing. Female sex was associated with poorer QOL specific to BMT concerns ($\beta = -0.118$, $p = .001$). **Conclusions:** Higher treatment cost burden is associated with poorer overall QOL and its physical, emotional, social, functional, and BMT-specific components one year following HSCT, after controlling for demographic and clinical characteristics. This reflects a critical barrier to equitable cancer care, suggesting that financial toxicity may perpetuate preexisting inequities in QOL, treatment, disease, and survival outcomes that disproportionately impact the underserved. Future research should prioritize 1) better understanding relationships among complex indicators of financial toxicity, QOL, and their underpinning mechanisms and 2) developing solutions to mitigate financial toxicity of HSCT and overall cancer care. Research Sponsor: U.S. National Institutes of Health.

1594 **Poster Session**

Early post-operative opioid fills after cancer-directed surgery among Medicare beneficiaries by race and ethnicity. First Author: Ashley Odai-Afotey, Dana-Farber Cancer Institute, Boston, MA

Background: Post-operative pain is often underestimated and undertreated. Researchers have shown that Black patients receive fewer opioids than White patients across multiple settings and conditions; however, little is known about whether post-operative opioid prescribing for cancer-directed surgery differs by race and ethnicity. We characterized racial and ethnic differences in opioid fills among Medicare beneficiaries undergoing cancer-directed surgery. **Methods:** Using 100% Medicare data for fee-for-service beneficiaries enrolled in parts A, B, and D, we identified episodes of cancer-directed surgeries from 2012-2021 among adults who survived > 30d after surgery and were discharged home. We used Part D claims to identify opioid prescriptions filled in the 30d after outpatient surgeries and the 30d after hospital discharge for inpatient surgeries, overall and among non-Hispanic White (NHW), Black (NHB), Hispanic, and Asian patients. **Results:** Among 981,702 surgical episodes (mean age 73 [SD 8] years, 36% male), 83% were NHW, 8% NHB, 4% Hispanic and 2% Asian patients. Most surgeries were for breast (38%), colorectal (15%), prostate (13%), or lung (10%) cancers. Most (67%) patients with surgical episodes had an opioid fill within 30d, with a mean dose of 246 morphine milligram equivalents (MMEs) in the first prescription, and a mean total dose of 360 MMEs filled within 30d of surgery or discharge. On average, patients filled 1.4 opioid prescriptions, with a mean of 9-days' supply in the 30d after surgery or discharge. NHB patients had the highest rate of opioid prescription, doses, and days' supply; Asian patients had the lowest rate of opioid prescriptions, doses, and days' supply (Table). Findings among Hispanic patients mirrored NHW patients. **Conclusions:** Among Medicare beneficiaries undergoing cancer-directed surgeries in 2012-2021, two-thirds of surgical episodes were associated with an opioid fill. In contrast to prior studies of opioid fills among cancer patients, we observed the highest opioid fills among Black patients. Future work is needed to understand the association of time and patient, physician, and healthcare factors on post-operative opioid prescribing and to understand the association of opioid prescribing with pain control. Research Sponsor: National Cancer Institute/U.S. National Institutes of Health.

Outcome in 30d Mean (SD)	Overall (n=981702)	NHW (n=815966)	NHB (n=77932)	Hispanic (n=42663)	Asian (n=21087)
Filling an opioid n (%)	653883 (67%)	538183 (66%)	58323 (75%)	28866 (68%)	12937 (61%)
MME, first prescription	246 (320)	245 (318)	271 (350)	243 (318)	211 (210)
Total MME in 30d	360 (566)	356 (563)	420 (620)	358.9 (565)	276 (374)
# of fills	1.4 (0.8)	1.4 (0.8)	1.5 (0.8)	1.4 (0.8)	1.3 (0.6)
Days prescribed	9 (9)	9 (9)	10 (10)	9 (9)	8 (7)

MME=morphine milligram equivalents.

1595 **Poster Session**

Disaggregating Asian American and Pacific Islander subgroups to evaluate disparities in breast cancer characteristics and outcomes. First Author: Shawn Michael Doss, Medical College of Georgia, Augusta, GA

Background: When Asian American and Pacific Islander (AAPI) subgroups are aggregated under the labels "AAPI" or "Asian," subgroup-specific differences in breast cancer (BC) presentation and outcomes may be masked. Potential overlooked disparities among these diverse groups remain understudied. We analyzed BC characteristics and outcomes among regional AAPI subgroups. **Methods:** From the National Cancer Database (2009–2020), we identified patients diagnosed with stage I–IV BC, excluding patients missing race or stage. Multivariate logistic regression examined odds of advanced stage (III–IV), high-grade histology, and triple-negative BC (TNBC) at diagnosis. Multivariate Cox regression assessed three-year overall survival (OS). Age, comorbidity index, diagnosis year, and zip code income quartile were analyzed to account for confounding. **Results:** Of 1,956,145 total patients, there were 61,731 pooled AAPI patients, comprised of East Asian (n=23,643), South Asian (n=13,642), Southeast Asian (n=19,000), and Pacific Islander (PI) (n=5,446) subgroups. Non-Hispanic White (NHW) (n=1,639,814) served as the reference group. Compared to NHW, pooled AAPI had higher odds of advanced stage (adjusted odds ratio [aOR] 1.09; 95% CI 1.07–1.12; p<0.001) and high-grade histology (aOR 1.21; 95% CI 1.17–1.25; p<0.001). There was no difference in odds of TNBC (0.98; 0.92–1.03; p=0.41). Despite this, AAPI had better three-year OS (hazard ratio [HR] 0.79 (0.76–0.82; p<0.001). Compared to NHW, each AAPI subgroup had higher odds of high-grade histology and better OS except for PIs, who had similar odds of both. South Asians and Southeast Asians had higher odds of advanced stage (aOR 1.27; 1.21–1.34; p<0.001 and 1.22; 1.17–1.27; p<0.001, respectively), while East Asians had lower odds (0.86; 0.83–0.90; p<0.001). South Asians showed increased odds of TNBC (aOR 1.11; 1.00–1.23; p=0.04), whereas Southeast Asians (0.82; 0.73–0.91; p<0.001) and PIs (0.81; 0.66–0.98; p=0.036) showed lower odds. **Conclusions:** Disaggregating AAPI subgroup data is necessary to understand disparities in BC among these heterogenous populations. Further studies are warranted to evaluate disparities in healthcare delivery and its efficacy in these subgroups. Research Sponsor: None.

Breast cancer characteristics by AAPI and subgroup.

	Advanced Stage (aOR, 95% CI)	High-Grade (aOR, 95% CI)	TNBC (aOR, 95% CI)	Three-Year OS (HR, 95% CI)
NHW (Reference)	1.00	1.00	1.00	1.00
AAPI	1.09 (1.07–1.12)**	1.21 (1.17–1.25)**	0.98 (0.92–1.03)	0.79 (0.76–0.82)**
East Asian	0.86 (0.83–0.90)**	1.12 (1.07–1.18)**	1.06 (0.97–1.15)	0.71 (0.67–0.75)**
Southeast Asian	1.22 (1.17–1.27)**	1.30 (1.24–1.38)**	0.82 (0.73–0.91)**	0.84 (0.78–0.89)**
South Asian	1.27 (1.21–1.34)**	1.28 (1.21–1.36)**	1.11 (1.00–1.23)*	0.75 (0.69–0.82)**
PI	1.31 (1.21–1.42)**	1.10 (0.99–1.21)	0.81 (0.66–0.98)*	1.06 (0.96–1.18)

*p-value <0.05.
**p-value <0.001.

1596 **Poster Session**

The development of the cost of cancer in 31 European countries. First Author: Andrea Manzano, IHE, Stockholm, Sweden

Background: The estimated number of new cancer cases in Europe has risen from 2.6 million in 1995 to 4.1 million in 2022. Around every fourth death is due to cancer, yet survival rates have been improving due to advances in early detection, diagnosis, and treatment. The implications of these epidemiological changes and medical advances for the overall cost of cancer are not well documented. **Methods:** This cost-of-illness study estimated the direct and indirect costs of cancer across 31 European countries (the EU-27 countries, plus Iceland, Norway, Switzerland, and the UK) from 1995 to 2023. For direct costs, information on cancer-specific health expenditure was searched for all countries and combined with data from Eurostat and the OECD. Extrapolations were made for countries with missing information. For indirect costs, productivity losses due to premature mortality were calculated using mortality data from the World Health Organization, Eurostat, and the Office for National Statistics, combined with labor market data from Eurostat. Productivity loss due to morbidity were estimated using data from prior studies and changes in population structure. The human-capital approach was employed to calculate indirect costs. Total costs, costs per capita, and costs per new case were estimated for Europe as a whole and for each individual country. **Results:** Between 1995 and 2023, the combined direct and indirect costs of cancer across all countries increased by 43% from EUR 159 billion to EUR 228 billion (all figures adjusted to 2023 prices). Direct costs grew by 135%, from EUR 62 to EUR 146 billion, while indirect costs, which fell below direct costs after 2005, decreased by 16% from EUR 97 to EUR 82 billion. The decline in indirect costs reflects a reduction in potential years of working life lost due to premature mortality of working-age patients. Direct costs of cancer accounted for 4-8% of total health expenditures in all countries, with modest increases over time in some but not all countries. Per capita costs for all countries combined rose by 35% from EUR 313 to 423. However, there was a seven-fold difference between countries in 2023 ranging from around EUR 150 in Bulgaria and Romania to EUR 1,011 in Switzerland. This disparity represents a reduction from the twelve-fold difference observed in 1995. The cost per new cancer case remained relatively stable in Europe as whole at around EUR 78,000 between 1995 and 2010, before declining slightly to EUR 72,000 in 2015 and stabilizing thereafter. **Conclusions:** The societal cost of cancer in Europe has been steadily increasing. The growing number of cancer patients is spurring this development, rather than changes in cost per patient, which has remained mostly stable for nearly 30 years. Although the direct costs of cancer have risen the most, this has been partially offset by reductions in indirect costs. Changes in indirect costs and epidemiological trends should be considered in debates about the rising costs of cancer. Research Sponsor: European Federation of Pharmaceutical Industries and Associations (EFPIA), Brussels, Belgium (unrestricted grant).

1597 Poster Session

Trends in female breast cancer among adolescent and young adults in Southeast Asia. First Author: Jenny Chen, Memorial Sloan Kettering Cancer Center, New York, NY

Background: Breast cancer is the leading cancer among women globally and poses a growing public health challenge, particularly in adolescents and young adults (AYAs), defined as individuals aged 15–39 years. In Southeast Asia (SEA), rising breast cancer rates among AYAs are compounded by unique biological, socioeconomic, and healthcare barriers, including late-stage diagnosis and limited access to screening and treatment. However, regional data on incidence and mortality trends remain scarce. This study aims to analyze temporal trends in AYA breast cancer incidence and mortality across 11 SEA countries from 1990 to 2021 using data from the Global Burden of Disease (GBD) database. **Methods:** We extracted breast cancer incidence and mortality data for AYAs in SEA from the GBD database (1990–2021) for Brunei, Cambodia, Indonesia, Lao PDR, Malaysia, Myanmar, the Philippines, Singapore, Thailand, Timor-Leste, and Vietnam. Age-standardized rates (ASRs) were calculated, and temporal trends were evaluated using Estimated Annual Percent Change (EAPC) based on log-linear regression. **Results:** Breast cancer incidence among AYAs increased significantly across SEA from 1990 to 2021. Thailand reported the highest ASR in 2021 (11.78 per 100,000) and the most pronounced rise in incidence (EAPC 4.06). Significant increases were also observed in Vietnam (EAPC 2.92), Cambodia (2.63), and Laos (2.57). Mortality trends were heterogeneous: Singapore achieved a significant decline (EAPC -2.00), attributed to advancements in early detection and treatment, while Thailand, Indonesia, Vietnam, and Cambodia experienced rising mortality rates. In 2021, the highest mortality rates were recorded in Myanmar (2.54 per 100,000), Thailand (2.36 per 100,000), and the Philippines (2.17 per 100,000). **Conclusions:** The growing burden of AYA breast cancer in SEA reflects a combination of epidemiologic transitions, socio-economic shifts, and regional healthcare disparities. Rising incidence is linked to changes in reproductive behavior, lifestyle factors, and urbanization, while increased mortality highlights gaps in healthcare access and screening infrastructure. Urgent public health interventions tailored to AYA populations are needed to enhance early detection, improve treatment accessibility, and address disparities across SEA. Regional collaboration and investments in healthcare systems are critical to mitigating the growing burden of breast cancer among AYAs in this dynamic region. Research Sponsor: None.

1598 Poster Session

The impact of race on the association between structural racism and the quality of non-small cell lung cancer (NSCLC). First Author: Jacquelyne Janean Gaddy, Yale School of Medicine, New Haven, CT

Background: Structural racism encompasses multiple intricate systems that generate and reinforce inequities amongst minoritized communities. Given the complexities associated with measuring structural racism, we sought to evaluate the relationship between structural racism and racial inequities amongst Black and White patients with NSCLC using an established structural racism index. **Methods:** We conducted a retrospective analysis using Surveillance, Epidemiology, and End Results -Medicare data. Outcomes were: localized stage at diagnosis, stage appropriate evaluation and treatment, and 2-year survival. We used the County Structural Racism (CSR) index, which assesses racial inequity within counties across various domains including criminal justice, education, employment, housing, and health care. We categorized counties into quintiles of the CSR index and estimated multivariable mixed effects logistic regression models to determine the adjusted association between structural racism and each outcome. We included interaction terms between patient race (Black versus White) and CSR to determine whether structural racism moderates the association between patient race and outcomes. We used the results of the regression models to calculate the adjusted predicted probabilities of each outcome across strata of patient race and CSR quintile. **Results:** The cohort included 54,344 individuals (10.3% Black, 89.7% White) diagnosed with NSCLC from 2013-2019. When compared to White patients, Black patients were less likely to be diagnosed at a localized stage (30.9% vs 38.4%), undergo stage appropriate evaluation and treatment (20.3% vs 28.0%), and survive two years after diagnosis (29.2% vs 37.3%) (all $p < 0.001$). Black patients were more likely to live in counties with higher structural racism (8.2% of the population in lowest quintile vs 19.2% in highest quintile). We did not find a clear association between structural racism and our outcomes. However, we did find that patient race moderated the association between structural racism and two-year survival. Specifically, Black patients in areas in the lowest quintile of structural racism had a predicted probability of two-year survival of 28.3% (95% CI, 25.2-31.4) compared to 31.1% (95% CI, 29.8-32.4) amongst White patients, a difference of 2.8% ($p = 0.08$). In areas with the highest structural racism, Black patients had an even more pronounced reduction in the probability of two-year survival (27.4%, 95% CI, 24.6-30.2 vs. 37.5, 95% CI, 34.9-40.1 for White patients), resulting in a disparity of 10.1% ($p < 0.001$). **Conclusions:** Increased structural racism exacerbates the racial disparity in two-year survival experienced by Black patients with NSCLC. Research Sponsor: R01MD017569.

1599 Poster Session

30 year trends in racial disparities for early stage lung cancer treatment. First Author: Olivia Frances Lynch, Yale School of Medicine, New Haven, CT

Background: Racial disparities in lung cancer treatment have been recognized for over 30 years. Our prior work showed that among Medicare beneficiaries diagnosed during 1992-2002, Black patients were less likely to receive curative therapy than White patients. As treatment approaches have evolved and increased attention has been paid to healthcare disparities, it is unclear whether this pattern has changed over time. We assessed temporal trends in racial disparities in receipt of curative therapy from 2005 to 2019, and compared findings to estimates from over 25 years earlier. **Methods:** Using the SEER-Medicare data linkage, we conducted a retrospective cohort study of Medicare fee for service beneficiaries diagnosed with stage I-II NSCLC during 3 time intervals: 2005-07, 2011-13, and 2017-19. Consistent with the prior study, we restricted the sample to Non-Latinx Black and Non-Latinx White patients. Curative therapy was defined as either surgery and/or radiation within 6 months of diagnosis. In our prior study, curative treatment was limited to surgery, as radiation was rarely used as curative therapy at that time. We performed multivariable logistic regression with receipt of any curative therapy as our outcome, controlling for sociodemographic and clinical covariates. We included a time*race interaction to evaluate whether receipt of treatment differed by race over time, and calculated the predicted probability of treatment across time and race group. **Results:** We identified 28,287 patients (7.5% Black) for study inclusion. Black and White patients were similar across most demographic variables; however, Black patients were more likely to have ≥3 comorbidities and to have been hospitalized in the year prior to diagnosis. Overall, receipt of curative therapy was lower among Black patients (69.9%) compared to White patients (83.3%) throughout the study period and across all time intervals (Table). In adjusted analyses, Black patients were less likely to receive curative treatment in all 3 time intervals, with a Black-White difference of -17.6% in 2005-07, -14.2% in 2011-13, and -9.7% in 2017-19 (p-value for time*race interaction = < 0.001). Compared to the 1992-94 and 2000-02 time intervals from the prior study where Black-White difference in receipt of treatment was -11.8% and -14.4% respectively, disparities have persisted. **Conclusions:** Racial disparities in receipt of curative treatment for early stage lung cancer in Medicare beneficiaries have persisted 30 years, with minimal improvement. Research Sponsor: None.

Receipt of curative treatment by race and time period, adjusted.

	1992-1994[a]	2000–2002[a]	2005-2007[b]	2011-2013[b]	2017-2019[b]
Black	73.1	64.9	66.2 (59.6, 72.7)	71.6 (65.8, 77.3)	77.7 (72.3, 83.1)
White	84.9	79.3	83.8 (82.4, 85.1)	85.8 (84.4, 87.1)	87.4 (86.2, 88.6)
Black:White Difference	-11.8	-14.4	-17.6 (-24.3, -10.9)	-14.2 (-20.1, -8.3)	-9.7 (-15.2, -4.2)

[a]Data from prior 2008 study.
[b]Current Study.

1600 Poster Session

At-risk cancer genetic syndrome identification (ARCAGEN-ID): Novel EHR integrated system to overcome disparities in identification and testing for cancer genetic syndromes. First Author: Vinit Singh, Roswell Park Comprehensive Cancer Center, Buffalo, NY

Background: Identifying individuals at-risk for a hereditary cancer syndrome (HCS) is crucial to prevent cancer deaths. While there are established guidelines for genetic testing, less than 30% eligible individuals are tested, with consistently worse rates among underserved. The complexity of guidelines and providers' unconscious bias contribute to these disparities. This project aimed to enhance the identification and testing of at-risk individuals, focusing on underserved populations. **Methods:** NCCN/ACMG criteria for genetic testing were translated into three distinct rule-based conditional logic statements in the EHR. A total of 218 rules that serially evaluate each aspect of an individual criteria, and together roll up into a logic statement of "at-risk for HCS. The rules evaluate personal and/or family history, determine age at onset, and categorize family relationships. A proof-of-concept automated outreach initiative was developed that allowed patients to opt into genetic testing after an informational video was watched was developed. Relevant data were extracted and compared using chi-square test. **Results:** Out of 1.3 million individuals, ARCAGEN-ID identified 59,377 (4.8%) at-risk of an HCS. Of those, 47,000 (79.2%) had not been previously evaluated: 43,051 (79.3%) at-risk for Breast, Ovarian, Pancreas, Prostate related mutation; 3,308 (70.2%) at-risk for Lynch syndrome, and 1,144 (80.5%) at-risk for other HCSs. Among previously identified individuals, 2,340 (18.9%) had a pathogenic variant (PV). Compared to overall population in health system, ARCAGEN group had a higher proportion of female (82% vs 55%, $p < 0.01$), White (78% vs 65%, $p < 0.01$) and non-Hispanic (89% vs 84%, $p < 0.01$) individuals, and had less often Medicaid (16.7% vs 28%, $p < 0.01$). Within ARCAGEN, comparing previously identified individuals with newly identified ones, the latter were significantly more often male (19.9 vs 11.13%, $p < 0.01$), younger (≤45y) (33.6% vs 27.2%, $p < 0.01$), Non-White (22.9& vs 20.5%, $p < 0.01$), and more often on Medicaid (31.5% vs 13%, $p < 0.01$). For the pilot, 126/504 outreached individuals (25%) viewed the video and completed a questionnaire. 43/504 (8.5%) pursued testing, and 7 (16%) had a PV. A total of 7% had prior testing not recorded in discrete fields; 2% declined testing; and 6% sought genetic counseling prior to testing. A higher proportion of African American (AA) individuals opted for testing through this strategy (11%) compared to the overall percentage of this population that was outreached (6%, $p = 0.05$). **Conclusions:** Through this automated system, we were able to identify more non-White individuals and add more Medicaid-insured individuals for testing. Uptake after outreach was higher among AA. Thus, a system like ARCAGEN can help overcome disparities in HCS identification without a relevant increase in resources. Research Sponsor: None.

1601 **Poster Session**

Clinical implications and prevalence of benign ethnic neutropenia (BEN) in breast cancer patients of Middle Eastern ethnicity. First Author: Shruti Prem Sudha, Bahrain Oncology Center, Muharraq, Bahrain

Background: Benign ethnic neutropenia (BEN) commonly affects patients of African and Middle-Eastern descent and is not a true neutropenic state. Patients with BEN have the Duffy-null phenotype on red cells and Duffy phenotyping has been used as a surrogate marker for diagnosis. There is evidence that cancer patients with BEN are not at increased risk of infection with chemotherapy. The primary aim of this study was to assess the prevalence of BEN among breast cancer patients in Bahrain using Duffy antigen phenotyping on red cells. The secondary aims were to study treatment delays and infectious complications in BEN patients. **Methods:** We conducted this retrospective study after obtaining IRB approval. We reviewed records of 493 consecutive breast cancer patients treated in our setting from January 2018 to January 2024. We included patients with neutropenia at presentation (defined as having an absolute neutrophil count [ANC] of $< 1.5 \times 10^3/\mu L$). Patients with Duffy-null phenotype and no identifiable secondary causes of neutropenia were presumed to have BEN. Clinical details studied included drug, and family history, treatment interruptions for neutropenia, filgrastim responsiveness, and episodes of febrile neutropenia. Overall survival (OS) and progression-free survival (PFS) estimation using the Kaplan-Meier method and Cox regression analysis of prognostic factors were performed using R software version 4.2.0. **Results:** Of 493 patients, 72 (14.6%) had a presumed diagnosis of BEN. The median age at presentation was 45 yrs, and the median follow-up duration was 3.6 yrs. 13% patients had metastatic disease at presentation and 11% had triple-negative breast cancer (TNBC). The median ANC at diagnosis was $1.2 \times 10^3/\mu L$ (range $0.4–2.1 \times 10^3/\mu L$). The 4-yr OS was 95% (95% CI, 89–100%) and the 4-yr PFS was 75% (95% CI, 63–89%). Treatment was interrupted due to low ANC in 65% of patients, and the median ANC at which treatment was delayed was $0.8 \times 10^3/\mu L$. 89% patients had received filgrastim and all were filgrastim responsive. Only one patient had uncomplicated neutropenic fever. On multivariable analysis, inferior PFS was seen in patients with metastatic disease (HR, 6.2; 95% CI, 2.17–17.9; $p < 0.001$), and TNBC (HR, 7.73; 95% CI 1.79–33.3; p = 0.006). We did not find any effect of treatment delay on the PFS. **Conclusions:** Ethnic neutropenia is prevalent among breast cancer patients in Bahrain. Duffy phenotyping can be used in place of more invasive tests to identify these patients. Treatment delays due to apparent neutropenia are common, however, response to filgrastim is universal, and febrile neutropenia episodes are rarely seen. Since these patients are not at increased risk of infection, larger studies to identify unique neutrophil thresholds for holding chemotherapy in BEN can help avoid compromising therapy. This can have far-reaching implications in populations with a high prevalence of BEN. Research Sponsor: None.

1602 **Poster Session**

Community-based patient navigation and preventative care among women surviving breast cancer. First Author: Anthony Zisa, Lombardi Comprehensive Cancer Center, Georgetown University Medical Center, Washington, DC

Background: Routine physical exams, mammograms, and Pap smears are essential to long-term follow-up for breast cancer survivors, enabling detection of recurrence and guiding overall health maintenance. Barriers to preventive care adherence over time can be addressed by community-based organizations (CBOs) by providing information and supportive services, including navigation to screening. We studied adherence to preventive care and screening among breast cancer survivors who engaged a national cancer control CBO–examining how sociodemographics, cancer care factors, and quality of life (QoL) were associated with adherence. **Methods:** A secondary data analysis was conducted among N = 777 breast cancer survivors who contacted a CBO for resources, including no-cost patient navigation. Patient-reported outcomes were assessed after 30 days, along with survivorship care planning (SCP) and QoL. An index score was created based upon women's self-reported adherence to receiving routine physical exams, mammograms, and Pap smears at recommended intervals. **Results:** Among survivors, 37% were age < = 46, 19% were non-white, 63% were in a partnered relationship, 23% rated their QoL (general health) as fair/poor, and 47% carried a pathogenic variant in *BRCA*. Medical providers caring for these survivors included primary care physicians (53.6%) and oncology specialists (46.4%). For index scores, 66% were adherent to all 3 recommendations for follow-up, 29% to 2 recommendations, and 6% to < = 1 recommendation. The most adhered to recommendation was a physical exam (97%), and the least was a Pap smear (73%): 88% of survivors reported mammograms at recommended intervals. At the bivariate level, breast cancer survivors who were younger (t, df = 4.59, 711, $p < .001$), non-white, (t, df = -3.27, 267, $p < .001$), in a partnered relationship (t, df = 1.76, 54, $p < .05$), and with better QoL (r = -.09 $p < .01$) were more adherent to guideline-based care. A trend was observed for SCP: survivors who received care summaries (56%), including follow-up instructions (64%), and in written form (45%), were more likely to adhere (r = 0.05, $p < .10$). In a multivariable regression model adjusting for partnership status and SCP, younger survivors (B = 1.13, $p < .001$), who were non-white (B = 1.0, $p < .01$), and with better QoL (B = .09, $p < .05$) were more adherent. **Conclusions:** Survivors can benefit from guideline-based cancer prevention and screening with CBO-led support. Tailored SCP is essential to reinforce life-saving health behaviors and enhance follow-up adherence. Research Sponsor: Centers for Disease Control and Prevention #U58DP005408; #P30CA051008.

1603 **Poster Session**

Mutation rate differences across populations and association with performance disparities in pathology AI diagnostic models. First Author: Po-Jen Lin, Department of Biomedical Informatics, Harvard Medical School, Boston, MA

Background: Previous studies have established artificial intelligence (AI) algorithms to classify cancer types, providing real-time diagnostic support. In addition, AI models have identified previously unknown pathology patterns associated with cancer genomic profiles. However, these models exhibit variable performance in different demographic groups, and the causes remain largely unknown. To address this challenge, we investigated the relationships between biases in AI diagnostic models and mutation rate disparities across populations and evaluated the efficacy of a fairness-aware contrastive learning (FACL) framework in reducing performance disparities. **Methods:** We obtained whole-slide pathology images, mutation rates of the 5 most frequently mutated genes in each cancer type, age, sex, and race from 9,217 patients in The Cancer Genome Atlas across 10 cancer types. We identified tasks with performance disparities across demographic groups, and employed generalized linear models to quantify the relationship between mutation rates and model bias in each cancer type. We further developed an FACL framework, and evaluated its effectiveness in mitigating these disparities using metrics including differences in accuracy (DIA) and equal opportunity. **Results:** Six genomic profile prediction tasks showed significant performance disparities across population groups (Table). Variations in TP53 mutation are associated with differential error rates in serous UCEC v. nonserous UCEC, mixed IDC v. ILC, LUAD v. LUSC, and GBM v. LGG classification tasks. Differences in CDH1 mutation rates were linked to racial disparity in mixed IDC v. ILC and age discrepancy in IDC v. ILC classification tasks. Our FACL framework mitigated performance disparities across demographic groups in 5 out of 6 tasks where standard AI model exhibited significant bias ($p < 0.05$). **Conclusions:** Biases in AI-driven cancer pathology diagnosis stem from disparities in somatic mutation prevalence across demographic groups. Addressing these biases is critical to ensuring fairness and the global applicability of AI tools. Our findings demonstrate that the FACL-based framework effectively reduces performance disparities, making AI-powered cancer diagnostics more reliable. Research Sponsor: None.

Tasks	Mutation	Sensitive Attribute	Groups and Mutation rates			Standard (S) v. FACL (F) models DIA
sUCEC v. nsUCEC	TP53	Race	W	0.34	$p<0.001$	S: 0.13±0.10, $p<0.001$
			B	0.45		F: 0.10±0.05, p=0.088
Mixed IDC v. ILC	CDH1	Race	W	0.29	$p<0.001$	S: 0.07±0.02, $p<0.001$
			B	0.46		F: 0.11±0.04, p=0.233
	TP53	Race	W	0.15	p=0.047	S: 0.12±0.02, p=0.023
			A	0.11		F: 0.10±0.05, p=0.196
IDC v. ILC	CDH1	Age	≥59 yrs	0.11	p=0.038	S: 0.05±0.02, p=0.001
			<59 yrs	0.17		F: 0.05±0.05, p=0.370
LUAD v. LUSC	TP53	Sex	F	0.75	p=0.002	S: 0.12±0.02, $p<0.001$
			M	0.58		F: 0.01±0.01, p=0.154
GBM v. LGG	TP53	Race	W	0.50	p=0.021	S: 0.20±0.01, $p<0.001$
			B	0.33		F: 0.29±0.02, p=0.005

W: White;
B: Black;
A: Asian.

1604 **Poster Session**

Gentian violet compared with methylene blue for sentinel lymph node biopsy in breast cancer: A retrospective analysis from a resource-limited setting. First Author: Mehwish Mooghal, Cancer Foundation Hospital, Karachi, Pakistan

Background: Sentinel lymph node biopsy (SLNB) minimizes morbidity in breast cancer surgeries compared to axillary lymph node dissection. Standard tracers like vital blue (VB), methylene blue (MB) and radioisotopes (RI) are effective but often costly and logistically challenging in low- and middle-income countries (LMICs). Gentian violet (GV), a low-cost alternative, offers potential for resource-constrained settings. **Methods:** A retrospective cohort study was conducted at Cancer Foundation Hospital Karachi, Pakistan between January 2023 - December 2024. The study included 28 patients with breast cancer who underwent SLNB using GV and RI. Sentinel lymph node (SLN) detection rates, concordance between GV and RI, and safety profiles were assessed. Detection was analyzed across tumor grades, histology, receptor statuses, and neoadjuvant chemotherapy (NACT) status. **Results:** The majority of patients were aged 41–50 years (n = 8) and > 70 years (n = 8) and had a BMI in the range of 21–30. Tumor size analysis revealed that T2 tumors were most common (57.1%, n = 16), followed by T3 tumors (21.4%, n = 6). Neoadjuvant chemotherapy (NACT) was administered to 35.7% (n = 10) of patients and all patients were clinically node-negative (cN0) at diagnosis with no distant metastases. Stage II disease predominated (78.6%, n = 22), and invasive ductal carcinoma (IDC) was the most common type (71.4%, n = 20), and 53.6% (n = 15) of tumors were poorly differentiated (Grade 3). Receptor status analysis showed ER/PR positivity in 64.3% (n = 18) of cases, triple positivity in 21.4% (n = 6), while HER2/neu-positive and triple-negative subtypes each accounted for 7.1% (n = 2). GV successfully identified SLNs in 96.4% of cases, with moderate concordance with RI (Kappa = 0.512). GV identified more nodes in 32.1% of patients, while RI identified more in 14.3%; both identified the same number in 50%. The false-negative rate for GV was low (4.2%). Detection rates were consistent across histological types (e.g., invasive ductal carcinoma: 1.94 nodes by GV vs. RI), tumor grades (Grade 3: 1.78 by both), and receptor statuses (triple-positive cases: ~2.4 nodes by GV vs. 2 by RI), with no significant differences. NACT did not impact SLN detection (p = 0.844). No complications or adverse events related to GV dye were observed intraoperatively or during the postoperative follow-up at days 0, 3–7, and 30. The safety profile of GV dye demonstrated no staining-related complications, dermatitis, tattooing, or skin necrosis. **Conclusions:** Gentian violet is a safe, effective, and affordable alternative to MB/VB for SLNB in breast cancer. It demonstrates high detection rates and a favorable safety profile, making it particularly suitable for LMICs. Broader studies are encouraged to validate these findings and further its clinical adoption. Research Sponsor: No funding received.

1605 Poster Session

Comparison of mobile mammography versus urban hospital-based breast cancer screening. First Author: Carla Zeballos Torrez, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA

Background: Breast cancer screening via mobile mammography units (MMU) is used to improve access in medically underserved communities. This study aims to evaluate factors associated with site of screening, recall rates and time to diagnostic resolution for MMU vs hospital-based sites. **Methods:** This retrospective study analyzed screening mammography examinations performed in a MMU and at our large, urban hospital sites during overlapping 2-week periods in 2022 and 2023. BI-RADS, recall and cancer detection rates were assessed. For BI-RADS 0 patients, time intervals between screening and diagnostic imaging and, when indicated, between diagnostic imaging and biopsy, were collected. Area of Deprivation Index (ADI), an index of socioeconomic status for communities, was calculated for each patient. Diagnostic resolution was defined as time from screening to completion of diagnostic work-up. Statistical analyses were performed with chi-square, analysis of variance, and Kruskal-Wallis tests. Cox regression analysis was used to assess factors associated with diagnostic resolution. **Results:** In the MMU cohort (n=516) vs the hospital-based cohort (n=2401), more patients identified as Non-Hispanic Black (68% vs 40%, $p < 0.001$), reported no insurance (71% vs 2.1% $p < 0.001$), had no PCP (35% vs 9.8%, $p < 0.001$), and were in the highest ADI percentile (70% vs 27%, $p < 0.001$). Regardless of screening site, most patients with longer time to diagnostic resolution had a higher ADI percentile; 58% of patients with > 80 ADI percentile ($p < 0.001$) had diagnostic resolution in > 60 days. The MMU cohort had a higher recall rate (18.8% vs 9.9%; $p < 0.001$) and trend towards a higher cancer detection rate (13.6 vs 8.7 per 1000 examinations, p = 0.32) than the hospital-based cohort. Among BI-RADS 0 patients (n=333), there were longer delays to diagnostic resolution in the MMU vs the hospital-based cohort (Table 1). Patients with no insurance were less likely to have diagnostic resolution compared to insured patients (HR: 0.43, 95%CI [0.26,0.71], p = 0.001). **Conclusions:** Compared to hospital-based screening, MMU-screened patients experienced longer times to diagnostic resolution and had higher recall rates. Although MMU offers an effective strategy to improve screening access, our study highlights opportunities for improved patient navigation, social work support, and financial assistance to promote more equitable follow-up of abnormal screening mammograms. Research Sponsor: None.

BI-RADS 0 outcomes.

	Facility N = 236	Mobile N = 97	Overall N = 333	p-value
Median Days from Screening to Diagnostic (IQR)	11 (7, 20)	28 (13, 43)	13 (7, 28)	<0.001
Median Days from Diagnostic to Biopsy (IQR)	12 (7, 18)	11 (6, 24)	12 (7, 19)	0.5
Median Days to Diagnostic Resolution (IQR)	14 (7, 29)	29 (16, 52)	17 (8, 34)	<0.001
Days to Diagnostic Resolution				<0.001
<=30	178 (75%)	42 (43%)	220 (66%)	
30-60	33 (14%)	20 (21%)	53 (16%)	
60+	16 (6.8%)	17 (18%)	33 (9.9%)	
No Follow up	9 (3.8%)	18 (19%)	27 (8.1%)	

1606 Poster Session

Radiotherapy utilization at the fourth most populous province in Indonesia: A single centre study. First Author: Vito Filbert Jayalie, Murni Teguh Memorial Hospital, Medan, North Sumatra, Indonesia

Background: Cancer continues to grow as a health burden in Indonesia, with the current cumulative cancer risk at 14.0%. Along with the rising rate of cancer discovery, treatment effectiveness should be constantly improved. This study was conducted to explore the actual radiotherapy utilization rate (aRUR) of the 10 most common cancers at Murni Teguh Memorial Hospital (MTMH), a cancer referral hospital in North Sumatra. **Methods:** This was a retrospective study utilizing MTMH medical records in 2019. Data on the 10 most common cancers in Indonesia (based on GLOBOCAN 2020) were collected. Completed data underwent double filtering and cleaning before analysis with the Statistical Package for the Social Sciences (SPSS) and Microsoft Excel to calculate aRUR. Further elaboration was made to compare with the Collaboration for Cancer Outcomes Research and Evaluation (CCORE) RUR data. **Results:** A total of 3,928 samples were collected with 74% of patients being female; the mean age is 50 (0,6 to 96) years old; 38% of cancer staging reported (6% stage I; 32% stage II; 34% stage III; and 28% stage IV). The most to least common cancers are breast, colon, rectal, nasopharynx, cervix, ovary, leukemia, prostate, lung, and lymphoma. Out of 457 irradiated cases, radiotherapy was most used in breast (36%), nasopharyngeal (23%), and cervical cancer (23%). There was gap between these three cancers' aRUR to their optimal RUR (oRUR) calculated by CCORE (54.4% for cervix; 52% for nasopharynx; 41.27% for rectum). Optimal radiotherapy utilization was reached only for colon and ovarian cancers. **Conclusions:** Our study shows that a gap between aRUR and oRUR was observed for most cancers treated at MTMH. Several factors may contributed to this result, including patient factors, clinical factors, and administrative/bureaucracy factors. Further study is needed to address the cause and to plan any measures to shorten the gap and optimize radiotherapy. Research Sponsor: None.

1607 Poster Session

Rates and predictors of cancer screening in California (CA) prisons. First Author: Christopher Manz, Dana-Farber Cancer Institute, Boston, MA

Background: Cancer is the leading cause of death in state prisons. Patients diagnosed with cancer in prison are more likely to have Stage IV diagnoses and have worse survival. Rates and predictors of cancer screening in prison and the relationship to stage at diagnosis are unknown. **Methods:** This retrospective study evaluated patients incarcerated in CA prisons in 2014-2023 who met screening criteria for breast, cervical, colon, liver and lung cancers during periods tracked by the prison system (Table). Correctional data were used to identify screening-eligible patients incarcerated during the study period, screening eligibility dates, receipt of screening and periods of incarceration. These data were matched to CA cancer registry data from 2014-2021 using name and date of birth; cancers were identified between the start of the tracking period for each cancer and 2021. For each cancer, we calculated the proportion of: patients who ever received cancer screening, time covered by a screening test (sum of non-overlapping time of screening intervals [e.g., 10 years for colonoscopy] divided by time eligible for screening), and patients diagnosed at Stage IV (stratified by ever-receipt of screening prior to diagnosis). Generalized estimating equations models with logit link adjusted for demographic and incarceration characteristics (e.g. incarcerated in the past year) clustered at the prison+yard level were used to determine predictors of receipt of screening for each cancer and the association of ever-receipt of screening with Stage IV diagnosis. **Results:** The study included 83,174 individuals who were 79% male, had a median age of 51 when first eligible for any screening, and were 33% Non-Hispanic White. Rates of ever receiving cancer screening ranged from 43-87%, and mean proportion of time covered ranged from 30-75% (Table). In adjusted models, receipt of outpatient mental health services, higher security level and recent change in prison or primary care clinician were associated with higher screening rates for most cancers. 597 screenable cancers were diagnosed from the start of each screening tracking period through 2021. 17% of cancers were diagnosed as Stage IV. In the adjusted model including all cancers, patients who ever received screening prior to diagnosis were 60% less likely to be diagnosed with Stage IV disease (OR 0.40, 95% CI 0.24-0.69). **Conclusions:** Cancer screening rates in CA prisons are high and may explain why rates of Stage IV diagnoses in CA prisons are comparable to the general population and lower than in other state prisons. Research Sponsor: None.

	Breast	Cervical	Colon	Liver	Lung
Start of tracking period (all end 6/2023)	1/2014	1/2016	1/2014	10/2015	7/2022
N	3,218	16,238	68,086	5,644	3,406
Ever screened, n (%)	2,408 (75)	11,326 (70)	49,023 (72)	4,935 (87)	1,479 (43)
Mean proportion of time covered	72%	74%	62%	75%	30%
Cancer diagnosed, n	58	12	280	247	-
Stage IV at diagnosis, screened, %	5%	0%	21%	12%	-
Stage IV at diagnosis, not screened, %	7%	0%	35%	21%	-

1608 Poster Session

Implementation of a clinical trial navigation program for cancer patients: Barriers and facilitators identified through stakeholder perspectives. First Author: Milica Paunic, Temerty Faculty of Medicine, University of Toronto, Toronto, ON, Canada

Background: Patient navigation has been highlighted as a solution to improve clinical trial access. The Clinical Trial Navigator (CTN) Program is a Canadian cancer clinical trial navigation program that can be accessed online by patients or healthcare professionals (HCP). Trained individuals search and provide patients and/or oncologists a report of potentially eligible trials for free. Over 550 patients have used the Program since its launch in 2019, but systemic implementation within cancer centers has yet to occur. We aimed to identify facilitators and barriers to implementing the CTN Program in Canadian cancer centers by gathering insights from key stakeholders. **Methods:** Thirty-three 45-minute, virtual, semi-structured interviews were conducted with healthcare/clinical research professionals (CRP; n = 9) and patient-focused stakeholders (n = 24). Interviews were guided by the Consolidated Framework for Implementation Research (CFIR) and analyzed by two independent researchers using thematic analyses with deductive and inductive coding. **Results:** Participants highlighted the importance of patient navigation to address barriers related to the limited availability of clinical trials and difficulty in identifying them, noting that navigation can significantly reduce this workload. *CRP: "We need a program dedicated to look at trials across the board. [The clinical trial unit team] has no time or tools to be able to do this for patients."* Key barriers to implementing navigation were the financial and logistical stressors for patients who may want to enroll onto trials that the navigator finds, particularly when only available in another institution. *HCP: "[Our province] covers only travel for the consultation, so [financing] is a big barrier and needs to be thought through."* Another commonly cited barrier was obtaining the required medical information for the CTN Program to perform high quality clinical trial searches. *Cancer advocacy group leader: "It's got to be very physician structured because [the CTN Program intake form] needs patient records. I'll ask patients what stage they are at and they don't know, so asking them for their medical information [to perform a clinical trial search], they just don't know that."* When the clinical trial search is initiated by patients and the report of potential eligible trials returned to them, patients felt they needed extra support in discussing the report with their oncologist. *Patient: "Every oncologist is different. Some are very easy to talk to...one was extremely difficult...so to have a discussion is very difficult."* **Conclusions:** Our findings provide critical considerations for the successful implementation of the CTN Program in cancer centers across Canada. We have planned program adaptations to address these results and will evaluate changes in uptake and effectiveness of the CTN Program. Research Sponsor: None.

1609 **Poster Session**

Association of West African ancestry, reproductive factors, and deprivation with incidence of triple-negative breast cancer among Black women in the U.S. First Author: Neha Hippalgaonkar, University of Illinois Chicago, Chicago, IL

Background: Black women have the highest incidence of triple negative breast cancer (TNBC) of any racial or ethnic group in the U.S. The TNBC incidence rate among Black women varies substantially by state of residence (Sung H, et al, JAMA Oncol 2023), and the underlying factors driving state level variation are unknown. Genetic ancestry of West Africans and U.S.-born Black Americans (whose ancestry is primarily admixed West African) is significantly different from East Africans, and approximately 10% of the U.S. Black population identify as African immigrants. We used state level data on the number of Black residents who identify as East African immigrants to estimate the proportion of the Black population in that state with West African ancestry (defined as not East African immigrant), and we conducted a mediation analysis of state TNBC incidence data to investigate whether West African ancestry, reproductive patterns, and socioeconomic deprivation influence the relationship between race and TNBC incidence. **Methods:** We obtained state level TNBC incidence rates for Black women (2011-2021) from the U.S. Cancer Statistics Public Use database. State level data on country of birth from the 2020 U.S. census, rates of breastfeeding and fertility for Black residents, and socioeconomic indicators (the 2015 official poverty measure (OPM) and Multidimensional Deprivation Index (MDI)) were obtained from the U.S. Census Bureau. Correlations between TNBC incidence rates and variables of interest were tested with Spearman's correlation test. Causal mediation analysis of TNBC incidence rate differences was performed by estimating coefficients for direct and indirect effects with linear regression models. We calculated estimates of the proportion mediated with 95% confidence intervals (CI) accounting for a priori confounders and potential effect modification at the state level. **Results:** State TNBC incidence rates among Black residents were inversely correlated with the proportion of residents identifying as East African immigrants ($r = -0.42$, $p = .006$) and the rate of breastfeeding ($r = -0.35$, $p = .03$). There was no correlation with fertility rates, OPM or MDI. In unadjusted analyses, East African immigrant proportion at the state level mediated 15.3% ($p = 0.01$) of the differences in TNBC incidence rates. After adjustment for rates of breastfeeding, fertility, and socioeconomic indicators, East African immigrant proportion was associated with 30.1% ($p = 0.02$) of the difference in TNBC incidence rates for Black women at the state level. **Conclusions:** Proportion of East African immigrants and rate of breastfeeding are inversely correlated with TNBC incidence rates in Black women. These factors transmit a portion of state level differences in TNBC incidence, suggesting that West African ancestry partially mediates the higher incidence of TNBC in Black women. Research Sponsor: None.

1610 **Poster Session**

Effects of socioeconomic status on access to next generation sequencing in patients with metastatic breast cancer. First Author: Conchita Martin de Bustamante, UT Southwestern Medical Center, Dallas, TX

Background: Metastatic breast cancer is difficult to treat and a major cause of mortality related to breast cancer. Standard treatment includes therapeutic options that target specific molecular signals and pathways responsible for cancer growth. For metastatic breast cancer, focused next-generation sequencing (NGS) on DNA isolated from the tumor tissue or circulating tumor DNA in the blood has quickly become standard of care to create actionable and personalized treatment plans. In ER+ disease, NGS helps to determine potential second-line therapies. However, these tests are often expensive, limiting their clinical implementation. We hypothesized that limited access to these therapies increases health disparities in clinical oncology. **Methods:** Data from 187 patients with recurrent MBC were obtained from the Dallas Metastatic Breast Cancer Study, a clinical database that was established in 2021 at a single academic medical system to track patient demographics, area deprivation index (ADI), treatments, and other variables. Commercial NGS testing was performed on patient tumor tissue or tumor DNA from blood samples by Tempus and FoundationOne between the years 2014 through 2022. **Results:** Overall, 39% of patients in our dataset received NGS testing. Patients who are not Hispanic/Latino (n=140, OR: 3.99, 95% CI: 1.66-9.61) are 4 times more likely to receive NGS compared to those who are Hispanic/Latino. We then explored whether ADI correlated with access to NGS testing. ADI measures education level, employment, housing quality, and income to rank neighborhoods by SES disadvantage; a higher quartile ADI equates to a greater disadvantage. Our data showed that patients in the lowest quartile ADI are 2.5 times more likely to have NGS testing compared to those in the highest quartile (OR: 2.54, 95% CI 1.07-6.20). To account for different clinical indications for receiving NGS testing, we then looked at NGS trends between tumor molecular subtypes. We observed that ER+ patients were 3 times more likely to have NGS testing compared to ER- patients (n=118, OR: 2.77, 95% CI: 1.45-5.29) and that TNBC patients were less likely to receive NGS testing compared to ER+ patients, however this difference was not significant (n=113, OR: 0.36, 95% CI: 0.13-1.01). In ER+ patient population, we found that Hispanics/Latinos were 79% less likely to undergo NGS testing compared to their non-Hispanic counterparts (n=76, OR: 0.21, 95% CI: 0.06-0.73). **Conclusions:** These results suggest that even in clinically indicated ER+ disease, NGS testing is disproportionately offered to patients with a higher SES, particularly those who are not Hispanic/Latino. Whether these discrepancies stem from the recent adoption of NGS as standard of care or from actual barriers to accessing care should be defined in future studies. However, identifying that these disparities exist promotes awareness for clinicians to offer NGS more broadly. Research Sponsor: None.

1611 **Poster Session**

Trust and communication among sexual and gender minority (SGM) cancer survivors. First Author: Brandon M. Godinich, Texas Tech Health Science Center El Paso, El Paso, TX

Background: Trust and effective communication in healthcare are essential for delivering high-quality cancer care, especially for marginalized groups like SGM patients. This study examines the differences in trust and communication among LGBTQIA cancer survivors and those without (w/o) a cancer history to inform strategies for improving cancer care equity. **Methods:** Data from the nationally representative Health Information National Trends Survey (HINTS) from 2018-2022 was used to evaluate questions on communication, quality of care, and trust in those who self-identified as homosexual, gay, or lesbian, bisexual, or "something else" for sexual orientation. Two cohorts compared SGM participants with prior cancer diagnosis (survivors) and those w/o cancer. Demographic data included: age, gender, race/ethnicity, education, employment, and household income. Analysis was done in STATA with Chi-squared and T-tests testing between SGM survivors and those w/o cancer and multivariate analysis (MVA) focused on SGM survivors. **Results:** In total, 1,258 SGM participants were included, of which 144 (11.4%) were SGM cancer survivors. SGM survivors were older than those w/o cancer history (median 64 vs. 46, $p < 0.001$) but had no significant differences in employment (25.0% vs. 47.2%) or race (White: 79.9% vs 69.5%; Black 21.9% vs 19.6%) (p = NS). Less than half of SGM survivors (44.9%) reported they always or usually had the chance to ask all of their health-related questions during provider visits, this was better than SGM w/o cancer (36.8%, $p = 0.03$). About a third reported that providers always/usually gave adequate attention to their emotions and feelings (37.2% survivors vs 37.5% w/o cancer, p = NS). Most felt they were always/usually adequately involved in decisions about their health care (82.5% survivors vs 82.0% w/o cancer, p = NS). Only 33.1% SGM survivors rated their overall quality of care as excellent/very good within the past year; this was slightly better than surveyed SGM w/o cancer (24.6%, p = NS). Half of SGM survivors (50.9%) trusted information about cancer from doctors, slightly more than for those w/o cancer (46.2%, p = NS). In a MVA limited to SGM survivors, only education was associated with decreased trust of cancer information from a doctor; those with at least some college (OR = 0.51 95% CI 0.26-0.99, $p = 0.048$) or postgraduate education (OR = 0.36 95%CI 0.14-0.92, $p = 0.034$) had less trust compared to those with a high school degree or less. **Conclusions:** This national study shows that patient-reported overall healthcare to SGM survivors is poor. Less than a third of SGM survivors reported good quality of care and less than half felt providers answered all their questions; only half trusted cancer information from a doctor. Concerningly, those with higher education levels were less likely to trust doctors. Future efforts should focus on ensuring that *all patients* benefit from high quality cancer care and communication. Research Sponsor: None.

1612 **Poster Session**

Quantifying financial toxicity in oncology: A comprehensive analysis of prescription cost disparities using public data from 2022. First Author: Charishma Bhimineni, Jefferson Einstein Montgomery, East Norriton, PA

Background: Financial toxicity in cancer care poses a significant burden for patients and healthcare systems. This study analyzed public data to evaluate the financial impact of oncology treatments, focusing on factors such as demographics, insurance type, gender disparities, or geographics. **Methods:** The 2022 Medical Expenditure Panel Survey (MEPS) data was analyzed, focusing on antineoplastic and immunologic agents. Cost distributions, payment sources, and financial burden—defined as prescription costs exceeding 20% of annual household income—were assessed across various insurances and demographic groups (age, gender, race, income, and education). Geographic analyses utilized Federal Information Processing Standard (FIPS) state codes. **Results:** The study included 1,379 oncology prescriptions. Prescription costs averaged 1,569 per prescription (median 388), ranging from 19 to 7,208. Annual costs spanned 2,507 (25th percentile) to 26,857 (75th percentile), with a median of 3,561 and a mean of 14,138. Non-prescription medical costs, such as procedures and hospitalizations, had a median of 45,475 and a mean of 47,509, with some exceeding 132,396 annually. Uninsured patients faced the highest average costs (78,439 annually), followed by Medicare patients (67,979). Medicaid patients had the lowest total costs (53,469). VA/TRICARE patients showed moderate costs (56,619) but higher prescription expenses (16,758). Low-income patients faced the greatest financial burden, spending 11.71% of their income on prescriptions, compared to 5.89% for middle-income and 2.66% for high-income patients. Private insurance beneficiaries faced the highest costs (5,500-6,000), particularly among Black and White patients, followed by Medicare (4,500-5,000). Medicaid beneficiaries incurred lower costs (3,500-4,000), while uninsured patients had the lowest mean costs (2,500-3,000), reflecting limited access to comprehensive treatments. Female patients had higher costs for breast and lung cancer treatments. Black and Hispanic patients relied more on Medicaid. Patients with graduate degrees had higher average costs (4,226) than those with a high school education or less (3,707). Geographically, financial burden was highest in the Midwest, moderate in the Northeast, and mixed in coastal and Southern states. **Conclusions:** Significant disparities in financial toxicity exist across demographics, insurance types, and regions. The gap between mean and median costs underscores the disproportionate financial strain faced by some patients. Policy interventions, including expanded insurance coverage, capped out-of-pocket costs, and targeted subsidies, are needed to improve equity and affordability in cancer care. Research Sponsor: None.

1613 Poster Session

Racial differences in cardiovascular outcomes among cancer patients receiving immune checkpoint inhibitors. First Author: Cho Han Chiang, Department of Medicine, Mount Auburn Hospital, Harvard Medical School, Cambridge, MA

Background: Immune checkpoint inhibitors (ICIs) increase the risk of major adverse cardiovascular events (MACE). We aimed to evaluate disparities in MACE across racial groups. **Methods:** We conducted a propensity score-matched study using the TriNetX Analytics Network database, which includes de-identified data from over 140 healthcare institutions. Adult cancer patients treated with ICIs were included and those with prior MACE were excluded. Patients were grouped into White, Black, Asian, and Hispanic cohorts. The primary outcome was incident MACE, defined as the composite of myocarditis, pericarditis, myocardial infarction, ischemic stroke, heart failure, atrial fibrillation, and venous thromboembolism (VTE) within 12 months of ICI. Matching was performed using variables: age, sex, cancer type, metastatic disease, comorbidities, and cardiovascular medication. **Results:** A total of 58,217 eligible patients were identified, including 44,151 White, 5,876 Black, 5,347 Asian, and 2,843 Hispanic individuals. After matching, cohorts were adequately balanced. Black patients had the highest risk for MACE, with an 18% increased risk compared to White (HR 1.18 [95% CI: 1.06-1.30]) and Hispanic patients (HR 1.18 [95% CI: 1.03-1.35]) and an 80% increased risk compared to Asian patients (HR 1.80 [95% CI: 1.57-1.35]). This increased risk among Black patients appeared to be driven by higher rates of heart failure and VTE. The risks of MACE were similar between White and Hispanic individuals while Asian patients had the lowest risk. **Conclusions:** There were racial differences in immune-related MACE, with Black patients experiencing the highest risk of cardiotoxicity following ICI treatment. Research Sponsor: None.

Hazard ratio for effects of race on cardiovascular outcomes.

	Black vs. White	Black vs. Hispanic	Black vs. Asian	White vs. Asian	White vs. Hispanic	Hispanic vs. Asian
Outcomes	n=5,109 each	n=2,636 each	n=3,095 each	n=2,842 each	n=4,876 each	n=2,157 each
MACE	1.18 (1.06-1.30)	1.18 (1.03-1.35)	1.80 (1.57-2.07)	1.44 (1.28-1.62)	0.98 (0.86-1.12)	1.60 (1.35-1.91)
Myocarditis	0.50 (0.20-1.23)	0.16 (0.04-0.69)	0.61 (0.15-2.57)	1.85 (0.74-4.63)	1.08 (0.49-2.37)	1.66 (0.61-4.58)
Pericarditis	1.10 (0.47-2.56)	1.36 (0.31-6.09)	2.31 (0.71-7.51)	2.99 (1.09-8.21)	1.20 (0.37-3.92)	0.99 (0.20-4.91)
Myocardial infarction	1.09 (0.86-1.39)	1.18 (0.83-1.67)	1.80 (1.28-2.53)	1.42 (1.06-1.91)	1.18 (0.84-1.65)	1.47 (0.96-2.24)
Ischemic stroke	1.23 (0.99-1.54)	1.13 (0.83-1.54)	1.34 (1.00-1.80)	1.17 (0.91-1.50)	0.81 (0.59-1.10)	1.45 (1.01-2.08)
Heart failure	1.33 (1.11-1.61)	1.32 (1.01-1.73)	1.78 (1.37-2.31)	1.38 (1.10-1.73)	1.05 (0.80-1.39)	1.33 (0.96-1.84)
Atrial fibrillation	0.96 (0.79-1.16)	1.19 (0.86-1.64)	1.29 (0.98-1.70)	1.36 (1.08-1.70)	1.26 (0.93-1.70)	0.95 (0.66-1.36)
Venous thromboembolism	1.28 (1.12-1.47)	1.19 (1.00-1.41)	2.34 (1.92-2.84)	1.62 (1.37-1.91)	0.97 (0.81-1.15)	2.09 (1.63-2.69)

1614 Poster Session

Impact of sociodemographic factors and Medicaid expansion on postoperative outcomes for glioblastoma, 2004-2021. First Author: Bhav Jain, Stanford University School of Medicine, Stanford, CA

Background: Glioblastoma (GBM), the most aggressive primary brain tumor in adults, has a median survival of ~15 months despite treatment and exhibits significant disparities in care access. Sociodemographic factors and policy interventions, such as Medicaid expansion under the ACA, show potential to mitigate inequities in other cancers. However, their impact on GBM outcomes remains underexplored. **Methods:** Using the National Cancer Database, we conducted a retrospective study of 85,631 GBM patients treated with surgery between 2004 and 2021. Multivariate regression models and Kaplan-Meier survival analyses evaluated associations between sociodemographic factors (e.g., race, income, education, rurality, insurance status) and outcomes, including postoperative hospital stay, 30-day readmission, 90-day mortality, and overall survival. All models adjusted for key clinical (e.g., tumor size, comorbidities, receipt of chemotherapy/radiation therapy) and patient (e.g., age, sex) covariates. A difference-in-differences analysis assessed the effects of Medicaid expansion on these outcomes. **Results:** Regarding postoperative length of hospital stay, disparities were observed by race (Black vs. White β = 1.45 days [1.22–1.68]; Asian American and Pacific Islander [AAPI] vs. White β = 0.86 days [0.50–1.22]), rurality (urban vs. metro β = -0.31 days [-0.47 to -0.15]), insurance status (private vs. uninsured β = -1.10 days [-1.41 to -0.80]), and education (highest vs. lowest quartile β = -0.28 days [-0.48 to -0.09]). Unplanned 30-day hospital readmission rates demonstrated disparities by race (Black vs. White OR = 1.19 [1.04–1.35]), income (highest vs. lowest quartile OR = 0.84 [0.75–0.96]), and education (highest vs. lowest quartile OR = 1.19 [1.05–1.34]). Moreover, 90-day mortality indicated disparities by race (Black vs. White OR = 0.85 [0.77–0.95]; AAPI vs. White OR = 0.64 [0.53–0.77]), income (highest vs. lowest quartile OR = 0.81 [0.74–0.89]), education (highest vs. lowest quartile OR = 1.13 [1.03–1.23]), and insurance status (private vs. uninsured OR = 0.71 [0.62–0.82]). Finally, overall survival demonstrated disparities by race (Black vs. White HR = 0.88 [0.85–0.91]; AAPI vs. White HR = 0.77 [0.73–0.82]), income (highest vs. lowest quartile HR = 0.83 [0.81–0.86]), education (highest vs. lowest quartile HR = 1.12 [1.09–1.15]), rurality (rural vs. metro HR = 1.06 [1.00–1.12]), and insurance status (Medicaid vs. no insurance HR = 1.09 [1.04–1.15]). Medicaid expansion did not significantly impact any outcomes, including overall survival (DID HR = 0.95 [0.84–1.07]). **Conclusions:** Significant sociodemographic disparities persist in GBM postoperative outcomes, with no improvement from Medicaid expansion. Targeted socioeconomic interventions are needed to address inequities in access to specialized neuro-oncological care and improve outcomes for underserved populations. Research Sponsor: None.

1615 Poster Session

Symptom burden, quality of life (QoL), social and behavioral characteristics in young patients (<40 years old) with cancer: A prospective cohort of 7323 patients across 110 sites in France and Belgium. First Author: Kaïssa Ouali, Gustave Roussy, Drug Development Department (DITEP), Villejuif, France

Background: Cancer in individuals under 40 years old is increasingly recognized as a public health concern, characterized by unique etiologies, biology, and clinical behaviors compared to older populations. Young patients may also face specific physical, psychosocial, and socioeconomic challenges that can influence outcomes which are often suboptimally addressed in routine care. Digital health and specifically remote patient monitoring (RPM) offer a way to track and manage these challenges effectively, increasing access to supportive care. **Methods:** Prospective, observational cohort of 7323 adult patients with cancer participating in an RPM pathway across 110 hospitals in France and Belgium between Jun-2022 and Dec-2024. Patients were grouped by age ($<$ 40 vs. $\geq$40). At baseline, demographic, clinical, and social and behavioral data were collected. Longitudinal symptom burden (e.g., anxiety, pain, nausea) was assessed using validated patient-reported outcomes (PRO-CTCAE). High symptom burden was defined as PRO-CTCAE grade $\geq$3. QoL was measured by EORCT QLQ-C30 summary score. Linear mixed models, adjusted for relevant covariates, were used to compare changes in symptom burden over 12 weeks between age groups. **Results:** Younger patients (n = 350 pts $<$ 40 years) were more often female (77 vs 62%, p $<$ 0.001) and with localized disease (55 vs 45%, p $<$ 0.001). The rate of breast, lung, colorectal and pancreatic cancers represented respectively 157%, 27%, 57% and 17% of the proportion in older adults (p $<$ 0.001). Younger patients also presented with more unfavorable social and behavioral characteristics including higher alcohol consumption (26.3 vs. 15.3%, p= 0.005), tobacco consumption (23.2 vs. 13.8%, p $<$ 0.001), unemployment (17.7 vs 7.2%, p $<$ 0.001) and financial insecurity (23.2 vs 10.9%, p $<$ 0.001). Similar QoL was found at baseline (mean [SD] 76.9 [16.8] vs 76.1 [17.0], p = 0.84). Adherence to RPM surveys was lower in the younger group (74 vs 84%, p = 0.001), who took also on average longer to answer (22 vs 10h, p$<$0.001). Younger patients had higher early (week 1 to 3) symptom burden (anxiety 16.7 vs 10.6%, p = 0.001], fatigue [36.1 vs 30.6, p = 0.05], nausea [30.4 vs 18.6%, p $<$ 0.001], anorexia [16.7 vs 10.6, p = 0.004] and performance status decline [26.8 vs 18.7%, p = 0.012). At 12 weeks, symptom burden improved in both groups, and the between-group difference was no longer significant. **Conclusions:** In this large, multi-institutional cohort, younger patients faced unique physical, psychological and behavioral challenges and experienced higher early symptom burden. Interestingly, by 12 weeks, both groups demonstrated symptomatic improvement, with no remaining differential across age groups. These findings suggest that RPM and supportive interventions may help mitigate disparities in symptom burden over time. Research Sponsor: Resilience Care.

1616 Poster Session

Prevalence of and factors associated with financial toxicity among gastrointestinal cancer patients in Pakistan. First Author: Sehar Salim Virani, Aga Khan University Hospital, Karachi, Pakistan

Background: Financial toxicity (FT) impacts cancer care in low- and middle-income countries (LMICs), affecting treatment adherence and quality of life. This study assesses FT prevalence and associated factors among gastrointestinal (GI) cancer patients across distinct healthcare systems in Pakistan. **Methods:** A cross-sectional study was conducted across three tertiary care centers in Karachi: Aga Khan University Hospital (AKUH, private, fee-for-service), Jinnah Postgraduate Medical Center (JPMC, public, free), and Cancer Foundation Hospital (CFH, private-philanthropy, subsidized). FT was assessed using the Urdu version of the Comprehensive Score for Financial Toxicity–Functional Assessment of Chronic Illness Therapy (COST-FACIT). Multivariable negative binomial regression identified factors linked to high FT. **Results:** Of 375 patients, 44.5% were from AKUH, 33.6% from JPMC, and 21.9% from CFH. Mean age was 50.8 $\pm$ 14.4 years, with 62.4% males. Only 8.3% had health insurance, and the median International Wealth Index (IWI) was 79.9 (IQR: 57.1–95.1). Catastrophic healthcare expenditure affected 41.7%. The mean COST-FACIT score was 16.0 $\pm$ 7.4, with 46.1% experiencing mild FT (score: 14–26) and 41.9% moderate FT (score: $\leq$14). Patients delaying or forgoing care had higher FT (p $<$ 0.001). Borrowing money, selling assets, or cutting essential expenses were strongly associated with increased FT (p $<$ 0.001). Patients at AKUH reported higher FT than JPMC (IRR = 0.84, 95% CI: 0.74–0.97). Younger patients (21–50 years) (IRR = 0.66, 95% CI: 0.46–0.95) and those receiving chemotherapy (IRR = 0.89, 95% CI: 0.81–0.98) experienced higher FT. Females (IRR = 1.36, 95% CI: 1.17–1.58) and higher socioeconomic status (IRR = 1.39, 95% CI: 1.06–1.83) were associated with lower FT. **Conclusions:** Nearly 85% of GI cancer patients faced FT. Younger age, male gender, lower socioeconomic status, and systemic therapy were associated with higher FT. Subsidized care, financial support, and institution-specific strategies are critical to mitigating FT in LMIC healthcare systems. Research Sponsor: None.

Patient characteristics and treatment costs across hospitals.

	AKUH	JPMC	CFH
Gender, n (%)			
Male	109 (65.3)	73 (57.9)	52 (63.4)
Female	58 (34.7)	53 (42.1)	30 (36.6)
Age (yrs), mean (SD)	54.3 (1.1)	44.2 (1.3)	53.6 (1.4)
IWI score, mean (SD)	84.0 (1.5)	52.8 (2.6)	80.4 (2.0)
COST-FACIT score, mean (SD)	16.7 (7.9)	15.3 (7.6)	15.7 (5.8)
EORTC QLQ summary score (Quality of Life score), mean (SD)	78.1 (15.5)	79.3 (17.9)	75.1 (16.0)
Monthly household income (USD), median (IQR)	358.4 (179.2-716.8)	107.5 (43.0-179.2)	233.0 (71.7-358.4)
Out of pocket costs (USD), median (IQR)			
Surgery and associated inpatient	2509.0 (1003.6-4569.89)	0 (0-0)	1433.7 (1075.3-1792.1)
Chemotherapy	1433.7 (573.5-3225.8)	0 (0-304.7)	1469.5 (358.4-1881.7)
Radiotherapy	896.1 (255.4-2150.5)	0 (0-0)	1075.3 (716.8-1792.1)

*Costs converted using 1 USD = 279 Pakistani Rupee.

1617 **Poster Session**

The effect of a vertically integrated health system on the disparity of socioeconomic status seen in cancer stage at presentation. First Author: Robert Michael Cooper, Kaiser Permanente Los Angeles Medical Center, Los Angeles, CA

Background: Earlier stage of diagnosis may lead to more curable disease and less intensive treatment. Vertically integrated health care systems through screening and integrated care delivery model may provide benefit in identifying cancer patients at earlier stage of disease. **Methods:** We examined an insured Southern California cohort of 503,279 patients diagnosed with invasive cancer between Jan 1 2015 and Dec 31 2020 provided by the state SEER Cancer Registry. Stage at diagnosis provided was SEER summary stage in which patients were defined as having local disease or advanced (regional or metastatic) disease. We used geocoded socioeconomic status, race/ethnicity, and hospital of diagnosis as independent variables. For hospital of diagnosis, patients were divided into those diagnosed in Kaiser Foundation Hospitals or not. The first cohort was for cancers with robust screening programs and included breast, cervical and colon (CBC group). The second cohort was all other cancers (non CBC group). We evaluated each of these groups independently. The prevalence of local disease was determined and multilinear regression was used to determine the adjusted odd ratios of being diagnosed with local disease. **Results:** Compared to patients not diagnosed in Kaiser Foundation hospitals (non KFH), patients diagnosed in Kaiser Foundation hospitals (KFH) were more likely to be diagnosed with local disease. 1.14 (95% Confidence Intervals 1.13, 1.16) for the total cohort. We looked at the adjusted interaction of being diagnosed in KFH for each quintile: Highest SES 1.03 (1.00, 1.07), Upper Middle SES 1.11 (1.08, 1.14), Middle SES 1.21 (1.18, 1.25), Lower-Middle SES 1.25 (1.21, 1.29) and Lowest 1.34 (1.29, 1.38). Compared to patients not diagnosed in Kaiser Foundation hospitals (non KFH), patients diagnosed in Kaiser Foundation hospitals (KFH) were more likely to be diagnosed with local disease in the CBC cohort 1.12 (1.09, 1.16) and in the non CBC cohort 1.16 (1.14, 1.17). **Conclusions:** Vertically integrated health care systems have shown advantages in preventive care. We show that insured patients diagnosed in Kaiser Foundation hospitals present with more localized and less advanced disease than patients diagnosed in non KF hospitals. This advantage was seen in a group of patients with established screening program and was also seen in diseases without screening programs. A sub analysis showed that the advantage more pronounced the lower the SES. How a vertically integrated care delivery system provides these advantages deserves further study. Research Sponsor: None.

1618 **Poster Session**

Dihydropyrimidine dehydrogenase (DPD) deficiency–related variants among Mexican patients with gastrointestinal (GI) malignancies. First Author: Enrique Soto Pérez de Celis, University of Colorado Anschutz Medical Campus, Aurora, CO

Background: DPD deficiency is the most important risk factor for developing fluoropyrimidine-related adverse events. Genetic variants causing DPD deficiency are found in 6-8% of Caucasian patients. However, there is limited information on their prevalence in underrepresented ethnic groups, such as Hispanics and Latinos, and testing for these variants is not routinely recommended in Latin America. Our goal was to assess the allele frequency of clinically actionable dihydropyrimidine dehydrogenase (*DPYD)* risk variants defined by the Clinical Pharmacogenetics Implementation Consortium (CPIC) and the European Medicines Agency (EMA) among admixed Mexican patients with GI malignancies. **Methods:** Patients with recently diagnosed GI cancer candidates for fluropyrimidine therapy were recruited from a single institution in Mexico City. After providing informed consent, a blood sample and clinical characteristics were collected. We utilized the Illumina Infinium Global Screening Array (GSA)-to genotype 34 DPYD variants, six of which are known to lead to an increased risk of fluoropyrimidine toxicity and are considered clinically actionable. **Results:** Two hundred and eight patients with a mean age of 62 years (SD 13.2) were included. 47% were female. The most common type of cancer was colorectal (38%) followed by pancreas (22%) and biliary tract (18%). DNA samples from 192 patients passed quality control, of which 156 (62%) received fluoropyrimidines during follow-up. Only 2 patients (1%) were heterozygous for actionable *DPYD* intermediate metabolizer risk variant alleles: one with *c.2846A > T (*rs67376798*, D949V)* and one with *c.1129–5923C > G [*rs75017182; HapB3 SNP *c.1236G > A;* rs56038477]. No patients were found to have other CPIC-listed *DPYD* risk variants. Additionally, we investigated the allele frequencies of other 30 *DPYD* variants and observed low-frequency variation (between 0.260 and 0.0032) in rs56038477, rs1801160, rs17376848, rs1801159, rs1801158, rs45589337, rs2297595, rs200562975, and rs1801265. Several of these may be related to decreased DPYD activity and warrant further analysis regarding their impact on adverse drug reactions. **Conclusions:** In contrast with reports from Caucasic populations, we found a very low allele frequency of *DPYD* actionable variants. Our findings highlight the limitation of current pharmacogenomic testing recommendations and panels, which may not be appropriate for admixed ethnic populations such as Hispanics/Latinos due to disparities in representation. There is a need to study the role of other *DPYD* variants in larger patient samples to understand their role in the toxicity risk of admixed populations in Mexico and Latin America, to explore the use of novel techniques such as Next Generation Sequencing, and to investigate the effect of other related genes on toxicity risk. Research Sponsor: AGA Research Foundation.

1619 **Poster Session**

State-level trends and associated disparities in melanoma burden in the United States. First Author: Furkan Bahar, Mount Auburn Hospital/Harvard Medical School, Cambridge, MA

Background: Melanoma, an aggressive skin cancer, poses a significant public health challenge in the United States despite advancements in detection and treatment due to its high mortality. This study analyzes trends in melanoma incidence, mortality, and disease burden in the US from 1990 to 2021. **Methods:** Data on incidence rates (IR), mortality rates (MR), disability-adjusted life years (DALYs), and estimated annual percentage changes (EAPCs) from 1990 to 2021 were extracted from the Global Burden of Disease 2021 database. Regional trends within the US were evaluated to identify state-level patterns and disparities. **Results:** In 2021, melanoma IR in the US was 27.2 per 100,000, far exceeding the global average of 3.8. Between 1990 and 2021, IR increased by 64.8%, compared to a global rise of 28.8%. Among US states, Maine had the highest IR at 37.8 per 100,000, while the District of Columbia reported the lowest IR at 8.3. Alaska showed the largest relative increase (EAPC of 81.5%), while New Jersey was the only state to report a decline in incidence, with an EAPC of -1.6%. The US melanoma mortality rate was 3.0 per 100,000 in 2021, compared to the global rate of 0.78. US mortality increased by 5.5%, while the global mortality rate rose by 25.8%. West Virginia recorded the highest mortality rate at 4.49 per 100,000, whereas the District of Columbia had the lowest rate at 1.20 and the most significant improvement, with an EAPC of -43.5%. In terms of DALYs, the US reported a rate of 79.2 per 100,000 in 2021, significantly higher than the global average of 21.27. Between 1990 and 2021, DALYs in the US declined by 14.4%, contrasting with an 8.5% increase globally. The DALY/incidence ratio in 2021 was 2.9 in the US, compared to 5.6 globally, indicating notable differences in disease burden across populations. Melanoma disproportionately affected males, with an IR of 33.9 per 100,000 compared to 20.7 in females (male-to-female ratio: 1.6). Mortality rates followed a similar pattern, with males experiencing a rate of 4.0 per 100,000 vs. 2.1 for females, consistent with global trends. **Conclusions:** Despite the decrease in DALYs, melanoma incidence and mortality continue to rise in the US, exceeding global averages. Significant disparities persist across states and genders, reflecting the complex interplay of risk factors and behavioral patterns. The lower DALY/incidence ratio in the United States highlights the likely effectiveness of US treatment options in mitigating disease burden per case. Variations among states may also be attributed to differences in ethnic distribution, which influence genetic susceptibility, healthcare access, and prevention efforts. Research Sponsor: None.

1620 **Poster Session**

Association of allostatic load (AL) and residential segregation with breast biopsy outcomes after screening mammography. First Author: Braelyn Wekwerth, Massachusetts General Hospital, Boston, MA

Background: Allostatic Load (AL) and residential segregation have been associated with the risk of breast cancer (BC). However, the independent effects of AL and measures of residential segregation (MRSs) on cancer detection and the false positive (FP) biopsy rate in a screening mammography population have not yet been assessed. **Methods:** We retrospectively identified women aged ³40 who underwent screening mammography between 1/1/2021-12/31/2021 and subsequent breast biopsy from the Mass General Brigham Biobank. We collected age and self-reported race/ethnicity. Each participant's zip code was geocoded to the corresponding census tract. We computed five MRS indices: Dissimilarity (DD), Isolation (BI), Delta (D), Absolute Centralization (AC), Spatial Proximity (SP). We collected the following biomarkers obtained within two years before the index screen: cardiovascular, metabolic, immunologic, renal lab values. AL was assigned one point for each lab value in the worst quartile and summed (continuous). We collected diagnostic breast imaging and biopsy encounters within 12 months after the index screen. Multiple imputation accounted for missing data. Multivariable logistic regression assessed age, race, AL and each of our MRSs association with cancer detection and FP rates. We applied Rubin's rules to estimate overall odds ratios (OR), confidence intervals (CI), and p-values for all covariates. **Results:** Of the 418 eligible women, 59.6% (N=249) had an FP biopsy, and 66.3% (N=277) had breast cancer, including cases of ductal carcinoma in situ. On average, women were 62 years old (SD=13); 85.6% White. DD was associated with a reduced risk of benign high-risk lesions (OR=0.69, 95% CI:[0.49-0.95]; p=0.025), and homogeneous, affluent census tracts—whether predominantly Black or White—were similarly protective (OR=0.85, 95% CI:[0.72, 0.99]; p=0.041). MRS indices were linked to lower benign high-risk outcomes (e.g. SP, OR=0.53, 95% CI:[0.31, 0.91]; p=0.021). Age and race significantly predicted adverse events (AEs). Older age was consistently associated with increased AEs across all models (OR = 1.09, 95% CI:[1.00, 1.18]). Cancer detection also increased with age (OR = 1.20, 95% CI: [1.10, 1.30]; $p < 0.001$). AL was significantly linked to cancer detection (OR = 1.13, 95% CI:[1.00, 1.28]). **Conclusions:** Some MRSs are associated with cancer detection and high-risk FP. AL remains associated with these cancer and high-risk FP, even accounting for these segregation measures. These factors may contribute to an increased risk of cancer, highlighting the significance of spatial and socioeconomic influences on screening outcomes. Clinical Relevance Statement: AL may serve as a biomarker to enhance biopsy selection following screen-detected mammographic abnormalities, potentially improving cancer detection rates. Research Sponsor: None.

1621 Poster Session

Racial differences in serious immune-related adverse events among cancer patients receiving immune checkpoint inhibitors. First Author: Cho Han Chiang, Department of Medicine, Mount Auburn Hospital, Harvard Medical School, Cambridge, MA

Background: Immune checkpoint inhibitors (ICIs) are associated with an increased risk of adverse events (irAEs). We aimed to evaluate disparities in serious irAEs among patients from different racial backgrounds. **Methods:** We performed a propensity score-matched study using the TriNetX Analytics Network database, which includes de-identified data from over 140 healthcare institutions. We included adult cancer patients treated with ICIs and grouped patients into White, Black, Asian, and Hispanic cohorts. The outcomes were incident composite irAEs, which included pneumonitis, colitis, thyroiditis, hypophysitis, adrenal insufficiency, Stevens-Johnson syndrome (SJS) / toxic epidermal necrolysis (TEN), and hepatitis within 12 months of ICI. Patients were matched using variables: age, sex, ICI type, cancer type, metastatic disease, and underlying comorbidities. **Results:** We identified 72,501 cancer patients who received ICIs, including 56,937 White, 7,027 Black, 5,623 Asian, and 2,914 Hispanic patients. Cohorts were adequately balanced across covariates after matching. White and Hispanic patients showed similar risks of irAEs, both having approximately 30% higher risk of developing serious irAEs compared with Black and Asian patients. Compared with Black patients, White and Hispanic patients had higher risks of colitis and adrenal insufficiency. Compared with Asian patients, White and Hispanic patients had higher risks of pneumonitis, colitis, and thyroiditis. **Conclusions:** White and Hispanic patients have the highest risks of developing serious irAEs. Further research is needed to explore the underlying causes and develop targeted interventions to mitigate these disparities. Research Sponsor: None.

Hazard ratio for the effects of race on irAEs.

	White vs. Black	White vs. Asian	White vs. Hispanic	Black vs. Asian	Hispanic vs. Black	Hispanic vs. Asian
Outcomes	n=7,207 each	n=5,562 each	n=3,314 each	n=3,839 each	n=2,680 each	n=2,224 each
Composite irAE	1.28 (1.16-1.41)	1.30 (1.16-1.45)	1.03 (0.91-1.18)	0.95 (0.82-1.10)	1.30 (1.11-1.52)	1.39 (1.16-1.67)
Pneumonitis	1.55 (0.77-3.12)	1.93 (0.93-4.01)	1.01 (0.42-2.44)	0.68 (0.24-1.91)	2.86 (0.78-11.1)	4.35 (0.96-20.0)
Colitis	1.44 (1.27-1.63)	1.72 (1.47-2.00)	1.04 (0.88-1.23)	1.12 (0.91-1.34)	1.22 (0.99-1.52)	1.69 (1.32-2.17)
Thyroiditis	1.01 (0.81-1.25)	1.61 (1.19-2.17)	1.09 (0.81-1.47)	1.31 (0.91-1.89)	1.41 (0.98-2.04)	1.85 (1.19-2.86)
Hypophysitis	0.34 (0.07-1.67)	0.50 (0.05-5.56)	0.68 (0.11-4.04)	2.00 (0.37-10.9)	0.65 (0.11-3.85)	1.47 (0.24-9.09)
Adrenal insufficiency	1.70 (1.13-2.55)	1.18 (0.79-1.75)	1.10 (0.69-1.77)	0.64 (0.36-1.11)	2.50 (1.20-5.26)	0.89 (0.48-1.67)
SJS/TEN	0.61 (0.15-2.54)	0.05 (0.01-0.40)	0.76 (0.17-3.40)	0.51 (0.15-1.68)	1.43 (0.24-8.33)	0.33 (0.07-1.61)
Hepatitis	1.11 (0.88-1.40)	0.74 (0.59-0.93)	0.88 (0.67-1.16)	0.68 (0.50-0.91)	1.41 (0.99-2.00)	0.97 (0.69-1.37)

1622 Poster Session

Survival disparities between patients with breast cancer with and without HIV at Jaramogi Oginga Odinga Teaching and Referral Hospital (JOOTRH). First Author: Harriet Fridah Adhiambo, Kenya Medical Research Institute, Nairobi, Kenya

Background: Breast cancer and HIV/AIDS pose significant public health challenges. Women living with HIV face higher mortality rates when diagnosed with breast cancer than HIV-negative women. Although advancements in treatment have improved survival outcomes, limited evidence exists on the impact of HIV on breast cancer outcomes in low-resource settings. This study examines survival disparities between breast cancer patients with and without HIV. **Methods:** We conducted a retrospective cohort study of breast cancer patients diagnosed at JOOTRH between January 2013 and September 2024. Data from paper-based records included demographics, clinical data and outcomes (survival status). Survival, defined as time from diagnosis to death or last follow-up, accounted for transfer out, death, being alive, or lost to follow-up. Variables with >20% missingness were excluded. Survival disparities by HIV status were estimated using Kaplan-Meier, with mortality relationships analyzed via Cox Proportional Hazards Model. **Results:** Out of 494 breast cancer patients, 101(20%) were HIV+, 219 (44%) had unknown HIV status, and 174(36%) were HIV-. At diagnosis, HIV+ patients were younger (median: 48, [IQR 40–56]) compared to HIV- patients (median: 51, [IQR 40–64], p=0.030) and had a lower median BMI (23.2 vs. 25.4, p=0.008). HIV positive patients had a longer median time to treatment initiation (56 days, IQR 25–127) compared to HIV-negative patients (44 days, IQR 20–94), although the difference was not statistically significant (p=0.4). In this cohort, 12% (60) of patients had died, with a higher mortality rate among HIV+ patients (17%, 17 out of 101) compared to HIV- patients (14%, 24 out of 174), while loss to follow-up was substantial in both groups (43% HIV+ vs. 37% HIV-, p<0.001). The crude 5-year survival probability was 14% lower in HIV+ patients (59%, [95% CI 38 – 91]) than HIV- patients (73%, [61–87]). Survival, adjusted for age, smoking, employment, and cancer stage, did not vary significantly by HIV status (HR for HIV+ vs. HIV-: 1.13, 95% CI: 0.51–2.50, p = 0.8). However, survival was significantly lower among patients with health insurance (HR = 0.35, 95% CI: 0.12–0.97, p = 0.044) and those with > primary/elementary school education (HR: 0.13, 95% CI: 0.02, 0.88, p = 0.037) compared to those with primary education only. Patients who did not receive treatment had a significantly higher mortality risk (HR = 3.52, 95% CI: 1.54–8.04, p = 0.003. **Conclusions:** In this study, breast cancer patients living with HIV had poorer crude 5-year survival probabilities compared to their HIV-negative counterparts, although the adjusted survival did not differ significantly by HIV status. Factors associated with significantly lower survival included lack of treatment, lower education levels, and absence of treatment. These findings underscore the need for targeted interventions to improve breast cancer outcomes among HIV-positive patients, particularly in low-resource settings. Research Sponsor: None.

1623 Poster Session

Association between Geriatric 8 frailty, guideline treatment, treatment adherence, and overall survival in older patients with cancer (PROGNOSIS-G8). First Author: Helena Møgelbjerg Ditzel, Department of Oncology, Odense University Hospital, Odense, Denmark

Background: Frailty is frequent among older adults with cancer and may affect oncologic treatment tolerance. Frailty screening, with tools such as the Geriatric 8 (G8), is recommended to help guide clinical decision-making. While the G8 has been strongly associated with survival, its relationship with treatment adherence remains less clear. This study aimed to evaluate the association between G8-identified frailty and treatment outcomes in a large cohort of older adults with diverse cancer types. **Methods:** This single-center prospective cohort included adults, age ≥70 years, with solid cancers who underwent G8 screening at their initial oncology consultation. Treatment-related outcomes included one-year overall survival, first-line oncologic treatment adherence within 9 months, and whether patients were offered guideline treatment. Guideline treatment was defined as regimens consistent with recommendations from national guidelines for first-line oncologic treatment, allowing add-on protocol treatment, while less-than-guideline treatment referred to regimens not among first choices, often deemed inferior. Adherence to the doctor-patient selected treatment plan was defined as the absence of discontinuations, dose reductions after treatment initiation, or un-administered treatments (i.e., excluding delays). Data on demographics, comorbidity, cancer diagnosis, treatment, and survival were extracted from medical records. Associations between G8 frailty (≤14/17 points) and outcomes were analyzed using multivariate logistic regression and Cox proportional hazards regression, adjusting (adj.) for confounders. **Results:** Among the 1,398 patients screened, 65% were frail. Frailty doubled the risk of death at one year (adj. HR 2.0, 95% CI 1.7-2.4, p < 0.001). Frail patients who adhered to less-than-guideline treatment had a 69% lower mortality risk compared to frail patients unable to adhere to guideline treatment (adj. HR 0.31, 95% CI 0.21-0.47, p < 0.001). Non-frail patients were more likely to adhere to treatment (adj. OR 2.38, 95% CI 1.49-3.81, p < 0.001) and were more often offered guideline treatment (adj. OR 1.98, 95% CI 1.28-3.06, p = 0.002) compared to frail patients. Lastly, when receiving guideline treatment, non-frail patients had significantly better adherence than frail patients (adj. OR 3.08, 95% CI 1.72-5.52, p < 0.001). **Conclusions:** G8 frailty screening effectively identifies older adults at a higher risk of treatment non-adherence and mortality, facilitating tailored treatment approaches. Our findings suggest that frail patients may benefit from initial less-intensive treatments with potential escalation to improve adherence and survival. Implementing G8 screening in routine practice addresses the unique challenges associated with frailty, ensuring more effective, equitable care for at-risk older adults. Research Sponsor: The Danish Cancer Society; Odense University Hospital; University of Southern Denmark; Agnes and Poul Friis Fond; Dagmar Marshalls Fond; Academy of Geriatric Cancer Research (AgeCare).

1624 Poster Session

Prognostic awareness in older adults with metastatic cancer: Secondary analysis of a randomized controlled trial. First Author: Cristiane Decat Bergerot, Oncoclínicas&Co, Sao Paulo, Brazil

Background: Prognostic awareness plays a key role in patient outcomes, particularly among older adults with metastatic cancer. This secondary analysis of a randomized controlled trial (RCT) evaluated the effect of a Geriatric Assessment-guided Intervention (GAIN-S) on patient responses to prognosis items over time between two arms. **Methods:** Eligible participants, aged 65+, diagnosed with metastatic solid cancers, and undergoing treatment across multiple Brazilian states, were randomized 1:1 into two arms. The GAIN-S included a geriatric assessment (GA), which devised tailored treatment based on identified impairments. Patients in the usual care (UC) arm received standard care. Both arms completed the Illness and Prognostic Awareness Impact Questionnaire (PAIS) at baseline (T1) and 12 weeks (T2), assessing Emotional (10 items; range 0-30) and Adaptive (12 items; range 0-36) domains; each rated on a 4-point Likert scale The change in PAIS (T2 - T1) was calculated for each participant in both the GAIN-S and UC arms, and then the mean changes in PAIS between the two arms were compared via independent t-test. **Results:** Eighty-six patients were approached; 80 provided consent (93% enrollment rate). At 12 weeks, the analytic sample included 77 patients. Demographic characteristics were well-balanced between arms, with a mean age of 74.5 years (SD=6.1), primarily female (55.8%), self-identified as White (71.4%), and 50.4% had at least a college education. The most common cancer types were genitourinary (29.9%), breast (24.7%), and gastrointestinal (22.1%). At T1, no significant differences were noted in PAIS between arms. However, there was significant improvement in PAIS Emotional (UC: mean change=-0.26, SD=1.6 vs GAIN-S: mean change=0.87, SD=1.4; P=0.002) and Adaptive (UC: mean change=-0.07, SD=0.6 vs GAIN-S: mean change=0.74, SD=1.7; P=0.008) domains between in the GAIN-S arm (Table). **Conclusions:** This secondary analysis highlights the impact of GA-guided care on improving prognostic awareness in older adults with metastatic cancer. GAIN-S resulted in significant improvements in Emotional and Adaptive domains compared to UC. Tailored interventions addressing the specific needs of older adults with metastatic cancer may enhance understanding of prognosis and improve adaptive responses. Studies are needed to determine whether these differences translate into meaningful improvements in outcomes. Research Sponsor: None.

Impact of GAIN-S intervention on prognostic awareness.

	Change over time			
	Arm 1 (T2-T1) Mean (SD)	Arm 2 (T2-T1) Mean (SD)	Difference Arm 2 - Arm 1 (SE)	p-value
Emotional Domain 10 items (range: 0-30)	-0.263 (1.62)	0.872 (1.44)	**1.135 (0.35)**	**0.002**
Adaptive Domain 12 items (range: 0-36)	-0.079 (0.67)	0.744 (1.73)	**0.823 (0.30)**	**0.008**

1625 **Poster Session**

National cancer system characteristics and global pan-cancer outcomes. First Author: Edward Christopher Dee, Memorial Sloan Kettering Cancer Center, New York, NY

Background: Approximately 29.9 million cancer cases and 15.3 million deaths are anticipated by 2040 globally. Health systems must invest in cancer system strengthening. A greater understanding of health system factors that can be leveraged to improve cancer control may guide health system planning. Therefore, we conducted a pan-cancer ecological study making use of most recent available national health system metrics for cancer outcomes and health system metrics, spanning the breadth of global income levels across 185 countries. **Methods:** Estimates of age-standardized mortality-to-incidence ratios were derived from GLOBOCAN 2022 for patients with cancer of all ages. Health spending (% of gross domestic product [GDP]), physicians/1000population, nurses and midwives/1000population, surgical workforce/1000population, GDP per capita, Universal Health Coverage Service Coverage Index (UHC index), availability of pathology services, human development index, gender inequality index, radiotherapy centers/1000population, and out-of-pocket expenditure as percentage of current health expenditure were collected. The association between MIR and each metric was evaluated using univariable linear regressions. Metrics with $P < 0.0045$ (Bonferroni corrected) were included in multivariable models. Variation inflation factor allowed exclusion of variables with significant multicollinearity. R2 defined goodness of fit. **Results:** On univariable analysis, all metrics were significantly associated with MIR of cancer ($P < 0.001$ for all). After including metrics significant on univariable analysis and correcting for multicollinearity, the final multivariable model had R2 of 0.8729. Therefore, the following variables were associated with lower (improved) MIR for cancer: 1) nurses/midwives per 1000 population ($\beta = -0.0049$, $P < 0.057$), 2) UHC index ($\beta = -0.0042$, $P < 0.001$), 3) radiotherapy centers per 1000 population ($\beta = -11.21$, $P = 0.072$), and 4) GDP per capita ($\beta = -1.7x10\text{-}6$, $P < 0.001$). On analysis stratified by sex, the following were associated with improved MIR for all cancers among females: 1) UHC index ($\beta = -0.0042$, $P < 0.001$), 2) GDP per capita ($\beta = -9.9x10\text{-}7$, $P = 0.02$), and 3) gender inequality index ($\beta = 0.13$, $P = 0.084$) (R2 0.8699). The following were associated with improved MIR for all cancers among males: 1) nurses/midwives per 1000 population ($\beta = -0.0053$, $P = 0.066$), 2) UHC index ($\beta = -0.0042$, $P < 0.001$), 3) radiotherapy centers per 1000 population ($\beta = -12.37$, $P = 0.076$), 4) GDP per capita ($\beta = -2.31x10\text{-}6$, $P < 0.001$) (R2 0.8485). **Conclusions:** This comprehensive pan-cancer analysis of health system metrics suggests progress towards UHC, strengthening the nursing/midwifery workforce, facilitating access to services such as radiotherapy, and mitigating gender inequality are key priorities in cancer control. These generalizable findings may guide efforts to strengthen cancer systems throughout the world. Research Sponsor: National Cancer Institute/U.S. National Institutes of Health; P30 CA008748; Prostate Cancer Foundation; National, Heart, Lung, and Blood Institute; 1R38HL167238-01 grant.

1626 **Poster Session**

Validating Navya Earthshot: An AI-enabled point-of-care solution for guideline-adherent treatment planning in a decentralized cancer care model. First Author: Umesh Mahantshetty, Tata Memorial Hospital, Homi Bhabha National Institute, Homi Bhabha Cancer Hospital & Research Centre, Visakhapatnam, India

Background: Adherence to guidelines increases overall survival, globally. In resource-constrained settings, ~ 30% of patients receive undertreatment or overtreatment. Despite significant investment in decentralized cancer care—with tertiary hub centers providing support to non-specialized spoke centers—shortage of oncologists creates a knowledge gap, which may be partially addressed by clinically validated AI solutions. Navya is a clinically validated AI solution for cancer patients in use since 2014 which matches patient-specific data to evidence and generates treatment recommendations vetted via asynchronous expert review. Navya Earthshot is a new, provider facing solution for point of care cancer treatment planning for non-specialized providers, and is built as an AI driven search interface on Navya's validated domain model supporting subspecialized expert opinions in oncology. **Methods:** This multicenter, prospective validation took place at 25 hospitals across India participating in a decentralized cancer care model. All patients with breast, oral and lung cancerbetween January and June 2024 with all decisions (curative and palliative; local and systemic therapies) were included. Navya Earthshot matched input patient data available in the patient medical record with National Cancer Grid (NCG) guidelines, and output evidence based treatment plans at the point of care. The output was shared at each center, and concordance was scored by the tumor board/treating oncologists, as well as by a group of domain experts experienced in analyzing NCG guidelines. **Results:** Navya Earthshot processed 1787 decisions in a decentralized cancer care system, pertaining to 40% (725) breast, 20% (351) oral, 40% (711) lung cancer diagnoses respectively. Patients were well represented with respect to age ($<$ 45 years (23%) and $>$ 45years (77%), and early stage (24%); advanced stage (58%) and incomplete diagnostic workup (18%)). Of the 1787 decisions, Navya Earthshot output referred 27% (478) to hub center tumor boards due to presence of uncommon histologies or scenarios not covered by the NCG guidelines (3rd line therapy etc.). In the remainder 73% (1309) decisions, Navya Earthshot output diagnostic or treatment plans. Of these, 85% (1114/1309) were scored concordant with NCG guidelines, and adopted by the local treating oncologist. The remaining 15% (195) decisions were referred to a hub center for treatment planning. **Conclusions:** Navya Earthshot can improve capacity of oncologists in resource-constrained settings and enhance adherence to guideline-driven care in a decentralized cancer care model. In a majority of cases, this point-of-care solution can improve access to care locally, reduce reliance on tertiary hub centers, and improve patient outcomes, globally. Research Sponsor: None.

1627 **Poster Session**

Advancing global equity in cancer care: Comparative environmental impacts of radiotherapy in Brazil and the U.S. First Author: Katie Lichter, Department of Radiation Oncology, University of California, San Francisco, San Francisco, CA

Background: Climate change poses a significant threat to global health, necessitating efforts to address the environmental impacts of oncology care, particularly in low- and middle-income countries (LMICs). Radiation therapy is a cornerstone of cancer treatment, yet its delivery often involves high energy consumption and resource use, contributing to environmental degradation and inequities in health outcomes. Despite these challenges, the environmental footprint of radiotherapy in the Global South remains largely unexplored. This study quantifies the environmental impacts of radiotherapy in Brazil, compares these findings to external beam radiation therapy (EBRT) delivery in the U.S., and explores how sustainable practices may promote equity by reducing operational costs and expanding access to radiation therapy in underserved regions. **Methods:** A life cycle assessment (LCA) of EBRT for ten cancer disease sites was conducted at a radiation oncology clinic (Vitta) in Brasília, Brazil, following ISO 14040 and 14044 standardized methodology. Data on medical supplies, equipment usage, building energy consumption, and staff and patient travel from 2018-2023 was analyzed to assess environmental impacts across nine categories, including greenhouse gas emissions, air pollution, and carcinogenic potential. These results were compared with a previously published LCA of EBRT across four U.S. healthcare centers. **Results:** Radiotherapy at Vitta had a lower environmental impact across all categories compared to U.S. centers. Transit-related emissions were the largest contributor at Vitta, though they remained lower than those in the U.S. due to shorter travel distances (median 15 miles/week by public transit at Vitta vs. 48–90 miles/week by car in the U.S.). Vitta's reliance on hydroelectric energy eliminated emissions from building heating and reduced cooling-related emissions to 9.3% of the clinic's total footprint, compared to 74.0% at U.S. sites using mixed-grid electricity and natural gas. However, impacts from medical supplies at Vitta were higher across all categories, reflecting opportunities for resource optimization. **Conclusions:** This study provides novel insights into the environmental impact of radiotherapy in an LMIC context, underscoring the importance of regional differences in care delivery. The reduced environmental footprint at Vitta highlights the value of sustainable practices, such as renewable energy and public transit, in mitigating the health sector's climate impact while reducing operational costs. These findings support the development of adaptable, scalable models for global radiation oncology, particularly in publicly funded and rural clinics, to expand access and promote equity in cancer care. Future research should prioritize environmentally sustainable strategies that align with the unique needs of LMICs and underserved populations. Research Sponsor: None.

1628 **Poster Session**

Achieving global breast cancer initiative key performance indices for breast cancer patients in Botswana by HIV status. First Author: Tara Friebel-Klingner, Johns Hopkins University, Baltimore, MD

Background: Low- to middle-income countries have disproportionately higher breast cancer (BC) mortality rates, partly due to late-stage diagnosis. In people with HIV (PWH), BC mortality is worse compared to those without HIV. The WHO's Global Breast Cancer Initiative (GBCI) proposes to reduce mortality through 3 identified pillars: (1) health promotion for early detection with at least 60% of invasive BC diagnosed at stage 1 or 2; (2) timely diagnosis, where evaluation, imaging, and pathology are completed within 60 days from first doctor's appointment; and (3) $\geq$80% of patients completing treatment. Few real-world data exist on these key performance indices in PWH. Understanding the influence of clinical and demographic factors associated with achieving the GBCI pillars can inform tailored interventions to increase BC survival. We aimed to assess pillars 1 and 2 in BC patients presenting to a referral hospital in Botswana, by HIV status. **Methods:** This prospective BC cohort included patients $>$18 years, presenting for BC care at Princess Marina Hospital between 2015 and 2023. Patients with unknown HIV status and/or unknown stage were excluded. Pillar 1 was assessed using the cancer stage documented in the medical chart. Pillar 2 was assessed using patient recall of first-contact with health facility and pathology report date. We characterized socioeconomically disadvantaged districts as those with poverty rate $\geq$20% and $<$ 100% of the population living within 5km from a health facility. Descriptive statistics and logistic regression were used. Results were stratified by HIV status. All p-values were two-sided. Data was analyzed using STATA 18.5. **Results:** 655 patients (median age: 51.2, IQR 42.4, 63.4) met eligibility criteria. 212 (31.8%) were PWH and 11 (1.7%) men. 180 (27.1%) attained pillar 1, and 59 (9.3%) attained pillar 2. PWH were younger (48.9 vs. 58.6; $p < 0.001$) and more likely to be single (70.3% vs. 47.3%; < 0.001). There was no significant difference between rates of PWH and those without HIV achieving both pillar 1 (23.1% vs 28.9%, p = 0.12) and pillar 2 (11.4% vs 8.3%, p = 0.2). However, PWH had a significantly shorter interval from first contact with the health facility to completed pathology (11.9 months vs. 20.1 months, p = 0.013). There was no significant difference between residents of socioeconomically disadvantaged districts versus non-residents in achieving pillar 1 (29.7% vs. 27.0%, p = 0.72) or pillar 2 (8.3% vs. 9.3%, p = 0.84). **Conclusions:** Majority of BC patients presenting to the referral hospital in Botswana did not achieve the GBCI pillars 1 and 2. However, PWH had significantly less diagnostic interval, which may be reflective of frequent contact for PWH in established care and may present an opportunity for care integration for PWH. Early detection and patient navigation interventions may potentially help Botswana achieve the WHO's GBCI goals and reduce BC mortality. Research Sponsor: Fogarty International Center K01TW011481 Award; Doris Duke Charitable Foundation Fund to Retain Clinical Scientists at Penn/CHOP.

1629 **Poster Session**

Disparities in exercise referral practices and barriers among oncologists in public and private institutions in Latin America. First Author: Paulo Gustavo Bergerot, Oncoclínicas&Co, Medica Scientia Innovation Research (MEDSIR), Sao Paulo, Brazil

Background: Exercise offers significant benefit for patients with cancer, improving physical function, quality of life, and treatment-related outcomes. However, barriers such as limited referral practices and insufficient knowledge hinder its integration into care. This study compared referral practices, exercise assessment, and physicians' perceptions in public (PUB) and private institutions (PRI). **Methods:** A cross-sectional survey of 454 physicians from 21 Latin American countries was conducted using a 25-item questionnaire on referral practices, patients' exercise habits, and perceived barriers and facilitators to implementing exercise programs. Descriptive statistics summarized respondent characteristics and adherence to exercise-related practices. Chi-square tests were used to compare differences in referral practices and perceived barriers/facilitators between physicians working in PUB versus PRI institutions. **Results:** Out of 454 participants, most were from PUB (52%), mainly from Mexico (17%), Brazil (12%), and Colombia (10%). In the PRI (48%), Brazil led with 51%, followed by Argentina (18%), and Peru (8%). Female representation was higher in PUB compared to PRI (57% vs. 43%, P = 0.01). Physicians in PUB were less likely than those in PRI to assess exercise habits (53% vs. 18%, P = 0.001), refer patients (72% vs. 36%, P = 0.001), or provide guidance (56% vs. 12%, P = 0.001). Resource limitations were more common in PUB (e.g., no referral location: 86% vs. 70%, P = 0.04). Barriers included treatment side effects (PUB: 66% vs. PRI: 40%, P = 0.001) and lack of knowledge on prescribing exercise (PUB: 63% vs. PRI: 27%, P = 0.001). Physicians in PUB emphasized facilitators like access to qualified professionals (90% vs. 66%, P = 0.001) and personal experience (90% vs. 80%, P = 0.01). **Conclusions:** This study reveals significant disparities in cancer exercise practices between oncologists in public and private institutions across Latin America. Oncologists in public institutions were less likely to assess exercise, refer patients to exercise programs, and provide guidance. They also reported greater barriers, such as treatment side effects and lack of knowledge on exercise prescription and resources. Facilitators such as access to qualified professionals were less prominent in public institutions. These findings highlight the need for targeted interventions to improve exercise integration in cancer care, particularly in resource-limited settings. Research Sponsor: None.

1630 **Poster Session**

Investigating gender demographics and equity among hematologists. First Author: Florence Broussais, Institut Carnot CALYM, Lyon, France

Background: Despite a substantial number of women in the field of hematology, representation in leadership roles remains inconsistent with ~50% of women among medical graduates in many countries. This survey of hematologists sought to examine gender demographics and explore experiences with professional development including mentorship, involvement in and leadership of clinical trials, and opportunities for career advancement. **Methods:** An international online survey of hematologists was developed collaboratively with the Women in Lymphoma (WiL) global organization in partnership with the HERmatology initiative (AstraZeneca). It was distributed to and by the membership of WiL. All participants were licensed medical practitioners, self-characterized on gender, age, years of practice, country of practice, and seniority of role. Statistical differences between males and females were calculated by pairwise z-tests with a significance level of 90%. **Results:** From October to December 2024, 237 hematologists from 34 countries were surveyed: 182 female and 55 male. The proportion of females to males in hematology practices significantly favored females (53% [51, 56] vs. 47% [44, 49]). Heads of Department (60% [55, 66] vs. 40% [35, 45]) and direct supervisors (59% [54, 64] vs. 41% [36, 46]) were significantly more likely to be male. Females reported serving as Principal Investigator significantly less frequently for industry-sponsored clinical trials over the past 12 months than males (2.1 vs 0.9, $p < 0.1$), but no significant differences as a Site Investigator (3.4 vs 2.4, p = 0.2). No differences were observed in female vs. male participation or leadership in cooperative group / academic clinical trials. There was a trend for fewer female physicians invited to write an article or publication in the past 12 months compared to males (2.7 vs. 4.2, p = 0.15), as well as fewer opportunities to receive public recognition from a senior colleague (1.1 vs. 1.9, p = 0.15). Females overall were significantly less likely to have clinical ($p < 0.1$) or career mentors ($p < 0.1$), but earlier-career females were more likely than later-career females to have both ($p < 0.1$). 'Family or caregiving responsibilities' was the top factor discouraging women from pursuing careers in hematology (86% agreed), followed by a 'Lack of representation of women in leadership positions' (59% agreed). **Conclusions:** Differences were noted between males and females across several career dimensions, including representation in leadership roles, involvement in industry-sponsored clinical trials, and access to mentorship. These results underscore the continued need for systematic efforts to reduce unconscious bias and promote greater diversity within hematology. Providing additional structured support, particularly to boost female leadership in industry-sponsored trials, will help advance gender equity, ultimately benefiting both medical progress and patient outcomes. Research Sponsor: None.

1631 **Poster Session**

Clinical profiles, patient expectations and outcomes from an integrative oncology clinic in India: A novel integrated model of care in oncology. First Author: Kanakavalli K. Kundury, JSS Academy of Higher Education & Research, Mysuru, India

Background: Integrative approaches are used in Oncology care, often as an auxiliary measure to the Standard of Care (SoC). There is paucity of data regarding Integrated oncology model approach combining alternate systems of medicines like Ayurveda & Siddha, Yoga and Dietary modification recommendations along with SoC . In this study, we present an audit of this novel Integrated oncology model of care provided by online and in-patient consultations at Isha Integrative Oncology Clinic (IIOC), Isha Health Solutions (IH), Coimbatore, India. **Methods:** A clinical audit was conducted for 514 patients who have received care through Integrated oncology consultations (in-person or online) at IIOC from January 2016 to July 2024. This abstract focuses on the statistical analysis of data of the initial 196 consecutive patients based on descriptive data from clinical proformas and follow-up visits for symptomatic response outcomes. Updated data will be presented at the conference. **Results:** Among 196 patients analysed, 99% of patients had online consultations. The median age was 52yrs (7-81yrs) and Male: Female ratio was 1: 1.3. 50% belonged to age group 40-60 yrs whereas 29% were between 60-85 yrs. Most common cancers in males were hematological cancers (20%), prostate cancers (11%), GI cancers (11%) and in females were breast (26%), ovary (10%) and colon (5%). The most common stage was Stage 4 (58%) followed by Stage 3 (40%). Most common symptoms were pain (49%), anorexia (43%), fatigue (42%), lack of sleep and anxiety (39%). Most common side effects of chemotherapy were fatigue (32%), constipation (25%), anorexia/weight loss (25%), pain (16%) etc. Most common expectations were cure/avoid relapse (32%), symptomatic relief (15%), reduction from chemotherapy side effects (11%), integration of Yoga (10%) etc. Only 6% of patients wished to avoid chemotherapy. Integrated oncology model based on complementary systems of medicine (Ayurveda & Siddha), dietary changes and yoga was provided to all patients (100%). After using this model of care, improvement in cancer-related symptoms was reported by 90% of patients and compliance seen in 73% of patients. **Conclusions:** Our study is one of the largest clinical audits in Integrative oncology in published literature. Younger patients and advanced cancer patients more often seek integrative oncology care and main expectation is to achieve better cure rates and symptomatic relief. In this study, all patients were provided a novel integrated oncology model with alternative medicines (Ayurveda & Siddha), yoga, and dietary modifications in addition to their ongoing SoC resulting in good symptomatic relief and high compliance rates. Integrative oncology model incorporating alternative medicine, yoga, and dietary changes can be effectively offered to cancer patients alongside standard treatment. Further prospective studies are warranted. Research Sponsor: None.

1632 **Poster Session**

How do health concerns present in cancer survivors who require interpreters? Database analysis of a structured survivorship clinic for early-stage cancer. First Author: Lawrence Kasherman, Concord Clinical School, Faculty of Medicine and Health, University of Sydney, Concord, NSW, Australia

Background: Cancer survivors (CS) of Culturally and Linguistically Diverse (CALD) backgrounds face disparities in care. We aimed to compare demographics and health concerns of CALD CS with non-CALD CS following completion of primary treatment. **Methods:** The Sydney Cancer Survivorship Centre (SCSC) database was analyzed to compare baseline differences in demographics and health concerns between early-stage CS of solid tumor or hematologic cancers requiring interpreters (CALD CS) during initial consultations to those who did not (non-CALD CS). Descriptive statistics were used to illustrate distribution by age, gender and tumour type. Survivors completed questionnaires on symptoms, quality of life (QoL), distress, exercise time and were assessed by a psychologist for fear of cancer recurrence (FCR). Univariate analyses were used to determine differences at presentation to the survivorship clinic between CALD and non-CALD groups. **Results:** From September 2013 to April 2024, 939 initial consultations (median 10.9 months from diagnosis) with consenting CS were conducted at SCSC. 15% (n = 137) required interpreters in 21 different languages (Mandarin (n = 48, 35%), Korean (n = 26, 19%) and Cantonese (n = 19, 14%)): 83 (61%) used professional interpreters, 25 (18%) family/friends. CALD CS were more likely to be female (58%), aged 40-64 (51%) and have colorectal cancer (55%). Common symptoms in CALD CS of at least moderate severity included fatigue (39%), numbness (32%), and pain (31%), not significantly different to non-CALD CS. Significantly lower proportions of CALD CS reported trouble concentrating (19 vs 29%, p = 0.023), hot flashes (14 vs 23%, p = 0.017) and problems with sexual function (12 vs 20%, p = 0.032). CALD CS were significantly more likely than non-CALD CS to report less minutes/week doing vigorous (13.2 vs 32.8; $p < 0.001$), moderate (32.3 vs 73.0; $p < 0.001$) and resistance exercise (4.6 vs 18.7; $p < 0.001$), but more light exercise (219.6 vs 115.5; p = 0.041). Mean global FACT-G QoL score for CALD CS was 77.4 (SD 20), with physical (mean 21.4, SD 6) and emotional (mean 17.6, SD 5) domains most impacted; these were not significantly different from non-CALD CS scores. There were no significant differences between groups in mean distress thermometer scores (3.09 vs 3.39/10; p = 0.288), rates of moderate-to-severe distress (36 vs 41%; p = 0.952) or rates of psychologist-assessed moderate-to-severe FCR (19 vs 28%; p = 0.228). **Conclusions:** CALD CS experience similar physical and psychosocial health concerns to non-CALD CS at initial survivorship clinic consultations but are less likely to report issues with sexual function, concentration and hot flashes, and are more likely to exercise less. Future work should focus on longitudinal effects and comparisons over time, with particular focus on addressing cultural sensitivities and increasing exercise intensity. Research Sponsor: Australian Government, National Health and Medical Research Council; 2021964; Cancer Institute New South Wales; 2021/ CBG0002; Australian Government, National Health and Medical Research Council; APP1176221.

1633 **Poster Session**

Living beyond cancer: The long-term impact of breast cancer diagnosis on cognitive function. First Author: Cheng Peng, Brigham and Women's Hospital, Boston, MA

Background: While some clinical studies report greater cognitive difficulties in middle-aged women diagnosed with and treated for breast cancer over the short-term, observational studies of older persons, with longer follow-up, found that a history of cancer was associated with lower Alzheimer's disease risk. We estimated the relation of breast cancer and treatment history with cognitive status and rate of decline among older women. We further divided breast cancer survivors by: (1) time since cancer diagnosis (assessing recency), (2) age of cancer onset (reflecting body aging at diagnosis), and (3) stage (capturing disease aggressiveness). To evaluate any overlap in shared or opposing genetic risk, we estimated cognitive status by breast cancer polygenic risk score (PRS). **Methods:** A cognitive sub-study was initiated in 1995-2001 in the Nurses' Health Study, including 1,378 breast cancer survivors and 14,196 cancer-free women. Breast cancer diagnoses were self-reported and confirmed by medical records; treatment was self-reported. Cognitive function was assessed up to 4 times (over a mean of 6.6 years) and combined into 4 outcomes: global composite score, Telephone Interview for Cognitive Status (TICS), verbal memory, and working memory. We used linear models to assess breast cancer history and treatment with cognitive status (averaged across follow-ups). We used mixed-effects models to assess breast cancer history and treatment with rate of cognitive decline. We computed a breast cancer PRS and evaluated cognitive function across quartiles of PRS. **Results:** The mean age of breast cancer diagnosis was 65.4 years, and the mean time between cancer diagnosis and baseline cognitive assessment was 8.6 years. We observed similar distributions of key risk factors for AD between women with and without history of breast cancer, including age, education, depression, and physical activity. No significant differences in global cognitive status were noted comparing women with a history of breast cancer with those who were cancer-free. Associations did not differ by age of cancer onset ($<$ 65 vs. $\geq$65 years), time since diagnosis ($<$ 5 vs. $\geq$5 years), or stage. Genetically predicted breast cancer risk was not associated with the global cognitive status. Women with breast cancer and treated with hormone therapy, chemotherapy, and/or radiation therapy had similar global cognitive status compared to cancer-free women. No significant differences by breast cancer history were observed for TICS, verbal memory, or working memory. Over the modest follow-up time, we observed no significant differences in cognitive decline between women with a history of breast cancer and cancer-free women. **Conclusions:** We observed no association of history of breast cancer or breast cancer treatment with cognitive function status or rate of decline, suggesting there is neither harm nor benefit of breast cancer diagnosis on long-term cognition. Research Sponsor: National Institute on Aging.

1634 **Poster Session**

Blended survivorship and palliative care for patients with advanced lung cancer receiving targeted therapy: An open pilot. First Author: Laura A. Petrillo, Massachusetts General Hospital, Boston, MA

Background: Targeted therapy improves survival and quality of life for patients with advanced non-small cell lung cancer (NSCLC) with driver alterations. However, advanced NSCLC remains incurable, and the timing of progression on targeted therapy is unpredictable. Thus, many patients live with an abiding, distressing sense of uncertainty. To better support patients with advanced NSCLC receiving targeted therapy, we 1) developed and refined a blended early palliative care and survivorship intervention and 2) conducted an open pilot to further refine the intervention. **Methods:** We conducted a review of evidence and prior palliative care and behavioral health interventions to inform the development of POISE, a structured, supportive care intervention for patients with advanced NSCLC receiving targeted therapy, in which trained palliative care clinicians aim to enhance patient coping with uncertainty, setting lifestyle goals, and prognostic awareness. To refine POISE, we first conducted qualitative interviews with 20 community partners, including patient/caregiver advocates, palliative care clinicians, psychologists, and oncologists. We elicited feedback on POISE intervention content and delivery. We used rapid analysis to analyze interview transcripts and identified themes, with which we finalized POISE (4 monthly one-hour palliative care visits). We then conducted an open pilot study of POISE among 10 patients diagnosed with advanced NSCLC with a targetable mutation (i.e., EGFR, ALK, ROS1 or RET) in the past 6 months who were receiving care at a single academic cancer center. All participants received POISE and completed self-report surveys at baseline and at 12 and 20 weeks. Participants rated their satisfaction with POISE and completed exit interviews at 20 weeks. We used a framework approach to analyze exit interviews and identify themes for further intervention refinement. **Results:** Qualitative interviews highlighted a need to strengthen the POISE clinician training and supervision plan to increase palliative care clinicians' behavior modification therapy skills. We revised the POISE manual to be more flexible to accommodate patient choice in session focus and added a list of community organizations to support ongoing behavior change. With the revised intervention, we then initiated the POISE open pilot. We approached 13 eligible patients, of whom 10 (mean age = 67 years, 5 female, 5 male) consented to participate. Most (8/10) patients completed all 4 sessions and all surveys. All (8/8) patients reported that POISE was helpful and would recommend it to others. In exit interviews, patients suggested incorporating caregivers in sessions and adding a patient-facing workbook to assist with skill acquisition. **Conclusions:** POISE warrants further study in a feasibility pilot randomized controlled trial. Clinical trial information: NCT04900935. Research Sponsor: National Cancer Institute.

1635 **Poster Session**

Experiences and preferences of cancer survivors across the immunotherapy journey. First Author: Shelley Fuld Nasso, National Coalition for Cancer Survivorship, Silver Spring, MD

Background: Immuno-oncology (IO) drugs are recommended by guidelines for several tumor types and can significantly improve survival in patients with cancer. As patients experience long-term care due to extended survival, it is important to understand the challenges of survivorship and experiences receiving IO. Here, we present IO treatment experiences and preferences for IO based on modes of administration among cancer survivors. **Methods:** A web-based survey was administered to US cancer survivors in the fall of 2024. Patients were recruited via physician referral and were eligible to participate if they were $\geq$ 18 years of age, diagnosed $\geq$ 1 year prior with any solid tumor cancer (any stage), and received IO within the past 5 years. The survey included the Quality of Life-Cancer Survivor (QoL-CS) scale (range 0–10; higher scores indicate better QoL) and a direct preference exercise. The preference exercise asked patients to indicate whether they would prefer IO be administered via subcutaneous (SC) injection or intravenous (IV) infusion and asked patients to rank the influence of common characteristics of each administration on preferences. Study variables were analyzed descriptively. **Results:** The mean (standard deviation [SD]) age of patients (N = 100) was 57.8 (7.2) years; 46% were White and 51% were male. The most common tumor types reported were lung (26%), melanoma (14%), kidney (12%), and colon (10%). Mean (SD) time since cancer diagnosis was 4.1 (2.7) years and mean time since starting IO was 2.4 (1.5) years. Most (72%) patients reported that a typical visit for receiving an infusion lasted between 1–2 hours and most (56%) traveled 30–60 minutes to receive their infusion. Some patients experienced interrupted access to their most recent IO treatment due to transportation delays (24%) and not having someone to accompany them to treatment (24%). The average QoL-CS score was moderate (mean [SD], 5.1 [1.3]) and 57% of patients agreed that IO improved their QoL. Yet, 42% and 48% noted that daily activities and physical health, respectively, were negatively affected by their most recent IO treatment. Most patients (92%) preferred a hypothetical SC injection over IV infusion; the top SC injection characteristics influencing this preference were no need to access the vein with an IV catheter, the amount of time it takes to be administered (described as 5 vs 30 minutes), and the potential for more flexibility in scheduling/location of receiving IO treatment. **Conclusions:** Our study found that IO treatment improved the QoL of most cancer survivors. However, challenges to receiving IO, including the time required for travel and administration, were common. Most patients in our sample would prefer a SC administration of IO over an IV infusion, suggesting that less-invasive modes of administration requiring less time and greater flexibility may present opportunities to improve the patient treatment experience. Research Sponsor: Bristol Myers Squibb.

1636 **Poster Session**

Health related social needs in an urban academic breast cancer survivorship program. First Author: Mumtu Lalla, Montefiore Einstein Comprehensive Cancer Center, Bronx, NY

Background: Health-related social needs (HRSN) impact cancer care and are associated with late stage at diagnosis (dx), prolonged time to therapy initiation, and poor outcomes. Little data exists regarding long-term impact of cancer dx and therapy on HRSN in late survivorship. We evaluated associations of cancer therapies with HRSN in a diverse cohort of breast cancer (BC) survivors seen in an urban academic medical center. **Methods:** HRSN screening was completed by BC survivors seen in the cancer center survivorship program in 2023. Survivors were 4 or more years (yrs) from dx of Stage 0 to III BC, with all therapy complete (including endocrine therapy) and no evidence of metastasis. HRSN screens were compared with those completed by newly diagnosed (dxed) BC patients (pts) and adult general medical pts. Charts of survivors were reviewed for details of BC dx and treatment [stage, hormone receptor (HR) and HER2 status, type of surgery, and use of chemotherapy, radiation, and endocrine therapy]; as well as demographic data (age, race, ethnicity, insurance status, ZIP code). Neighborhood distress was categorized using Distressed Communities Index (DCI). Associations of clinical and demographic factors with HRSN in BC survivors were evaluated by Chi-Square and ANOVA tests. **Results:** 465 BC survivors [177 (38%) Black, 228 (49%) Hispanic] completed HRSN screening. Median age at assessment was 68 (range 43-98) and at dx was 57 (range 27-89); median time from dx was 11.25 yrs (range 4-35). 63.5% resided in distressed ZIP codes; 26.4% in at-risk ZIP codes. Most common HRSN in survivors completing their first HRSN screen (n = 395) were housing quality (5.3%) and food insecurity (4.8%). BC survivors were less likely to endorse HRSN than newly dxed BC pts (16.7% vs 24.0%, p = 0.03), but had similar HSRN as general medical pts (16.7% vs 14.6%, NS). Among survivors, younger age at BC dx (p = 0.006) and at HRSN screen (p = 0.004) was associated with greater risk of HRSN, with pts dxed prior to 57 almost twice as likely to endorse HRSN as those dxed after 57 (22.7% v 12.6%, p = 0.004). Younger survivors with HRSN were more likely to reside in distressed ZIP codes (p = 0.03). Hispanics seen in new survivorship visits were more likely to endorse HRSN than Hispanics seen in follow-up and than non-Hispanics seen in new or follow-up visits (p = 0.03). Race, insurance status, time from BC dx, stage, HR and HER2 status, extent of surgery, and use of chemotherapy, radiation, or endocrine therapy were not significantly associated with HRSN in survivors. **Conclusions:** In this diverse cohort, late BC survivors had similar HRSN prevalence as general medical pts. Younger age was associated with greater HRSN in survivors, while BC stage, receptor status, and extent of treatment were not. Hispanics presenting for first survivorship visit endorsed greatest HRSN. These findings have implications for interventions targeted to young survivors and for culturally sensitive survivorship care. Research Sponsor: None.

1637 **Poster Session**

Feasibility trial of health coaching-based navigation after breast cancer treatment. First Author: Ruvarashe Rumano, The Ohio State University, Columbus, OH

Background: Following breast cancer diagnosis, 25% of survivors experience psychosocial needs like depression, anxiety, and fear of recurrence. Integrative survivorship support services address these needs, but participation is lower among Black women, who report higher psychosocial distress. Patient navigation has emerged as a strategy to reduce these barriers. This study piloted a navigation-based intervention aimed at improving psychosocial symptom management over 6 months. **Methods:** A single-arm feasibility trial was conducted with Black breast cancer survivors from November 2022-June 2024. Women aged 18+ with non-metastatic breast cancer were recruited. A trained lay navigator provided personalized support and resource facilitation to address psychosocial and healthcare challenges. Interactions were analyzed qualitatively to assess preliminary impact. Surveys administered at baseline and post-intervention included the Life and Longevity after Cancer, Patient Reported Outcomes Measurement Information System, and Breast Cancer Survivorship Experience Survey, with responses measured on a Likert scale. Quantitative data were analyzed descriptively. **Results:** Of 21 Black women who consented (mean age 64), 18 began the study while 3 did not proceed beyond consent. Of these, 44.4% completed all six months, while 61.1% completed three months. Eight participants completed post-surveys. All participants found the study easy to join, 5/8 found its length appropriate, and 6/8 were satisfied with session intervals. All would recommend the program, and 4 preferred in-person sessions. Participants reported confidence in accessing future support programs. Key benefits included managing stress, family stressors, and improving community support. Qualitative analysis of 108 transcripts from 17 participants identified six themes: managing health challenges, communication, emotional well-being, resilience in daily life, program support, and future planning. Survey results showed improvements in well-being and self-efficacy. LILAC scores increased from 52.7 to 63.9, PROMIS physical scores rose from 12.4 to 13.3, and mental scores improved from 13.3 to 15.6. Self-efficacy decreased slightly in BCSES scores from 53.6 to 52.5. **Conclusions:** Among Black breast cancer survivors, 61% completed biweekly sessions during the first 3 months, with a drop in participation after transitioning to monthly sessions. Participants reported benefits in addressing distress and accessing support programs. Future efforts should focus on tailored strategies to enhance engagement and retention. Research Sponsor: OSUCCC Intramural Research Program; Speilman Fund.

1638 **Poster Session**

Predicting overall survival in adults with cancer in the US using machine learning approaches integrating comprehensive social risk factors. First Author: Yiwang Zhou, St. Jude Children's Research Hospital, Memphis, TN

Background: Adults with cancer in the U.S. face an elevated mortality risk compared to the general population, with social risk factors playing a critical role – particularly among those with comorbidities. However, traditional mortality risk prediction models often focus on treatment exposures and basic demographic factors, overlooking social risk factors. We aim to develop a machine learning (ML) model that integrates comprehensive social risk factors with traditional predictors to predict overall survival for adults with cancer in the U.S. **Methods:** We analyzed data from 6,181 nationally representative adults diagnosed with cancer from the National Health Interview Survey (NHIS; 2013-2014). A total of 74 risk factors, including basic demographics (e.g., age at the survey, sex, marital status, body mass index [BMI]), personal and household socioeconomic status (SES; e.g., education, food insecurity), lifestyle, social support, and health status (e.g., chronic health conditions [CHCs], disability), were included in modeling. The primary endpoint was 5-year overall survival from the survey completion date, with secondary endpoints of 1- and 2-year survival. Death from any cause after the survey was defined as an event, and subjects were censored 5 years post-survey. The sample was randomly split into 70% training and 30% testing. A random survival forest (RSF) model predicted survival. The time-dependent area under the receiver operating characteristic (AUROC) curve and the Brier score (BS) assessed the model performance. Both AUROC and BS range from 0 to 1, with higher AUROC for higher accuracy (discrimination) and lower BS for better alignment between predicted and observed risk (calibration). The Shapley additive explanations (SHAP) values were used to interpret variable importance in the established RSF model. **Results:** The mean age of subjects during the survey was 65.6$\pm$13.8 years, and 40.2% were male. For the established RSF model, the AUROC (mean $\pm$ standard deviation) for predicting 1-, 2-, and 5-year survival was 0.795 $\pm$ 0.026, 0.810 $\pm$ 0.018, and 0.831 $\pm$ 0.011, respectively, reflecting high and improved predictive accuracy over time. The BS for 1-, 2-, and 5-year survival was 0.039 $\pm$ 0.004, 0.065 $\pm$ 0.005, and 0.119 $\pm$ 0.005, respectively, indicating excellent calibration. The top five variables ranked by SHAP values include age at the survey (0.048), use of special equipment due to health problems (0.029), employment status (0.020), number of CHCs (0.016), and BMI (0.015). **Conclusions:** By integrating social risk factors with traditional risk predictors, we developed an ML model that predicts overall survival with high accuracy and excellent calibration for adults with cancer in the U.S. Identifying key risk social factors enables targeted interventions, potentially improving health outcomes and management for the adult cancer population. Research Sponsor: None.

1640 **Poster Session**

Pioneering cancer survivorship care in Latin America: Early results from the OC sobre VIVER program in Brazil. First Author: Luciana Landeiro, Oncoclínicas&Co, Salvador, Brazil

Background: Cancer survivorship poses a growing challenge, especially in low- and middle-income settings. The OC SobreVIVER program, launched in October, 2020 by the Oncoclínicas Group, addresses survivorship care gaps by providing structured, multidisciplinary care. Initially piloted for breast cancer survivors in two Brazilian units, the program expanded in 2023 to include colorectal and prostate cancer survivors across eight states. This study presents preliminary data. **Methods:** This descriptive, observational study assessed the OC SobreVIVER program's impact on survivorship care. Multidisciplinary consultations involving oncologists, nurses, psychologists, and nutritionists addressed late toxicities, recurrence risk, and quality of life, following international survivorship guidelines. Telehealth and digital tools improved accessibility. Data from July, 2023 to December, 2024 included clinical characteristics, program metrics, and patient-reported satisfaction via EORTC PATSAT 33 and Net Promoter Score (NPS). Descriptive statistics summarized key outcomes. **Results:** From July 2023 to December 2024, the program supported 577 survivors (518 breast, 47 colorectal, 12 prostate) across 11 practices in eight states, with 490 initial consultations, 91 follow-ups, and over 20 support groups conducted.Virtual consultations were available to all patients, enhancing accessibility for underserved regions. Patient-reported satisfaction was high, with 95% of respondents classified as Promoters (scores 9–10) in the NPS, demonstrating strong program loyalty. Based on EORTC PATSAT 33 evaluations, over 80% of respondents rated their medical care experience in the highest satisfaction range (41–50), and over 80% rated their nursing care experience in the highest category (29–35). Minimal dissatisfaction was reported, with less than 2% of responses falling into the lowest satisfaction ranges ($<$ 20 for medical care and $<$ 14 for nursing care). **Conclusions:** The OC SobreVIVER program demonstrates the feasibility of a structured, multidisciplinary survivorship model in a private network across Brazil. Preliminary data highlight its effectiveness in addressing complex survivorship needs, enhancing accessibility through telehealth, and maintaining high satisfaction.This integrated, patient-centric approach ensures continuity of care across physical, social, psychological, spiritual, and nutritional dimensions, fostering a more comprehensive and holistic survivorship experience. Research Sponsor: None.

1641 **Poster Session**

Oncology primary care clinics for comprehensive care of high-risk adolescent and young adult (AYA) cancer survivors. First Author: Alique Gabrielle Topalian, University of Cincinnati, Cincinnati, OH

Background: Adolescent and young adult (AYA) cancer survivors experience early development of chronic medical conditions compared to healthy peers. Due to their young age at diagnosis and living decades beyond treatment, they are also at higher risk for second primary malignancies (SPM) and late effects than older adult-onset cancer survivors. Primary care providers are responsible for most long-term care of survivors and many are unfamiliar with the effects of cancer treatment in younger populations. Oncology primary care providers are uniquely positioned to address increased needs of AYA patients because of their additional survivorship expertise. **Methods:** In 2020, the University of Cincinnati Cancer Center established an oncology primary care clinic. An accompanying clinical registry was developed to track patient outcomes longitudinally Electronic medical records of all patients seen between 1/2021 and 1/2025 (n = 901) were extracted and entered in REDCap. Records of AYA cancer survivors, defined as cancer diagnosis between the ages of 18-39, were queried and analyzed (9%, n = 85). **Results:** The patient population's mean age was 36 yrs (range 20-74; std dev = 11.3). Hematologic cancers (37%) were most common followed by breast (13%) and brain (9%). Additionally, 14% were diagnosed with a SPM. Comorbid conditions were prevalent with 60% of patients having cardiovascular disease such as hypertension. Neurologic (46%), endocrine (44%), and psychologic (71%) co-morbidities were also common. Over half of patients were overweight/obese (68%) and many patients were former (19%) or current (7%) smokers. Eligible patients received their recommended cancer screening including breast (82%), colon (60%), and cervical (40%). Due to treatment exposures, 53% of patients were eligible for cardiomyopathy screening and 73% received recommended echocardiograms. A reduced ejection fraction was found in 26% of patients screened. **Conclusions:** Comprehensive primary care services and longitudinal monitoring are imperative in this high-risk population. Oncology primary care provides necessary survivorship-informed care and longitudinal monitoring for early onset comorbidities and SPMs. Tailored education and outreach efforts for providers and patients should address preventative health services needed in this high-risk population. Research Sponsor: None.

1642 **Poster Session**

Risk and predictors of late second primary malignancies in long-term breast, prostate, colon, and rectal cancer survivors. First Author: Tendai Kwaramba, Department of Medical Oncology, Yale Cancer Center, Yale School of Medicine, New Haven, CT

Background: In older, long-term (5-year) cancer survivors, mortality risks from aging and treatment-related effects may surpass those of their index cancer. Second primary malignancies (SPMs) occurring 5-10 years post-diagnosis are understudied in older patients. This study aims to quantify SPM risk, identify predictors, and describe prevalent SPM sites in older survivors of breast, prostate, colon, and rectal cancer to guide survivorship care. **Methods:** This retrospective cohort study analyzed patients aged 66+ with stage I-III cancer diagnosed between 2003-2011 using the SEER-Medicare database. Eligible patients survived ≥5 years post-diagnosis and had continuous Medicare Parts A & B enrollment from 1 year pre-diagnosis to 1 year post-diagnosis. The primary outcome was late SPMs occurring 5-10 years after index cancer diagnosis. Covariates included demographics, comorbidities, index cancer characteristics, treatment, and early SPMs (diagnosed within 5 years). Least absolute shrinkage and selection operator for variable selection and 5-year restricted mean survival time regression models were used. Cumulative late SPM incidence was calculated with mortality as a competing risk. The prevalence of specific SPMs was calculated as a proportion relative to the total number of SPMs within each cohort, and categorized as hematologic, predominantly screen-detected (breast, prostate, colorectal), or other solid tumors. **Results:** Of the 88,227 long-term survivors included with median age of 73.3 (IQR 69.5-78), 6.2% developed early SPMs and 8.2% (7,231) developed late SPMs. The 5-year cumulative incidence of late SPMs was 8.6%, highest in prostate (9.2%) and lowest in breast (6.7%) cancer survivors. Non-screenable cancers had the highest 5-year risk (6.2%), followed by screen-detected (1.3%) and hematologic malignancies (1.1%). Lung was the most common SPM overall (18.4% of SPMs), including in survivors of breast (21%), rectal (19.2%) and colon (16.5%) cancers, while prostate was most common in rectal cancer survivors (17.0%). Diagnosis of SPM in the early (< 5 years) survivorship cohort was associated with shorter time to a new late SPM, particularly in prostate cancer survivors (RMST Ratio 0.97, 95% CI 0.96-0.98). Treatments and high-risk disease features showed no significant associations with occurrence of late SPMs. **Conclusions:** Late SPMs were diagnosed in 8.6% of older, long-term cancer survivors. Lung cancer was the most common SPM overall. Some screen-detected SPMs, such as prostate were also common which is notable in a population aging out of screening guidelines. Prediction of SPMs was limited by the absence of modifiable risk factors, genetic data, and family history in SEER-Medicare data. Early SPMs were the sole predictor of late SPMs while treatment and index cancer features showed no effect, suggesting other drivers of late SPM development in older survivors. Research Sponsor: American Cancer Society.

1643 **Poster Session**

Subtype-specific trends in lung cancer incidence and survival: A SEER analysis (2004–2021). First Author: Shubhank Goyal, University of Texas Rio Grande Valley, Mcallen, TX

Background: Lung cancer remains a leading cause of cancer mortality, with adenocarcinoma, squamous cell carcinoma (SCC), and small cell lung cancer (SCLC) as key subtypes. Advances in early detection (e.g., low-dose CT screening post-2013) and systemic therapies (e.g., targeted agents and immunotherapies [IO], approved 2015 for adenocarcinoma/SCC, 2018 for SCLC) have transformed care. However, links between incidence trends and survival outcomes remain unclear.This study leverages SEER data (2010–2021) to extend prior analyses (Howlader et al. 2000-2017, NEJM 2020) and evaluate subtype-specific trends, focusing on the post-2015 era of IO adoption and updated screening eligibility. **Methods:** Age-adjusted incidence and 3-year relative survival rates for adenocarcinoma, SCC, and SCLC were analyzed using SEER data (2004–2021), stratified by stage. Joinpoint regression identified significant trend changes. Survival shifts >2% annually were temporally linked to key milestones: low-dose CT screening (2013), EGFR/ALK inhibitors (2013), and IO (2015). **Results:** For adenocarcinoma, distant-stage survival rose from 12.8% (2011) to 23.0% (2018), with a sharp +3.1% annual increase in 2018 aligning with immunotherapy adoption. Localized and regional survival improved by 5.3% and 6.5%, respectively, over the study period. These trends probably reflect the combined impact of early detection and systemic therapies. In SCC, localized-stage survival increased from ~56% to ~66% after 2015, driven by earlier detection and reduced late-stage incidence. However, regional and distant-stage survival saw only modest gains (~7%), highlighting limited advancements for advanced disease. SCLC showed the least survival improvements despite declining incidence, largely attributed to reduced smoking. Distant-stage survival stagnated at ~4–6%, while localized-stage survival improved transiently by 17% from 2010 to 2012, likely reflecting temporary improvements in early-stage management. However, overall outcomes for SCLC remain poor, underscoring an urgent need for new therapies. **Conclusions:** Advancements in lung cancer treatment and cancer screening have led to significant survival gains. Adenocarcinoma's distant-stage survival improvements highlight the transformative impact of immunotherapy, while localized SCC gains emphasize the role of early detection and screening. SCLC remains a major challenge, with survival rates stagnating despite a steady decline in incidence. Further innovation in SCLC therapies, along with equitable access to both screening and novel treatments, is crucial to improving outcomes across all lung cancer subtypes. Survival data beyond 2018 for metastatic disease and post-2024 for localized disease (following IO approvals for respective indications) will provide deeper insights into the real-world impact of these therapeutic advancements. Research Sponsor: None.

1644 **Poster Session**

Telehealth and cancer care delivery: An updated real-world analysis of the impact of telehealth on patient access and treatment utilization at a comprehensive cancer center. First Author: Kelsey H. Natsuhara, University of California, San Francisco Helen Diller Family Comprehensive Cancer Center, San Francisco, CA

Background: Telehealth in oncology (onc) has persisted due to its convenience and potential to improve equitable access to care. Data on telehealth's impact on treatment (tx) access are needed to guide long-term telehealth policies. **Methods:** We identified adult patients (pts) who completed ≥1 medical, surgical, or radiation onc visit with an associated cancer diagnosis at our center from 2017-2019 (pre-telehealth) vs 2021-2023 (post-telehealth). Data from 2020 was excluded, given COVID irregularities. We selected 3 disease groups with varying telehealth use – breast (low), GI (medium), and GU (high) – allowing us to better control for external factors (eg COVID). We compared changes in visit distribution, sociodemographic, and tx patterns within and between disease groups pre- vs post-telehealth using Chi-square and ANOVA tests. Logistic regression analyses identified post-telehealth predictors of receiving tx, including the percentage (%) of in-person (IP) visits per pt. **Results:** We analyzed 109,200 encounters and 26,907 pts pre-telehealth vs 143,159 encounters and 50,168 pts post-telehealth. Pt volume increased in all groups post-telehealth (+99% breast, +55% GI, +104% GU). Post-telehealth, the % of video visits (VVs) increased in breast (1.5% to 28.8%), GI (2.0% to 55.2%), and GU (3.0% to 80.9%). In all groups, the % of pts seen from outside the SF Bay Area decreased (-7.5 breast, -1.4 GI, -6.1 GU). In breast and GU, the % of pts receiving cancer tx decreased (-5.2, -16.0, $p<0.01$), while the % of pts receiving GI tx was stable (-0.9). For infusion tx, predictors of tx receipt included metastatic disease (OR 3.9, 95% CI 3.6-4.2) and higher % of IP medical onc visits (OR 3.6, 95% CI 3.3-3.9); while living outside the Bay Area was negatively associated with infusion tx (OR 0.5, 95% CI 0.4-0.5). For surgery, the % of IP surgical onc visits (OR 0.7, 95% CI 0.6-0.7) and living outside the Bay Area (OR 0.8, 95% CI 0.7-0.9) were negatively associated with tx receipt. For radiation tx, metastatic disease (OR 2.8, 95% CI 2.5-3.1), but not living outside the Bay Area (OR 0.6, 95% CI 0.5-0.7), was associated with tx receipt. The % of IP radiation onc visits was not significant (OR 1.1, 95% CI 1.0-1.4). **Conclusions:** Among 3 disease groups with varying telehealth use, pt volume increased in all groups, while the % of pts receiving tx at our center decreased. This suggests that providers may be providing collaborative care while pts receive care locally. In regression analyses, higher % of IP medical onc visits was positively associated with receiving infusions, highlighting the importance of IP visits during active medical onc tx. However, this was not seen for surgery and radiation tx. For these time-limited interventions, pts seen virtually are still likely to access tx at our center. Further analyses are needed to identify pts and visit types best suited for telehealth. Research Sponsor: Conquer Cancer Foundation Young Investigator Award.

1647 **Poster Session**

Pilot study of an enhanced telehealth program for patients with prostate cancer. First Author: Erin Mary Bange, Memorial Sloan Kettering Cancer Center, New York, NY

Background: The time required for cancer treatment is considerable. Telehealth (TH) with home monitoring can minimize travel burden but patients' perceptions regarding tradeoffs of clinic visits versus enhanced telehealth (ET) are uncertain. We piloted an ET intervention offering patients on androgen deprivation therapy (ADT) for prostate cancer up to four components of care at home. **Methods:** Prostate cancer patients on ADT were offered participation in 4 at home services: 1) TH oncologist visits; 2) remote BP monitoring (BP); 3) home phlebotomy (HP); and 4) self-injection of ADT or denosumab at home with RN support via TH as needed. Clinicians referred eligible patients and specified frequency of each service. Completion rates were evaluated for each component. Patient perspectives, preferences for subsequent care, and assessments of the feasibility, acceptability, and appropriateness of each component were collected after participation in eligible services at least once over the course of the pilot. Feasibility, acceptability, and appropriateness were measured by validated measures (scores from 1-5). Patient satisfaction with ET was measured using a net promoter score. All results are based on the last completed patient survey. **Results:** Between 6/2023 and 6/2024, 39 patients enrolled in the pilot, the median age was 70 (IQR: 61.5-76.7), 62% were white, and 69% (N = 27) lived with family or a partner. Table 1 shows the %/(N) of patients who chose to participate in each at home component with completion rates at the patient and visit level. 73% (145/198) of remote monitoring failures were due to patient inability to execute the at home task. > 75% of patients reported that each service was convenient and saved time. Most patients reported no problems with completing the visit (TH 89%, BP 89%, HP 91%, injections 67%). Patients were either very likely or somewhat likely to participate again (TH 97%, BP 100%, HP 96%, injections 100%) and the majority preferred ET for future care (TH 79%, BP 79%, HP 87%, injections 100%). 62% (24/39) of patients found at-home visits to be equally or less stressful than in-person care. Patients found each service to be feasible, acceptable, and appropriate (mean score > 4.7 for all services) and gave ET a net promotor score of 79. **Conclusions:** Patients found ET for the management of prostate cancer on ADT to be feasible, acceptable, and appropriate, providing a more patient-centered and convenient alternative to traditional clinic-based care. Future studies will explore scalability and applicability across diverse patient populations and treatment regimens. Research Sponsor: National Cancer Institute/U.S. National Institutes of Health; P30 CA008748; National Cancer Institute/U.S. National Institutes of Health; P50 CA271357.

	% (N) Patients opting in for each component	% (N) Patients completing each component (at least once)	% (N) Total episodes completed
TH visits	100% (39)	59% (23)	90% (53/59)
Remote BP monitoring	92% (36)	94% (34)	60% (296/494)
Home phlebotomy	69% (27)	100% (27)	97% (143/148)
Home injections	28% (11)	73% (8)	90% (9/10)
All 4 components	18% (7)	29% (2)	70% (501/771)

1648 **Poster Session**

Impact of telehealth utilization on adherence to endocrine therapies in privately insured breast cancer patients: A claims-based cohort study. First Author: Shaimaa Elshafie, Clinical and Administrative Pharmacy, College of Pharmacy, University of Georgia, Athens, GA

Background: Adherence to endocrine therapies is essential for reducing recurrence and improving survival in breast cancer patients. However, nonadherence remains a significant challenge, particularly among young women. Telehealth has emerged as a promising tool to address barriers to care, yet its impact on long-term adherence to endocrine therapies is poorly understood. This study evaluated the association between telehealth utilization and adherence to endocrine therapies among privately insured women with nonmetastatic breast cancer. **Methods:** Using medical and pharmacy claims data from the Merative MarketScan database, we identified women under 65 years old who were newly diagnosed with nonmetastatic breast cancer in 2018 and were commercially insured for at least one year before diagnosis and five years after initiating endocrine therapy. Telehealth utilization was identified through billing codes, and adherence was measured by the proportion of days covered (PDC) with adherence defined as $\geq$80% prescription coverage. Generalized linear mixed models were used to estimate odds ratios (ORs) and 95% confidence intervals (CIs) while adjusting for relevant patient-level covariates. **Results:** The study cohort included 1,141 patients with the majority (53%) aged 45-54 years and 92% exhibited moderate severity of comorbidities. All patients initiated endocrine therapy in 2018 with 34% receiving tamoxifen, 33% receiving an aromatase inhibitor, and 33% switching between agents during follow-up. Telehealth utilization increased sevenfold during the second year of treatment (coinciding with the COVID-19 pandemic) and peaked in the third year when 48% of patients used telehealth and 2,178 visits were recorded. Adherence rates declined steadily over time: from 75% in the first year to 36% by the fifth year. Patients who utilized telehealth were 58% more likely to be adherent compared to those who did not utilize telehealth (OR = 1.58; 95% CI: 1.31-1.91; $p < 0.0001$). Geographic region, insurance plan type, and endocrine therapy agent were also significant predictors of adherence. **Conclusions:** Telehealth utilization was significantly associated with improved adherence to endocrine therapies among privately insured breast cancer patients. These findings highlight the potential of telehealth to mitigate barriers to long-term treatment adherence. Future research should explore strategies to sustain adherence and evaluate the broader clinical and economic implications of telehealth in this population. Research Sponsor: None.

1649 **Poster Session**

Comparative effectiveness of delivering early palliative care via video versus in-person on end-of-life outcomes in patients with advanced lung cancer. First Author: Jessica R. Bauman, Fox Chase Cancer Center, Philadelphia, PA

Background: Findings from our prior large-scale comparative effectiveness trial showed the equivalent effect of delivering early palliative care via video versus in-person on quality of life among patients with advanced non-small cell lung cancer (NSCLC). We now report on whether the two care delivery modalities were equivalent with respect to patient-reported communication with clinicians about their end-of-life (EOL) care preferences and hospice utilization. **Methods:** Between 6/14/2018 and 5/4/2023, we enrolled 1250 patients with newly diagnosed advanced NSCLC in a randomized trial of early palliative care across 22 US cancer centers. Patients were randomly assigned to meet with a palliative care clinician every 4 weeks from enrollment through the course of the disease, either via video or in the outpatient clinic. Participants completed self-report surveys at baseline and weeks 12, 24, 36, and 48, including an item asking if they had discussed with their clinicians the care they would want to receive if dying (yes/no); patients' final assessments prior to death or last follow up were analyzed. We reviewed patients' health records to collect data on hospice referral and length of stay. To test the equivalence in these outcomes, we used a binomial generalized linear model with the identity link function (pre-specified equivalence margin of $\pm$8% for patient-reported communication about EOL care) and linear regression (pre-specified equivalence margin of $\pm$6 days for mean length of stay in hospice). P-values were adjusted for multiplicity using a Bonferroni correction. **Results:** Of the 1250 enrolled participants, 888 (71.0%) completed at least one survey post baseline regarding whether they communicated with clinicians about EOL care preferences. Among those, 29.1% of the video group and 26.0% of the in-person group reported "yes," indicating that they recalled such EOL care discussions (difference = 3.1%, 95% CI: -1.8%, 8.1%; p = 0.26 for equivalence). During the course of the trial, 733/1250 (58.6%) patients died, of whom 537/733 (73.3%) were referred to hospice. Mean lengths of hospice stay were 25.3 days for the video group versus 25.1 days for the in-person group (difference = 0.2, 95% CI: -7.0, 7.4; p = 0.46 for equivalence). When excluding outlying patients receiving hospice services $>$ 180 days (n = 13), the mean lengths of hospice stay were 19.1 (video group) versus 19.7 (in-person group) days (difference = -0.6, 95% CI: -4.6, 3.3; p = 0.06 for equivalence). **Conclusions:** Although thresholds were not met to confirm equivalence statistically, the two modalities for delivering early palliative care demonstrate very similar outcomes with respect to patient-clinician communication about EOL care and hospice utilization. These findings provide further evidence of the utility of video visits for providing high quality palliative and EOL care. Clinical trial information: ClinicalTrials.gov Identifier (NCT03375489). Research Sponsor: Patient-Centered Outcomes Research Institute; PLC-1609-35995.

1650 **Poster Session**

Assessing circadian rhythms and chemotherapy safety in remote patients with pancreatic ductal adenocarcinoma (PDAC) using a multidimensional digital platform (MultiDom, NCT04263948). First Author: Francis Albert Lévi, UPR Chronotherapie, Cancers et Transplantation, Université Paris Saclay, Hôpital Paul Brousse ID Isco 13918, Villejuif, France

Background: The disruption of circadian clocks is associated with reduced survival and treatment tolerability in cancer patients (pts). Here, real-time analyses of telemonitored circadian rhythms and electronic Pt-Reported Outcome (ePRO) are integrated within a multidimensional telemonitoring-telecare digital platform that triggers proactive telecare toward improved quality of life (QoL) and treatment safety. **Methods:** The multicentre, interventional, prospective, longitudinal, single-arm study recruited pts receiving mFOLFIRINOX chemotherapy (CT) q2-weeks for pancreatic ductal adenocarcinoma (PDAC). Early warning signals of circadian disruption, body weight loss, and ePROs severity are extracted from real time analysis and graphical displays of (i) continuously telemonitored rest-activity and chest surface temperature (chestemp) rhythms using a chest sensor, and (ii) daily body weight (e-balance), and (iii) daily self-rating of 23 symptoms using a GPRS tablet (MD Anderson Symptoms Inventory, MDASI). Pts participate for 1 week before (baseline) and 6 weeks after 1st CT course. Circadian disruption is defined by an ($I < O$) value $<$ 96%. ($I < O$) is the % accelerations per min In-Bed that are below median accelerations per min Out-of-Bed for 3 days; ($I < O$) range in controls, 97-100%). Automatic alerts are sent via internet for decision of proactive intervention by the oncology team, in case of circadian disruption, chestemp increase by 1.5°C, weight loss $>$ 5%, or MDASI symptom $\geq$ 7. **Results:** From 6/2021 to 7/2024, 58 pts with advanced PDAC were selected (male, 52%), median age, 58 y.o. (range, 33-82); WHO performance status (PS) 0/1/2, 36%/53%/10% of the pts; metastatic sites 0/1/ $>$ 2, 38%/24%/8%; liver metastases, 50%). Early PDAC-related complications prevented platform use in 5 pts. The platform was used by 53 pts during a median of 45.5 days (IQR, 38-50], with $>$ 85% compliance. At baseline, large between-pts differences in circadian rhythms were found for both rest-activity $I < O$ (median [IQR]), 98.4 accelerations/min [95.8-99.6]); range, 75 to 100), and chestemp circadian amplitude (median, 1.1°C [IQR, 0.7-1.4], range, 0.3°C to 2.7°C). Baseline circadian disruption was larger in male pts (56% vs 31%; p = 0.07) and in those with PS 1-2 (47% vs 14%; p = 0.02). Consistently, median chestemp circadian amplitude was less in males compared to females (0.8°C vs 1.3°C, $p < 0.01$) and in pts with PS = 1-2 compared to PS = 0 (0.8°C vs 1.3°C; $p < 0.01$). Maximum toxicities of CT were circadian disruption (100% of the pts), body weight loss $>$ 5% (59%), and MDASI symptom $\geq$7 (46%), without any influence of baseline pt characteristics. **Conclusions:** The use of this multidimensional digital platform combining circadian and other physiology metrics with ePROs was feasible and accepted by the pts. Its implementation seemed to be clinically relevant toward improving the care of remote pts at risk of adverse events. Clinical trial information: 04263948. Research Sponsor: Education and Research Direction of Ramsay-Santé.

1651 **Poster Session**

Remote physiologic and behavioral monitoring to predict early treatment response in metastatic cancer: High-Definition Oncology study (HDOs) preliminary results. First Author: Leire Paz-Arbaizar, Department of Signal Theory and Communications, University Carlos III, Leganés, Spain

Background: Emerging evidence suggests that behavioral, physiologic or emotional factors may act as real-time indicators of treatment response, with potential as modifiable factors. Advances in remote monitoring technologies provide passive (e.g., heart rate, sleep patterns) and active (e.g., self-reported emotions) data. HDOs collects such data and serial -omics from 300 women with metastatic cancer to identify novel markers, understand disease trajectories and develop a digital twin for individualized care. We present data from 25% accrual. **Methods:** Women receiving first-line treatment for metastatic colorectal, lung, or hormone-positive breast cancer were eligible. Patients continuously wore a smartwatch and used the EB2 App to capture step count (SC), sleep duration (SL), phone usage (PU), time at home (TH), location clusters (LC), mean (MHR) and minimum (mHR) heart rate, mean (MSHR) and minimum (mSHR) sleeping heart rate and sleeping oxygen saturation (SOS). Emotional valence was self-reported from a list of 20 emotions and classified as negative (-1), neutral (0) or positive (+1). Aim 1: to explore the relationship between the variables and response (CB: CR+PR+SD vs. PD) at the first CT scan at day +90 analyzing data from days 1-15 and 75-90 (Mann-Whitney U). Aim 2: to find Response-Associated Behavioral Patterns (RABPs) associated with CB or PD. First, Daily Behavioral Profiles (DBPs) are obtained using unsupervised learning models from $>$ 2 million days of smartwatch and App data (external set). After identifying 256 DBPs with the VQ-VAE model, Latent Dirichlet Allocation defined RABPS based on the frequency and abundance of DBPs per patient. RABPs were compared among classes (response type, age group) using X^2. Bilateral P values $<$ 0.01 were deemed significant. **Results:** from May 2023 to April 2024, 77 female patients (median age 61; 28-80) were accrued (46 Breast, 23 Lung, 8 Colorectal). At first CT, 72 (93.5%) achieved CB while 5 (6.5%) had PD. During days 1-15, CB patients showed lower PU (2.4 vs. 3.9 hours; P = 0.002), TH (18.5 vs. 22 hours; P = 2* $10^{\wedge-7}$), MHR (78 vs. 88 bpm), mHR (59 vs 70 bpm), MSHR (75 vs 88 bpm) mSHR (66 vs 78 bpm) (all Ps $< 10^{\wedge-10}$) and reported more negative EV. The trends persisted in days 76-90 in addition to SC (7235 vs 4038 steps/day; P = 0.00001) and decreased SOS (90.1% vs. 92.6%; P = 1.5*$10^{\wedge-8}$). Six RABPS were identified. Patients $<$ 60 yo displayed more often RABPs 1, 2 and 5 (84% vs. 16%; P = 0.02). RABP1 breast cancer and RABP5 lung cancer patients were more likely to experience PD vs. CB (75% vs. 24%; P = 0.08; and 69% vs.19%, P = 0.07, respectively). **Conclusions:** Behavioral and physiologic data in days 1-15 and 76-90 were strongly associated with treatment response, independent of tumor type, age or treatment. RABPS identifying patients at high risk of PD can be detected, highlighting their value as markers for early intervention. Research Sponsor: None.

1652 **Poster Session**

Administration of tarlatamab in an outpatient setting utilizing remote patient monitoring: Mayo Clinic experience. First Author: Ashley Potter, Mayo Clinic Rochester, Rochester, MN

Background: Tarlatamab is a bispecific T-cell engager targeting DLL3 that has shown promise as a therapy in small cell lung cancer. Administering tarlatamab requires careful consideration of immune-related adverse events (AE), including cytokine release syndrome (CRS) and immune effector cell-associated neurotoxicity syndrome (ICANS). Prescribing information recommends patients to be monitored for 22-24 hours in an appropriate healthcare setting for cycle 1 (C1), days 1 and 8. At Mayo Clinic in Rochester MN (MCR), tarlatamab is initially administered in a hospital-based outpatient (HBO) setting utilizing an innovative remote patient monitoring system (RPM). In this study, we describe our RPM process and patient outcomes thus far. **Methods:** We retrospectively reviewed records of patients treated with tarlatamab from August through December 2024. All patients received tarlatamab in the HBO setting and were enrolled into RPM for C1, days 1–10. Patients attended daily HBO visits on days 1–3 and 8–10 of C1 and were required to stay within 30 minutes of the hospital with a 24-hour caregiver for 48 hours following infusion days in C1-2. Data on patient characteristics, frequency of RPM alerts, escalations, rate of CRS & ICANS, and need for hospitalizations were reported using descriptive metrics. **Results:** As part of RPM, patients are provided with a kit containing preconnected Bluetooth-enabled devices to measure vital signs (VS), including blood pressure (BP), heart rate (HR), temperature (T), and pulse oximetry (SpO2). The kit also includes a cellular-enabled tablet for electronic ICANS questionnaires, which upload directly into our electronic medical record system. Patients are required to log VS four times daily, monitored in real-time by a centralized virtual RPM nursing (RN) team. Embedded decision trees trigger alerts, prompting the RN team to contact patients and follow care pathways for escalations as needed. Among the 16 patients treated, the median age was 68 years, and the median ECOG PS was 1. During the 10-day RPM period, a total of 2,233 VS entries were recorded. Of these, 88% (14/16) of patients had alerts triggered, with a median of 2 alerts per patient. Alerts were mostly for out-of-range systolic BP (56%), HR (56%), and T (25%), with none for SpO2. The RN team escalated alerts in 50% (8/16) of the patients. Overall, 38% (6/16) of patients were managed entirely in the HBO setting. Among the 63% hospitalized, 56% had CRS limited to grade (G) 2, and 31% had ICANS limited to G3. Two patients were hospitalized for other indications. The mean length of stay was 2.6 days, with no ICU admissions. **Conclusions:** Our experience shows that frequent monitoring required with tarlatamab can be safely and effectively executed in an outpatient setting with the utilization of an RPM system. It can potentially minimize the burden of hospitalizations for patients and the healthcare system. Research Sponsor: None.

1653 **Poster Session**

Teledermatology-dermoscopy: Expanding access to skin cancer screening to reduce healthcare disparities. First Author: Brenda Santellano, Georgia Cancer Center, Augusta University, Augusta, GA

Background: Skin cancer, the most common malignancy in the United States, continues to rise in incidence. Underserved populations face significant barriers to care, including lack of insurance, language differences, and limited access to specialists. The Augusta Free Dermatology Clinic, a student-run clinic, collaborates with the Teledermatology in Rural Georgia program to address these challenges through store-and-forward (SAF) teledermatology-dermoscopy. This approach involves transmitting dermoscopic images to a dermatologist for remote analysis. Implemented during Community Health Fairs (CHFs), this initiative aims to enhance access to skin cancer screening in underserved communities. **Methods:** Volunteer medical students (MS) from the Medical College of Georgia (MCG) and general physicians underwent training to use a dermatoscope effectively. Trained MS collected brief medical histories and dermoscopic images for SAF referrals during CHFs serving individuals with incomes below 200% of the federal poverty line. Polarized dermoscopic images were captured using iPhones equipped with magnetic dermatoscope attachments and were securely transmitted to a board-certified dermatologist via a teledermatology platform. Dermatological recommendations were provided within one hour and communicated to patients, with Spanish translators facilitating communication. **Results:** Across two CHFs (~8 hours each), 10 MS volunteered in shifts under the supervision of a general physician (n = 1) or dermatology resident (n = 1). A total of 141 patients presented with dermatological concerns, of whom 24 (17.02%) were referred for SAF consultations due to suspicious skin lesions. Among these, 17 (70.83%) had benign lesions, while 7 (29.17%) were identified as potentially malignant and referred for in-person follow-up at the Augusta Free Dermatology Clinic for further evaluation or biopsy. Comprehensive data were available for 112 patients (79.43%), most of whom were female (58.04%, n = 65) and Latino/Hispanic (98.21%, n = 110). The majority were uninsured (73.21%, n = 82), Spanish-speaking (98.21%, n = 110), and required translation services (98.21%, n = 110). Nearly all participants worked in skilled agricultural roles (98.21%, n = 110) and reported a median of two household dependents (range: 0–9). Common diagnoses among follow-up patients included healthy skin (45.54%, n = 51), acne (5.36%, n = 6), melasma (5.36%, n = 6), benign nevi (5.36%, n = 6), dermatitis (4.46%, n = 5), and folliculitis (3.57%, n = 4). Other less common conditions were diagnosed in 30.36% (n = 34) of patients. **Conclusions:** The implementation of teledermatology-dermoscopy at CHFs effectively addressed barriers to dermatological care in underserved populations. This approach demonstrated the potential to improve early detection of skin cancer, facilitate timely care, and reduce healthcare disparities. Research Sponsor: United States Department of Agriculture Rural Utilities Service (USDA).

1654 **Poster Session**

Patient-reported experience with an immunotherapy telehealth platform. First Author: Robert Michael Daly, Memorial Sloan Kettering Cancer Center, New York, NY

Background: The Making Teleheath Delivery of Cancer Care at Home Effective and Safe for Immunotherapy (MATCHES-IO) intervention seeks to improve the efficiency and patient experience for those treated with single agent pembrolizumab. Because pembrolizumab is administered as an outpatient infusion every 3-weeks, patients require up to 18 clinic visits per year to receive treatment, which is arduous. During the COVID-19 pandemic, the FDA granted accelerated approval for an extended interval dosing administered every 6 weeks, but despite this approval every 3-week dosing remains the standard (65% of prescriptions) as clinicians perceive this schedule enables them to identify and manage toxicity early. Telehealth may be the impetus to change the standard to the more convenient 6-week in person schedule, but evidence is needed. **Methods:** We conducted a single arm pragmatic trial to evaluate the efficiency and patient experience of a telehealth immunotherapy platform (MATCHES-IO) in patients with non-small cell lung, genitourinary, or melanoma cancers receiving single agent pembrolizumab. MATCHES-IO evaluates whether in-person visits for pembrolizumab therapy q6wk (rather than q3wk) with interim telehealth toxicity checks between in-person treatments for the first six months of therapy is more efficient and enhances patient experience relative to the standard q3wk infusion visits. The components of the platform include clinician-patient virtual visits, labs at home, biometric devices at home for vital sign monitoring, and electronic patient-reported outcomes to monitor for common IO-related toxicities. Patient experience was assessed after each MATCHES-IO televisit for up to two televisits. We measured experience with a patient experience survey that included how likely are they to recommend this intervention to similar patients (scale 0-10). **Results:** Between July 2023 and January 2025, 59 patients were enrolled, median age 69 (range 25–85), 81.5% White, 11.1% Black, 7.4% Asian, and 61.1% male. Cancer types included thoracic (50.9% of patients), genitourinary (30.5%), and melanoma (18.6%). 45 patients (76.3%) have completed a MATCHES-IO televisit and completed a patient experience survey. The median score for likelihood to recommend was 10 (range 4-10). 97.8% patients perceived a benefit to the MATCH-IO televisit including saved time (82.2% of respondents), patient convenience (71.1%), convenience for caregiver/family (44.4%), saved money (44.4%), and better monitoring of cancer and treatment (24.4%). 57.8% of patients found the at home visit less stressful than the in-person visit. **Conclusions:** Patients endorsed an enhanced experience with an immunotherapy telehealth platform for extended dosing of pembrolizumab. Further follow-up is needed to confirm these experience findings and determine whether this platform improved efficiency through fewer in-person visits. Research Sponsor: National Cancer Institute; Emerson Collective Digital Oncology Care.

1655 **Poster Session**

Outcomes of germline expedited point of care (POC) genetic testing through telehealth in the Veterans Health Administration (VA). First Author: Akiko Chiba, Department of Surgery, Duke University Medical Center, DUMC, Durham, NC

Background: Germline genetic testing is standard of care for treatment planning for several malignancies. To increase access to genetic testing for Veterans, VA developed and disseminated educational materials, laboratory portal access, and templates for ordering and documenting consent and testing in the electronic health record to facilitate POC testing by oncology providers. Here, we describe the outcomes of POC testing. **Methods:** POC tests ordered between 2/24/23-11/18/24 by oncology providers at VA sites or with National TeleOncology (NTO) were identified through the VHA's Corporate Data Warehouse and the VINCI (VA Informatics and Computing Infrastructure) research environment. Pathogenicity of variants was determined by the classification provided by the laboratory. Providers are recommended to use the POC testing for patients actively being treated for the following cancers: metastatic/high risk prostate, breast, ovarian, exocrine pancreatic/ampullary, colon $<$ 50 years of age, medullary thyroid, and pheochromocytoma/paraganglioma. **Results:** POC tests were ordered at 45 different VAs for 1293 patients. Total of 1364 tests were ordered, and 1195 (87.5%) tests were . The tests ordered included 854 (62.6%) curated multigene panel and 510 (37.4%) targeted cancer panels. Demographics are summarized in Table. Among 1382 diagnoses listed as the indication for testing (some patients had multiple), the most common cancer diagnoses were prostate (831, 60.1%), breast (206, 14.9%), and pancreatic (94, 6.8%). Most tests were ordered for patients who met POC indications, but 13.6% of orders were for other indications. A total of 77 (6.4%) patients were found to have pathogenic/likely pathogenic variants (PV) in dominantly inherited cancer predisposition genes. Seventy-one (5.9%) patients had PVs in high/moderate penetrance cancer predisposition genes. **Conclusions:** POC testing is feasible and being widely adopted across the VA. Further work is needed to determine if patients found to have actionable PVs through the POC mechanism have changes in treatment or are referred for follow-up genetic counseling. A significant, minority of tests were ordered for patients with diagnoses not eligible for POC testing. Continued education and support is planned to increase utilization of POC testing in oncology across the VA. Research Sponsor: None.

Demographics of veterans with a point of care genetic testing order (n=1293).

White/Other races	**701 (54.2%)/ (45.8%)**
Non-Hispanic/Hispanic	1225 (94.7%)/29 (2.2%)
Male/Female	1034 (80%)/259 (20%)
Rural/Urban	369 (29.5%)/915(70.8%)
POC test orders	
Testing completed (n=1364)	1195 (87.6%)
Comprehensive panel/targeted panel (n=1364)	854 (62.6%)/510(37.4%)
POC eligible cancer diagnosis (n=1382)	1194 (86.4%)
Pathogenic/likely pathogenic variant in a dominant high/moderate risk gene (n=1195)	71 (6.4%)

TPS1656 **Poster Session**

DIPCAN, a multidimensional approach to precision oncology: Harnessing genomic, clinical, pathological and radiographic data to advance personalized cancer treatment. First Author: Enrique Grande, Department of Medical Oncology, MD Anderson Cancer Center Madrid, Madrid, Spain

Background: Advances in big data analytics and artificial intelligence (AI) are enabling novel approaches to patient classification in oncology. While existing studies often correlate only a few data types, the DIPCAN Study (Digitalisation and Integral Management of Personalised Medicine in CANcer) seeks a comprehensive, integrated analysis combining phenotypic, clinical, pathological, radiomic, and genomic data from patients with metastatic cancer in Spain. DIPCAN aims to deepen insights into cancer's multifactorial nature, driving personalized care and more precise therapeutic strategies. **Methods:** DIPCAN was initiated through a consortium comprising five technology and healthcare SMEs—Genomcore, Quibim, Pangaea Oncology, Artelnics, and Atrys Health—alongside Eurofins Megalab and the non-profit MD Anderson International Foundation Spain. Funding was secured via the Spanish Ministry of Economic Affairs and Digital Transformation under the EU-funded Recovery, Transformation, and Resilience Plan (R&D Missions Program in Artificial Intelligence, File No. MIA.2021.M02.0006). DIPCAN's primary objective is to characterize and map clinical, phenotypic, genomic, and radiomic profiles of metastatic cancer patients across Spain. Secondary goals involve developing Big Data, AI, and machine learning tools to enable multidimensional analysis of these patients. Eligible patients are 18 years or older, have histologically confirmed metastatic solid tumors, a life expectancy exceeding three months, and available tumor material for histological and molecular analyses. Participants consent to undergo a comprehensive set of diagnostic and imaging procedures outlined in the study protocol. If recent tumor tissue ($<$3 years) is unavailable, patients may opt for a current biopsy or liquid biopsy. At no cost, participants receive consultations with oncology and drug development specialists, who document baseline characteristics and compile structured medical histories. Additional diagnostics include bloodwork emphasizing lipid metabolism, digital pathology, extensive NGS sequencing on tissue or blood, and a full-body MRI. All participants receive digital access to their data and a clinical report with tailored recommendations for their physicians. With ethics approval in place, DIPCAN has enrolled 1,500 patients since June 14, 2022. Data collection is ongoing, with anticipated advancements in AI-driven analysis aimed at refining precision oncology approaches for metastatic cancer in Spain. Clinical trial information: 2021.M02.0006. Research Sponsor: European Union; MIA.2021.M02.0006.

TPS1657 **Poster Session**

A pilot single-arm, pragmatic trial in progress of in-home versus in-clinic subcutaneous nivolumab administration through Cancer Care (connected access and remote expertise) Beyond Walls (CCBW) program. First Author: Dina Elantably, Mayo Clinic, Jacksonville, FL

Background: Cancer treatments are traditionally administered in clinical settings, which can isolate patients from their familiar environments and exacerbate physical, psychosocial, and financial burdens. Travel requirements further amplify these challenges, particularly for underserved populations. Studies indicate that patients prefer receiving care at home, and international models have demonstrated the safety of home-delivered chemotherapy since the 1990s; however, no U.S. clinical trial data exists. In response, Mayo Clinic has developed the *Cancer CARE (Connected Access and Remote Expertise) Beyond Walls (CCBW)* program, a distributed cancer care delivery model that expands access to quality cancer care by bringing it to the home environment, providing in-home cancer treatment, lab testing, telemedicine, and community paramedic support. This trial evaluates the safety, acceptability, and impact of home-based subcutaneous (SC) nivolumab (Nivo) administration compared to in-clinic treatment within the CCBW initiative. **Methods:** This open-label, single-arm trial evaluates the impact of SC Nivo administration location—home versus infusion center—on patient reported cancer care experience, patient-preferred treatment location, acceptability, safety, and patient-reported outcomes. Eligible adult patients (ECOG 0-1) receiving IV Nivo for an FDA-approved indication and residing within 75 miles of Mayo Clinic Florida will transition to SC Nivo, receiving two initial in-clinic cycles. If tolerated without injection reactions, four cycles will be administered at home before resuming in-clinic treatment. Exclusion criteria include concurrent investigational/standard treatments or contraindications to immunotherapy. Fifty patients will be enrolled, with an estimated 75% (n=38) providing cancer care ratings after 8 weeks in-clinic and 8 weeks at-home, offering 85% power to detect a mean difference in ratings of 0.50 standard deviations. The primary endpoint is within-patient change in cancer care rating (0–10 scale, CAHPS Cancer Care Survey) comparing 8 weeks of in-clinic vs. at-home care. Secondary endpoints include patient-preferred treatment location, comfort with home injections, safety (grade 3+ adverse events), function (EORTC QLQ-F17), symptoms (PRO-CTCAE), side effect impact (GP5), and healthcare utilization (ER visits, hospitalizations). Cost will be assessed as a tertiary endpoint. The trial has FDA approval (IND #170079), Mayo Clinic IRB approval (#23009663), and ClinicalTrials.gov registration (NCT06265285). Enrollment began in April 2024, with an expected accrual period of 24 months. To date, 10 patients have been enrolled, and final analysis is expected 2.5 years after trial activation. Clinical trial information: NCT06265285. Research Sponsor: BMS; Mayo Clinic.

TPS1658 **Poster Session**

Trial in progress: Evaluating the effectiveness of Blue-button—A tool for institution-agnostic, EHR-integrated regional automated clinical trial prescreening and matching. First Author: Waddah Arafat, Simmons Comprehensive Cancer Center, University of Texas Southwestern Medical Center, Dallas, TX

Background: Clinical trial enrollment is essential for advancing cancer treatment and improving patient outcomes. Despite the benefits, only 7% of adult cancer patients in the US enroll in clinical trials due to barriers such as limited awareness, the time-intensive nature of manual prescreening and lack of relevant on-site clinical trials. This contributes to insufficient enrollment, causing approximately 20% of trials to fail. Automated prescreening using electronic health records (EHRs) offers a promising solution to streamline trial identification and improve access. This study builds on our published feasibility study (Cancer 2023; doi: 10.1002/cncr.35022) that demonstrated the potential of an open-source clinical trial matching tool, developed in collaboration with ACS CAN and MITRE Corporation, to improve locoregional trial identification for patients. **Methods:** Trial Design: This prospective, randomized, two-arm pilot study is being conducted at two sites: University of Texas Southwestern Medical Center (UTSW), an academic center, and Tampa General Hospital (TGH), a community hospital. Patients are randomized to usual care or an intervention arm utilizing Blue-button, an automated prescreening tool. This SMART-on-FHIR tool automatically extracts deidentified patient data (e.g., cancer type, stage, biomarkers) from the site EHR system and uses them to query external matching services via the FHIR mCODE standard. Using the standard FHIR ResearchStudy resource format, research coordinators review potential trial matches returned within a specified radius of the practice for eligibility and discuss them with patients. At UTSW, this includes prostate, bladder, breast cancer and colon cancer cohorts. At TGH, the trial includes breast, prostate, and colorectal cancers, as well as glioblastoma and multiple myeloma. Statistical Methods:The primary endpoint is the proportion of patients enrolling in trials, comparing intervention and usual care arms. Secondary objectives include evaluating usability, barriers to enrollment, and participant diversity. A total of 1200 patients (600 per arm) will be enrolled, with 81% power to detect a 75% relative increase in enrollment from 9.0% (control) to 15.8% (intervention) at a one-sided alpha of 0.05. Trial Progress:The first phase of the trial addressed institutional approvals, security compliance, and complex server and EHR integrations. The later phase addressed integration of the automated tool into diverse clinical workflows, engagement with site staff and participating patients. Both sites have enrolled approximately 200 patients to date, half on the intervention arm. The final phase will address primary and secondary outcomes as per trial design. Clinical trial information: NCT05885880. Research Sponsor: American Cancer Society Cancer Action Network.

TPS1659 **Poster Session**

DISCO App: A patient intervention to reduce the financial burden of cancer in a diverse patient population. First Author: Lauren M. Hamel, Karmanos Cancer Center, Wayne State University, Detroit, MI

Background: Financial toxicity, the material and psychological burden of treatment cost, affects up to half of people with cancer and can affect adherence and survival. Financial toxicity is a health equity issue, disproportionately affecting Black patients. Patient education about cost and patient-provider cost discussions are recommended to mitigate financial toxicity but occur infrequently. Our goal is to mitigate financial toxicity through a tailorable education and communication intervention, the DISCO App. The DISCO App was shown to be feasible, acceptable, and preliminarily effective at prompting cost discussions and improving related outcomes in a pilot trial. The aim of the ongoing trial is to test the effectiveness of the DISCO App on short- and longer-term outcomes for Black and White patients with cancer. **Methods:** This study is a longitudinal RCT. Oncologists are eligible if they treat patients with solid tumors at the trial site. Patients of participating oncologists are eligible if they are $\geq$ 18 years of age; identify as Black or White; can read and write in English; have an email address; and were diagnosed with a solid tumor for which systemic therapy is a likely recommended treatment. Strata were created to balance arms by patient race, income, age, and sex. Upon consent, patients are randomized to one usual care arm (1) or one of two intervention arms (2 and 3). All patients are asked to allow one treatment discussion with their oncologist to be video recorded for analysis. Prior to the recording, intervention patients utilize the DISCO App on an iPad. The DISCO App includes a video about treatment costs, ways to manage costs, and the importance of discussing costs with oncologists. Once patients enter their socio-demographic information (e.g., employment, insurance) and any financial concerns, they receive a tailored list of questions to ask their oncologist. Arm 3 patients receive an intervention booster via email two months after the recording. Patients complete measures at baseline, right after the recording, and at 1, 3, 6 and 12 months after the recording. Measures assess outcomes including cost discussions, communication quality, cost knowledge, self-efficacy for cost management, referrals for support, short- and longer-term financial toxicity, and treatment adherence. The patient-oncologist interaction is the unit of analysis and we will use multi-linear models to compare outcomes by arm. We anticipate recruiting up to 15 oncologists and 240 patients. Data collection began in March 2021 and will continue until July 2025. Participants to date include 13 oncologists and 192 patients (116 Black, 76 White). Most patients completed the baseline assessment (n=164), the post-interaction assessment (n=137), and at least 1 follow-up assessment (n=132); 125 treatment discussions have been recorded. The IRB reviewed the trial in December 2024 and approved continuation. Clinical trial information: NCT04766190. Research Sponsor: American Cancer Society; ACS RSG-20-026-01-CPHPS.

TPS1660 **Poster Session**

RACED (Reduction of Cervical Cancer Disparities): The impact of navigators and racial literacy training. First Author: Abna Faustina Sousa Vieira, Instituto do Câncer do Estado de São Paulo, Faculdade Medicina da USP, São Paulo, Brazil

Background: Cervical cancer is the third most prevalent cancer in Brazilian women. Approximately 17,000 new cases are expected for Brazil's 2023-2025 triennium. The complex multimodality treatment of locally advanced cervical cancer (LACC), which relies on platinum-based chemoradiotherapy (CRT) and brachytherapy (BT), in addition due to the significant healthcare demands of patients with cervical cancer, creates challenges for a public-funded health system. The Black population experiences the highest cancer mortality rates compared to the general population, partly due to inequalities in social, economic, political, and health areas spheres. Data showed that, compared to White women, the mean age-adjusted mortality rates according to race/skin color were 27% higher in Black women. Around 60% of Black patients have a cervical cancer diagnosis in locally advanced or advanced stages. The incidence rate among Black women was found to be significantly higher than that of their White counterparts, with a relative risk of incidence nearly 50% higher. This disparity cannot be ignored. **Methods:** Our study is based on Critical Racial Praxis for Public Health. It is inspired by the ACCURE (Accountability for Cancer Care Through Undoing Racism and Equity) initiative trial, composed of 3 anti-racist actions: 1- oncology navigation with racial literacy, 2- real-time medical record alert system, and 3- race-specific feedback. Our intervention, in turn, consists of oncology navigation with racial inequities training and improving interprofessional team knowledge about race and diversity through race-specific feedback. This prospective, single-center, non-randomized clinical trial of anti-racist actions and treatment support will compare prospective patients with a historical control from the same hospital. The primary endpoint is to increase the completion rate of definitive treatment with CRT+BT for 100 patients with IB2 to IVA cervical cancer (convenience sample). The secondary endpoints are to analyze the implementation policy of this strategy and to make an economic assessment of the use of this implementation (we hypothesize that such measures reduce both visits to the emergency room due to toxicity, as well as admissions to wards and ICU). Patient inclusion is expected to begin in March 2025. Nurses are receiving training in oncology navigation and racial literacy in healthcare. As this is a race-conscious trial, the researchers plan to prospectively compare outcomes between the intervention group's Black/Brown and non-Black/Brown populations. In addition, given critical race theory, the research team comprises Black women in creation, design, and throughout the entire study continuum. Clinical trial information: 85819325.0.0000.0068. Research Sponsor: Bristol Myers Squibb Foundation.

TPS1661 **Poster Session**

Practical geriatric assessment (PGA) implementation strategies and correlative evaluations (PACE-70): A hybrid implementation-effectiveness study in 3 community practices. First Author: Gabriel Aleixo, University of Pennsylvania, Philadelphia, PA

Background: The use of a geriatric assessment to inform oncologic care for older persons with cancer is an evidence-based practice that improves patient-clinician communication, reduces treatment-related toxicity, and is recommended by national guidelines. However, the implementation of a geriatric assessment can be time-consuming and burdensome, leading to suboptimal use in clinical practice. Developed and endorsed by the American Society for Clinical Oncology (ASCO), the Practical Geriatric Assessment (PGA) is designed to improve clinical usability and adoption, but its implementation in real-world settings has not been evaluated. The PACE-70 study aims to evaluate PGA implementation and resultant chemotherapy dose modification among older adults with advanced cancer treated in a community setting. An exploratory aim will evaluate how the PGA, body composition and step count monitoring correlate with chemotherapy toxicity and other clinical outcomes. **Methods:** The PACE-70 study is a Type III hybrid implementation-effectiveness study enrolling at three community sites within a large academic health system. Eligible participants will be 70 years or older, have a diagnosis of advanced or metastatic solid malignancy, and be starting a new line of palliative-intent systemic therapy, where the expected prevalence of grade 3 toxicity exceeds 50 percent. The PGA will be administered via the electronic health record (EHR), available for patients to complete independently prior to an initial medical oncology visit, or during the visit with staff assistance. Results from the PGA will be shared automatically with clinical teams via the EHR, including a Best Practice Alert highlighting any identified geriatric impairment(s) and ASCO's recommendation for PGA-adapted care. The primary outcome will be the PGA completion rate. The secondary outcome will be the rate of chemotherapy dose modification among those with any identified geriatric impairment. Clinician perspectives on PGA implementation will be assessed via structured interviews among a sub-sample of participating clinicians. In a subsample of patients consenting to additional data collection, exploratory analyses will examine correlations between the PGA, step counts (measured via FitBit) and body composition (measured via standard abdominal CT scans) with clinical outcomes, including toxicity, hospitalization, and death. PACE-70 will be the first study to report on real-world implementation of the PGA in a multisite community oncology setting. It will provide insights on the facilitators and barriers of the PGA to inform chemotherapy dose modification, as well as its potential predictive value for clinical outcomes. It will lay the foundation for larger trials of effectiveness seeking to encourage PGA implementation and PGA-adapted care. Clinical trial information: pending. Research Sponsor: None.

TPS1662 **Poster Session**

Patient Priorities Care for older breast cancer survivors: A patient-centered approach to improve quality of breast cancer survivorship. First Author: Dana Elena Giza, The University of Texas Health Science Center at Houston, Houston, TX

Background: Older adult breast cancer survivors have higher rates of chronic conditions compared with other cancer survivors and may have a higher treatment burden. High treatment burden is associated with poor quality of life and increased healthcare utilization. Aligning care with patient priorities can reduce the treatment burden during survivorship care. Patient Priorities Care (PPC) is an approach designed to align care around each patient's goals to help decrease treatment burden. Although the PPC approach was previously designed for patients with multiple chronic conditions, we sought feedback from stakeholders, including older patients with a history of breast cancer, to adapt the PPC approach to breast cancer survivorship context. This quality improvement project aims to use PPC and patient's self-defined goals to improve the quality of survivorship care for older adults breast cancer survivors. **Methods:** We are conducting a multicenter, randomized quality improvement project with a hybrid implementation-effectiveness design to evaluate the impact of the adapted PPC approach compared to standard survivorship care on treatment burden and quality of life (NCT06478589). We are recruiting 120 older adult breast cancer survivors from outpatient oncology and primary care clinics. Eligible patients are: (1) $\geq$65 years of age; (2) stage I-III breast cancer, who had finished active breast cancer treatment and are in the first year of survivorship care; (3) have evidence of burdensome care; (4) English-speaking; and (5) able to provide informed consent. Enrollment started in December 2024. Patients are stratified based on treatment burden at baseline; patients with a score of $>$ 15 on the treatment burden questionnaire (TBQ) undergo simple randomization with a 2:1 ratio to either the PPC or standard survivorship care group. The PPC for Breast Cancer Survivorship intervention consists of: (1) a 30-minute priorities identification visit with a facilitator, 2) delivery of a structured patient priorities report to the survivorship care team, 3) survivorship care alignment using the patient's priorities. The primary outcome measures are differences in treatment burden (TBQ) and quality of life (FACT-B) from baseline at 3 to 6 months. Secondary outcomes include goal attainment achievement at 3,6 months for patients in the intervention group and adherence to standard and priorities-based breast cancer survivorship recommendations at 12 months for both groups. Descriptive statistics will be used to report patients' baseline and clinical characteristics. All analysis will be intention to treat. The effect of the intervention on changes (baseline to 3, 6 months) in the TBQ and FAST-B scores using Bayesian analysis. For the goal attainment differences, we will compare the differences in goal ratings from baseline at 3, 6 months within the Patient Priorities Group. Clinical trial information: NCT04513977. Research Sponsor: NIA.

TPS1663 **Poster Session**

Impacting quality of life and pancreatic cancer survivorship through a telehealth intervention. First Author: Vincent Chung, City of Hope, Duarte, CA

Background: Pancreatic cancer patients experience significant debilitating symptoms as a direct or indirect result of disease, treatment, and co-morbidities resulting in higher symptom burden compared to other cancer types. The presence of comorbidities, declines in organ function, and increased need for assistance with daily function complicates the care of older adults with pancreatic cancer. Cancer not only affects the patient but also the entire family, especially the one that assumes the role of the family caregiver (FCG). Robust evidence suggests that survivors with pancreatic cancer and their FCGs experience high symptom burden and reduced quality-of-life (QOL). Despite robust evidence pointing to potential benefits of palliative care, many pancreatic cancer patients never receive any due to the workforce shortage. A scalable method of providing palliative care is needed. **Methods:** We are conducting a randomized pilot study to determine the feasibility, acceptability, and preliminary efficacy of a centrally administered telehealth, self-management survivorship care intervention in patients with pancreatic cancer and their FCGs. Patients within 8 weeks of initiating first line treatment for metastatic disease are eligible. Prior to initiating the intervention sessions, an advanced practice nurse (APRN) will complete separate comprehensive survivor/FCG QOL assessments using baseline surveys. The assessments will focus on QOL needs for survivors/FCGs and will include geriatric assessment for all regardless of age (activities of daily living, physical mobility, falls, social activity limitations, social support). Based on the QOL and geriatric screenings, the Intervention APRN will complete a personalized care plan for the patient, and a personalized self-care plan for the FCG. This provides for tailoring of the care plan to the participant's needs and preferences and will be shared with each participant's oncology care team after session completion. Both care plans will be organized around the four QOL aspects of care (physical, psychological, social, spiritual). Cultural aspects of care are taken into account and integrated appropriately within the four QOL aspects of care. A fully developed intervention resource manual with support reference materials and intervention content are provided to each patient and FCG. The patient and FCG coaching sessions are bi-weekly, centrally administered and separate but parallel to allow participants to freely discuss their QOL needs. Clinical trial information: NCT06524973. Research Sponsor: U.S. Department of Defense.

LBA2000 **Oral Abstract Session**

Efficacy and safety of STUPP regimen with or without anlotinib for newly diagnosed glioblastoma: Results of a multicenter, double-blind, randomized phase II trial. First Author: Yuanyuan Chen, State Key Laboratory of Oncology in South China, Sun Yat-Sen Univercity Cancer Center, United Laboratory of Frontier Radiotherapy Technology of Sun Yat-sen University and Chinese Academy of Sciences Ion Medical Technology Co., Ltd., Guangzhou, China

The full, final text of this abstract will be available at meetings.asco.org on the day of presentation and in the online supplement to the June 10, 2025, issue of the *Journal of Clinical Oncology*.

2001 **Oral Abstract Session**

A prognostic classification system for extent of resection in IDH-mutant grade 2 glioma: A report by the RANO resect group. First Author: Philipp Karschnia, Department of Neurosurgery, Uniklinikum Erlangen, Friedrich-Alexander-University Erlangen-Nuremberg, Erlangen, Germany

Background: The effects of resection in IDH-mutant grade 2 gliomas remain controversial since terminology for extent of resection was inconsistently applied across trials. We aimed to (I) establish a standardized classification system for extent of resection and (II) assess the impact of supramaximal resection on survival in IDH-mutant astrocytomas and 1p19q-codeleted oligodendrogliomas. **Methods:** Patients with newly diagnosed grade 2 IDH-mutant glioma meeting the WHO 2021 criteria were identified across sixteen centers in the USA, Europe, and Asia as part of the RANO *resect* effort. Additional patients from UCSF served for validation. Kaplan-Meier analyses and log-rank tests were applied to calculate survival, and Cox's proportional hazard regression model to adjust for multiple variables (significance level: $p \leq 0.05$). **Results:** We identified 1391 newly diagnosed IDH-mutant gliomas grade 2 between 1993-2024, of which 728 patients (379 astrocytoma, 349 oligodendroglioma) received no adjuvant treatment and allowed to study the effects of resection. Smaller post-operative T2/FLAIR tumor remnants were favorably associated with outcome. We classified those patients according to residual T2/FLAIR tumor volumes: patients with 'maximal T2/FLAIR resection' (class 2; 0-5 cm^3 remnant) had superior progression-free and overall survival compared to 'submaximal T2/FLAIR resection' (class 3; 5-25 cm^3 remnant) or 'minimal T2/FLAIR resection' (class 4; $>$25 cm^3 remnant), with 10-year survival rates of 82.2% *vs*. 75.0% *vs*. 45.6% (respectively; $p = 0.001$). Resection of non-infiltrated structures beyond T2/FLAIR borders provided an additional survival benefit as characterized by a 10-year survival rate of 97.5%; thus defining class 1 'supramaximal T2/FLAIR resection' (HR for OS *vs.* class 2: 0.24, CI 0.1-0.5 / in astrocytoma: 0.26, CI 0.1-0.7 / in oligodendroglioma: 0.21, CI 0.1-0.9). Effects of extensive resection on survival unfolded after 3 years in astrocytomas, whereas survival curves separated after 6-8 years in oligodendrogliomas. The prognostic relevance of the four-tier classification was conserved in a multivariate analysis controlling for clinical markers including pre-operative tumor and 1p19q-codeletion, in subgroups of either astrocytomas or oligodendrogliomas, and in a separate cohort of 586 patients who received adjuvant chemo-/radiotherapy. The prognostic value of the classification was further validated in the external UCSF cohort of 381 grade 2 IDH-mutant gliomas ($p = 0.001$). **Conclusions:** The proposed 'RANO classification for extent of resection' serves as prognostic tool for patient stratification in grade 2 IDH-mutant gliomas. While effects of extensive surgery are evident earlier in astrocytomas, 'supramaximal' resection translates into a survival benefit for both astrocytomas and oligodendrogliomas and should be characterized in clinical trials. Research Sponsor: None.

2002 **Oral Abstract Session**

Final clinical and molecular analysis of the EORTC randomized phase III intergroup CATNON trial on concurrent and adjuvant temozolomide in anaplastic glioma without 1p/19q codeletion: NCT00626990. First Author: Martin J. Van Den Bent, Erasmus MC Cancer Institute, Rotterdam, Netherlands

Background: The 1st and 2nd interim analyses of the CATNON trial on anaplastic glioma (NCT00626990) showed benefit from adjuvant (adj) temozolomide (TMZ) on overall survival (OS) in patients with IDH mutant (mt) tumors, but no benefit of concurrent (conc) TMZ regardless of Isocitrate dehydrogenase 1 and 2 (IDH) mutation (mt) status. We now present the final analysis and the exploratory molecular marker analysis of the study. **Methods:** The 2x2 factorial design phase III CATNON trial randomized 751 adult patients with newly diagnosed non-codeleted anaplastic glioma to either 59.4 Gy radiotherapy (RT) alone; the same RT with concTMZ; the same RT and 12 cycles of adjTMZ or the same RT with both concTMZ and adjTMZ. Methylation status including *MGMT* promoter methylation status were assessed with the Infinium MethylationEPIC Beadchip. IDH mutation (mt) status and glioma specific alterations were assessed with a glioma targeted panel using Agilent SureSelect baits. **Results:** After a median follow-up of 10.9 years and with 499 events observed, in the intent-to-treat population the hazard ratio (HR) for OS adjusted for stratification factors after concTMZ was 0.906 (95%CI 0.760, 1.082; p=0.28) and after adjTMZ 0.647 (95%CI 0.541, 0.773; p $<$0.0001). In 660 patients IDH status could be determined: IDH was mt in 444 tumors and wild type (wt) in 216 tumors. Median OS was 1.7 yrs in patients with IDHwt tumors and 8.5 years in patients with IDHmt tumors. Benefit to TMZ was limited to patients with anaplastic glioma IDHmt of which 199 were still alive (45%). For patients with IDHmt tumors the HR for concTMZ was 0.81 (95% CI 0.63-1.04; p=0.09) and for adjTMZ 0.54 (95% CI 0.42-0.69,p $<$ 0.0001). No benefit was observed of concTMZ in IDHmt glioma patients that also received adjTMZ (HR 0.92 95% CI 0.63-1.36; p=0.69). In patients with IDHmt tumors that had received any TMZ median OS was 10.3 years, the median OS in patients treated with adjTMZ was 12.5 years (95% CI 9.4-15.0; p$<$0.0001). In exploratory analysis, high-copy number Amplification of *PDGFR* and *CDK4*; Homozygous deletion of the *CDKN2A/B* locus, total copy number alterations, methylation subtype (A_IDH vs A_IDH_HG, G-CIMP high versus low, *MGMT*-promoter methylation as determined by methylation arrays) were all associated with outcome but none was predictive for benefit to TMZ. **Conclusions:** Despite more follow-up, concTMZ did not improve OS regardless of IDH status. AdjTMZ increased OS in patients with IDHmt tumors but not in patients with IDHwt tumors. Molecular factors of known prognostic significance for IDHmt 1p/19q intact anaplastic glioma did not predict benefit to TMZ. Median OS in patients with IDHmt glioma having received adjTMZ after RT was 12.5 years. Standard of post-operative care in patients with high grade IDHmt astrocytoma should be RT followed by 12 cycles adjTMZ. Funding Source: MSD. Clinical trial information: NCT00626990. Research Sponsor: MSD; Dutch Cancer Socierty; 10685; Brain Tumor Charity; GN-000577; Stijd van Salland.

2003 **Oral Abstract Session**

A phase 2 study of pemigatinib for pre-treated glioblastoma or other gliomas with activating FGFR1-3 alterations: Results from FIGHT-209. First Author: Enrico Franceschi, IRCCS Istituto delle Scienze Neurologiche di Bologna, Bologna, Italy

Background: FGFR genomic alterations occur in approximately 8% of gliomas. Inhibition of FGFR1-3 with pemigatinib showed antitumor activity in a multihistology basket trial (FIGHT-207) in which approximately 10% of participants (pts) had recurrent/progressive FGFR-altered glioblastoma (GBM). We further investigated pemigatinib activity in primary brain tumors by conducting an international, multicenter, single-arm, 2-cohort, phase 2 study specifically in adults with FGFR-altered pretreated gliomas (FIGHT-209; NCT05267106). **Methods:** Pts were enrolled in 2 cohorts: A, histologically or molecularly defined GBM; or B, other gliomas, glioneuronal tumors, and neuronal tumors. Eligible pts had tumors harboring a FGFR1-3 fusion/rearrangement or mutation detected by an accredited laboratory that had recurred/progressed after $\geq$1 prior therapy. Pemigatinib (oral, 13.5 mg on days 1-14/21) was intended to continue until progression by Response Assessment in Neuro-Oncology (RANO) criteria determined by an independent review committee (IRC) or unacceptable toxicity. Efficacy of each cohort was evaluated independently. The primary endpoint was objective response rate (ORR; partial plus complete) per RANO (cohort A), with a goal of $>$ 28%. Key secondary and exploratory endpoints were ORR in cohort B, ORR by investigator assessment, progression-free survival (PFS) by IRC, overall survival (OS), safety, neurologic function by Neurologic Assessment in Neuro-Oncology (NANO), and efficacy correlations with diagnosis and specific FGFR-alterations. **Results:** Between May 2022 and December 2023, 74 pts were enrolled in cohort A and 9 in cohort B. FGFR1-3 fusions/rearrangements were the most common genomic alterations in cohort A (n = 65 [88%]) and in cohort B, FGFR1 mutations (n = 8 [89%]). Pts had a median (range) age of 56 (20-79) years; 60% were male. On September 27, 2024 (data cutoff), 16 pts remained on treatment (cohort A, n = 11 [15%]; cohort B, n = 5 [56%]); 67 discontinued, primarily due to progressive disease (n = 59 [71%]). In cohort A, ORR was 8% (6 partial responses [PR], 0 complete responses [CR]); 21 pts (28%) had stable disease (SD); estimated 6-month PFS rate was 17% (95% CI, 8.7-27.8) and 12-month OS rate 48% (95% CI, 35.6-60.2). In cohort B, the ORR was 22% (1 CR, 1 PR); 3 (33%) SD. Most treatment-emergent adverse events (AEs) were low grade in severity (grade $\geq$3, 36.1%). Hyperphosphatemia, a class effect of FGFR inhibitors, was the most common AE (75%); 6 pts (7%) required dose reduction and 4 pts (5%) discontinued due to AEs. **Conclusions:** ORR did not meet the pre-specified goal of $>$ 28% among pts with GBM harboring pemigatinib-sensitizing FGFR alterations. However, durable disease stabilization was observed, notably in pts with CNS tumors other than GBM, and toxicities were manageable. More mature PFS and OS data will be presented with exploratory molecular correlations. Clinical trial information: NCT05267106. Research Sponsor: Incyte Corporation.

2004 Oral Abstract Session

A phase II study of asandeutertinib (TY-9591) in advanced NSCLC patients with EGFR-positive mutations and brain metastases. First Author: Pu-Yuan Xing, National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences & Peking Union Medical College, Beijing Key Laboratory of Clinical Study on Anticancer Molecular Targeted Drugs, Beijing, China

Background: Asandeutertinib (TY-9591), a deuterated osimertinib derivative, is a new central nervous system-active 3rd generation epidermal growth factor receptor tyrosine kinase inhibitor (EGFR-TKI), that can potently and selectively inhibit *EGFR*- sensitizing mutations (EGFRm+) and T790M resistance mutation. The phase I study for asandeutertinib (NCT04204473) showed had a very superior clinical efficacy on the NSCLC with *EGFR* mutations. This phase II study (NCT05146219) aimed to further evaluate the efficacy and safety of asandeutertinib in patients with locally advanced or metastatic EGFRm+ NSCLC with brain metastases (BM). **Methods:** 29 patients were enrolled and received asandeutertinib treatment at a dose of 160 mg once daily. The 27 patients with *EGFR*-sensitizing mutations (19 Del or L858R) did not take any EGFR-TKI previously, while the 2 patients with *EGFR* T790M resistance mutation previously received 1st or 2nd-generation EGFR-TKIs therapy. The primary endpoints were the intracranial objective response rate (iORR) assessed by investigator (INV) per RANO-BM and the extracranial objective response rate (eORR) assessed by INV per the RECIST v1.1. **Results:** At the time of data cutoff at March 21,2024, the median follow-up time was 16.4 months. The confirmed INV-iORR was 93.1% (95% CI: 77.2%-99.2%) (n = 29). The confirmed INV-iORR for those who were treated with asandeutertinib as first line was 92.6% (95% CI : 75.7%-99.1%) (n = 27). The 2 patients with previous EGFR-TKI therapy were intracranial partial response (iPR). The median intracranial duration of response (iDoR) and intracranial progression-free survival (iPFS) were not reached. The 12-month iDoR was 82.8%, and the 12-month iPFS was 96.6%. The median PFS was 13.5 months (95% CI: 12.5-NA) (n = 29) and 15.1 months (95%CI : 12.5 - NA) (n = 27) for those without previous EGFR-TKI therapy. Any intracranial or extracranial progression was evaluated as systemic progression, which may lead to underestimation of the systemic PFS. The mean treatment was 402.9 days (n = 29). 27 (93.1%) patients experienced treatment-related adverse events (TRAEs). The most common TRAEs (≥10%) included decreased white blood cell count, decreased absolute neutrophil count, decreased platelet count, elevated serum creatine phosphokinase, diarrhea, etc (majority grade 1/2). Grade 3 TRAEs occurred in 27.6% patients while no grade 4/5 adverse event. Six serious adverse events were reported by five patients (17.2%), of which two patients (6.9%) were study drug-related. The interstitial lung disease, cardiomyopathy and keratitis were not reported. **Conclusions:** Asandeutertinib is highly effective and well-tolerated in locally advanced or metastatic EGFRm+ NSCLC patients with BM. Pivotal phase II study (NCT05948813) and phase II trials (NCT05382728) are onging. Keywords: TY-9591; Deuterated osimertinib derivative; Brain metastases. Clinical trial information: NCT05146219. Research Sponsor: None.

2005 Oral Abstract Session

Patritumab deruxtecan (HER3-DXd) in active brain metastases (BM) from metastatic breast (mBC) and non–small cell lung cancers (aNSCLC), and leptomeningeal disease (LMD) from advanced solid tumors: Results from the TUXEDO-3 phase II trial. First Author: Matthias Preusser, Division of Oncology, Department of Internal Medicine I, Medical University of Vienna, Vienna, Austria

Background: BM and LMD are common and severe complications of solid cancers with high morbidity, poor prognosis, and limited treatment options. Antibody drug conjugates (ADCs) have shown high intracranial overall response rates (IC-ORR) in HER2-positive mBC and *EGFR*-mutated NSCLC patients (pts). HER3-DXd, an ADC combining an anti-HER3 antibody with a topoisomerase (topo) I inhibitor, has shown promising results in mBC and aNSCLC pts. Since HER3 is highly expressed in aNSCLC and mBC CNS metastases, we hypothesized HER3-DXd may have clinical activity in BM from mBC and aNSCLC pts, and LMD from any solid tumor. **Methods:** TUXEDO-3 (NCT05865990) is an international, multicenter, multicohort, single-arm, phase II trial enrolling pts with BM from mBC (cohort 1), aNSCLC (cohort 2), and LMD from any solid tumor (cohort 3). Key inclusion criteria were: Pts ≥18 years old, histologically documented disease, ECOG PS 0-2, and left ventricular ejection fraction ≥50% in all cohorts; newly diagnosed/progressing BM with ≥1 brain lesions ≥10mm by MRI, and ≥1 line of prior systemic treatment, in cohorts 1 and 2; LMD per EANO-ESMO in cohort 3. Pts received HER3-DXd 5.6 mg/kg IV Q3W until disease progression, unacceptable toxicity or withdrawal for any reason. Primary endpoint was IC-ORR per local investigator according to RANO-BM in cohorts 1 and 2, and 3-month OS in cohort 3. Sample size was based on Simon's two-stage design. Primary endpoint was met if ≥3 IC responses (H0: ≤5%; H1: ≥25%) in cohort 1 and 2; and if ≥3 pts with 3-month OS (H0: ≤5%; H1: ≥25%) in cohort 3. Overall sample size was 60 pts with a target population of 20 pts per cohort. **Results:** Between December 2023 and July 2024, 61 evaluable pts were enrolled from 8 Austrian and Spanish sites. Median age (min; max) was 57.0 (35.0; 75.0), 59.5 (37.0; 72.0) and 51.5 (40.0; 66.0) years in cohorts 1, 2 and 3, respectively. At data cut-off, median follow-up (min; max) was 4.4 (1.4; 10.1), 4.3 (0.2; 11.0) and 3.5 (0.8; 8.6) months in cohorts 1, 2 and 3, respectively. Primary endpoints were met in all three cohorts. In cohort 1, 5/21 (23.8%) pts had IC response irrespective of BC subtype; 2 (40.0%) responders had received previous topo I based ADCs. In cohort 2, 5/20 (25.0%) pts had IC response. In cohort 3, 11/20 (55.0%) pts achieved 3-month OS irrespective of the LMD type. No new signals of toxicity were observed and neurological symptoms, QoL and neurocognitive function remained stable or improved over the treatment period. Tumoral HER3 expression did not correlate with treatment response. **Conclusions:** TUXEDO-3 is the first trial evaluating efficacy and safety of HER3-DXd in pts with BM or LMD. HER3-DXd showed substantial CNS activity in parenchymal metastases and LMD, and may be a potential novel treatment for CNS disease in cancer pts. Clinical trial information: NCT05865990. Research Sponsor: Daiichi Sankyo Company, Limited; Merck Sharp & Dohme LLC, a subsidiary of Merck & Co.

2006 Oral Abstract Session

A phase II study of an anti-telomerase CD4+ T-helper vaccine (UCPVax) with or without temozolomide in newly diagnosed glioblastoma. First Author: Antoine Carpentier, Hôpital Saint-Louis, Paris, France

Background: UCPVax is a therapeutic vaccine designed to stimulate CD4+ helper T cell responses against telomerase (TERT), a protein highly expressed in glioblastoma (GBM). Temozolomide (TMZ), a standard chemotherapeutic agent in the treatment of GBM, has been shown to induce CD4+ T-cell lymphopenia, which could potentially impair the immune response to the vaccine. We conducted a multicenter, 2-cohort, phase IIa study to evaluate the immunogenicity and efficacy of UCPVax, with or without TMZ, as adjuvant therapy in patients with newly diagnosed GBM following chemoradiation. **Methods:** Patients with non-mutated IDH1 glioblastoma (GBM) were enrolled one month after completing concurrent radiotherapy and temozolomide (TMZ). Cohort A received the vaccine alone, without additional TMZ, while Cohort B was treated with both the vaccine and six monthly cycles of TMZ. The primary endpoint was the induction of TERT-specific CD4+ T cell responses, assessed ex vivo using the INF-γ ELISpot assay. Secondary endpoints included epitope spreading, clinical outcomes, and safety. **Results:** Thirty-one GBM patients with unmethylated MGMT status were included in cohort A, and 30 patients (50% with unmethylated MGMT status) were included in cohort B. The vaccine was well tolerated, with no vaccine-related serious adverse events. Vaccine-expanded TERT-specific CD4+ T cells were detectable *ex vivo* in 25/30 (83%) of patients in cohort A (no additional TMZ) and in 18/26 69% of patients in cohort B (treated with additional TMZ). Epitope spreading was induced in 29 out of 55 evaluable patients (52.7%), corresponding to 15/26 (57.7%) in cohort A and 14/29 (48%) in cohort B. Median overall survival (OS) was significantly improved in patients who developed an epitope spread response compared to those who did not (19.3 vs. 12.8 months, P = 0.03). In the 44 patients with measurable disease at the time of inclusion, the radiological response rate (RR) was 34%, including minor responses. In patients who developed epitope spreading after vaccination (n = 22), the RR was 50%, compared to 18.7% in patients without epitope spreading (P = 0.05). Furthermore, tumor-infiltrating lymphocytes against TERT were detected in 3 vaccinated patients who underwent surgery at recurrence. **Conclusions:** UCPVax demonstrated robust immunogenicity, even when co-administered with TMZ, and was associated with improved overall survival (OS) in GBM patients who developed an epitope spreading response. These findings support further clinical investigation of TERT-derived CD4+ helper vaccine in GBM patients. Clinical trial information: NCT04280848. Research Sponsor: French Eastern Interregional Group of Clinical Research and Innovation (GIRCI-Est - APJ2017); Oligocyte.

2007 Oral Abstract Session

INB-200: Phase 1 study of gene-modified autologous gamma-delta (γδ) t cells in newly diagnosed glioblastoma multiforme (GBM) patients receiving maintenance temozolomide (TMZ). First Author: Mina Lobbous, Cleveland Clinic, Cleveland, OH

Background: Recent cell therapy and CAR-T initiatives for GBM have shown initial responses but durability has been disappointing. We developed a novel approach to treat newly diagnosed GBM using innate γδ T cells following forced upregulation of tumor stress-associated targets. **Methods:** We leveraged the TMZ-induced activation of the DNA damage response (DDR) pathway to transiently upregulate NKG2D-L targets on GBM. Co-administration of TMZ chemotherapy with γδ T cells engineered for TMZ resistance by insertion of a methylguanine-DNA methyltransferase (MGMT)-expressing lentivector (DeltEx Drug Resistant Immunotherapy – DRI) enables the targeting of residual GBM cells during the standard-of-care Stupp regimen. A total of 23 patients were enrolled, with 13 treated and (62% male; median age 66 (range: 21-74); 92% IDH-WT, 54% MGMT-unmethylated). Cohorts (C) 1, 2 and 3 received 1, 3 or 6 doses (1×10^7 DRI cells/dose) into the resection cavity with 150 mg/m^2 of IV TMZ on Day (D) 1 of each Stupp regimen maintenance cycle. **Results:** No Dose limiting toxicities (DLTs) were seen nor were occurrences of cytokine release syndrome (CRS) or neurotoxicity (ICANS). Most common adverse events were related to underlying TMZ and Stupp regimen. As of January 24, 2025, median follow-up is 16.9 months (m). The median PFS for patients is 8.3m for those who received a single dose of INB-200, 9.9m for all patients (a 44% increase over the 6.9m mPFS of the Stupp) and 14.0m for patients who received repeated doses, an 102.4% improvement over Stupp and 69% over single dose patients. A patient with IDH mutant tumor remains progression free for almost 44 months and one with MGMT-unmethylated tumor for 18 months. Biopsy specimens from three patients are available with general immune activation having been demonstrated. **Conclusions:** To date all patients had manageable toxicity with outpatient treatment and a continued encouraging trend in longer PFS from treatment with DRI γδ T cells. Clinical trial information: NCT04165941. Research Sponsor: IN8Bio, Inc.

Subject	Age/ Sex	IDH/ Methylation	Resection	Dose level	TMZ Maint. Cycles Received	Response	PFS (mos)	OS (mos)
001	69/M	IDH-WT, MGMT-unmethylated	Total	1	5	SD	8.3	15.6
003	75/F	IDH-WT, MGMT-methylated	Total	1	6	SD	11.9	17.7
004	21/F	IDH-WT, MGMT-unmethylated	Total	1	3	SD	7.4	9.6
007	75/M	IDH-WT, MGMT-unmethylated	Total	2	2	Un-evaluable	-	5.1
009	32/M	IDH-mutant, MGMT-methylated	Total	2	12	SD		43.7+
011	56/F	IDH-WT, MGMT-methylated	Total	2	6	SD	22.2	28.6
014	73/F	IDH-WT, MGMT-unmethylated	Subtotal	2	6	SD	8.7+	8.7 without progression
015	73/M	IDH-WT, MGMT-methylated	Subtotal	3	5	SD	7.1	11.8
017	74/F	IDH-WT, MGMT-methylated	Subtotal	3	3	SD		21.5+
020	66/M	IDH-WT, MGMT-methylated	Subtotal	3	3	SD		19.6+
021	57/M	IDH-WT, MGMT-unmethylated	Total	3	6	SD		18.1+
022	53/M	IDH-WT, MGMT-unmethylated	Subtotal	3	6	SD	10.0	13.6
023	52/M	IDH-WT, MGMT-unmethylated	Subtotal	3	1		4.2	5.4

2008 Oral Abstract Session

Immunological correlates from phase I study of CARv3-TEAM-E in patients with recurrent glioblastoma (GBM): INCIPIENT trial. First Author: Bryan D. Choi, Massachusetts General Hospital, Boston, MA

Background: Chimeric Antigen Receptor (CAR) T cells for glioblastoma (GBM) have been limited by the challenge of targeting a single tumor antigen in a heterogeneous disease. To address this barrier, we generated a novel engineered T-cell product (CARv3-TEAM-E) that targets the EGFRvIII antigen while also secreting T-cell-Engaging Antibody Molecules (TEAMs) against wild-type EGFR. **Methods:** The INCIPIENT clinical trial is a first-in-human study of CARv3-TEAM-E in patients with recurrent GBM (NCT05660369). Patients were treated with intraventricular CARv3-TEAM-E T cells (10E6 cells per infusion). A subset of patients were conditioned with lymphodepleting chemotherapy (LDC) consisting of cyclophosphamide and fludarabine. Immune cells were profiled in the cerebrospinal fluid (CSF) and peripheral blood of patients by flow cytometry. **Results:** CAR T cells were detected in the CSF of all patients for an average of 33.6 days (*SD* = 10.33). Granulocytes, NK cells, B cells, and monocytes appeared in the CSF immediately after infusion, decreasing to low levels over the course of several weeks. TEAM-positive T cells persisted in CSF until (median) day 33.6 (*SD* = 10.8) with a range of 21-56 days. CAR T cells were transiently detected in the peripheral blood of 9/10 patients at an average of 14 days (*SD* = 3.5) after infusion. Prior to infusion, CAR T cells were predominantly CD4-positive and remained as such in the CSF over time. Those in the periphery exhibited CD4-to-CD8 polarization. Of patients who received multiple infusions, 3 out of 6 had CAR-positive T cells in the CSF after a second infusion, although their persistence was short-lived and was not detected in the periphery following repeat infusions. LDC increased engraftment of CAR T cells in CSF but not in peripheral blood. Patients with poor CAR persistence demonstrated the development of anti-CARv3-TEAM-E antibodies in the CSF and serum, which increased with reinfusion. **Conclusions:** Following initial infusion, intraventricularly delivered CARv3-TEAM-E T cells were detected in the CSF and peripheral blood in patients with recurrent GBM. Reduced persistence was observed with subsequent infusions. This corresponded with the emergence of anti-CARv3-TEAM-E antibodies in treated patients. Clinical trial information: NCT05660369. Research Sponsor: Gateway for Cancer Research; National Cancer Institute/U.S. National Institutes of Health; 1R01CA294071-01A1.

2009 Clinical Science Symposium

Multicenter trial of microbubble-enhanced transcranial focused ultrasound (MB-FUS) with monthly adjuvant temozolomide for patients with high-grade gliomas. First Author: Graeme Woodworth, University of Maryland School of Medicine, Baltimore, MD

Background: High-grade gliomas (HGGs) have few effective therapies targeting tumor cell recurrence, which remain shielded by blood-brain barrier (BBB). MB-FUS allows for controlled BBB opening (BBBO) enabling localized drug delivery and increased tumor biomarker release into systemic circulation. **Methods:** MR-guided MB-FUS with real-time feedback was evaluated for HGG patients in multicenter phase 1/2 trial (BT008: NCT03551249, NCT03616860) for adverse events (AEs) and feasibility [primary endpoints], efficacy [secondary endpoint], and plasma cell-free DNA (cfDNA) post-procedure [exploratory]. After resection and 6 weeks of chemoradiation, peri-resectional infiltrative regions were targeted with MB-FUS during monthly adjuvant temozolomide cycles (MB-FUS+TMZ). For efficacy, overall survival (OS) and progression-free survival (PFS) were compared with an external cohort, created using restriction and coarsened exact matching (CEM). **Results:** Trial cohort had 34 patients enrolled and evaluated from 5 sites in North America. No serious procedure-related AEs were seen, with the most common AEs being mild, self-resolving. BBBO was seen in 100% of treatments, covering 82% targeted volumes with ≤3mm accuracy. Trial cohort had longer mPFS (univariate 13.5 vs. 9.6 months, multivariate HR 0.62, 95%CI: 0.39-0.99, p=0.048) and mOS (36.4 vs. 19.1 months, multivariate HR 0.50, 95%CI: 0.26-0.95, p=0.036), with treatment effect robust in sensitivity analyses. Disease state correlated closely with longitudinal plasma cfDNA changes. **Conclusions:** MB-FUS+TMZ is a safe and feasible therapeutic approach for HGG, potentially improving survival and enabling longitudinal non-invasive monitoring. Clinical trial information: NCT03551249, NCT03616860. Research Sponsor: Insightec Inc; U.S. National Institutes of Health; R21NS113016.

Variables	Trial cohort	Matched Cohort †	
Patients (N)	34	158	
Baseline characteristics used in CEM			SMD†
Age, years, mean±SD	51.5 ±13.0	51.6 ±13.0	0.0
MGMT, Unmethylated, N (%)	16 (47.1%)	74 (47.1%)	0.0
IDH, Wild type, N (%)	29 (85.3%)	135 (85.3%)	0.0
Characteristics tackled through restriction			SMD†
Received resection & 6 weeks of chemoradiotherapy	34 (100%)	158 (100%)	0.0
Non-Hispanic, N (%)	34 (100%)	158 (100%)	0.0
Complete resection, N (%)	34 (100%)	158 (100%)	0.0
KPS ≥70 – N (%)	34 (100%)	158 (100%)	0.0
Other characteristics not used in CEM			wSMD†
Sex, male – N (%)	16 (47.1%)	101 (63.9%)	0.34
Race, White – N (%)	28 (82.4%)	137 (86.7%)	0.13
Preoperative tumor size, median cm^3 (IQR)	19.8 (6.9, 42.9)	47.0 [30.0, 53.0)	0.61
Clinical Outcomes			P
Unadjusted mOS, months (95%CI)	36.4 (21.1, NR)	19.1 (16.2, 22.8)	<0.001
OS HR for treatment adjusted for tumor size, IDH, & MGMT (95%CI)	0.50 (0.26, 0.95)		0.036
Unadjusted mPFS, months (95% CI)	13.5 (9.9, 25.4)	9.6 (7.8, 11.9)	0.032
PFS HR for treatment adjusted for tumor size, IDH, & MGMT (95%CI)	0.62 (0.39, 0.99)		0.048

SMD, weighted standardized mean difference.
†Estimated using CEM weights.

2010 Clinical Science Symposium

Leveraging stimulated Raman histology-based cellularity for random forest prediction of glioblastoma recurrence. First Author: Sanjeev Herr, Drexel University College of Medicine, Philadelphia, PA

Background: Glioblastoma is a universally fatal diagnosis with extent of resection being one of the most significant predictors of overall and progression-free survival. Most patients eventually experience recurrence, with sixty percent recurring along the resection cavity. Recent work leveraging Stimulated Raman histology (SRH) and artificial intelligence (AI) has approximated glioma cellularity within the infiltrative margins. It remains unknown if these estimates of glioma burden at the infiltrative margins influence glioblastoma recurrence. This study aims to evaluate a predictive model of focal recurrence in patients with glioblastoma using SRH and AI-generated cellularity scores from tissue samples taken at the resection cavity margins. **Methods:** A multi-center, retrospective cohort study was conducted on patients diagnosed with glioblastoma who underwent resection followed by spatial annotated tissues acquired from the resection cavity margins. Tissues were analyzed using SRH optical imaging, and histopathology analysis was performed using confocal microscopy. Tissue cellularity was measured histologically and by optical imaging. **Results:** Over 400 patients and 2,200 specimens were analyzed, of which a nested subset of 60 patients were selected based on selection criteria. Using preoperative and postoperative imaging, margin samples were determined to be in an area of recurrence (n=58) or nonrecurrence (n=220). Cellularity was significantly higher in the recurrent margin sample group when compared to the nonrecurrent group (p = 0.026), which was further confirmed by a pathologist-determined cellularity score (0-3) that demonstrated similar findings (p = 0.026). Results were validated across three medical centers. Six classifiers were then trained for recurrence prediction. Using nineteen of the most predictive variables, random forests (RF) performed best with an AUC of 0.848. RF screening for the minimum practical number of variables demonstrated an AUC of 0.805 using only FastGlioma, age and extent of resection as variables. **Conclusions:** AI-generated cellularity scores have the potential to predict focal recurrence of glioblastoma, allowing for more tailored approaches to surgical resection and radiotherapy to increase progression-free survival. Research Sponsor: None.

2011 Clinical Science Symposium

Stereotactic radiation versus hippocampal avoidance whole brain radiation in patients with 5-20 brain metastases: A multicenter, phase 3 randomized trial. First Author: Ayal Aizer, Brigham and Women's Hospital/Dana-Farber Cancer Institute, Boston, MA

Background: Radiation therapy forms the mainstay of management for patients with brain metastases. Published randomized trials have found improved quality of life with stereotactic radiation (SRS/SRT) over whole brain radiation (WBRT) in patients with ≤ 4 brain metastases; comparative trials in patients with >4 brain metastases are lacking. In addition, prior randomized trials have demonstrated the superiority of hippocampal avoidance WBRT (HA-WBRT) over traditional WBRT, but no study has compared SRS/SRT to HA-WBRT. Accordingly, we conducted a multicenter, phase 3 randomized trial comparing SRS/SRT to HA-WBRT in patients with 5-20 brain metastases. **Methods:** Eligible patients were age 18-80 with 5-20 brain metastases secondary to a solid primary other than small cell lung cancer, were naïve to prior brain-directed radiation, and lacked leptomeningeal disease. The primary endpoint was the average of patient-reported symptom severity and interference over the first six months post-baseline relative to baseline, using the MD Anderson Symptom Inventory–Brain Tumor (MDASI-BT) module, a validated instrument assessing 22 symptoms and 6 interference measures integral to quality of life, each scored 0-10 with higher scores indicating greater symptomatology/interference in function. The target effect size was a symptom severity of 0.70, corresponding to 50% of the observed difference between patients with a good (90-100) versus poor (≤80) Karnofsky performance status; with 80% power and a two-sided alpha of 0.05, 196 patients were required. **Results:** Between 4/2017-5/2024, 196 patients enrolled, 98 in each arm. The median number of brain metastases was 14 (IQR 11-18); 25% of patients underwent prior neurosurgical resection. Baseline mean MDASI-BT symptom severity scores were 2.2 (SRS/SRT arm) and 1.9 (HA-WBRT arm), p=0.20; respective interference scores were 3.5 and 3.2 (p=0.40). The average of weighted post-baseline severity and interference scores relative to baseline indicated lower symptomatology/inference in the SRS/SRT arm, meeting the primary endpoint of the study (difference between SRS/SRT and HA-WBRT: -1.06, p<0.001). Averaged post-baseline symptom severity scores minus baseline were -0.03 and 0.59 in the SRS/SRT and HA-WBRT arms, respectively (difference -0.62, with lower symptom severity in the SRS/SRT arm, p<0.001); respective interference estimates were -0.62 and 0.89 (difference -1.50, with lower interference in the SRS/SRT arm, p<0.001). Median survival was 8.3 and 8.5 months in the SRS/SRT and HA-WBRT arms, respectively (p=0.30). **Conclusions:** This phase 3 randomized trial indicates that patients with 5-20 brain metastases experience fewer symptoms and less interference in function after SRS/SRT as opposed to HA-WBRT, without compromise of survival, supporting SRS/SRT as the standard of care in this population. Clinical trial information: NCT03075072. Research Sponsor: Varian.

2012 Rapid Oral Abstract Session

Utidelone in combination with etoposide and bevacizumab in HER2-negative breast cancer patients with brain metastasis: A prospective, single-arm, phase II trial. First Author: Yehui Shi, Tianjin Medical University Cancer Institute and Hospital, Tianjin, China

Background: For advanced HER2 negative breast cancer patients with brain metastasis, systematic therapy has failed to yield satisfied efficacy, although bevacizumab and etoposide have shown some effectiveness as mono- or combination therapy. Novel microtubule inhibitor utidelone demonstrated good efficacy in advanced breast cancer patients in several clinical trials, and was also suggested a capability of blood-brain barrier penetration. Therefore, utidelone in combination with bevacizumab and etoposide would be a promising regimen for HER2 negative breast cancer patients with brain metastasis. **Methods:** Breast cancer patients with brain metastasis were enrolled and Simon's two-stage optimal trial design was used for this trial. If more than 3 out of 13 patients showed central nervous system (CNS) response, 30 more patients would be further enrolled. The acceptable ORR was set to be 40% for the trial. Utidelone (30mg/m^2/day, iv, d1-5), and etoposide (100mg/m^2, iv, d1-3) were concurrently administered with bevacizumab (10mg/kg iv, d1) every 21 days for 6 cycles, followed by maintenance treatment with utidelone and bevacizumab until disease progression or unacceptable toxicity. The primary endpoint is CNS-ORR. Secondary endpoints include CNS-clinical benefit rate (CNS-CBR), CNS-PFS, PFS, and safety. **Results:** 34 female HER2 negative patients were enrolled, including 11 triple negative breast cancer patients and 23 patients of luminal subtype, with a median age of 52 years (range 34-74) and a median treatment lines of three. Five patients had prior brain radiotherapy and 2 patients were previously treated with brain surgery. As of December 2, 2024, the median follow up duration was 11.5 months. The CNS-ORR was 67.6% (23/34), and the CNS-CBR was 88.2% (30/34). The median PFS was 6 months (95% confidence interval [CI], 4.265-7.735). The median CNS-PFS was 15 months (95% CI, 6.760-23.240), with supportive treatment for some of the patients after extracranial progression which included etoposide re-administration, or abraxane, endocrine therapy, radiotherapy and immunotherapy. The major AE was peripheral neuropathy with 8.8% (3/34) of Grade 3, primarily classified as sensory. Most of the treatment-related AEs were grade 1 or 2 and were considered manageable and reversible. **Conclusions:** Utidelone in combination with etoposide and bevacizumab has shown promising anti-tumor activity and manageable toxicity in HER2 negative breast cancer patients with brain metastasis, and a randomized control trial is warrantied. Clinical trial information: NCT05781633. Research Sponsor: Tianjin Science and Technology Funding; 18ZXXYSY00070; Tianjin Municipal Education Commission Funding; 2016YD03; Beijing Biostar Pharmaceuticals; "358"Project, TJMUCH; 358-2023-06.

2013 Rapid Oral Abstract Session

Phase 1 study of HMPL-306, an inhibitor of mutant IDH1/IDH2 (mIDH1/2), in western patients (pts) with advanced mIDH solid tumor, including glioma. First Author: Jordi Rodon Ahnert, The University of Texas MD Anderson Cancer Center, Houston, TX

Background: Isocitrate dehydrogenase (IDH) 1 or IDH2 mutations or co-mutations have been associated with various tumors, including glioma. HMPL-306 ('306) is a novel, small-molecule, orally available, highly selective, and potent dual inhibitor of both mIDH1 and mIDH2. This is a phase 1 study of '306 in pts with locally advanced or metastatic solid tumors with mIDH. Here, we report the results of the dose escalation stage. **Methods:** Pts with locally advanced or metastatic solid tumors with any mIDH were enrolled to receive '306 once daily (QD) for 28-day cycles. The mTPI-2 design was used for dose escalation, having explored in 8 successive cohorts (50-400 mg). The study aims to determine the maximum tolerated dose (MTD)/recommended phase 2 dose (RP2D), evaluate safety, tolerability, preliminary efficacy and pharmacokinetics/pharmacodynamics (PK/PD). **Results:** As of Aug 9, 2024, 42 pts were administered '306 across 8 doses (n = 3, 3, 5, 12, 6, 4, 4, 5 in 50, 100, 150, 200, 250, 300, 350, 400 mg QD cohorts, respectively), with 17 (40.5%) lower-grade glioma (LGG, grade 2 and grade 3 glioma) pts, 3 (7.1%) grade 4 glioma pts and 22 (52.4%) non glioma pts. The median age was 55 years, and 25 (59.5%) pts were male. During the dose escalation from 50 mg to 400 mg QD cohort, 1 pt given 250 mg QD experienced a dose-limiting toxicity (DLT) of grade 3 lipase increased. MTD was not reached. 12 (28.6%) pts reported grade $\geq$3 adverse events (AEs), which reported in $\geq$ 2 pts was abdominal pain. Efficacy signals were observed especially in LGG pts, in the efficacy evaluated set (N = 14), objective response rate (ORR) was 7.1%, disease control rate was 100%; in the safety analysis set (N = 17), median progression-free survival (PFS) was 20.5 months (95% confidence interval [CI]; 5.5-not estimable). One grade 2 glioma pt with multiple previous treatment on the 200 mg QD achieved minor response lasting 16.8 months. The ORR of grade 4 glioma pts and non glioma pts were not reached, the disease control rate were 33.3% and 25%, respectively. Drug exposures were dose-proportional from 50 mg to 400 mg. Steady-state with ~5-fold accumulation was reached after ~28 days of repeated daily dosing. In non-glioma pts, 2-HG inhibition plateaued after ~28 days, increasing with dose, reaching ~90% at $\geq$150 mg at C2D1. **Conclusions:** '306 was well-tolerated in pts with mIDH1/2 solid tumors, showing target inhibition and durable responses in LGG. Clinical trial information: NCT04762602. Research Sponsor: HUTCHMED Limited.

2014 Rapid Oral Abstract Session

Vaccination by homologous antigenic loading with DOC1021 as adjuvant therapy for glioblastoma: Phase I clinical trial results. First Author: Joseph Georges, Banner University Medical Center, Phoenix, AZ

Background: Glioblastoma is a devastating tumor for which median overall survival (mOS) remains 14-18 months despite aggressive standard of care (SOC) treatment. Clinical studies of dendritic cell (DC) vaccination for GBM have shown promise but have been largely inconclusive. DC homologous antigenic loading leverages p38MAPK and mTORC1 signaling cascades to initiate cDC1-like skewing of monocyte-derived DC, leading to potent downstream induction of tissue-homing cytolytic memory effector T cells. Here we report results of a completed phase I study for glioblastoma (IDH-wt). **Methods:** This clinical trial evaluated autologous DC vaccine DOC1021 prepared from mobilized peripheral blood mononuclear cells (PBMC), loaded with autologous tumor lysate and amplified tumor mRNA, and administered bilaterally near deep cervical lymph nodes. Three courses of vaccine every 2 weeks plus weekly peg-IFN were administered after completion of chemoradiation. Four dose levels from 3.5 x 10^6 to 3.6 x 10^7 total vaccine cells were tested. Patients with subtotal resection or tumor progression prior to vaccination were not excluded. **Results:** Sixteen newly diagnosed patients completed treatment, median age 61 years (range 47-73), 94% MGMT unmethylated, 25% subtotal resected. OS at 12-months was 88% compared to expected ~60% for SOC and 5 patients are still alive at 19-30 months of follow-up. Two recurrent glioblastoma patients were also treated and survived for 10-12 months. Most common AEs were mild flu-like symptoms and injection-site reactions, and there were no dose limiting toxicities. Analysis of post-vaccination PBMC indicated expansion of $CD4^+$ (13/13 patients) and $CD8^+$ (11/13) central memory T-cell compartments ($p < 0.00006$ and $p < 0.003$, respectively) as well as expansion of $CD8^+CD127^+$ MPECs (12/13; $p < 0.002$). Among 3/3 patients analyzed by spatial transcriptomics, intense $CD25^+$ foci correlating with co-expression of effector memory T-cell and migratory microglial markers were observed in post-vaccination but not pre-vaccination samples. For 8 patients who were observed rather than re-operated for worsening T1-weighted signal on MRI in the 23 weeks after vaccination, signal gradually resolved and GBM-specific mOS is not yet reached compared to 15.1 months for 8 patients who received reoperation despite comparable clinical characteristics, suggesting an immune-reactive microenvironment manifesting as pseudo-progression. **Conclusions:** DOC1021 combined with SOC is safe and potentially efficacious in this challenging population that included subtotal resections, pre-treatment progression and 15/16 MGMT unmethylated. A randomized phase II trial is being launched including criteria to avoid early re-operation for enhancing T1-weighted signal that may be pseudo-progression. Clinical trial information: NCT04552886. Research Sponsor: Cancer Cures 4 Kids; N/A; Diakonos Oncology; N/A.

2015 Rapid Oral Abstract Session

Results from phase 1 study of mycophenolate mofetil with chemoradiation in newly diagnosed glioblastoma to target de-novo purine metabolism to overcome treatment resistance. First Author: Yoshie Umemura, Ivy Brain Tumor Center at Barrow Neurological Institute, Phoenix, AZ

Background: Mycophenolate mofetil (MMF) inhibits IMPDH and disrupts *de novo* purine synthesis which is preferred by glioblastoma (GBM) whilst normal brain prefers resource efficient salvage pathway. A phase 0 study demonstrated the active drug metabolite reaching both enhancing and non-enhancing GBM tissues in humans, and effective target engagement, noted by reduced GTP/IMP ratio. This phase 1 trial assessed the tolerability of MMF with chemoradiation in newly diagnosed GBM patients (NCT04477200). **Methods:** Thirty adult patients with newly diagnosed GBM were given MMF, dosed BID, 1 week prior to and concurrently with standard of care (SOC) radiotherapy (RT) of 60 Gy in 30 fractions with concomitant temozolomide (TMZ) 75mg/m2, followed by MMF 1 day before + 5 days of each SOC TMZ 150-200mg/m2 x 5/28-day cycle up 12 cycles. Optune was optional. Primary endpoint was dose limiting toxicity (DLT) and maximally tolerated dose (MTD) of MMF combined with SOC GBM chemoradiation. Time-to-event continual reassessment method was used to determine MMF dosing, with MTD defined as estimated rate of dose-limiting toxicity (DLT) closest to but not exceeding 30%. DLT periods were during and up to 4 weeks after concurrent chemoradiation (DLT1), and first two 28-day cycles of MMF with temozolomide (DLT2). Transient grade 4 neutropenia x $<$ 7 days and asymptomatic grade 4 lymphopenia were excluded from DLT. Kaplan Meier method was used to estimate overall survival (OS). **Results:** The median age was 57 (range 20-75). The majority had KPS $>$ 80 (67%) at baseline, and unmethylated MGMT (70%). During DLT1 period, 5 DLT1 was noted out of 16 subjects on 2000mg BID (grade 3 hemiparesis, cognitive disturbance, fatigue, and grade 4 thrombocytopenia x2), and none at 1500mg (N = 10) and 1000mg (N = 4). During DLT2 period, 1/6 subjects at 1500mg BID experienced DLT of grade 3 fatigue, and none at 1000mg (N = 4) and 2000mg (N = 16). All DLTs were reversible. Four patients did not receive MMF during DLT2 period due to withdrawal from the study (N = 2) and progression of disease (N = 2). The most common treatment related adverse events were fatigue (77%), leukopenia (67%), and nausea (53%). Of the dose levels studied, the MTD for DLT1 and DLT2 were both 2000mg BID (posterior probability of DLT1: 18.5%, posterior probability of DLT2: 7.5%), however, due to frequent fatigue and nausea, DLT1 period starting dose was lowered to 1500mg BID for the last 7 subjects. The recommended phase 2 dose is 1500mg BID combined with concurrent RT+TMZ followed by TMZ. Median OS was 16.8 months with 25.5 months median follow up duration (NR & 25.5 months in MGMT methylated, 14.2 & 24.9 months in MGMT unmethylated respectively). **Conclusions:** MMF can penetrate enhancing and non-enhancing GBM with evidence of successful inhibition of *de-novo* purine synthesis in humans, and is reasonably well tolerated when combined with chemoradiation newly diagnosed GBM patients. These promising results have led to a planned phase 2/3 randomized controlled trial through Alliance for Clinical Trials in Oncology. Clinical trial information: NCT04477200. Research Sponsor: Gateway for Cancer Research.

2016 **Rapid Oral Abstract Session**

Use of lucicebtide (ST101) in glioblastoma patients by antagonism of C/EBPβ-dependent mesenchymal cell transition and immunosuppressive M2 macrophage polarization. First Author: Fabio Massaiti Iwamoto, Columbia University Irving Medical Center, New York, NY

Background: C/EBPβ is a master regulator of the mesenchymal phenotype in GBM and has an essential role in the maintenance of immunosuppressive M2 tumor-associated macrophages (TAMs). Lucicebtide is a first-in-class antagonist of C/EBPβ that has shown direct anti-tumor activity in GBM as well as the ability to reprogram TAMs in the TME toward immunostimulatory M1 macrophages. In a recent recurrent GBM (rGBM) P2 study, lucicebtide was well-tolerated and resulted in disease control in 9/30 patients, including two PRs lasting > 1 year. With strong rationale for targeting C/EBPβ in GBM, additional cohorts we explored in a window-of-opportunity (WoO) study (NCT04478279). **Methods:** The WoO study enrolled 2 cohorts; 9 pts with rGBM that received 2-4 doses of lucicebtide 500mg QW prior to surgery and resumed lucicebtide after surgery to progression and 9 ndGBM pts that received 2-3 doses of lucicebtide 500mg QW prior to surgery and resumed lucicebtide + chemoradiation after surgery until progression. Endpoints include efficacy parameters of PFS and OS, safety as a single agent and in combination with chemoradiation, and pharmacodynamic analyses including spatial transcriptomics and TME characterization. **Results:** Lucicebtide was well-tolerated as a single agent and in combination with chemoradiation. Tissue analysis indicates penetration past the BBB and tumor uptake, as well as C/EBPβ target engagement. Lucicebtide + chemoradiation in ndGBM extended PFS beyond historic benchmarks, with the majority of patients remaining on study without progression (7-22+ months). As of January 25, 2025, mOS could not be evaluated, with 8/9 patients alive. In rGBM, lucicebtide improved mPFS to 3.4 months and mOS to at least 11.8 months, exceeding historical data with chemotherapy (historic mPFS ~ 2 months and mOS 5.6-9.8 months). Pathologic evidence of treatment effect, i.e. geographic necrosis, was observed in 5/6 pts including otherwise treatment naïve ndGBM patients. Spatial transcriptomics analysis revealed a significant reduction in the mesenchymal gene signature following lucicebtide, consistent with on-target antagonism of C/EBPβ. Further, immune activation in the TME, as indicated by increased M1/M2 ratio and CD8+ T cell infiltration, was associated with disease control. **Conclusions:** Lucicebtide is well-tolerated as monotherapy and in combination with SoC. Improvements in PFS and OS in GBM patients following lucicebtide exposure demonstrated penetration across the BBB and target engagement, resulting in on-target pharmacodynamic activity including a dramatic reduction in mesenchymal gene signature in tumor cells and a remodeling towards a more permissive immune TME. These data provide the mechanistic rationale for continued clinical evaluation of lucicebtide as a novel approach for patients with GBM. Clinical trial information: NCT04478279. Research Sponsor: None.

2017 **Rapid Oral Abstract Session**

Safety and tolerability of intraventricular CARv3-TEAM-E T cells following lymphodepleting chemotherapy in recurrent glioblastoma: INCIPIENT trial. First Author: Elizabeth R. Gerstner, Massachusetts General Hospital, Boston, MA

Background: CAR T therapy is a novel, promising approach in glioblastoma (GBM) but tumor heterogeneity can limit efficacy when a single antigen is targeted. We designed a second-generation CAR T molecule that targets epidermal growth factor receptor vIII (EGFRvIII) and also secretes a T-cell–engaging antibody molecule (TEAM) against wild-type EGFR. **Methods:** In a phase 1, first-in-human study (INCIPIENT, NCT05660369), patients with recurrent GBM with EGFRvIII mutation and/or EGFR amplification were eligible to receive up to 6 intraventricular doses of 10x106 CAR T cells via Ommaya catheter after lymphodepleting chemotherapy (LDC) with fludarabine and cyclophosphamide. Primary objective was safety and tolerability and secondary objective was preliminary tumor response determined by iRANO criteria. **Results:** CAR T manufacturing was successful for all patients. Seven patients (5 male) received at least 1 intraventricular infusion. Two patients received 2 infusions (1 for progressive disease (PD) and 1 without PD). One patient received 3 infusions after experiencing initial PD. No DLTs occurred. All patients experienced cytokine release syndrome (CRS) grade 1 lasting 0-9 days with only 1 patient experiencing CRS grade 2 for 1 day. One patient experienced ICANS grade 1 that lasted 2 days. All patients experienced tumor inflammation-associated neurotoxicity grade 1 with a duration of 2-9 days. Adverse events (grade 3-4) at least possibly related to CAR T were febrile neutropenia (N = 1) and neutrophil count decrease (N = 1). Toxicity was managed with supportive care without need for ICU monitoring and 3 patients received at least 1 dose of anakinra (max duration = 4 days, median = 1 day). Best response was stable disease (SD) in 5 patients with 1 patient achieving SD for 6 months after a single infusion and another experiencing a 33% decrease in tumor diameter after 2 infusions. All patients are alive 3-8 months after first infusion. From the preceding safety run-in arm of the study (without LDC), one patient survived 12 months and another is still alive > 20 months after infusion. **Conclusions:** Intraventricular CARv3-TEAM-E infusions were well tolerated, even with multiple doses, and no DLTs were noted. Toxicity was manageable in all patients with supportive care and anakinra was administered to 3 patients. Steroids were not required to manage toxicity. A subset of patients experienced SD for several months. Clinical trial information: NCT05660369. Research Sponsor: Gateway for Cancer Research; National Gene Vector Biorepository at Indiana University, which is funded under National Cancer Institute contract HSN261201500003I Task Order No. HHSN26100077; Philanthropic support to the Cellular Therapy Program at MGH.

2018 **Rapid Oral Abstract Session**

A phase 1 study of B7H3 CAR-T cells administered intracranially in recurrent glioblastoma. First Author: Gordon Li, Stanford University, Stanford, CA

Background: Glioblastoma (GBM) is an aggressive malignancy with median survival of approximately 2 years from initial diagnosis and 9 months after first progression. Effective treatments in the recurrent setting following upfront chemoradiation and adjuvant temozolomide are limited. The transmembrane glycoprotein B7H3 is over-expressed in GBM and chimeric antigen receptor T cells targeting B7H3 (B7H3-CART) have shown activity in several preclinical cancer models. Intracranial delivery of B7H3-CART may optimize targeting the immune response to the tumor microenvironment while limiting systemic toxicity. **Methods:** We conducted a single-arm phase 1 study in patients with recurrent GBM undergoing repeat resection. B7H3-CART was administered via intratumoral and intraventricular Ommaya reservoirs monthly for a planned 6 months or until confirmed disease progression. When possible per investigator discretion, the dose was divided evenly between the two reservoirs. The primary endpoints were safety and manufacturing feasibility, with secondary endpoints focused on preliminary efficacy. Dose escalation was planned according to a standard 3+3 design (dose level 1: $10x10^6$ cells; level 4 (max): $100x10^6$). Adverse events within 28 days of first dose and at least possibly related to B7H3-CART were considered dose-limiting toxicities (DLTs) if meeting additional criteria: any grade 5 toxicity, grade 4 cytokine release syndrome, neutropenia, or thrombocytopenia lasting > 14 days, or any non-hematologic grade 3 toxicity lasting > 72 hours. Neurotoxicity was considered a DLT if grade 4 for > 96 hours or new-onset grade 3 for > 28 days. Serial CSF and serum samples were collected for translational studies to determine immune cell kinetics and the mechanisms of activity and resistance. **Results:** Eleven patients were enrolled, underwent apheresis, and had B7H3-CART successfully manufactured. Nine received at least one dose of B7H3-CART and were evaluable in the dose escalation cohort. One patient in dose level 2 ($25x10^6$ cells) experienced a DLT (grade 3 hypertension). No additional DLTs were observed in this dose level after expansion to 6 patients, and the recommended phase 2 dose was established at $25x10^6$ cells. Toxicity otherwise has been primarily related to tumor inflammation-associated neurotoxicity (TIAN), observed after 29 of 36 infusions (81%), and managed acutely with anakinra and dexamethasone. The median overall survival (mOS) from date of enrollment for patients receiving at least one dose of B7H3-CART is 14.6 months (95% CI: 2.3 - 26.8 months). One patient is currently receiving B7H3-CART and 4 others are being clinically followed up to 22 months from enrollment. **Conclusions:** Intracranial administration of B7H3-CART in recurrent GBM is technically feasible and safe. TIAN was common but manageable and reversible with immunomodulators. Correlative analyses on surgical tissue, CSF, and serum are ongoing. Clinical trial information: NCT05474378. Research Sponsor: California Institute for Regenerative Medicine; CLIN2-15094.

2019 **Rapid Oral Abstract Session**

Tirabrutinib for the treatment of relapsed or refractory primary central nervous system lymphoma: Efficacy and safety from the phase II PROSPECT study. First Author: Lakshmi Nayak, Dana-Farber Cancer Institute, Boston, MA

Background: Primary central nervous system lymphoma (PCNSL) is a rare, aggressive form of non-Hodgkin lymphoma localized to the brain, cerebrospinal fluid, or eyes. For patients with PCNSL, treatment options are limited, standard of care is not well established, and prognosis is poor, particularly in the relapsed or refractory (r/r) setting. Tirabrutinib, a highly potent selective second-generation Bruton's tyrosine kinase inhibitor, is approved in Japan, Taiwan, and South Korea based on a phase I/II study that demonstrated clinical activity in Japanese patients with r/r PCNSL. There are no currently approved drug therapies for PCNSL in the US or Europe. Here we report results from the PROSPECT study (NCT04947319) conducted in the US. **Methods:** In this open-label phase II study, patients with r/r PCNSL received oral tirabrutinib 480 mg as monotherapy once daily until disease progression or unacceptable toxicity. The primary endpoint was overall response rate (ORR) assessed by Independent Review Committee. Secondary endpoints included duration of response (DOR), time to response (TTR), best overall response (BOR), and safety. Overall survival (OS) and progression-free survival (PFS) were exploratory endpoints. **Results:** Forty-eight patients were enrolled. Median age was 65.5 y (range, 34-87). With a median follow-up of 11.2 mo as of November 1, 2024 (data cut-off), ORR was 66.7% (n = 32), with a complete response rate (CRR), confirmed (CR) + unconfirmed (CRu), of 43.8% (n = 21) and a partial response rate of 22.9% (n = 11). Median DOR was 9.3 mo (range, 0.0-23.5), and median TTR was 0.95 mo (range, 0.9-3.7). Median OS was not reached (range, 1.0-33.0); median PFS was 6.0 mo (range, 0.0-26.0). Overall incidence of any-grade treatment-emergent adverse events (TEAEs) was 97.9% (n = 47) and grade ≥3 was 56.3% (n = 27). Any-grade treatment-related adverse events (TRAEs) were experienced by 75.0% (n = 36), most frequently anemia (18.8%), fatigue (14.6%), neutrophil count decreased (14.6%), pruritus (14.6%), rash (14.6%), and maculo-papular rash (14.6%). Grade ≥3 TRAEs were experienced by 27.1% (n = 13), most frequently neutrophil count decreased (8.3%) and rash maculo-papular (4.2%). Deaths related to TEAEs occurred in 2 (4.2%) patients: 1 patient died from seizure and pneumonia, and the other from a fall; these grade 5 TEAEs were considered unrelated to study treatment. At data cutoff, 27.1% (n = 13) of patients remain on tirabrutinib treatment. Main reasons for discontinuation were disease progression (54.2%, n = 26) and death (8.3%, n = 4), and 1 (2.1%) patient discontinued due to an AE; deaths included the 2 patients with grade 5 TEAEs. **Conclusions:** With an ORR of 66.7%, CR/CRu rate of 43.8%, median DOR of 9.3 mo, and a manageable safety profile, the PROSPECT trial supports tirabrutinib monotherapy as a potentially effective treatment option for patients with r/r PCNSL. Clinical trial information: NCT04947319. Research Sponsor: ONO Pharmaceutical Co., Ltd.

2020 Rapid Oral Abstract Session

Using single-cell transcriptomics to reveal CD226 upregulation and enhancement of CD19-CAR-T function in the inhibitory CNS microenvironment of refractory CNS lymphoma. First Author: Ulrike Gerdemann, Dana-Farber/Boston Children's Cancer and Blood Disorders Center, Boston, MA

Background: Refractory CNS lymphoma (CNSL) has a poor prognosis, with 5-year survival of ~30%. We conducted a trial of axi-cel for CNSL, where we achieved a CR of 67%. To deeply interrogate the immune mediators of response, we collected daily paired CSF and peripheral blood (PB) samples post-CAR T infusion. This enabled single-cell transcriptional profiling at an unprecedented depth, identifying key drivers of CD19 CAR T responses and compartment-specific mechanisms of CAR T function. **Methods:** CNSL patients were enrolled in the 'Axi-cel in CNS Lymphoma' Trial, NCT04608487. PB and CSF samples were collected daily from Day 0–14 post-infusion, and 5'10x scRNA /TCR-Seq was performed. This analysis focused on peak CAR T expansion (Day 5-10) and included 1,224,178 T cells from 17 patients. Samples were tested for compartment (CSF vs PB) and response-specific (CR vs PD) transcriptomic differences using a mixed-effects model and GSEA. Functional assays were conducted with CD19 CAR Ts and CD19 CAR+ Jurkat-NFAT reporter cells. **Results:** Transcriptomic analysis identified distinct compartmental differences in CAR Ts, with PB CAR Ts displaying a robust proliferation signature, while CSF CAR Ts were enriched for type I interferon and T-cell dysfunction signatures, including upregulation of inhibitory genes PD-1, TIGIT, TIM3, LAG3. *In vitro*, CSF-exposed CD19-CAR Ts showed increased expression vs culture-media controls for TIGIT (up 40.1%, SEM 7.4), PD-1 (18.9%, SEM 3.8), and Tim3 (60.6%, SEM 7.5). CAR T NFAT expression was reduced from 18.4, 0.1 SEM (media) to 7.2, 0.2 SEM (CSF) relative to unstimulated controls. Differential expression analysis comparing CSF CD8+ CAR Ts from patients achieving CR (n = 11) or PD (n = 4) showed upregulation of Type I interferon signaling (IFIT1, IFIT3) in PD patients. In contrast, CR patients exhibited increased expression of counter-inhibitory genes (TCF7, CD226) in CSF CAR Ts, suggesting a functional advantage of these CAR Ts in the inhibitory CNS environment. Functional assays of CD19-CAR Ts overexpressing the costimulatory molecule CD226, demonstrated higher lymphoma-cell killing vs WT-CAR Ts (48.6%, SEM 4.1 vs 24%, SEM 2.2, p = 0.01) and greater IFNγ production (63.2%, SEM 1.6 vs 49.4%, SEM 1.7, P = 0.006). CD226 acts as a costimulatory receptor and counteracts TIGIT signaling by competing for its shared ligands, CD112 and CD155. Notably, scRNA-Seq receptor-ligand analysis identified CD112 exclusively expressed in myeloid cells, highlighting a critical myeloid-CAR T interaction that enhances CD226^{high} CAR T efficacy. **Conclusions:** ScRNA-Seq suggests tissue-specific CAR T dysfunction in the CNS microenvironment, with CR patients demonstrating upregulation of counter-inhibitory genes, including CD226. This study offers novel insights into axi-cel's mechanism of efficacy and identifies targets to improve CNSL CAR T therapy. Research Sponsor: Kite/Gilead.

2021 Poster Session

Brain metastasis: Incidence, trend analysis, and impact on survival using SEER database (2010-2020). First Author: Shaimaa Fadel, Faculty of Medicine, Suez Canal University, Ismailia, Egypt

Background: Brain metastasis has a poor prognosis in cancer patients with high morbidity and mortality rates. An updated comprehensive analysis of patients with brain metastasis across all primary cancer sites is lacking. So, the study aims to provide the literature with updated evidence about recent trends and survival analysis of brain metastasis. **Methods:** Data of 75,797 patients with brain metastasis, diagnosed in 2010-2020, were extracted using the Surveillance, Epidemiology, and End Results (SEER) software. We used a rate session to calculate the incidence, percent change (PC), and annual percentage change (APC). Rates are per 100,000 and age-adjusted to the 2000 US Std population. Confidence intervals (CI) are 95% per rate with statistical significance at $P > 0.05$. We used SPSS version 23 for data analysis and Kaplan Meier Curve and log-rank test for survival analysis. **Results:** Brain metastasis represented 1.9% of all cancer cases with a mean age of 64.4 (Sd = 11.2). The age-adjusted incidence rate of brain metastasis was 7.1 with a PC of -9.6 from 2010 to 2020 (APC = -0.60; 95% CI: -1.2-0.001, $P < 0.05$). The APC was significantly declining in Caucasians (-0.70; $P > 0.05$) and African Americans (-1.2; $P < 0.05$) with a significant decrease in males (-1, $P < 0.05$) while the Asian or Pacific islanders (API) race had PC of 11.7 and APC of 1.30 ($P < 0.05$). Lung, breast, skin melanoma, and kidneys were the most common primary sites for brain metastasis (78.5%, 3.8%, 3.7%, and 3.2%). The 5-year relative survival of patients with brain metastasis was 6.1% compared to the non-metastatic group 71.5%. The 5-year age standardized relative survival was 5.7% for the metastatic group. The 5-year relative survival of brain metastasis was higher in the API race compared to Caucasians and African Americans (10.1%, 5.9%, and 5.3%). **Conclusions:** The results of this study show a very poor survival outcome for brain metastasis. However, there was a significant decline in brain metastasis trends over the years, which highlights promising improvements in the early detection of primary cancers. Further stratifications showed disparities according to race and primary cancer site. These data may have clinical-directed variations in screening and counseling for subpopulations with cancer. Research Sponsor: None.

2022 Poster Session

A phase I/II study to assess safety and preliminary evidence of a therapeutic effect of azeliragon combined with stereotactic radiation therapy in patients with brain metastases (ADORATION). First Author: Rupesh Kotecha, Miami Cancer Institute, Baptist Health South Florida, Miami, FL

Background: Azeliragon is an oral, brain penetrating small molecule inhibitor of the receptor for advanced glycation end-products (RAGE), reducing neuroinflammation by inhibiting peritumoral edema/vascular leakage and overcoming radiation resistance. The primary objective of this study is to evaluate the safety and tolerability of azeliragon plus stereotactic radiosurgery (SRS) for patients with brain metastasis substituting for peri-procedural corticosteroids (loading dose [LD] and corticosteroid taper [CT]) and secondarily to assess the potential efficacy of this novel therapeutic combination. **Methods:** ADORATION (NCT05789589) is a single center, open-label, phase I/II trial. Eligible adults have a confirmed cancer diagnosis within 5 years, maximum brain metastasis diameter of $\leq$2 cm, and have discontinued corticosteroids at least 5 days prior to SRS. In phase I, participants were enrolled into sequential cohorts, starting with azeliragon + SRS + LD; depending on dose-limiting toxicities (DLTs), the next cohorts could be either azeliragon + SRS or azeliragon + SRS + LD + CT. A DLT was defined as any CNS-specific Grade $\geq$ 2 toxicity requiring corticosteroid treatment or any Grade $\geq$ 3 events not clearly due to the underlying disease or extraneous causes. **Results:** In the completed phase 1 portion, 3 patients were initially treated with azeliragon at 30 mg twice daily for 6 days followed by SRS+LD within 7 days of starting drug then a continuous dose of 20 mg daily for at least 8 weeks. As no DLTs were observed, the second cohort of 3 patients was treated with azeliragon and SRS without any corticosteroids (LD or CT). Of the 6 evaluable patients treated to 46 brain metastases, the most common primary histology was lung adenocarcinoma (n = 4). At data cutoff (1/8/2025), the median follow-up was 4.9 months (3.8-9.4 months) and no DLTs were observed. Early response rate (RR) to the combination therapy was assessed at week 8, with a per-patient RANO RR of 100% (partial response [PR] for all 100%), and a per-lesion RANO RR for all RANO-defined target lesions (n = 18) of 100% (PR 95.5%, complete response [CR] 4.5%). For all brain metastases treated (n = 46) the RR was 93.5% (PR for 69.6% and CR for 23.9%). Neurocognitive function batteries, symptom inventories, and quality of life evaluations remained stable during the 8-week early assessment period. **Conclusions:** Azeliragon was safely substituted for corticosteroids in this phase 1 study with no DLTs observed. The early response rate appears encouraging and accrual to the phase II expansion cohort (n = 40) with a primary endpoint of objective response rate is ongoing. Clinical trial information: NCT05789589. Research Sponsor: Cantex Pharmaceuticals.

2023 Poster Session

Efficacy of immune checkpoint inhibitors (ICI) in patients (pts) with central nervous system (CNS) metastases (mets) from solid tumors: A systematic review and meta-analysis. First Author: Soraia Martins, Université libre de Bruxelles (ULB), Hôpital Universitaire de Bruxelles (H.U.B), Institut Jules Bordet, Brussels, Belgium

Background: Brain metastases, a common complication of solid tumors, are associated with poor outcomes. The role of ICIs in this setting remains unclear. This meta-analysis aims to assess intracranial efficacy of ICI-based systemic treatment in pts with CNS mets from solid tumors. **Methods:** A systematic literature search of PubMed, Embase, CENTRAL, and conference proceedings (ESMO and ASCO) up to 15-Mar-24 (PROSPERO: CRD42021242755), was conducted to identify single-arm phase II or III, or randomized controlled trials of pts with CNS mets from solid tumors at baseline treated with ICI-based systemic treatment. The primary objective, CNS efficacy, was measured by pooled CNS objective response rate (CNS-ORR) and weighted median CNS progression-free survival (mCNS-PFS). Subgroup analyses evaluated the impact of disease and treatment characteristics. Overall effects were pooled using random-effects models. **Results:** Out of 1 690 records screened, a total of 1 224 pts enrolled in 32 clinical trials were included. Overall, ICI-based systemic therapy led to a CNS-ORR of 38.0% (95% confidence interval [CI] 31.8-45.5) and a mCNS-PFS of 9.1 months (mos). CNS efficacy was numerically higher in pts with non-small cell lung cancer (NSCLC, n=383, CNS-ORR 45.8% [34.4-60.9]; mCNS-PFS 9.6 mos) and melanoma (n=554, CNS-ORR 37.7% [30.6-46.5]; mCNS-PFS 11.4 mos) vs multi tumors (n=128, CNS-ORR 24.8% [7.7-80.1] and mCNS-PFS 2.8 mos). Efficacy was also greater in first-line therapy (n=553, CNS-ORR 45.2% [36.7-55.7]; mCNS-PFS 8.6 mos) vs second or later lines (n=190, CNS-ORR 14.9% [7.6-29.2]; and mCNS-PFS 2.6 mos). Dual ICI (n=279, CNS-ORR 43.9% [35.5-54.2]; mCNS-PFS 17.8 mos) and ICI plus non-ICI agents (n=432, CNS-ORR 48.7% [39.6-59.9]; mCNS-PFS 7.1 mos) were more effective than single ICI (n=419, CNS-ORR, 20.4% [11.9-34.9]; mCNS-PFS 4.8 mos). Subgroup analyses showed superior CNS outcomes in cerebral mets, treated lesions, asymptomatic pts, and low/no steroid use (table). **Conclusions:** ICI-based regimens demonstrate CNS efficacy in pts with solid tumors, particularly in pts with NSCLC and melanoma treated with first-line combination therapies. Research Sponsor: None.

Subgroup analyses by CNS characteristics	Category (*n* of pts for CNS-ORR)	CNS-ORR, % (95% CI)	mCNS-PFS, mos
Type of CNS mets	Cerebral (1063)	38.3 (31.9-45.9)	9.6
	Leptomeningeal (51)	34.6 (15.9-75.2)	2.4
CNS local therapy	Treated (197)	37.6 (26.8-52.8)	8.9
	Untreated (307)	43.1 (35.0-53.0)	5.2
Symptoms	Asymptomatic/mild (832)	40.4 (34.5-47.3)	10.3
	Symptomatic (80)	31.3 (18.3-53.4)	2.5
Concomitant steroids	No (391)	30.6 (21.6-43.4)	15.1
	Low dose (434)	40.7 (31.5-52.6)	7.6
	Any dose steroids (144)	41.6 (31.7-54.7)	3.3

2024 **Poster Session**

Irradiated tumor volume as a predictor of local recurrence and radionecrosis in lung cancer with brain metastases treated with stereotactic radiosurgery. First Author: Andreas Koulouris, Karolinska University Hospital, Solna, Sweden

Background: Stereotactic radiosurgery (SRS) is a standard local treatment for brain metastases (BM), but it may result in local recurrence (LR) or radionecrosis (RN). This study evaluates irradiated tumor volume as a predictor of LR and RN in SRS-treated lung cancer patients with BM. **Methods:** We retrospectively analyzed 431 lung cancer patients with BM who underwent SRS at Karolinska University Hospital, Sweden, (2009-2020), encompassing all-comers from the Stockholm region. Associations among irradiated tumor volume and risks of RN, symptomatic RN, as well as LR at 6 and 12 months, were assessed using Cox regression models. Furthermore, we evaluated the diagnostic performance of Methionine PET-CT in differentiating RN from LR. **Results:** 40 patients (9.2%) developed asymptomatic RN, 37 (8.3%) symptomatic RN, and 67 (15.5%) LR. Larger tumor volumes significantly increased the risks of RN and LR. At 6 months, a tumor volume of 4.75 cm^3 was associated with an RN risk reaching the upper limit of 20%. By 12 months, substantially smaller volumes, such as 1.13 cm^3, were related to same risk levels. Symptomatic RN followed a similar trend, with a volume of 13.58 cm^3 presenting a risk of up to 20% at 6 months, while at 12 months, considerably smaller volumes, such as 3.8 cm^3, corresponded to a symptomatic RN risk as high as 40%. 20% risk of LR was observed with volumes of 5.66 cm^3 and 3.28 cm^3 at 6 and 12 months, respectively. The sensitivity and specificity of Methionine PET-CT are 0.909 and 0.600 when MRI was considered the gold standard. **Conclusions:** Larger irradiated tumor volumes were positively correlated with an increased risk of both RN and LR. At 12 months post-SRS, smaller tumor volumes were associated with higher RN and LR risks in comparison with 6 months. Methionine PET-CT, when used alongside MRI, did not demonstrate a clear advantage in differentiating LR from RN. Research Sponsor: European Society for Medical Oncology (ESMO); Hellenic Society of Medical Oncology (HeSMO); Elena Iliopoulou Giama (EIG) Cancer Research & Scholarship Foundation; Scholarship - Legacy "M. M. Manassaki" by the University of Crete; Region Stockholm (clinical postdoctoral appointment); Stockholm Cancer Society; 204053.

2025 **Poster Session**

Efficacy of systemic therapy in breast cancer with CNS metastases: "Real-world" experience. First Author: Bipin Ghimire, Henry Ford Health System, Detroit, MI

Background: The incidence of CNS metastases in breast cancer is rising. While local therapies such as surgery and radiation remain standard, data on upfront systemic therapies for active brain metastases, especially HER2-negative patients, is limited. This study examines upfront systemic therapy efficacy for CNS metastases in breast cancer patients at a single institution, including a majority African American (AA) population. **Methods:** A retrospective chart review included breast cancer patients with CNS metastases treated at Henry Ford Health (January 2014–July 2024). Eligible patients had not received concurrent local therapy; prior local therapy was permitted if unrelated to the studied lesions. CNS response was to be assessed using RANO-BM (defines measurable disease as lesions $>$ 10 mm) for parenchymal and modified RANO-LM criteria for leptomeningeal disease (LMD). **Results:** Among 35 patients (20 AA, 13 Caucasian), with a median age of 54 years, HER2-positive was the most common receptor type (49%), followed by HR-positive (37%) and triple-negative (14%); nearly half (46%) had HER2-low disease. Parenchymal metastases were predominant (86%); three had co-existing LMD, and two others had only LMD. Most metastases were multiple; 91% had lesions $<$ 10 mm. 43% had prior WBRT or SRS to unrelated lesions. HER2-positive patients had the highest CNS overall response rate (ORR, 53%) and disease control rate (DCR, 94%), followed by HR-positive (ORR 31%, DCR 69%) and triple-negative (ORR and DCR 20%). Median PFS did not significantly differ between receptor groups (p = 0.130). Trastuzumab-deruxtecan (T-Dxd) was the most common regimen (10/35) and within HER2-positive and HR-positive groups. T-Dxd achieved CNS ORR of 60%, DCR of 90%, and median PFS of 16 months. Tucatinib-based regimens showed a 100% DCR with median PFS of six months. Other therapies, including sacituzumab, abemaciclib, and trastuzumab-emtansine, showed stable disease as the best response. Among AAs, HR-positive was the most common receptor type (50%). These patients had ORR of 35% and DCR of 65%. T-Dxd maintained ORR of 60% and DCR of 80%. Of five patients with LMD, three were HER2-positive, and two were HR-positive, with an ORR of 60%, and DCR of 80%. **Conclusions:** This "real-world" experience highlights that, at our institution, most patients with breast cancer and CNS metastases considered for upfront systemic therapy lack measurable disease (91% having lesions $<$ 10 mm) typically required for clinical trials. Nonetheless, the response rate aligns with published experiences. In addition, we included patients with LMD, who are often excluded in trials. Our data also suggests impressive CNS responses with T-Dxd, both overall and in AA patients. The management of brain metastases and LMD in these patients is best approached in a multidisciplinary format. Research Sponsor: None.

2027 **Poster Session**

Whole brain radiotherapy and intrathecal injection of thiotepa, combined with systemic treatment for the primary tumor, to treat solid tumor leptomeningeal metastasis: A prospective, single center, single arm, phase II clinical study. First Author: Siyu Guo, Zhejiang University, Hangzhou, China

Background: To evaluate the efficacy and toxicity of a triple therapy regimen consisting of Hippocampal-sparing whole-brain radiotherapy (HS-WBRT), intrathecal Thiotepa (ITT), and primary lesion treatment for solid tumor leptomeningeal metastasis (LM). (NCT06376292). **Methods:** Based on the comprehensive results of MRI and cytology evidence, patients diagnosed with LM according to the diagnostic criteria in the EANO-ESMO guidelines meet the criteria. Patient began ITT twice a week, and underwent HS-WBRT as soon as possible. Before each ITT, cerebrospinal fluid (CSF) pressure is measured and CSF is collected for testing, including protein, tumor markers, IgG, albumin levels of CSF, and albumin ratio. MRI re-examination is conducted every three months, and the RANO-LM criteria is used to evaluate the response of patients after treatment. Besides,the LM-PROG SCORE we designed can be used as an indicator to evaluate the treatment effect and adjust the medication frequency or switch the treatment line of intrathecal Pemetrexed (IP). The primary endpoint is overall survival. **Results:** As of December 1, 2024, a total of 57 patients have been enrolled. 40 patients were included in the statistics. Most cases are lung cancer (27, 67.5%), in addition to breast cancer(8, 20%), gastric cancer (3, 7.5%), rectal cancer (1, 2.5%) and cervical cancer (1, 2.5%). The mOS was 7.8 months (95% CI 2.06-13.54 months). The mPFS was 5.63 months (95% CI 0.76-10.51 months). The RANO-assessed ORR to treatment was 62.5% (10/16), DCR was 87.5% (14/16), with 24 patients (60%) not reaching the follow-up time. The three longest survival among alive patients are 21.3 months, 14.9 months, and 12.7 months. The most significant effect of combination therapy is the rapid relief of symptoms. 25% of patients (10/40) had already experienced unconsciousness (RASS≠0) at the time of diagnosis. After our treatment, all patients regained consciousness (RASS = 0). The long-term therapeutic effect also significantly reduces tumor markers, protein content, albumin and IgG content, pressure drop, and albumin ratio in CSF, indicating the recovery of the blood-brain barrier. 85% of patients experience varying degrees of bone marrow suppression during treatment, but most are mild and can tolerate subsequent ITT maintenance after treatment. **Conclusions:** Under the efficacy guidance of LM-PROG SCORE we designed, our combination therapy can greatly improve patients' overall survival, progression free survival, and quality of life. And it was found that in addition to imaging, indicators such as protein content, IgG and albumin content, Albumin Ratio and tumor markers in CSF can serve as efficacy evaluation indicators. Clinical trial information: NCT06376292. Research Sponsor: None.

2028 **Poster Session**

Effect of CD4+PD-1+CXCR6+ T cells on the response of immune checkpoint inhibitor therapy in brain metastases of NSCLC. First Author: Yang-Si Li, Guangdong Lung Cancer Institute, Guangdong Provincial People's Hospital, Guangzhou, China

Background: Brain metastases (BrM) in non-small cell lung cancer (NSCLC) presented a significant challenge due to poor prognosis. While immune checkpoint inhibitors (ICIs) have been standard treatments for NSCLC, their efficacy in BrM is variable, emphasizing the urgent need for predictive biomarkers and fundamental mechanisms. **Methods:** We prospectively collected 20 cerebrospinal fluid (CSF) and 4 BrM tumors from 18 NSCLC patients with BrM undergoing ICI therapy for single-cell RNA sequencing (scRNA-seq), complemented by integrating data from multiple published datasets. Three independent cohorts (8 and 25 CSF, and 31 BrM tumors) underwent flow cytometry, proteomics, and multiplex immunohistochemistry for validation, respectively. **Results:** Our study provided a high-resolution atlas of cellular dynamics in the CSF and BrM during ICI therapy in NSCLC patients with BrM. Notably, we identified a key immune cell subset, $CD4^+PD\text{-}1^+CXCR6^+$ T cells, as a positive predictor of ICI intracranial tumor responses, which presented highly functional and transcriptomic similarities in both CSF and BrM tumor environment. Moreover, CXCR6 could serve as a specific marker for $CD4^+PD\text{-}1^+$ T cells linked to ICI response. Further, we revealed that the novel cluster of $CD4^+PD\text{-}1^+CXCR6^+$ T cells was closely associated with lymphocyte activation and aggregation in CSF and BrM of ICI responders, and cDCs of ICI responders interacted with $CD4^+PD\text{-}1^+CXCR6^+$ T cells for enhanced antigen presentation and inflammatory activation. **Conclusions:** Our findings revealed critical insights into the immune landscape of NSCLC BrM under ICI therapy, highlighting $CD4^+PD\text{-}1^+CXCR6^+$ T cells in CSF as a promising biomarker and illuminating fundamental mechanisms underlying ICI efficacy. Research Sponsor: None.

2029 Poster Session

IT-IO: Intrathecal administration of nivolumab and ipilimumab in combination with systemic combination of nivolumab and ipilimumab in patients with non-small cell lung cancer or melanoma and newly diagnosed leptomeningeal metastasis, a multicentric phase I study. First Author: Emilie Le Rhun, University Hospital Zurich, Zurich, Switzerland

Background: The optimal management of patients with leptomeningeal metastases (LM) from non-small cell lung cancer (NSCLC) or melanoma remains controversial. IT-IO (NCT05598853) is a prospective phase I, multicenter, open label, interventional clinical study aiming at determining the recommended phase 2 dose (RP2D) of intrathecal nivolumab and ipilimumab in patients with newly diagnosed LM from NSCLC or melanoma. **Methods:** The diagnosis of LM had to be confirmed or probable by EANO ESMO criteria. Planned whole brain radiotherapy (WBRT) was not allowed. Planned or prior craniospinal irradiation were not allowed. The treatment regimen consisted of intrathecal nivolumab (fixed dose 50 mg) / ipilimumab (increasing doses) in combination with systemic combined nivolumab/ipilimumab. Three dose levels of IT ipilimumab were planned: 5 mg (dose level 1), 10 mg (dose level 2), and 20 mg (dose level 3). RP2D, the primary endpoint, was determined in a 3+3 design. Secondary endpoints included compartmental efficacy and survival. **Results:** A total of 19 patients, 6 female and 13 male patients, 12 with melanoma and 7 with NSCLC, were enrolled between February 2022 and August 2024. Median KPS at study entry was 80, 12 patients had a positive CSF. The dose escalation phase (n = 12) was completed without dose-limiting toxicity until dose level 3. The RP2D is nivolumab 50 mg and ipilimumab 20 mg. Sixteen SAE were noted, all unrelated or unlikely related to intrathecal therapy. Three patients are still alive. For the whole cohort, median overall survival was 3 (range 0.6-10.3) months, for patients with a diagnosis of melanoma 2.9 (range 0.6-8.2) and for patients with NSCLC 4.5 (range 0.8-10.3) months. OS at 6 months was 20% (one patient ongoing at 5.1 months). Translational research is ongoing. **Conclusions:** No safety issue was noted. Efficacy data are preliminary and need to be confirmed in larger trials. Clinical trial information: NCT05598853. Research Sponsor: Bristol Myers Squibb.

2030 Poster Session

Evaluating the utility of DNA methylation signatures in tissue and biofluids for lung adenocarcinoma brain metastasis prediction and non-invasive detection. First Author: Jeffrey Zuccato, Oklahoma University Health Sciences Center, Oklahoma City, OK

Background: Brain metastases (BM) are common and arise in 30% of lung adenocarcinoma (LUAD) patients. Patients with LUAD that develop BM have significantly poorer outcomes, with a 10-16 month median overall survival. Unfortunately, current clinical practice for BM prediction is limited and so BM are typically detected after they develop and grow to cause neurological symptoms. Once BM are detected, currently neurosurgical tumor biopsies are performed to enable BM diagnosis via neuropathological evaluation. The aims of this study were to develop DNA methylation-based models that predict LUAD BM and non-invasively detect BM in blood to enable early diagnosis and treatment. **Methods:** DNA methylomes were acquired from 402 tumor tissue and plasma samples in a cohort of 346 LUAD and BM patients. Machine learning models were built using DNA methylation signatures that stratify BM risk in tissue and detect BM in plasma. Models were evaluated in independent validation datasets. A predictive nomogram was developed using the BM prediction model together with clinical factors to provide composite patient-specific scores reflecting BM risk. **Results:** The methylation-based BM predictor accurately stratified BM risk in a univariable Cox model using validation set data (HR = 5.65, 95%CI 1.85–17.2, p = 0.0023). Model utility was independent of the predictive value of clinical factors in a multivariable Cox model using validation set data (Table 1: HR = 8.92, 95%CI 1.97–40.5, p = 0.0046). The 5-year model accuracy was 0.81 and significantly higher than a similarly built cancer stage-based model (0.65), demonstrating utility over current practice. The combinatorial clinical-methylomic predictive nomogram had enhanced utility with an accuracy of 0.82 univariable Cox HR of 17.2 (95%CI 4.13–71.3, $p < 0.0001$), demonstrating comprehensive patient-specificity. The plasma-based model accurately classified BM from gliomas and lymphomas (AUROC=0.80), as typical clinical differential diagnoses, in validation set data. The models were validated further in additional external data. **Conclusions:** DNA methylation-based modeling of BM can accurately predict LUAD patients at risk for BM development and can non-invasively detect BM that develop. Future treatment approaches may tailor initial LUAD treatment and ongoing cancer surveillance to a patient's BM risk, allowing for the potential to prevent and treat BM early. Research Sponsor: None.

DNA methylation-based BM prediction is independent of clinical factors in a multivariable Cox proportional hazards model.

Variable		HR	95% CI	p
Methylome risk score		8.92	1.97–40.5	0.005
Age	Years	0.96	0.92–1.02	0.177
Smoking	Pack-years	0.99	0.95–1.03	0.496
EGFR	Mutant vs wildtype	0.92	0.25–3.34	0.895
T	T2 vs T1	1.58	0.41–6.04	0.505
	T3−4 vs T1	1.49	0.28–7.98	0.642
N	N1 vs N0	1.05	0.31–3.58	0.943
	N2−3 vs N0	1.00	0.27–3.69	0.995
M	M1 vs M0	145	12.2–1730	<0.001

2031 Poster Session

Effect of early integrated neuropsychological care in patients with brain metastases: A phase 2 randomized controlled trial (ATHENA trial). First Author: Haley Kopp Perlow, Department of Radiation Oncology, Seidman Cancer Center University Hospitals/Case Western Reserve University, Cleveland, OH

Background: Advancements in radiotherapy delivery through both hippocampal sparing whole brain radiotherapy (WBRT) and stereotactic radiosurgery (SRS) can better preserve QOL and reduce cognitive decline. However, even patients treated with advanced brain radiotherapy techniques have a reduction in their QOL and cognitive abilities either due to their radiation treatment, systemic therapy, or progression of disease. This Phase 2 Randomized Controlled Trial (NCT05503251) aims to evaluate the impact of a neuropsychological evaluation and intervention with a certified neuropsychologist on QOL and cognitive function for brain metastases patients treated with radiotherapy. **Methods:** Brain metastases patients were randomized 1:1 to either neuropsychology evaluation and intervention plus brain radiotherapy or brain radiotherapy alone. The intervention arm included five appointments with the neuropsychology team for testing, evaluation, and counseling over a three-month period. Patients with any number of brain metastases and an estimated survival of $\geq$ 6 months were included. Exclusion criteria included prior WBRT and pre-existing mental disability. Stratification factors for randomization were Karnofsky performance status (KPS, $>$ 70 vs. $\leq$ 70) and radiation cohort ($>$ 15 brain metastases received WBRT, $\leq$15 received SRS). All patients receiving WBRT were prescribed memantine. The primary endpoint was deterioration of QOL at 3 months as measured by Fact-Br. Repeated measures analysis of variance was used to measure QOL. Cognition was measured by Hopkins Verbal Learning Test-Revised, Controlled Oral Word Association Test, and Trail Making Test A/B, with cognitive decline defined as decline on at least one assessment using reliable change index. **Results:** Between August 2022 and June 2024, 110 patients were randomized. Baseline characteristics were balanced between arms and included a median KPS of 90 (IQR 80, 90), median age of 62.5 (IQR 54, 70), 53% female patients, 43% of patients with a primary lung cancer, and most patients (74%) with $\leq$15 brain metastases. The median overall survival or time to last follow-up was 8.5 months. The primary endpoint, deterioration of QOL at 3 months, was not different between the control and intervention arms (p = 0.93). Cognitive decline differences at 3 months were not significant between the control and intervention arms (24.1% vs. 27.3%, p = 0.33). Additionally, there were no differences at 3 months with verbal fluency, executive function, immediate recall, delayed recall, or delayed recognition between arms. **Conclusions:** This study did not meet its primary endpoint, better preserved QOL at 3 months for patients receiving early integrated neuropsychological care. Further evaluation of the delayed impact ($>$ 6 months) of neuropsychology intervention on QOL and cognitive function will be reported when data are available. Clinical trial information: NCT05503251. Research Sponsor: None.

2032 Poster Session

Intrathecal deferoxamine in patients with leptomeningeal metastases: Phase 1a analysis. First Author: Jessica Wilcox, Memorial Sloan Kettering Cancer Center, New York, NY

Background: Leptomeningeal metastases (LM), the spread of cancer to the cerebrospinal fluid (CSF), is associated with high morbidity and mortality. LM employ the iron-binding transporter and receptor system, lipocalin-2/SLC22A17, to scavenge iron from the CSF to sustain their metabolic needs. In preclinical models of LM, intrathecal administration of deferoxamine (IT-DFO), an iron chelator, resulted in reduction of LM growth and improvement of survival. We evaluated this novel treatment strategy in this first-in-human clinical trial in patients with solid tumor LM. **Methods:** This is a phase 1a, single-institution, clinical trial to determine safety and maximum tolerated dose (MTD) of IT-DFO in patients with LM. Eligibility criteria included LM from any solid tumor, age $\geq$ 18 years, Karnofsky Performance Status $\geq$ 60, life expectancy $\geq$ 8 weeks, and Ommaya reservoir. Patients were enrolled in an accelerated 3+3 dose escalation design with a primary endpoint of dose-limiting toxicity (DLT), defined as a grade 3 non-hematologic or grade 4 hematologic toxicity in the first cycle of treatment. All patients received IT-DFO twice weekly (cycle 1), once weekly (cycle 2), then once every two weeks (cycle 3+) in 28-day cycles. Patients were monitored for LM progression by neurological examination, neuraxial magnetic resonance imaging, and CSF cytology as per modified Response Assessment in Neuro-Oncology LM criteria. **Results:** A total of 8 patients received treatment with IT-DFO from May 2022 to January 2025 at the time of data cut-off. The median age at enrollment was 50 years (range, 26-69). The primary malignancy included breast (n = 4), lung (n = 2), colon (n = 1), and sarcoma (n = 1). Patients were treated with IT-DFO at doses of 10 mg (level 1, n = 4) and 30 mg (level 2, n = 4). IT-DFO was well tolerated, and the majority of adverse events (AEs) were grade 1-2. The most common any grade AEs were vomiting (50%), nausea (37.5%), chills (25%), myalgias (25%), and tremor (25%). Two patients experienced DLTs at 30 mg (grade 3 vomiting, grade 3 syncope). No grade 4-5 AEs were observed. The MTD was determined to be 10 mg. In this heterogenous heavily pretreated population, median overall survival for the evaluable cohort (n = 7) was 10.0 months (95% CI, 6.5 – NA). **Conclusions:** IT-DFO is a novel, well tolerated investigational treatment for LM. A phase 1b dose expansion study at a dose of 10 mg is currently underway to better define safety and efficacy endpoints. Clinical trial information: NCT05184816. Research Sponsor: MSK Center for Experimental Therapeutics; F. M. Kirby Foundation; ASCO Conquer Cancer Young Investigator Award 2021.

2033 Poster Session

Improving adherence to cancer care for socioeconomically disadvantaged patients with central nervous system tumors. First Author: Joshua Amit Budhu, Memorial Sloan Kettering Cancer Center, New York, NY

Background: Socially disadvantaged patients often face significant barriers to adhering to and completing cancer treatment. Patients with central nervous system (CNS) tumors experience cognitive, neuropsychiatric, speech, motor, sensory, and gait symptoms that exacerbate socioeconomic barriers to care. The Integrated Cancer Care Access Network (ICCAN) is a multi-institutional program developed by Memorial Sloan Kettering Cancer Center's Immigrant Health and Cancer Disparities Service (IHCD). Through ICCAN, patients are provided with patient navigation and resources to mitigate barriers to treatment adherence and completion. While ICCAN has been shown to increase treatment adherence and completion for patients with other cancers, it has not historically enrolled patients with CNS tumors. **Methods:** Under this pilot ICCAN-CNS program, 58 patients with either primary brain tumors or brain metastases were referred to the program. Of these, 45 patients enrolled, 5 patients died before contact was made, 2 patients declined participation, and 4 patients could not be reached. The patient population was evenly split between primary brain tumors (mainly glioblastomas and low-grade gliomas) and brain metastases. Patients were eligible if they were 18 years or older and receiving active treatment or were under active surveillance. If a patient was eligible, they were administered an extensive needs assessment survey that took 60 minutes to complete. The interviews consisted of basic demographic questions, Alliance Distress Screening Tool, Health Related Social Needs (HRSN) Assessment, Essential Needs Assessment, Patient Satisfaction with Cancer Care questionnaire, and an ICCAN-CNS specific questionnaire for patients with brain tumors. Caregivers were allowed to assist patients with neurocognitive or speech deficits in completing the survey questions. Patients were then provided with both patient navigation and resources depending on their needs. Follow-up assessments were conducted at the 2-, 4-, and 6-month marks. **Results:** Patients with CNS tumors completed the initial needs assessments and additional questionnaires. Trends of delayed responses and the need for questions to be repeated were observed, however, patients were still able to express socioeconomic needs. The main needs expressed among these patients were income, employment issues due to lack of ability to work from their cancer, food access, and transportation to appointments. Overall, the response to the program was positive from patients, with many patients accessing resources with the assistance of the access facilitator. **Conclusions:** This pilot demonstrates the feasibility and value of including CNS tumor patients in patient and resource navigation programs. Future plans include a randomized controlled trial using the ICCAN intervention for patients with glioblastoma. Research Sponsor: None.

2034 Poster Session

Risk of intracranial hemorrhage with DOACs vs LMWH in patients with cancer-associated thrombosis and brain metastases. First Author: Ali Mushtaq, Cleveland Clinic Foundation, Cleveland, OH

Background: Intracranial hemorrhage (ICH) is a major and often devastating complication in patients with brain metastases requiring therapeutic anticoagulation for cancer-associated thromboembolism (CAT). While direct oral anticoagulants (DOACs) provide a convenient alternative to low-molecular-weight heparin (LMWH), their safety in this population remains unclear. Comparing ICH risk between DOACs and LMWH is crucial for optimizing anticoagulation in these high-risk patients. **Methods:** This retrospective cohort study utilized TriNetX, a multi-institutional database, to analyze adults with solid tumors who developed CAT within six months of brain metastasis diagnosis. Patients receiving therapeutic-dose DOACs (apixaban, rivaroxaban, edoxaban) or LMWH within ten days of venous thromboembolism diagnosis were compared. 1:1 propensity score matching for over 50 covariates, including age, sex, and cancer type (Table 1). We assessed ICH incidence, bleeding events, ICU admissions, and all-cause mortality using Kaplan-Meier survival analysis and Cox proportional hazards models. Subgroup analyses examined ICH risk by cancer type. **Results:** After matching, 4,275 patients were included in each group. DOACs were associated with a statistically significant lower risk of ICH (HR 0.855, 95% CI 0.731-0.999, p=0.049). Additionally, significantly lower rates of ICU admission (16.7% vs. 20.3%; $p<0.001$) and all-cause mortality at 12 months (42.4% vs. 48.9%; $p<0.001$) were observed in the DOAC group. Subgroup analyses showed a trend toward lower ICH with DOACs in lung cancer (5.9% vs. 6.1%, p=0.726), melanoma (13.7% vs. 15.9%, p=0.432), and renal cell carcinoma (5.7% vs. 9.0%, p=0.103), but these differences were not statistically significant. No significant differences were found for breast (3.6% vs. 4.5%, p=0.375) or colorectal cancer (4.0% vs. 5.4%, p=0.331). **Conclusions:** DOACs were associated with significantly lower ICH, ICU admission, and mortality compared to LMWH in patients with brain metastases requiring anticoagulation, supporting their role as a viable and well-tolerated alternative. While subgroup analyses did not show significant differences in ICH risk by cancer type, the overall findings indicate a favorable profile for DOACs. These results highlight the need for individualized anticoagulation strategies and warrant further prospective validation. Research Sponsor: None.

Baseline characteristics after matching.

Characteristic	DOAC (n=4275)	LMWH (n=4275)
Age (years), mean ± SD	63.4 ± 11.9	63.5 ± 11.9
Female, n (%)	1969 (46.1%)	1958 (45.8%)
Lung Cancer, n (%)	2218 (51.9%)	2229 (52.1%)
Breast Cancer, n (%)	692 (16.2%)	672 (15.7%)
Melanoma, n (%)	280 (6.5%)	279 (6.5%)
Renal Cell, n (%)	241 (5.6%)	244 (5.7%)
Colorectal, n (%)	408 (9.5%)	413 (9.6%)

2035 Poster Session

Risk factors (RF) for brain metastases (BM) in patients (pts) with metastatic breast cancer (MBC): An analysis of US electronic health records (EHRs). First Author: Jose Pablo Leone, Dana-Farber Cancer Institute, Boston, MA

Background: BM are a significant clinical challenge in pts with MBC yet risk stratification for early identification is suboptimal. We leveraged a large, contemporary, real-world database to characterize RF associated with BM to inform strategies for enriched surveillance and early detection. **Methods:** Selected pts from the nationwide Flatiron Health de-identified EHR-derived database had MBC, had initiated first-line treatment (1L tx) before March 2023 (allowing for > 1 year [yr] of potential follow-up [FU]), and were free of BM at tx initiation. Clinical characteristics were examined as potential RF for BM incidence at any time during FU, using univariate sub-distribution (sd) and cause-specific (cs) hazard ratios. Additional analyses focused on BM risk at 3 yrs from tx initiation and included longitudinal data sequential Cox models with landmarks at every 6 months of FU, and a nested case-control (NCC) design for concurrent BM detection. Analyses were conducted on complete cases, no imputation method was used for missing data, and regression methods using multivariate analyses were used to mitigate confounding. Predictive, modeling-based machine learning (LASSO Cox regression, random survival forests) was conducted using cs hazard ratios to identify potential predictors amongst 90 candidates (data-driven approach using most of the dataset). Analyses were conducted in the overall cohort and stratified by subtype: HER2-negative/hormone receptor-positive (HER2−/HR+), HER2-positive/HR-negative (HER2+/HR−), HER2+/HR+, and triple-negative breast cancer (TNBC). **Results:** The study included 21,368 female pts initiating 1L tx (n = 14,898 HER2−/HR+, 1006 HER2+/HR−, 3468 HER2+/HR+, 1996 TNBC), with 2,530 BM events. Younger age, HER2+ and TNBC subtypes, and more extensive metastasis (≥2 organ sites, particularly liver, lung, or lymph nodes) were associated with higher BM risk (Table); bone-only metastases conferred a lower risk. sd and cs hazard ratios were largely concordant. NCC analyses identified similar predictors for concurrent BM. LASSO Cox modeling yielded a C-index of 0.74 overall (HER2+ 0.70; HER2−/HR+ 0.73; TNBC 0.62). Similar C-indices were seen with random survival forests. **Conclusions:** Clinical characteristics, including metastatic distribution and tumor subtype, can help identify pts at higher BM risk within 3 yrs of initiating MBC tx. Competing risks (of BM and death) did not appear to substantially affect results, except for recurrence time and ECOG PS. Although these findings are encouraging, further refinement of predictive models is needed to improve discrimination and guide targeted neuroimaging and early intervention strategies. Research Sponsor: F. Hoffmann-La Roche Ltd.

		sd hazard ratio
Age, yrs (reference [ref]: <45)	45–55	0.81
	56–65	0.62
	66+	0.31
Subtype (ref: HER2−/HR+)	HER2+/HR+	2.45
	HER2+/HR−	3.40
	TNBC	2.33
Metastatic sites, n (ref: 1)	2–3	1.55
	4+	2.63

2036 Poster Session

Memantine in radiation-induced cognitive dysfunction in brain metastases: A double-blinded, randomized, placebo-controlled trial (CTRI/2022/01/039599). First Author: Haripriya Parapparambil Surendran, Amrita Institute of Medical Sciences and Research, Kochi, India

Background: Prospective double-blinded, placebo-controlled randomized study to evaluate the role of memantine in brain metastasis (BM) in preserving cognitive function. **Methods:** Clinic-radiologically diagnosed of BM patients planned for radiation therapy (RT) (SRS or whole brain RT) were randomized to receive memantine or placebo (20 mg/day) over 24 weeks. Cognitive function assessed by Addenbrooke's Cognitive Examination (ACE). Secondary outcomes included QoL, white matter volume changes (MRI T2 FLAIR), and plasma memantine levels (by LC-MS/MS). Safety was assessed using CTCAE v5.0 criteria. **Results:** 130 BM patients were enrolled after randomization [placebo 64 & memantine (experimental arm n = 66]. In placebo and memantine arm mean age was 56.5 & 56.7; female 39 & 40; high school education status 39 (30%) & 37 (28%); SRS in 40 (30%) & 35 (27%); frontal lobe lesion 43 (33%) & 55 (42%); PS 0-1 55 (42%) & 54 (41%) respectively. In the placebo arm, ACE scores at baseline in placebo and memantine arm 83.0 ± 10.1 and 77.7 ± 12.7 (p = 0.78) respectively. At 4 months, ACE score in placebo and memantine arm 76.2 ± 14.3 and 82.2 ± 12.7 (p = 0.04). At 6 months in placebo and memantine arm were 72.9 ± 20.2 and 83.9 ± 10.8 (p = 0.005). At 24 weeks, ACE scores change was +4.0 in memantine & -9.5 in placebo arm; p = 0.001. Memantine arm had better preservation of memory (-3 vs. -2.5, $p < 0.001$), delayed recall (-1 vs. -1, $p < 0.001$), and verbal fluency (-1 vs. 0, p = 0.007). In the SRS subgroup, ACE scores in placebo and memantine at baseline, 4 and 6 month was 83.5 (± 9.5) & 79.7 (± 12.5); 76.6 (± 14.7) & 85.3 (± 10.6); 72.5 (± 23.1) & 86.4 (± 9.5) respectively. At 24 weeks, memantine arm improved ACE scores by +4 (0 to 12) compared to placebo -8 (-15.5 to -2.5) ($p < 0.001$). At 24 weeks in WBRT, memantine arm sustained cognitive improvement (ACE score +3) compared to further decline in placebo (-9.5, $p < 0.001$). At 24 weeks, percentage change in global health status in placebo & memantine arms were -5.57%. & +63.3% respectively. 21% required dose reductions due to adverse events. Loss of appetite (25.7% vs. 12.5%, p = 0.05); gastric irritation (0 vs 7.5%; p = 0.02) were higher in memantine arm. White matter volume changes in the placebo group correlated negatively with cognitive decline (r = -0.544, p = 0.055), suggesting a potential role of edema in radiation-induced cognitive dysfunction. Memantine at a 5 mg BID dose achieved a median trough concentration of 118.06 ng/mL (IQR: 68–211), within the desirable therapeutic range (70–150 ng/mL). 10 mg BID dose trough was 172 (85-290) and peak concentration 397 (258-499 ng/mL) exceeded alert threshold of 300 ng/mL. **Conclusions:** Memantine preserved cognitive function and QoL in RT for BM. Cognitive benefits were more in SRS than HA/WBRT. White matter volume change was negatively correlated to cognitive outcomes. 5 mg BID dose optimally balances efficacy with tolerability. Clinical trial information: CTRI/2022/01/039599. Research Sponsor: None.

2037 **Poster Session**

Predictors of overall survival in patients with brain metastases from HER2+ breast cancer. First Author: Qinmei Xu, Stanford University School of Medicine, Stanford, CA

Background: Predictors of overall survival (OS) after brain metastasis (BM) in HER2-positive breast cancer (BC) are not well characterized. This study aimed to identify clinical and imaging-derived (radiomic) features that predict OS and develop a combined model for better prognostic performance. **Methods:** Our retrospective study analyzed 289 patients initially diagnosed with non-metastatic HER2-positive BC who later developed BM. We used 25 clinical characteristics and 12 treatment parameters to develop a Clinical model. We developed an Imaging model using a subset of 120 patients, who possessed evaluable pre-treatment brain MRI for delineating tumor segmentations on all brain metastatic lesions. We extracted 1078 radiomic features from each tumor segmentation using PyRadiomics, generating 8 feature sets based on 2 segmentation strategies (largest tumor per patient versus all tumors combined) and 4 tumor feature types (entire tumor, solid component, necrotic component, combined solid and necrotic features with statistical transformations). Morphological features, including lesion number, total size/volume, and necrotic-to-solid ratios, were also incorporated, along with tumor intracranial location. Cox proportional hazards regression model with Coxnet, integrating LASSO and Elastic Net regularization, was used to predict OS. For fair comparison, we randomly selected 30% (n = 31) of the smallest subset (n = 103, largest brain metastasis with both necrotic and solid components), all of which overlap with other model subsets, as validation cohort. Three model types—Clinical, Imaging and Combined—were compared using the concordance index (C-index) to assess performance based on validation cohort. **Results:** Clinical model, built on the whole cohort (286 women, 3 men; mean age 54.52 $\pm$ 12.79 years), identified 3 predictors of OS. Imaging model, built on a subset of 120 patients with brain MRI data, identified a radiomic signature (RS) consisting of 4 radiomic features most predictive of OS. Using the same subset, the Combined model (C-index: 0.728 [95% CI: 0.590–0.855]) outperformed Clinical (C-index: 0.62 [95% CI: 0.44–0.78]) and Imaging (C-index: 0.62 [95% CI: 0.46–0.77]) models in the held-out validation cohort (n = 31). Significant features associated with increased mortality risk in the Combined model included a higher RS, absence of tucatinib treatment for the primary BC prior to BM development, elevated Ki-67 expression, Black race, higher N stage, and brainstem metastases. Among these factors, RS, with the largest absolute coefficient in the Combined model (0.38), emerged as the most important predictor of OS (hazard ratio: 20.03 [95% CI: 4.92–81.48], $p < 0.005$). **Conclusions:** A distinct RS from brain MRI is the strongest predictor of OS in patients with BM from HER2-positive BC, surpassing clinical factors. RS may refine risk stratification and guide treatment or clinical trial prioritization. Research Sponsor: Susan G. Komen.

2038 **Poster Session**

Hippocampal-avoidance whole-brain radiotherapy with dose escalation on metastases: A prospective randomized trial (HIPPORAD). First Author: Anca-Ligia Grosu, Department of Radiation Oncology, Medical Center - University of Freiburg, Faculty of Medicine, Freiburg, Germany

Background: The HIPPORAD trial aimed to evaluate a new method of whole brain radiation therapy (WBRT) with simultaneous integrated boost (SIB) to the metastases, with versus without hippocampal avoidance in patients with brain metastases. **Methods:** We conducted a prospective, multicentre, randomised, double-blind trial (DRKS00004598). Patients with 4-10 brain metastases > = 5mm were randomised at 13 centres in Germany 1:1 between WBRT+SIB with hippocampus avoidance (HA-WBRT+SIB) (arm A) and WBRT+SIB (arm B). Patients and assessors of outcome were blinded to the randomised arm. All patients received WBRT with 30 Gy and SIB with 51 Gy or 42 Gy in 12 fractions, 5x/week. The primary endpoint was the change in neurocognitive function (assessed by the Verbal Learning and Memory Test [VLMT]) 3 months after treatment. Secondary endpoints included neurocognitive changes at 9 and 18 months, development of anxiety and depression, quality of life and measures of oncological outcome. **Results:** Between August 2nd, 2016 and September 7th, 2021, 170 patients were recruited and 136 were randomised between HA-WBRT+SIB (n = 67) and WBRT+SIB (n = 69). Of these, 38 patients in arm A and 42 in arm B were known to be alive 3 months after treatment and were included in the primary endpoint analysis. The change in overall learning performance at 3 months was not significantly different between arms (p = 0.83). VLMT-scores decreased after 3 months, but improved at 9 and 18 months, with HA-WBRT+SIB showing an overall superior trend over WBRT+SIB. At 18 months, VLMT-scores improved to values above baseline in both arms. Patients treated with HA-WBRT+SIB had significantly less depression compared to patients treated with WBRT+SIB at 3 (p = 0.047) and 18 months (p = 0.048). The 12-month-tumor control for boosted metastases was 96% in Arm A and 88% in Arm B, while for the WBRT area it was 78% in both arms. Time to hippocampal tumour progression was comparable between arms (p = 0.98). After 12 months, 4% of patients in arm A and 12% in arm B had suffered neurological death. **Conclusions:** To our knowledge, this is the first prospective trial to show that hippocampal avoidance during WBRT leads to significantly lower rates of depression. The development of VLMT values after HA-WBRT+SIB and WBRT+SIB with 30 Gy in 2.5 Gy-fractions was comparable and a good recovery was observed at 18 months in both arms. The method showed a considerably higher intracerebral tumour control with lower neurological mortality rates compared to historical cohorts. Clinical trial information: DRKS00004598. Research Sponsor: German Cancer Aid.

2039 **Poster Session**

Initial report of memory avoidance whole brain radiotherapy to treat brain metastases: A prospective phase 2 trial. First Author: Joshua David Palmer, Department of Radiation Oncology, Ohio State University, Columbus, OH

Background: A common approach for patients with extensive brain metastases requiring radiation is hippocampal avoidance whole brain radiotherapy (HA-WBRT) prescribed with memantine; this was proven to be efficacious based on NRG CC001. However, a subset of patients who receive HA-WBRT with memantine still experience cognitive decline. Other brain structures with important roles in memory and cognition include the corpus callosum, fornix, amygdala, hypothalamus, and pituitary; these structures all have a low propensity for brain metastases and therefore can be safely spared in a radiotherapy plan without increasing the risk of relapse. A subset of patients enrolled on a Phase 2 Randomized Controlled Trial (NCT05503251) received an advanced "memory-avoidance WBRT (MA-WBRT) approach that spared these substructures in addition to the hippocampus, with a primary endpoint of improved cognition compared to a historical control (NRG CC001). **Methods:** All patients with > 15 brain metastases on a prospective clinical trial, which randomized patients to either neuropsychology evaluation and intervention plus brain radiotherapy or brain radiotherapy alone, received MA-WBRT. Exclusion criteria included prior WBRT, pre-existing mental disability, and metastases within the avoidance neurocognitive substructures. All patients received 30 Gy in 10 fractions of MA-WBRT and were prescribed memantine. Cognition was measured by Hopkins Verbal Learning Test-Revised, Controlled Oral Word Association Test, and Trail Making Test A/B, with cognitive decline defined as decline on at least one assessment using reliable change index (same tests and definition as NRG CC001). **Results:** Between August 2022 and May 2024, 29 patients received MA-WBRT. Baseline characteristics included a median KPS of 80 (IQR 70, 90), median age of 64 (IQR 54, 69), 62% female patients, and a plurality of patients with a primary lung cancer (48%), The median overall survival or time to last follow up was 7.9 months. The three-month decline in neurocognitive function comparing the control and intervention groups for patients receiving MA-WBRT was 15.4% and 18.8%, respectively (p = 0.39). There was one failure in the right fornix 10 months after enrollment, but this was associated with concurrent distant intracranial failure outside the memory avoidance zone. **Conclusions:** The cognitive decline rate of approximately 17% at three months for patients receiving MA-WBRT compares favorably to a 3-month cognitive decline rate of 50% seen on NRG CC001. Additionally, MA-WBRT does not appear to significantly increase the risk of intracranial failure. Further evaluation of the delayed impact (> 6 months) of MA-WBRT on cognitive function will be reported when data are available. A direct comparison of MA-WBRT plus memantine vs. HA-WBRT plus memantine is forthcoming with a randomized phase 3 trial. Clinical trial information: NCT05503251. Research Sponsor: None.

2040 **Poster Session**

Genomic predictors of brain metastases in breast cancer. First Author: Anton Safonov, Memorial Sloan Kettering Cancer Center, New York, NY

Background: Despite therapeutic advances in metastatic breast cancer (MBC), the rising incidence of brain metastases (BM) remains a major challenge, contributing to poor prognosis and significant morbidity. Due to the absence of consensus screening strategies for BM, they are often detected only after clinical symptoms emerge. There is therefore a pressing need for predictive biomarkers to identify breast cancer patients at risk of BM. **Methods:** This study included 3908 patients who underwent sequencing of primary tumor (n = 1885) or non-brain metastasis (n = 2023) with MSK-IMPACT, a custom tumor-normal next generation sequencing assay. First, we performed penalized logistic regression on a gene level to identify alterations in extracranial metastases or primary tumors associated with development of BM. We adjusted for multiple hypothesis testing using Benjamini-Hochberg. Lastly, we developed a lasso machine-learning (ML) model, incorporating baseline genomic and clinicopathologic features, to predict onset and timing of BM from initial diagnosis (for early stage cases) or metastatic disease (for MBC). Each analysis was stratified by receptor status, and repeated to account for loss of heterozygosity (LOH) of tumor suppressor genes. **Results:** Our cohort included 528 BM events over a median follow-up of 58 mos. Pathogenic variants in several genes were associated with subsequent BM development. In the HR+/HER2- subset (n = 2624), pathogenic variants in the following genes portended the onset of BM: *RB1* (OR 2.59 [1.39 - 4.81], q = 0.011), *NF1* (OR 2.22 [1.21 - 4.06], q = 0.039), *TP53* (OR 1.91 [1.43 - 2.54], q < 0.001), *PIK3CA* (OR 1.47 [1.21-4.06], q = 0.028). Pre-existing LOH of *RB1,* in the absence of an *RB1* functional alteration, was associated with BM development (OR 1.37 [1.03 - 1.83], q = 0.090). *TP53* LoF .OR 5.14 [2.21 - 11.9], q < 0.001) was enriched in the BM group in HER2+ tumors, while amplification of *CDKN2A* (OR 11.6 [2.44 - 55.5], q = 0.01) or *EGFR* (OR 4.60 [1.54 - 13.8], q = 0.03) were enriched in TNBC. *TP53* emerged as an important feature across all receptor subtypes in our machine-learning model; *RB1* LoF was also selected as an important feature in the HR+/HER2- group. Validation of the ML model in an external cohort will be presented at the meeting. **Conclusions:** In a large cohort of genomically profiled breast cancer samples, we found several biologically plausible candidates for molecular harbingers of BM. For instance, the recurrent involvement of genes involved in cell cycle regulation (*RB1, CDKN2A, TP53)* has been implicated as candidates for BM tropism in other cancer types. Our approach also uncovers several alterations for which targeted therapies exist or are actively in development *(NF1, PIK3CA).* Our clinically actionable multimodal model of BM risk is poised to facilitate the development of early detection strategies and guide-high risk patient selection for novel clinical trials to intercept this devastating complication. Research Sponsor: None.

2041 Poster Session

Characterizing functional connectivity in brain tumor patients. First Author: Alexander B. Remsik, University of Wisconsin System, Madison, WI

Background: Brain tumors (affecting 25,500 individuals in the US alone) cause unique changes to neural function and connectivity resulting in impairments in various functional domains, including cognition. **Methods:** Between 2012 and 2018, as part of their preoperative surgical planning, 91 brain tumor patients with tumors in right (R) or left (L) temporal (T), parietal (P) or frontal (F) lobes received resting-state functional magnetic resonance imaging (rs-fMRI) and the COWAT verbal fluency (VF) test. UW Hospital and Clinics uses 1.5 T (112 axial slices, 1.0 × 1.0 × 1.5 mm) and 3 T (136 axial slices, 1.0 × 1.0 × 1.2 mm) GE MRI scanners and includes high-resolution 3D BRAVO T1-weighted imaging, and rs-fMRI scans (eyes closed, 28 axial slices, 3.75×3.75×5.0mm) were also acquired during this imaging protocol. These individuals were compared to each other and to 40 age-matched non-tumor controls (Cs). **Results:** Groups were similar in age, and sex ($p>0.05$), but different in education ($p=0.028$) and VF scores ($p=0.001$). There were significant differences in post-hoc p-values when comparing VF scores between Cs and RT tumor patients ($p=0.039$). Qualitative observations indicate Cs are more integrated have greater network strength and connectivity higher transitivity, efficiency, and modularity index compared to patients. There were significant differences in VF scores between Cs, LF ($p=0.001$), RF ($p=0.012$), RT ($p=0.021$), RP ($p=0.015$). Patients show hypo-frontality of hubs and a unique cerebellar module. LF patients showed correlation to transitivity at 25% ($R=0.404$, $p=0.041$), and patients with RP tumors had significant correlations to transitivity ($R=0.654$, $p=0.029$) and global efficiency ($R=0.607$, $p=0.048$). Cs and L tumors did not show any significant correlation to VF scores, R tumors showed correlation with global efficiency at 25% sparsity ($R=0.374$, $p=0.025$). All remained significant after FDR correction. **Conclusions:** Tumor location impacts rs-fMRI-derived GT network structure and VF scores, suggesting tumors in left hemisphere and frontal areas caused the greatest impact to cognition. These methods may be used in future research and clinical care to map, track, and predict functional connectivity changes resulting from brain tumor and can help inform clinicians and care trajectories. Research Sponsor: NIH (NINDS); T32CA009206, R01NS117568, R01NS123378, TL1TR002375, R01CA264017, R01CA277728, UL1TR002373, P30CA014520; WI Partnership Program; VA; BX005842-01A2; Wisconsin Alumni Research Foundation; MSN281757.

2042 Poster Session

AI-driven transcriptomic classification of glioblastoma: Associations with survival and tumor microenvironment. First Author: Juan Manuel Fernandez-Muñoz, SphereBio, Mendoza, Argentina

Background: Glioblastoma (GBM) is the most lethal primary brain tumor in adults, with a median survival of ~15 months despite current therapies (surgery, radiation, temozolomide). Advances like immune checkpoint inhibitors, anti-angiogenic agents, and tumor vaccines have shown suboptimal results. The 2021 WHO classification highlights molecular markers (e.g., IDH, MGMT) for better stratification, but these fail to fully capture tumor microenvironmental dynamics. Using an AI-driven transcriptomic approach, we identified novel prognostic subtypes in IDH-wildtype GBM, aiming to refine stratification, enhance understanding of tumor biology, and guide personalized therapeutic strategies. **Methods:** We accessed microarray data from The Cancer Genome Atlas (TCGA) (n=353 newly diagnosed, IDH-WT GBM) for a training set and RNA-seq data from the Chinese Glioma Genome Atlas (CGGA) (n=170 primary and n=106 recurrent tumors) for validation. A proprietary SphereBio machine learning–based algorithm was used to derive transcriptomic signatures with prognostic relevance. Subtypes were assessed via Kaplan–Meier analyses in the training cohort and tested in both primary and recurrent validation cohorts. Immune/stromal infiltration was quantified using a tumor deconvolution tool (DA_505), and pathway enrichment (GAGE) was performed on the validation sets. **Results:** AI-driven clustering revealed three transcriptomic subtypes with significant survival differences in both the training ($p<0.0001$) and primary validation ($p=0.0004$) cohorts. In the recurrent cohort, a similar survival trend by subtype was observed, though significance was diminished ($p=0.12$), likely due to limited sample size and therapy-related changes. Immune/stromal deconvolution showed distinct infiltration patterns: subtypes enriched for CD4+ and CD8+ T cells correlated with prolonged survival. Pathway enrichment analysis in both primary and recurrent tumors highlighted potential targets involving embryogenesis, immune modulation, cell cycle, and stress response. The persistence of a consistent survival trend and comparable microenvironment and pathway patterns suggest that these transcriptomic subtypes remain biologically relevant even after standard treatment. **Conclusions:** Our integrated transcriptomic and microenvironment-focused approach identified three prognostically distinct GBM subtypes, validated across independent cohorts. These findings underscore the utility of AI-driven transcriptomic signatures for personalized stratification, with the potential to guide targeted therapeutic strategies and inform clinical trial design in GBM. Research Sponsor: None.

2043 Poster Session

Impact of neuroradiologists' input on peer review meetings for CNS radiotherapy treatment planning. First Author: Abhishek Mahajan, The Clatterbridge Cancer Centre NHS Foundation Trust, Liverpool, Merseyside, United Kingdom

Background: Evidence shows radiologists' involvement improves planning accuracy, especially in complex anatomical areas. However, their participation remains limited. This prospective observational study evaluates the impact of neuroradiologists' input on changes to radiotherapy (RT) plans during peer review meetings. **Methods:** Data were collected from 205 patients with CNS tumours planned for radiotherapy between May 2022 and October 2023. We recorded demographics, diagnostic and RT planning scans, and therapy received. All images were reviewed by a neuroradiologist, with RT changes classified as major (affecting cure or disease control) or minor (affecting target volumes or organs at risk). Summary statistics were calculated, and Pearson chi-squared tests assessed whether changes in RT plans varied by tumour type, time since diagnosis, and neuroradiologist findings. Data were analyzed using STATA SE v.17. **Results:** Of 205 patients, 81 (40%) had gliomas, 77 (38%) had brain metastases, 23 (11%) had meningiomas, 17 (8%) had schwannomas, and 7 (3%) had pituitary tumours. The mean age was 60 years (SD 14), 56% were male, and 36% were treatment-naïve. All but one had MRI scans, 128 (62%) had CT scans, and 9 (4.4%) had PET scans. The median number of diagnostic scans per patient was 2 (IQR 2-3), and all had two planning scans. The median interval between diagnosis and RT planning scans was 35 days (IQR 21-61). Disease progression was observed in 67 (33%) patients. Major and minor changes to RT plans were reported in 35 (17%) and 78 (38%) patients, respectively. A higher proportion of RT plans changed for brain metastasis (26% & 40%) and glioma (11% & 43%). Changes were not associated with tumour type ($p = 0.07$) or time since diagnosis ($p = 0.12$), but were significantly associated with neuroradiologist findings ($p < 0.0001$). **Conclusions:** Neuroradiologists' assessments led to major and minor changes in RT plans, regardless of tumour classification or interval since diagnosis. This expertise can enhance RT plan accuracy, improving patient outcomes. Research Sponsor: None.

Changes to radiotherapy treatments as per RCR categories and by tumour type, time interval, and neuroradiologist findings.

	Changes to radiotherapy plan			
	Major change (N= 35)	Minor change (N= 78)	No change (N=92)	P value*
Total	17 %	38%	45%	
Tumour classification				0.07
Glioma	9 (11.1)	35 (43.2)	37 (45.7)	
Meningioma	3 (13.0)	7 (30.4)	13 (56.5)	
Schwannoma	2 (11.8)	3 (17.7)	4 (57.1)	
Pituitary tumour	1 (14.3)	2 (28.6)	4 (70.6)	
Metastasis	20 (26.0)	31 (40.3)	26 (33.8)	
Time interval, weeks				0.12
Less than 8	27 (77.2)	61 (78.2)	59 (64.1)	
8-	4 (11.4)	10 (12.8)	20 (21.7)	
16-	1 (2.9)	3 (3.9)	7 (7.6)	
24-	-	2 (2.6)	1 (1.1)	
30-	-	2 (2.6)	3 (3.3)	
38-	3 (8.6)	-	2 (2.2)	
Neuroradiologist findings				<0.0001
Stable disease	17 (48.6)	35 (44.9)	71 (77.2)	
Residual disease	3 (8.6)	6 (7.7)	6 (6.5)	
Disease progression	15 (42.8)	37 (47.4)	15 (16.3)	

**Pearson chi-squared test.*

2044 Poster Session

Identification and validation of potential diagnostic plasma biomarkers for diffuse gliomas by multiplex immunoassays. First Author: Miyo K. Chatanaka, University of Toronto, Toronto, ON, Canada

Background: Diffuse gliomas are aggressive malignant tumors with poor prognosis. The current standard of care includes measurement of molecular biomarkers in biopsy samples. One unmet clinical need is to identify non-invasive biomarkers that may be used for differential diagnosis of gliomas from other brain tumors. Pre-clinical and clinical validation of such biomarkers could eliminate the need for biopsy, and support the implementation of more personalized and/or emerging treatments and the earlier enrolment of patients into clinical trials. Our objective is to use multidimensional proteomics to identify and validate potential plasma biomarkers for glioma management. **Methods:** We used the proximity extension assay from Olink Proteomics to analyze 3,000 proteins in plasma of patients with diffuse gliomas and meningiomas (as controls). By data visualization, we identified several plasma proteins that were increased or decreased in gliomas in comparison to meningiomas. Several candidate markers were selected for validation with an independent set of retrospectively collected samples by using quantitative research-use-only electrochemiluminescence assays available from Meso Scale Discovery. In the validation set, which included longitudinal data from patients, patient information included biopsy-requiring molecular tumor abnormalities such as IDH1 status, ATRX expression, MGMT promoter methylation, CDKN2A/B/p16 status, V1p 19q co-deletion and NF1 status. In the validation stage, we focused on diffuse gliomas. **Results:** In the discovery phase, associations between proteins were plotted to determine potential predictive ability for discriminating diffuse gliomas vs. meningiomas. A partitioning algorithm was fit to determine the optimal combination of GFAP (the strongest biochemical marker), age and sex, as well as with other candidate proteins. Differential expression was seen for a few other proteins such as NEFL, PROK1, FABP4, MMP3 and LMOD1. In the cross-sectional validation phase, we verified strong associations between GFAP and FABP4 plasma concentration and GBM, astrocytomas, oligodendrogliomas and meningiomas, where these markers could differentiate between the groups. Within diffuse gliomas, NEFL, GFAP, FABP4 and IL13 were significantly different. **Conclusions:** This study highlights the potential of plasma biomarkers to revolutionize glioma patient management through liquid biopsy applications. The strong associations observed between plasma protein concentrations and glioma subtypes support a diagnostic power that addresses a critical unmet need in neuro-oncology. More specifically, these biomarkers can help with patient differential diagnosis at initial presentation, with future aims to investigate the prognostic value and the possibility of acting as surrogates of molecular changes that are currently used for optimizing therapy. Research Sponsor: Canadian Institutes for Health Research, The Canadian Brain Foundation, Canadian Cancer Society Research Institute; CCS707057; National Cancer Institute; P50CA221747.

2045 **Poster Session**

Association of plasma biomarkers with diagnostic molecular markers for potential diagnosis and prognosis of diffuse gliomas. First Author: Leonardo Macedo Filho, Penn State College of Medicine, Hershey, PA

Background: Diffuse gliomas were recently reclassified based on the 2021 WHO Classification criteria. Several molecular changes which carry diagnostic and prognostic power have been added to the classification parameters, including IDH1 mutation and MGMT promotor methylation. To characterize these molecular changes, however, an invasive biopsy is required. Our goal was to examine the relationship between seven plasma biomarkers for diffuse glioma and the established molecular changes and delineate if these markers can be used as surrogates of these molecular changes. **Methods:** Seven candidate markers, namely glial fibrillary acidic protein (GFAP), neurofilament light (NEFL), matrix metalloproteinase 1, 3, 9 (MMP1, MMP3, MMP9), total Tau (tTau) and fatty acid binding protein 4 (FABP4) were evaluated by quantitative research-use-only electrochemiluminescence assays available from Meso Scale Discovery by comparing the protein concentration distribution with non-parametric Wilcoxon rank sum tests and multiple testing adjustment. The molecular markers tested were IDH1, MGMT promotor and ATRX. The discovery cohort consisted of 49 IDH1 mutant (39%) and 77 IDH1 wildtype (61%) gliomas. Among this retrospective cohort were 103 primary samples (collected at diagnosis) and 23 recurrent samples (collected at time of recurrence). The retrospective validation cohort consisted of 36 IDH1 mutant (22%) and 129 IDH1 wildtype (78%), with 64 primary samples and 76 recurrent samples. **Results:** Several of the proteomic markers showed significant associations with genetic markers at an adjusted significance level of $P < 0.05$. For IDH1 status, the strongest association was with NEFL, with IDH1 wildtype samples showing higher levels of the protein. For ATRX expression, high FABP4 was correlated with ATRX retention. As expected, survival analysis based on molecular markers yielded that IDH1 status was most predictive of survival both in primary tumors and recurrent tumors. MGMT promotor methylation was predictive of survival in primary cases but not recurrent cases. When combining the genetic markers with protein concentrations, we were able to see some improvement in survival prediction. **Conclusions:** We demonstrate that some plasma biomarkers, particularly NEFL and FABP4, show significant associations with key molecular changes in diffuse gliomas, including IDH1 status and ATRX retention/loss. Future research will determine whether these proteomic markers can serve as surrogates for molecular alterations and assist in potentially improved diagnosis and monitoring of diffuse gliomas. Research Sponsor: None.

2046 **Poster Session**

A multicenter randomized phase III study for recurrent glioblastoma comparing bevacizumab alone with dose-dense temozolomide followed by bevacizumab: JCOG1308C. First Author: Motoo Nagane, Department of Neurosurgery, Kyorin University Faculty of Medicine, Tokyo, Japan

Background: Temozolomide (TMZ) is an alkylating agent commonly used as the standard therapy for newly diagnosed glioblastoma (GBM), with the DNA repair enzyme O^6-methylguanine-DNA methyltransferase (MGMT) serving as a key prognostic and predictive factor. Despite treatment, GBM almost always recurs with limited therapeutic options, leading to poor prognosis. Since MGMT is consumed during the repair of TMZ-induced O^6-methylguanine lesions in DNA, dose-intensified TMZ regimens are designed to deplete MGMT, thereby enhancing tumor sensitivity to TMZ. Bevacizumab (BEV), an anti-VEGF agent, has shown efficacy in recurrent GBM (re-GBM), but no effective therapies exist after BEV failure. Introducing an active agent before BEV may improve outcomes. To test this, we conducted a multicenter, phase III study comparing BEV monotherapy with dose-dense TMZ (ddTMZ) followed by BEV in re-GBM. **Methods:** Patients (pts) aged 20-75 years with KPS $\geq$60 and histologically confirmed GBM at first recurrence were enrolled from 31 Japanese hospitals. Participants were randomized to BEV monotherapy (10 mg/kg every 2 weeks; arm A) or ddTMZ (120-150 mg/m^2, 7 days on/7 days off) followed by BEV at progression (arm B). Treatment continued until progression or unacceptable toxicity. The primary endpoint was overall survival (OS). A planned sample size of 146 pts provided 70% power to detect a hazard ratio (HR) of 0.73 (median OS (mOS): 8 vs. 11 months) at a one-sided alpha of 10%. *MGMT* promoter methylation and *IDH* mutation status were analyzed. **Results:** From July 2016 to April 2022, 146 pts (73 per arm) were randomized. *MGMT* promoter methylation was observed in 78 pts, while 49 were unmethylated. *IDH1* mutations were identified in 8 of 129 pts to be tested. The mOS was 11.0 months (95% CI: 9.0-12.8) in arm A and 10.8 months (95% CI: 8.6-12.5) in arm B, with no significant difference (HR 0.922, 95% CI: 0.655-1.297, one-sided p = 0.320). No significant OS difference was observed between arms based on *MGMT* methylation status. The median progression-free survival (PFS) was 4.0 months (95% CI: 3.8-5.7) in arm A and 2.0 months (95% CI: 1.9-2.1) in arm B (HR 1.632, 95% CI: 1.168-2.281). Most pts in arm B exhibited progression at their first MRI. From the start of BEV treatment, mOS was 10.8 months (95% CI: 8.8-12.6) in arm A, and 8.0 months (95% CI: 6.1-9.1) in arm B. Grade 3-4 adverse events included hypertension (19.4%) in arm A and lymphopenia (52.1%) and leukopenia (8.2%) during ddTMZ in arm B. Grade 4 toxicities were rare. **Conclusions:** While ddTMZ was well-tolerated, this study failed to demonstrate a survival benefit for ddTMZ followed by BEV in re-GBM. BEV remains the preferred treatment at first recurrence. Further research is needed to develop effective therapies beyond the current standard for re-GBM. Clinical trial information: NCT02761070. Research Sponsor: Japan Agency for Medical Research and Development; 17824890.

2047 **Poster Session**

Use of brain protein I3 (BRI3) to predict disease fate in glioblastoma. First Author: Ifeanyichukwu Ogobuiro, The University of Miami Sylvester Comprehensive Cancer Center, Miami, FL

Background: Genome-wide characterization has illuminated the molecular complexity of human gliomas. Genetic alterations help predict the clinical behavior of gliomas, but variability persists. Accordingly, there is a need to expanding molecular signatures that refine prognostication. The Brain Protein I3 (BRI3) gene, localized on chromosome 7, is associated with high-grade glioma, yielding the highest hazard ratio among all high-risk genes in an in-silico glioma model. Given GBM's known chromosome 7 gain and BRI3's chromosomal location, we hypothesized that gene dosage gains and overexpression serve as prognostic biomarkers. **Methods:** We used the Rembrandt (n = 461 patients) and TCGA low-grade glioma (LGG) and GBM (n = 1,148 patients) databases for multi-omic analyses. RNA sequencing (Illumina HiSeq) and DNA methylation profiles (Illumina 450K) were analyzed in a combined LGG and GBM cohort, with high/low expression and hyper/hypomethylation defined by median values. CNV analysis (GISTIC 2.0) classified 2 copies as gene-copy neutral and > 2 as gene dosage gain. Somatic mutation data (SNPs/INDELs) were derived from whole-exome sequencing to decipher IDH-wt and IDH-mutant gliomas. Univariate and adjusted Cox models, Kaplan-Meier estimates, and receiver operating characteristic (ROC) curve analysis were performed. **Results:** Of 461 Rembrandt patients, 47.29% were GBM, 31.89% astrocytoma, 14.53% oligodendroglioma, and 6.29% normal brain. Among 1,148 TCGA LGG/GBM patients, 551 had complete molecular and clinical data, with 28% IDH-wt status, 49% MGMT hypermethylation, and 36.66% BRI3 gene dosage gains. BRI3 expression was significantly higher in GBM, grade IV tumors, IDH-wt, and mesenchymal subtypes. Among the IDH-wt cases, 75% showed BRI3 gene dosage gains with significantly elevated mRNA expression. EGFR, co-amplified in 80% of IDH-wt cases, did not affect survival (25.27 vs. 17.90 months, p = 0.346). Conversely, BRI3 gene dosage gain correlated with worse survival (79.3 vs. 17.93 mo, p = 0.001), as did BRI3 high vs. low expression (17.90 vs. 25.27 months, p = 0.015) and MGMT hypermethylation (25.27 vs. 18.63 mo, p = 0.021). Univariate analysis linked patient age (HR: 2.858 [1.781–4.586], $p < 0.001$), MGMT hypermethylation (HR: 2.632 [1.307–5.301], p = 0.007), BRI3 high expression (HR: 1.938 [1.131–3.320], p = 0.016) and BRI3 gene dosage gain (HR: 2.504 [1.425–4.398], p = 0.001) to worse OS. Adjusted multivariate Cox regression confirmed BRI3 gene dosage gain, age, and MGMT methylation as independent OS predictors in IDH-wt cases. ROC analysis revealed stronger prognostic performance for BRI3 gene dosage gain than MGMT hypermethylation (AUC: 0.737 vs. 0.616, $p < 0.001$) in IDH-wt cases. **Conclusions:** Elevated BRI3 gene dosage and expression portend poor prognosis and could be incorporated into models predicting disease fate in GBM. Research Sponsor: None.

2048 **Poster Session**

Effect of armed oncolytic adenovirus on immunotherapy for primary and metastatic brain tumors. First Author: Jiasen He, The University of Texas MD Anderson Cancer Center, Houston, TX

Background: Oncolytic viruses have shown promise in clinical trials for solid tumors, including glioma and melanoma, but only a subset of patients benefits. We previously showed that arming the oncolytic adenovirus Delta-24-RGD with OX40L can enhance antitumor immunity. To further boost efficacy, we developed Delta-24-RGDOX-IL15, co-expressing OX40L and IL-15, and tested it in preclinical models of primary and metastatic brain tumors. **Methods:** To evaluate IL-15 and its receptor (IL15RA) expression in patients with glioma and melanoma, we conducted gene expression and survival analysis using the GEPIA web server, integrating RNA sequencing data from TCGA and GTEx. Transgene expression in Delta-24-RGDOX-IL15 was assessed via flow cytometry and ELISA, while viral potency was evaluated using replication and cell viability assays. Anti-tumor activity was tested in syngeneic intracranial models derived from mouse diffuse midline (DMG) glioma and melanoma cell lines in C57BL/6 mice, both of which expressed GD2 and luciferase. Tumor growth was monitored with bioluminescent imaging, survival with Kaplan-Meier analysis, and immune profiling of the tumor microenvironment using flow cytometry. **Results:** GEPIA analysis showed that melanoma had higher expression of IL-15 and IL-15RA compared to glioma. In melanoma patients, higher expression of IL-15RA or IL-15 was linked to better overall survival ($P < 0.005$), while no survival difference was found in patients with glioma. Delta-24-RGDOX-IL15 infected and co-expressed OX40L and IL-15 effectively in mouse glioma and melanoma cells, and induced potent oncolysis. Delta-24-RGDOX-IL15-infected tumor cells significantly enhanced the oncolysis activity of GD2 CAR T cells in culture. Intratumoral injection of the virus also resulted in better tumor reduction and improved survival in C57BL6 mice with gliomas derived from mouse DMG cells while no significant toxicity was observed. Additionally, locoregional therapy with Delta-24-RGDOX-IL15 induced a systemic inflammatory response in the tumor microenvironment, characterized by increased frequency of T cells and reduced that of myeloid cells. **Conclusions:** Higher expression of IL-15/IL-15RA is associated with better survival in patients with melanoma. Delta-24-RGDOX-IL15 demonstrates potent oncolytic activity in both glioma and melanoma cell lines. In the intracranial brain tumor mouse model, it exhibited promising anti-tumor effects with enhanced T cell stimulation and minimal toxicity. Delta-24-RGDOX-IL15 is a promising candidate for combination with cellular therapies in both primary and metastatic brain tumors. Research Sponsor: ChadTough Defeat DIPG Foundation.

2049 **Poster Session**

A phase I clinical trial on combined (neo-)adjuvant intravenous plus intracranial administration of ipilimumab and nivolumab in recurrent glioblastoma (NEO-GLITIPNI). First Author: Iris Dirven, Department of Medical Oncology, Laboratory for Medical and Molecular Oncology (LMMO), Translational Oncology Research Center (TORC), Vrije Universiteit Brussel (VUB), Universitair Ziekenhuis Brussel (UZ Brussel), Brussels, Belgium

Background: Intravenous (IV) administration of ipilimumab (IPI) and nivolumab (NIVO) has shown limited activity in recurrent glioblastoma (rGBM). Intracerebral (iCer; within the brain tissue lining the resection cavity) and intracavitary (iCav; through an Ommaya reservoir) administration (admin) of IPI and NIVO was proven to be safe and resulted in promising survival outcomes (Duerinck et al. Neuro-Oncol 2024). Adding a neoadjuvant (NEOADJ) treatment phase to iCer/iCav IPI/NIVO may further improve outcome. **Methods:** In the Neo-Glitipni trial (NCT06097975), a single center, phase I clinical trial, patients (pts) with resectable rGBM (WHO grade 4, IDH wild type) who progressed after radiotherapy and temozolomide, with a baseline ECOG performance status of 0-2 and $\leq$8 mg methylprednisolone daily, received 2 NEOADJ cycles of IV IPI 1 mg/kg + NIVO 3 mg/kg followed by maximal safe resection (MSR) in week 5 with iCer admin of IPI 5 mg + NIVO 10 mg and iCav admin of IPI 1 mg + NIVO 10 mg. The adjuvant phase consists of biweekly postoperative iCav admin of IPI 1 mg + NIVO 10 mg and IV NIVO 240 mg for 12 cycles, followed by monthly NIVO 480 mg IV maintenance for up to two years. **Results:** 5 pts (4 male, median age 57 years (44-65); 1st recurrence in 3 pts) were enrolled. All pts received the 1st and 4 pts also the 2nd NEOADJ dose of IV IPI/NIVO. Out of the 5 pts, 3 were not amenable to MSR with iCer/iCav IPI/NIVO admin according to the protocol because of disease progression during the NEOADJ treatment phase and required corticosteroids (1 pt in week 2, 2 pts in week 4). Two pts successfully underwent MSR with iCer/iCav admin of IPI/NIVO per protocol. One pt initiated adjuvant treatment with iCav IPI/NIVO and IV NIVO. There were no unexpected adverse events (AE). Two pts experienced an immune-related AE that required corticosteroids and interruption of study treatment (grade 4 hepatitis in 1 pt, onset 8 days after MSR and grade 2 colitis in 1 pt, onset 28 days after MSR). One pt developed a thyroiditis during the NEOADJ treatment phase and 2 pts experienced a grade 3 treatment related AE that was not immune-related (seizure and Ommaya reservoir infection). None of the rGBM were characterized by a high tumor mutational burden on next generation sequencing. Gene expression profiling, and pharmacokinetic analysis of NIVO and IPI in the cerebrospinal fluid and blood are ongoing. After a median follow-up of 15 weeks (9-35w) all pts are alive, one pt remains free of progression (median progression free survival: 4.3 weeks). **Conclusions:** Four weeks of NEOADJ IV IPI/NIVO (comprising 2 admin) is safe, but symptomatic disease progression was observed in 3 out of 5 rGBM pts prior to the planned MSR with iCer/iCav IPI/NIVO admin in week 5. Therefore, the trial is being amended by shortening the NEOADJ treatment phase to 2 weeks (1 admin) and planned MSR with iCer/iCav IPI/NIVO admin in week 3. Clinical trial information: NCT06097975. Research Sponsor: None.

2050 **Poster Session**

Effect of 18F-DOPA-PET and advanced MRI on treatment response assessment in IDH1/2-mutant gliomas treated with IDH inhibitors. First Author: Diego Martín Prost, Hopital La Pitié Salpetriere, Paris, France

Background: Small-molecule inhibitors targeting IDH1/2-mutant proteins (IDHi) have shown promise as treatments for *IDH1/2*-mutant gliomas. However, accurate assessment of response using morphological magnetic resonance imaging (MRI) measurements remains difficult, and the potential of PET imaging with radiolabeled amino acids in this context is yet to be explored. Here, we investigated 3,4-Dihydroxy-6-[18F]-fluoro-L-phenylalanine PET (^{18}F-DOPA-PET) and MRI responses in *IDH1/2*-mutant glioma patients receiving IDHi. **Methods:** *IDH1/2*-mutant glioma patients receiving IDHi as part of trials or expanded access programs were included. Patients had pre- and post-treatment MRI and ^{18}F-DOPA-PET. Centralized evaluations included 2D/3D measurements on T2-weighted FLAIR images, T1-post contrast, perfusion, and diffusion imaging for MRI, and metabolic tumor volume (MTV), total lesion glycolysis (TLG), and tumor-to-background ratios (TBRs) for ^{18}F-DOPA-PET. Disease response evaluation using volumetric assessments, RANO 2.0 and PET RANO 1.0 criteria were compared and confronted to outcomes. **Results:** From 2021 to 2024, 10 patients with *IDH1/2*-mutant glioma (3 astrocytoma, 7 oligodendroglioma) receiving IDHi (4 ivosidenib, 6 vorasidenib) were analyzed. Significant reductions in ^{18}F-DOPA-PET parameters including TBRmean, TBRmax, and MTV were observed in 8/10 patients, aligning with observed changes in perfusion and diffusion imaging. Seven partial responses and one complete response were identified using ^{18}F-DOPA-PET, while both volumetric and standard 2D morphological MRI assessments indicated stable disease as best response. PET response was correlated with prolonged tumor control. **Conclusions:** This study highlights the potential of ^{18}F-DOPA-PET and advanced MRI sequences as valuable complements to standard RANO 2.0 MRI evaluations for assessing treatment response in glioma patients undergoing IDHi therapy. Research Sponsor: None.

2051 **Poster Session**

Phase I/II study of maintenance therapy with metformin and temozolomide for newly diagnosed glioblastoma. First Author: Yoshitaka Narita, Department of Neurosurgery and Neuro-Oncology, National Cancer Center Hospital, Tokyo, Japan

Background: Glioblastoma (GBM) is an aggressive primary brain tumor with poor prognosis. A potential strategy for overcoming therapeutic resistance involves the development of novel therapies that target cancer stem/initiating cells. Our previous research demonstrated that metformin (MF), an antidiabetic drug, induces the differentiation of stem-like glioma-initiating cells and suppresses tumor formation via AMPK-FOXO3 activation (Stem Cells Transl Med, 2012). We conducted a phase I/II study to evaluate the clinical efficacy of MF combined with standard maintenance temozolomide (TMZ). Our phase I findings indicated that MF at doses of up to 2,250 mg/day combined with maintenance TMZ was well tolerated (Cancers, 2022). Here, we present the complete results of the phase I/II study. **Methods:** Patients aged 20–74 years with supratentorial GBM, Karnofsky Performance Status $\geq$ 70, and a history of initial chemoradiotherapy with TMZ were eligible. During the phase II study, patients received MF monotherapy for 14 days, followed by six cycles of TMZ combined with daily MF (2,250 mg) for 365 days. The primary endpoint was the 1-year progression-free survival (PFS) rate from the initiation of chemoradiotherapy with TMZ (target; one-sided alpha 10%, power 70%, threshold 1-year PFS, 27%; expected 1-year PFS, 50%, based on the historical EORTC/NCIC study (Stupp et al, 2005)). **Results:** From 2021–2023, 22 patients were enrolled in 5 hospitals and 21 patients received TMZ combined with daily MF. The cohort included 12 men and nine women, with a median age of 50 years (32–69 years). According to the WHO 2016 classification, the initial histology revealed 18 IDH-wild-type and 3 IDH-mutant GBMs. The 1-year PFS was 47.6 % (90% CI; 29.2–64.0), achieving the primary endpoint. The 2-year overall survival rate was 54.5%. Grade $\geq$ 3 adverse events included lymphocytopenia (19%), thrombocytopenia (4.8%), appetite loss (4.8%), body weight loss (4.8%), nausea (4.8%), and seizures (4.8%). **Conclusions:** Maintenance therapy with 2,250 mg/day of MF combined with TMZ for newly diagnosed GBM is promising. A phase III study comparing MF combined with TMZ vs. TMZ alone for the treatment of GBM is planned. Clinical trial information: jRCTs031200326. Research Sponsor: Japan Agency for Medical Research and Development; AMED 21ck0106623h0002.

2052 **Poster Session**

Modification of the novel RANO clinical risk score for low- and middle-income countries without access to MGMT methylation testing. First Author: Imdat Eroglu, Gazi University School of Medicine, Department of Medical Oncology, Ankara, Yenimahalle, Turkey

Background: The RANO Resect Group developed a new risk score using simple variables, including age, Karnofsky performance scale (KPS), RANO resection class (RRC), and MGMT methylation (MGMTm), for patients with IDH-wildtype glioblastoma (GBM). Although this score is easy to apply and demonstrates high prognostic accuracy, routine testing for MGMTm remains inaccessible in many low- and middle-income countries. In this study, we aimed to modify the RANO risk score by excluding MGMTm. **Methods:** This is a single-center, retrospective analysis of IDH-wildtype GBM patients. We applied the same scoring system established by the RANO Resect Group, excluding MGMTm. The point (p) allocations were as follows: RRC1 = 0p, RRC2 = 1p, RRC3 = 2p, RRC4 = 5p; KPS $>$ 80 = 0p, KPS $<$ 80 = 3p; age $<$ 65 = 0p, and age $>$ 65 = 1p (age was not scored if RRC = 1p). The relationship between overall survival (OS) and the variables (age, KPS, and RRC) was evaluated using univariate and multivariate Cox regression analyses. Three risk classes were defined as numerical scores derived through ROC analysis. The primary endpoint was overall survival, and the secondary endpoint was progression-free survival (PFS). **Results:** A total of 119 patients were included in the study. Of these, 100 patients received chemoradiotherapy with temozolomide followed by adjuvant temozolomide (CRT-TMZ), while 13 received CRT only, 1 patient received temozolomide only, and 1 received radiotherapy only. Four patients were unable to undergo any treatment. RRC, age, and KPS classifications were all significantly associated with overall survival in both univariate and multivariate analyses ($p < 0.001$).Based on ROC curve analysis, three risk classes were identified: low risk (0–1 points, n:47, 39.5 %), intermediate risk (2–3 points, n:27, 22.7 %), and high risk ($\geq$4 points, n:45, 37.8 %). The median OS was 35.5 months (95% CI: 21.1–50) for the low-risk group, 16 months (95% CI: 9.9–22.1) for the intermediate-risk group, and 5 months (95% CI: 3.8–6.1) for the high-risk group ($p < 0.001$). Similarly, the median PFS was 16.3 months (95% CI: 12.3–20.2) for the low-risk group, 9.9 months (95% CI: 7.2–12.6) for the intermediate-risk group, and 4.1 months (95% CI: 3.4–4.8) for the high-risk group ($p < 0.001$). **Conclusions:** The modification of the novel RANO clinical risk score by omitting MGMTm remains highly prognostic for patients with IDH-wildtype GBM. Since it relies on very basic parameters and is easy to use, the modified RANO score can serve as a practical tool in countries where MGMTm testing is inaccessible. Research Sponsor: None.

2053 **Poster Session**

The impact of IDH mutation and 1p/19q codeletion on immune-checkpoint inhibitor efficacy in recurrent gliomas. First Author: Shameel Shafqat, Mayo Clinic Comprehensive Cancer Center, Rochester, MN

Background: Recurrent gliomas are highly aggressive brain tumors, often resistant to conventional treatments. Immune checkpoint inhibitors (ICI) have emerged as promising therapeutic agents by targeting tumor cells through immune modulation. However, clinical trials have demonstrated limited efficacy in recurrent gliomas. This study aimed to identify potential factors influencing treatment efficacy of ICIs in recurrent gliomas. **Methods:** This retrospective study, conducted across the Mayo Clinic following IRB approval, included patients $\geq$ 18 years diagnosed with adult-type diffuse gliomas. Eligible patients received treatment with at least 2 cycles of ICI for recurrent glioma between 2014 – 2024. Patients treated with ICIs as initial therapy were excluded. Clinical, radiographic, histological, and molecular data were analyzed, with missing information excluded. Responders to ICI were defined as patients who did not meet iRANO criteria for progressive disease based on first radiographic response assessment (and confirmatory follow up imaging as needed for possible pseudo-progression). Survival outcomes [Progression-Free Survival (PFS) and Overall Survival (OS)] and potential predictive variables were analyzed using the Kaplan-Meier method and Cox-Regression Analyses. **Results:** 67 patients met eligibility criteria (mean age: 45.1 $\pm$ 15.0 years; 64.2% male; 94% white). 64 (95.5%) patients received Pembrolizumab, 2 (3%) Nivolumab, and 1(1.5%) combined Ipilimumab/Nivolumab, with a median treatment duration of 2.77 (1.39 – 19.4) months. All had prior alkylating chemotherapy. The OS (from diagnosis) for IDH wildtype (IDH-WT, n = 36), IDH mutant, 1p/19q non-co-deleted (IDH-MUT, n = 17) and IDH mutant, 1p/19q co-deleted (OLIGO, n = 14) gliomas were 3.1, 9.2, and 18.6 years, respectively. The median PFS from time of ICI was 2.23 (0.69 – 27.3) months. 24 (36.9%) patients were identified as Responders. PFS was not significantly different between patients with IDH-MUT and IDH-WT gliomas (2.30 vs 2.07 months, p = 0.593). However, patients with OLIGO gliomas had a significantly higher PFS compared to IDH-WT gliomas (5.16 vs 2.07 months, p = 0.021). The proportion of responders was greatest in OLIGO gliomas, however, did not reach statistical significance (IDH-WT, 31.4%; IDH-MUT, 29.4%; OLIGO, 61.5%, p = 0.120). Overall PFS was not impacted by patient age, sex, and extent of initial resection. When analyses were limited to Responders, the PFS for IDH-WT, IDH-MUT and OLIGO gliomas were 5.75, 7.01 and 10.8 months, respectively (p = 0.434). **Conclusions:** Patients with recurrent OLIGO gliomas may have a longer PFS with ICI therapy compared with recurrent IDH-WT and IDH-MUT gliomas. However, there is significant variability in ICI treatment efficacy between patients. Further molecular profiling is in progress to evaluate additional predictive biomarkers of response. Research Sponsor: None.

2054 **Poster Session**

Factors influencing clinical trial enrollment in glioblastoma patients: A retrospective study at the University of Vermont Medical Center. First Author: Leena Ziane, Larner College of Medicine, Burlington, VT

Background: The standard of care for patients with glioblastoma (GBM) is a combination therapy of radiation and temozolomide. NCCN guidelines recommend clinical trials should be offered to glioblastoma patients when appropriate. This study aims to investigate the number of patients enrolled in clinical trials at the University of Vermont Medical Center (UVMMC) and/or referred to larger academic centers for trials. This study sought to identify and analyze characteristics of patients enrolled in trials at UVMMC and other outside academic centers. **Methods:** A retrospective review was undertaken of the electronic health records of ninety patients with GBM from 2021 to 2023 who were followed at UVMMC. Patient age, gender, and educational and employment status were collected. We assessed all comers who were offered a clinical trial, patients who proceeded to enroll in a clinical trial, and factors that influenced enrollment. We also assessed location where the trial was conducted (UVMMC vs Outside Center) and the trial interventions provided at the various centers. **Results:** We assessed 90 patients diagnosed with GBM at UVMMC from 2021-2023. 87% of all patients were offered the opportunity to enroll in a clinical trial. 17% of patients who were offered a trial successfully enrolled. Amongst enrolled patients, 62% completed their clinical trial at UVMMC while 38% were referred and treated at nearby academic centers in the New England Area including Mass General Hospital and Dana-Faber Cancer Institute (DFCI). Intrinsic barriers to enrollment included poor Karnofsky performance scale (KPS) scores, MGMT negative status, presence of leptomeningeal disease, and deep tumor locations precluding resection. Extrinsic factors included distance to academic centers, trial closure to accrual, and socioeconomic status. There was a correlation between socioeconomic status and trial enrollment. Of the thirty-eight patients identified with higher educational attainment (college or higher), 87% were offered a clinical trial and 18% eventually enrolled. Among the non-college educated group of thirty-six, 92% were offered a trial. However, only 14% enrolled. Further analysis on age, gender, and clinical trial intervention will be reported in future publications. **Conclusions:** Expanding access to clinical trials is critical to optimizing care for GBM patients. Our findings highlight access to academic centers is crucial to clinical trial enrollment. Further studies analyzing modifiable barriers to clinical trial accrual are needed. Research Sponsor: None.

2055 **Poster Session**

Safety and tolerability of olaparib, temozolomide, and pembrolizumab in a phase 2 trial in patients with progressive glioblastoma. First Author: Luis Nicolas Gonzalez Castro, Dana-Farber Cancer Institute, Boston, MA

Background: Glioblastoma is the most aggressive primary brain tumor of adults, with patients obtaining limited survival benefit from standard-of-care therapies. We are conducting a phase 2, surgical window-of-opportunity study evaluating the combination of pembrolizumab (anti-PD-1 immunotherapy), olaparib (PARP inhibitor), and temozolomide (alkylating chemotherapy) in patients with progressive glioblastoma. Olaparib and temozolomide have the potential of synergistically enhancing the tumor's susceptibility to immune checkpoint immunotherapy through DNA damage and activation of immune pathways, potentially amplifying the efficacy of pembrolizumab. We provide a preliminary report on the safety and tolerability of the olaparib, temozolomide, and pembrolizumab combination. **Methods:** We enrolled patients with radiographically progressive glioblastoma, IDH-wildtype, MGMT promoter unmethylated, on 2mg daily or less of dexamethasone. Patients participating in the safety lead-in (Cohort 1) did not require surgically-resectable disease, while those enrolled in the surgical arm (Cohort 2) did. Treatment is provided in consecutive 42-day cycles with olaparib 200mg BID and temozolomide 50mg QD given on days 1-7 and 22-29, and pembrolizumab 400mg IV given on day 1. Adverse events (AEs), dose-limiting toxicities (DLTs), and high-frequency toxicities ($\geq$50% occurrence) were assessed, along with dose modifications or delays required to manage treatment-related toxicities. AEs were graded according to CTCAE v5.0 criteria, with pre-specified measures to address reversible toxicities through dose adjustments. **Results:** Six patients were enrolled in the safety lead-in (Cohort 1), which followed a 3+3 design. Grade 1–2 leukopenia, lymphopenia, and neutropenia were observed in 3 patients and resolved without intervention. Grade 4 neutropenia was observed in two patients (starting in cycle 2 for one patient, and on cycle 5 for the other). This resolved with dose delays, reduction in temozolomide dose or discontinuation of temozolomide (1 patient). In Cohort 2, which is ongoing (25 patients currently enrolled), toxicity profiles remain consistent with those observed in Cohort 1 patients. Grade 4 neutropenia has been observed in 1 (6%) of the enrolled patients, improving with dose delays and temozolomide dose reduction. **Conclusions:** The combination of olaparib, temozolomide, and pembrolizumab demonstrates a tolerable safety profile in patients with progressive glioblastoma. Observed hematologic toxicities are reversible with appropriate management, supporting the ongoing evaluation of this regimen to assess its efficacy and therapeutic potential. Clinical trial information: NCT05463848. Research Sponsor: Merck & Co.

2057 **Poster Session**

Efficacy and safety of bevacizumab in combination with radiotherapy and temozolomide in patients with glioblastoma: A meta-analysis and meta-regression of randomized controlled trials. First Author: Ibrahim Khalil, Dhaka Medical College & Hospital, Dhaka, Bangladesh

Background: Glioblastoma (GBM), the most common primary brain tumor in adults, has a poor prognosis despite standard treatment. This meta-analysis evaluates the efficacy and safety of Bevacizumab, a VEGF inhibitor, when combined with radiotherapy and Temozolomide in terms of progression-free survival (PFS), overall survival (OS), and treatment-related adverse events. **Methods:** A systematic search of PubMed, Cochrane Library, Embase, and ClinicalTrials.gov identified randomized controlled trials (RCTs) evaluating Bevacizumab with radiotherapy and Temozolomide. Ten RCTs involving 4,425 patients (2,249 in the Bevacizumab arm and 2,176 in the control arm) met the inclusion criteria. A random-effects model calculated mean differences (MD) for continuous outcomes and risk ratios (RR) for dichotomous outcomes with 95% confidence intervals (CI). **Results:** Bevacizumab significantly improved PFS by a mean difference of 2.39 months (95% CI: 1.34 to 3.44; P = 0.0005), but no significant benefit was observed in OS (MD: 0.46 months, 95% CI: -0.53 to 1.45; P = 0.318). The therapy increased the risk of vascular adverse events (RR: 1.52, 95% CI: 1.10 to 2.11; P = 0.023). While trends towards increased hematologic adverse events (RR: 1.24, 95% CI: 0.95 to 1.60; P = 0.093) and hypertensive events (RR: 2.17, 95% CI: 0.91 to 5.16; P = 0.066) were observed, they did not reach statistical significance. Other adverse events, including serious adverse events (RR: 1.21, 95% CI: 0.84 to 1.76; P = 0.221), grade 3-4 thrombocytopenia (RR: 1.05, 95% CI: 0.44 to 2.52; P = 0.858), visceral perforation (RR: 1.92, 95% CI: 0.54 to 6.90; P = 0.202), and thromboembolic incidents (RR: 1.32, 95% CI: 0.88 to 2.00; P = 0.120), showed no significant increase. Meta-regression analysis indicated that study-level covariates, including patient age, sex distribution, and histologic differences did not significantly influence the primary outcomes. However, MGMT methylation status demonstrated borderline significance (P $<$ 0.1), suggesting potential prognostic relevance. **Conclusions:** Bevacizumab modestly improves PFS but not OS, with an increased risk of vascular toxicities. Personalized treatment strategies and further research are essential to optimize its role in glioblastoma management. Research Sponsor: None.

Adverse event outcomes associated with bevacizumab in glioblastoma patients.

Adverse Event Outcomes	RR	95%CI	P value
Any Adverse events	1.18	[0.64,2.16]	0.364
Hematologic adverse events	1.24	[0.95,1.60]	0.093
Any serious adverse events	1.21	[0.84,1.76]	0.221
Any vascular adverse events	1.52	[1.10,2.11]	0.023
Any grade 3-4 thrombocytopenia	1.05	[0.44,2.52]	0.858
Visceral perforation	1.92	[0.54,6.90]	0.202
Any arterial or venous thromboembolic incidents	1.32	[0.88,2.00]	0.120
Any hypertensive events	2.17	[0.91,5.16]	0.066

2058 **Poster Session**

Assessment of age in the clinical risk stratification of patients with IDH-mutant gliomas. First Author: Michal Nisnboym Ziv, Duke University Medical Center, Durham, NC

Background: Prognosis for mutant isocitrate dehydrogenase (mIDH) gliomas is influenced by tumor type, size, neurologic deficits, and age. Traditionally, patients over 45 are considered high-risk, prompting consideration of early chemoradiation. Recent promising results with the mIDH inhibitor vorasidenib challenge traditional age-based risk stratification, sparking debate over its role in treatment decisions. We evaluated survival relative to age and molecular data obtained from next-generation sequencing (NGS). **Methods:** Tumor specimens from 598 mIDH gliomas were analyzed using NGS and WTS at Caris Life Sciences (Phoenix, AZ). Samples were stratified by age at diagnosis into four groups: 12-26y, 27-40y, 41-60y, and $>$ 60y. Real-world overall survival (calculated from initial diagnosis to last contact) was obtained from insurance claims data and analyzed using Kaplan-Meier and Cox proportional hazards models. Covariates in the multivariate regression analysis included radiation treatment, temozolomide treatment, and mutation status of different biomarkers. **Results:** In mIDH astrocytoma group, age distribution was 12-26y, n = 74 (12.4%); 27-40y, n = 271 (45.3%); 41-60y, n = 205 (34.3%); and $>$ 60y, n = 48 (8.0%). In mIDH oligodendroglioma group, age distribution was 12-26y, n = 18 (5.5%); 27-40y, n = 76 (23.2%); 41-60y, n = 137 (41.8%); and $>$ 60y, n = 57 (17.4%). For each subtype, comparisons in survival were made between patients 27-40y vs. 41-60y given larger sample size, and patients with temozolomide treatment before biopsy were excluded (about 10%). Univariate analysis showed that 27-40y patients had shorter survival in astrocytoma (HR = 1.63, 95% CI: 1.07 – 2.50, p = 0.022). However, after adjusting for confounding factors in multivariate analysis, age was not associated with survival. In contrast, TP53 (HR = 4.0, 95% CI: 1.43-11.24, p = 0.008 – mutation rate = 95.4%) and TERT-promoter (HR = 10.36, 95% CI: 4.05-26.45, p $<$ 0.0001 – mutation rate = 9.0%) mutations were independently associated with poorer survival in astrocytoma patients. Univariate analysis showed that age was not associated with survival in oligodendroglioma (HR = 1.07, 95% CI: 0.79-3.65, p = 0.168). KRAS mutations were independently associated with poorer survival in oligodendroglioma patients (HR = 4.36, 95% CI: 1.12-16.92, p = 0.033 - mutation rate = 3%). **Conclusions:** In this enriched dataset of mIDH low grade glioma patients, which included NGS, age did not contribute to survival differences when comparing patients between 27-40 years with those aged 41-60 years. Rather, selected genetic alterations such as KRAS for oligodendroglioma and TP53 and TERT mutations for astrocytoma were associated with poorer survival. The results suggest that NGS, rather than age, may drive prognosis for mIDH glioma patients. Research Sponsor: None.

2059 **Poster Session**

The tumoral molecular landscape of long-term survivors with isocitrate dehydrogenase wildtype glioblastoma: Lessons from ETERNITY (EORTC 1419). First Author: Michael Weller, Department of Neurology, University Hospital Zurich, and Brain Tumor Centre, University Hospital and University of Zurich, University Hospital Zurich, Zurich, Switzerland

Background: Predictors of long-term survival in patients with isocitrate dehydrogenase (IDH)-wildtype glioblastoma remain incompletely understood. ETERNITY (EORTC 1419) is the largest registry study of glioblastoma patients surviving for 5 years or more worldwide. **Methods:** Here we characterized the DNA methylation and mutational landscapes of 142 tumors from ETERNITY patients and compared the findings with different reference cohorts. **Results:** The majority of tumors of the ETERNITY cohort showed molecular profiles corresponding to established methylation subclasses of IDH-wildtype glioblastoma. ETERNITY tumors were enriched for the mesenchymal subclass, depleted of the receptor tyrosine kinase 1 subclass, and showed a high frequency of *MGMT* promoter methylation. While large chromosomal alterations were remarkably similar in all cohorts, circumscribed homozygous deletions on chromosome 10q including the *MGMT* gene were enriched in ETERNITY tumors. Gene panel sequencing showed similar types and frequencies of gene alterations as in the reference cohorts with a trend towards more frequent *RB1* mutations. Deconvolution analyses of global DNA methylation data revealed fewer monocytes in the MES methylation class in ETERNITY compared with the reference cohort. ETERNITY tumors from patients without documented relapse showed no specific molecular profile. Small subgroups of tumors corresponded to rare incompletely defined tumor entities. **Conclusions:** The present study illustrates the profound association of *MGMT* gene alterations with outcome, but also suggests as yet unidentified clinical or molecular pathways and potential host-dependent features in long-term survival with glioblastoma. Clinical trial information: NCT03770468. Research Sponsor: Brain Tumor Funders' Collaborative Consortium.

2060 **Poster Session**

Efficacy and safety of depatuxizumab mafodotin (ABT-414) in EGFR-amplified glioblastoma: A systematic review and Bayesian network meta-analysis. First Author: Sunjida Amin Promi, Chittagong Medical College Hospital, Chittagong, Bangladesh

Background: Glioblastoma (GBM) is a highly aggressive brain tumor with a poor prognosis, typically resulting in a median survival of 12–15 months. Epidermal growth factor receptor (EGFR) alterations, present in half of GBM cases, are key therapeutic targets. Depatuxizumab mafodotin (Depatux-M, ABT-414), an EGFR-targeting antibody-drug conjugate, represents a novel therapeutic option. This Bayesian network meta-analysis assessed the efficacy and safety of Depatux-M in EGFR-amplified GBM. **Methods:** Eight randomized controlled trials (RCTs) involving 1,183 patients were analyzed. Trials evaluating Depatux-M as monotherapy or combined with temozolomide (TMZ) and/or radiotherapy (RT) were included. Outcomes included overall survival (OS), progression-free survival (PFS), and safety (grade 3/4 adverse events and keratitis). Bayesian models estimated mean differences (MDs) and relative risks (RRs) with 95% credible intervals (CrI), while SUCRA values ranked treatments. **Results:** Depatux-M plus TMZ showed modest OS improvement over TMZ alone (MD: 0.91 months; 95% CrI: -11.83 to 13.86; SUCRA: 62.09%). Depatux-M monotherapy showed minimal OS benefit (MD: 0.07 months; 95% CrI: -12.69 to 12.95; SUCRA: 51.2%), and the combination of Depatux-M, TMZ, and RT had the lowest OS benefit (MD: -2.17 months; 95% CrI: -19.83 to 15.74; SUCRA: 35.48%). For PFS, Depatux-M monotherapy performed best (MD: 1.46 months; 95% CrI: -4.92 to 7.78; SUCRA: 81.00%), while Depatux-M plus TMZ (MD: -0.45 months; 95% CrI: -6.85 to 5.89; SUCRA: 40.03%) and Depatux-M, TMZ, and RT (MD: -1.54 months; 95% CrI: -10.34 to 7.24; SUCRA: 28.32%) were less effective. Depatux-M monotherapy had a lower RR for grade 3/4 adverse events (RR: 1.38; 95% CrI: 0.23 to 8.07) and keratitis (RR: 2.62; 95% CrI: 0.43 to 15.63) compared to combination regimens, with the highest keratitis risks observed in Depatux-M, TMZ, and RT. **Conclusions:** Depatuxizumab mafodotin offers limited survival benefits in EGFR-amplified GBM, with monotherapy showing the most favorable PFS. However, significant safety concerns, particularly keratitis, warrant further research to optimize its therapeutic potential and identify more tolerable regimens. Research Sponsor: None.

Efficacy and safety outcomes of depatuxizumab mafodotin in EGFR-amplified glioblastoma.

Regimen	Overall Survival (OS)	Progression-Free Survival (PFS)	Grade 3/4 Adverse Events (RR)	Keratitis (RR)
Depatux-M + TMZ	0.91 (-11.83 to 13.86); SUCRA 62.09	-0.45 (-6.85 to 5.89); SUCRA 40.03	1.54 (0.20 to 13.53); SUCRA 41.75	4.40 (0.51 to 31.10); SUCRA 33.07
Depatux-M	0.07 (-12.69 to 12.95); SUCRA 51.20	1.46 (-4.92 to 7.78); SUCRA 81.00	1.38 (0.23 to 8.07); SUCRA 49.06	2.62 (0.43 to 15.63); SUCRA 62.34
Depatux-M + TMZ + RT	-2.17 (-19.83 to 15.74); SUCRA 35.48	-1.54 (-10.34 to 7.24); SUCRA 28.32	0.98 (0.09 to 9.65); SUCRA 68.37	6.63 (0.62 to 66.40); SUCRA 12.73

ABSTRACT WITHDRAWN

2062 Poster Session

Relationship between aperiodic dynamics and transcriptomic alterations and a neural signature of glioma-induced excitation-inhibition dysregulation. First Author: Youssef Sibih, University of California, San Francisco, San Francisco, CA

Background: Diffuse gliomas disrupt neuronal dynamics, leading to excitation-inhibition (E/I) imbalance and associated functional impairments. The aperiodic component of the power spectral density (1/f slope) has emerged as a proxy for estimating E/I balance, offering a novel framework for understanding glioma-induced neural dysregulation. This study is the first to validate the relationship between 1/f slope and E/I dysregulation in glioma by integrating electrophysiological, genomic, and behavioral data. **Methods:** Resting-state intraoperative subdural electrocorticography (ECoG) data were recorded from 13 glioma patients. Power spectral analysis at a frequency of 70–150Hz (high-gamma) computed 1/f slopes, and electrodes were classified as glioma-infiltrated or normal-appearing based on preoperative MRI T2-FLAIR. Linear mixed-effects models assessed E/I balance across tissue and glioma subtypes. Single-nucleus RNA sequencing (snRNA-seq) was performed on 14 spatially annotated glioma tissue samples from regions classified as inhibitory or excitatory by 1/f slope. Behavioral analysis of language tasks examined functional correlates of E/I imbalance. **Results:** The cohort included 23.0% WHO grade 2 IDH-mutant oligodendrogliomas, 38.5% WHO grade 2-3 IDH-mutant astrocytoma, and 38.5% glioblastoma (GBM). Glioma-infiltrated electrodes (n=142) exhibited significantly lower 1/f slopes than normal-appearing electrodes (n=518;$p < 0.0001$), reflecting an excitation-dominant state. Subtype analysis revealed hierarchical E/I imbalance, with GBM showing the steepest reductions in 1/f slope compared to astrocytoma and oligodendroglioma (glioma-infiltrated: $p<0.0001$; normal-appearing: GBM vs. oligodendroglioma, p=0.012; GBM vs. astrocytoma, p=0.019). SnRNA-seq revealed elevated excitatory and reduced inhibitory signaling gene expression in glutamatergic and GABAergic neuronal populations across glioma-infiltrated (n=12; n=4 per subtype) and normal cortex (n=2) samples. Excitatory module scores were significantly higher in excitatory 1/f samples compared to inhibitory 1/f samples, validating the 1/f slope as a genomic correlate of E/I imbalance in human cortical tissue. Behavioral analysis of language tasks demonstrated error-related reductions in 1/f slope ($e > i$), emphasizing the functional impact of glioma-induced dysregulation. **Conclusions:** Diffuse gliomas are associated with a profound shift toward excitation dominance in both glioma-infiltrated and normal-appearing cortex. For the first time, the 1/f slope is validated as a robust measure of E/I imbalance through electrophysiological, genomic, and behavioral analyses. These findings position the 1/f slope as a physiologically relevant biomarker of glioma-induced neural dysregulation, offering significant potential to inform therapeutic strategies. Research Sponsor: None.

2063 Poster Session

Comparing ERK signaling and tumor microenvironment in BRAF-altered gliomas. First Author: Lucy Chen, Johns Hopkins School of Medicine, Baltimore, MD

Background: Many patients with BRAF-altered glioma (V600E mutations, fusions) respond to BRAF inhibitors (BRAFi), but some—particularly those with high-grade gliomas (HGG)—progress on treatment. Here, we aim to assess MAPK/ERK activation associated with various BRAF alterations in a large dataset of adult and pediatric patients with low-grade (LGG) and HGG using previously validated transcriptomic signatures. **Methods:** Samples underwent next-generation sequencing and whole transcriptome sequencing at Caris Life Sciences (Phoenix, AZ). The MAPK Pathway Activity Score (MPAS, Wagle 2018, NPJPO) and two MEK inhibitor sensitivity signatures (Dry 2019, Cancer Res & Pratilas 2009, PNAS) were calculated from RNA-seq data. Tumor immune microenvironment was assessed using immune deconvolution (quanTIseq) and the Tumor Inflammation Signature (TIS). Results were compared for HGG in two age groups (AYA: 0-39y; adult: $>$ 39y) in V600E mutation, fusions, or controls (BRAF-WT/IDH-WT/NF1-WT). For LGG 0-39y, V600E were compared to fusion, but not to BRAF-WT due to near-universal enrichment of MAPK alterations in LGG. There were insufficient LGG $>$ 39y for analysis. Mann-Whiney U tests were used at $\alpha = 0.05$. **Results:** In adult HGG (V600E: n = 35, fusions: n = 11, WT: n = 3235), both V600E and fusions showed significantly higher MAPK/ERK signatures than WT (all $p < 0.01$), with no significant difference between V600E and fusions. In AYA HGG (V600E: n = 32, fusions: n = 11, WT: n = 235), all three MAPK/ERK signatures were significantly higher in V600E compared to WT (all $p < 0.01$), while fusions fell in between BRAF V600E and WT ($p > 0.05$). In both AYA and adult HGG, B cells were higher in WT compared to V600E, while among infiltrated cells only M1 and M2 macrophages were elevated in fusions compared to WT ($p < 0.05$). Comparison of MAPK/ERK signatures in LGG (V600E: n = 28, fusions: n = 54) revealed no significant difference between V600E and fusions. TIS did not differ among BRAF alterations in any groups. Pathway analysis revealed RAS signaling and inflammation were enriched in BRAF V600E compared to WT in both HGG and LGG (NES $>$ 2; FDR $<$ 0.005), regardless of age. When comparing all V600E HGG patients (0-90y) previously treated with BRAFi (n = 21) to those who were not (n = 46), no difference in MAPK/ERK signatures were seen. Pathway analysis revealed samples with prior BRAFi had upregulated complement activation, B-cell activation, and opsonization (NES $>$ 3.5; FDR $<$ 10e-5), while treatment-naïve samples had higher BRAF/MAPK signaling (NES $>$ 2, FDR $<$ 0.03). **Conclusions:** These data confirm higher MAPK/ERK dependence signatures and RAS signaling in BRAF-altered HGG (V600E, fusion) compared to BRAF-WT controls. Differences in immune cell infiltration were observed between BRAF alteration classes. Changes in humoral immunity may be correlated with acquired resistance to BRAFi, in line with previous reports of increased B-cell infiltration in BRAFi-resistant melanomas. Research Sponsor: None.

2064 Poster Session

Phase II propensity-matched controlled trial evaluating metformin as an adjunct to neo-adjuvant, concomitant, and adjuvant temozolomide and hypofractionated-accelerated radiotherapy (M-HART) in glioblastoma patients (NCT02780024). First Author: George Shenouda, McGill University Health Centre, Montréal, QC, Canada

Background: Phase II, propensity-matched trial, to assess feasibility and toxicity of adding Metformin (MTF) to neo-adjuvant, concomitant and adjuvant Temozolomide (TMZ) and hypofractionated accelerated radiotherapy (M-HART), for patients with Glioblastoma (GBM). We compared median survival time (MST), and progression-free-survival (PFS) of M-HART versus a contemporaneous cohort of propensity-score matched controls (PSMC) who received standard of care (SOC). **Methods:** Eligible patients were $\geq$ 18 years with newly diagnosed GBM, ECOG score $\leq$ 2, with known MGMT status, gross total or partial resection, and residual surgical cavity $>$ 15 mm from brainstem, or optic apparatus. Four weeks from surgery, M-HART patients started 2 weeks of neo-adjuvant MTF/TMZ followed by concomitant MTF/TMZ + HART 60 Gy/20 daily fractions, and 6 cycles of adjuvant MTF/TMZ. The PSMC patients received Stupp's regimen. We used a nearest neighbor matching with a caliper width of 0.2 SD and compared patients' characteristics using chi-square test (Table). Propensity scores were estimated using logistic regression model, with probability of M-HART treatment as dependent variable. **Results:** From April 2015 to November 2020, 50 patients participated in the M-HART trial and matched with 50 PSMC cohort treated during the same period, with a median follow up of 24.1 (M-HART) vs 17.6 months PSMC, respectively. M-HART patients had significantly longer MST of 24.1 (95% CI, 15.2- 30.3) vs. 17.7 months for PSMC patients (95% CI, 12-20) (HR, 0.62 [95% CI, 0.40-0.93]; P = 0.02), and significantly longer PFS of 13.7 (95% CI, 11.7 to 18.8) vs. 11.0 months (95% CI, 9-12) (HR, 0.63 [95% CI, 0.42-0.95]; P = 0.02). M-HART treatment was an independent predictor of survival. M-HART patients with methylated-MGMT and gross total resection had significant longer MST of 41.9 vs. 17.8 months for PSMC (95% CI, 15.1-20.5 months) (HR 0.21 [95% CI, 0.09-0.49]; P = 0.001). **Conclusions:** M-HART protocol is novel, feasible, and well-tolerated approach with significantly longer MST and PFS as compared to propensity-matched SOC controls. These results add to growing evidence for the use of Metformin as an adjunct to HART and TMZ especially in M-MGMT GBM. Clinical trial information: NCT02780024. Research Sponsor: No funding was received.

Characteristics of M-HART versus propensity-matched standard of care control patients.

	M-HART N=50 (%)	CONTROLS N=50 (%)	P-value
Age (years)			
≤ 60	34 (68)	27 (54)	0.218
> 60	16 (32)	23 (46)	
Sex			
Male	22 (44)	30 (60)	0.161
Female	28 (56)	20 (40)	
ECOG-score			
0-1	43 (84)	47 (94)	0.318
2	7 (14)	3 (6)	
Surgery			
Gross Total	41 (82)	39 (78)	0.803
Subtotal	9 (18)	11 (22)	
MGMT status			
Unmethylated	34 (68)	29 (58)	0.015
Methylated	16 (32)	21 (42)	
Re-operation			
Yes	24 (84)	18 (36)	0.077
No	26 (52)	32 (64)	
Chemotherapy at recurrence			
Yes	14 (28)	27 (54)	<0.001
No	36 (74)	23 (46)	

2065 Poster Session

Association of MGMT status with survival in low and high-grade IDH-mutant astrocytomas. First Author: Katherine E. Schwetye, Washington University, St. Louis, MO

Background: The role of MGMT promoter methylation status on survival for IDH-mutant astrocytomas is less known than for glioblastoma, IDH-wildtype (GBM). Further, different laboratories utilize a variety of techniques to measure methylation of the MGMT gene promoter region, including pyrosequencing, methylation-specific polymerase chain reaction (PCR), and direct Sanger sequencing; these techniques are limited by low quantitative accuracy, short read length, and low sample throughput. In the current study, we used a large database of next-generation sequencing (NGS) and whole-transcriptome sequencing (WTS) performed in a single laboratory to determine the role of MGMT status on survival in IDH-mutant astrocytomas (CNS WHO grades 2-3 and 4), as well as in GBM. **Methods:** 10,181 glioma samples were analyzed by NGS (592, NextSeq, or WES, NovaSeq) and WTS (NovaSeq) at Caris Life Sciences (Phoenix, AZ), including determination of methylation status of the MGMT promoter region by pyrosequencing. Real-world overall survival was obtained from insurance claims data and calculated from initial diagnosis to last contact, while TMZ-OS was calculated from first dose of temozolomide to last of treatment. Hazard ratios (HRs) were analyzed using Cox proportional hazards model and p values (log-rank test). Multivariate regression analysis was performed on age, gender, radiation treatment, temozolomide treatment, and mutations in different biomarkers. Fisher's exact tests was used at a significance level of 0.05. **Results:** 693 IDH-mutant astrocytomas CNS WHO grades 2 or 3 ("g2/3"), 251 IDH-mutant astrocytoma CNS WHO grade 4 ("g4"), and 4469 glioblastoma ("GBM") met inclusion criteria. Univariate and multivariate survival analysis showed that MGMT promoter methylation (mMGMT vs. unmethylated, uMGMT) was associated with improved OS only in GBM (HR = 0.62, 95% CI: 0.57 – 0.67, $p < 0.0001$), but not in astrocytoma-g2/3 and g4. Similarly, TMZ-OS was only significantly longer in mMGMT vs. uMGMT in GBM (HR = 0.53, 95% CI: 0.48 – 0.58, $p < 0.0001$). In astrocytoma-g2/3, ATRX mutation was more prevalent in mMGMT than uMGMT (73.9% vs. 62.6%, $p < 0.05$), and SETD2 was more prevalent in uMGMT than mMGMT (4% vs. 1.1%, $p < 0.05$). Tumor mutational burden (TMB)-high was more prevalent in mMGMT than uMGMT in astrocytoma-g4 (14.8% vs. 2.7%, $p < 0.05$) and in GBM (5.4% vs. 1.9%, $p < 0.0001$). In GBM, many genes had different mutational rates between mMGMT and uMGMT groups, including MSH6 (2% vs. 0.7%, $p < 0.001$), ATRX (3.1% vs. 1.6%, $p < 0.01$), and CDKN2A (4.3% vs. 2.5%, $p < 0.01$). **Conclusions:** mMGMT was not associated with better survival in IDH-mutant astrocytoma-g2/3 or g4with respect to OS or TMZ-OS, whereas mMGMT conferred improved survival in GBM. These results, derived from a large database using same platform (next-generation sequencing at a single laboratory), support similar findings from recent, smaller cohort studies. Research Sponsor: None.

2066 Poster Session

Prognostic impact of DDR mutations (mt) in IDH mutant high-grade gliomas (HGG). First Author: John L. Villano, University of Kentucky Markey Cancer Center, Lexington, KY

Background: The oncometabolite 2-hydroxyglutarate (2HG) produced by *IDH1/2* mt in HGG has profound effects on numerous pathways including DNA damage repair (DDR). We investigated the prognostic effect of DDR mt in *IDH* mutant vs. wild type (wt) tumors in a large cohort using a real-world database. **Methods:** A total of 4894 HGG tumors tested at Caris Life Sciences (Phoenix, AZ) with NextGen sequencing of DNA (592-gene panel or whole exome sequencing) were included in the study. DDR alteration was defined as a pathogenic mutation in one of $>$ 20 DDR genes. Patient survival was obtained by insurance claims data and calculated from the initiation of tissue collection (rwOS). Cox proportional hazards model was used to calculate hazard ratios (HR) and log-rank tests to calculate p values, which were adjusted for multiple comparisons. Significance was set at $p<0.05$. **Results:** In the 1121 HGG carrying either *IDH1* or 2 mutations, 100 carried a DDR mutation (8.9%) . When comparing DDR mutant (mt) vs. wild type (wt), no difference was seen in patient age (median 39 vs. 38 yrs; p = 0.8); gender (female 45% vs. 42%, p = 0.9), race or ethnicity ($p > 0.1$). The most frequent mutations were seen in *MSH6* (24% of the DDR mt), *ATM* (18%), *MLH1* (15%), *MSH2* (13%), *MSH3* (10%) and *BRCA2* (10%). When comparing the rwOS of DDR mt vs. wt, a significantly shorter survival was seen (24m vs. 51m, HR = 1.87, 95% CI [1.41-2.48], $p < 0.001$); the effect persisted in the subset of tumors collected prior to temozolomide treatment (26m vs. 64m, HR = 1.92 [1.35-2.74], $p < 0.001$). In contrast, in IDH wt tumors, patients with (N = 223) or without DDR mutation (N = 3550) showed similar survival (17.5m vs. 20.6m, p = 0.1). In the *IDH* mutant cohort, DDR mt was associated with an increased tumor mutational burden (TMB) compared to DDR wt tumors (median = 6 vs. 4 mutations/mb, by Wilcoxon). Multivariate analysis within the IDH mutant tumors indicated that both TMB and DDR status were independently associated with poorer rwOS, with TMB showing an adjusted HR of 1.01 per unit increase (p = 0.005) and DDR status with an adjusted HR of 1.59 (p = 0.028). **Conclusions:** In a large real-world database, we demonstrate IDH mt HGG with a DDR mutation exhibit significantly poorer survival compared to DDR wt. This is not seen in IDH wt, where survivals of the two groups are similar. These results stand in sharp contrast to reported prognostic effect of DDR mutation in many other solid tumors. The data suggest that DDR mutations in the context of 2HG accumulation in IDH mt HGG may be an indicator of profound genomic instability that confers severe negative impact on patient survival. Clinicians managing high-grade gliomas should consider the presence of DDR mutations in IDH mutant patients as a poor prognostic category in this overall favorable prognostic group and consider therapeutic approaches accordingly. Research Sponsor: None.

2067 Poster Session

Prognostic value of inflammatory markers in glioblastoma: A meta-analysis of NLR and PLR stratified by cutoff values. First Author: Abril Carrillo, UT Southwestern Medical Center, Dallas, TX

Background: Glioblastoma (GBM) is the most aggressive primary brain tumor in adults, with an unfavorable prognosis. Identifying prognostic markers is crucial to stratify patients and tailor therapeutic approaches. The neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) are inflammatory markers that have gained attention as outcome predictors in various cancers. While numerous studies have demonstrated associations between elevated NLR, PLR, and poor GBM outcomes, consensus on standardized cutoff values remains elusive, limiting their clinical application. In this meta-analysis, we stratified the data based on preoperative NLR and PLR cutoff values, aiming to identify the most accurate cutoff thresholds to predict overall survival (OS) outcomes. **Methods:** We performed a systematic search on PubMed, Medline, OVID, Embase, and Cochrane in November 2024 to identify cohort studies reporting hazard ratios (HR) for OS associated with preoperative NLR and/or PLR in patients with histopathologically confirmed GBM. Two reviewers screened articles; discrepancies were resolved by consensus. Data analysis was conducted using a random-effects model. Pooled HRs with 95% confidence intervals (CI) were calculated and subgroup analysis were performed. **Results:** From 227 studies initially identified, 22 studies met our inclusion criteria, encompassing a total population of 3,423 patients with GBM. In our general cohort, when compared to lower PLR, a higher PLR yielded a pooled HR of 1.30 (95% CI: 1.12-1.50, $p < 0.001$). Specific cutoff subgroup analysis revealed that, the $<$ 135 cutoff group had a HR of 1.09 (95% CI: 0.62-1.93, p = 0.60), in the $>$ 135 cutoff group, the HR was 1.42 (95% CI: 1.19-1.70, p = 0.0001). Regarding the NLR analysis, cutoff subgroup analysis showed that for NLR with a cutoff of $<$ 3, the HR was 1.39 (95% CI: 0.96–2.02, p = 0.08), for NLR with a cutoff between 3 and 4.9, the HR was 1.56 (95% CI: 0.98–2.51, p = 0.06). For studies with a NLR cutoff of 4, the HR was 1.40 (95% CI: 1.23–1.58, p = 0.01). For studies with a NLR cutoff $>$ 4.9, the HR was 1.85 (95% CI: 1.37–2.50, $p < 0.0001$). The overall pooled HR for elevated NLR regardless of cutoff value was 1.40 (95% CI: 1.23–1.58, $p < 0.00001$). **Conclusions:** Elevated preoperative NLR and PLR are significant prognostic markers for worse OS in GBM patients. Stratifying data by cutoff values revealed that PLR $>$ 135 and NLR $>$ 4.9 were more consistently correlated with poor survival outcomes. These findings suggest that higher cutoff values for these markers may better predict OS, particularly for NLR where values $>$ 4.9 demonstrated a stronger association than the commonly used cutoff of 4. The results highlight the potential utility of NLR and PLR as accessible, cost-effective prognostic tools. Future prospective studies are warranted to validate these findings, refine optimal cutoff thresholds, and explore their applicability. Research Sponsor: None.

2068 Poster Session

A phase 1, first-in-human study of regorafenib plus temozolomide with or without radiotherapy in patients with newly diagnosed MGMT methylated, IDHwt glioblastoma: The REGOMA-2 trial. First Author: Marta Padovan, University of Padua, Padua, Italy

Background: Regorafenib (REG) is an oral multikinase inhibitor and in vivo studies demonstrated a synergistic antitumor effect when combined with radiotherapy (RT) and temozolomide (TMZ) against glioblastoma (GBM). We conducted a phase 1 study to evaluate the safety, dose limiting toxicity (DLT), maximum tolerated dose (MTD) of REG, pharmacokinetics (PK), preliminary activity of this combination. **Methods:** This phase 1 multicenter academic study used a "3 + 3" design to evaluate REG doses of 80mg (Level 1), 120mg (Level 2), 160mg (Level 3) in 2 different cohorts of pts with histologic diagnosis of MGMT-methylated, IDHwt GBM (WHO 2021) and ECOG PS 0-1. In cohort A, pts who completed the concurrent chemoradiotherapy (CT-RT) regimen received REG in combination with standard maintenance TMZ; cohort B received REG concurrently with standard CT-RT and continued REG with maintenance TMZ. REG was administered according to the standard schedule of 3 weeks on/1 week off. The DLT evaluation period for cohort A was during the first two maintenance cycles and for cohort B during the concurrent CT-RT phase. During the DLT period, blood and clinical assessments were performed weekly. Toxicity was assessed by CTCAE v 5.0. RANO criteria were used for neuroradiologic assessment. Pharmacokinetics (PK) was also evaluated. **Results:** In cohort A, none of the 9 pts enrolled (median age 52ys) had a DLT at any dose; 1 pt in Level 2 had REG delayed and TMZ dose reduced due to grade (G) 2 thrombocytopenia. At Level 1 and 2, 1 G3 haematological toxicity, respectively. At Level 3, 1 pt had a G3 gastrointestinal toxicity. In cohort B, 12 pts were enrolled (median age 53ys); at Level 3, 2 of 6 pts reported a DLT (n=1 G3 hypertransaminasemia with a dose reduction of REG (51%) and TMZ (50%) and n=1 G4 thrombocytopenia at the last day of RT). One case of G3 hypertension and 1 case of G3 hypertransaminasemia were also reported. REG was reduced in another pt due to G2 pain (no DLT); at Level 2 there was 1 case of G3 hyperbilirubinemia. There were no G3-4 AEs at Level 1. PK analysis of REG alone or in combination with TMZ showed a significant reduction (P=0.038) in the AUC, with a geometric mean ratio (GMR) of 80% (CI_{90} 64 – 98%) when given together with TMZ. PK analysis of TMZ showed a slight but significant reduction in the Cmax and AUC (P = 0.003 and 0.015, respectively) when given with REG, with GMR of 72% (CI_{90} 57 – 91%) and 86% (CI_{90} 79 – 92%), respectively. These results suggest a weak PK interaction between the two drugs. **Conclusions:** The MTD of REG for cohort A was 160mg, for cohort B 120mg with a weak PK interaction between the two drugs. The MTD of 120mg can be considered the recommended dose of REG in combination with standard Stupp therapy for the phase 2 study. Preliminary activity analyses are ongoing. Clinical trial information: NCT06095375. Research Sponsor: None.

2069 Poster Session

Azeliragon, a RAGE inhibitor, in combination with temozolomide and radiotherapy in patients with newly diagnosed glioblastoma: Preliminary results of phase Ib/II CAN-201 NDG trial. First Author: Juan Manuel Sepulveda, Medical Oncology Service, Hospital Universitario 12 de Octubre, Madrid, Spain

Background: Azeliragon is an orally available inhibitor of the receptor for advanced glycation end-products (RAGE). RAGE pathway promotes cell proliferation and angiogenesis, contributing to glioblastoma (GBM) progression and resistance to temozolomide (TMZ) and radiation (RT). Azeliragon has extensive clinical safety data in patients (pts) with Alzheimer's disease. Our hypothesis was that azeliragon may enhance the efficacy of Stupp regimen in newly diagnosed GBM. **Methods:** CAN-201 NDG is an open-label, single arm, phase Ib/II trial in Spain. Newly diagnosed IDH wild-type pts with GBM, MGMT methylation locally available and with tumor resection were recruited. Pts received azeliragon in combination with standard radiotherapy and TMZ followed by maintenance with azeliragon. The trial consists of an initial dose finding phase in a 6 dose escalation strategy with a subsequent expansion phase (up to 14 additional pts) at the recommended phase 2 dose (RP2D). The dose levels were: 5 mg/day (L1), 10 mg/day (L2) and 20 mg/day (L3). The primary objective is to determine the RP2D, defined as the dose for which $<$ 33% pts experience a dose limiting toxicity (DLT) within 28 days from initiation of dosing. Main secondary endpoints include progression-free survival (PFS), overall survival (OS) and changes in corticosteroid requirements. **Results:** From Oct 2023 to Jul 2024, 20 pts were included, 6 in L1, 8 in L2 and 6 in L3. The median age was 52 years (range: 40-69). Most pts were male (65%), ECOG 0-1 (95%) and MGMT unmethylated (60%). No DLTs were observed. Serious adverse events, all considered unrelated to azeliragon, were reported in 4 pts (20%), being hemiplegia, pyrexia, infectious meningoencephalitis, epilepsy and neurological decompensation. Non-serious Grade 3-4 adverse events (AE), also considered unrelated, were G3 hematological AEs in 33.3% in L1 and 37.5% in L2. G1-2 azeliragon-related AEs were reported in 33.3%, 25% and 66.7% of pts in L1, L2 and L3, respectively. Azeliragon treatment was ended due to progression in 83.3% and 62.5% of pts in L1 and L2, respectively. All pts on L3 are still on treatment. With a median follow-up time of 8.4 months, pts in L1 showed a median PFS of 5.2 months (95% CI, 4.4-Not Reached [NR]) and 9.8 months (95% CI, 6.2-NR) in L2. No progression of disease was observed in L3 with a range of follow-up of 4.9-7.0 months. Median OS in L1 was 11.1 months (95% CI, 9.4-NR). Data was not mature enough to calculate OS in L2 and L3. **Conclusions:** Azeliragon in combination with standard RT and TMZ is safe, with no dose-limiting toxicities reported so far at the initial three dose levels. To further explore the safety and efficacy profile of azeliragon, we are now expanding the study to include two additional dose levels of 30 mg/day (L4) and 50 mg/day (L5). Enrollment is currently open for level L4. Clinical trial information: NCT05635734. Research Sponsor: CANTEX Pharmaceuticals, Inc.

2070 **Poster Session**

From retrospective analysis to real-world impact: Mismatch repair deficiency detection in gliomas by tissue and liquid ctDNA NGS in glioma management. First Author: Suman Suryanarayana Karanth, FMRI, Gurugram, India

Background: Tissue biopsy remains the gold standard for Microsatellite Instability and MMR (mismatch repair) gene alteration assessment. The regulatory approval of immune checkpoint inhibitors is for mismatch repair-deficient cancers, regardless of tumor type. Surgical resection or biopsy is challenging when the glioma is located deep in the brain or brainstem. Circulating tumor DNA (ctDNA) next-generation sequencing (NGS) offers a non-invasive alternative, garnering attention in extracranial cancers, however not so in gliomas due to the lower concentrations of tumor-derived biomarkers. While Cerebrospinal fluid (CSF) provides superior sensitivity and specificity for gliomas, it is not a standard test in gliomas with its own technical issues. **Methods:** A retrospective analysis was conducted using databases to evaluate the prevalence of pathogenic inactivating alterations in MMR genes in glioma tissue samples. Data were queried from the MSK, Clin Cancer Res 2019 database for targeted sequencing on MSK-IMPACT and FMI panels, comprising 1004 tissue samples (837 with matched normal) from 923 glioma patients through the cBioPortal platform. Frequencies of MMR gene alterations were assessed. **Results:** A total of 850 patients (out of 923) were retrospectively analyzed for MMR gene alterations, with 40.3% (343) being female and 59.6% (507) male. Primary samples constituted 79.8% (679), and recurrent samples 20.2% (172). OncoKb level alterations were categorized as Level 1 (0.5%), Level 2B (16.6%), Level 3B (13.6%), Level 4 (32.8%), and none (36.4%). MMR gene alterations were found in 35 samples (4%), with MSH2 and MSH6 each detected in 2%, MLH1 in 1%, and PMS1, PMS2, and MSH3 in less than 1% of samples. In a specific case, ctDNA NGS was performed on a 9-year-old boy diagnosed with diffuse intrinsic pontine glioma as tissue biopsy was not feasible. Survivals are 9 to 11 months despite multimodality treatment. ctDNA NGS identified a truncating MSH6 alteration at 100% Variant Allele Frequency, suggesting biallelic inactivation of MSH6. Additionally, an IDH R132C activating mutation, a TP53 splice site SNV and high tumor mutational burden (bTMB) at 132.33 Mut/Mb were detected. Post radiation resulted in no change in tumor size. Injection pembrolizumab 3 weekly was initiated. Follow up MRI revealed further reduction in size and tumor has remained stable with ongoing therapy. **Conclusions:** Identifying MMR alterations potentially broadens the therapeutic options for glioma. The compelling case of the 9-year-old boy highlights the clinical utility of ctDNA NGS in identifying actionable MMR gene alterations, leading to successful immunotherapy with pembrolizumab and continued stable disease beyond 13 months. While few studies exist on utility of ctDNA in gliomas, it is time for bigger studies in both primary and recurrent gliomas where biopsy is not feasible. Research Sponsor: None.

2071 **Poster Session**

Immunohistochemical and gene expression profiles as predictors of survival in recurrent high-grade glioma treated with intracranial nivolumab, ipilimumab, and autologous CD1c(BDCA-1)$^+$/CD141(BDCA-3)$^+$ myeloid dendritic cells (myDC). First Author: Cleo Bertels, Universitair Ziekenhuis Brussel (UZ Brussel), Brussels, Belgium

Background: Innovative treatments are needed for recurrent high-grade glioma (rHGG) patients (pts) as current salvage therapies fail to improve overall survival (OS). Immune checkpoint inhibitors lack efficacy in rHGG when administered IV. This single center, multicohort phase I trial (Glitipni, NCT03233152) investigated intracerebral (iCer) administration of ipilimumab (IPI) +/- nivolumab (NIVO) +/- myDC after maximal safe resection (MSR), followed by adjuvant intracavitary (iCav) IPI/NIVO through an Ommaya reservoir. **Methods:** Eligible pts (ECOG $\leq$ 2, $\leq$ 8mg/day methylprednisolone) with rHGG (WHO 2021 grade 3/4, IDH-1/2 wild type (wt) or mutant) after standard postoperative radiotherapy (RT) and temozolomide (TMZ) were included. Pts underwent MSR or stereotactic biopsy (if unresectable) $<$ 24h after receiving NIVO IV (10mg), followed by iCer injection of varying doses of IPI +/- NIVO +/- myDC and Ommaya catheter placement depending on the cohort (C). NIVO was administered IV (all cohorts) +/- iCav (C3-7) biweekly up to 12 cycles. Baseline tumor microenvironment characteristics were assessed by immunohistochemical (IHC) analysis and gene expression profiling (GEP). **Results:** Between 2016 and 2023, 110 pts (68% male, median age 57, 92% ECOG 0/1) were enrolled. At primary diagnosis, the majority (85%) were glioblastoma pts (WHO grade 4, IDH-wt), treated with the standard of care (MSR + RT + TMZ) (71%). All pts received 10mg NIVO IV preoperatively. Ninety percent of the pts who underwent the neurosurgical procedure started the postoperative treatment. Early discontinuation of study treatment occurred in 76% of pts, mainly due to tumor progression (86%). Treatment-related adverse events (TRAE) were mild (CTCAE grade 1/2), no grade 5 TRAE occurred. Most frequent TRAE were fatigue, headache and fever. At database lock (Jan 1st, '25), 9 pts remained progression-free. When including durable benefit from bevacizumab at first progression (13 pts), PFS and OS were significantly higher in C5/6 (+myDC) compared to other cohorts (-myDC) of our trial with resectable rHGG, and to a historical control group treated with VEGF(R)-inhibitors (descriptive $p < 0.05$ for each pairwise comparison). Absence of B7H3 on resected tumor tissues as demonstrated by IHC (C4, 5, 7) showed longer median OS, which was consistent with GEP. PD-L1 expression and density of CD8, Granzyme B or FOXP3 positive cells/mm^2 did not correlate with survival. A proliferative gene signature on GEP was significantly correlated with shorter PFS and OS. **Conclusions:** Intracranial administration of IPI/NIVO co-administered with myDC was feasible and safe, resulting in encouraging survival in pts with resectable rHGG. Baseline B7H3 levels and a proliferative gene signature correlated with survival. Clinical trial information: NCT03233152. Research Sponsor: None.

2072 **Poster Session**

Development and validation of a droplet digital PCR (ddPCR) assay to detect MGMT promoter methylation in FFPE tumors of glioblastoma (GBM) patients. First Author: Mahrukh M Syeda, NYU Langone Medical Center, New York, NY

Background: Methylation of the MGMT gene promoter (MGMTp) is a critical biomarker to inform GBM prognosis and guide treatment decisions, including clinical trial eligibility. Rapid reporting of MGMTp methylation can help stratify patients early and facilitate clinical trial referral during the crucial post-operative period where treatment options are being considered by patients and physicians alike. **Methods:** We developed a probe-based ddPCR method to detect and quantify MGMTp methylation. Assay specificity was assessed using bisulfite-converted, unmethylated DNA. Assay linearity and Limit of Detection (LoD) were determined using MGMTp methylated cell line DNA samples of decreasing fractional abundances (35%, 5%, and 0.5%) and decreasing DNA inputs (30ng, 10ng, 3ng,1ng and 0.5ng). The limit of Blank (LoB) was calculated using 16 replicates of unmethylated bisulfite-converted PBMC DNA, and DNA from tonsil FFPE samples (n = 9). Reproducibility studies were conducted on two different days with two different operators. Accuracy and concordance were assessed using an in-house MGMTp methylation pyrosequencing assay as an orthogonal method to analyze11 melanoma and one glioblastoma cell line. Preliminary clinical validation was conducted via analysis of FFPE tumor DNA from 34 GBM patients with clinical MGMTp methylation pyrosequencing results. **Results:** The MGMTp methylation ddPCR assay demonstrated 100% specificity to detect promoter methylation. The method linearly quantified both total DNA and methylated DNA along a range of input DNAs with conserved fractional abundances. The LoB was 0.036% and 0.034% using PBMC and tonsil FFPE DNA, respectively. The LoD was 0.075%. The bisulfite conversion and assay were highly reproducible, with a coefficient of variation $<$ 20%. Among the 12 cell lines analyzed by both pyrosequencing and ddPCR the concordance was 100%. Ten of 11 GBM tumor samples identified as MGMTp methylated by the clinical pyrosequencing assay were also identified as methylated by the ddPCR assay. Five of 23 clinically unmethylated tumors were positive in the ddPCR assay with generally very low fractional abundances (0.08%, 0.12% 0.3%, 0.97% and 10.11%). **Conclusions:** We report preliminary validation of a highly sensitive and specific ddPCR assay to detect MGMTp methylation. Given the minimal sample requirements and rapid turnaround time for ddPCR assays, this test could eventually be utilized in clinical laboratories to quickly report MGMTp methylation status for GBM patient management. Research Sponsor: None.

2073 **Poster Session**

Combining abemaciclib, temozolomide, and radiation in DIPG PDOX models: Insights from single-cell RNA-seq on cellular subtypes and genes critical for responsiveness and resistance. First Author: Zilu Huang, Robert H. Lurie Comprehensive Cancer Center, Feinberg School of Medicine, Northwestern University, Chicago, IL

Background: Diffuse intrinsic pontine glioma (DIPG) is a highly aggressive pediatric brain tumor, with two-year survival less than 10%. Radiation therapy (XRT) offers limited survival benefits, and effective therapies are urgently needed. This study investigates the FDA-approved CDK4/6 inhibitors-Abemaciclib, XRT, and temozolomide (TMZ) as a therapeutic regimen for DIPG using organoids and patient-derived orthotopic xenograft (PDOX) models, aiming to improve survival outcomes and gain insights into the underlying cellular and molecular mechanisms of DIPG treatment responsiveness and resistance to support rapid translation into clinical trials. **Methods:** The efficacy of Abemaciclib, XRT, TMZ, and their combinations was evaluated in DIPG organoids and PDOX models (IBs-A0317DIPG and IBs-9119DIPG, H3.3K27M mutation). In vitro, PDOX organoids were treated with Abemaciclib, TMZ, with/without XRT. Synergy was assessed using the Bliss Independence model. In vivo, six treatment arms were tested: (1) control, (2) XRT (2 Gy/day $\times$ 5), (3) Abemaciclib (75 mg/kg, p.o., 14 days), (4) Abemaciclib + XRT, (5) TMZ (50 mg/kg, p.o., 5 days) + XRT, (6) Abemaciclib + TMZ + XRT. Single-cell RNA sequencing and IHC were used to assess cellular subtypes responses, gene expression changes, and resistance mechanisms. **Results:** In DIPG organoids, the combination treatment yielded Over Bliss values $>$ 0 (0.25 and 0.58 in A0317DIPG and 9119DIPG models, respectively) demonstrating synergistic activities. In PDOX models, the triple therapy showed improved median survival compared to other treatment arms and significant survival advantage over control (p = 0.0157) and Abemaciclib alone (p = 0.0461) in A0317DIPG, and control ($p < 0.0001$), XRT alone (p = 0.0032), Abemaciclib alone (p = 0.0006), Abemaciclib + XRT (p = 0.0046), and TMZ + XRT (p = 0.0001) in 9119DIPG models. Single-cell RNA sequencing revealed six tumor subtypes: AC-like, NPC-like, OPC-like, MES-like, mitotic, and radiation-resistant cells. The triple therapy increased NPC-like and mitotic cell populations while decreasing AC-like and OPC-like cells in both models. Additionally, we identified a novel radiation-resistant subpopulation that expanded after XRT treatment. Dynamic gene expression analysis in different cell types identified key target genes and cell-type specific pathways that mediate therapy responsiveness and resistance. **Conclusions:** Our study demonstrates that the combination of Abemaciclib, TMZ, and XRT offers a novel, synergistic approach for DIPG, significantly improving survival in preclinical PDOX models. Single-cell RNA sequencing reveals the roles of different cell types and molecular changes underlying resistance, highlighting potential targets for future anti-resistance strategies in DIPG management. Research Sponsor: The Lou and Jean Malnati Brain Tumor Institute (MBTI).

2074 **Poster Session**

MRI-based radiomics for prediction of isocitrate dehydrogenase subtype in glioblastoma multiforme through artificial intelligence models: A systematic review and meta analysis. First Author: Sonali Belankar, M. S. Ramaiah Medical College, Bangalore, India

Background: Gliomas are aggressive tumours with poor prognosis. Isocitrate Dehydrogenase (IDH) mutations are present in approximately 12% of all Glioma tumours and are considered biomarkers for prognosis and response to chemotherapeutic agents. IDH mutant gliomas have better prognosis in comparison to IDH wild type Gliomas. IDH mutant Gliomas exhibit features like T2-Flair mismatch sign, reduced blood flow seen on perfusion-weighted images and reduced enhancement on MRI, which aid in identification of IDH mutation. Radiomic imaging techniques extract quantitative features from medical images like MRI and CT scans with the help of advanced algorithms and the extracted data can be utilized in the development of specific artificial intelligence (AI) models like Neural Networks for the prediction of IDH mutation. Thus, MRI based Radiomics is an emerging non invasive technique in comparison to conventional biopsy, for the determination of IDH mutation. The meta-analysis conducted aims to analyse the diagnostic potential of Radiomic imaging in predicting IDH mutations in Gliomas. **Methods:** A systematic search was conducted in PubMed, Google Scholar and Scopus. PRISMA guidelines were followed. A boolean expression was constructed to retrieve and select articles from major medical databases. The R Studio package was used to evaluate the potential of the diagnostic test. The Meta, Metadata and Mada packages were utilised to evaluate Pooled accuracy, sensitivity and specificity. **Results:** A total of 35 studies and 7522 radiomic features were assessed through this meta analysis. The Pooled Sensitivity and Specificity were estimated to be 86.70% ([74.85; 87.51], 95% CI, $p< 0.0001$, I^2 = 92.7% [90.9%; 94.1%]) and 82.75% ([0.7912; 0.8587], 95% CI, $p<0.0001$, I^2 = 82.8% [77.4%; 86.9%]) utilising the random effects model. The pooled Accuracy was found to be 81.28% ([0.6037; 0.9253], 95% CI, $p>0.01$, I^2 = 0.0% [0.0%; 45.4%]). **Conclusions:** Through the compilation of previously conducted studies, MRI based Radiomics show High Pooled Sensitivity of 86.70% and High Pooled Specificity of 82.75% in the detection of Isocitrate Dehydrogenase mutations in Gliomas. Pooled Accuracy rate of 81.8% indicates steady reliability of Radiomics in the prediction of IDH mutations. MRI based Radiomics is a dependable and consistent non invasive technique in the detection of IDH mutations in GBM and can be utilized for the generation of predictive models, enhancing clinical diagnosis and tailored management based on IDH mutation. Research Sponsor: None.

2075 **Poster Session**

Correlative and spatial transcriptomic analysis of olaparib and durvalumab in patients with recurrent/refractory *IDH*-mutant gliomas. First Author: Xin Wang, Department of Medical Oncology, University of Toronto, Sunnybrook Health-Sciences Centre, Toronto, ON, Canada

Background: Combination of immune checkpoint and PARP inhibition has potential synergistic effects in *IDH*mt gliomas in pre-clinical models. Durvalumab and olaparib demonstrated objective responses in a subset of patients (pts) with *IDH*mt gliomas (NCT03991832). We report mutational, transcriptomic, and spatial correlative analysis of pts samples from baseline and at time of progression. **Methods:** Pts with recurrent/refractory *IDH*mt gliomas received olaparib 300 mg twice daily and durvalumab 1500 mg IV every 4 weeks until disease progression as determined by RANO 2.0 criteria. Whole exome sequencing (WES, n = 28) and total RNA sequencing (RNA-seq, n = 21) were performed on baseline archival formalin-fixed, paraffin-embedded tumor samples. Baseline tumor microenvironment was characterized with multiplex-immunohistochemistry (n = 29). Matched responders (n = 4) and non-responders (n = 6) were further profiled using 10X Visium HD for spatial transcriptomics. An unsupervised deconvolution method was applied using consensus non-negative matrix factorization for *de novo* discovery of expression programs corresponding to cell types and cell states. Associations with objective response (OR) to therapy were determined using either Fisher's exact test or rank-sum test. **Results:** In the 29 pts enrolled between January 2020–February 2023, median age was 40.5 (range 23–66) and 41% were female. The initial tumor grade was 2 (n = 9), 3 (n = 8), and 4 (n = 12). The OR rate was 14% (95% CI 3.9–32%), 1 complete response and 3 partial responses. All cases were mismatch repair proficient. The median tumor mutation burden (TMB) was 16.5, with TMB $>$ 10 in 21 pts (75%). Baseline TMB was not associated with response. The most common co-mutations were *TP53* (n = 21, 75%), *ATRX* (n = 20, 71%), *ARID1A* (n = 7, 25%), *CIC* (n = 4, 14%), and *NF1* (n = 3, 11%), none were associated with response. There were no canonical mutations in *BRCA1*, *BRCA2*, or *PALB2*. Pathway analysis on differentially expressed genes between responders and non-responders showed convergence on interferon signaling and inflammation among responders ($p <$ 0.001). Lower pre-existing M2-polarized tumor associated macrophages/microglia (high expression of CD68, PDL1, CD163) was associated with response ($p < 0.01$). These findings were supported by metaprograms in the HD spatial data, which showed higher levels of CD8+ cytotoxic T-cells at baseline in responders. Conversely, M2-polarized macrophage/microglia were enriched in non-responders. Paired progression samples will additionally be presented. **Conclusions:** Responders to olaparib and durvalumab had decreased baseline M2-polarized macrophages/microglia and increased pre-existing immunogenicity (interferon signaling). Several spatially conserved expression metaprograms targeting baseline immune infiltration were associated with response. Clinical trial information: NCT03991832. Research Sponsor: None.

2076 **Poster Session**

The utilization of palliative care services by patients with glioblastoma: A cross-sectional study with care partners of patients with GBM recruited from Facebook support groups. First Author: Lauren Robbins, UNC Wilmington, Wilmington, NC

Background: Glioblastoma(GBM) is a terminal brain cancer that has a rapid onset and results in symptoms such as headaches, vomiting, seizures, anxiety, depression, agitation, speech impairment, memory impairment, infections, brain bleeds, mobility changes, changes in sleep patterns and cognitive changes. Palliative care helps patients diagnosed with an incurable or chronic disease manage physical, social and psychological symptoms while undergoing treatment, and has been shown to increase survival for patients with cancer. Previous data of former care partners of patients with GBM indicated only 30% of patients used palliative care during the disease trajectory, whereas 90% engaged hospice during the end of life stage. **Methods:** To better understand the reasons for underutilization of palliative care, primary caregivers of patients with GBM recruited from a Facebook support group in February 2024 completed a 38-question survey about where care was received, who was on their care team, and whether they had discussions around palliative care. Inclusion criteria: current primary care partner of a patient with GBM over the age of 18, and willing to participate (IRB exempt;H24-0393). The care partner was excluded if their patient was no longer living. **Results:** Of the 77 care partners who participated in the study, the median age of the caregivers was 56 years (98% female) and the median age of the patients with GBM was 60 years (87% female). Patients with GBM were initially diagnosed in community hospitals, major medical centers, university medical centers, brain tumor centers, and as part of incidental findings. Approximately $^{1}/_{4}$ of patients pursued second opinions. Of the 21 patients initially diagnosed in community medical centers, over half received treatment in other facilities. Medical care team members differed by facility type with a marked difference in palliative care utilization. Only 27% of care partners reported palliative care was part of the care team. Notably,when care team members discussed palliative care with patients and their care partners (n = 21), 71% of the dyads utilized palliative care. In contrast, when palliative care was not discussed (n = 56), only 7% of the care partners used these services ($p < 001$). Participants reported they would have benefited from additional supportive services provided by patient navigation and palliative care. **Conclusions:** This data highlights the value of discussions about palliative care in its utilization among GBM patients and their care partners. These conversations should take place early in the disease's progression to ensure that care partners receive the necessary education and resources in a timely manner. Research Sponsor: None.

2077 **Poster Session**

Identification of novel electrophysiologic biomarkers of cognition in glioma-infiltrated cortex. First Author: Vardhaan Ambati, University of California, San Francisco, San Francisco, CA

Background: Diffuse gliomas, the most common primary brain cancers, often invade speech-critical areas. Maximal resection improves survival, but damage to functional cortex may cause permanent impairments. Direct cortical stimulation (DCS) differentiates functional (DCS+) from nonfunctional (DCS-) cortex by temporarily disrupting neuronal activity, yet it remains unknown how DCS+ sites elicit transient impairments. DCS is technically challenging and resource-intensive. As a result, fewer than 50% of glioma patients receive optimal surgical care. This translational study aims to identify electrophysiologic biomarkers of DCS+ cortex to 1) aid in safe resection by avoiding functional cortex and 2) to elucidate causal relations behind these transient impairments. **Methods:** Local field potentials of subdural array data from glioma infiltrated cortex was annotated as DCS+ or DCS- prospectively. We compared spectral electrophysiologic variations (mean Theta [4-8 Hz], Alpha [8-13 Hz], Beta [13-30 Hz], and Full Gamma [30-150 Hz] ranges) at resting state between DCS+ and DCS- sites using linear mixed-effects models (to account for patient-level differences). **Results:** 1421 cortical sites of language were studied in 91 patients including 21 Oligodendroglioma WHO grade 2-3, 19 Astrocytoma WHO 2-3, 3 Astrocytoma WHO 4, 48 IDHwt glioblastoma [GBM] WHO 4). 115 (8.0%) were DCS+. After alignment to ECoG electrode arrays, 512 cortical sites (49 DCS+) were assigned to electrodes. In oligodendrogliomas, DCS+ (N=16) vs DCS- (N=132) sites had higher alpha (77.7 ± 111.9 vs 38.6 ± 39.8, p=0.018), beta (23.1 ± 18.1 vs 11.9 ± 17.9, p=0.033), and full gamma (0.6 ± 0.6 vs 0.3 ± 0.3, $p<0.001$) power. Similarly, in astrocytoma, DCS+ (N=13) vs DCS- (N=147) sites had significantly higher theta (98.5 ± 94.9 vs 57.1 ± 67.2, p=0.020), alpha (83.5 ± 76.3 vs 39.9 ± 42.4, p=0.003), beta (55.9 ± 58.4 vs 16.3 ± 17.8, $p<0.001$), and gamma (0.9 ± 0.9 vs 0.4 ± 0.4, p=0.006) power. Interestingly, when comparing DCS+ (N=20) and DCS- (N=237) sites in GBM patients, no significant differences were found in any studied ranges (all $p>0.05$). **Conclusions:** This study is the first of its kind to identify unique electrophysiological biomarker differences (at resting state) for oligodendroglioma and astrocytoma speech cortex. It has two key implications. First, clinically, the identification of electrophysiologic biomarkers may improve direct cortical stimulation (DCS) mapping: It can make surgeries faster by identifying cortex critical for cognition (speech) based on these biomarkers, safer by helping neurosurgeons avoid resecting critical regions, and more accessible. Second, this research suggests that different tumor types (low-grade gliomas vs. GBM) remodel speech areas differently, prompting further investigation into tumor-specific effects on neural circuits. Research Sponsor: None.

2078 **Poster Session**

A single-institution retrospective study of multicentric gliomas stratified by *IDH* mutational status. First Author: Chuyin Yang, University of California, Los Angeles, Los Angeles, CA

Background: Multicentric glioma (MCG) is a subset of diffuse glioma that can be synchronous or metachronous and is defined as the occurrence of two or more tumor foci, with separation of FLAIR (Fluid-attenuated Inversion Recovery) hyperintensity on MRI. MCG has not been extensively studied in studies stratifying *IDH* wild-type and mutant gliomas. This large single-institution study investigates the prevalence of MCG, examines the prognostic implications of MCG, and characterizes metachronous MCG (mMCG) in a cohort that has been stratified by *IDH* mutational status. **Methods:** In this IRB approved UCLA study, we identified diffuse glioma patients with known *IDH* mutational status and adequate MRI studies. Patients with multiple lesions on the MRI study pre-surgery or up to 3 months post-surgery were considered synchronous MCG (sMCG). Patients who developed a new independent lesion at least 6 months after initial surgery were considered mMCG. To qualify as MCG, we identified additional tumors on MRI that had no overlapping FLAIR borders and met one or more of the following: pathologically confirmed with biopsy, exhibited growth and thickening over time, and developed or increased in enhancement. Difference in prevalence was compared using Student's t-test. Kaplan-Meier and Cox-multivariate analyses were used to analyze OS and time to metachronous (TtM) appearance. **Results:** We identified 911 consecutive *IDH* wild-type, high-grade diffuse glioma patients from 2013-2023 and 515 consecutive *IDH* mutant patients from 2007-2024 with pre-surgical MRI or MRI within three months of initial surgery. From the examined cohort, we found 39 *IDH* mutants with 21 sMCG and 18 mMCG and 153 *IDH* wild types with 95 sMCG and 63 mMCG. In eight *IDH* wild-type cases but no *IDH* mutant cases, mMCG arose from sMCG patients. We found that MCG had higher prevalence in *IDH* wild-types than in mutants (WT = 16%, Mut = 7%, $p < 0.0001$), and *IDH* mutant MCG showed more male predominance than *IDH* wild-type MCG (Mut = 73%, WT = 58%, $p < 0.0001$). In *IDH* mutant patients, mMCG, but not sMCG, was associated with lower OS (mMCG: HR = 2.476, p = 0.0115; sMCG: HR = 0.6437, p = 0.5027). However, in *IDH* wild types both sMCG and mMCG and were associated with lower OS (mMCG: HR = 1.589, p = 0.0025; sMCG: HR = 1.347, p = 0.0332). There was no difference in TtM between the two groups (HR = 0.5738, p = 0.5318). Amongst patients with multiple biopsied lesions, *IDH* wild types had consistent pathologies between lesions in all examined patients (29/29), but 71% of *IDH* mutants exhibited different pathologies between lesions (5/7). **Conclusions:** Our study examined a cohort of adult diffuse gliomas stratified by *IDH* mutational status and shows MCG is less common in *IDH* mutant gliomas and sMCG is not associated with worse prognosis. Further studies to identify molecular features underlying MCG will be valuable. Notes: For mMCG, FLAIR overlap might have occurred had the new lesion been observed synchronously. Research Sponsor: Bradley Zankel Foundation; NIH/NCI P50 CA211015-01A1 (UCLA SPORE in Brain Cancer).

2079 **Poster Session**

Diagnostic accuracy of machine learning models in glioma classification: A meta-analysis. First Author: Maya Gowda, Cornell University, New York, NY

Background: Machine learning (ML) is promising in IDH-based glioma classification using magnetic resonance imaging (MRI), but variability in methods and algorithms necessitates a comprehensive evaluation. This meta-analysis assesses the pooled diagnostic performance of ML-based approaches. **Methods:** A literature search was conducted in January 2025 across PubMed, MEDLINE, and Cochrane. MICCAI, RSNA, and SNO meeting abstracts were additionally reviewed. Eligible studies evaluating ML models for IDH-based glioma classification using MRI were included. Data were pooled using a random-effects model, analyzing sensitivity, specificity, heterogeneity, and publication bias via Egger's test and funnel plots. Leave-one-out analysis was conducted. **Results:** A total of 5982 cases were analyzed. Gliomas were classified as WHO Grades II (11.5%), III (23.1%), and IV (65.4%). Histopathology-based reference standards, including genetic and molecular testing, were used in 73.1% of studies, while immunohistochemistry, pathology, biopsy-proven markers, and immunohistopathologic diagnosis were each used in 3.8–7.7%. Deep learning models, including CNNs and ResNet, were the most used classifiers (30.8%), followed by Support Vector Machines (26.9%). Ensemble methods, such as Random Forest accounted for 19.2%, regression-based approaches (LASSO, logistic regression) for 15.3%, and other techniques like multilayer perceptron and AdaBoost for 7.7%. This meta-analysis included 25 studies for sensitivity and 26 for specificity, using a random-effects model with DerSimonian-Laird estimation. Pooled sensitivity was 83.0% (95% CI: 79.5–86.5%) and specificity was 78.6% (95% CI: 73.7-83.4%), both statistically significant ($p < 0.0001$). Substantial heterogeneity was found (I^2 = 100% for both), with Cochran's Q values of 1.9e+06 for sensitivity and 4.2e+06 for specificity ($p < 0.001$). Leave-one-out analysis showed minimal variation in pooled estimates (sensitivity: 82.6–83.8%, specificity: 77.6–79.4%). Egger's test revealed significant small-study effects (p = 0.0001 for both), suggesting potential publication bias. **Conclusions:** ML models demonstrated moderate diagnostic performance in IDH-based glioma classification, achieving a sensitivity of 83.1% and specificity of 78.6%. However, substantial heterogeneity and potential biases pose significant challenges to their clinical implementation. To enhance the reliability and broader applicability of ML models in IDH-based glioma diagnosis, standardization of imaging protocols and external validation are imperative. Research Sponsor: None.

Meta-analytical findings.

Metric	Sensitivity (%)	Specificity (%)
Pooled Estimate	83.0 (79.5–86.6)	78.6 (73.7–83.4)
Z-Value	46.4	31.76
P-Value	<0.0001	<0.0001
I^2 (%)	100	100
T^2	80.0	159.0
Cochran's Q	1.9e+06 (df=24, p<0.001)	4.2e+06 (df=25, p<0.001)
Leave-One-Out Range	82.6–83.8	77.6–79.4
Egger's Test (P-value)	0.001	0.001

2080 **Poster Session**

Identifying key molecular drivers of survival and therapeutic targets in glioblastoma through integrated transcriptomic analysis. First Author: Mohammad Kashkooli, Harvard-MIT Health Sciences and Technology, Boston, MA

Background: Glioblastoma multiforme (GBM) remains one of the most aggressive brain tumors, characterized by poor survival rates and limited therapeutic success. Advancing treatment requires identifying molecular drivers of tumor progression and therapy resistance. Integrated transcriptomic analyses offer a powerful means to uncover pathogenic pathways, therapeutic targets, and refine prognostic tools. This study aimed to explore GBM's molecular landscape to identify survival-relevant genes and actionable pathways, ultimately paving the way for precision therapies to improve outcomes. **Methods:** RNA-sequencing data from TCGA, CGGA, CPTAC, GLASS, GSE121720, and GSE147352 datasets, encompassing 783 samples, were analyzed. Only primary, untreated GBM tumors with survival data were included. Data normalization was performed using the voom function in limma, and batch effects were corrected using ComBat while preserving survival-related and gender-specific variations. Differential expression analysis (DEA) was used with thresholds of $|\log FC| > 1$ (two-fold expression change) and adjusted $p < 0.001$, accounting for age, gender, race, and IDH1 mutation. Protein–protein interaction (PPI) networks were constructed using STRING, and Cox regression identified survival-related genes. DrugBank was used to link survival-associated genes to potential therapeutics. **Results:** Of the 783 samples, 488 met inclusion criteria (473 tumor, 15 non-tumor). DEA identified 1,453 differentially expressed genes (DEGs) with significant differences between tumor and non-tumor samples. PPI analysis highlighted 270 hub genes, of which 47 were significantly associated with survival. Notably, CDK1, RRM2, and BIRC5 showed negative prognostic effects (hazard ratio [HR] > 1.7, adjusted $p < 0.05$), while RPL3L, RPL21, and RPL9 exhibited protective effects (HR < 0.5, adjusted $p < 0.001$). DrugBank analysis identified gallium nitrate (targeting RRM2) and Alsterpaullone (inhibiting CDK1) as promising therapeutic candidates. **Conclusions:** This study provides a comprehensive bioinformatics analysis of GBM, integrating multiple transcriptomic datasets to identify critical survival-related genes, including CDK1, RRM2, and BIRC5, as key therapeutic targets. Notably, it highlights the protective roles of ribosomal proteins (RPL7, RPL9, RPL21), challenging the traditional view that ribosomal upregulation solely drives tumorigenesis. These findings emphasize the dual nature of ribosomal dysfunction, which has been implicated in both oncogenic and tumor-suppressive pathways. Through rigorous data normalization, batch correction, and PPI analysis, the findings offer robust insights into GBM biology and its molecular drivers. These results lay a strong foundation for future studies to validate their clinical relevance, refine prognostic models, and advance precision therapy strategies for GBM patients. Research Sponsor: None.

2081 **Poster Session**

Effect of ivosidenib and vorasidenib on 2-hydroxyglutarate levels in low grade glioma: An in vivo MR spectroscopy study. First Author: Max Saint-Germain, Johns Hopkins University School of Medicine, Baltimore, MD

Background: IDH-mutant gliomas are slow-growing infiltrating tumors of astrocytic (AS) or oligodendroglial (OG) origin (WHO grade 2/3). The mutations occur in genes that encode the metabolic enzyme IDH1 or, more rarely, IDH2 and lead to production of 2-hydroxyglutarate (2-HG) that can be measured with optimized in-vivo MRS. Small-molecule IDH inhibitors (IDHi) ivosidenib (inhibits mIDH1 enzyme) and vorasidenib (inhibits mIDH1 and mIDH2 enzymes) showed good tumor penetrance and ~95% 2-HG reduction measured in tumor biopsies. Both ivosidenib and vorasidenib have evidence of responses in tumor growth rate. As volume reductions are often observed, but after a delay of several months, thus an early response biomarker highly desired. The aim of this study was to explore whether MRS measurements of 2-HG can be used to non-invasively monitor response to treatment with IDHmut-inhibiting drugs and compare this response to changes in tumor volume. **Methods:** 14 patients (Age ≥18y) with a histomolecularly confirmed IDH1 mutated diffuse glioma (AS or OG) received ivosidenib (n = 12) or vorasidenib (n = 2) therapy as part of their routine clinical care. MRI was performed before treatment (*baseline*) and repeated (*follow-up*) with a median on-drug follow-up of 6 months [4, 12 IQR]. Tumors were segmented from FLAIR images in 3D Slicer and volumes were calculated in cm^3. All MRS data were processed in Osprey with the built-in LCModel fitting module. Comparisons between baseline and follow-up measured metabolite levels were conducted using paired t-tests or (in cases where the normality assumption was not met) non-parametric Wilcoxon tests. **Results:** We analyzed spectra from 11 patients with both baseline and follow-up sessions. All spectra exhibited characteristic tumor features: reduced total N-acetylaspartate (tNAA) and elevated levels of total choline (tCho), lactate (Lac), and myo-inositol (mI), along with a 2-HG peak at 2.25 ppm that is visibly smaller after treatment. The decrease in 2-HG levels was highly significant ($p < 0.001$) across all included patients undergoing ivosidenib/vorasidenib therapy, regardless of reference standard. Volumetric assessment revealed tumor growth arrest and a subtle reduction in tumor growth in some individuals. **Conclusions:** This is the first in-vivo evidence using MRS that ivosidenib/vorasidenib reduces 2-HG. We found that 2-HG levels respond specifically and rapidly to treatment, while volumetric changes manifest slowly and more gradually, consistent with previous studies. This preliminary study suggests that in vivo MRS-derived 2-HG estimates could serve as sensitive and specific biomarkers for monitoring low grade gliomas in vivo in response to small-molecule IDH inhibitor therapy after initiation of treatment. Longitudinal volumetric and radiomic analyses are underway. Research Sponsor: None.

2082 Poster Session

Vault proteins as prognostic biomarkers and therapeutic targets in lower-grade gliomas. First Author: Sebawe Syaj, Division of Hematology and Oncology, Department of Medicine, University of Pittsburg Medical Center, and UPMC Hillman Cancer Center, Pittsburgh, PA

Background: Vault proteins, including MVP, VPARP, and TEP1, are components of the vault complex, and are involved in drug resistance, DNA repair, and cell survival. However, their role in low-grade gliomas (LGG) remains unclear. This study explored the expression and prognostic significance of LGG with the aim of uncovering their potential as biomarkers. **Methods:** Using the TCGA-LGG cohort, Kaplan Meier (KM) and uni/multivariate Cox proportional hazards regression (CPH) analyses were performed using R 4.3.3, and hazard ratios (HR) with 95% confidence intervals (CI) were reported. MVP, TEP1, and VPARP (PARP4) expression levels were further stratified according to the LGG subtype. Multi-gene KM plots were generated to stratify overall survival (OS), progression-free survival (PFS), and disease-specific survival (DSS) using gene set variation analysis (GSVA) scores. "ImmuCellAI" algorithm was utilized for immune infiltration analysis. The GDSC and CTRP databases were used for drug sensitivity analyses. **Results:** As indicated by KM and univariate CPH analyses, MVP (hazard ratio [HR] = 1.5, 95% CI: 1.3-1.8), TEP1 (HR = 1.7, 95% CI: 1.4-2.0), and VPARP (HR = 1.6, 95% CI: 1.3-1.9) predicted poor OS. MVP, in multivariate CPH model adjusted to tumor grade and histology, remained significant (HR = 1.37, 95% CI: 1.14-1.70). The expression of MVP, TEP1, and VPARP was the highest in astrocytomas and the lowest in oligodendrogliomas ($p < 0.05$), with oligoastrocytomas in between. 3-gene KM signature analysis revealed a negative association between higher GSVA scores and OS, PFS, and DSS (log-rank $p < 0.01$) (Table). Immune infiltration analysis indicated positive macrophage, Th1, Th2, and dendritic cell infiltration with higher GSVA (derived from MVP, TEP1, and VPARP) ($r > 0.40$, FDR < 0.05) and negative infiltration of naive CD8+ and neutrophils ($r < -0.30$, FDR < 0.05). Drug analysis revealed vincristine resistance with higher MVP expression (r = 0.44, FDR < 0.001). **Conclusions:** MVP, TEP1, and VPARP were associated with poor survival outcomes and distinct immune infiltration patterns in LGG. These findings highlight the potential of vault proteins as biomarkers and therapeutic targets for LGG. Research Sponsor: None.

Univariate Cox proportional hazards ratios for the different survival types for GSVA scores of the three major proteins of the vault (MVP, TEP1, and VPARP).

Survival type	Hazard Ratio	Cox P value	Logrank P value	Higher risk of death
OS	1.7	<0.001	24E-2.03	Higher GSVA
PFS	1.43	0.01	9.09E-03	Higher GSVA
DSS	1.75	<0.001	2.18E-03	Higher GSVA

2083 Poster Session

Accelerator-based boron neutron capture therapy, a randomized controlled trial for refractory recurrent high-grade meningiomas. First Author: Shin-Ichi Miyatake, Kansai BNCT Medical Center, Osaka Medical and Pharmaceutical University, Takatsuki, Japan

Background: High-grade meningiomas (HGMs) recurred after X-ray treatment showed pessimistic prognosis. We conducted "A phase II investigator-lead RCT using accelerator-based BNCT system for refractory recurrent high-grade meningioma". **Methods:** We prepared 2 study arms, BNCT test treatment arm (12 subjects) and control best supportive care arm (6 subjects) in RCT fashion. PFS judged by the third-party committee was primary endpoint and PFS judged by investigators themselves and OS of BNCT arm and so on were secondary endpoints. Rescue BNCT was permitted for control group patients, if they were judged as PD by investigators. First patient-in and last patient-in were August 2019 and August 2021, respectively. Last patient visit was February 2024 and final OS survey and final observation for effectiveness and safety in BNCT arm were performed in July 2024. These results were compared to EORTC's RCT of trabectedin. **Results:** Three and 2 grade 3 subjects were included in BNCT and control arm, respectively. Others were grade 2 subjects. All cases were confirmed relapse after some radiotherapy in follow-up images. One subject allocated in BNCT arms was excluded after enrollment due to protocol violation. At the end of the observation, as primary endpoint, PFS of each arm judged by committees showed statistical significance (p=0.0157, Log-rank). As one of the secondary endpoints, PFS of each arm judged by investigators also showed statistical significance (p=0.0002). Median PFS judged by committees were 14.4 (95% CI:7.9-26.4) and 1.4 (1.0-9.0) months for BNCT and control arm, respectively. Median PFS judged by investigators showed 14.7 (7.6-22.8) and 1.5 (1.0-9.0) months, respectively. Five out of 6 cases in control arm received rescue BNCT after PD assessments. Other endpoints are listed in the table. **Conclusions:** As primary endpoint, PFS judged by committee showed statistical significance between treatment and control arms. Recently, the results of RCT of "Trabectedin" for recurrent HGMs, organized by EORTC, (EORTC-1320-BTG) was reported. Unfortunately, there was no effect of Trabectedin not only in PFS but in OS. Therefore, EORTC's report seems to be natural course of recurrent refractory HGMs. Our current BNCT shows extremely excellent results in comparison with EORTC's RCT in mPFS, PFS-6 months, mOS, OS-1 year and ORR (Table). Clinical trial information: 2051190044. Research Sponsor: AMED.

Comparison of both RCT (current study and EORTC trabectedin).

	Current study (n=18)		EORTC trabectedin (n=90)	
	BNCT	Control	Trabectedin	Control
mPFS (months)	14.4	1.4	2.43	4.17
PFS-6 months (%)	100	44.4	21.1	29.1
mOS (months)	46.9	-	11.4	10.6
OS-1 year (%)	100.0	-	48.1	43.0
OS-2 year (%)	90.9	-	-	-
ORR (CR+PR) (%)	27.3	0	1.6	0

2084 Poster Session

Phase 2 study of nivolumab for patients with meningiomas refractory to surgery and radiotherapy with immune-related response criteria. First Author: Hikaru Sasaki, Tokyo Dental College Ichikawa General Hospital, Ichikawa, Japan

Background: The majority of meningiomas, which are the most common central nervous system (CNS) tumors, are benign and often cured by surgical resection alone. However, 20%–30% of meningiomas can be malignant tumors of CNS WHO grade II or III that are refractory to repetitive resection and radiotherapy. Moreover, a proportion of grade I meningiomas is associated with an aggressive clinical course reminiscent of grade II tumors. Reports of effective medical therapy for those tumors are extremely rare. **Methods:** A single-arm, open-label, phase 2 study was conducted to evaluate the efficacy and safety of nivolumab for meningiomas refractory to surgery and radiotherapy. Nivolumab (480 mg) was administered intravenously every 4 weeks and continued until tumor progression or unacceptable toxicity for up to 365 days. The primary endpoint was the objective response rate (ORR) determined by a central independent review committee. With a one-sided significance level of 5%, a power of 80%, a threshold response rate of 5%, and an expected response rate of 20%, the required sample size was calculated to be 27 patients using the exact binomial test. Considering a 10% attrition rate, the target sample size was set at 29. To avoid premature discontinuation of potentially effective immunotherapy, response was evaluated based on the iRANO (meningioma) criteria, which is based on the RANO (meningioma) criteria (Neuro Oncol 21(1):26-36, 2019) with the integration of the immune-related response criteria outlined previously (Lancet Oncol 16(15):e534-e542, 2015). Archival tumor specimens from all 29 cases were obtained for biomarker analyses. **Results:** A total of 29 patients started the study therapy. Response assessment by the central review committee was performed for 28 patients: grade I meningioma in 5, grade II in 19, and grade III in 4 by definition of the 2016 WHO criteria. The best overall response was PR in 1, SD in 13, and uPD/cPD in 14. The ORR was 3.6% and progression-free survival at 6 months was 23.9%. Biallelic inactivation of the *NF2* gene was detected in 20/27 cases (74%), whereas biallelic inactivation of the *CDKN2A* gene was identified in 7/27 cases (26%). One patient who had multiple grade I meningiomas with biopsy-proven lung metastases showed near CR following initial radiological progression. The TMB of the tumor was 8.1/MB. Next-generation sequencing found that none of the tumors had mutations of the DNA mismatch repair genes. Nivolumab was well tolerated. **Conclusions:** Although nivolumab monotherapy failed to meet the prespecified primary endpoint, our study demonstrated that a subset of patients could benefit from the therapy and that immune-related response criteria are necessary to evaluate immunotherapy for meningiomas. Clinical trial information: jRCT2031190074. Research Sponsor: Ono pharmaceuticals.

2085 Poster Session

Analysis of genetic mutation profile and CNS pharmacokinetics in relapsed/refractory primary CNS lymphoma patients responding to novel emavusertib (IRAK4i) and BTKi combination. First Author: Christian Grommes, Department of Neuro-oncology, Memorial Sloan Kettering Cancer Center, New York, NY

Background: Primary Central Nervous System Lymphoma (PCNSL) is a rare and aggressive non-Hodgkin lymphoma with no approved treatments for relapsed/refractory (R/R) patients, representing a critical unmet need. MyD88 mutations in ~70% of PCNSL patients drive Interleukin-1 receptor associated kinase 4 (IRAK4) activation, promoting NF-κB signaling, inflammation, and tumor progression. Emavusertib, a potent oral IRAK4 inhibitor, crosses the blood-brain barrier and shows preclinical synergy with Bruton tyrosine kinase inhibitors (BTKi), re-sensitizing BTKi-resistant cell lines. This study evaluates the molecular and pharmacokinetic (PK) data associated with responses to emavusertib + ibrutinib combination therapy in R/R PCNSL patients. **Methods:** The safety, clinical activity, and potential biomarkers of emavusertib in R/R PCNSL are being investigated in the ongoing open-label, Phase 1/2 TakeAim Lymphoma trial (NCT03328078). Pre-dose and 1.5-hour post-dose plasma samples were collected on Cycle 3 Day 1, Cycle 5 Day 1 and Cycle 7 Day 1. Cerebrospinal fluid (CSF) samples were obtained via a lumbar puncture within 1.5 hrs of collection of the post-dose plasma PK sample on Cycle 3 Day 1. Mutation analysis was based on patients' molecular pathology reports provided by trial sites. Sequencing of archival tissues, CSF and plasma are in progress. **Results:** As of 06 December 2024, CSF concentration data were available for 7 PCNSL patients. The mean emavusertib concentration in CSF was 81.3 ng/ml (54.7-104.0) in patients receiving 100 mg emavusertib BID (n = 4). In patients receiving 200 mg emavusertib BID (n = 3), the mean emavusertib concentration in CSF was higher at 175.7 ng/ml (114.8-209.4), which is 2.2X the mean value in patients who received 100 mg emavusertib BID (p-value = 0.02). All 7 patients received 560 mg ibrutinib QD, and the ibrutinib concentrations in the CSF were consistent with findings from previously published clinical studies. MyD88 mutation status was available for 7 patients of which all had prior exposure to BTKi regimens. Among these, 6 patients had MyD88 mutation of which 4 patients had responded (3 complete responses and 1 partial response) to emavusertib + ibrutinib combination with duration of response (DOR) up to 18.9 months with data collection ongoing. **Conclusions:** Preliminary CNS pharmacokinetic data demonstrates that emavusertib concentration in CSF increases with increasing emavusertib dose. Patients with MyD88 mutations showed expected promising preliminary efficacy to emavusertib + ibrutinib combination and may overcome BTKi resistance. Enrollment in this trial is ongoing. Clinical trial information: NCT03328078. Research Sponsor: None.

2086 **Poster Session**

Unraveling survival disparities in primary central nervous system (CNS) lymphoma: An analysis of race, socioeconomic factors, and treatment outcomes using the Surveillance, Epidemiology, and End Results program (2000–2021). First Author: Imran Khan, NYC Health and Hospitals/Woodhull, Brooklyn, NY

Background: Primary central nervous system lymphoma (PCNSL) is a rare B-cell non-Hodgkin lymphoma with survival outcomes influenced by treatment, demographic, and socioeconomic factors (Villano JL et al., Br J Cancer, 2011). This study evaluated survival disparities associated with race, socioeconomic status (SES), and treatment modalities in PCNSL patients using a large U.S. population database. **Methods:** This retrospective cohort study used the SEER-17 database to analyze data from 7,068 patients diagnosed with PCNSL between 2000 and 2021. Demographic, socioeconomic, and treatment data were collected. Kaplan-Meier analysis was used to compare survival across groups, and Cox proportional hazards models identified independent prognostic factors. **Results:** The cohort included 7,068 patients (52.3% male; mean age: 63 years, SD $\pm$ 15). Racial distribution was 63.9% Caucasians, 16.0% Hispanics, 12.2% Asian/Pacific Islanders, 7.3% African Americans, and 0.4% American Indian/Alaskan Natives. Among these, 27.3% received radiation, and 64.3% received chemotherapy. During the study period, 73.5% of patients died from PCNSL. Survival analysis revealed that Asian/Pacific Islanders had the longest median overall survival (OS) at 22 months (95% CI: 16.5–27.5), followed by Hispanics (16 months; 95% CI: 11.8–20.2), Caucasians (11 months; 95% CI: 9.8–12.2), and American Indian/Alaskan Natives with the shortest survival at 5 months (95% CI: 0–11.2) ($p<0.001$). Socioeconomic analysis showed a direct association between higher income and improved OS: patients with household incomes $\geq$75k had a median OS of 13 months (95% CI: 11.2–14.8), compared to 6 months (95% CI: 4.2–7.8) in those earning $<$50k ($p<0.001$). Multivariable Cox regression identified male sex (HR 1.21, $p<0.001$) and older age (HR 1.027, $p<0.001$) as adverse prognostic factors, while chemotherapy significantly improved survival (HR 0.43, $p<0.001$). Radiation provided a modest benefit (HR 0.913, p=0.005). **Conclusions:** This large study demonstrates that lower income levels and racial disparities are associated with reduced survival in PCNSL. Findings underscore the need for equitable healthcare access and tailored therapeutic strategies to address these inequities. Keywords: CNS lymphoma, survival disparities, socioeconomic status, race, treatment outcomes, public health oncology. Research Sponsor: None.

2087 **Poster Session**

Predicting survival in malignant meningiomas: A machine learning approach. First Author: Mustafa Alshwayyat, Jordan University of Science and Technology, Irbid, Jordan

Background: Intracerebral meningiomas account for over 90% of all meningioma cases, with only 1–3% classified as malignant. Malignant meningiomas remain understudied compared with other brain tumors. This study is the first to apply machine learning (ML) to identify prognostic factors and improve outcomes of malignant intracerebral meningiomas. **Methods:** Data were obtained from the SEER database (2004-2021). Patients who met any of the following criteria were excluded: diagnosis not confirmed by histology; previous history of cancer or other concurrent malignancies; or unknown data. To identify prognostic variables, we conducted Cox regression analysis and constructed prognostic models using ML algorithms to predict the 5-year survival. Patient records were randomly divided into training (70%) and validation (30%) sets. A validation method incorporating the area under the curve (AUC) of the receiver operating characteristic curve was used to validate the accuracy and reliability of the ML models. We also investigated the role of multiple therapeutic options using Kaplan-Meier survival analysis. **Results:** A total of 1,363 patients were included. Most patients were White (71.8%) or female (56.7%). The median patient age was 62 years, and the median tumor size was 4.8 cm. Most of the tumors were localized (67.8%). Adjuvant radiation therapy was administered to 50.2% of the patients. Patients aged $<$ 62 years exhibited better 5-year survival rates, with an overall survival (OS) of 79.4% and cancer-specific survival (CSS) of 82%, compared to those aged $\geq$ 62 years, who had an OS of 40.9% and CSS of 50.6%. Tumors smaller than 4.5 cm were associated with higher survival rates (OS: 67.7%, CSS: 72.4%) than larger tumors (OS: 53.6%, CSS: 61.9%). The impact of adjuvant radiation therapy showed an OS of 59.9% and 64.5%, respectively, compared with those who did not receive radiation, with an OS of 59.5% and CSS of 68.7%. Multivariate Cox regression analysis identified older age (HR: 3.6, 95% CI: 3.03–4.4) and large tumor size (HR: 1.4, 95% CI: 1.22–1.7) as poor prognostic factors. The Random Forest and MLP classifiers were the most accurate models. The ML models identified age as the most significant prognostic factor. The performance metrics for all the ML algorithms are summarized in Table. **Conclusions:** This study underscores the transformative potential of ML in enhancing personalized medical approaches for malignant intracerebral meningiomas. Furthermore, whether the benefits of adjuvant radiotherapy outweigh the risks remains unclear, indicating the need for further targeted research to investigate its therapeutic impact on these rare tumors. Research Sponsor: None.

ML Model	Accuracy	Precision	Recall	F1 score	AUC
LR	63%	50.8%	61.2%	55.6%	0.696
KNN	63.3%	51.2%	45.1%	48%	0.660
RFC	69.1%	58.9%	60.2%	59.5%	0.743
GBC	66.2%	55.6%	52.6%	54.1%	0.723
MLP Classifier	67.48%	57.47%	53.76%	55.56%	0.716

TPS2088 **Poster Session**

Phase IIa study of αDC1 vaccines targeting HER2/HER3 combined with pembrolizumab in patients with asymptomatic brain metastasis from breast cancer. First Author: Shipra Gandhi, Roswell Park Comprehensive Cancer Center, Buffalo, NY

Background: Brain metastases develop in up to 50% of patients (pts) with metastatic breast cancer. Overexpression of HER3 in brain metastatic breast cancer (BMBC) is a resistance factor to HER2-targeted therapies and a driver of brain metastasis. Disease progression is associated with loss of anti-HER2 and anti-HER3 immunity. Previously, we have demonstrated that glioma-specific peptide-loaded αDC1 which produces CXCL9, CXCL10, CXCL11, and CCL5, the chemokines that attract CXCR3- and CCR5-expressing cytotoxic T-lymphocytes (CTLs) and T-helper 1 (Th1) cells, induce clinical responses and long-term disease stabilization in pts with aggressive recurrent primary brain tumors (Okada et al. JCO 2011. PMID: 21149657). We hypothesized that anti-HER2/3-loaded αDC1 combination with PD1 blockade will result in a strong Th1/CTL response against HER2/3 epitopes (Basu A et al. Cancer Immunol Res. 2022 PMID: 34785506) that will translate into anti-cancer benefit in the central nervous system (CNS) and systemically. **Methods:** This is a phase II single-arm, non-randomized multicenter study (NCT04348747). Eligibility includes pts with BMBC $\geq$18 years, ECOG PS $\leq$1, normal marrow and organ function with asymptomatic untreated brain metastases $\geq$ 5 mm. The study subjects receive αDC1 q3 weeks x 3 along with pembrolizumab every 3 weeks. Thereafter, αDC1 booster doses can be administered every 3 months until disease progression, intolerable side effects, or withdrawal from study, up to 24 months. Baseline and 9-week post-αDC1 peripheral biopsies (non-CNS) are required for six pts. The primary endpoint is CNS response rate (RR) by RANO-BM criteria. If no CNS response is observed after 12 pts, the study will be terminated. If $\geq$ 1 response is observed, then 9 more pts will be enrolled, for a total of 21 pts. If $\geq$ 3 CR are observed, the proposed therapy will be considered promising for further evaluation. Secondary endpoints include non-CNS RR per RECIST v1.1, median CNS, non-CNS and overall progression-free survival, overall survival, and safety. Exploratory endpoints include changes in intratumoral biomarkers (CTLs, PDL1, chemokines) in pre- and post-treatment peripheral tumor biopsies and immune changes in the blood. So far, 7 of the planned 21 pts have been enrolled. Clinical trial information: NCT04348747. Research Sponsor: U.S. Department of Defense.

TPS2089 **Poster Session**

A multicenter, randomized, controlled, pivotal trial of microbubble-enhanced transcranial focused ultrasound for patients with NSCLC brain metastases (LIMITLESS). First Author: Manmeet Singh Ahluwalia, Miami Cancer Institute, Baptist Health South Florida, Miami, FL

Background: The efficacy of systemic therapies for brain metastases (BM) is hindered by the blood-brain barrier (BBB) and brain-tumor barrier. Transcranial low-intensity focused ultrasound combined with IV microbubble oscillators (MB-FUS), allows for localized, controlled, non-invasive and temporary BBB opening, which has been shown to enhance tumor drug delivery of systemic therapies, as well as impro efficacy of immunotherapies. Non-small cell lung cancer (NSCLC) is the most common cause of BM, and this randomized controlled trial (RCT) aims to evaluate the safety and efficacy of MB-FUS-mediated BBB opening combined with standard of care (SOC) systemic therapy versus systemic therapy alone for patients with NSCLC BM. **Methods:** LIMITLESS is prospective, multicenter, parallel-arm, RCT, ongoing at up to 30 centers, that randomizes patients with NSCLC BM, in a 2:1 ratio to either: (i) Arm 1: MR-guided MB-FUS plus all FDA approved on-label use of immune checkpoint inhibitors (ICIs) with or without chemotherapy regimen (SOC systemic therapy), or (ii) Arm 2: SOC systemic therapy alone. Included patients are $\geq$18 years aged, with normal organ function, KPS $\geq$70, and have $\geq$0.5 cm size BM meeting measurable disease criteria as per RANO-BM. Patients on both arms receive standard-of-care therapy, while those on arm 1 also undergo MB-FUS. Patients undergo pre-treatment brain MRI, followed by IV administration of microbubbles for enhanced sonication effects. BBB opening is performed using a transcranial 220 kHz device with 1024-element phased array transducer with real-time acoustic feedback-based power control for maintaining effective microbubble activation. The primary study outcome is the overall objective response rate (ORR) at 6 months as assessed using RANO-BM criteria. Using a Bayesian design for power analysis, a superior ORR of 60% is assumed for MB-FUS arm versus 30% in the control arm for a total sample size of N = 96, 64 participants in MB-FUS and 32 in control arm, for 80% power using a two-sided chi-square test with an alpha of 0.05. For the upper-bound estimate, ORR of 45% in MB-FUS arm and 30% in the control arm, the study needs N = 369 participants: 246 in LIFU arm and 123 in control arm. The secondary outcomes are best objective response rate and median time-to-response per treatment arm. Exploratory outcomes are median progression-free survival (PFS), overall survival (OS), median intracranial PFS, median extracranial PFS, and quality of life. Patient enrollment commenced in 2022 and is ongoing (ClinicalTrials.Gov Registration: NCT05317858). Clinical trial information: NCT05317858. Research Sponsor: Insightec Inc.

TPS2090 Poster Session

Delayed or upfront brain radiotherapy in treatment-naïve lung cancer patients with asymptomatic or minimally symptomatic brain metastases and ALK rearrangements (DURABLE). First Author: Joshua David Palmer, Department of Radiation Oncology, Ohio State University, Columbus, OH

Background: Patients with non-small cell lung cancer (NSCLC) with ALK rearrangements have a high frequency of brain metastases. Alectinib was shown to be superior to crizotinib in the first-line treatment of patients with ALK-positive NSCLC in the ALEX trial, and the intracranial response rate (CNS ORR) was 85.7% with alectinib versus 71.4% with crizotinib in patients who received prior radiotherapy and 78.6% versus 40.0%, respectively, in those who had not. Alectinib has also shown benefit in earlier stages of NSCLC. Given the high intracranial efficacy rate demonstrated by alectinib, as well as the known toxicities of cranial irradiation, the role of early irradiation of CNS disease vs delaying radiation in favor of treatment with alectinib needs to be defined to inform clinical practice. **Methods:** NCT05987644 is a multi-center, multi-cohort study consisting of a Phase 1b and Phase 2 portion. The Phase 1b portion of the study is a single-arm, open label study of alectinib in patients with CNS disease. Twelve subjects will be enrolled in the Phase 1b portion of the study and treated with alectinib alone; patients with PD will come off study treatment and move on to standard of care treatment per national guidelines. The phase 2 portion will be a randomized, non-blinded, open-label study. Forty-four subjects will be enrolled and randomized 1:1 to either alectinib upfront (Arm A) or alectinib + SRS (arm B). A group sequential design will be implemented with one interim analysis for futility and, and one final analysis using the composite outcome. The primary objective of phase 1b is to determine the safety and feasibility of delayed brain radiation in patients with ALK fusion positive NSCLC and CNS metastases. The primary objective of the phase 2 study is to determine whether treatment with alectinib results in preserved neurological status and control of CNS disease at 12 months compared to alectinib plus SRS. Secondary endpoint will be intracranial progression free survival at 12 months (icPFS12), response rate and icPFS, OS, and safety and tolerability. The study is open and accruing at 4 sites. Clinical trial information: NCT05987644. Research Sponsor: Genentech.

TPS2091 Poster Session

FORTE: A phase 2 master protocol assessing plixorafenib for BRAF-altered cancers. First Author: Karisa C. Schreck, Johns Hopkins School of Medicine, Baltimore, MD

Background: Plixorafenib (FORE8394; PLX8394) is a novel, oral, small-molecule BRAF inhibitor highly selective for BRAF V600 monomers and BRAF-containing dimers. Plixorafenib binding disrupts RAF dimerization, targeting both BRAF V600 mutations and fusions, thereby preventing paradoxical activation and avoiding the need for combination with a MEK inhibitor. In a phase 1/2a study, plixorafenib demonstrated promising safety and clinical activity across a range of doses tested in tumors with BRAF V600 mutations or fusions. The most common adverse events (AEs) included predominantly low-grade liver function test changes and grade 1 fatigue, nausea, diarrhea, and vomiting. **Methods:** The FORTE Phase 2 basket study is currently enrolling patients ≥10 years of age into 4 sub-protocols. Study details are shown in theTable. Eligible patients have received prior therapy for advanced disease, have measurable disease, and have a Karnofsky (≥16 years) or Lansky (<16 years) Performance Score of ≥60 at study entry. All patients receive plixorafenib continuous dosing, in some cohorts coadministered with cobicistat, a pharmacokinetic (PK) booster. Prior MAPK inhibitor therapy is excluded unless otherwise specified below. As of January 2025, the trial is recruiting participants in 9 countries globally, with 54 sites activated. Clinical trial information: NCT05503797. Research Sponsor: Fore Biotherapeutics.

	Sub-Protocol A	Sub-Protocol B	Sub-Protocol C	Sub-Protocol D
Patient Population	Advanced solid and primary CNS tumors harboring BRAF fusions	BRAF V600-mutated recurrent primary CNS tumors	Rare[1] BRAF V600-mutated advanced solid tumors	BRAF V600-mutated melanoma[2] or thyroid cancer without anaplastic or undifferentiated components
Planned Enrollment	~100	~50	~75	~12
Design	Single-arm, open-label, Bayesian optimal phase 2 design			1:1 randomized, open-label crossover design to compare plixorafenib administered alone and with PK booster
Planned Efficacy Interim Analyses	N=25 N=50	N=25	N=25 N=50	None
Primary Endpoint	ORR[3]			Intra-patient PK
Key Secondary Endpoints	DOR, DCR, PFS, OS, PK, Safety			Safety, ORR, DOR, DCR, PFS, OS, Safety
Key Exploratory Endpoint	Longitudinal ctDNA assessments[4]			

[1]BRAF V600-mutated tumors occurring in ≤40,000 US patients annually (eg, ovarian/gynecologic cancers, cholangiocarcinoma, small intestinal/gastrointestinal cancers other than colorectal adenocarcinoma, neuroendocrine cancers).
[2]Patients with melanoma should have received and not tolerated a prior BRAF inhibitor.
[3]Response assessed by BICR using RECIST v1.1 for solid tumors or RANO HGG or LGG for primary CNS tumors. ORR for primary CNS tumors using RANO 2.0 is an exploratory endpoint. Tumors assessed at cycle 1 day 1, every 9 weeks for 48 weeks, then every 12 weeks.
[4]Plasma for all patients; plasma and CSF for patients with primary CNS tumors.

TPS2092 Poster Session

Retifanlimab with bevacizumab and hypofractionated radiotherapy to treat recurrent glioblastoma. First Author: Nishika Karbhari, Mayo Clinic, Rochester, MN

Background: Glioblastoma (GBM) is the most common primary brain malignancy in adults. GBM is universally recurrent and associated with dismal outcomes. Re-irradiation (reRT) is ideal for evaluating combination therapy for recurrent GBM (rGBM) due to its multifactorial mechanism of action, including downstream immunomodulatory activity. RT (especially multi-fraction) increases immunogenicity in preclinical models by promoting immune activation, immune migration, and antigen uptake. Additionally, a recent study demonstrated enhanced PD-L1 expression in the glioma tumor microenvironment (TME) following RT, and combining stereotactic RT with a PD-1 inhibitor improved survival in murine models. Retifanlimab is a humanized monoclonal anti-PD1 IgG4 antibody that received FDA approval for adults with metastatic or recurrent locally advanced Merkel cell carcinoma. Bevacizumab, an anti-VEGF antibody, is a treatment for radiation necrosis/cerebral edema with less immune suppression than corticosteroids. In a previous Phase 2 study, hypofractionated RT (HFRT), retifanlimab, and bevacizumab was associated with a 9-month overall survival (OS) rate of 71.4%. To demonstrate the efficacy of this regimen compared to HFRT and bevacizumab, we have designed a new randomized controlled Phase 2 trial. We hypothesize that combination reRT with retifanlimab will produce a more robust anti-tumor immune response and improve OS compared to reRT without retifanlimab. **Methods:** This is a multicenter, open-label, randomized, controlled Phase 2 study of retifanlimab, bevacizumab, and HFRT for adult patients with rGBM. Patients are randomized 1:1 to the experimental (bevacizumab + retifanlimab + HFRT) or control cohort (bevacizumab + HFRT). Key eligibility criteria include age ≥ 18 years, Karnofsky performance status ≥ 60, ≥ 4 months since administration of any prior bevacizumab, and dexamethasone dose ≤ 4 mg at the time of randomization. The primary endpoint is 9-month OS. Secondary endpoints include OS, progression-free survival, objective response rate, neurologic assessment by NANO criteria, and adverse events profile. Protocol treatment will continue up to two years, or until progression or intolerable toxicity. Survival follow up will continue every two months, up to four years. Seven of the planned 94 patients have been enrolled as of submission on 1/28/25. Clinical trial #: NCT06160206. Funding provided by Incyte. Clinical trial information: NCT06160206. Research Sponsor: Incyte Corporation.

TPS2093 Poster Session

PEAR-GLIO: Clinical evaluation of an AI-driven functional precision medicine platform for therapeutic efficacy in gliomas. First Author: Matthew Williams, Ourotech Ltd t/a Pear Bio, London, United Kingdom

Background: Gliomas and other primary brain tumors remain a leading cause of cancer-related mortality, with limited predictive biomarkers to guide therapy selection. The PEAR-GLIO trial investigates the use of Pear Bio's AI-driven ex vivo platform to assess the therapeutic sensitivity of FDA-approved and experimental treatments on patient-derived 3D immune-microtumors. This observational study seeks to validate whether this platform can provide actionable insights for patient stratification and treatment optimization in subsequent trials. The trial also incorporates patient and public involvement and engagement (PPIE) to understand perspectives and enhance study design and accessibility. **Methods:** PEAR-GLIO (NCT06038760) is a UK-based, observational study enrolling 50 patients diagnosed with operable primary brain tumors, including grades 2–4 gliomas. Inclusion criteria require histologically confirmed malignancy, the ability to provide ≥0.4g of tumor tissue and 40mL of whole blood, and consent for data and sample use. Exclusion criteria include pre-surgical chemotherapy or radiotherapy within 30 days and inoperable disease. Tumour-extracted and immune patient cells are cultured as physiologically-relevant 3D immune-microtumors and exposed to FDA-approved and experimental treatments. Phenotypic and molecular responses, including changes in tumour viability, cell death, migration, immune cell infiltration are assessed using live imaging and computer vision. The study uniquely integrates real-time confocal imaging and omics analyses to evaluate drug mechanisms of action. This includes correlation of ex vivo responses with biomarkers such as MGMT methylation, IDH mutation, and 1p/19q co-deletion, alongside exploratory analysis of experimental therapies. Recruitment began in October 2023, with 12 patients of the target 50 enrolled thus far. Data from the first cohort will inform platform optimization and scalability. All biological samples are anonymized, with outcomes tracked per RANO guidelines. Even at this early stage, PPIE has helped improve trial design. We are concurrently validating the platform in other high-unmet-need indications including early-stage breast cancer (NCT05435352), metastatic breast cancer (NCT06182306) and metastatic kidney cancer (NCT06264479) hoping to shift the paradigm in precision treatment selection. Clinical trial information: NCT06038760. Research Sponsor: Ourotech (t/a Pear Bio).

TPS2094 **Poster Session**

A multicenter, pivotal trial of microbubble-enhanced transcranial focused ultrasound (MB-FUS) for plasma-based liquid biopsy in patients with glioblastoma (LIBERATE). First Author: Manmeet Singh Ahluwalia, Miami Cancer Institute, Baptist Health South Florida, Miami, FL

Background: Liquid biopsy in glioblastoma (GBM) is hindered by a lack of requisite circulating tumor (ct) and cell-free (cf) DNA levels in blood due to the blood-brain barrier (BBB). This limits the identification of blood-based tumor biomarkers along with the development and use of biomarker-driven systemic therapies. Low intensity focused ultrasound combined with intravenously administered microbubble oscillators (MB-FUS), leads to non-invasive BBB opening. This trial aims to evaluate the utility of LIFU for bolstering blood ctDNA and cfDNA for enhance liquid biopsy in patients with GBM. **Methods:** LIBERATE is an ongoing, prospective, multi-center, self-controlled, pivotal trial evaluating safety and technical efficacy of transcranial MR-guided MB-FUS for increasing blood ctDNA and cfDNA levels in adults, aged 18-80 years with GBM. Patients with suspected GBM planned for tumor biopsy or resection at 17 centers in US and Canada are being enrolled. Patients with multifocal tumors or tumors arising from deep midline, thalamus, cerebellum, or brainstem are excluded. Patients are administered IV microbubbles for enhanced sonication, after which MR-guided BBB opening using a 220 kHz device, with 1024-element phased array transducer, is performed with real-time acoustic feedback control for effective cavitation. Pre- and post-procedure, phlebotomy and MRI brain are done. Patients are offered optional 2nd procedure during adjuvant chemotherapy phase if willing. Primary efficacy endpoint is correlation between biomarker patterns in tumor tissue collected during surgery/biopsy and blood collected following MB-FUS procedure. Confirmatory secondary efficacy endpoint is ratio between greatest yield of cfDNA in blood post-MB-FUS compared to cfDNA level in blood pre-MB-FUS. The primary study hypothesis is that agreement rate on biomarker pattern between resected/biopsied tumor tissue and blood is $>$ 70%. The secondary hypothesis is that MB-FUS BBBO leads to a $\geq$2-fold rise in blood cfDNA. Assuming the true agreement rate expected is 89%, a sample of N = 50 patients will provide 90% power to meet the primary endpoint (Exact test, Binomial Proportion, one-sided Alpha = 0.025). Exploratory endpoints include (1) sensitivity of detection of known specific somatic mutations in ctDNA from blood samples collected before and after MB-FUS, (2) estimation of ctDNA levels in samples collected at 30-minutes, 1-hour, 2-hour, and 3-hour post-MB-FUS to determine time of greatest yield, (3) correlation of MRI parameters related to grading of BBB opening and ctDNA-based biomarkers from post-MB-FUS blood samples, (4) biomarker correlation between plasma cfDNA sampled during adjuvant chemotherapy phase and tumor tissue harvested at surgery. Patient enrollment commenced in 2022 and is ongoing (NCT05383872). Clinical trial information: NCT05383872. Research Sponsor: Insightec Inc.

TPS2095 **Poster Session**

Liposomal curcumin and standard radiation and temozolomide for newly diagnosed high-grade gliomas: A phase 1/2 study. First Author: Matthias Holdhoff, Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins, Baltimore, MD

Background: Curcumin, derived from turmeric (Curcuma spp.), exhibits anti-inflammatory and antitumoral activity in preclinical studies, including inducing cell cycle arrest, apoptosis, autophagy and disrupting key cancer signaling pathways (e.g., STAT-3, AKT, VEGF, NF-κB, and IDO). Despite its promise, oral curcumin has limited bioavailability. Liposomal curcumin (LC), a novel intravenous formulation, achieves plasma curcumin levels over 1000 times higher than oral administration and preferentially accumulates in tumor cells. In preclinical glioma models, LC has antitumoral efficacy, particularly when combined with cytotoxic therapies. Previous trials in healthy volunteers and cancer patients demonstrated LC's safety, pharmacokinetics, and manageable adverse effects, with doses up to 300 mg/m² being well-tolerated. However, a case of hemolytic anemia was observed in a prior study at this dose in a patient who was also taking several known hemolytic drugs, suggesting the need for further safety evaluation at this and potentially higher doses. **Methods:** This Phase I/II open-label, study evaluates LC combined with standard radiation (RT) and concomitant and adjuvant temozolomide (TMZ) in newly diagnosed HGG patients (NCT05768919). The primary endpoints are MTD, RP2D and safety. Secondary endpoints include treatment feasibility ($\geq$80% adherence to LC, RT, and $\geq$60% to TMZ), and exploratory efficacy measures (PFS, OS by RANO criteria). The study has two phases: (1) dose-escalation using the TITE-BOIN method to determine MTD, and (2) dose-extension to evaluate RP2D safety and feasibility. Up to 50 patients will be screened to enroll 30. LC is given weekly at 4 dose levels (240, 300, 350, and 400 mg/m²) alongside standard adjuvant TMZ (150–200 mg/m² x 5 days every 28 days) and RT. Treatment continues for up to 6 TMZ cycles, with LC monotherapy possible afterward until progression or toxicity. MRI is done before and 4 weeks post-chemoradiation, then every 2 cycles of TMZ, as per standard of care. DLTs are evaluated over 10 weeks to determine the MTD which will be determined by TITE-BOIN dose escalation rule and Safety Review Committee's guidance. A separate exploratory protocol is offered to patients interested in additional imaging, which uses chemical exchange saturation transfer (CEST) MRI to visualize liposome accumulation in tumor tissue non-invasively. As of 1/24/2025, 14 patients have been enrolled in the dose-escalation part of this study. Clinical trial information: NCT05768919. Research Sponsor: SignPath Pharma.

TPS2096 **Poster Session**

A global phase 3, open-label, randomized 2-arm study comparing the clinical efficacy and safety of niraparib with temozolomide in adult participants with newly-diagnosed, MGMT unmethylated glioblastoma. First Author: Nader Sanai, Ivy Brain Tumor Center at Barrow Neurological Institute, Phoenix, AZ

Background: Glioblastoma (GBM) is associated with dismal prognosis and poor quality of life. In approximately 60% of tumors, the O6-methylguanine methyltransferase (MGMT) promoter is unmethylated and the prognosis is even more dire, with a median overall survival (OS) of 12.7 months following surgical resection, temozolomide (TMZ), and fractionated radiotherapy (RT). Poly (ADP-ribose) polymerase (PARP) mediates DNA damage response in GBM and niraparib is an investigational PARP1/2-selective inhibitor. At ASCO 2024, we reported on a Phase 0/2 study of niraparib plus radiotherapy in newly-diagnosed, MGMT-unmethylated glioblastoma (GBM), demonstrating superior tumor pharmacokinetic and pharmacodynamic performance compared to other studied PARP inhibitors and a median overall survival (OS) of 21.7 months. Based on the proof-of-concept data, a global registrational Phase 3 study (Gliofocus) was initiated. **Methods:** This Phase 3, open-label, randomized 2-arm study (NCT06388733) will compare niraparib versus TMZ in 450 adult participants with newly-diagnosed, MGMT-unmethylated GBM. Participants must have a biopsied or resected GBM, per 2021 World Health Organization classification. MGMT promoter methylation status is determined locally by validated pyrosequencing or quantitative methylation-specific polymerase chain reaction assays. Other key inclusion/exclusion criteria include: (1) Karnofsky performance status of $\geq$70, (2) no prior treatment for GBM (including brachytherapy or BCNU wafers), (3) no tumor-treating field therapy, and (4) suitability for RT of 60 Gy in 30 fractions using ESTRO-EANO 'single phase' targeting approach. Following 1:1 randomization, niraparib (Arm A) or TMZ (Arm B) is administered concomitantly with RT and then adjuvantly until disease progression by Blinded Independent Central Review (BICR) or until completion of 6 cycles of TMZ. . The primary endpoints of the study are progression-free survival (PFS) (per RANO 2.0; HR = 0.612, 90% power, 1-sided alpha = 0.001) and overall survival (OS) (HR = 0.698, 90% power, 1-sided alpha = 0.0239). Secondary endpoints include overall response rate, health-related quality of life, neurocognitive function, and the safety and tolerability of niraparib compared to TMZ. The first patient was accrued in June 2024 and an interim futility analysis is planned in 2025. This study, sponsored by the Ivy Brain Tumor Center and with drug and funding provided by GSK, is expected to enroll in a minimum of 115 clinical sites across 11 countries. Clinical trial information: NCT06388733. Research Sponsor: GSK.

TPS2097 **Poster Session**

Personalized targeted glioblastoma therapies by *ex vivo* drug screening: Advanced brain tumor therapy clinical trial (ATTRACT). First Author: Anna Sophie Berghoff, Division of Oncology, Department of Medicine I, Medical University of Vienna, Vienna, Austria

Background: Targeted therapies used in a personalized treatment concept have revolutionized the management of several solid cancers. So far, various clinical trials aiming to introduce the concept of personalized targeted therapies in glioblastoma have failed, as no clinically meaningful responses were observed. Importantly, most clinical trials investigating molecular targeted therapies included all-comers and concentrated on genetic biomarkers to predict treatment response. Given the biological complexity of glioblastoma, genetic biomarkers might give only an insufficient insight into the response of a given patient, and more personalized approaches are warranted. As novel approaches to guide personalized treatment in glioblastoma are urgently needed, we designed a prospective clinical trial to investigate the novel approach of cultivated patient-derived tumor cells (PDCs) for *ex vivo* drug screening. **Methods:** In this randomized phase 2 study, we are testing the ability of PDC-based *ex vivo* drug screening to formulate a personalized recommendation for maintenance treatment in patients with newly diagnosed glioblastoma with unmethylated MGMT promoter after neurosurgical resection followed by combined radio-chemotherapy. Based on overall survival as the primary endpoint, we plan to include 240 patients (120 per group) to show with a power of 80% that we can increase the median survival from 12 to 17 months (hazard ratio 0.7). Patients are randomized 1:1 to either the standard group (no drug screening) or the intervention group (drug screening and personalized recommendation for maintenance treatment). In the intervention group, automated drug screening is performed on PDCs with 28 drugs used for treatment of solid tumors and hematological malignancies. Based on the cytotoxic/cytostatic activity of these drugs, as quantified by relative viability based on adenosine triphosphate levels, a molecular tumor board recommends a personalized treatment regimen. The first patient was enrolled in July 2024. Interim analysis of the ATTRACT study (NCT06512311) is expected in late 2027, and final results in 2030. Moreover, the clinical trial is accompanied by a comprehensive translational research program to gain insights into the biological underpinnings of treatment response in glioblastoma. Clinical trial information: NCT06512311. Research Sponsor: Ludwig Boltzmann Society.

TPS2098 **Poster Session**

Trial in progress: Feasibility of CSF and plasma ctDNA in BRAF-altered glioma during treatment with plixorafenib. First Author: Karisa C. Schreck, Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins, Baltimore, MD

Background: Gliomas with BRAF alterations are often difficult to treat in the recurrent setting due to emergent resistance to FDA-approved targeted therapies. Additionally, it can be difficult to assess response to treatment given the limitations of radiographic techniques and the infeasibility of serial tissue sampling. This protocol serves as a prototype for determining the feasibility of using CSF and plasma circulating tumor DNA (ctDNA) as biomarkers for response to a novel-BRAF inhibitor, plixorafenib. Plixorafenib is a small-molecule selective inhibitor of BRAF-V600E and BRAF-fusion alterations that does not induce paradoxical reactivation of MAPK signaling. **Methods:** This study is a single institution trial of plixorafenib in patients (18+ years of age) with BRAF-V600E mutant glioma following progression on prior BRAF-targeted therapy who are recommended for a clinically-indicated diagnostic or debulking surgery. Eligible patients have recurrent BRAF-V600E mutant glioma (any grade) with measurable disease (by RANO 2.0), have a Karnofsky performance status >70, and are able to undergo surgery. Leptomeningeal disease is allowed. A total of 12 evaluable patients will be enrolled. Enrolled patients undergo clinically-indicated resection or biopsy for confirmation of disease progression and characterization of putative resistance alterations. All patients have a ventricular reservoir placed at time of surgery with CSF and plasma sampling. Patients will initiate oral plixorafenib 900mg daily with cobicistat, a CYP3A inhibitor and PK enhancer, when clinically recovered from surgery. Patients will take the drug continuously under fasting conditions. MRI, CSF, and plasma assessments will occur approximately every two months to evaluate disease status. The primary endpoint is proportion of samples with detectable tumor ctDNA baseline and after one month of treatment with plixorafenib. Secondary endpoints include the correlation of ctDNA with disease status over time and response rate to plixorafenib. The trial is IRB approved and currently open to enrollment. Clinical trial identifier NCT06610682. Clinical trial information: NCT06610682. Research Sponsor: Ivy Brain Tumor Foundation; Fore Biotherapeutics.

TPS2099 **Poster Session**

Neuro-oncology anywhere 242: Pilot study evaluating telehealth and in-person assessments in patients with glioma receiving oral chemotherapy—Clinical trial in progress. First Author: Ugur Sener, Division of Neurology, Mayo Clinic, Rochester, MN

Background: Gliomas are the most common primary central nervous system (CNS) malignancy in adults, accounting for 26.3% of all brain tumors. Care at high volume centers is associated with an overall survival benefit, but access to in-person evaluations can be challenging due to disease-related neurological disability and loss of income. Telehealth represents a convenient and efficient alternative to in-person evaluations, but acceptability and comparative safety of this care delivery modality has not been prospectively evaluated among glioma patients undergoing chemotherapy. **Methods:** This single-arm non-randomized pragmatic clinical trial evaluates patient satisfaction with, and safety of video-enabled telehealth assessments compared to in-person evaluations for patients with glioma undergoing temozolomide chemotherapy. The study includes adult patients with a diagnosis of glioma requiring adjuvant temozolomide chemotherapy. Participants act as their own controls, alternating between in-person and telehealth assessments while undergoing chemotherapy dosed per standard of care. Monitoring labs are completed locally and transmitted electronically. For participants without access to Wi-Fi or a device (e.g. mobile phone or computer), cellular-enabled tablet devices are provided to facilitate appointments and completion of electronic study components. All participants who travel to in-person appointments are reimbursed for travel expenses. The primary outcome measure is patient satisfaction with care delivered, as measured by institutional Press-Ganey survey scores obtained following telehealth and in-person assessments. A key secondary outcome measure is completion rate of planned oral chemotherapy, tracked using a digital pill diary incorporated into our institutional electronic health record. The digital diary allows real-time tracking of chemotherapy adherence and adverse events experienced by participants. Other secondary outcomes include acute care utilization days following telehealth and in-person visits (defined as emergency department evaluations and days of inpatient stay), neurologic disability as measured by the Neurologic Assessment in Neuro-Oncology (NANO) scale, and disease related quality of life measured by the EORTC QLQ-C30. All participant surveys are self-reported and completed electronically. This decentralized pragmatic clinical trial provides unprecedented, prospective real-world data on utilization of telehealth services compared to in-person visits for patients undergoing chemotherapy for glioma. We expect the data generated to inform the design and conduct of future decentralized interventional neuro-oncology trials. NCT06625047 opened for enrollment in October 2024, 16 of 30 intended participants were accrued as of January 2025. Clinical trial information: NCT06625047. Research Sponsor: Mayo Clinic.

TPS2100 **Poster Session**

Update on GBM AGILE: A global, phase 2/3 adaptive platform trial to evaluate multiple regimens in newly diagnosed and recurrent glioblastoma. First Author: Emma Maria Viktoria Hyddmark, Global Coalition for Adaptive Research, Larkspur, CA

Background: GBM AGILE (Glioblastoma Adaptive, Global, Innovative Learning Environment) is a biomarker based, multi-arm, international, seamless Phase 2/3 response adaptive randomization platform trial designed to efficiently identify investigational therapies that improve overall survival and confirm efficacious therapies and associated biomarker signatures to support drug approvals and registration. GBM AGILE is a collaboration between academic investigators, patient organizations, and industry to support new drug applications for newly diagnosed and recurrent glioblastoma. **Methods:** The primary objective of GBM AGILE is to identify therapies that improve overall survival in patients with newly diagnosed or recurrent glioblastoma. Operating under a Master Protocol, GBM AGILE allows multiple drugs from different pharmaceutical/biotech companies to be evaluated simultaneously and/or over time against a common control. New investigational therapies are added as new information about promising drugs is identified, while other therapies are removed as they complete evaluation. Bayesian response adaptive randomization is used within subtypes of the disease to assign participants to investigational arms based on their performance. GBM AGILE has screened over 2300 patients and enrollment continues to be robust. An estimated 25% of all US glioblastoma patients enrolled in clinical trials participate in GBM AGILE. The trial is open at select sites in the United States, Canada, Switzerland, France, Germany, and Australia. In addition to the efficient evaluation of investigational arms, a primary goal of GBM AGILE is to expand knowledge of glioblastoma to support advancements in treatment using the data collected within the trial (learning environment). Over 7 million data points are currently available for inclusion in the development of a longitudinal model. Such a model may be able to inform randomization by providing earlier and continuous information regarding patient and arm performance. In addition, serial magnetic resonance imaging scans and biospecimens from baseline through patient progression are being collected for further analysis. An initial 500 baseline tissue samples are being characterized using whole genome sequencing and whole transcriptome analysis. Clinical trial information: NCT03970447. Research Sponsor: None.

TPS2101 **Poster Session**

Dual targeting of VEGF and PD-1: A phase I/II trial of ivonescimab, a novel bispecific antibody, in recurrent glioblastoma. First Author: Anuj Dilip Patel, University of Texas MD Anderson Cancer Center, Houston, TX

Background: Patients with recurrent glioblastoma have limited effective treatment options due to the highly immunosuppressive microenvironment and rapid proliferation fueled by neoangiogenesis. Anti-angiogenic therapy, including targeting vascular endothelial growth factor (VEGF) with bevacizumab, and immune checkpoint inhibition with programmed cell death protein 1 (PD-1) inhibitors, have independently had limited efficacy in these tumors. Ivonescimab is a humanized tetravalent bispecific antibody against PD-1 and VEGF, which has demonstrated cooperative binding *in vitro* leading to increased binding of PD-1 in the presence of VEGF and vice-versa[1]. Ivonescimab has shown activity in multiple phase 3 trials conducted in China in non-small cell lung cancer, including one trial which demonstrated activity in patients with brain metastases, but has not yet been evaluated in patients with primary brain tumors. This trial evaluates ivonescimab in patients with recurrent glioblastoma. **Methods:** This investigator-initiated study consists of a phase I and II component; the primary objectives are safety and tolerability for phase I and determining progression-free survival for phase II. The phase I component evaluates 3 dose levels of ivonescimab (7.5, 10, and 20 mg/kg every 3 weeks), employing a Bayesian optimal interval (BOIN) design for assessing toxicity. Once the recommended phase II dose is determined, the phase II portion will follow a Bayesian optimal phase II (BOP2) design, with interim analyses at pre-specified enrollment points allowing for monitoring of efficacy as well as ongoing evaluation of toxicity. The maximum accumulative sample size at the target dose will be 30 patients. Radiographic assessment will utilize the Response Assessment in Neuro-Oncology 2.0 criteria. Key eligibility criteria include adults with recurrent glioblastoma, IDH-wildtype (by WHO CNS 2021 classification) at first or second recurrence with Karnofsky Performance Scale ≥ 60 and normal blood counts and organ function. Prior therapy with anti-angiogenic agents (including bevacizumab) or checkpoint inhibitors is excluded, as well as concurrent corticosteroids $\geq$ 2 mg/day dexamethasone or equivalent. Samples of archival tumor, blood and stool microbiome will be collected for correlative studies as an exploratory evaluation of predictive biomarkers of response or resistance to ivonescimab. The study has been approved by the institutional review board and accrual to phase I will commence in the first quarter of 2025. 1. Zhong T, Huang Z, Pang X, et al. 1194 Mechanism of action of ivonescimab (AK112/SMT112): a first-in-class tetravalent Fc-silent bispecific antibody with dual blockade of PD-1 and VEGF that promotes cooperative biological effects. Journal for ImmunoTherapy of Cancer 2023;11: doi: 10.1136/jitc-2023-SITC2023.1194. Clinical trial information: NCT06672575. Research Sponsor: Summit Therapeutics.

TPS2102 **Poster Session**

Regorafenib versus local standard of care in patients with grade 2-3 meningioma no longer eligible for loco-regional treatments: The MIRAGE trial.

First Author: Alberto Bosio, Veneto Institute of Oncology IOV, IRCCS, Padua, Italy

Background: Meningiomas are the most common intracranial tumors. Standard treatment involves surgical resection with curative intent. When gross total resection is not achievable, or in case of recurrence, RT is frequently utilized. On the other hand, the role of systemic treatments remains poorly supported by evidence.Regorafenib is an oral multi-tyrosine kinase (RTK) inhibitor. It exhibits high selectivity for VEGFR1/2/3, while also inhibiting PDGFRβ, FGFR1, and c-RAF/RAF1 and BRAF pathways, highly expressed in high-grade meningiomas. **Methods:** TheMIRAGE Trial (NCT06275919) is a multicenter, open-label, randomized phase 2 clinical trial evaluating grade 2/3 meningioma pts who have progressed following surgery and RT. A total of 94 pts are being randomized (1:1) to receive either Regorafenib (160 mg orally for 3 weeks on, 1 week off) or local standard-of-care therapies (e.g., bevacizumab, hydroxyurea, somatostatin analogues).Major inclusion criteria include histological confirmation of WHO 2021 grade 2-3 meningioma, radiologically documented progression at least 24 weeks from RT (estimated planar growth $>$ 25% in two dimensional tumor areas within the prior 12 months or development of a new lesion) with at least 1 measurable lesion (minimum 10 x 10 mm) on baseline MRI, ineligibility for further surgery and/or radiotherapy, absence of extracranial lesions and a WHO performance status of 0-1.The primary endpoint is 6-month PFS (6m-PFS). Assuming a 6m-PFS of 20% in the control arm and 40% in the regorafenib arm (corresponding to a HR = 0.57) with a = 5%, b = 85%, 104 patients are needed to assess the targeted efficacy. Response to treatment will be assessed by using RANO criteria. Secondary endpoints include OS, ORR, DCR, volumetric analysis of the target lesions, safety and health-related quality of life. Multi-omics exploratory analysis will also be performed to investigate possible prognostic and predictive biomarkers. Radiomics analysis will also be performed. MIRAGE, initiated in September 2024, is an academic trial promoted by the Istituto Oncologico Veneto, IOV-IRCCS and will recruit patients across 15 neuro-oncology Centers in Italy with an estimated study duration of 18 months. Discussion: MIRAGE is the first randomized phase 2 trial analyzing the role of a RTK inhibitor (regorafenib) in prolonging PFS in pts with grade 2-3 meningioma who are ineligible for further surgery and/or radiotherapy. Clinical trial information: NCT06275919. Research Sponsor: None.

2500 Oral Abstract Session

Assessment of efficacy of LBL-024, a novel and uniquely designed bispecific antibody against PD-L1 and 4-1BB, combined with etoposide/platinum-based chemotherapy in treatment-naive advanced extrapulmonary neuroendocrine carcinoma (EP-NEC): A multicenter phase Ib/II trial. First Author: Ming Lu, Peking University Cancer Hospital /Beijing GoBroad Hospital, Beijing, China

Background: The prognosis for patients with EP-NEC is very poor. A recognized 1L treatment for advanced disease is etoposide/platinum-based chemotherapy with no standard 2L/3L treatment. LBL-024 blocks the immunosuppressive pathway of tumor cells by targeting PD-L1 and effectively co-stimulates T cells by targeting 4-1BB, to improve the anti-tumor immune response. Here we report the safety and efficacy of LBL-024 combined with etoposide and cisplatin or carboplatin (EP/EC) as first line treatment in patients with advanced NEC. (NCT06157827). **Methods:** This is a phase Ib dose escalation and phase II dose optimization/expansion clinical trial. Phase Ib enrolled previously untreated advanced EP-NEC and SCLC patients, phase II enrolled previously untreated advanced EP-NEC patients. Three dose levels of LBL-024 (6, 10 and 15 mg/kg, i.v. Q3W) plus EP/EC in phase Ib were evaluated, 2 dose levels (6 and 15 mg/kg, i.v. Q3W) of LBL-024 plus EP/EC were evaluated in a randomized dose optimization. The primary endpoints were tolerability, safety, efficacy (RECIST 1.1) and RP2D, the secondary endpoints were PK, PD and ADA. **Results:** As of December 26, 2024, a total of 53 patients were enrolled, with 13 patients in Phase Ib and 40 patients in dose optimization stage of Phase II. Phase Ib included 2 patients with SCLC, 1 with MiNEN, and 10 with EP-NEC. All 40 patients in Phase II were EP-NEC. During the Dose escalation stage, no DLTs were observed. During the Dose optimization stage, 15 mg/kg of LBL-024 was selected as RP2D based on PK/PD, efficacy, safety and ER analysis. Out of 49 patients, the ORR across all dose levels is 77.6% and the DCR is 93.9% among which 9 patients were unconfirmed. The ORR in 21 EP-NEC patients at RP2D dose is 81.0% and DCR is 95.2% among which 3 patients were unconfirmed. Additionally, 2 patients with SCLC achieved 100% ORR. LBL-024 TRAEs of all-grade occurred in 53 patients (100%), with grade ≥3 TRAEs in 17/53 patients (32.1%). **Conclusions:** LBL-024 combined with chemotherapy was well-tolerated. The extremely improved response observed in EP-NECs is significantly higher than the historic reports (about 30%~55%). Data including ER analysis of this ongoing study will be updated by a follow-up submission to ASCO. Clinical trial information: NCT06157827. Research Sponsor: None.

Clinical benefits of first line treatment in evaluable patients bin phase Ib/II.

	Phase Ib (Dose escalation)			Phase II (Dose optimization)		15 mg/kg (N=21) EP-NECs	Total (N=49)
	6 mg/kg (N=3)	10 mg/kg (N=4)	15 mg/kg (N=6*)	6 mg/kg (N=18)	15 mg/kg (N=18)		
ORR, N (%)	2 (66.7%)	3 (75.0%)	4 (66.7%)	14 (77.8%)	15 (83.3%)	17 (81.0%)	38 (77.6%)
DCR, N (%)	3 (100.0%)	4 (100.0%)	4 (66.7%)	17 (94.4%)	18 (100.0%)	20 (95.2%)	46 (93.9%)

*2 patients with SCLC, 1 with MiNEN and 3 with EP-NEC.

2501 Oral Abstract Session

First-in-human phase I/II trial evaluating BNT142, a first-in-class mRNA encoded, bispecific antibody targeting Claudin 6 (CLDN6) and CD3, in patients (pts) with CLDN6-positive advanced solid tumors. First Author: Timothy A. Yap, The University of Texas MD Anderson Cancer Center, Houston, TX

Background: CLDN6 is an oncofetal cell surface protein silenced in normal adult tissues but aberrantly activated in testicular, ovarian, non-small cell lung (NSCLC) and other cancers. The investigational therapeutic BNT142 is a novel lipid nanoparticle (LNP)-encapsulated mRNA encoding the anti-CLDN6/CD3 bispecific antibody RiboMab02.1. After intravenous administration, BNT142 RNA-LNPs are taken up by liver cells and are translated into RiboMab02.1. The first results of the dose escalation part of the BNT142-01 trial testing 7 dose levels (DL) are presented here. **Methods:** BNT142-01 (NCT05262530) is a Phase I/II, open-label, multi-center trial to evaluate weekly BNT142 treatment with premedication (antipyretics, antihistamines, fluids) at the investigators' discretion in pts with CLDN6+ (≥10% of cells with at least weak membrane positivity) advanced solid tumors. Primary objectives include safety, tolerability and identifying the recommended Phase 2 dose (RP2D), secondary and exploratory objectives include pharmacokinetics, pharmacodynamics and preliminary efficacy (RECIST 1.1). **Results:** As of 02 Dec 2024, 65 pts (median age 57 years [range 18 – 79]; 75% female; 60% ECOG 1; 44 ovarian, 10 testicular, 5 NSCLC, 6 rare cancers) received ≥1 dose (median 7, range 1 – 38) of BNT142. Of 65 pts, 46 (71%) had ≥4 prior lines of systemic therapy. Mostly mild to moderate treatment-related adverse events (TRAEs) occurred in 41 (63%) pts, including 15 (23%) pts with ≥G3 TRAEs. Most common (≥10%) TRAEs were cytokine release syndrome (CRS) in 14 (22%) pts (1 pt [2%] ≥G3), aspartate or alanine aminotransferase (AST, ALT) increased in 12 (19%) pts (8 pts [12%] ≥G3), and pyrexia, chills or fatigue in 8 (12%) pts (0/0/2 pts [0%/0%/3%] ≥G3, respectively). TRAEs leading to dose reduction, treatment interruption or discontinuation occurred in 1 (2%), 12 (19%) or 2 pts (3%), respectively (mostly G3; most common related terms AST or ALT increased and infusion related reaction). Two (3%) pts had a dose limiting toxicity (G4 ALT increased [DL5], leading to dose reduction, and G5 CRS [DL6]). BNT142 led to transient, dose-dependent increases in inflammatory cytokines. Translated RiboMab02.1 was detected in serum in a dose-dependent manner, peaking 24 – 72 h post-dose. Across all DLs, the disease control rate (DCR) was 58% with a tendency of higher efficacy in the higher DLs. In ovarian cancer, there were 7 RECIST 1.1 partial responses (PRs) and the DCR was 75%. **Conclusions:** BNT142 demonstrated a manageable safety profile and promising anti-tumor activity at the higher DLs, with 7 RECIST 1.1 PRs in CLDN6+ ovarian cancer, a tumor usually refractory to immunotherapy. We provide the first clinical proof-of-concept for an mRNA encoded bispecific antibody. Dose optimization is ongoing. Clinical trial information: NCT05262530. Research Sponsor: BioNTech SE.

2502 Oral Abstract Session

Efficacy and safety results of a first-in-class PD-1/IL-2$^{\alpha\text{-bias}}$ bispecific antibody fusion protein IBI363 in patients (pts) with immunotherapy-treated, advanced acral and mucosal melanoma. First Author: Bin Lian, Peking University Cancer Hospital & Institute, Beijing, China

Background: Despite great success of immunotherapy (IO) in advanced melanoma, there remains an unmet clinical need for resistant tumors. Pts with acral and mucosal melanomas show limited benefit from current therapies. IBI363, a first-in-class PD-1/IL-2$^{\alpha\text{-bias}}$ bispecific antibody fusion protein that blocks PD-1 and activates α-bias IL-2 to rejuvenate exhausted tumor-specific T cells, has shown encouraging efficacy in pts with advanced melanoma. Here, we present results of IBI363 from a phase 1 study (NCT05460767) and a phase 2 study (NCT06081920) of pts with IO-treated, advanced acral and mucosal melanoma. **Methods:** Eligible pts with IO-treated advanced acral and mucosal melanoma were enrolled. IBI363 was administered intravenously at 0.1 mg/kg every week, 0.3/0.6/1 mg/kg every 2 weeks (Q2W), or 1/1.5/2/3 mg/kg every 3 weeks (Q3W). Primary endpoints for the phase 1 study were dose-limiting toxicity (DLT) and safety, and for the phase 2 study were safety and investigator-assessed objective response rate (ORR), disease control rate (DCR), duration of response (DoR) and progression-free survival (PFS) according to RECIST v1.1. **Results:** As of December 6, 2024, 91 pts were enrolled across the phase 1 (n = 76) and phase 2 (n = 15) studies (male: 47%; median age: 57 years; Asian: 100%; ECOG PS 1: 66%; stage IV: 89%); 47 pts had acral melanoma and 44 had mucosal melanoma. Median follow-up time was 8.2 months. Median treatment duration was 13.4 weeks (range: 2.0-72.4). Treatment-emergent adverse events (TEAEs) occurred in 90/91 (98.9%) pts including 27 (29.7%) pts with grade ≥3 (≥G3) TEAEs. TEAEs led to treatment discontinuation in 3 (3.3%) pts, and 1 (1.1%) pt had a TEAE leading to death which was considered to be treatment-related (sepsis). Most common TEAEs were arthralgia (59.3%, with 4.4% ≥G3), rash (42.9%, with 3.3% ≥G3), and anemia (42.9%, with 2.2% ≥G3). Among all pts with at least one post-baseline tumor assessment (n = 87), 1 pt had a complete response, 22 had partial responses, 33 had stable disease, 31 had progressive disease. ORR was 26.4% (95% CI: 17.6-37.0) with 16 responses confirmed and 2 pts still waiting for confirmation; DCR was 64.4% (95%CI: 53.4-74.4). Among pts treated at 1mg/kg and above (n = 74), the ORR was 28.4% (95%CI: 18.5-40.1) and DCR was 68.9% (95%CI: 57.1-79.2). Patients treated at 1 mg/kg Q2W (n = 30) had median DOR 14.0 months with a median follow-up of 9.1 months and 50.0% events; the median PFS was 5.7 (95% CI, 3.6-6.7) months with a median follow-up of 11.0 months and 73.3% events. **Conclusions:** IBI363 showed encouraging efficacy in pts with IO-treated advanced acral and mucosal melanoma. The safety profile was acceptable and manageable. Further global clinical development of IBI363 in melanoma is ongoing. Clinical trial information: NCT05460767 and NCT06081920. Research Sponsor: Innovent Biologics (Suzhou) Co., Ltd.

2503 Oral Abstract Session

A therapeutic vaccine for fibrolamellar hepatocellular carcinoma. First Author: Marina Baretti, Johns Hopkins Sidney Kimmel Comprehensive Cancer Center, Baltimore, MD

Background: Fibrolamellar hepatocellular carcinoma (FLC) is a rare form of liver cancer affecting children and young adults that is driven by a chimeric protein, DNAJ-PKAc. The development of molecular inhibitors of DNAJ-PKAc has been hampered by unacceptable on-target toxicity, but the chimera results in a tumor-specific antigen (neoantigen) that may be targeted immunologically. **Methods:** We conducted a phase 1 clinical trial of a therapeutic vaccine targeting DNAJ-PKAc (FLC-Vac), in combination with nivolumab and ipilimumab, in children and adults with advanced FLC. The primary objectives were safety and T cell responses, defined as 2.5-fold increase of interferon gamma (IFN-γ)-producing DNAJB1-PRKACA chimera-specific T cells in the peripheral blood after week 10 (priming phase). The study was planned with 12 evaluable patients. FLC-Vac, consisting of a peptide encoding the DNAJB1-PRACA fusion plus poly-ICLC adjuvant, was administered on weeks 0, 1, 2, 3, 6, 9 during the priming phase of the study. Nivolumab, 3 mg/kg, followed by ipilimumab, 1 mg/kg, was administered every 3 weeks for 4 doses during the priming phase. After completion of the priming phase, FLC-Vac and nivolumab were continued in maintenance. Key exclusion criteria include age < 12 years and prior treatment with immune checkpoint inhibitors. The trial incorporated a safety lead-in portion in which the first 3 patients received vaccine monotherapy for 3 weeks prior to receiving combination therapy. **Results:** Among 16 patients enrolled, 12 completed the vaccine priming phase and were evaluable for both immunological and clinical endpoints. The median age was 24 years (range: 12-47). Grade 3 treatment-related adverse events were reported by six patients (37.5%). DNAJ-PKAc-specific T cell responses were detected in 9/12 patients after treatment. In the subset of patients who completed the initial priming phase the disease control rate (DCR) was 75% (9/12), with three partial responses (25%). All 3 responding patients are without evidence of active cancer after undergoing surgical debulking of residual disease. All patients with clinical responses also had DNAJ-PKAc-specific T cell responses, from whom we identified multiple class II-restricted T cell receptors (TCRs) with specificity for DNAJ-PKAc. Correlates of response included both functional neoantigen reactivity and changes in TCR repertoire features over time. In two patients who experienced eventual progression after initial clinical response, we found evidence that the loss of efficacy was likely due to T cell exhaustion, and in one case was restored with checkpoint rechallenge. **Conclusions:** Our findings demonstrate the potential for therapeutic vaccines targeting DNAJ-PKAc in FLC and suggest a rubric for evaluating effective anti-neoantigen immunity. Clinical trial information: NCT04248569. Research Sponsor: ASCO CDA (Dr Yarchoan); Fibrolamellar Cancer Foundation; BMS; R01-CA265009.

2504 **Oral Abstract Session**

Clinical responses to SYNC-T therapy: In situ personalized cancer vaccination with intratumoral immunotherapy in patients with metastatic castration-resistant prostate cancer (mCRPC). First Author: Charles J. Link Jr., Lankenau Institute for Medical Research, Wynnewood, PA

Background: Metastatic castration-resistant prostate cancer (mCRPC) has a poor response to immunotherapy limited by both a low ORR and high frequency of severe immune-related adverse events. SYNC-T is a novel *in situ* therapy that synchronizes the presence of tumor antigens, an immune therapy drug, and immune cells in the tumor and locoregional lymph nodes. SYNC-T Therapy combines device-induced partial cryolysis of a targeted tumor to create a personalized multi-antigen vaccine, followed immediately by intratumoral infusion of the multitarget novel drug candidate SV-102, leading to T-cell activation and an effective systemic immune response. **Methods:** 15 subjects, 13 with bone metastases, and documented failure to prior hormonal therapy (n = 10) or refused therapy (n = 5) were recruited to a single-arm study (NCT05544227). Image-guided partial cryolysis of a tumor was followed by intratumoral infusion of SV-102, comprised of fixed low dose of anti-PD-1 mAb, anti-CTLA4 mAb, CD40 agonist mAb, and TLR9 agonist CpG-ODN. All subjects received the same dose of SV-102. Subjects received SYNC-T Therapy q4 weeks for up to 12 cycles (median = 6). One site of primary prostate or soft tissue metastasis was targeted at each cycle. Primary objective was to evaluate safety and tolerability with a secondary objective to assess tumor response by PCWG3 and RECIST 1.1. **Results:** 15 subjects were treated and evaluable. Median age was 61 (48-74). Prior treatments included one or more of 1st, 2nd generation hormonal blockade, chemotherapy, immunotherapy, or radiation therapy. Within 15 evaluable subjects there were 8 radiographic CRs (53%, the two-sided 95% CI is 29.4% to 78.7%, rejecting 20% CR null hypothesis; p = 0.0085) with complete resolution of primary, bone, and soft tissue metastases and 5 PRs with an ORR of 87%. Median time to response was 3 months with a median duration of 12 months to date (range 1.2 -14.6). Among the 15 subjects, 3 have died resulting in 80% survival with 14 months median follow-up. SYNC-T Therapy was well-tolerated with 41 TEAEs in 13 subjects. The majority (95%) of TEAEs were Grade 1 or 2, most commonly fever and hematuria. There were 2 Grade 2 irAEs of hepatitis and hypothyroidism and 2 Grade 3 TEAEs of urinary retention and spinal cord compression. PSA analysis during and post SYNC-T Therapy will be presented. PK analysis revealed minimal systemic exposure to SV-102 components. PD analysis showed induction of inflammatory cytokines and the emergence of multiple, novel T-cell clones. **Conclusions:** SYNC-T Therapy was well-tolerated achieving an 87% ORR in subjects with mCRPC or who refused ADT. These encouraging clinical results have led to further study of SYNC-T SV-102 in a US, multicenter, Phase 2a trial for subjects with mCRPC. Clinical trial information: NCT05544227. Research Sponsor: Syncromune, Inc.

2505 **Oral Abstract Session**

Phase 1 study of B440, an oral *Bifidobacterium*-engineered WT1 cancer vaccine, in patients with metastatic urothelial cancer. First Author: Toshiro Shirakawa, Kobe University, Kobe, Japan

Background: B440 is an innovative oral cancer vaccine comprised of recombinant *Bifidobacterium* engineered to express WT1 tumor-associated antigen. By delivering the WT1 protein to dendritic cells in gut-associated lymphoid tissue, B440 is designed to induce a tumor-specific cellular immunity. Preclinical data demonstrated effective WT1-specific T-cell induction and anti-tumor activity in murine models of urothelial, prostate, and renal cancers. **Methods:** This open-label, single-arm, phase 1 study evaluated the safety and preliminary efficacy of B440 in patients with metastatic urothelial cancer who had progressed after all standard therapies, including cytotoxic chemotherapy, PD-1/PD-L1 inhibitors, and antibody-drug conjugates. Twelve patients were enrolled in two dose cohorts (800 mg or 1,600 mg, *n* = 6 each), administered once daily for five consecutive days per week over four weeks (20 total doses). The primary endpoint was dose-limiting toxicity (DLT), assessed during the treatment. Secondary endpoints included safety (adverse events [AEs] graded by CTCAE v5.0), best overall response (BOR), and progression-free survival (PFS) by RECIST v1.1. WT1-specific immune responses were measured via ELISPOT assays detecting interferon-γ-producing T cells. **Results:** All 12 patients completed the treatment: (median age: 74.5 years [range: 39–81]; primary tumors in bladder [*n* = 5], renal pelvis [*n* = 4], ureter [*n* = 3]). No DLTs were observed in either dose cohort. Treatment-related AEs were generally mild (Grade 1), with the most common events being transient IL-6 elevations and cold-like symptoms (n = 3 each). The disease control rate (DCR) was 50%, as six patients achieved stable disease (SD) as their BOR. Six patients also demonstrated WT1-specific T-cell induction confirmed by ELISPOT. ELISPOT-positive patients had a significantly longer PFS compared to ELISPOT-negative patients (median PFS: 113 days vs. 57 days; *P* = 0.0033). Although not included in the study protocol, six patients subsequently underwent pembrolizumab rechallenge at the discretion of their physicians. Of these, three achieved clinical responses (one complete response [CR] and two partial responses [PR]). Spider plot analyses indicated early tumor shrinkage among ELISPOT-positive patients, with maximum reductions of −100%, −49%, and −32.7% from baseline. Notably, three of the four ELISPOT-positive patients achieved objective responses upon rechallenge. **Conclusions:** B440 exhibited a favorable safety profile and no DLTs up to 1,600 mg. The induction of WT1-specific immunity correlated with improved PFS during B440 therapy and enhanced responses upon pembrolizumab rechallenge. These data support further investigation of B440 in larger, randomized trials and potential combination with other immunotherapies in WT1-expressing malignancies. Clinical trial information: jRCT2051220143. Research Sponsor: Japan Agency for Medical Research and Development (AMED); 23ym0126081h0002; Immunorock Co., Ltd.

2506 **Oral Abstract Session**

Effect of erythrocyte-antibody conjugates on cancers resistant to checkpoint blockade immunotherapy: A phase I trial. First Author: Xiaoqian Nie, Westlake University, Hangzhou, Zhejiang, China

Background: Despite the clinical success of immune checkpoint blockade therapy, the majority of patients do not benefit due to inadequate efficacy as well as immune-related adverse toxicities. We have previously developed WTX-212, an erythrocyte-antibody conjugate that covalently links anti-PD-1 antibodies to erythrocyte membranes. Unlike conventional antibodies, WTX-212 accumulates in the spleen, where it effectively remodels splenic immune landscape by expanding effector T cells and reducing the reservoir of immunosuppressive myeloid cells. These changes further reprogram the tumor microenvironment and suppress tumor growth in syngeneic mouse models. Based on promising preclinical results, we have investigated WTX-212 in cancer patients resistant to checkpoint blockade therapy (NCT06026605). **Methods:** This is an investigator-initiated trial designed to assess the safety, tolerability, and preliminary efficacy of autologous WTX-212 monotherapy in patients with advanced malignancies. The primary outcome measures include safety and tolerability according to NCI-CTCAE v.5.0. Secondary outcome measures preliminary efficacy based on RECIST 1.1 criteria. As of January 15, 2025, 14 heavily treated patients with 11 types of solid tumors, who had received PD-1/PD-L1 antibody-containing regimens as their last line of treatment but developed resistance, were enrolled. These patients received WTX-212 monotherapy in two dose cohorts (2×10^{11} or 3×10^{11} cells, with 6-10 mg of conjugated antibody). **Results:** Repeated WTX-212 treatment showed no DLTs or TRAEs ≥3. No patient discontinued treatment due to AEs. WTX-212 monotherapy demonstrated promising anti-tumor activity, with a DCR of 78.6% (11/14) and an ORR of 42.9% (6/14), including 1 CR and 5 PR. In the higher-dose cohort (3×10^{11} cells), DCR and ORR increased to 85.7% (6/7) and 57.1% (4/7), respectively, suggesting dose-dependent efficacy. Additionally, responders (CR+PR) exhibited higher baseline levels of circulating polymorphonuclear myeloid-derived suppressor cells (PMN-MDSCs) compared to non-responders (PD+SD), indicating that patients with elevated PMN-MDSCs may benefit more from treatment. Importantly, WTX-212 treatment rapidly reduced PMN-MDSCs in the peripheral blood of responders compared with non-responders, consistent with preclinical data. These preliminary results suggest that WTX-212 is safe, well-tolerated, and effective at low doses, supporting further investigation into WTX-212 monotherapy and combination therapies. **Conclusions:** Our study suggests that PD-1 blockade in the spleen using erythrocyte-antibody conjugates triggers systemic anti-tumor responses while maintaining a favorable safety profile. Erythrocyte-drug conjugates represent a novel approach for targeting immune cells in the spleen, with broad implications for cancer treatment and drug development. Clinical trial information: NCT06026605. Research Sponsor: None.

2507 **Oral Abstract Session**

RETRACTED: Phase 1 clinical trial of EpCAM CAR-T cell therapy in patients with gastrointestinal cancers. First Author: Tianhang Luo, Shanghai Changhai Hospital, Shanghai, China

2508 Oral Abstract Session

Phase 1 clinical update of IMA203, an autologous TCR-T targeting PRAME in patients with PD1 refractory metastatic melanoma. First Author: Martin Wermke, University Hospital Carl Gustav Carus, Dresden, Germany

Background: Frequent recurrence and limited long-term survival in unresected or metastatic melanoma after relapse from 1L checkpoint inhibitor treatment highlight the critical need for new therapies that deliver deeper, more durable responses. ACTengine IMA203 is an autologous TCR-T targeting PRAME, an intracellular protein displayed as peptide antigen at high density on the surface of multiple solid tumors, including melanoma. **Methods:** Patients treated in this ongoing Ph1a/b trial (NCT03686124) are ≥18yo, HLA-A*02:01+, PRAME+, have recurrent and/or refractory solid tumors with no additional standard of care treatments available, measurable disease (RECIST1.1) and ECOG PS 0-1. Patients receive Cy/Flu (500 mg/m^2 & 30 mg/m^2 x4 d) lymphodepletion prior to infusion, followed by low-dose IL-2 for 10 days. **Results:** As of Aug 23, 2024: 70 heavily pretreated patients with solid tumors (median 3 prior systemic therapies) across all dose levels (median total infused dose 2.09x10^9 TCR-T cells (0.08-10.02x10^9)) were enrolled and assessed for safety. Baseline tumor burden (median sum of diameter): 11.78 cm; LDH > 1 x ULN: 64% of patients. IMA203 had an overall favorable tolerability profile. Most common TEAEs: chemotherapy-related cytopenias (100%), mild to moderate CRS (G1-2: 83%, G3: 11%), infrequent ICANS (G1: 6%, G2: 4%, G3: 4%), no G5 events. Objective responses were observed in melanoma, ovarian cancer, synovial sarcoma, and other tumor types. Successful trafficking of IMA203 cells to various organs was evidenced by their ability to shrink metastatic tumor lesions in the lung, liver, pleura, peritoneum, skin, lymph nodes, adrenal gland, bladder, kidney, spleen, and muscle. Across patients treated in dose escalation and dose expansion, higher doses of IMA203 TCR-T cells were associated with a higher rate of confirmed responses (p = 0.018), whereas tolerability profile remained favorable. Exposure data (C_{max}, AUC) demonstrated a clear dose-dependent improvement in clinical efficacy: Patients with confirmed PR had a higher concentration of IMA203 TCR-T cells in the periphery, compared to patients with unconfirmed PR, SD, and PD. In heavily pretreated patients (median 2 prior systemic therapies) with melanoma at RP2D (1-10x10^9) in Ph1b, cORR was 54% (14/26), with tumor shrinkage in 88% (23/26) of patients. Median DOR was 12.1 months with 7/14 confirmed responses ongoing (longest > 2 years). Median PFS was 6 months and median OS not reached at 8.6 months mFU. Updated data with longer follow-up will be presented. **Conclusions:** IMA203 TCR-T was well tolerated and showed durable objective responses in patients with advanced melanoma. Given its promising risk/benefit profile and high PRAME prevalence in melanoma, a registration-directed Phase 3 trial (SUPRAME; NCT06743126) is underway to further evaluate its efficacy in patients with previously treated (2L) advanced cutaneous melanoma. Clinical trial information: NCT03686124. Research Sponsor: None.

2509 Clinical Science Symposium

Phase III randomized study comparing ultra-low dose immunotherapy to standard cytotoxic chemotherapy for solid tumors in second line and beyond setting (DELII: Development of Low dose Immunotherapy in India). First Author: Vanita Noronha, Tata Memorial Hospital, Mumbai, India

Background: Although immunotherapy (IO) is approved in the second line and beyond setting for most solid tumors, cost limits its accessibility. Lower doses of IO have been shown to achieve adequate target occupancy, persisting for 3 months post administration. We hypothesized that nivolumab would retain efficacy at one-twelfth the approved dose. **Methods:** Open-label, phase III randomized superiority study in 500 patients with solid tumors, whose disease had progressed on at least one line of systemic treatment, with performance status 0-1. Patients were randomized 1:1 to ultra-low-dose nivolumab (20 mg intravenously every 2 weeks) or standard chemotherapy. Standard chemotherapy options for lung and head-and-neck cancers were docetaxel 75 mg/m^2 every 3 weeks or paclitaxel 175 mg/m^2 every 3 weeks or paclitaxel 80 mg/m^2 once-a-week; esophageal and urothelial cancers: paclitaxel 175 mg/m^2 every 3 weeks or 80 mg/m^2 once-a-week. Therapy continued until progression or intolerable toxicity. Primary endpoint was overall survival (OS). **Results:** Between Jun 2020 and Feb 2024, we enrolled 500 patients: 250 to each arm. Median age was 49.5 years (IQR, 42-58), 408 (81.6%) patients were male. Primary cancers included head and neck (259, 51.8%), lung (182, 36.4%), esophagogastric (31, 6.2%), urothelial (14, 2.8%), and microsatellite instability-high colorectal cancers (14, 2.8%). Patients had received a median of one prior line of systemic therapy (range: 1-8); 144 (28.8%) patients had received at least two prior lines of systemic therapy. PD-L1 positivity (TPS or CPS > 0) was noted in 66.2% patients. Radiologic response was 7.7% and 8.1% in IO and chemotherapy arms, respectively; P = 0.882. Disease stabilization rate was 37.7% and 39.3% in IO and chemotherapy arms, respectively; P = 0.761. Median PFS was similar between the two arms: 2.04 months (95% CI, 2.0-2.1) in IO arm, and 2.09 months (95% CI, 2.04-2.17) in chemotherapy arm (HR, 1.03; 95% CI, 0.86-1.23; P = 0.77). Median OS was 5.88 months (95% CI, 4.99-7.13) in IO arm, versus 4.70 months (95% CI, 3.91-5.65) in chemotherapy arm; P = 0.022; HR, 0.80 (95% CI, 0.66-0.97). One-yr OS in IO and chemotherapy arms was 27.28% (22.19-33.54) and 16.88% (12.75-22.34), respectively; 2-yr OS was 11.19% (7.59-16.50) and 6.55% (3.95-10.89), respectively. Grade 3 and higher treatment-related adverse events were significantly lower in IO arm (42%) than chemotherapy arm (60.3%); P < 0.001. **Conclusions:** Ultra-low dose immunotherapy dosed at one-twelfth the standard approved dose is efficacious and significantly prolongs survival in patients with solid tumors in the second line and beyond setting, as compared to standard cytotoxic chemotherapy. Low dose IO should be tested in various settings and multiple malignancies. This will substantially increase global accessibility to IO. Clinical trial information: CTRI/2020/02/023441. Research Sponsor: R G Manudhane Foundation for Excellence; Trilokchand Papriwal Trust; Tata Memorial Hospital, Mumbai, India.

2510 Clinical Science Symposium

Overall survival according to time-of-day of combined immunochemotherapy for advanced non-small cell lung cancer: A bicentric bicontinental study. First Author: Francis Albert Lévi, UPR Chronotherapie, Cancers et Transplantation, Université Paris Saclay, Hôpital Paul Brousse ID Isco 13918, Villejuif, France

Background: Circadian rhythms moderate immune cells trafficking and function over the 24 hours. This could account for the near doubling of overall survival (OS) in patients (pts) receiving immune checkpoint inhibitors (ICIs) as single agents at early times-of-day of administration (ToDA) in retrospective studies. Yet, (i) the cut-off time that differentiates ICI efficacy according to ToDA ranges from 11:30 to 16:30, and (ii) the relevance of ICI timing for OS is unknown in pts receiving immunochemotherapy (ICI-chemo). **Methods:** These issues are addressed using OS as the primary endpoint in retrospectively-included pts receiving 1st-line ICI-chemo for stage IIIc-IV non-small cell cancer (NSCLC) in France (Cohort 1) or in China (Cohort 2). The median ToDA of the initial four ICI-chemo infusions was computed for each patient. Hazard ratio (HR) functions of an earlier death or an earlier progression were computed for each cohort and for the pooled one, using ToDA cut-off times ranging from 10: 30 to 13:00, with 30-minutes increments. Median ToDA of ICI-chemo determined the allocation of patients to "Before" or "After" treatment groups. The temporal relations between HRs and ToDA as a continuous variable were further determined, using Cox models incorporating periodic restricted cubic splines. Patients were dichotomized according to the best cut off ToDA candidate, with OS and PFS being estimated using Kaplan-Meier and compared using log-rank. The association between ToDA and OS, PFS and response rates were evaluated using the Cox and logistic models controlling for main patient characteristics. **Results:** A total of 713 pts started treatment between 01/2018 and 10/2023 (Cohort 1, 165 pts; Cohort 2, 548 pts; median age, 62 y.o., male sex, 84%; pembrolizumab as ICI, 51%; pemetrexed-carboplatin/cisplatin, 49%; paclitaxel-carboplatin, 51%). HR functions in each cohort and in the pooled one, and the fitted curve using ToDA as a continuous variable identified 11:30 as a likely best cut off time. Median OS was 33.0 months (mo.) [95% CI, 27.5 - 41.0] in the 345 patients, who received 2-4 immunochemotherapy courses before 11:30) compared to 19.5 mo. [18.0 - 22.5] in those, who received 2-4 courses after 11:30 (N = 368) (p<0.0001). In the multivariable analysis, a median ToDA before 11:30 was associated with prolonged OS with an adjusted HR of 0.47 [0.37-0.60]. Statistically significant differences in ToDA effects were found for OS, PFS in each cohort, and for response rate in each cohort and in the pooled data. **Conclusions:** In this large bi-continental study, ToDA of immunochemotherapy administration before 11:30 was associated with improved OS, PFS and response rates, compared to later ToDA in pts receiving standard first line immunochemotherapy for NSCLC. Randomized trials are needed to confirm this important finding and inform recommendations for clinical practice. Research Sponsor: None.

2511 Clinical Science Symposium

Safety and efficacy of immune checkpoint inhibitors in solid organ transplant recipients: A systematic review and individual patient data meta-analysis. First Author: Muntaser Al Zyoud, University of Jordan, Amman, Jordan

Background: Immune checkpoint inhibitors (ICIs) have revolutionized cancer treatment but pose unique challenges in solid organ transplant (SOT) recipients. Transplant rejection remains the predominant safety concern. We systematically evaluated the safety (focusing on allograft rejection) and efficacy of ICIs across all organ transplant types and ICI classes, providing updated evidence-based insights for clinical decision-making. **Methods:** A systematic review of PubMed, EMBASE, and SCOPUS databases was conducted in accordance with PRISMA guidelines. Studies reporting rejection or efficacy outcomes in SOT recipients treated with any class of ICI were included. The primary endpoints were the incidence of transplant rejection and survival following ICI therapy. Secondary endpoints included objective response rate (ORR) and progression-free survival (PFS) for malignancies. Analysis was performed using SPSS (V26.0) and R (V4.3.0). **Results:** Of 2682 screened abstracts, 198 studies involving 331 SOT recipients met inclusion criteria. The transplanted organs were liver (n=175), kidney (n=136), and heart (n=15). Rejection rates were highest in Kidney at 46.3% (63/136), followed by heart (40.0%, 6/15) and liver (26.9%, 47/175). Across ICI classes, rejection rates were: Anti-CTLA4 (25%) Anti-PD1 (40.6%) and Anti-PDL1 (0%). Rejection rates were lower in patients receiving ICI pre-transplant (25.9%) compared to post-transplant (40.9%). ORR varied by ICI class: Anti-CTLA4 (25%), Anti-PD1 (41.8%), Anti-PD1 + CTLA4 (28%), and Anti-PDL1 (72.7%). Cutaneous squamous cell carcinoma (cSCC) showed the highest ORR (49.1%), followed by hepatocellular carcinoma (40.8%) and melanoma (25.3%). Post-transplant rejection risk was lower with Anti-CTLA4 (OR 0.22), 3rd-line ICI therapy (OR 0.24), and corticosteroids (OR 0.46). Pre-transplant rejection risk decreased with >60-day washout periods (OR 0.10). Multivariate analysis identified key factors influencing rejection risk (Table 1). **Conclusions:** ICI therapy in SOT recipients is high-risk yet promising. Key strategies include prolonged washout periods, Anti-CTLA4 therapy, and late-line ICI use. Prospective studies are needed to refine protocols and identify predictive markers to improve outcomes in this population. Research Sponsor: None.

Multivariate analysis results.

Factor	Total (OR)	P-Value	Pre-Transplant ICI administration (OR)	P-Value	Post-transplant ICI administration (OR)	P-Value
Age (<60 vs > 60)	0.79	0.42	0.85	0.82	0.62	0.18
Sex (M vs F)	1.12	0.75	1.36	0.7	1.23	0.63
CTLA-4	0.21	0.03	-	-	0.22	0.04
Third line and later (vs 1st line)	0.26	0.01	0.17	0.44	0.24	0.01
NSCLC (vs HCC)	6.87	0.03	-	-	3.59	0.23
RCC (vs HCC)	9.9	0.04	-	-	5.88	0.11
Multiple tumors	19.18	0.01	-	-	9.3	0.06
Washout period (<60 vs>=60)	-	-	0.1	<0.001	-	-

LBA2512 **Rapid Oral Abstract Session**

The phase II NIBIT-ML1 study of nivolumab plus ipilimumab and ASTX727 or nivolumab plus ipilimumab in PD-1 resistant metastatic melanoma: Tumor methylation landscape and correlation with clinical outcomes. First Author: Anna Maria Di Giacomo, University of Siena, Center for Immuno-Oncology, University Hospital of Siena, NIBIT Foundation Onlus, Siena, Italy

The full, final text of this abstract will be available at meetings.asco.org on the day of presentation and in the online supplement to the June 10, 2025, issue of the *Journal of Clinical Oncology*.

2513 **Rapid Oral Abstract Session**

Durable responses in ICI-refractory or acquired resistance: Phase 2 study of NP-G2-044 combined with anti-PD-1 therapy. First Author: Anup Kasi, University of Kansas Cancer Center, Fairway, KS

Background: Although immune checkpoint inhibitors (ICIs) have transformed cancer treatment, many patients still develop primary or acquired resistance. NP-G2-044 is a first-in-class, oral fascin inhibitor that disrupts cancer cell motility, invasion, and metastasis while promoting intratumoral dendritic cell (DC) activation and CD8+ T-cell proliferation. Preclinical studies indicate NP-G2-044 synergizes with anti-PD-1 therapy to convert nonresponsive tumors into responsive ones. Early-phase clinical data support the feasibility of NP-G2-044 at pharmacologically active doses and its potential to prevent metastasis when used as monotherapy. **Methods:** In this open-label Phase 2 trial (NCT05023486), patients with advanced or metastatic solid tumors and documented primary or acquired resistance to anti-PD-(L)1 therapy received NP-G2-044 plus standard-of-care anti-PD-1. Efficacy was assessed using RECIST, with the primary endpoint being objective response rate (ORR). Secondary endpoints included progression-free survival (PFS), duration of response, disease control rate (DCR), and safety. **Results:** Forty-five patients were enrolled, with 33 evaluable for efficacy. No dose-limiting toxicities were observed. Objective responses occurred in 7/33 patients (21%) [95 % CI 9 - 38.9%], including 4 complete responses (CRs)—2 by RECIST in cervical and endometrial cancers, and 2 pathological CRs in pancreatic and gastroesophageal junction adenocarcinomas—and 3 partial responses (cutaneous squamous cell carcinoma, non-small cell lung cancer, and cholangiocarcinoma). Three patients have been cancer-free for over 7 months, and 5 have remained on therapy for more than 15 months. The DCR was 76%, and 55% of patients showed no new metastases during the study. One-year PFS is projected at 30%. The most common adverse events were diarrhea, fatigue, nausea, and transaminitis (~30%), which was transient, reversible, and preceded tumor response. Mechanistic analyses using multiplex immunofluorescence and immunophenotyping revealed enhanced intratumoral cytotoxic T-cell infiltration, proliferation, and granzyme B expression, along with an increase in activated DCs—consistent with a strong immunomodulatory effect. **Conclusions:** NP-G2-044, in combination with anti-PD-1 therapy, appears to have clinical activity across multiple cancer types, overcoming both primary and acquired ICI resistance while producing durable responses. Ongoing expansion cohorts and biomarker analyses aim to refine patient selection. These findings underscore NP-G2-044's potential to address metastatic disease and improve cancer immunotherapy outcomes, offering a promising therapeutic option for patients with limited alternatives. Clinical trial information: NCT05023486. Research Sponsor: Novita Pharmaceuticals.

2514 **Rapid Oral Abstract Session**

Preliminary results from the dose-escalation stage of a phase I trial of an anti-CCR8 antibody in patients with relapsed/refractory cutaneous T-cell lymphoma (R/R CTCL). First Author: Zhiming Li, Sun Yat-sen University Cancer Center, Guangzhou, China

Background: Mycosis fungoides (MF) and Sézary syndrome (SS) are the most common cutaneous T-cell lymphomas (CTCL). CCR8 is expressed in the skin resident memory T cells. ICP-B05 (CM369) is a humanized monoclonal antibody against CCR8 with potent ADCC activity. Here we report safety, efficacy and PK/PD findings for ICP-B05 during the dose-escalation stage of a Phase I study. **Methods:** Patients with R/R CTCL received ICP-B05 at 150 mg, 300 mg, 450 mg and 600 mg I.V. Q2W. Patients with R/R CTCL who failed at least 1 prior standard systemic regimen. Primary objectives included safety and tolerability of ICP-B05, MTD and RP2D. Secondary Objectives included the PK/PD and objective response per investigator. **Results:** By the cutoff date of 6th Jan, 2025, a total of 13 patients with R/R CTCL were treated, with 4 patients in 150 mg, and 3 patients each in 300 mg, 450 mg and 600mg, respectively. Eleven patients had a diagnosis of MF, one had SS and one had pcALCL. The median age was 46 years, and the median prior lines of therapy were 3 (2-6). There were 10/13 (76.9%) patients had lymph nodes involvement and 1/13 (7.7%) patient with SS had above 90% Sézary cells in peripheral blood at baseline. TEAEs occurred in 12 (92.3%) patients, and ≥Grade 3 TEAEs occurred in 6(46.2%) patients. The most common≥Grade 3 TEAEs is hematological AEs, including lymphopenia (8.3%), neutropenia (8.3%) and thrombocytopenia (8.3%). Two patients (16.7%) reported serious TEAEs, including edema and cardiac failure reported by the SS patient which was assessed as not related to ICP-B05, and thrombocytopenia and anemia reported by a MF patient. There was no fatal TEAE reported. There were 12 patients received at least one skin lesion assessment followed the mSWAT. 4/12 patients (33.3%) achieved PR, and 7patients (7/12, 58.3%) were assessed as SD with reduction (medium: - 27%) in skin lesion. The 6-month PFS rate was 82.5% (95% CI: 46.1%-95.3%). At baseline, CCR8+ in skin lesions (medium: 8.38%, range: 3.22–49.6%) was assessed in 11 out of 13 patients. Among the five patients with CCR8+ levels exceeding 10%, four (80%) achieved PR. PK analysis showed that serum exposure (C_{max} and $AUC_{0\text{-}14D}$) increased with dose escalation. PD analysis demontrated significant depletion of CCR8-expressing cells in CTCL skin lesions. Significant reduction of CCR8+ malignant T cells (-80%) and CCR8+ regulatory T cells (Treg, -68%) were observed at C3D1 compared with baseline in the skin lesion. Similar PD effects were observed in the peripheral blood as well with an average decrease of 91% in CCR8+ malignant T cells and 16% in Treg at C3D1 when compared with baseline. **Conclusions:** The current study is the first and only report on the preliminary efficacy data of anti-CCR8 targeted therapy for CTCL patients. The effectiveness of ICP-B05 was supported by the PD effects in both skin lesions and peripheral blood in the depletion of CCR8+ cells. ICP-B05 is safe and well tolerated and its safety profile made it a good candidate for combo therapies for CTCL patients with lymph node and other organ involvement. Clinical trial information: NCT05690581. Research Sponsor: None.

2515 **Rapid Oral Abstract Session**

An open-label, phase I trial of the SIRPα monoclonal antibody, BI 770371, alone and in combination with the PD-1 inhibitor ezabenlimab in patients with advanced solid tumors. First Author: Judy S. Wang, Florida Cancer Specialists & Research Institute, Sarasota, FL

Background: The signal regulatory protein alpha (SIRPα)/CD47 axis is a critical regulator of myeloid cell activation and serves as a myeloid-specific immune checkpoint, making it a potential therapeutic target. The pan-specific SIRPα monoclonal antibody, BI 770371, blocks the SIRPα/CD47 interaction, leading to reactivation of innate antitumor immune responses. This Phase I trial (NCT05327946) aimed to determine the maximum tolerated dose (MTD) and recommended dose for expansion of BI 770371 ± ezabenlimab in patients (pts) with advanced solid tumors. **Methods:** Pts with ≥1 measurable lesion and ECOG PS of 0/1 were enrolled. Pts received escalating doses ofBI 770371 alone or in combination with ezabenlimab 240 mg once every 3 weeks. Treatment continued until progressive disease, unacceptable toxicity, or pt withdrawal. BI 770731 dose escalation was guided by a Bayesian Logistic Regression Model with overdose control. Primary endpoint was dose-limiting toxicities (DLTs) in the MTD evaluation period (Days 1–21). Secondary endpoints were adverse events (AEs) and DLTs in the on-treatment period. **Results:** At data cut-off (Nov 22, 2024), 21 pts had received BI 770371 monotherapy across 6 dose levels, and 15 pts had received BI 770371 in combination with ezabenlimab (combination group) across 5 dose levels. In the monotherapy group, median age was 63 years (range: 26–77) and 95% of pts had received ≥3 prior lines of therapy. In the combination group, median age was 61 years (range: 27–78), and 80% had received ≥3 prior therapies. No DLTs were reported during the MTD evaluation period with BI 770371 monotherapy or with the combination; 1 pt in the monotherapy group had a DLT (grade 2 encephalitis, which resolved within 1 week) during the on-treatment period (likely due to prior nivolumab and ipilimumab treatment). In total, 14 (67%) and 10 (67%) pts in the monotherapy and combination groups, respectively, had a treatment-related AE (TRAE). Most common TRAEs with BI 770371 monotherapy were pruritus (24%) and fatigue (19%). Most common TRAEs with the combination were fatigue and decreased appetite (each 20%). Most TRAEs were grade 1/2, one pt in the combination group had two grade 3 TRAEs (diarrhea and fatigue); there were no grade 4/5 TRAEs. Two suspected unexpected serious adverse reactions were seen: grade 2 encephalitis (monotherapy) and grade 3 diarrhea (combination). One pt had an AE leading to discontinuation (grade 2 encephalitis). One pt in the combination group had a partial response; 13 (62%) and 8 (53%) pts in the monotherapy and combination groups, respectively, had stable disease. **Conclusions:** These preliminary data indicate that BI 770371 is well tolerated alone and in combination with ezabenlimab, with promising antitumor activity seen in heavily pretreated pts with advanced solid tumors. The MTD of BI 770371 was not reached in either group. Clinical trial information: NCT05327946. Research Sponsor: Boehringer Ingelheim.

2516 **Rapid Oral Abstract Session**

A novel application of deep learning (DL)-based MRI with liquid biomarkers for immune effector cell-associated neurotoxicity syndrome (ICANS) after chimeric antigen receptor (CAR) T-cell therapy. First Author: Kathryn Ries Tringale, UC San Diego, La Jolla, CA

Background: ICANS is a complication of CAR T-cell therapy, yet risk factors and quantitative diagnostic criteria, particularly neuroimaging criteria, remain incompletely characterized. We implemented a novel application of a deep learning (DL)-based MRI approach alongside clinical and liquid biomarkers to better characterize neurotoxicity after CAR T-cell therapy. **Methods:** We analyzed all patients with non-Hodgkin lymphoma (NHL) or acute lymphoblastic leukemia (ALL) who underwent CAR T-cell therapy at UCSD with a commercial product from 2018-2024. ICANS was graded as per American Society for Transplantation and Cellular Therapy (gr1-4). Variables included stage, performance status, and prior receipt of high-dose methotrexate (HD MTX), intrathecal (IT) chemotherapy, central nervous system (CNS) involvement, CNS-directed radiotherapy (CNS RT), and extracranial RT. Labs obtained pre-infusion, 3 days post-infusion, and during ICANS (or 7 days post-infusion for those without ICANS) were evaluated. Available post-infusion brain MRIs were processed with a 3D U-Net convolutional neural network to quantify T2 FLAIR hyperintensity volumetrics. Linear mixed regression models accounting for zero inflation assessed longitudinal DL-derived FLAIR. Multivariable regression models assessed factors associated with ICANS. **Results:** Of 163 patients (89% NHL, 11% ALL), 52 had IT chemotherapy, 27 had HD MTX, 24 had prior CNS disease, and 22 had prior CNS RT. Most (106) received axicabtagene ciloleucel (34 tisagenlecleucel, 23 brexucabtagene autoleucel) and most had CRS (133, 82%). ICANS occurred in 73 (45%) at a median of 7 days post-infusion (39 gr1-2, 34 gr3-4). Post-infusion, 21 patients had ³1 brain MRI (93 MRIs total). Baseline factors associated with ICANS were lactate dehydrogenase (LDH; odds ratio [OR] 1.03 p = 0.002) and prior IT chemotherapy (OR 2.5 p = 0.01). There was a trend toward association of gr3-4 ICANS with HD MTX (OR 2.8 p = 0.07). Post-infusion, CRS grade was associated with ICANS (OR 2.8 $p < 0.001$). LDH (1.02 p = 0.004) and C-reactive protein (OR 1.2 $p < 0.001$) were elevated during ICANS. Patients with ICANS had significantly greater FLAIR (intercept 23.8 cm^3 $p < 0.001$) and there was increased FLAIR over time across all patients (b = 3.3 cm^3 p = 0.05). There was a trend toward association between higher ICANS grade and DL-derived FLAIR (p = 0.09). **Conclusions:** Here, we demonstrate a novel application of DL-based MRI quantification of ICANS post-CAR T-cell therapy. This metric, along with clinical features, emerged as potential quantitative biomarkers of ICANS. These findings warrant further investigation and have informed a prospective study, including standardized brain MRI pre- and post-infusion, to develop a comprehensive phenotype of neurotoxicity following CAR T-cell therapy. Research Sponsor: None.

2517 **Rapid Oral Abstract Session**

Role of autoimmune reactivity in neurotoxicities (N-Tox) in melanoma patients treated with immune-checkpoint inhibitors (ICI). First Author: Agrima Dutt, New York University Grossman School of Medicine, New York, NY

Background: N-Tox is a grossly understudied immune-related adverse event (irAE), despite its association with mortality (e.g. encephalitis) and morbidities (e.g. peripheral neuropathy). We reported that pre-treatment sera autoantibodies (auto-Abs) are implicated in the pathogenesis of irAEs (Johannet *et al. CCR* 2022). We here examined the rate and patterns of N-Tox in melanoma patients who received ICI in the adjuvant setting and whether baseline specific serum auto-Abs are associated with N-Tox. **Methods:** We examined clinicopathological features and baseline auto-Abs of 965melanoma patients (551 male and 414 female) enrolled in two phase III clinical trials: Checkmate 238 and Checkmate 915 (797 resected stage III, 166 resected stage IV, and 2 unknown). Patients received ipilimumab (n = 423), nivolumab (n = 347), or both (n = 195). We compared pre-treatment serum auto-Ab profiles using the HuProt Human Proteome Microarray v4.0 (CDI Laboratories, Mayaguez, PR) that has 21,000+ individually purified full-length human proteins and protein isoforms in duplicate, in patients who developed at least a single incidence of N-Tox grade $\geq$2 to those who developed only other types of irAEs grade $\geq$2. We used a threshold of logFC $>$ 0.3 and false discovery rate (FDR) adjusted P value $<$ 0.05 to determine differentially expressed auto-Abs in patients with N-Tox. **Results:** 329/965 (34%) patients developed N-Tox. There were 426 total incidences of N-tox (grade 1 n = 258, grade 2 n = 132, grade 3 n = 34, grade 4 n = 2). 97/329 patients developed more than one grade of N-Tox. Patients who received ipilimumab were more likely to experience any grade N-Tox (P = 0.002) in a multivariate model. Any grade N-tox was also associated with a lower recurrence rate (P = 0.004). Gender and melanoma stage were not associated with N-Tox ($P > 0.05$). A signature of 160 auto-Abs, including those targeting mitochondrial proteins (ATP5PO, COX6C, NDUFA3, NDUFB6), calcineurin (PPP3CC, PPP3R1), cellular architecture (RAC1), and inflammation/apoptosis (TRAF2) were significantly overexpressed in the N-Tox grade $\geq$2 cohort (n = 143) compared to non-N-Tox grade $\geq$2 (n = 569). Pathway analysis revealed these auto-Abs were enriched in several pathways involved in neuroinflammation and neurodegeneration, including TNF-a signaling, B cell receptor signaling, interleukin-2 production, natural killer cell mediated cytotoxicity, and cellular senescence. **Conclusions:** Our data demonstrate that the incidence of N-Tox is higher than previously reported, possibly due to stringent assessment and follow up in clinical trial settings. The multiplicity of pathways involved, some of them directly involved in neurodegeneration and neuroinflammation, suggests a complex N-tox pathogenesis that requires further clinical and pre-clinical investigations. Research Sponsor: National Cancer Institute; P50CA225450.

2518 **Rapid Oral Abstract Session**

Natural killer cell transcriptomic expression and prediction of survival after immune checkpoint blockade across cancers. First Author: Hirotaka Miyashita, Dartmouth Cancer Center, Lebanon, NH

Background: Preclinical and clinical evidence has suggested the role of natural killer (NK) cells in tumor immunity and prognosis across various cancer types, but their significance during immune checkpoint blockade (ICB) treatment is poorly understood. This study investigated the impact of tumor-infiltrating NK cells, surrogated by the RNA expression of genes related to NK cells in the tumor microenvironment, on the outcomes of the patients who undergo ICB, using real-world, pan-cancer data. **Methods:** We analyzed RNA sequencing data of 395 immune-related genes from 514 patients with various cancers included in the Study of Personalized Cancer Therapy to Determine Response and Toxicity (NCT02478931). After excluding 25 patients ineligible for survival analysis, we defined two distinctive cohorts: patients who received ICB (ICB cohort, N = 217) and those who did not (non-ICB cohort, N = 272). Among the 395 immune-related genes, 43 were selected as NK-related genes according to the Human Protein Atlas. Patients in each cohort were clustered into two groups based on the NK-related gene expression. The associations between the clusters and the clinical outcomes, including overall survival (OS) and progression-free survival (PFS), were analyzed using univariate and multivariate analyses. In the multivariate analysis, cancer types, line of immunotherapy, positive programmed-death ligand 1 immunohistochemistry (PD-L1 IHC, $\geq$ 1%), high tumor mutational burden (TMB, $\geq$ 10/Mb), and microsatellite instability (MSI) were adjusted. **Results:** The ICB cohort (N = 217) was divided into two clusters (hot vs. cold), characterized by general abundance and paucity of NK-related gene transcripts (N = 101 and 116, respectively). The clusters were not significantly associated with histology, positive PD-L1 IHC, high TMB, or MSI. Those in the hot cluster demonstrated significantly longer overall survival (OS) after starting ICB compared to those in the cold clusters in univariate analysis (hazard ratio [HR] and 95% confidence interval [CI]: 0.65 [0.45-0.92], p = 0.015) and multivariate analysis (HR and 95% CI: 0.57 [0.34-0.87], p = 0.010). The cluster was not significantly associated with PFS. The non-ICB cohort (N = 272) was similarly divided into two clusters (hot vs. cold), with the characteristics of generally high and low NK-related gene RNA expressions. (N = 114 and 158, respectively). However, in the non-ICB cohort, patients in the hot clusters did not demonstrate significantly prolonged OS compared with those in the cold cluster either with univariate or multivariate analysis (HR and 95% CI: 0.93 [0.65-1.32], p = 0.67 and 0.97 [0.76-2.01], p = 0.90 respectively). **Conclusions:** Transcriptomic expression of NK-related genes in tumor tissue independently and significantly predicted longer survival after ICB treatment, which implies a role of tumor infiltrating NK cells in immunotherapy outcome. Research Sponsor: U.S. National Institutes of Health; CA023100.

2519 **Rapid Oral Abstract Session**

Tumor-wide RNA splicing aberrations and their potential as therapeutic neoantigen targets. First Author: Darwin Kwok, University of California, San Francisco, San Francisco, CA

Background: Tumor heterogeneity and low mutational burden limits the availability of effective immunotherapy targets. Aberrant RNA-splicing (neojunctions) represents an underexplored yet promising source of neoantigens. To address this, we developed a neoantigen discovery platform (SNIPP) that characterizes a novel class of clonally-expressed, splicing-derived neoantigens. Furthermore, we validated the immunogenicity of these neoantigens by identifying specific TCRs that drive CD8+ T-cell-mediated tumor killing. **Methods:** SNIPP identified public neojunctions by analyzing TCGA RNA-seq data, selecting neojunctions with a positive sample rate (PSR) $>$ 10% and filtering out those found in GTEx normal tissue RNA-seq data (PSR $<$ 1%) across 12 cancer types. To characterize intratumorally conserved neojunctions, we performed maximally-distanced multi-site biopsies (n = 535) within glioma patients (n = 56) and generated RNA-seq data for each intratumoral site. Two independent algorithms were utilized to predict peptide processing likelihood and HLA-binding affinity of splicing-derived neoantigen candidates. Neoantigen-specific TCR sequences were identified via *in vitro* sensitization of PBMCs and subsequent 10x V(D)J scRNA-seq. These TCRs were transduced into CD8+ T-cells, which were tested downstream for immunogenicity and cytotoxicity against glioma cell lines. **Results:** Our pipeline identified 789 public neojunctions, including 32 neojunctions concurrently detected in transcriptomic and proteomic glioma datasets and confidently predicted to be presented by HLA-A*02:01. IVS and subsequent 10x V(D)J scRNA-seq identified TCR clonotypes reactive against neojunctions in *RPL22* (n = 7) and *GNAS* (n = 1), with the latter exhibiting high intratumoral conservation (detected in $>$ 90% of spatially-mapped biopsies across 17/56 patients (26.78%)). TCR-transduced CD8+ T-cells recognized and were immunogenically activated and demonstrated cytotoxicity against endogenously processed and presented neoantigens in GBM and melanoma lines. Additionally, IDH1-mutant oligodendrogliomas exhibited significantly higher neojunction expression compared to IDH1-mutant astrocytomas and IDH1wt subtypes. Differential gene expression analysis (DESeq2) revealed reduced expression of splicing factors in oligodendrogliomas, attributed to their specific co-deletion of chromosomes 1p and 19q. CRISPRi-mediated knockdown of these splicing factors (e.g. SF3A3, SNRPD2) in IDH1wt glioma cells resulted in significantly increased expression of corresponding neojunctions. **Conclusions:** Our study highlights a novel class of neoantigens derived from tumor-wide aberrant RNA splicing. The SNIPP platform effectively identifies public intratumorally-conserved neojunctions with strong therapeutic potential. Furthermore, elevated neojunction expression in oligodendroglioma underscores the mechanistic link between dysregulated splicing factor expression and RNA splicing abnormalities. Research Sponsor: None.

2520 Rapid Oral Abstract Session

Perturbational single-cell RNA sequencing of patient tumors in Merkel cell and small cell lung carcinomas. First Author: Curtis J. Perry, Yale School of Medicine, New Haven, CT

Background: Despite the transformational impact of immune checkpoint blockade, many cancer patients do not experience long-term survival. T cells with innate immune signatures can secrete inflammatory cytokines/chemokines and deliver potent cytotoxic signals potentially ideal for tumor immunity. The novel double-stranded RNA sensor RIG-I agonist SLR14 improved the control of murine melanoma. We tested the hypothesis that SLR14 transforms T cells to a cytotoxic state in immunologically "cold" human tumor specimens. **Methods:** We developed an approach, called PERCEPT, to directly test the response of patient tumor and immune samples to novel and established therapies *ex vivo* using perturbational single-cell RNA sequencing (Table). We obtained 9 surgical resections from primary or metastatic melanoma and Merkel Cell Carcinoma (MCC) tumors and lymph node metastases and made suspension replicates of tumor and infiltrating immune cell co-cultures. We stimulated for 42-48 hours (Table). We Flouresscently Activated Cell Sorted live cells and then barcoded for multiplexed single-cell sequencing using 10x scRNAseq. We used CINEMA-OT to identify factors associated with response and resistance to the perturbations tested. We developed and validated CRISPR-KO MCC and small cell lung cancer (SCLC) cell lines, and co-cultured with CD14+ monocytes or monocyte-derived DCs. **Results:** Stimulation with RIG-I agonist SLR14 induced expression beyond canonical IFN-stimulated genes in tumor cells, NK cells, and T cells. SLR14 stimulates tumor-infiltrating T cells into antiviral states in tumor-immune co-cultures and primes *in vitro* T-cell production of IFNγ. However, MCC immune infiltrate responsiveness to IFN or SLR14 was notably decreased compared to the melanoma samples, and perturbational computational analyses with CINEMA-OT identified the cytokine midkine (MDK) associated with nonresponse in MCC. Knockout of MDK restored response to IFN and SLR14 by MCC and SCLC tumor cell lines, as well as co-cultured CD14+ monocytes or monocyte-derived DCs. **Conclusions:** Our approach revealed that midkine, a multifunctional cytokine, suppresses innate immune sensing of IFN and SLR14 in both tumor and immune cells, disrupting the tumor immunity cycle at multiple points. We show that this effect, while comparatively infrequent in melanoma, is pronounced in MCC and SCLC. Our study thus uses a direct assessment of patient tumor and immune samples to identify a novel resistance mechanism enriched in neuroendocrine tumors MCC and SCLC. Research Sponsor: Conquer Cancer/ASCO Young Investigator Award 2023; Astrazeneca; U.S. National Institutes of Health; 1R37CA279834-01A1.

Therapeutic class	Stimulation	Target	Clinical development
Immune checkpoint inhibitor	αPD-1	PD-1	Standard of care
Cytokine	IFNγ	IFNGR	Early-phase clinical trials
	IFNβ	IFNAR	or
Innate immune agonist	Poly(I:C)-NT	TLR3	Pre-clinical
	Poly(I:C)-T	MDA5/TIG-I/TLR3	
	ADU-S100	STING	
	SLR14	RIG-I	
Combination	αPD-1 + IFNβ	PD-1/IFNAR	

2521 Poster Session

Phase 1/2, open-label, first-in-human study of the anti-GPC3 T-cell engager SAR444200 in patients with advanced solid tumors: Updated efficacy and biomarker analysis. First Author: Ecaterina Elena Dumbrava, Department of Investigational Cancer Therapeutics, The University of Texas MD Anderson Cancer Center, Houston, TX

Background: SAR444200 is a novel NANOBODY T cell engager that simultaneously binds TCR$\alpha\beta$ and glypican-3 (GPC3) to co-engage T cells with GPC3+ tumor cells, resulting in T cell-dependent cellular cytotoxicity. We present updated safety, efficacy, and biomarker data from the dose escalation cohort (Part 1A) of a multicenter, first-in-human, Phase 1/2 trial (NCT05450562). **Methods:** Patients (Pts) with GPC3+ refractory solid tumors received SAR444200 intravenously (IV) weekly with lead-in doses at dose levels (DLs) 1 (3 mg), 1A (1 mg), 2A (2.5 mg), 3A (4.5 mg), 4A (18 mg), 5A (36 mg), 6A and 7A (different lead-in doses, target dose 70 mg). Pts with ECOG PS $\leq$1, and $\geq$1 measurable lesion per RECIST 1.1, were eligible. Primary objective for Part 1A was safety. Key secondary objectives included efficacy and PK/PD. Levels of interleukin-6 (IL-6) and interferon gamma (IFNγ) were evaluated with a multiplex ECL-based assay. Study imaging was performed every 9 weeks following first infusion. Circulating tumor (ct) DNA was analyzed in blood samples using a mutational profiling NGS approach. **Results:** As of October 15, 2024, 33 pts (23 pts with hepatocellular carcinoma [HCC]) were treated with SAR444200 (premedicated with dexamethasone 15 mg IV or equivalent) for a median of 23 cycles (range, 1–32). Median lines of prior therapies were 3–4. Most pts (32 [97%]) experienced $\geq$1 AE of any Grade. Grade $\geq$3 TEAEs in 16 (48.5%) pts and serious TRAEs in 8 (24.2%) pts were reported. 2 Grade 3 cytokine release syndrome events were reported as DLTs at DL6A and 1 at DL7A during the lead-in dosing. Key efficacy data are summarized in Table 1. An increase in IL-6 and IFNγ (maximum of 1326 pg and 461 pg on average per DL, respectively) was observed during lead-in-doses in pts from DL1 to DL5A, supporting CRS diagnosis. Cytokine levels declined after Cycle 1. Of 18 HCC pts with baseline alpha fetoprotein (AFP) $\geq$20%, 5 (27%) pts showed $\geq$50% AFP reduction. Median time of observing any AFP decrease was 4 weeks post-treatment. Among these, 3 pts had sustained decrease over 13 cycles. Stable disease (SD) was reported in 10 (30.3%) pts including 2 who were on study drug for 12 and 22 months. Of the 18 pts with measurable ctDNA, 4 (including 3 pts at DL5 and above) had reductions in ctDNA (18%–48%) from baseline. **Conclusions:** SAR444200 was tolerated at the investigated DLs in pts with GPC3+ advanced solid tumors. Decrease in AFP post treatment along with SD in a subset of pts is suggestive of preliminary anti-tumor activity. Clinical trial information: NCT05450562. Research Sponsor: Sanofi.

Efficacy analysis.

n (%)	DL1 3 mg 2W n=4	DL1A 1 mg 2W n=4	DL2A 2.5 mg 2W n=4	DL3A 4.5 mg 2W n=4	DL4A 18 mg 3W n=4	DL5A 36 mg 3W n=6	DL6A 70 mg 3W n=3	DL7A 70 mg 3W n = 4	All (N = 33)
BOR	1 (25.0)	1 (25.0)	1 (25.0)	1 (25.0)	2 (50.0)	3 (50.0)	1 (33.3)	0	10 (30.3)
Stable Disease	3 (75.0)	3 (75.0)	3 (75.0)	2 (50.0)	2 (50.0)	2 (33.3)	1 (33.3)	2 (50.0)	18 (54.5)
Progressive disease									

BOR, best overall response; DL, dose level; W, weeks.

2522 Poster Session

Lacutamab in patients with relapsed and refractory Sézary syndrome: Long term follow-up from the TELLOMAK phase 2 trial. First Author: Pierluigi Porcu, Sidney Kimmel Cancer Center, Thomas Jefferson University, Philadelphia, PA

Background: Sézary syndrome (SS) is a rare and aggressive cutaneous T-cell lymphoma, which commonly expresses KIR3DL2, a killer immunoglobulin-like receptor, reported in $\geq$ 85% of patients. SS is characterized by erythroderma, significant blood involvement, lymphadenopathy and poor prognosis (10-20% 5-year survival). Lacutamab is a first-in-class monoclonal antibody designed to specifically deplete KIR3DL2-expressing cells via antibody-dependent cell-cytotoxicity and phagocytosis. **Methods:** TELLOMAK is an international, Phase 2 trial with multiple cohorts (NCT03902184). We report here long term follow-up results from Cohort 1, evaluating lacutamab in patients with relapsed/refractory (R/R) SS after at least 2 prior systemic therapies including mogamulizumab. Lacutamab 750 mg is administered until progression or unacceptable toxicity. Primary endpoint was Objective Response Rate (ORR) based on the evaluation of 4 compartments: skin, blood, lymph nodes and viscera according to the International Consensus criteria Olsen 2011. Secondary endpoints included but were not limited to duration of response (DOR), progression free survival (PFS), safety, and quality of life assessments. **Results:** As of October 17, 2024, recruitment was completed with 63 SS patients enrolled. Median age was 69 years (range: 42-86), the median prior lines of systemic therapies were 5.0 (range: 2-13), 65.1% and 34.9 % patients had stage IVA1 and stage IVA2 at baseline respectively, all patients had blood involvement (B2), 63.5% had confluence of erythema covering $\geq$ 80% body surface area (T4), 34.9% had lymph node lymphoma involvement (N3). Median follow-up was 25.1 months (95% CI 21.0-29.4). Global confirmed ORR was 42.9% (CI 31.4-55.1) including 6 (9.5%) CRs who are all still in CR; with a median time to response of 2.8 months (range 1-10) and a median duration of response of 25.6 months (CI 11.0, NE). According to each compartment, ORR in skin was 52.4% (CI 40.3-64.2) including 9 (14.3%) CRs, ORR in blood was 50.8% (CI 38.8-62.7) including 21 (33.3) CRs, and ORR in lymph nodes was 28.8% (CI 18.3-42.3) including 9 (17.3) CRs. Median PFS was 8.3 months (CI 5.1-18.7). Grade $\geq$ 3 related Treatment-Emergent Adverse Events (TEAEs) were observed in 20.6% patients. Serious related TEAEs were observed in 9.5% patients and related TEAEs leading to study drug discontinuation in 6.3% patients. Data from additional key endpoints will be presented. **Conclusions:** The long term follow-up data from TELLOMAK study in a R/R SS population previously treated with 2 or more prior systemic therapies including mogamulizumab, confirm that lacutamab shows promising clinical activity with ORR 42.9% (95% CI 31.4-55.1) and median duration of response of 25.6 months (11.0, NE) and an overall favourable safety profile. These data support the further development of lacutamab in an effort to bring improved treatments to patients with SS. Clinical trial information: NCT03902184 // EU CT number: 2023-507777-18-00. Research Sponsor: Innate Pharma.

2523 Poster Session

Lacutamab in patients with relapsed and/or refractory mycosis fungoides: Long-term follow-up and translational data from the TELLOMAK phase 2 trial. First Author: Pierluigi Porcu, Sidney Kimmel Cancer Center, Thomas Jefferson University, Philadelphia, PA

Background: The most common type of cutaneous T-cell lymphoma is Mycosis Fungoides (MF) accounting for 50-60% of cases. Extracutaneous involvement occurs mainly in lymph nodes or blood; 25% of patients are diagnosed at advanced stage with a 5-year survival of 15-25%. Lacutamab is a first-in-class monoclonal antibody designed to specifically deplete KIR3DL2-expressing cells via antibody-dependent cell-cytotoxicity and phagocytosis. KIR3DL2 is a killer immunoglobulin-like receptor expressed in MF patients. **Methods:** TELLOMAK is an international, multi-cohort phase 2 trial (NCT03902184). MF patients who had received at least 2 prior systemic therapies were treated with lacutamab 750 mg until disease progression or unacceptable toxicity. Primary endpoint was Objective Response Rate (ORR) by global response score based on the evaluation of 4 compartments: skin, blood, lymph nodes and viscera according to the International Consensus criteria Olsen 2011. Key secondary endpoints included duration of response (DoR), progression free survival (PFS), safety, and quality of life. Here we report long term follow-up data of MF patients. **Results:** As of October 17, 2024, recruitment was completed, with 107 MF patients enrolled. The median age was 62 years. The median number of previous systemic lines was 4 (range: 1-14). Median follow-up was 22.1 months (m) (95% CI 19.4, 23.6). Global confirmed ORR was 19.6% (CI 13.2, 28.1; Olsen 2011), and response in skin was 29.0% (CI 21.2, 38.2). Median time to response was 2.8 m (min, max 1-37) and median DoR was 13.8 m (7.4, NE), median PFS was 10.2 m (CI 8.0, 15.4). Among the KIR3DL2 $\geq$1% pts (N = 48), ORR was 20.8% (CI 11.7, 34.3; Olsen 2011), and response in skin was 33.3% (CI 21.7, 47.5), median DoR was 13.8 m (CI 4.6, NE) and median PFS 11.8 m (CI 5.6, 16.8). Among the KIR3DL2 $<$ 1% pts (N = 59), ORR was 18.6% (CI 10.7;30.4; Olsen 2011), and response in skin was 25.4 (CI 16.1, 37.8), median DoR was 15.7 m (CI 5.1, NE) and median PFS 9.5 m (CI 6.5;16.6). Grade $\geq$ 3 related Treatment-Emergent Adverse events (TEAEs) were observed in 5/107 (4.7%) patients, serious related TEAEs in 4/107 (3.7%) patients and related TEAEs leading to study drug discontinuation in 3/107 (2.8%) patients. The most common ($>$ 10%) related TEAEs were fatigue (12.1%), nausea (13.1%), asthenia (11.2%) and arthralgia (11.2%). Data from additional key endpoints and translational data will also be presented. **Conclusions:** The long-term follow-up data from the heavily pre-treated MF population enrolled to the TELLOMAK study confirms promising clinical activity of lacutamab regardless of KIR3DL2 expression, with ORR 20.8%, a median duration of response of 13.8 m, a median PFS of 10.2 m and a favorable safety and tolerability profile. These data support the further development of lacutamab in an effort to bring improved treatments to patients with MF. Clinical trial information: NCT03902184 // EU CT number: 2023-507777-18-00. Research Sponsor: INNATE PHARMA.

2524 Poster Session

Safety and efficacy of OR502, an antibody targeting leukocyte immunoglobulin-like receptor B2 (LILRB2), ± cemiplimab in patients with advanced solid tumors from a phase 1 study. First Author: Shiraj Sen, NEXT Oncology, Dallas, TX

Background: OR502 is a humanized IgG1 antibody that targets LILRB2, blocking its binding to HLA ligands A, B and G. OR502 prevents and reverses myeloid cell-mediated immune suppression and rescues T cell effector functions. Preclinical data demonstrate best-in-class properties. We report on the completed monotherapy and combination dose escalation cohorts from the ongoing, first-in-human, phase 1-2 study of this novel antibody. **Methods:** Patients had progressive, histologically confirmed, metastatic/unresectable solid tumors with ≥ 1 prior systemic standard of care treatments. Primary objectives were OR502 safety/tolerability and identifying a dose for future study supported by LILRB2 receptor occupancy (RO) and pharmacokinetics (PK). Secondary objectives included assessment of anti-tumor activity. We used a modified toxicity probability interval-2 design with a 25% dose-limiting toxicity (DLT) rate and a 20–30% equivalence interval. Patients received OR502 IV (100–1600 mg) over 30 minutes, every 3 weeks (Q3W) as monotherapy (n = 19) or with cemiplimab (350 mg) (n = 20). **Results:** In dose escalation (n = 39), there were no DLTs, treatment-related deaths, related SAEs, grade ≥ 3 treatment-related AEs or signals from vital signs, ECGs or laboratory results. One patient (monotherapy, 400 mg) discontinued due to grade 2 AEs. Infusion-related reactions (IRRs) occurred in 6 patients (3 monotherapy [1 at 800 mg and 2 at 1600 mg] and 3 combination [400, 800 and 1600 mg]). All IRRs were grade ≤ 2 and were mitigated by extending infusion duration to 60 minutes, with secondary prophylaxis if necessary (acetaminophen, diphenhydramine). All but 4 patients were evaluable for efficacy, see table. Monotherapy responses were seen at 200 and 800 mg in melanoma and non-small cell lung cancer (NSCLC), respectively. In combination, 1 patient with soft tissue sarcoma (1600 mg) had a cPR. There were 13 deaths due to progressive disease. Durable stable disease (SD) was seen in: sarcomas, cutaneous squamous cell carcinoma, thymoma, thyroid, melanoma, hepatocellular carcinoma and colorectal cancer. OR502 RO was near-complete at ≥ 200 mg and PK was roughly dose-proportional. Combination with cemiplimab did not affect RO or PK. **Conclusions:** OR502 has excellent safety and tolerability ± cemiplimab. Based on efficacy, predictable PK and near-complete RO, two mini-expansion cohorts are evaluating OR502 800 mg Q3W ± cemiplimab in patients with cutaneous melanoma or NSCLC who have failed or progressed after ≥ 12 weeks of anti-PD-(L)1. Clinical trial information: NCT06090266. Research Sponsor: OncoResponse, Inc.; The Cancer Prevention and Research Institute of Texas.

Best objective response (RECIST 1.1), PK and RO.

	OR502 (n=17)	OR502 + cemiplimab (n=18)
PR	2	1
cPR	1	1
SD	9	8
Durable SD (≥ Week 12)	7	4
Best overall response rate %	12	6
Disease control rate (CR+PR+SD)%	65	50
PK (100–1600 mg) $t^1/_2$ (day)	7.6–15.9	8.4–12.4
Peripheral RO% (100–1600 mg)	91–101	88–99
Classical monocytes		
Neutrophils	89–100	84–100

2525 Poster Session

A phase 1 study of the OX40 agonist BGB-A445, with or without tislelizumab, an anti-PD-1 monoclonal antibody, in patients with advanced NSCLC, HNSCC, or NPC. First Author: Min Hee Hong, Yonsei Cancer Center, Yonsei University College of Medicine, Seoul, South Korea

Background: BGB-A445 is a monoclonal antibody OX40 agonist that does not compete with the natural OX40 ligand, reducing the likelihood of a hook effect and distinguishing it from other OX40-targeting therapies. Here, we present results from the dose expansion portion of a ph 1, open-label, dose escalation/expansion trial of BGB-A445 in pts with advanced solid tumors (NCT04215978). Ph 1a results were previously presented (Desai *et al. J Clin Oncol.* 2023). **Methods:** Previously treated pts with NSCLC (Part A1), HNSCC (Part A2), or NSCLC with PD-L1 ≥50% (Part C) received BGB-A445 monotherapy, while pts with treatment-naïve recurrent/metastatic NPC (Part B) received BGB-A445 combined with tislelizumab and chemotherapy. Primary endpoints included ORR per investigator (RECIST v1.1); secondary endpoints were to assess PFS, DOR and DCR, safety/tolerability, PK, and host immunogenicity. **Results:** As of Sep 25, 2024, 54 pts were enrolled in Part A1, 19 in Part A2, 12 in Part B, and 7 in Part C. In the efficacy evaluable analysis set, ORR was 0% in Parts A1, A2, and C, and 70% (7/10; all confirmed PRs, one unconfirmed CR) in Part B. In Parts A1, A2, B, and C, confirmed DCR was 49.0%, 33.3%, 100.0%, and 57.1%, respectively. TEAEs occurred in the majority of pts (Table). The most common treatment-related TEAEs were pyrexia (10.0% [8/80]), chills (5.0% [4/80]), and anemia (5.0% [4/80]) in the monotherapy cohorts, and anemia (75.0% [9/12]), decreased WBC (66.7% [8/12]), decreased neutrophils, and decreased platelets (58.3% [7/12], each) in the combination cohort. Treatment-related serious TEAEs occurred in 2.5% (2/80; pyrexia and asthenia in a single pt each) of pts in the monotherapy cohorts and 8.3% (1/12; febrile neutropenia) in the combination cohort. There were no BGB-A445 or tislelizumab-related TEAEs leading to treatment discontinuation or death. The most common imAE was rash (2.5% [2/80] in the monotherapy cohort; 33.3% [4/12] in the combination cohort). No Gr ≥3 imAEs or IRRs were reported. **Conclusions:** BGB-A445 alone or in combination with tislelizumab and chemotherapy was generally well tolerated across all doses in pts with advanced NSCLC, HNSCC, and NPC, and showed preliminary antitumor activity. Clinical trial information: NCT04215978. Research Sponsor: BeOne Medicines Ltd.

Safety.

	Part A1 NSCLC (N=54)	Part A2 HNSCC (N=19)	Part B NPC (N=12)	Part C NSCLC and PD-L1 ≥50% (N=7)
Any treatment-emergent AE	47 (87.0)	16 (84.2)	12 (100.0)	7 (100.0)
Gr ≥3	17 (31.5)	5 (26.3)	11 (91.7)	3 (42.9)
Serious	21 (38.9)	4 (21.1)	2 (16.7)	4 (57.1)
Leading to death	4 (7.4)	2 (10.5)	0 (0)	0 (0)
Leading to treatment discontinuation	8 (14.8)	3 (15.8)	2 (16.7)	0 (0)
Any treatment-related treatment-emergent AE	28 (51.9)	7 (36.8)	12 (100.0)	3 (42.9)
Gr ≥3	1 (1.9)	0 (0)	11 (91.7)	0 (0)
Any immune-mediated AE	6 (11.1)	1 (5.3)	6 (50.0)	1 (14.3)
Infusion-related reactions	6 (11.1)	3 (15.8)	3 (25.0)	1 (14.3)

Pts with multiple adverse events (AEs) are counted once. All AEs are listed as n (%).

2526 Poster Session

Phase 1b dose extension study of a next-generation anti-CD47 monoclonal antibody IMC-002 combined with lenvatinib in patients with advanced hepatocellular carcinoma (HCC). First Author: Jung Yong Hong, Division of Hematology-Oncology, Department of Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, South Korea

Background: IMC-002 has shown significant preclinical efficacy and safety, which are attributed to its unique binding site and distinct mechanism of action. These preclinical findings strongly support its clinical development as a cancer therapeutic. Phase 1a trial confirmed its superior safety and tolerability. Here we present initial results from the phase Ib trial, focusing on safety, efficacy, PK, and biomarker. **Methods:** Eligible pts had advanced HCC that progressed following at least 1 prior systemic therapy and ECOG PS ≤1. IMC-002 was administered at 20 mg/kg Q3W in combination with Lenvatinib, continuing until disease progression. Tumor assessments were conducted every 6 weeks using RECIST 1.1 and iRECIST. A target-mediated drug disposition (TMDD) PK model incorporating FcRn recycling was developed to predict PK values for Q3W dosing and evaluated for consistency with observed data. Immunohistochemistry (IHC) images of CD47 expression were analyzed using Lunit SCOPE uIHC, an AI-based platform capable of distinguishing staining positivity and cell types at the single cell level. **Results:** A total of 13 pts with refractory HCC received IMC-002 in combination with Lenvatinib. Most patients had received prior anti-PD-(L)1 therapy (11 pts) and had an ECOG PS of 1 (9 pts). Among the 10 pts evaluable for efficacy, the ORR was 30%, and the DCR was 70%. The median TTP was 8.3 months. AI-driven analysis of CD47 membrane specificity, using a subcellular model, revealed that samples with a high proportion of non-membrane-specific cells were associated with poor clinical outcomes (ORR 0%, DCR 33%). In contrast, samples with a low proportion demonstrated improved responses (ORR 60%, DCR 80%). We confirmed that 96.3% of the observed concentrations of IMC-002 in Phase 1b not only fell within the 90% prediction percentiles of PK model developed for Q3W dosing schedule but also demonstrated steady-state achievement (after cycle 2 of Q3W) and consistent C_{trough} exposure above the MEC (> 24 μg/mL). All TRAEs were grade 1-2 (100%), with 92% occurring during cycle 1. TRAEs reported in more than one patient included skin rash and transient vitreous floaters. Anemia was observed in only one patient, while no cases of neutropenia, thrombocytopenia, or treatment-related SAEs were reported. **Conclusions:** IMC-002, when combined with Lenvatinib at a dose of 20 mg/kg Q3W, demonstrated a promising efficacy and safety profile. AI-driven biomarker analysis identified potential predictive value, supporting the need for further investigation in larger clinical trials. Clinical trial information: NCT05276310. Research Sponsor: ImmuneOncia Therapeutics Inc.

Tumor response by CD47 non-specific cell proportion.

Cohort	Non-specific cell proportion Mean (±SD)	ORR	DCR
A	0.24 (±0.05)	0%	33%
B	0.05 (±0.05)	60%	80%
p-value	0.00	0.03	0.14

Cohort A: High proportion (≥15%) of 'non-specific' cells; Cohort B: Low proportion (<15%) of 'non-specific' cells.

2527 Poster Session

Safety and efficacy of QLS31905 in patients with advanced solid tumors: Updated data from phase 1 study. First Author: Yakun Wang, Key Laboratory of Carcinogenesis and Translational Research (Ministry of Education/Beijing), Department of Gastrointestinal Oncology, Peking University Cancer Hospital and Institute, Beijing, China

Background: QLS31905 is a Claudin18.2/CD3 bispecific antibody. Here we report the updated data of a phase 1 study of QLS31905. **Methods:** This multicenter phase 1 trial (NCT05278832) recruited patients (pts) with advanced solid tumors who had progressive disease or were intolerable to or inapplicable of standard therapy. In dose-escalation stage adopting accelerated titration and interval 3+3 design, pts regardless of Claudin18.2 status were administered QLS31905 via intravenous infusion in 11 sequential single doses (0.5, 1.5, 5, 15, 45, 100, 200, 350, 500, 800, 1200 μg/kg qw or q2w) with priming dose from 350 μg/kg. In dose-expansion stage, Claudin18.2-positive (≥1% tumor cells) pts were recruited. The primary endpoint was dose limiting toxicities (DLT) and maximum tolerated dose (MTD) in dose-escalation stage, and was objective response rate (ORR) in dose-expansion stage. **Results:** As of Jul 26, 2024, 31 pts were included from 0.5 μg/kg qw to 1200 μg/kg q2w in dose-escalation stage, and 48 pts were included in five cohorts (100~200 μg/kg qw and 350~800 μg/kg q2w) in dose-expansion stage. The 1200 μg/kg q2w cohort is ongoing. There were 43 (54.4%) pts with gastric or gastro-esophageal junction (G/GEJ) cancer and 26 (32.9%) with pancreatic adenocarcinoma (PAC). Over half of (61.8%) pts had received ≥2 lines of prior treatment. No DLT occurred. MTD was not reached. Treatment-related adverse events (TRAEs) occurred in 79 (100%) pts, of whom 34 (43.04%) were ≥grade 3. The most common ≥grade 3 TRAEs (≥3%) were lymphocyte count decreased (21.5%), γ-glutamyl transferase increased (3.8%), neutrophil count decreased (3.8%), cytokine release syndrome (CRS [3.8%]), and anemia (3.8%). CRS occurred in 17 (21.52%) pts including two pts with grade 3 and one with grade 4, and all recovered. Two pts (2.53%) discontinued treatment due to TRAEs of abdominal pain and CRS, respectively. No TRAE leading to death occurred. In 33 Claudin18.2-positive pts in 350~1200 μg/kg q2w cohorts, six pts (three with G/GEJ cancer and three with PAC) had partial response. ORR was 18.18% (95% confidence interval [CI]: 6.98%, 35.46%), disease control rate (DCR) was 87.88% (95% CI: 71.80%, 96.60%), median progression-free survival (PFS) was 4.21 months (95% CI: 2.99, 5.55), and median overall survival (OS) was 9.53 months (95% CI: 7.69, not evaluable). Among the Claudin18.2-positive pts in 350~1200 μg/kg q2w cohorts, ORR, DCR, median PFS, median OS was 15.79%, 89.47%, 4.40 months, 9.20 months in 19 pts with G/GEJ cancer, and was 25.00%, 91.67%, 3.94 months, not reached in 12 pts with PAC, respectively. QLS31905 exposure was generally linear with the administered dosage. There was no tendency of accumulation after multiple administrations. **Conclusions:** QLS31905 was safe and tolerable, and showed encouraging efficacy in Claudin18.2-positive pts with gastrointestinal tumors. QLS31905 is worthy of further exploration in combined therapy in phase 2 trials. Clinical trial information: NCT05278832. Research Sponsor: None.

2528 **Poster Session**

Epigenetic and phenotypic signatures of T-cell response to blinatumomab in pediatric relapsed and refractory B-ALL. First Author: Tyler G. Bruno, St. Jude Children's Research Hospital, Memphis, TN

Background: By forming an immunological synapse between T cells and tumor antigen, bispecific T cell engagers (BiTEs) like blinatumomab have shown great promise in treating B-cell acute lymphoblastic leukemia (B-ALL). However, many relapsed and refractory (R/R) patients fail to achieve long-term survival, with 40% not surviving past 24 months. Prolonged T cell activation with blinatumomab therapy may lead to changes in differentiation that leave the T cell population unable to elicit a sustained anti-tumor response. A deeper understanding of the dynamics of the T cell compartment in R/R B-ALL patients will lead to improved treatment strategies and optimized patient selection for blinatumomab therapy. **Methods:** To characterize T cell persistence and response in this context, we assessed memory and exhaustion phenotypes in blinatumomab-treated T cells isolated from 10 R/R pediatric B-ALL patients treated with blinatumomab. CD8+ T cells were isolated from peripheral blood and bone marrow samples and analyzed for memory and exhaustion phenotypes via flow cytometry. Absolute lymphocyte counts were measured and linked to the sample flow cytometry data to assess expansion and contraction of T cell memory subsets throughout the course of therapy. Whole genome enzymatic methyl sequencing was performed on post-treatment PD-1 High and PD-1 Low CD8 T cells to determine the multipotency of the patient T cell compartment after blinatumomab treatment. **Results:** After 7 days of continued blinatumomab infusion, patient T cells demonstrated a significant expansion of terminally differentiated and effector memory T cells. Notably, we observed that non-responders had a high tumor burden at the start of the therapy and possessed a large population of naïve CD8 T cells that failed to expand. These CD8 T cells exhibited a significant increase in expression of TIM-3 and PD-1 compared to responders after the 7-day infusion. Methylation analysis of post-treatment CD8 T cells showed decreased methylation of exhaustion regulators IKZF1 and CD300a in non-responders compared to the responders. Additionally, *in vitro* treatment of T cells with blinatumomab induced T-cell exhaustion in a target-dependent manner. **Conclusions:** Blinatumomab therapy in pediatric B-ALL patients induced variable epigenetic and phenotypic changes to the T cell compartment indicative of exhaustion, corresponding to differences in T cell expansion and persistence between patients. Our study is the first to link epigenetic changes in exhaustion regulators with response variability in blinatumomab-treated patients. Furthermore, our findings highlight a potential role of baseline T cell composition and tumor burden in determining therapeutic outcomes. These insights provide a novel framework for improving patient stratification and treatment strategies to mitigate T cell exhaustion in blinatumomab therapy. Research Sponsor: American Lebanese Syrian Associated Charities (ALSAC), St. Jude Children's Research Hospital.

2529 **Poster Session**

PD-1 blockade in combination with bevacizumab and nab-paclitaxel for second-line treatment in cancer of unknown primary (Fudan CUP-002): A prospective, single-arm phase II study. First Author: Zhiguo Luo, Department of Medical Oncology, Fudan University Shanghai Cancer Center, Shanghai, China

Background: Cancer of unknown primary (CUP), a heterogeneous tumor characterized by histologically confirmed metastases with undefined primary, accounts for 2-5% of all malignancies. Our previous study, Fudan CUP-001, confirmed that site-specific first-line treatment improves progression-free survival (PFS) in patients with CUP compared to empirical treatment. However, no evidence-based standard of care currently exists for second-line treatment of CUP. We conducted the Fudan CUP-002 study by Simon's two-stage design to evaluate the efficacy and safety of co-administration of F520 injection (anti-PD-1 antibody), bevacizumab, and nab-paclitaxel in patients with CUP who have progressed after first-line treatment. **Methods:** In this prospective, single-arm phase II study (ClinicalTrials.gov, NCT04848597), patients with previously treated CUP received intravenous F520 injection at a dose of 200 mg and bevacizumab 7.5 mg/kg every 3 weeks for up to 2 years, and intravenous nab-paclitaxel 125 mg/m^2 administered on day 1 and day 8 every 3 weeks for up to 8 cycles. The primary endpoint was confirmed objective response rate (ORR) by blinded independent central review (BICR) per Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1. The secondary endpoints included PFS, overall survival (OS), disease control rate (DCR), and safety. **Results:** Between June 2, 2021, and January 10, 2025, a total of 48 eligible subjects were enrolled in the study. In the overall population, the median age was 60 (range: 29 to 72) years, with 31 males (64.6%) and 17 females (35.4%). At the data cutoff on January 10, 2025, the median follow-up was 27.1 months (95% CI, 20.2 to 37.2) and 3 (6.3%) cases continued treatment. The ORR was 54.2% (95% CI, 40.3 to 67.4), and the DCR was 95.8% (95% CI, 86.0 to 98.9), as assessed by BICR per RECIST version 1.1. The median PFS was 16.7 months (95% CI, 12.6 to not available (NA)), with the 12- and 24-month PFS rates at 68.6% and 38.5%, respectively. The median OS was 24.6 months (95% CI, 14.6 to 29.5), and the 12- and 24-month OS rates were 72.5% and 53.0%, respectively. The median duration of response (DoR) was 22.5 months (95% CI, 12.5 to NA), with the 12- and 24-month DoR rates at 78.9% and 47.5%, respectively. Treatment-related adverse events (TRAEs) of any grade were reported by 46 (95.8%) patients. Hematologic toxicity (43, 89.6%) and liver injury (25, 52.1%) of any grade were the most frequently reported TRAEs, and grade 3-4 TRAEs were observed in 25 (52.1%) patients. Grade 3-4 immune-related adverse events (irAEs) occurred in 8 (16.7%) participants, with pneumonitis (2, 4.2%) and endocrine disorders (2, 4.2%) being the most common. **Conclusions:** Second-line PD-1 blockade in combination with bevacizumab and nab-paclitaxel is an effective and well-tolerated treatment regimen for patients with CUP. Clinical trial information: NCT04848597. Research Sponsor: Clinical Research Plan of SHDC.

2530 **Poster Session**

Comprehensive analysis of NSAIDs use and oncological outcomes in non-small cell lung cancer patients treated with immune checkpoint inhibitors. First Author: Yanlin Li, Second Affiliated Hospital of Xi'an Jiaotong University, Xi'an, China

Background: The effect of non-steroidal anti-inflammatory drugs (NSAIDs) on immune checkpoint inhibitors (ICIs) efficacy in non-small cell lung cancer (NSCLC) remains controversial. Although the COX-2/PGE2 pathway, a primary target of NSAIDs, has been implicated in diminished immunotherapy response, direct clinical association with NSAIDs and ICIs in real world has yet to be established. This study aims to evaluate the impact of NSAIDs use—considering types, duration, and timing—on ICI efficacy, alongside its effects on PGE2 and immune cell profiles. **Methods:** We included stage III-IV NSCLC patients receiving PD-1/PD-L1 antibodies in 5 centers. Blood and tumor samples were collected in perspective cohort. NSAIDs were categorized based on selectivity (non-selective COX inhibitors, selective COX-2 inhibitors) and chemical structure (salicylates, propionate derivatives, others). PGE2 and cytokines were measured in blood by ELISA. RNA sequencing data were obtained from databases. Tumor tissues were collected for immunohistochemical staining of immune cells. Multivariate Cox and logistic regression were used in analyses of progression-free survival (PFS) and objective response rate (ORR). **Results:** 883 patients were included, with 140 NSAIDs users and 743 non-users. 196 patients were enrolled prospectively with samples. Multivariate analysis showed that NSAIDs use was significantly associated with improved PFS (HR 0.67, 95% CI 0.51-0.88, P = 0.005) and ORR (OR 1.87, 95% CI 1.29-2.72, P = 0.001). Subgroup analyses indicated that non-selective COX inhibitors, salicylates, long-term use, and pre-ICI initiation were correlated with better outcomes. In contrast, selective COX-2 inhibitors, propionate derivatives, others, short-term use, and post-ICI initiation showed no effect on PFS or ORR. Blood analyses indicated that NSAIDs significantly lowered PGE2 levels, particularly salicylates and long-term use. Higher PGE2 was associated with worse outcomes. For immune cells, RNA sequencing revealed that COX-2 and mPGES-1 were significantly correlated with neutrophil enrichment and neutrophil-related cytokines. Single-cell RNA-seq showed high expression of COX-2 and mPGES-1 in neutrophils. Analysis of samples confirmed that NSAIDs use was associated with reduced neutrophils and neutrophil-related cytokines in blood and less neutrophil infiltration in tumor. **Conclusions:** NSAID use is an independent predictor of improved PFS and ORR in NSCLC patients receiving ICIs. Specifically, non-selective COX inhibitors, salicylates, long-term use, and pre-ICI initiation are associated with better clinical outcomes. NSAID use may enhance ICIs efficacy by reducing serum PGE2, which could serve as a predictive biomarker. Furthermore, NSAIDs decrease neutrophils in both blood and tumor, potentially contributing to the improvement in ICI efficacy. Research Sponsor: Basic Research Funds for Central Universities; National Natural Science Foundation of China; Shaanxi Province "Sanqin Scholars" Innovation Team Support Program; Shaanxi Province Health and Medical Research Innovation Team Support Program.

2531 **Poster Session**

Preliminary monotherapy efficacy of novel immune checkpoint blockade GV20-0251 (anti-IGSF8) in advanced melanoma patients with primary resistance to anti-PD1. First Author: Kristopher Wentzel, The Angeles Clinic and Research Institute, A Cedars-Sinai Affiliate, Los Angeles, CA

Background: GV20-0251 is an AI-designed, first-in-class, cross-species reactive, Fc-attenuated IgG1 antibody that targets the novel cancer immune checkpoint IGSF8 which is broadly expressed across solid tumors. In syngeneic tumor models, anti-IGSF8 alone or with anti-PD1 inhibits tumor growth by increasing cytotoxicity and infiltration of natural killer cells (NK) and antigen cross-priming by dendritic cells which in turn activates T cells. **Methods:** The phase 1 portion of this first-in-human, phase I/IIa study (NCT05669430) was conducted across multiple U.S. centers. The study utilized a standard 3+3 design to evaluate the safety, pharmacokinetics (PK), pharmacodynamics, immunogenicity, and preliminary efficacy of GV20-0251, and to establish a preliminary recommended phase 2 dose (RP2D). **Results:** Forty-two patients with advanced solid tumors (median age 61 years, median 4 prior treatment lines) were enrolled across six dose levels (0.5, 1, 3, 6, 10, and 20 mg/kg) and two schedules (D1/D8 Q3W and D1 Q3W). GV20-0251 demonstrated favorable safety and tolerability across all doses and schedules with no dose-limiting toxicities, and 10 and 20 mg/kg D1 Q3W were selected as the preliminary RP2D. Treatment-related adverse events occurred in 55% of patients, predominately grade 1/2, with a single grade 3 event of pneumonitis. The most common treatment-related AEs were fatigue and rash (12% each), with no dose-dependent trends. Full target occupancy and half-life of 26 days with linear PK were observed at ≥10 mg/kg, without significant serum cytokine elevation or anti-drug antibody signals. Among 38 efficacy-evaluable patients, 17 had cutaneous melanoma, all of whom progressed on prior anti-PD1 therapy and 16 progressed on prior anti-CTLA4 therapy. Among the 9 melanoma patients with primary resistance to anti-PD1, confirmed partial response (PR) was achieved in 3 (33%) patients and tumor shrinkage was observed in an additional 3 patients. Notably, responses were observed in 2 patients with liver metastases, which are typically refractory to immunotherapy. Although no responses were seen in the melanoma patients with acquired resistance to anti-PD1 (n = 8) or in patients with other tumor types (n = 21), potentially due to the lower frequency of IGSF8 protein expression in these tumors, tumor shrinkage was observed in one non-small cell lung cancer (n = 4) and one cervical cancer (n = 1) patient. Preliminary immunohistochemistry analyses of trial patient biopsies suggest IGSF8 high tumors have low anti-PDL1 at baseline, and GV20-0251 treatment increases tumor-infiltrating NK and T cells. **Conclusions:** GV20-0251 demonstrated a favorable safety profile in heavily pretreated patients with advanced solid tumors and showed promising monotherapy efficacy in cutaneous melanoma patients with primary resistance to anti-PD1. Clinical trial information: NCT05669430. Research Sponsor: GV20 Therapeutics.

2532 Poster Session

Prophylactic infusion of allogeneic double-negative T cells as immune modulators to prevent relapse in high-risk AML patients after allo-HSCT: A phase I trial. First Author: Xiaoyu Zhu, The First Affiliated Hospital of University of Science and Technology of China, Hefei, China

Background: Our previous study demonstrated that double-negative T cells (DNTs) hold potential for treating relapsed or refractory acute myeloid leukemia (r/r AML) following allogeneic hematopoietic stem cell transplantation (allo-HSCT). In a first-in-human Phase I trial (ChiCTR-IPR-1900022795), we reported a complete response (CR) rate of 50% (5/10) with a favorable safety profile. This Phase I/II study aims to evaluate the safety and efficacy of off-the-shelf allo-DNTs in preventing relapse in AML patients following allo-HSCT. **Methods:** Six high-risk AML patients undergoing allo-HSCT were enrolled and assigned to two dosage groups: 1×10^8 DNTs/kg and 1.5×10^8 DNTs/kg. Each patient received three infusions at one-month intervals without prior lymphodepleting chemotherapy. The median time from transplantation to the first infusion was 3.1 months. Primary endpoint was the occurrence of adverse events and dose-limiting toxicities, while the secondary endpoint was cumulative incidence of relapse (CIR). GMP-grade DNTs were expanded ex vivo from healthy donor PBMCs and cryopreserved in liquid nitrogen until infusion. **Results:** As of January 20, 2025, with a median follow-up of 17.55 months post-HSCT, four of six patients (66.7%) remained in MRD-negative CR, with the longest recurrence-free survival exceeding 17 months. The two relapsed patients both carried high-risk genetic mutations (TP53 mutation) and were MRD-positive prior to transplantation. They succumbed at 11.4 and 14.2 months post-HSCT respectively. Donor-derived DNTs were detectable in peripheral blood shortly after each infusion, peaking at 1–4 days and persisting for up to 28 days. In two patients with MRD-negative CR, infused DNTs remained detectable for up to 360 days post-infusion. Elevated levels of IFN-γ, IL-6, and IL-10 post-infusion indicated immune activation. Importantly, no dose-limiting toxicities, neurotoxicity, cytokine release syndrome greater than Grade 2, or graft-versus-host disease were observed. In contrast to the two relapsed patients, MRD-negative CR patients showed expanded levels of CD4+, CD8+, and DNT cells, particularly those with the effector memory T cell phenotype. Both the infused DNTs and the recipient's CD4+ and CD8+ T cells in these patients secreted higher levels of granzymes A and K. To investigate the interaction between CD8+ T cells and allo-DNTs in MRD-negative CR patients, co-culture experiments were conducted. CD8+ T cells exhibited an increase in the secretion of granzyme B and IFN-γ within 3–4 days. Transcriptome sequencing and multi-cytokine analyses revealed strong immune activation. **Conclusions:** The dual ability of DNTs to suppress GvHD while preserving the graft-versus-leukemia effect, along with its potential for off-the-shelf availability, makes it a transformative therapy in the post-transplant setting. Clinical trial information: NCT05858814. Research Sponsor: National Natural Science Foundation of China; # U23A20453, 82270223 and 82170209; Anhui Provincial Key Research and Development Project; # 2022e07020015; Anhui Health Research Project; # AHWJ2022a011; Anhui Provincial Department of Education Scientific Research Project; 2023AH010079; Anhui Provincial Natural Science Foundation; 2308085J09; the Fundamental Research Fund for the Central Universities; YD9110002047.

2533 Poster Session

Targeting cancer leptomeningeal metastasis with allogeneic chimeric antigen receptor γδ T-cell therapy. First Author: Peiwen Ma, National GCP Center for Anticancer Drugs, National Cancer Center/Cancer Hospital, Chinese Academy of Medical Sciences & Peking Union Medical College, Beijing, China

Background: Leptomeningeal metastasis (LM) occurs in 1–10% of patients with advanced solid tumors during disease progression. LM significantly worsens prognosis due to the rapid onset and progression of symptoms associated with elevated intracranial pressure. Currently, no therapies specifically targeting LM have been approved. Here, we report our clinical observations from two patients treated with intrathecal infusion of allogeneic B7H3-targeted CAR-γδT cells(QH104). **Methods:** This is an open-label, single-arm clinical study designed to evaluate the safety and efficacy of QH104 in patients with LM originating from B7H3-positive solid tumors(NCT06592092). Eligibility criteria included a diagnosis of LM from any B7H3-positive solid malignancy. QH104 was administered as a single dose of 3×10^7 cells via lumbar puncture or Ommaya reservoir infusion. Treatment-emergent adverse events were graded using CTCAE v5.0 and ASTCT criteria. Efficacy was assessed using the RANO-LM criteria. **Results:** As of January 2025, two female lung adenocarcinoma patients were enrolled. They had previously received treatments targeting LM, including intrathecal chemotherapy and oral EGFR tyrosine kinase inhibitors. No adverse events higher than grade3 were reported. One patient experienced a transient episode of absence seizures on Day 1 after cell infusion, which was considered treatment-related. At the Day 30 assessment post-infusion, both patients had stable disease, with a reduction or complete elimination of tumor cells in the CSF and improvement in clinical symptoms associated with LM. CSF component analysis demonstrated the persistence of CAR-γδ T cells for one week post-infusion. CSF cytokine analysis revealed increased levels of interleukin-5, -6, -9, -13, and -22, TNF-α and IFN-γ post-infusion compared to baseline. No significant increases in CAR-γδ T cells or cytokines were detected in peripheral blood. **Conclusions:** Our initial clinical experience with the first two patients with leptomeningeal metastasis (LM) provides preliminary evidence supporting the safety and efficacy of B7H3-targeted CAR-γδT cell immunotherapy in this patient group. A longer follow-up period and a larger patient cohort are necessary for a comprehensive evaluation of therapeutic efficacy and response durability. Clinical trial information: NCT06592092. Research Sponsor: National Natural Science Foundation of China; 82272953; The National Key Research and Development Program of China.

Patients' baseline character, administration routes and treatment evaluation.

	Diagnosis	Sex	Age	Genetic mutation	B7H3 Score	B7H3+ CAR -γδT cells infused	Administration route	Treatment response at Day 30
Patient 01	Lung adenocarcinoma with LM	F	53	EGFR 21 exon L858R mutation	70	3×10^7	Lumbar puncture	Stable disease (CSF cytology: remain positive CNS imaging: Stable Symptoms assessment score:6 to 4)
Patient 02	Lung adenocarcinoma with LM	F	58	EGFR 21 exon L858R mutation	40	3×10^7	Ommaya reservoir	Stable disease (CSF cytology: turned negative CNS imaging: Stable Symptoms assessment score:4 to 2)

2534 Poster Session

Safety and efficacy of non-viral aPD1-MSLN JL-lightning–CAR-T in advanced malignant mesothelioma in a phase I trial. First Author: Yan Sun, Shanghai Cell Therapy Group Co., Ltd, Shanghai, Shanghai, China

Background: CAR-T cells face challenges in solid tumors, including weak in vivo proliferation, immunosuppressive tumor microenvironments (TME), and limited tumor infiltration. We firstly developed an innovative non-viral JL-Lightning-CAR-T fast process to enhance CAR-T stemness, in vivo expansion, and persistence. The autologous non-viral aPD1-MSLN JL-Lightning-CAR-T cells were manufactured in just 30 hours, targeting mesothelin (MSLN) and secreting anti-PD-1 antibodies to counteract the immunosuppressive TME and improve the efficacy of solid tumor treatment. Here, we report the safety and preliminary efficacy of this novel CAR-T therapy in advanced malignant pleural mesothelioma (MPM) in a first-in-human phase I pilot study (ClinicalTrials.gov: NCT06249256). **Methods:** A single-arm, open-label, dose-escalation study was designed and enrolled MPM patients who had failed standard therapies and had confirmed MSLN and PD-L1 expression on tumors by IHC. Patients received a single dose of non-viral aPD1-MSLN JL-Lightning-CAR-T cells following lymphodepletion (Flu 30 mg/m²/day, Cy 300 mg/m²/day) for 2-3 days. The dose escalation was designed as DL1 (0.5-0.6×10^6/kg) and DL2 (0.8-1.0×10^6/kg). Adverse events were evaluated using CTCAE v5.0, and clinical responses were assessed by mRECIST 1.1 or RECIST 1.1. CAR expression was analyzed by qPCR, and anti-PD-1 antibodies were detected by MSD. **Results:** Patients: Seven advanced MPM patients were enrolled and received single dose CAR-T cell infusion. Efficacy: In DL1 (0.5-0.6×10^6/kg), one patient achieved partial response (PR) with a disease control rate (DCR) of 75% (3/4). In DL2 (0.8-1.0×10^6/kg), all of three patients achieved objective response (ORR 100%, 3/3), with one patient achieving complete response (CR) at 3 months and maintaining it for over 9 months. Pharmacokinetics: Anticipated CAR-T cell expansion and anti-PD-1 antibodies increase detected in circulation. CAR-T Cmax reached up to 47,307 copies/μg, detectable for over 3 months. Anti-PD-1 antibody Cmax reached up to 376,938 pg/ml, detectable for over 6 months. Tmax for MSLN-CAR-T and anti-PD1 nanobody occurred between Day 7 and Day 14 post infusion. IFN-γ and IL-6 levels also increased during this period. Safety: In DL1, CRS was observed in 1 of 4 patients (Grade 1), with no ICANS or DLT. In DL2, CRS was observed in 2 of 3 patients (Grade 3-4), with no ICANS. Grade 3 immune-mediated pneumonia occurred in 2 of 3 patients in DL2, managed by clinical intervention strategies. All patients experienced Grade 3-4 hematologic toxicity, reversible with supportive care. **Conclusions:** Non-viral aPD1-MSLN JL-Lightning-CAR-T cells demonstrated robust proliferative capacity, manageable safety profile, and significant anti-tumor potential, offering a promising therapeutic approach for advanced MPM patients. Clinical trial information: NCT06249256. Research Sponsor: None.

2535 Poster Session

Phase I trial of personalized AI-identified TCR-transduced T cell therapy in advanced solid tumors. First Author: Shuhang Wang, Department of Clinical Trial Center, National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China

Background: TCR-T cell therapy shows promise in treating solid tumors but is limited by the need for personalized TCR identification. We developed TCR-XFinder, a deep learning model using a 3-stage transfer-learning strategy, to rapidly identify personalized tumor-reactive TCRs within 10 days after tumor tissue acquisition. This study reports the first-in-human phase I trial of KSX01, a TCR-transduced T cell therapy identified by TCR-XFinder. **Methods:** We conducted a phase I, dose-escalation study (NCT06150365) to evaluate the safety and efficacy of KSX01 in patients with advanced solid tumors. Tumor tissues were subjected to single-cell RNA sequencing and TCR sequencing to identify tumor-reactive TCRs using TCR-XFinder. These TCRs were validated and transduced into autologous T cells, which were expanded and infused back into patients. Patients received preconditioning with cyclophosphamide (500 mg/m²/day) and fludarabine (30 mg/m²/day) for 3 days, followed by intravenous infusion of KSX01 TCR-T cells at two dose levels ($5\times10^9 \pm 30\%$ and $1\times10^{10} \pm 30\%$ cells). Safety was assessed by monitoring adverse events and cytokine release syndrome (CRS). Efficacy was evaluated by RECIST v1.1 criteria. **Results:** Four patients with advanced solid tumors (alveolar soft part sarcoma, epithelioid sarcoma, colon cancer, and clear cell renal cell carcinoma) were enrolled. KSX01 TCR-T cells were well-tolerated at both dose levels, with no dose-limiting toxicities (DLTs) observed. All patients experienced Grade 3–4 pancytopenia, which was expected following lymphodepletion. One patient developed Grade 2 CRS, resolved with tocilizumab. No Grade 3 or higher AEs related to KSX01 were noted. At the first tumor assessment (Day 28), all patients showed disease control, with one patient achieving a partial response (PR) and a 46% reduction in target lesion size. Another patient achieved PR with second infusion at higher dose. qPCR analyses confirmed the infiltration and long-term anti-tumor effect of infused TCR-T cells. A transient post-infusion increase in interferon-γ (IFN-γ), interleukin-6(IL-6), IL-10, IL-4, tumor necrosis factor-α (TNF-α), and CRP levels was observed in all patients. While the C_{max} and T_{max} values varied among cytokines, the first T_{max} for 80% of cytokines and CRP occurred within the first week post-infusion. Re-biopsy of tumor lesions showed infiltration of infused TCR-T with persistent cytotoxic function and ameliorate the microenvironment for the endogenous tumor-reactive T cells. **Conclusions:** The first-in-human phase I trial of KSX01 TCR-T cell therapy demonstrated promising safety and efficacy in patients with advanced solid tumors. TCR-XFinder enabled rapid identification of personalized tumor-reactive TCRs, supporting the clinical feasibility of this approach. Further studies are warranted to explore optimal dosing and combination strategies to maximize clinical benefit. Clinical trial information: NCT06150365. Research Sponsor: National Natural Science Foundation of China; 82272953; The National Key Research and Development Program of China.

2536 **Poster Session**

Artificial intelligence (XGBoost) in predicting outcomes among CAR-T therapy patients: The impact of malnutrition and comorbidities using the National Inpatient Sample (2020-2022). First Author: Tong Ren, University of South Florida (USF) Morsani College of Medicine/HCA Florida Oak Hill Hospital, Brooksville, FL

Background: Chimeric Antigen Receptor T-cell (CAR-T) therapy has revolutionized hematologic malignancy treatment but remains costly, with limited access and complications like prolonged hospitalization, sepsis, and mortality. Malnutrition, common in cancer patients, worsens these outcomes. Despite AI's growing role in oncology, its use in risk stratification for malnourished CAR-T recipients is underexplored. This study leverages the National Inpatient Sample (NIS) 2020-2022 to develop AI-driven models predicting length of stay (LOS), mortality, and sepsis, incorporating the Charlson Comorbidity Index and other factors. **Methods:** Using the NIS database, adult CAR-T therapy patients were identified with ICD-10 codes. Key variables included demographics (age, gender, race/ethnicity, income), clinical factors (Charlson Comorbidity Index, sepsis, admission type), and hospital characteristics (size, teaching status). AI models (XGBoost, Random Forest, Neural networks) were trained on the 2020 dataset and validated on 2020-2022 data. Hyperparameter tuning via grid search was performed to optimize model performance. LOS was modeled as a continuous outcome, while mortality and sepsis were classified as binary outcomes. Data preprocessing included handling missing values, one-hot encoding of categorical variables, and standardizing continuous variables. SHapley Additive exPlanations (SHAP) were used to interpret feature importance. **Results:** The study analyzed 1,912 CAR-T hospitalizations over three years, with 11.5% identified as malnourished. AI models demonstrated strong predictive performance, with XGBoost (RMSE: 3.5 days, R^2 = 0.82) for LOS, Random Forest (AUC: 0.91) for mortality, and Neural Networks (AUC: 0.87) for sepsis. Malnutrition significantly worsened outcomes, increasing LOS by 14.2 days ($p < 0.001$) and mortality risk by 3.2-fold ($p < 0.001$). Patients with Charlson Comorbidity Index scores $\geq$3 had 9.8-day longer LOS and 2.9-fold higher mortality risk ($p < 0.001$). Racial disparities were evident, with Black patients at 25% higher risk of prolonged LOS and Hispanic patients at increased risk of sepsis ($p < 0.05$). Malnourished patients in non-teaching hospitals with high comorbidity burdens had the worst outcomes, emphasizing the need for targeted interventions in high-risk populations. **Conclusions:** AI-driven models incorporating malnutrition and Charlson Comorbidity Index accurately predict LOS, mortality, and sepsis in CAR-T patients. Early identification and management of malnutrition and comorbidities, particularly in racially diverse populations, are critical to improving outcomes. Future research should focus on prospective validation and AI integration into clinical workflows to mitigate disparities. Research Sponsor: None.

2537 **Poster Session**

A novel cellular immunotherapy using vaccine generated neoantigen-specific effector T cells. First Author: Andrew Edward Sloan, Piedmont Healthcare and Case Western Reserve University School of Medicine, Atlanta, GA

Background: Cellular immunotherapy languished in obscurity until genetically engineered chimeric antigen receptor T cells were shown to effectively treat B lymphocyte cancers. Genetic studies also revealed that some cancer cell mutations produce neoantigens, which are consistent with historical studies demonstrating that cancer cell vaccination generates neoantigen specific immune responses in rodents and humans. Vaccination leads to an increase in neoantigen-specific T cells in lymphoid tissue that are released into the blood, which carries them to sites of disease activity, e.g., cancer tissue. TVAX Biomedical hypothesized that the natural power of the patient's immune system could be exploited using a novel neoantigen-specific cellular immunotherapy. **Methods:** Patients are vaccinated with their own attenuated cancer cells plus an immunologic adjuvant, e.g. GM-CSF, to increase the number of circulating neoantigen primed T cells. Patients are leukapheresed to collect the T cells. The collected T cells are exposed to activation and proliferation stimulating agents to generate the neoantigen-specific effector T cells that are used for treatment. TVAX is currently testing this treatment paradigm for efficacy and safety in newly diagnosed (MGMT-negative) glioblastoma patients when they have minimized immunosuppression and minimal residual disease, TVI-AST-008. **Results:** For this novel cellular immunotherapy to be effective, T cell mediated immune responses must be generated in vaccinated patients. Delayed type hypersensitivity skin testing, a method for detecting T cell mediated immunity in humans, showed reactions in patients with leukemia, brain, breast, colon, lung, kidney, melanoma, ovarian, prostate and sarcoma (data to be presented). Multiple autologous vaccinations led to detectable responses in all patients. The combination of cancer cell/immunologic adjuvant vaccination plus neoantigen-specific T cellular immunotherapy has been shown to be highly effective against a wide range of cancer types in preclinical studies and to be effective against the least immunogenic cancers. **Conclusions:** The possibility that neoantigen-specific T cells could effectively treat some human cancers has been documented through studies with tumor infiltrating lymphocytes (TILs). However, TIL efficacy is limited to a small number of (hot) cancers. Preclinical model studies demonstrated that neoantigen-specific effector T cells enter cancer tissue, initiating a cascade of T cell mediated immunologic events that ultimately leads to killing of cancer cells by cytotoxic T cells and cytokine activated accessory cells. The benefit of the vaccine enhanced neoantigen-specific effector T cell therapy (TVAX Immunotherapy) is that it expands the range of human cancers that could be safely and effectively treated. Clinical trial information: 05685004. Research Sponsor: NIH Grant, Office of Orphan Products.

2538 **Poster Session**

Engineering iPSC-derived mesenchymal stem cells (i MSCs) to secrete IL-7/IL-15 for modulation of the tumor microenvironment in a "cold" ovarian tumor model. First Author: Sandeep Singh, University of Texas MD Anderson Cancer Center, Houston, TX

Background: We previously discovered that bone marrow derived Mesenchymal stromal cells (BM-MSCs) migrate to the stroma of numerous cancers and their metastases, forming tumor-associated fibroblasts (TAFs) and can be modified to secrete proteins within the tumor microenvironment (TME). MSCs have not been utilized extensively in cancer therapy due to their immunosuppressive properties, limited replicative capacity, and variable quality depending on the source. **Methods:** Here, we report the characterization of induced mesenchymal stromal cells (iMSCs) derived from pluripotent stem cells (iPSCs), which were uniquely generated from adult skin fibroblasts using a transient mRNA transfection technique. Notably, iMSCs demonstrated superior proliferative capacity under both normoxic and hypoxic conditions, while preserving their trilineage differentiation potential. Comprehensive molecular profiling, including RNA sequencing, single-cell mass cytometry (CyTOF), and Luminex assays, revealed strong phenotypic and functional similarities between iMSCs and BM-MSCs. Crucially, no evidence of sarcoma formation was observed in NSGS mice following intraperitoneal, subcutaneous, or intravenous administration of iMSCs, highlighting their robust safety profile. We engineered a DNA cassette into these cells to enable constitutive superphysiological expression of interleukin(IL)-7 and IL-15, expressed as either individual molecules (P2A) or a single fused molecule (FUS). Both, P2A and FUS iMSCs demonstrate the capacity to drive T cell proliferation autonomously in co-culture experiments. **Results:** IL7/IL15-modified iMSCs induced tumor cell death in a triple co-culture system comprising iMSCs, the ovarian cancer cell line ID8, and human PBMCs. In a syngeneic mouse model of ovarian cancer (ID8 cells in C57BL/6 mice), intraperitoneal administration of P2A or FUS-iMSCs resulted in reduced tumor burden and extended survival. Immunohistochemical and flow cytometric analyses revealed massive infiltration of activated T cells, macrophages, and other immune cells into the tumor microenvironment (TME) in both FUS or P2A groups, but not in unmodified iMSC controls, or in PBS injected animals. The TME in P2A- and FUS-treated mice showed enrichment in tumoricidal M1-type macrophages, with no detection of exhausted or regulatory T cells, in contrast to controls. **Conclusions:** IL7-IL15-secreting iMSCs migrate into solid tumors, induce massive immune cell infiltration into the TME and enhance antitumor immunity in a syngeneic mouse model of cancer. These cytokine-producing iMSCs represent a potentially promising anticancer immunotherapy by converting "cold" into "hot" tumor microenvironments. Research Sponsor: Eterna Therapeutics, Inc.

2539 **Poster Session**

Universal solid tumor therapy with CD5-deleted, DSG2-directed CAR-T cells. First Author: Robert D. Carlson, Thomas Jefferson Universiy, Philadelphia, PA

Background: CAR-T cell therapy has been curative for many patients with refractory, progressive hematologic cancers, resulting in several FDA approvals. However, this therapy has not been successful for solid cancers, reflecting the need for suitable antigen targets for each disease and solutions to immunological barriers in solid tumors. Here, we have identified the desmosomal cadherin, desmoglein 2 (DSG2), as an effective CAR-T cell therapy target in epithelia-derived solid tumors. DSG2 contributes to cell proliferation, migration, and other emerging tumor-promoting pathways, resulting in its upregulation in nearly all solid cancers and correlating with poor prognosis. Moreover, we explored CRISPR-Cas9-mediated elimination of the inhibitory receptor CD5 to enhance in vivo CAR-T cell expansion and solid tumor efficacy. **Methods:** DSG2-directed CAR-T cells were generated from human T cells using a scFv derived from a murine hybridoma targeting the extracellular domain of DSG2 in a 3rd generation CAR design with CD28, 4-1BB, and CD3ζ signaling domains. CD5 elimination employed electroporation of complexed gRNA-Cas9 ribonucleoprotein (RNP). DSG2 expression was characterized in human cancers and cell lines and CAR-T cell activity was examined in vitro by cytokine production and target cell cytolysis. In vivo efficacy studies employed cancer xenografts in NSG mice treated with CAR-T cells. Safety studies employed a human DSG2 transgenic mouse treated with syngeneic murine CAR-T cells for clinical, serum biomarkers, and histopathological evaluation. **Results:** In vitro studies revealed recognition and lysis of solid cancer cell lines and effector cytokine production. Administration of DSG2-directed CAR-T cells eliminated metastatic cell-derived xenografts, patient-derived xenografts, and orthotopic tumors derived from various solid cancers, including colorectal, pancreatic, lung, prostate, breast, and liver. Moreover, elimination of CD5 enhanced the expansion of DSG2-directed CAR-T cells in vivo, resulting in curative efficacy at sub-therapeutic CAR-T cell doses. Safety studies revealed no toxicity in any human DSG2 transgenic mouse tissues. **Conclusions:** These studies reveal the robust antitumor activity of DSG2-directed CAR-T cells in solid tumors, which is enhanced by CD5 deletion, without toxicity in a human transgenic mouse model. Thus, CD5-deleted DSG2-directed CAR-T cells are a promising therapeutic approach that may be safe and effective for all solid cancers. Research Sponsor: Kleberg Foundation; U.S. Department of Defense; W81XWH-19-1-0263; U.S. Department of Defense; W81XWH-22-1-0207; DeGregorio Family Foundation; U.S. National Institutes of Health; 1R21 CA267087; U.S. National Institutes of Health; 1R21 CA286339; The Courtney Ann Diacont Memorial Foundation and Lorraine and David Swoyer; U.S. National Institutes of Health; T32 GM008562; U.S. National Institutes of Health; T32 CA236736.

2540 **Poster Session**

Mayhem under the microscope: T cell cytotoxicity and serial killers captured in situ. First Author: Greg Sawyer, Moffitt Cancer Center, Tampa, FL

Background: Developing a deeper understanding of the dynamics of immune cell-mediated cytotoxicity is critical to advancing immunotherapy and cell therapy. The results from the multidisciplinary effort reported here include numerous measurements and movies of immune cell-mediated cytotoxicity with striking examples of serial killing, foraging, path-tracking, triple killing events, measurements of cytokine gradients at tumor margins, and other dynamics. Some cytotoxic events revealed peak apoptotic signatures just minutes after T Cell engagement. **Methods:** In vitro studies of immune cell killing are traditionally performed using time-lapse imaging and biochemical assays, but these methods are often limited by spatial and temporal resolution, throughput, and the ability to extract the dynamics of cellular interactions. This study integrates high-resolution and high-speed laser scanning confocal microscopy with artificial intelligence (AI), and machine learning (ML) approaches to provide a high-resolution data-driven analysis of immune cell killing dynamics in vitro. In these studies, we use human CAR T cells with an anti-cd19.28z and Burkitt Lymphoma. **Results:** We have engineered a perfusion-enabled 3D culture system integrated microscopy to assess cellular dynamics for extended periods of time. Perfusion culture maintains the interstitial flow of liquid culture media, clearing the microenvironment of toxic metabolites and reactive oxygen species. This platform uses a Liquid-Like Solids (LLS) to mimic the transport dynamics of a capillary bed. Integrated microscopy allows in situ quantification of spatiotemporal cytokine concentrations, immune cell tracking, immune cell killing dynamics, and invasion dynamics. Cytokine on and off-rates were referenced alongside measured bead fluorescence intensities and positions to fit spatiotemporal reaction-diffusion models out to a 1,600 um radius. Fast-scanning confocal microscopy facilitated in-situ observation of the evolutionary dynamics of tumor progression. In-situ cytokine measurements revealed local IL-8 concentrations reached a maximum value of 2 ng ml-1 after 10 hours. A cellular production rate was estimated at 2 molecules cell-1 s-1. **Conclusions:** T Cell cytotoxicity is shown to be incredibly heterogeneous spanning from minutes to hours. The platform developed in this study demonstrates a powerful method for real-time, high-resolution imaging of cancer-immune interactions within a controlled 3D environment. By leveraging in situ fast-scanning fluorescence microscopy, the platform enables precise quantification of spatiotemporal cytokine concentrations, T cell motility, proliferation, cytotoxic activity, and tumor invasion patterns. Research Sponsor: None.

2541 **Poster Session**

Impact of stromal-targeting antitumor CAR T cells in solid tumors. First Author: Abdul Khan, Roswell Park Cancer Institute, Buffalo, NY

Background: While chimeric antigen receptor (CAR) T cells have shown tremendous success in hematological malignancies, but such efficacy has not been achieved in the setting of solid tumors. One of the hurdles to CAR T cells therapy in solid tumors is the presence of physical stroma and cancer associated fibroblasts (CAFs), which inhibit the entry of activated T cells to the tumor sites. Membrane bound protein Leucine-rich repeat containing 15 (LRRC15) has been shown to be highly expressed on CAFs in many solid tumors including pancreatic cancer as well as directly expressed on tumors of mesenchymal origin including sarcomas, glioblastomas and melanomas. LRRC15 has very limited expression in normal tissues. The goal of the current study was to explore the impact of stromal targeting antitumor (STAT) in solid tumors using LRRC15-directed CAR T cells. Herein we demonstrate that CAR T cells directed to tumor stroma can eradicate solid tumor. **Methods:** LRRC15-directed CAR T cells were validated in *in vitro* assays that included specific lysis, cytokine secretion, and proliferation. STAT CAR T cells were administered intravenously into NSG mice after engrafted with osteosarcoma SaOS2 and pancreatic PANC1 tumor cell lines as well as patient derived tissues (PDXs). The efficacy of STAT CAR T cells was also assessed in syngeneic mouse model engrafted with murine OS F420 and pancreatic KPC tumor cell lines. Tumor was harvested from mice at various timepoints and analyzed for LRRC15 expression as well as for the presence of T cells. **Results:** LRRC15-directed CAR T cells specifically lysed SaOS2 cells. Upon stimulation with SaOS2 cell line, LRRC15-directed CAR T cells resulted in robust expansion and secreted cytokines including IL2, IFN-Υ, GM-CSF and TNFα. The LRRC15-directed CAR T cells were able to eliminate tumor in NSG mice xenografted with SaOS2 cell line as well as OS PDX. LRRC15-directed CAR T cells significantly increased the survival of mice. Next, we sought to test the efficacy of LRRC15-directed CAR T cells in NSG mice engrafted with LRRC15$^-$ tumor/CAFs$^+$ cell line and PDX. We showed that the NSG mice injected with the LRRC15$^-$ PANC1 cell line acquired stroma with CAFs positive for LRRC15 within 2-3 weeks. LRRC15-directed CAR T cells were able to significantly inhibit the progression of both PANC1 tumors as well as PDAC PDX in NSG mice. In syngeneic mouse model, LRRC15-directed CAR T cells resulted in tumor regression of both LRRC15$^+$ sarcoma F420 and LRRC15$^-$ pancreatic KPC tumors. **Conclusions:** To our knowledge this is the first study demonstrating targeting stroma in solid tumors using STAT CAR T cells. LRRC15-directed CAR T cells showed antitumor efficacy in mouse models engrafted with LRRC15$^+$ as well as LRRC15$^-$ tumors. Collectively, we show that targeting LRRC15$^+$ CAFs in the tumor with CAR T cells has the potential to inhibit solid tumor progression as well to circumvent the challenge of limited penetration of T cells into the tumor site by disrupting the stroma. Research Sponsor: None.

2542 **Poster Session**

Association of lymphopenia rescue and CA19-9 levels with overall survival following IL-15 superagonist N-803 and PD-L1 t-haNK chemo-immunotherapy for 3rd line or greater metastatic pancreatic cancer. First Author: Tara Elisabeth Seery, Chan Soon-Shiong Institute for Medicine, El Segundo, CA

Background: Lymphopenia and high CA19-9 levels are associated with poor prognosis in pancreatic cancer patients. N-803 (ANKTIVA), an IL-15 superagonist is the first FDA approved molecule with a mechanism of action of rescuing lymphopenia by proliferating lymphocytes (NK and T cells). In QUILT-88, a Phase 2 multi-center study (NCT04390399), participants with 2nd line or greater locally advanced or metastatic pancreatic cancer (mPC) received N-803 and PD-L1-targeted high-affinity natural killer (PD-L1 t-haNK) cell therapy in combination with low-dose chemotherapy as $\geq$ 3rd line therapy. The absolute lymphocyte count (ALC), CA19-9 level, and correlation with overall survival (OS) was assessed. **Methods:** Patients (n = 84) received low-dose SBRT and low-dose chemotherapy in combination with N-803 and PD-L1 t-haNK cells to orchestrate responses of the innate and adaptive immune system, a paradigm change in the treatment of mPC. The association between OS and ALC $<$ or $\geq$ median 1.045 x 10^9 cells/L and CA19-9 $<$ or $\geq$ median 4079.6 U/mL at baseline was assessed. **Results:** Median OS for 3rd line patients (n = 43) was 6.2 months (95% CI 5.0 - 7.1;) and for all patients $\geq$ 3rd to 6th line patients (n = 84) was 5.7 months (95% confidence interval [CI] 4.3 – 6.4). OS was positively associated with both higher ALC and lower baseline CA19-9 levels. OS was significantly higher for participants (median OS: 7.1 months) with ALC $\geq$ 1.045 x 10^9 cells/L and CA19-9 $<$ 4079.6 U/mL than for those participants (median OS: 3.1 months) with ALC $<$ 1.045 x 10^9 cells/L and CA19-9 $\geq$ 4079.6 U/mL (HR 3.6, p $<$ 0.001). Higher ALC count was associated with prolonged OS over the course of the study. Grade 3 or higher TEAEs occurred in 95% of patients and were largely chemotherapy-associated. **Conclusions:** The multimodal chemo-immunotherapy protocol to induce immunogenic cell death resulted in OS that exceeded 6 months for both 3rd and $\geq$ 5th line patients, exceeding OS achieved by other therapies in this setting by ~2 months. It is notable that both favorable baseline ALC/CA19-9 and on-study higher ALC was associated with prolonged survival, given N-803's ability to increase both NK and CD8+/CD4+ T cells, the first FDA approved agent that proliferates lymphocytes in the face of lymphopenia. These findings support further investigation of this novel therapeutic regimen that includes PD-L1 t-haNK, and N-803 that, as an IL-15 superagonist, may be able to overcome lymphopenia and improve prognosis. Clinical trial information: NCT04390399. Research Sponsor: ImmunityBio, Inc.

2543 **Poster Session**

Predictors and clinical outcomes of CMV reactivation in CAR-T therapy: A systematic review. First Author: Faiza Humayun Khan, Montefiore St.Luke's Cornwall, Collaborative Opportunities for Research, Training, And Excellence in Innovation (CORTEX), Newburgh, NY

Background: Cytomegalovirus (CMV) reactivation is a common complication in immunocompromised patients, particularly those undergoing chimeric antigen receptor T-cell (CAR-T) therapy. CMV reactivation has been linked to increased morbidity and mortality due to immune dysregulation, relapses, and treatment-related toxicity. This systematic review investigates the predictors and outcomes of CMV reactivation in CAR-T recipients, focusing on survival, relapses, and non-relapse mortality (NRM). **Methods:** A systematic review was conducted following PRISMA guidelines to compare characteristics and outcomes between CMV reactivation (R) and non-reactivation (NR) groups. A comprehensive search of PUBMED, EMBASE, and CENTRAL identified 172 studies, of which only four met the inclusion criteria after screening. A descriptive statistical analysis was performed to calculate frequencies and percentages. **Results:** Among 462 patients with CAR-T therapy, 114 (24.7%) experienced CMV reactivation. The median time from CAR-T therapy to CMV reactivation was 20 days (Range: -1 to 73), with an incidence of CMV disease with end-organ damage at 1.73%. Most patients received axicabtagene ciloleucel (71%) and had lymphoma (88%). Our analysis identified a higher proportion of patients receiving BCMA-targeted CAR-T therapy (7% vs. 2.9% in NR) and a greater prevalence of prior allogeneic hematopoietic stem cell transplantation (allo-HSCT) in the R group (35% vs. 7% in NR). Severe CRS (Grade $\geq$3) was more common in the R group (11.4% vs. 8.6%), as was severe ICANS of $\geq$3 (37.7% vs. 26.7%). Immunosuppressive therapy use, including steroids (56% vs. 42.8%) and combination therapy with tocilizumab and anakinra (12% vs. 5%), was significantly higher in the R group. Outcomes varied across studies, with Lin et al. and Khawaja et al. reporting higher one-year mortality in R vs. NR groups (57% vs. 23%, P = .001; 53% vs. 38%). Khawaja et al. also noted higher NRM (48% vs. 33%). Chen et al. identified CMV reactivation (HR 2.3, 95% CI: 1.2–4.5, P = .02) as an independent mortality predictor, with relapse rates of 71.4% in R and 41.2% in NR. **Conclusions:** CMV reactivation is a significant complication in CAR-T therapy, linked to worse outcomes, including increased mortality, relapse, and NRM. Predictors include BCMA-targeted CAR-T therapy, prior allogeneic HSCT, severe CRS/ICANS, and associated treatments. Targeted CMV monitoring, prophylaxis, and immunosuppressive strategies are essential for mitigating reactivation risks and improving outcomes in CAR-T recipients. Research Sponsor: None.

2545 **Poster Session**

Validation of an optimized tissue-agnostic genome-wide methylome enrichment assay to predict clinical outcomes in patients treated with pembrolizumab. First Author: Enrique Sanz Garcia, Princess Margaret Cancer Centre, University Health Network, University of Toronto, Toronto, ON, Canada

Background: Recent work from the INSPIRE study (PMID38393391) suggests that kinetics of cell-free DNA (cfDNA) methylation profiles reflect immunotherapy treatment response in solid tumors. Here we provide validation data of a tissue-agnostic, genome-wide methylation enrichment assay based on cell free methylated DNA immunoprecipitation and high throughput sequencing (cfMeDIP-seq) designed for clinical use, to determine response to immunotherapy. **Methods:** This study utilizes samples and clinical data from the INSPIRE study, a single-institution investigator-initiated phase II study of pembrolizumab in multiple solid tumors given every 3 weeks (NCT02644369). A prior published analysis of cfMeDIP used TCGA to develop a classifier and demonstrated an association of response to immunotherapy. In contrast, in this analysis, a novel quantitative and highly specific measurement of ctDNA was estimated using a generative machine learning model trained on differentially methylated regions identified from a large cfMeDIP methylome atlas from individuals with and without cancer. In a blinded validation analysis, Firth's logistic regressions were used to test differences in objective response (ORR) and clinical benefit rate (CBR) defined as complete or partial response or stable disease $>$ / = 6 cycles between patients with a decrease in ctDNA from baseline to cycle 3 of treatment, and those with an increase in ctDNA. Sensitivity for no objective response, specificity for objective response, and positive and negative predictive values (PPV and NPV) were summarized. Cox regressions and log-rank tests were used to evaluate differences in progression-free survival (PFS) and overall survival (OS) between the two groups. **Results:** The analysis included 64 unique patients with a median follow up of 18.43 months (a total of 128 samples), including head & neck (n = 9), triple negative breast (n = 10), ovarian (n = 11), melanoma (n = 7), and other mixed solid tumor types (n = 27). A decrease in ctDNA was associated with significantly better objective response than an increase [odds ratio (OR) 33.89 (4.07, 44426.47), p = 0.0001], 58% sensitivity, 100% specificity, 100% PPV and 35% NPV. Significantly better CBR [OR 10.17 (2.74, 55.74), p = 0.0002] was also observed. A decrease in ctDNA was associated with significantly better PFS [hazard ratios (HR) 0.28 (0.15, 0.49) p $<$ 0.0001] and OS [HR 0.42 (0.24, 0.76) p $<$ 0.003]. **Conclusions:** A clinical tissue-agnostic, genome-wide methylome enrichment approach using cfMeDIP-seq accurately predicts clinical outcomes in patients treated with pembrolizumab in multiple advanced solid tumors. This test provides relative quantification of methylated ctDNA to predict response to immmunotherapy and does not require tumor tissue. This analysis highlights potential generalizability across tumor types in response monitoring. Clinical trial information: NCT02644369. Research Sponsor: Adela, Inc; Merck.

2547 **Poster Session**

Personalized tumor-informed circulating tumor DNA as predictor of progression risk after long-term responses to immunotherapy in advanced non-small-cell lung cancer. First Author: Fang Wu, Department of Oncology, The Second Xiangya Hospital, Central South University, Changsha, China

Background: Immune checkpoint inhibitors (ICIs) have remarkably improved survival in advanced non-small-cell lung cancer (NSCLC), with about 30% ~ 40% of patients achieving long-term responses. However, biomarkers for predicting progression remain undefined. Circulating tumor DNA (ctDNA) has demonstrated its ability to predict recurrence in resected NSCLC, but its potential to forecast progression following prolonged responses to ICIs requires investigation. **Methods:** CR1STAL study is a multicenter, prospective cohort study investigating ctDNA surveillance to monitor progression risk in advanced NSCLC treated with first-line ICIs (NCT05198154). Patients with advanced NSCLC with long-term responses, defined as a PFS of about 1 year, were enrolled. Peripheral blood samples were collected alongside radiographic evaluations. ctDNA was detected using a personalized tumor-informed assay. Somatic variants were identified using a targeting 1,021 genes, followed by the design of individualized target-capture. ctDNA-positive was defined as the detection of ctDNA at any time during surveillance. The primary endpoint was PFS, defined as the time from enrollment until progression or death. Secondary endpoints included OS and ORR. Exploratory endpoints included the association between ctDNA features and survival, and comparison to other biomarkers. **Results:** We analyzed 199 sample from 42 NSCLC patients. The median age was 60.5 years with 88.1% male, and 64.3% at stage IV. The median number of sample collections was 4, with a median follow-up time of 24.7 months. ctDNA was detected in 54.8% of patients (23/42), with 82.7% of patients (19/23) showing ctDNA-positive occurring within 2 years of ICIs treatment. A total of 23 PFS events were observed. The ctDNA-positive group showed significantly worse PFS compared to the negative group (HR: 7.65, p $<$ 0.001), with a positive predictive value of 90.0% and a specificity of 88.2%. Additionally, ctDNA-positive provided a median lead time of 6.6 months prior to radiological progression. ctDNA-positive significantly associated with poorer OS (HR: 68.42, p = 0.003) and lower ORR (60.9% vs 89.5%, p = 0.036). 18 exhibited clonal mutations. Compared to the ctDNA-negative group, the patients with clone had significantly worse PFS (HR: 9.38, p $<$ 0.001) than those with subclone (HR: 4.16, p = 0.063). The ctDNA positivity rate was 84.6% in cases of local progression, 80.0% in distant metastases with brain exhibiting lower positivity rates. Additionally, peripheral CEA showed inferior predictive value for PFS (HR: 1.76, p = 0.303) than ctDNA. **Conclusions:** ctDNA has emerged as a promising biomarker for predicting progression risk of ICIs in advanced NSCLC patients with long-term responses. ctDNA surveillance enables earlier detection of progression and supports treatment adjustments through adaptive therapy. Clinical trial information: NCT05198154. Research Sponsor: None.

2548 **Poster Session**

Novel dynamic circulating biomarkers for predicting therapeutic efficacy of PRaG regimen in advanced refractory solid tumors. First Author: Yuehong Kong, The Second Affiliated Hospital of Soochow University, Suzhou, Jiangsu, China

Background: Common biomarkers for predicting the efficacy of immune checkpoint inhibitors (ICIs), such as programmed death-ligand 1 (PD-L1) expression, face notable challenges with tumor tissue sampling and the inability to enable dynamic monitoring. Circulating T lymphocyte subset classification and cytokines offers a promising alternative, reflecting T cell functionality and predicting ICI responses. The PRaG regimen, combining PD-1 inhibitors, radiotherapy, and granulocyte-macrophage colony-stimulating factor (GM-CSF), has shown efficacy in patients with metastatic or refractory solid tumors unresponsive to standard therapies. This study seeks to develop an efficacy evaluation model by intergrating dynamic peripheral blood lymphocyte subsets and cytokines, based on comprehensive analysis of clinical data from the PRaG studies. **Methods:** Data from the PRaG 1.0 (ChiCTR1900026175), PRaG 2.0 (NCT04892498), and PRaG 3.0 (NCT05115500) studies were analyzed to evaluate the objective response rate (ORR) by RECIST 1.1. Machine learning models, including linear, sequential, attention-based, and hybrid models, were employed to predict disease progression. These models utilized dynamic peripheral blood data from thirty-five lymphocyte subsets and seven cytokines, collected across treatment cycles. Model efficacy was further validated using independent data from two additional PRaG studies (NCT05790447 and NCT06112041). **Results:** As of November 30, 2023, 132 patients were included in the study, with a median age of 63 years. Patients over 65 accounted for 41.7%, and 60.4% had more than five metastatic sites. Patients with an ECOG score of 2-3 made up 59.7% of the cohort. The ORR was 20.13%, and the disease control rate was 48.19%. Dynamic monitoring of peripheral blood features across treatment cycles facilitated the development of an LSTM-HeterGNN model, which integrates long short-term memory (LSTM) networks with heterogeneous graph neural networks (heterGNN). This model outperformed ten other models, achieving a ROC AUC of 0.818. Independent validation further demonstrated robust performance, with a ROC AUC of 0.801. **Conclusions:** This study underscores the potential of the PRaG regimen as an effective salvage therapy for advanced solid tumors after the failure of standard treatments. The LSTM-HeterGNN model, leveraging dynamic peripheral blood biomarkers, provided precise efficacy predictions, surpassing traditional models. These findings lay the groundwork for dynamic treatment monitoring and optimization. Larger sample sizes are required to further validate the model's generalizability. Research Sponsor: None.

2549 **Poster Session**

An exploratory study to predict the efficacy and prognosis of immunotherapy for extensive-stage small cell lung cancer based on peripheral blood dynamic immune profiles. First Author: Lin Wu, Hunan Cancer Hospital, Changsha, China

Background: The high-dimensional classification information of peripheral blood mononuclear cells can provide abundant efficacy and prognosis-related data. However, in the field of immunotherapy for extensive-stage small cell lung cancer (ES-SCLC), the biomarkers that can predict the efficacy and prognosis need to be explored and clarified. **Methods:** Cytometry by Time-Of-Flight (CyTOF) was applied to the dynamic monitoring of immunotherapy using clinical resources such as dynamic peripheral blood from ES-SCLC patients. By labeling the following proteins: CD45, CD3, CD4, CD8, CD25, CD127, CD45RA, CD45RO, CCR7, TCRγδ, CD19, CD66b, CD14, CD56, CD16, CD11c, CD123, HLA-DR, CD38, CD57, CXCR3, CCR6, CCR4, CXCR5, CD95/Fas, LAG-3, Tim-3, CTLA-4, PD-L1, PD-1, CD278/ICOS, and TIGIT, this study performed high-dimensional fine-phenotyping of peripheral blood immune cells from ES-SCLC patients. We further explored the dynamic immune profile of peripheral blood that could predict the efficacy and prognosis of immunotherapy in combination with efficacy assessment and survival indicators. **Results:** 81 dynamic peripheral blood samples (baseline, after two cycles of treatment[C2], and progressive disease) were collected from ES-SCLC patients who received first-line immunotherapy combined with chemotherapy (n = 20) and chemotherapy alone (n = 7) in this study. In the immunotherapy group, a high percentage of senescent CD4+TEM/CD4+TEM at baseline (P = 0.029) was significantly associated with longer PFS. High TIGIT expression at baseline (P = 0.016) was significantly associated with shorter PFS. In addition, PD-1 (CD4+TCM, P = 0.017; Naive CD4+T, P = 0.031; pDCs, P = 0.031; NK, P = 0.007; Early NK, P = 0.007; Late NK, P = 0.02) and TIGIT (CD8+TEM, P = 0.046; NK, P = 0.038) expression levels at baseline in multiple cell subpopulations were significantly negatively correlated with OS. In contrast, the above peripheral blood immune profile was not a predictor in the chemotherapy group. In the immunotherapy group, peripheral blood dynamic monitoring showed that increased γδT cell percentage after treatment was significantly associated with longer PFS and OS (PFS, P = 0.035; OS, P = 0.032). Increased CD4+ TEM and CD4+ TCM percentage after treatment was significantly associated with shorter PFS and OS (CD4+ TEM: PFS, P = 0.021, OS, P = 0.036; CD4+ TCM: PFS, P = 0.01; OS, P = 0.014). Meanwhile, CTLA-4 and ICOS expression in total cells at progressive disease was significantly higher than C2, suggesting that it might be related to immunotherapy resistance. In the chemotherapy group, the above peripheral blood dynamic immune profile did not predict the efficacy and prognosis of chemotherapy. **Conclusions:** Dynamic peripheral blood immune profile can predict the efficacy and prognosis of immunotherapy in ES-SCLC. Research Sponsor: None.

2550 **Poster Session**

Longitudinal tumor-informed cfDNA whole genome sequencing to capture residual disease during neoadjuvant immune checkpoint inhibition in resectable gastroesophageal cancer. First Author: Blair V. Landon, Sidney Kimmel Comprehensive Cancer Center, Johns Hopkins School of Medicine, Baltimore, MD

Background: Although circulating tumor DNA (ctDNA) detection represents a promising approach to capture minimal residual disease (MRD), the clinical performance of ctDNA MRD during neoadjuvant immune checkpoint inhibition (ICI) remains understudied. Here we employ a tumor-informed whole genome sequencing (WGS) approach to capture residual disease and link ctDNA dynamics with pathologic response and clinical outcomes. **Methods:** WGS was performed on tumor (n = 28), matched WBC (n = 28), and longitudinal plasma samples (baseline, post-ICI cycle 1, post-ICI cycle 2 and pre-op; n = 97) from 28 patients with resectable gastroesophageal cancer treated with neoadjuvant ICI and chemoradiation prior to surgical resection (NCT03044613). Tumor-specific single nucleotide variants were identified from tumor and WBC datasets, from which a high confidence candidate variant set was used to determine the presence of ctDNA through a random forest machine learning model. ctDNA status and tumor fraction (TF) were determined based on the level of signal compared to a reference population of noncancerous donor plasma samples (n = 80). Serial ctDNA TF dynamics were correlated with overall (OS) and recurrence-free survival (RFS) in comparison to a tumor-naïve targeted NGS gene panel liquid biopsy approach. **Results:** Twenty-four of the 28 patients (86%) with evaluable specimens had ctDNA detected in a least one timepoint: 22 of 25 (88%) evaluable patients had ctDNA detected at baseline, 20 of 25 (80%) evaluable patients had ctDNA detected post-ICI cycle 1, 18 of 26 (69%) evaluable patients had ctDNA detected post-ICI cycle 2, and 5 of 21 (24%) evaluable patients had ctDNA detected at the pre-op timepoint. In contrast, the tumor-naïve targeted NGS approach detected 13 of 30 (43%), 12 of 30 (40%), 11 of 30 (37%) and 5 of 25 (20%) patients at baseline, post-ICI cycle 1, post-ICI cycle 2 and pre-op respectively. A ctDNA TF peak was detected at either the post-ICI cycle 1 or cycle 2 timepoint for 50% of the patients. A 50% reduction in ctDNA TF at the post-ICI cycle 2 timepoint showed a sensitivity of 80% and specificity of 69% for prediction of complete pathologic response, which was improved compared to the tumor-naïve liquid biopsy approach and importantly showed a significantly higher evaluable rate (86% vs 62% for tumor-informed and tumor-naïve respectively). Similar trends were observed between major pathologic response and ctDNA TF. A dramatic reduction of ctDNA TF ($\geq$65%) at the pre-op timepoint predicted longer OS and RFS (log-rank p = 0.0035 and p = 0.0032 respectively). **Conclusions:** Tumor-informed cfDNA whole genome sequencing analyses showed reliable and sensitive detection and quantification of ctDNA during neoadjuvant ICI and adds to the body of evidence supporting the clinical utility of ctDNA residual disease in interpreting clinical outcomes. Research Sponsor: Bristol-Myers Squibb; U.S. National Institutes of Health; CA121113; Cancer Research Institute.

2551 **Poster Session**

Plasma extracellular vesicles as biomarkers of primary versus acquired resistance to immune checkpoint inhibitors (ICI) in patients (pts) with solid tumors. First Author: Scott Strum, Princess Margaret Cancer Centre – University Health Network, University of Toronto, Toronto, ON, Canada

Background: Plasma extracellular vesicles (pEVs) have emerged as promising biomarkers in the field of oncology. They can be obtained through minimally invasive methods, and hold the potential to help differentiate the clinically relevant subgroups of primary (PR) vs acquired resistance (AR) to ICI treatments. We hypothesized that individual pEV-derived protein cargo, or combinations thereof, associate with PR vs AR to ICI. **Methods:** A cohort of patients was derived from the Immune Resistance Interrogation Study (IRIS; NCT04243720), with plasma collected at the time of progression on ICI in advanced or adjuvant settings (n = 69; n = 44 primary resistance [PR], n = 25 acquired resistance [AR]). Plasma-derived extracellular vesicles (pEVs) were isolated using serial ultracentrifugation and characterized per ISEV guidelines. All samples were analyzed using OLink Immuno-Oncology proteomics to evaluate 92 proteins. Statistical analyses included the Mann–Whitney U test, binary logistic regression, and log-rank tests. Primary and acquired resistance were defined according to trial protocol. **Results:** A total of 57 out of 69 samples (n = 37 PR, n = 20 AR) generated evaluable proteomics data. Of the 92 proteins analyzed, 11 were significantly overexpressed in AR compared to PR (ADGRG1, CD28, FGF2, IL10, IL12RB1, IL2, IL33, IL4, MCP3, PD-L2, PTN) ($p < 0.05$), with IL10 and IL33 showing the strongest associations ($p< 0.01$). When stratified by cancer type, 9/11 proteins were overexpressed in AR vs PR among melanoma pts (n = 39; ADGRG1, CD28, FGF2, IL10, IL33, IL4, MCP3, PD-L2, PTN) ($p < 0.05$), whereas only IL12RB1 ($p < 0.01$) was overexpressed in HNSCC pts (n = 16). Analysis of 5 proteins most strongly associated with AR (IL10, IL33, IL4, MCP3, CD28) yielded a sensitivity of 70% and specificity of 95% for AR vs PR, with a positive and negative predictive value of 88% and 85%, respectively; AUC 0.853 ($p < 0.001$; 95% CI 0.742-0.963). **Conclusions:** In summary, 11 pEV-derived proteins from blood samples at progression on ICI independently statistically associated with AR vs PR, and a combination of 5 of them generated a highly accurate predictive model for AR. Immunomodulatory cytokines IL10 and IL33 held the strongest associations, known to activate signaling cascades implicated in ICI resistance through the JAK-STAT and NF-Kappa-B/MAPK pathways, respectively. Differentially expressed proteins may signify distinct mechanisms of ICI escape. Despite requiring validation, our results highlight the potential of pEV-derived proteins as predictive biomarkers for ICI resistance in solid tumors. Future studies of pEV proteomics in the pre-treatment setting, as well as exploring other cargo such as RNA, may provide additional insights into the biology of resistance, and discover minimally invasive clinically relevant biomarkers. Clinical trial information: NCT04243720. Research Sponsor: BMO Chair in Precision Genomics, Dr. Lillian Siu.

2552 **Poster Session**

Precision medicine research on chemo-immunotherapy combination treatment for locally advanced or metastatic non-small cell lung cancer based on deep plasma proteomics. First Author: Qiuchi Chen, Cancer Center, Union Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China

Background: For locally advanced or metastatic non-small cell lung cancer (NSCLC) patients lacking specific genetic mutations, chemotherapy combined with anti-programmed death-1/programmed death-ligand 1 immunotherapy has become standard first-line treatment with enhanced therapeutic efficacy and prolonged survival. However, 40-50% of patients do not benefit from chemo-immunotherapy and develop resistance. Currently, there is a lack of predictive biomarkers for the efficacy of combined therapy in NSCLC, and research on the regulatory mechanisms and drug targets is insufficient, either. We leveraged an advanced proteomics platform to profile serum in NSCLC patients, aiming to identify chemo-immunotherapy biomarkers and uncover resistance mechanisms. **Methods:** This study collected pre-treatment plasma samples from 103 patients with locally advanced or advanced NSCLC receiving chemo-immunotherapy. These samples were analyzed using a deep proteomics platform that integrates antibody arrays and mass spectrometry. Patients were classified into "responders" (R, complete/partial response or stable disease $>$ 6 months) and "non-responders" (NR, progressive disease or stable disease $\leq$6 months) based on treatment efficacy. Differentially expressed serum proteins were identified between the groups, and weighted gene co-expression network analysis (WGCNA) was applied. Cox survival analysis was conducted on prognosis-related modules, leading to the identification of key proteins associated with treatment efficacy and survival. **Results:** Through our high throughput blood proteomics platform, a total of 1,397 proteins were detected. The median progression-free survival was 9 months, and the median overall survival was 32 months. A total of 175 differentially expressed proteins were identified between the R and NR groups. WGCNA identified 12 distinct modules, with ME4 associated with poor prognosis, enriched in inflammation, gene activation, and apoptosis suppression pathways, while ME8 correlated with favorable prognosis and ERK1/ERK2 cascade regulation. In the NR group, upregulated proteins associated with poor prognosis included erythropoietin receptor (HR: 1.41, $p < 0.01$), fibrinogen gamma chain (HR: 1.90, p: 0.03), Fc alpha receptor (HR: 2.63, $p < 0.01$), and prion protein (HR: 1.30, p: 0.04). In contrast, upregulated proteins in the R group linked to favorable prognosis were insulin-like growth factor-binding protein 2 (HR: 0.77, p: 0.02), keratin 19 (HR: 0.61, p: 0.02), and retinol-binding protein 4 (HR: 0.74, p: 0.03). **Conclusions:** Through in-depth proteomics analysis, this study systematically characterized the plasma proteomic landscape of patients undergoing chemo-immunotherapy, identifying potential novel biomarkers, and providing new insights to optimize clinical decision-making. Research Sponsor: Beijing Xisike Clinical Oncology Research Foundation; Y-Young2023-0125.

2553 **Poster Session**

T-cell exhaustion and pre-existing T-cell immunity in circulation as predictive biomarkers for immunotherapy in NSCLC patients. First Author: Anastasia Xagara, Laboratory of Oncology, School of Health Sciences, University of Thessaly, Larissa, Greece

Background: Pre-existing cancer-antigen specific T-cells describe the endogenous adaptive immunity before any treatment that may represent a valuable novel predictive biomarker for ICI. In a recent publication we have shown a positive correlation of pre-existing cancer-antigen specific $CD8^+$ T-cells with the response to ICI. Here, we analyze the major differences of exhausted T-cells between pre-existing positive ($PreI^+$) and pre-existing negative immunity ($PreI^-$) NSCLC patients as well as, between different stages of the disease. **Methods:** Blood was collected from 82 patients with NSCLC, 38 with stage III and 44 with stage IV, before ICI therapy. PBMCs were isolated with *Ficoll* density gradient centrifugation from patients and 15 healthy donors (HD). PreI was calculated by detecting endogenous IFNg expressing cells with FACS after in-vivo co-cultures of PBMCs with mixes of hTERT, MAGEA1, NY-ESO-1 και Survivin cancer-associated antigens. T-exhausted signatures were detected by multi-color flow cytometry using antibodies against CD3, CD4, CD8, PD-1 and TCF1. **Results:** 47% (18/38) of patients with stage III disease and 41% (18/44) of stage IV had peptide specific T-cells ($PreI^+$ patients). Survival analysis revealed better OS only in stage III $PreI^+$ compared to $PreI^-$ patients (Log-rank = 0.04), while for stage IV (p=0.081) there was only a trend. The percentages of CD8 T-cells that were $PD\text{-}1^+TCF1^+$(p=0.030) and $PD\text{-}1^+TCF1^-$(p=0.041) were higher in patients compared to HD, and additionally both T-cell populations harbored higher levels of PD-1 protein expression (p=0.003 and p=0.032 for stage III) as it was shown with mean fluorescence intensity (MFI). Moreover, low percentages of $PD\text{-}1^+TCF1^+$ ware associated with longer survival (p= 0.037) only in stage III patients. By subgrouping stage III patients, we observed that all patients with $PreI^+$ harboring low percentages of exhausted $PD\text{-}1^+TCF1^+$ were alive at the end of the follow up. **Conclusions:** Combinatorial analysis of Pre-existing tumor-antigen specific immunity and the status of T-cells before initiation of ICI in stage III NSCLC could serve as a good predictive factor of response. The study is ongoing. Research Sponsor: None.

2554 **Poster Session**

Effect of fusobacterium nucleatum on NF-κB/HIF-1α/CCL20 pathway and M2 macrophages infiltration in esophageal squamous cell carcinoma. First Author: Yu Su, The Fourth Hospital of Hebei Medical University, Shijiazhuang, China

Background: Esophageal squamous cell carcinoma (ESCC) is one of the most common digestive malignant tumor with the highest mortality rate in China.Recent studies have shown that Fusobacterium nucleatum (F. nucleatum) can attenuate the efficacy of immunotherapy in ESCC patients through various mechanisms.One of them is recriuting more M2-like macrophages through tumor-derived cytokines such as CCL20. **Methods:** From January 2022 to June 2023, a total of 30 patients with ESCC from 4th Hospital of HeBei Medical University were enrolled.All of the pateints did not apply any neoadjuvant therapy before and received radical resection.Real-time reverse transcriptase - PCR(RT-PCR) were performed to examine the expressions of F. nucleatum in tumor tissues.According to the CT values,the level of the F. nucleatum infection could be seperated in two groups - positive group and negative group. Immunohistochemistry (IHC) staining were used to examine the expressions of CCL20、CD206 and HIF-1α in both groups. Immunofluorescence(IF) was characterised CD206 on $CD68^+$ macrophages.In addition,transwell assay was carried on to quantify macrophages migration ability in vitro.At last,Western blot was used to determine the expression level of CCL20, HIF-1α and p65/p-p65 on ESCC cells. **Results:** F. nucleatum DNA positivity was significantly associated with higher expression of CCL20, HIF-1α and accumulation of $CD68^+CD206^+$ macrophages.IHC showed that the expression of CCL20 and HIF-1α were higher in F. nucleatum positive tumor tissue. After coculture with F. nucleatum and Eca109 cells in vitro, CCL20 and HIF-1α production by ESCC cells were accelerated.Transwell assay showed using siCCL20, CCL20-Nab or siCCR6 could decline the macrophages invasion level caused by CCL20. Otherwise, siHIF-1α could lowered the CCL20 expression level caused by F. nucleatum.In addition,Western blot revealed NF-κB pathway was highly activated in Fn educated Eca109 cells.Using BAY11-7082 could decline both CCL20 and HIF-1α level triggered by F. nucleatum. **Conclusions:** Fusobacterium nucleatum promotes esophageal squamous cell carcinoma progression via NF-κB/HIF-1α/CCL20 pathway-mediated migration of M2-like macrophages into the tumour micro-environment and deteriorates the suppression of the local immune micro-environment within the tumor.Such bacteria may be a biomarker to predict the efficacy of immunotherapy in ESCC. Research Sponsor: None.

2555 **Poster Session**

Monitoring PD-L1 expression in cancer-associated macrophage-like cells as predictor of clinical outcomes in metastatic cancer patients treated with PD-L1 immunotherapies. First Author: Dimpal M. Kasabwala, Creatv MicroTech, Inc., Monmouth Junction, NJ

Background: Studies have described the efficacy of immunotherapies (IMT) utilizing programmed death 1 receptor and its ligand (PD-L1) for treating solid tumors. However, many patients (pts) fail to respond to IMT, necessitating better predictive biomarkers for improved stratification. Poor IMT responses are often attributed to the dynamic nature of PD-L1 likely changing after chemotherapy or radiation, but typically quantified by static immunostaining. Recent studies have described PD-L1 upregulation in giant phagocytic stromal cells, i.e. Cancer associated macrophage-like cells (CAML), circulating macrophages that engulf tumor before entering circulation and may predict IMT responses. We conducted a pilot study to monitor the peripheral blood of n = 111 metastatic cancer pts undergoing systemic treatment with IMT in combination with other therapies, to evaluate CAML PD-L1 prior to & post IMT induction with clinical correlation at 2 years. **Methods:** In a prospective pilot study of n = 111 metastatic cancer pts, breast (n = 42), lung (n = 46), renal cell (n = 10), prostate (n = 5), esophageal (n = 5) & colon (n = 3), all starting new lines of systemic chemotherapy in combination with IMT (pembrolizumab [n = 69], nivolumab [n = 23], Durva [n = 4], or atezolizumab [n = 13]) for new recurrent metastasis (n = 45) or with previously treated progressive metastatic disease (n = 66). We isolated CAMLs from 7.5 ml baseline (T0) blood using the LifeTracDx PD-L1 test and scored PD-L1 as high or low. If possible, a follow-up sample (T1) was taken (~56 days) after IMT induction. Pts' progressive free survival (PFS) and overall survival (OS) hazard ratios (HRs) were analyzed by censored univariate analysis based on RECIST v1.1 over 2 years. **Results:** T0 PD-L1 CAML data was available for 78% (n = 86/111) of pts, with 34% (n = 29/88) having high CAML PD-L1 which was not correlated with improved PFS (HR = 0.99, p = 0.9416, CI = 0.6-1.6) or OS (HR = 1.1, p = 0.9472, CI = 0.6-1.8). T1 PD-L1 CAML data was available for 74% (n = 82/111) of pts, with 44% (n = 36/82) having high CAML PD-L1, which significantly correlated with improved PFS (HR = 3.1, p = 0.0002, CI = 1.8-5.5) & OS (HR = 6.6, $p < 0.0001$, CI = 3.4-12.7). In comparing CAML PD-L1 change post IMT, it was found that consistently low PD-L1 at T0 & T1 had the poorest responses, median PFS (mPFS) = 4.9 months & median OS (mOS) = 7.2 months. In contrast, consistently high PD-L1 at T0 & T1 had better responses, mPFS = 8.4 months & mOS = 18.3 months. Further, pts who increased in CAML PD-L1 after IMT had the best OS response rates, mPFS = 3.8 months & mOS = 20.9 months. **Conclusions:** We utilized a cancer agnostic blood-based biopsy to monitor PD-L1 changes in circulating tumor immune cells and predict clinical benefit to PD-L1 IMTs in several cancer types. While this initial pilot study appears to stratify pts with better IMT responses, larger validation studies are needed. Research Sponsor: Creatv MicroTech.

2557 **Poster Session**

The classification of uncertain histologies based on cfDNA fragmentomic analysis in patients with uncommon cancers screened for NCI-MATCH. First Author: Chris Alan Karlovich, Molecular Characterization Laboratory, Frederick National Laboratory for Cancer Research, Frederick, MD

Background: The NCI Molecular Analysis for Therapy Choice (NCI-MATCH) was a precision medicine trial that assigned targeted treatments to patients independent of histology. We sequenced > 2500 NCI-MATCH ctDNA samples of uncommon histology (excludes colon, breast, non-small cell lung, and prostate) using the TruSight Oncology 500 (TSO500) v2 ctDNA assay. We generated a probabilistic model from ctDNA fragment sizes to assign histology to patient samples designated as "not otherwise specified (NOS)" in pathology reports. **Methods:** Fragmentomics data were computed by binning the segment-level data to each exon, followed by Shannon entropy calculation. The Least Absolute Shrinkage and Selection Operator (LASSO) algorithm was then used to build the histology classifier for each of 29 histologies (n = 1614 samples of known histology) using a 9:1 random training and validation separation for validation accuracy estimation. The 9:1 training/validation was repeated 10 times. During each training/validation step, another 10-fold cross validation within the training set was used to find the best hyperparameter. The final model was re-trained on total samples which combined 29 classifiers and final predicted histology was determined using a winner-take-all approach. Mutation data was generated by Illumina's DRAGEN TSO500 ctDNA analysis pipeline and annotated using the OncoKB knowledge base. **Results:** The fragmentomics-based classification model achieved 98.2 validation accuracy across 1614 evaluable samples. The accuracy was increased to 99.6% on a subset of samples (n = 1413) with high confidence prediction defined as prediction probability > 0.5. The model was further used to classify 232 samples with NOS histology. Although there were no ground truth cases, those where a histology was predicted with high confidence were closely aligned with their broader annotations. For example, among 37 pancreatic cancer (excluding Islets) NOS patient samples, 18/19 high-confidence predictions were adenocarcinoma of the pancreas. The model was further explored on female reproductive system cancer NOS, which includes several rare histologies with limited or no representation in the prediction model. In this analysis, 17/23 high-confidence predictions were designated as ovarian epithelial cancer (OEC) or related histologies. Interestingly, one oncogenic *BRCA2* mutation (p.T1388fs) was detected in a predicted ovarian epithelial cancer sample. **Conclusions:** The validation accuracy was high in this exploratory analysis of uncommon histologies. High-confidence prediction was achieved for adenocarcinoma of the pancreas although prediction confidence was lower in OEC or related histologies . This study may support an expanded role for large cfDNA targeted panels beyond the identification of clinically actionable mutations to the classification of tumor histologies. Research Sponsor: National Cancer Institute.

2558 **Poster Session**

A molecular biomarker for longitudinal monitoring of therapeutic efficacy in a real-world cohort of advanced solid tumors treated with immune checkpoint inhibitors. First Author: John Guittar, Tempus AI, Chicago, IL

Background: Clinical validation studies have shown that early dynamic changes in circulating tumor DNA (ctDNA) tumor fraction (TF) can predict clinical outcomes. Yet few studies have evaluated the clinical value of longitudinal monitoring throughout the course of treatment. Here we evaluate longitudinal changes in ctDNA TF and clinical outcomes in an advanced real-world pan-cancer cohort of patients (pts) treated with immune checkpoint inhibitors (ICIs). **Methods:** The cohort included deidentified pts from the Tempus clinicogenomic database with stage IIIB or IV solid tumors who underwent ctDNA NGS and were treated with an FDA-approved ICI +/- chemotherapy (CT). Pts had a pre-treatment baseline liquid biopsy (T0) and ≥1 on-treatment sample Ti within 21-180 days of ICI. xM for treatment response monitoring estimates TF via an ensemble algorithm that incorporates variant and copy number information. Response status was determined at each on-treatment timepoint Ti relative to T0. Pts were classified as a Molecular Responder (MR) if TF < 1% at T0 and Ti or if TF decreased by ≥ 50% from T0 to Ti; otherwise, they were classified as a Molecular Non-Responder (nMR). Pts with TF < 0.09% at T0 and Ti were classified as ctDNA not detected. The longitudinal cohort included pts with ≥2 on-treatment timepoints, further classified based on the most frequent classification across each Ti as longitudinal MR, longitudinal nMR and longitudinal ctDNA not detected. If no classification was dominant, the most recent classification was used. Real-world overall survival (rwOS) was defined from T1 to death and assessed by log-rank test. **Results:** The full cohort of 84 pts with > 10 solid tumors included 34.5% (n = 29) NSCLC and 16.7% (n = 14) SCLC. The majority of pts (59.5%, n = 50) received ICI+CT, (64.0% first-line [1L]), and 40.5% (n = 34) ICI-only (35.3% 1L). rwOS was longer for 53 MRs vs. 18 nMRs (median not reached vs. 7.0 months, P < 0.005); 13 pts had no ctDNA detected. The longitudinal subcohort of 35 pts was 31.4% (n = 11) NSCLC, 20.0% (n = 7) prostate cancer, and 14.3% (n = 5) SCLC; 45.7% (n = 16) ICI+CT (56.3% 1L), 54.3% (n = 19) ICI-only (31.6% 1L). On average, pts had 3 on-treatment liquid biopsies, with a median time between on-treatment samples of 91 days. Twelve pts were longitudinal nMRs (10 MR or ctDNA not detected at T1), 18 longitudinal MRs, and 5 longitudinal no ctDNA detected. There were 6 death events in the longitudinal nMRs, 3 in the longitudinal MRs (all > 18 months after T1), and no death events in the longitudinal no ctDNA detected group. Longitudinal MRs had longer rwOS than longitudinal nMRs (median 37.4 months vs 8.7 months, P < 0.005). **Conclusions:** Longitudinal nMR was associated with worse survival compared to longitudinal MR. Longitudinal, molecular biomarker dynamics may be a useful clinical treatment decision tool for monitoring treatment response to ICI therapy. Research Sponsor: Tempus AI.

2559 **Poster Session**

Predictive imaging of the immunotherapy and radioimmunotherapy response by immunoPET via a new target (CD103) and innovative protein formats in preclinical NSCLC. First Author: Léa Zimmermann, Université Paris-Saclay, CEA, CNRS, Inserm, BioMaps, SHFJ,, Orsay, France

Background: Immune checkpoint immunotherapies (ICI) have transformed cancer treatment, but patients have varied responses and potential risks of autoimmune disease. To improve ICI, we need to identify biomarkers to select responding patients and research new approaches. To this, resident memory T cells (TRM) LT $CD8^+$ $CD103^+$, have been identified as a promising tumor-specific biomarker for studying therapeutic efficacy involving ICI. Internal radiotherapy appears to be a promising approach. Our objective is to develop new therapeutic approaches combining radiotherapy and ICI (radioimmunotherapy) using $CD8^+CD103^+$ immunoPET imaging as a predictive biomarker of efficacy. **Methods:** After developing and characterizing a new CD103 radiotracer and validating the dual ^{18}F PET-Scan imaging for $CD8^+$ and $CD103^+$ in C57BL/6 mouse models, we implanted mice subcutaneously with MC38 and othotopically syngenetically with LLC. We evaluated the efficacy of radioimmunotherapy vs ICI and the predictive effect of TRM in this syngeneic orthotopic model. To this, we implanted two syngeneic NSCLC cell lines, either LLC for a cold tumor or CMT167 for a warmer tumor. We performed double imaging prior to treatment with [^{18}F]-CD8 mutated FcRn and [^{18}F]-CD103 minibody on 2 consecutive days. We treated our mice 3 times, 3 days apart, with the first dose of either cold Avelumab or [^{177}Lu]-Avelumab (8MBq). The second and third doses were cold Avelumab. We performed double post-treatment imaging with [^{18}F]-CD8 mutated FcRn and [^{18}F]-CD103 minibody on 2 consecutive days, as well as ex vivo analyses and a survival study. **Results:** There was a trend towards improved survival in [^{177}Lu]-Avelumab treated mice vs Avelumab treated mice but more markedly in the immunogenic model (30d vs 21d). The impact on tumor growth was assessed by comparing the two treatment groups with untreated mice. Radioimmunotherapy induced a significant decrease in overall tumor growth compared with mice treated with ICI (0.45 ccm vs 0.68 ccm, *$p < 0.05$ turkey's multiple comparison test) in the immunogenic model. In the cold tumor model, there was a significant difference in the tumor size ratio before and after treatment, for mice treated with radioimmunotherapy vs ICI (12.96 vs 26.08, ***$p < 0.001$ Uncorrected Fisher's LSD). An increase in immune infiltration was validated by PET and flow cytometry for the immunogenic model (pre-treatment: 5.00%ID/cc max, versus post-treatment 8.23%ID/cc max for CD8, *$p < 0.05$ two way-Anova). More heterogeneous results were observed in the cold tumor model. **Conclusions:** Radio-immunotherapy reduces tumour growth and stimulates the immune system by circulating LT_{CD8}. The dual ^{18}F PET-Scan imaging for $CD8^+$ and $CD103^+$ offer a promising non-invasive visualization of tumor-infiltrating $CD103^+$ TRMs. We need to correlate $LT_{CD8+/CD103+}$ infiltration with therapeutic response. Research Sponsor: None.

2560 **Poster Session**

Ultrasensitive ctDNA profiling to identify long-term survivors in phase I immunotherapy trials. First Author: Oriol Mirallas, Vall d'Hebron University Hospital and Vall d'Hebron Institute of Oncology (VHIO), Barcelona, Spain

Background: Patients (pts) included in early clinical trials (ECT) typically show a median overall survival of 8-10 months (PMID: 18042834 and 21975023), with long-term survivors (LTS) rarely encountered. While prognostic scores have been developed to identify short-term survivors (STS) in ECT, predictors of LTS remain largely unexplored. Ultrasensitive circulating tumor DNA (uctDNA) serves as a reliable surrogate for tumor burden (Toledo R *et al*, ASCO 2024), and may provide insights into LTS. This study aims to identify key determinants of LTS. **Methods:** A case-control study was conducted on pts treated at VHIO's phase I unit between 2013 and 2023, as part of the institutional translational study RIO360. Pts with an overall survival (OS) $>$ 3 years after C1D1 were classified as LTS and compared to STS with OS $<$ 1 year, matched for age, sex, stage, prior immunotherapy (IO), and ECOG. Clinical, histopathological, uctDNA, and treatment outcomes were collected. uctDNA analysis was performed prior to C1D1 and throughout treatment (every 3 to 4 weeks) in the subset of patients treated with IO. Comparisons between LTS and STS were performed using univariate binomial generalized linear models. **Results:** Of 1282 pts, a total of 117 pts (9.1%) were classified as LTS (median OS 5.2 years) and compared with 117 matched STS pts (median OS 0.6 year). The most common tumor types among LTS were HNSCC (18%), melanoma (10%), and breast (9.1%), while in STS were colorectal (27%), breast (12%), and melanoma (11%). Treatment with 3+ prior lines was more common in STS (45%) than LTS (24%) ($p = 0.002$). Visceral metastases were present in 59% LTS and 77% STS ($p = 0.010$). Higher neutrophil count and dNLR were associated with STS ($p < 0.05$). LTS had lower mean uctDNA at baseline (7.5 vs 10.9 ppm; $p < 0.001$). Two consecutive uctDNA decreases were observed in 92% of LTS pts, while 80% of STS pts showed two consecutive uctDNA increases ($p < 0.001$). **Conclusions:** In ECT, predictors of long-term survival include the absence of visceral metastasis, less prior treatment exposure, low baseline uctDNA levels, and early decreases in uctDNA. This study further explores uctDNA dynamics during treatment, with detailed findings to be presented. Research Sponsor: BBVA.

2561 **Poster Session**

Ultrasensitive ctDNA monitoring to reveal early predictors of immunotherapy success in advanced cancer. First Author: Daisuke Nishizaki, UC San Diego Moores Cancer Center, La Jolla, CA

Background: The potential of immune checkpoint inhibition (ICI) therapy is constrained by the inability to predict patient response. Circulating tumor DNA (ctDNA) has emerged as a promising tool for real-time response tracking and early prediction of therapeutic outcomes. However, the clinical utility of ctDNA-based liquid biopsy faces a critical challenge: reliable detection in low-shedding tumors and during dramatic therapeutic responses when ctDNA levels approach the analytical threshold. We overcome this technical limitation, achieving the precise longitudinal monitoring needed to optimize ICI therapy. **Methods:** We analyzed longitudinal plasma samples from 43 patients with treatment-refractory metastatic cancers spanning 8 distinct groups, composed primarily of GI (n = 17) and gynecological cancers (n = 6). Patients underwent a median of 1 previous line of therapy (range 0-8). Using NeXT Personal, an ultra-sensitive personalized liquid biopsy approach, we tracked up to 1,800 patient-specific somatic variants per case across 250 plasma samples. This methodology achieves exceptional analytical sensitivity, detecting circulating tumor DNA at levels as low as 1-3 parts per million (PPM). **Results:** ctDNA was detected across five orders of magnitude (2.0-239,315 PPM, median LOD: 1.76 PPM), with 31% of positive signals falling in the ultrasensitive range below 100 PPM. Early molecular response, measured by $>$ 50% ctDNA reduction or sustained ctDNA negativity from baseline to first follow-up (median 23 days), strongly predicted improved progression-free survival (PFS) (HR = 0.22, 95% CI 0.07-0.70, p = 0.006), representing a 3-fold increase in 1 year PFS rates. Achievement of durable molecular complete response (dmCR), defined as sustained ctDNA clearance $>$ 120 days, emerged as a powerful predictor of PFS, with dmCR patients maintaining 100% progression-free status at 12 months compared to 63% in non-dmCR patients (HR = 0.10, 95% CI 0.01-0.92, p = 0.017). This survival advantage persisted at 18 months with 80% PFS in dmCR patients versus 21% in non-dmCR patients. **Conclusions:** Early ctDNA kinetics predict long-term ICI outcomes across multiple advanced cancer types. The ability to detect ultra-low ctDNA levels proved critical for accurate minimal residual disease assessment, even in this heavily pretreated cohort. These results establish high-sensitivity ctDNA monitoring as an essential tool for precise, real-time evaluation of immunotherapy response to guide clinical decision-making. Clinical trial information: NCT02478931. Research Sponsor: Personalis.

2562 **Poster Session**

Role of pelareorep in activating anti-tumor immunity in PDAC. First Author: Richard Trauger, Oncolytics Biotech, San Diego, CA

Background: Pancreatic ductal adenocarcinoma (PDAC) is highly lethal cancer with limited immunotherapeutic options. Pelareorep (pela) is an intravenously delivered unmodified reovirus containing a double stranded RNA genome that has been studied as an immunotherapeutic in multiple cancers including breast, anal, colorectal and pancreatic. We previously reported high tumor response rates in first-line metastatic PDAC patients treated with pela combined with gemcitabine, nab-paclitaxel and atezolizumab. We report here the immunologic effects of pela in a cohort of first-line metastatic PDAC subjects treated with pela plus chemotherapy and atezolizumab and the correlation of these effects with tumor response. **Methods:** To examine its effects on pancreatic cancer, a phase 1/2 Simon 2-stage platform study (GOBLET) was performed that included patients with first-line locally advanced/metastatic unresectable PDAC. Anti-reovirus T cell activity was assessed by interferon gamma secretion (ELISPOT). Changes in the expression of plasma proteins were analyzed by Olink Response panels. T cell receptor sequencing (TCR-seq; ImmunoSEQ Assay, Adaptive Biotechnologies) was performed on tissue collected prior to the start of therapy and on blood from baseline through 3 treatment cycles to identify TILs expansion. Tumor responses were scored according to the modified RECIST v1.1 criteria. **Results:** Increases in anti-reovirus T cell activation as determined by ELISPOT after cycle 3 of therapy were observed in 6/8 subjects. Three subjects with maximum responses ($>$ 300 spots) showed $>$30% decreases in tumor volume. Significant changes in plasma proteins as determined by Olink included PD-L1, CXCL9, CXCL10, CXCL11 and IFN-γ. Pre-treatment tumor tissue was used to identify the TIL clonal populations prior to therapy. Increased TIL clones in the blood pre-treatment was associated with tumor responses. Pela treatment increased the expansion of pre-existing and new TIL clones in the blood after one cycle of treatment. Sustained increases in pre-existing TIL clonal populations in the blood through cycle 3 of therapy were observed in subjects who exhibited reductions in tumor volume. **Conclusions:** These findings, while preliminary, demonstrate that pela induces not only anti-reovirus T cells but also activates innate and adaptive anti-tumor immunity in PDAC subjects treated with chemotherapy and atezolizumab. Tumor responses are associated with both the presence of TIL clones in the blood prior to treatment and the expansion of pre-existing TILs in the blood on treatment. These findings provide additional insights into the immunologic mechanisms by which pela-based therapy may provide clinical benefit in patients with metastatic PDAC. Research Sponsor: None.

2563 **Poster Session**

ctDNA features of acquired resistance to immunotherapy in advanced NSCLC. First Author: Sofiane Taleb, Gustave Roussy Cancer Center, Villejuif, France

Background: Acquired resistance to systemic therapies, including immune checkpoint inhibitors (ICIs) and tyrosine kinase inhibitors (TKIs), is a major clinical challenge in advanced non–small cell lung cancer (NSCLC). While mechanisms of resistance to targeted therapies are well-documented, the genomic alterations associated with resistance to immunotherapy remain poorly understood. Circulating tumor DNA (ctDNA) profiling offers a non-invasive approach to identify real-time genomic changes driving resistance, providing novel insights into the underlying biology of immunotherapy failure. **Methods:** We performed a prospective ctDNA sequencing study in 57 advanced NSCLC patients from two cohorts: STING (n = 30, NCT04932525) and COPE (n = 27, NCT04258137). Plasma samples were collected before treatment initiation and at disease progression following objective response to anti–PD-1 therapy or TKIs. ctDNA analysis was conducted to detect emergent genomic alterations, evaluate tumor mutation burden (TMB), and quantify circulating tumor fraction (TF). **Results:** The study included 57 patients, with a median age of 62 years [IQR: 54.5–70], and 54.4% (31/57) were male. At disease progression, 64.9% (37/57) of patients exhibited emergent ctDNA alterations associated with secondary resistance, independent of therapy type. Among these, 70% (26/37) harbored multiple newly arising mutations. In the non–oncogene-addicted NSCLC cohort receiving anti–PD-1 therapy (n = 30), 56.6% (17/30) exhibited emergent resistance alterations, with 76.5% (13/17) harboring multiple mutations. Frequently observed aberrations included mutations in NOTCH1/3 (n = 3), KEAP1 (n = 3), KMT2B (n = 2), POLE (n = 2), SETD2 (n = 2), TYRO3 (n = 2), STK11 (n = 2), TSC2 (n = 1), TGFBR2 (n = 1), PTPN11 (n = 1), SPEN (n = 1), STAG (n = 1), CDH1 (n = 1), and CTNNB1 (n = 1). The median progression-free survival (mPFS) was 7.0 months [95% CI: 5.0–10.3]. In the anti-EGFR TKI cohort (n = 13), 84.6% (11/13) displayed emergent ctDNA alterations, including mutations in EGFR (n = 2), PIK3CA (n = 2), and MET (n = 1). The mPFS was 8.6 months [95% CI: 6.7–11.2]. TMB and circulating TF did not significantly change between baseline and progression in both cohorts. **Conclusions:** This study highlights the high prevalence of emergent genomic alterations detected by ctDNA in advanced NSCLC patients developing resistance to ICIs and TKIs. In the ICI-treated cohort, mutations in NOTCH1/3, KEAP1, and STK11 emerged as significant resistance drivers, consistent with their roles in immune evasion, oxidative stress regulation, and impaired immune cell infiltration, as supported by prior studies. Notably, this is the first study investigating features of ctDNA at acquired resistance to immunotherapy using an FDA-approved assay. These findings underscore the heterogeneous and polyclonal nature of resistance to ICIs. Research Sponsor: None.

2564 **Poster Session**

Mutation profiling of appendiceal cancer: Distinguishing tumor grades, comprehensive mutation landscape, and ctDNA as a discovery tool. First Author: Sefali Patel, AHN Cancer Institute, Pittsburgh, PA

Background: Appendiceal cancer (AC) encompasses rare tumors with varying clinical behavior. Histologic grade is a key determinant of disease biology and prognosis. This study utilized an in-house circulating tumor DNA (ctDNA) biomarker discovery pipeline to assess genetic determinants of histologic grade in AC, analyzing both peripheral blood and tumor tissue. **Methods:** Paired peripheral blood and solid tumor samples were collected from 52 patients undergoing surgery for AC (18 low-grade and 34 intermediate/high-grade). Comprehensive genomic profiling (CGP) using the TSO500 assay was performed on ctDNA, tissue-derived DNA and buffy-coat (germline)-derived DNA. Tumor-specific and germline mutations were analyzed using OncoKB, which classifies variants as oncogenic, likely oncogenic, or actionable (Level 1 therapeutic mutations with an approved therapy). The concordance of mutations between solid tumor and plasma CGP assays was assessed, categorizing variants as detected in both tumor and ctDNA, ctDNA only, or tumor only. **Results:** ctDNA exhibited 82% concordance with tumor tissue for known actionable mutations. Among 26 patients that were identified to have Level 1 therapeutic mutations, 88% (n = 23) had matching mutations in plasma. Frequently detected mutations included *KRAS (40%), GNAS (30.8%), SMAD4 (28.8%),* and *TP53 (28.8%)*. Germline analysis revealed additional variants, including *RUNX1 (71.2%), NOTCH4 (50%),* and *BARD1* (48.1%). Tumor-specific *TP53* and SMAD4 mutations correlated with high-grade tumors; while *GNAS* was more prevalent in low-grade tumors. Germline analysis identified *NOTCH3* and *SPEN* mutations predominantly in high-grade tumors, suggesting that inherited determinants may determine tumor grade (23.5% each). Plasma samples exhibited lower variant allele frequencies, limiting sensitivity for novel biomarker discovery. Concordance analysis revealed some mutations were exclusive to solid tumors, while others were plasma-specific, highlighting the need for a multi-modal genomic assessment. **Conclusions:** Tumor *TP53, GNAS,* and *SMAD4* mutations serve as molecular classifiers for histologic grade differentiation in AC, while germline *NOTCH3, SPEN, RUNX1, NOTCH4,* and *BARD1* variants may influence histologic grade. ctDNA showed strong concordance for actionable mutations but had reduced efficacy for novel mutation discovery in the plasma samples. These findings underscore the value of integrating tumor and germline profiling for classification and treatment stratification, while refining liquid biopsy methodologies to enhance sensitivity in AC research. Research Sponsor: None.

2565 **Poster Session**

Investigating the association of blood-to-tissue tumor mutation burden (TMB) ratio with overall survival and intratumor heterogeneity (ITH) in advanced NSCLC. First Author: Leeseul Kim, University of Chicago, Chicago, IL

Background: High tumor mutation burden (TMB) measured via tissue-based next-generation sequencing (NGS) (tTMB) has been shown to predict better survival outcomes in certain cancers treated with immune checkpoint inhibitors (ICIs). With the increasing use and sensitivity of blood-based NGS, blood-based TMB (bTMB) is frequently employed as an alternative. However, the prognostic significance of bTMB relative to tTMB and its correlation with intratumoral heterogeneity remain poorly understood. **Methods:** This study included advanced-stage NSCLC patients who underwent both pre-treatment blood-based NGS (collected between October 2020 and February 2024) and tissue-based NGS. Intratumoral heterogeneity (ITH) was assessed using the mutant-allele tumor heterogeneity (MATH) approach, with blood based NGS (bMATH). The highest allele frequency (HAF) was obtained from blood-based NGS. Survival analyses were conducted using Kaplan-Meier curves and Cox proportional hazards models, focusing on the bTMB/tTMB ratio. **Results:** A total of 102 patients met the inclusion criteria, 55 of whom had complete data for bTMB, tTMB, bMATH, and HAF. The median follow-up time was 12 months. Treatment regimens included ICI combined with chemotherapy (19 patients), ICIs alone (15), targeted therapy (16), and cytotoxic chemotherapy (5), with 33 receiving first-line treatment and 22 receiving second-line or beyond. The median interval from blood NGS to treatment initiation was 20 days (IQR 8–28), and from tissue NGS to treatment initiation was 65 days (IQR 28–255). Multivariable Cox proportional hazards analysis—adjusting for gender, smoking status, stage, ECOG, regimen type, line of therapy, and numeric values of bMATH, bTMB, tTMB, and the bTMB/tTMB ratio—revealed that a higher bTMB/tTMB ratio was independently associated with inferior overall survival (OS) (HR 1.16, 95% CI 1.03–1.30, p=0.01) but showed no significant difference in progression-free survival (PFS) (HR 1.10, 95% CI 0.94–1.29, p=0.23). The cutoff for the bTMB/tTMB ratio that best stratified OS was 0.81. Patients below this cutoff experienced significantly longer OS (median OS 10 vs. 49 months, HR 0.23, 95% CI 0.05–0.96, p=0.02). Additionally, a moderate positive correlation was observed between bMATH and the bTMB/tTMB ratio (Spearman's r=0.33, p=0.02). **Conclusions:** A higher bTMB/tTMB ratio was associated with poorer overall survival in advanced-stage NSCLC, highlighting its potential prognostic value. Moreover, the moderate correlation between bMATH and bTMB/tTMB suggests an interplay between TMB and intratumor heterogeneity. Future studies are needed to confirm these findings and to explore their potential therapeutic implications. Research Sponsor: None.

2566 **Poster Session**

Identifying peripheral cancer-associated TCR signals for the early-detection of lung cancer. First Author: Chen Huang, China-Japan Friendship Hospital, Beijing, China

Background: Tumor-associated antigens and neoantigens play a critical role in eliciting anti-tumor immune responses, leading to a significant amplification of tumor-specific T cell clones. Consequently, the detection of tumor-associated immune signaling in peripheral blood is expected as a promising strategy for cancer screening. Notably, due to the amplification effect of the immune response, the identification of tumor-related immune signals demonstrates higher abundance compared to the direct detection of tumor-derived molecules, such as circulating tumor DNA (ctDNA). This increased abundance allows for the extension of the screening time window, underscoring its potential for early cancer detection. The present study aims to identify lung cancer-associated T cell receptor (TCR) signatures, and develops a predictive model for to recognize lung cancer based on TCR repertoire sequencing. **Methods:** Peripheral blood samples were collected from 2,699 lung cancer patients and 3,360 healthy individuals. The TCR repertoires were profiled using a multiplex-PCR-based sequencing of the TCR-β chains. The frequency of TCR clonotypes were calculated using MiXCR tools by aligning against human TCR-β gene segments. The cancer-enriched TCR sequences were identified by comprehensively considering the distribution and frequency of clonotypes in the comparison between the lung cancers and the healthy controls. We proposed an lung cancer-enriched TCR score (LCS) to evaluate the risk for lung cancer based on the CDR3 sequences alignment. A robust machine learning model was developed integrating multiple TCR repertoire characteristics and LCS. **Results:** The UMAP clustering based on TCR repertoire features revealed distinct TCR characteristics in lung cancer patients compared to healthy individuals. 3,840 TCR clones were identified to be significantly enriched in lung cancer cases. Among these, the CDR3β 'CATSRDTGGREKLFF' was identified as the most highly enriched clone specific to lung cancer patients. Furthermore, a significantly higher LCS was observed in lung cancers ($p < 0.001$). To validate the utility of LCS, we applied the LCS measurement to an independent public TCR dataset with 382 lung cancer patients, 195 healthy individuals, and 1,034 COVID-19 cases. The external validation demonstrated that lung cancers show a significantly increased LCS compared with healthy controls ($p < 0.001$), while no significant difference in LCS between COVID-19 cases and healthy controls (p = 0.25). The detection performance of model using integrated TCR features and LCS demonstrated a sensitivity of 0.96 and a specificity of 0.95. **Conclusions:** Cancer-related immune signals in peripheral blood can inform the anti-tumor responses. This study identified lung cancer-enriched TCR signatures, highlighting the potential as promising biomarkers for lung cancer detection. Clinical trial information: ChiCTR2200055761. Research Sponsor: None.

2567 Poster Session

Dietary compounds and patterns associated with immune checkpoint inhibitor (ICI) outcomes in advanced non-small cell lung cancer (NSCLC). First Author: Edmond Rafie, Research Center of the Centre Hospitalier de l'Université de Montreal, Montreal, QC, Canada

Background: The gut microbiome is a modulator of ICI activity. Diet is among the most important factors influencing the gut microbiome. We previously showed that high fiber was not associated with outcome in NSCLC, in contrast to melanoma. However, the impact of dietary patterns and specific nutrients on ICI outcomes in NSCLC is unknown. **Methods:** At the CHUM Microbiome Centre, a nutritionist prospectively collected dietary history using a validated DHQ-II survey from 147 patients (pts) with advanced NSCLC treated with ICI alone or in combination with chemotherapy. Global dietary patterns and a systematic screen of 72 macro- and micronutrients (cut-offs defined by median) were examined for their association with progression-free survival (PFS) in univariable and multivariable cox-regression analyses. Associations between diet and immune-related adverse events (irAE) were examined. In 69 pts, shotgun metagenomic sequencing (WMS) was performed on fecal samples to determine differential abundance of bacteria using linear discriminant analyses, heatmaps, and MaAsLin2. **Results:** Median age was 68, 46% were male. Median follow-up was 13 months. Total caloric intake adjusted for basal metabolic rate (Mifflin-St Jeor equation using BMI and activity level) was not associated with PFS (p = 0.3). In univariable analyses, the following nutrients were associated with improved PFS: vitamin K (HR 0.62, p = 0.03), fat (HR 0.65, p = 0.04); while the following were associated with inferior PFS: starch (HR 1.61, p = 0.03), carbohydrates (HR 1.56, p = 0.04), sucrose (HR 1.62, p = 0.03), and iron (HR 1.7, p = 0.016). In a multivariable analysis examining all macro- and micronutrients and adjusting for BMI, vitamin K intake was significantly associated with improved PFS (HR 0.60, 95% CI 0.37, 0.97, p = 0.04). Fat-based diets such as keto-like diet (high fat, low starch) was associated with improved PFS in univariable (HR, 0.47, p = 0.008) and multivariable analyses (HR 0.37, 95%CI 0.2, 0.68, p = 0.001). Compared to high starch diet, western diet (high fat, high starch) was associated with increased risk of any grade irAE (24% vs 54%, respectively, p = 0.01). WMS analyses revealed biologically relevant signals; fat-based diets were associated with enrichment of favorable commensal bacteria such as *Ruminococcus lactaris*, *Butyricimonas faecihominis*, *Lachnospiraceae* spp, with low fat associated with deleterious *Veillonella atypica*. Starch-based diets were associated with high *Prevotella* spp. Sucrose-enriched diets were enriched with *Candidatus saccharibacteria*, a known sucrose-fermenting bacteria. **Conclusions:** Our results demonstrate the importance of diet on ICI outcomes in NSCLC and WMS results suggest this is mediated by the gut microbiome. Diet is a modifiable lifestyle factor which may be targeted to improve ICI activity, meriting study in a randomized trial. Research Sponsor: Terry Fox Research Institue; Institut de Cancer de Montréal.

2568 Poster Session

The role of lipid-laden Kupffer cells in immunosuppression and immunotherapy response in MASLD-related hepatocellular carcinoma. First Author: Junzhe Jacky Zhao, Duke-NUS Medical School, Singapore, Singapore

Background: Hepatocellular carcinoma (HCC) related to metabolic dysfunction-associated steatotic liver disease (MASLD) is a rising global health burden. Despite systemic immunotherapy being the first-line treatment for advanced HCC, clinical observation shows that immune checkpoint inhibitors (ICI) offer lower benefit to patients with non-viral HCC, including MASLD-HCC. Macrophages, especially Kupffer cells (KCs), are the major PD-L1+ liver cells. With previous studies showing that more KCs are associated with poorer survival, we hypothesise that KCs in MASLD-related HCC show an immunosuppressive phenotype secondary to lipid accumulation, contributing to the poorer ICI responses in patients. **Methods:** As proof-of-concept, we characterised macrophage phenotypes and lipid accumulation in matched tumour and non-tumour tissues from HBV+ and non-viral HCC patients (n = 6 / group). We next assessed the functional consequences of lipid loading using induced pluripotent stem cell (iPSC)-derived KCs in vitro, followed by validation in KC-containing iPSC- and patient-derived HCC organoids. We evaluated lipid accumulation, paracrine signalling, transcriptomic changes, and cell-cell interactions in these organoids. **Results:** In patient samples, macrophage lipid accumulation is associated with a PD-L1 high, TREM2 high, KC-like phenotype in both non-tumour and tumour (Cohen's $d > 1.0$, power $>$ 99%). In non-viral HCC samples, lipid-laden macrophages, with an M2-KC phenotype, are enriched twofold in non-tumour (Cohen's $d > 1.0$, power = 72%) and tumour (Cohen's d = 0.3, power = 6%). Light-sheet microscopy confirmed colocalization of lipids and PD-L1+ immune cells. Exposing iPSC-KCs to free fatty acids and IL-6 suppressed antigen presentation, while enhancing phagocytosis and T-cell exhaustion ($p < 0.05$) – effects not reversed by ICI alone but alleviated when combined with tocilizumab or a CD36 inhibitor. These changes are likely independent of lipophagy or FASN-mediated fatty acid synthesis. Our HCC organoid models preserve KCs and recapitulate their immunosuppressive phenotype. scRNA-seq and CellPhoneDB analysis of HCC organoids highlighted significant KC-hepatocyte crosstalk, mediated by IL-6, SPP1, and other cytokines, corroborated by Luminex assay. **Conclusions:** These findings suggest that MASLD-associated lipid loading promotes a distinctly immunosuppressive KC phenotype, contributing to diminished ICI responsiveness in HCC. Targeting the lipid-KC axis, for instance with IL-6 blockade or CD36 inhibitors, may help restore immune competence and improve ICI-based treatment outcomes. Future studies, especially with a larger patient cohort and with our organoid platform, should determine whether lipid-laden KCs can serve as a biomarker for ICI responsiveness and further delineate the pathways driving their immunosuppressive behaviour. Research Sponsor: National Medical Research Council, Singapore; MOH-STaR21nov-0002; National Medical Research Council, Singapore; NMRC/OFLCG/003/2018; National Research Foundation, Singapore; NRF-CRP26-2021RS-0001.

2569 Poster Session

The economics of cancer immunotherapy: A five-year Medicare B expenditure analysis of checkpoint inhibitors. First Author: Sharanya Tripathi, Saint Vincent Hospital, Worcester, MA

Background: Immune checkpoint inhibitors (ICIs) have transformed cancer treatment, prompting a comprehensive analysis of Medicare Part B spending trends from 2018 to 2022. **Methods:** We conducted a detailed examination of Medicare Part B claims data, focusing on spending per dosage unit, total expenditure, and beneficiary utilization across multiple ICI drugs. **Results:** Our analysis revealed significant variations in ICI utilization and spending, with Keytruda (Pembrolizumab) emerging as the leading drug, totaling 4.94 billion and serving 67,022 beneficiaries in 2022. Notably, Opdivo (Nivolumab) demonstrated substantial market presence with 1.85 billion in spending and 26,957 beneficiaries. Price changes varied considerably, with Pembrolizumab experiencing a 12.9% price increase, Durvalumab rising 8.0%, and Atezolizumab increasing 10.1%. Interestingly, Libtayo showed a modest 1.5% price decrease. Other significant drugs included Tecentriq (Atezolizumab) with 777.8 million in spending and 12,812 beneficiaries, and Imfinzi (Durvalumab) with 562.7 million and 10,517 beneficiaries. **Conclusions:** Medicare Part B spending on immune checkpoint inhibitors reflects complex market dynamics, characterized by significant variations in drug pricing, beneficiary utilization, and total expenditure, highlighting the evolving landscape of cancer immunotherapy. Research Sponsor: None.

Cost trajectories and utilization patterns of eight immune checkpoint inhibitors (2018-2022).

Brand Name	Generic Name	Average Spending per Dosage Unit 2022	Annual Growth Rate in Average Spending per Dosage Unit (2018-2022)	Total Spending 2022	Total Beneficiaries 2022	Average Spending per Beneficiary 2022	Average Sales Price (ASP) 2022
Bavencio	Avelumab	$85.86	2.10%	$111,862,815	1,591	$70,310	$87.91
Imfinzi	Durvalumab	$75.86	1.60%	$562,741,221	10,517	$53,508	$77.53
Jemperli	Dostarlimab-Gxly	$216.09		$4,502,157	79	$56,989	$217.87
Keytruda	Pembrolizumab	$52.18	4.70%	$4,935,971,049	67,022	$73,647	$53.42
Libtayo	Cemiplimab-Rwlc	$27.02	0.10%	$203,832,304	3,187	$63,957	$27.45
Opdivo	Nivolumab	$28.78	4.10%	$1,849,938,540	26,957	$68,626	$29.43
Opdualag	Nivolumab and relatlimab-rmbw	$176.43		$42,513,402	680	$62,520	$180.64
Tecentriq	Atezolizumab	$79.07	1.50%	$777,758,575	12,812	$60,705	$80.79

2570 Poster Session

Phase I study of hV01, a recombinant human IL-21-expressing oncolytic vaccinia virus, as monotherapy in advanced solid tumors. First Author: Jian Zhang, Fudan University Shanghai Cancer Center, Shanghai, China

Background: Oncolytic viruses have shown an excellent safety profile and can initiate antitumour immunity through in-situ tumor lysis and systemic immune response, thereby gaining significant attention in cancer immunotherapy. Here, we conducted a phase I study of hV01, a genetically engineered oncolytic vaccinia virus expressing IL-21, in patients with advanced malignant solid tumors. **Methods:** This open-label, single-dose escalation study evaluated four dosing levels (range, 1×10^7 - 8×10^8 PFU) of intratumoral (i.t) injection of hV01, with a 28-day treatment cycle (NCT05914376). The primary aims were to determine the maximally tolerated dose (MTD), dose-limiting toxicities (DLTs) and safety. Treatment response was evaluated by RECIST v1.1 criteria on day 28 using a CT scan.Peripheral blood samples were analyzed for immune cell phenotypes with FACS and viral shedding with Q-PCR after the hV01 regimen. **Results:** Thirteen patients with advanced solid tumors were enrolled; most had failed multiple prior therapies. Twelve patients completed at least one treatment cycle, with three in each dosing cohort. Six of the twelve patients (6/12, 50%) achieved stable disease (SD), while the rest had progressive disease (PD), evaluated at the end of the first treatment cycle. Among the six patients with SD, one patient with pulmonary spindle cell carcinoma in the 1×10^7 PFU cohort had progression-free survival (PFS) for 138 days, and one patient with dedifferentiated liposarcoma in the 6.0×10^8 PFU cohort had a PFS for 206 days. One patient with nasopharynx cancer in the 8.0×10^8 PFU cohort achieved a partial response (PR) after four treatment cycles. No DLTs occurred during the observation period of this study. The most commonly treatment-related adverse events (TRAE) were fever and anemia, which were reported as grade 1-2 events in eleven patients (11/13, 84.6%) and six patients (6/13, 46.2%), respectively. The only grade 3 event was decreased lymphocyte count in one patient in the 6.0×10^8 PFU cohort. FACS analysis found a decrease in T cells and natural killer (NK) cells in the peripheral blood in all patients on the day following hV01 administration, and later, the levels of T cells and NK cells gradually rebounded. Notably, four patients had significantly higher (more than doubled or tripled) levels of NK cells compared to their baseline on day 15 after the hV01 regimen. **Conclusions:** Single-dosing of hV01 per treatment cycle was well tolerated and safe. hV01 i.t. injection demonstrated primary efficacy in patients with advanced tumors. The data support further study of multiple-dosing regimens and future trials evaluating the benefits of combining hV01 with other antitumor therapies. Clinical trial information: NCT05914376. Research Sponsor: Hangzhou ConVerd Co., Ltd.

2571 **Poster Session**

Influence of salmonella-IL2 in combination with FOLFIRINOX on overall and progression-free survival in stage IV metastatic pancreatic cancer. First Author: Daniel Saltzman, Salspera Inc, Oakdale, MN

Background: Salmonella-IL2 is an attenuated Salmonella Typhimurium strain carrying the human gene for IL-2. When orally administered, the bacterium colonizes tumors and locally releases IL-2, triggering immunologically-mediated tumor cell killing without untoward side effects. Salmonella-IL2 was tested in a phase 2 clinical trial in which patients with stage IV metastatic pancreatic cancer were treated with standard of care chemotherapy (SOC) combined with Salmonella-IL2. **Methods:** A Health Canada and local IRB approved, non-randomized, two-arm human study evaluated the combination of Salmonella-IL2 with standard of care (SOC) chemotherapy; Arm One patients received Salmonella-IL2 plus FOLFIRINOX (FFX). Arm Two patients received Salmonella-IL2 plus Gemcitabine/nab-Paclitaxel (GEM/nabP). Overall survival (OS), progression-free survival (PFS), safety, and biomarker data in each arm were compared to corresponding values for reference patients (SOC Controls) receiving care at the study site in the four years preceding the clinical trial (2016 to 2020). Four patients with stage IV pancreatic cancer were treated via Salspera's Expanded Access Program (EAP) using the Arm One regimen. **Results:** In total, 34 patients (30 in the trial, 4 via EAP) were enrolled: 26 received Salmonella-IL2 with FOLFIRINOX (average age 58.7 years, range 32-74, 54% born female) and eight received Salmonella-IL2 with GEM/NabP (average age 68 years, range 56-82, 54% born female). SOC Control patients comprised 37 administered FOLFIRINOX (average age 58 years; range 33-75 years; 46% born female) and 31 given GEM/nabP (average age 65.1 years; range 45-84 years; 42% born female). Patients receiving more than five doses of Salmonella-IL2 with FOLFIRINOX (n = 20) had a mPFS of 15 months vs. 5.8 months in control patients who had received only FOLFIRNOX ($p < 0.0001$, 95% CI, HR 0.3, Concordance Index 0.64). For those same compared cohorts, the mOS was 20.3 months vs. 11.5 months (p = 0.07, 95% CI. HR 0.59, Concordance Index 0.59). Only eight patients were enrolled in the GEM/NabP Arm thus limiting useful conclusions. Overall, 41 serious adverse events were noted and attributed to SOC chemotherapy agents but none to Salmonella-IL2. **Conclusions:** Addition of Salmonella-IL2 to FOLFIRINOX for treating stage IV pancreatic cancer is associated with increased mPFS and mOS. A multicenter, randomized, phase III trial is warranted. Clinical trial information: NCT04589234. Research Sponsor: None.

2572 **Poster Session**

Initial safety and efficacy results from a first-in-human, phase 1/2 study of SAR445877, an anti-PD-1/IL-15 fusion protein, for patients with advanced solid tumors. First Author: Aung Naing, The University of Texas MD Anderson Cancer Center, Houston, TX

Background: SAR445877 is a fusion protein of an PD-1 antibody combined with a detuned IL-15, designed to selectively expand and activate CD8+ T and NK cells expressing both PD-1 and IL-2/15R$\beta\gamma$. Preclinical studies demonstrated the efficacy of SAR445877 in neoplastic models. Here, we present initial safety and efficacy observations from a first-in-human, dose escalation of SAR445877 monotherapy in patients (pts) with advanced solid tumors. **Methods:** This open-label, multicenter, Phase 1/2 study in adult pts with any type of measurable, advanced unresectable or metastatic solid tumors (NCT05584670) comprised two parts: dose escalation (Part 1) and dose expansion (Part 2). In Part 1, SAR445877 was administered intravenously at two dosing schedules (Q2W and QW). Pts with advanced solid tumors that do not typically respond or were resistant/refractory to immune checkpoint inhibitors (ICI), and with at least 1 measurable lesion per RECIST 1.1, were eligible. Tumor biopsy was performed at baseline and on treatment. The primary objective for Part 1 was safety. Secondary objectives included efficacy, pharmacokinetics, pharmacodynamics, and immunogenicity. **Results:** Thirty-two pts (Q2W) and 17 pts (QW), respectively, were enrolled. Median lines of prior therapy were 3 for both schedules. The Q2W schedule was tested at 6 dose levels (DLs) and QW schedule at 3 DLs. Median exposure to SAR445877 was around 9 weeks (Q2W range: 2–55 weeks; QW range: 1–46 weeks). All pts reported at least one treatment-emergent adverse event (TEAE). Treatment-related AEs (TRAEs) were reported in 47 pts (Grade $\geq$3: 12 pts [Q2W]; Grade $\geq$3: 5 pts [QW]). Most common TRAE was cytokine release syndrome (CRS), which was mainly Grade 1 or 2. Six pts discontinued treatment due to any TEAEs. DLTs occurred in 4 pts in the Q2W cohort (n = 1 each metabolic acidosis, pneumonia, hyperbilirubinemia, and GI hemorrhage) and in 2 pts in the QW cohort (both CRS). Serious TEAEs were reported in 23 pts (Q2W) and 7 pts (QW). All toxicities were manageable/reversible, and no TEAEs leading to death were observed. Confirmed partial response was reported in 5 pts (Q2W) and in 2 pts (QW) bearing melanoma, CRC, SCC of the scalp, penile cancer, adnexal carcinoma, urothelial carcinoma, and myxofibrosarcoma, with benefits lasting $>$ 1 year. Five of the 7 pts had progressed on prior immunotherapy. Stable disease $\geq$ 6 months was observed in 3 pts (Q2W) and 3 pts (QW). Antidrug antibodies (ADAs), detected in 23 pts (Q2W) and 13 pts (QW), did not correlate with clinical benefit or toxicity. A trend of dose dependent increase of cytokine (IFNγ, TNFα, IL-6, IL-8, IL-10) and chemokine (CCL2, CXCL10, MIP1α, MIP1ß) release were detected at both dosing schedules. **Conclusions:** SAR445877 monotherapy demonstrated a tolerable safety profile and promising antitumor activity in pts with advanced solid tumors unresponsive or resistant to ICI. Clinical trial information: NCT05584670. Research Sponsor: Sanofi.

2573 **Poster Session**

SLAMF8 as a potential therapeutic target for modulating tumor-associated macrophages in colorectal cancer. First Author: Han Xingzhi, The Comprehensive Cancer Center of Drum Tower Hospital, The Affiliated Hospital of Nanjing University Medical School, Nanjing, China

Background: Reprogramming or repolarizing tumor-associated macrophages (TAMs) has emerged as a novel strategy in tumor immunotherapy, leveraging their remarkable plasticity. Our previous studies have demonstrated that SLAMF8, predominantly expressed in macrophages, is a promising biomarker for predicting the efficacy of immune checkpoint inhibitor (ICI) therapy in colorectal cancer (CRC). This study aims to elucidate further the regulatory role of SLAMF8 in TAMs and its influence on the tumor immune microenvironment. **Methods:** In vitro, M2 macrophage and TAM models were established to investigate the regulatory role of SLAMF8 in macrophage immunophenotypic transition and its impact on CD8+ T cell function using qRT-PCR, flow cytometry, and co-culture assays. Additionally, pathway enrichment analysis of RNA-seq data and western blotting were conducted to elucidate the underlying molecular mechanisms. In vivo, SLAMF8-specific small interfering RNA (siSLAMF8) was utilized to inhibit SLAMF8 expression in subcutaneous colorectal cancer (CRC) tumor models. Subsequent observations included tumor growth monitoring and analysis of immune cell infiltration via flow cytometry. Furthermore, two subcutaneous tumor models, one sensitive and one resistant to PD-1 therapy, were constructed to explore potential synergistic effects between SLAMF8 inhibition and anti-PD-1 treatment. **Results:** In vitro studies reveal that SLAMF8 facilitates the polarization of macrophages toward the M2 phenotype, contributing to the immunosuppressive characteristics of TAMs and dysfunction of CD8+ T cells. Inhibiting SLAMF8 in vivo significantly delayed colorectal cancer (CRC) progression. Flow cytometry analysis confirmed that the infiltration of anti-tumor TAMs (CD86+ F4/80+) and cytotoxic CD8+ T cells (IFNγ+ GZMB+ CD8+ T cells) was augmented, while the infiltration of pro-tumor TAMs (CD206+ F4/80+) and exhausted CD8+ T cells (PD1+ LAG3+ CD8+ T cells) was reduced in tumors treated with SLAMF8-specific small interfering RNA (siSLAMF8). Additionally, targeting SLAMF8 enhances the efficacy of anti-PD-1 therapy. Mechanistically, Western blotting experiments confirmed that the phosphorylation levels of key molecules in the PI3K/AKT and JAK/STAT3 signaling pathways were significantly increased in SLAMF8-overexpressing macrophages. **Conclusions:** Inhibition of SLAMF8 delays tumor growth, enhances the sensitization to ICI therapy, and reverses the immunosuppressive microenvironment by modulating TAMs via the PI3K/AKT and JAK/STAT3 pathways in CRC. These findings reveal the potential of SLAMF8 as a therapeutic target for immunotherapy focused on TAMs. Research Sponsor: National Natural Science Foundation of China; 82303970.

2574 **Poster Session**

Preclinical development of GNTbm-38, a novel class I histone deacetylase inhibitor, while combined with anti-VEGFR TKI or anti-PD-1 Ab: Assessment of immune activation and immune memory in cancer immunotherapy. First Author: Jia-Shiong Chen, New Drug Research and Development Center, Great Novel Therapeutics Biotech & Medicals Corporation (GNTbm), Taipei City, Taiwan

Background: Several clinical trials explored ICI-based combinations in MSS mCRC patients, and the promising outcomes are lacking. Histone deacetylase inhibitors (HDACis) for cancer therapy may boost antitumor immune activity, reduce immunosuppressive cells, and play a crucial role in controlling tumor progression. Therefore, rational drug combinations, containing class I HDACi or other immune-modulating drugs, may provide opportunities in immunotherapy. **Methods:** The activities of GMTbm-38 were assessed in vitro, including H3 acetylation and cancer cell growth inhibition, etc. The murine colon cancer CT-26 model was used to test antitumor efficacy in wild type and transgenic humanized PD1/PD-L1 mice. GNTbm-38 was combined with an anti-VEGFR TKI or murine/human PD1 antibody to test the antitumor synergistic effect. RNA-seq, flow cytometry, and IHC were performed to illustrate the potential mechanisms. **Results:** GNTbm-38 induced histone 3 acetylation and inhibited the cell growth of varieties of human cancer cells. By using CT-26 model, GNTbm-38 showed a superior efficacy profile in WT mice compared to immune-deficient mice. The antitumor activity related to induced immune activation and immune memory was dependent on $CD8^+$ T cell activation. Treatment with GNTbm-38 showed an increased number of intratumoral $CD8^+$ CTLs, a decreased number of MDSCs, and induced normalization of tumor vessels. GNTbm-38 substantially induced the expression of IFN-γ response genes and enhanced antigen processing and presentation signatures. GNTbm-38 acts as a TME reprogramming regulator in immunotherapy. When combined with TKI, GNTbm-38 significantly improved tumor response rate and survival rate through synergistic effect by normalizing tumor vessels, increasing tumor antigen presentation, increasing activated $CD8^+$ T cell infiltration into tumors, inducing memory T cell persistence, and inhibiting mobilization of immunosuppressive cells into tumors. Treatment with GNTbm-38 plus anti-PD-1 Ab in the CT-26 model showed greatly improved tumor response rate and survival rate with a strong synergistic effect. Furthermore, in B-hPD-1/hPD-L1 mice (humanized model) subcutaneously injected with B-hPD-L1 CT-26 cells, treatment of pembrolizumab and GNTbm-38 resulted in a 46.5% inhibition on tumor growth. Therefore, our data provided a strong rationale to explore the combination of GNTbm-38 with anti-VEGF TKI with or without ICI. **Conclusions:** Collectively, our data show that GNTbm-38 exhibits markedly superior pharmacokinetics, tolerability, and efficacy in animal models. GNTm-38 has been shown to display powerful induction of immune activation and immune memory in combination therapy with TKI/ICI against colon CT-26 cold tumor. Research Sponsor: Great Novel Therapeutics Biotech & Medicals Corporation (GNTbm).

2575 **Poster Session**

Inhaled KB707, a novel HSV-based immunotherapy, as a monotherapy in patients with advanced solid tumor malignancies affecting the lungs: Efficacy and safety results from a phase 1/2 study. First Author: Wen Wee Ma, Cleveland Clinic Taussig Cancer Institute, Cleveland, OH

Background: The development of potent anti-tumor cytokines has been hindered by the systemic toxicity of intravenous administration. KB707 is a novel gene therapy designed to deliver high doses of cytokines to the local tumor microenvironment. The agent is a replication-defective herpes simplex virus type 1 (HSV-1)-based vector engineered to deliver human interleukin (IL)-12 and IL-2 with complementary anti-tumor effects. This replication-defective vector platform enables repeated dosing without significant toxicity or clinically relevant immunogenicity while allowing for localized, sustained IL-12 and IL-2 delivery to induce both innate and adaptive anti-tumor immunity. This study evaluates whether KB707 administered by inhalation will deliver efficacious dose to the lung while minimizing systemic exposure in advanced solid tumor patients with predominantly lung disease. **Methods:** KB707-02 is a Phase 1/2, open-label, multicenter, dose escalation (3+3 design) and expansion study of inhaled KB707 (NCT06228326). Eligible patients (pts) with at least one measurable lung lesion at screening and histological confirmation of advanced solid tumor malignancy in the lungs received nebulized KB707 once weekly for up to 3 weeks followed by treatment every 3 weeks. The primary objective is to assess safety and tolerability, with a secondary objective to evaluate preliminary efficacy per RECIST 1.1. **Results:** As of 08 Jan 2025, a total of 39 pts were enrolled and received at least one dose of inhaled KB707. Monotherapy dose escalation and expansion was completed. The doses evaluated were 10^8 and 10^9 PFU and the maximum tolerated dose (MTD) was not reached. Treatment-emergent adverse events have been consistent with known adverse event profiles of IL-2 and IL-12. The majority of treatment-related adverse events have been mild to moderate in severity and transient, with no Grade 4 or 5 adverse events observed. The 11 response-evaluable NSCLC pts were of advanced age (median 71 [54-77] years old) and heavily treated (4 median lines of prior therapies; all received at least 1 line of prior immunotherapy). The ORR was 27% (3/11) and DCR was 73% (8/11) with 7 out of 11 pts remaining on study. The response rate of the target lesions in the lungs was 36%. The median duration of response was not reached; treatment duration ranged from 10.3 to 33.3 weeks. **Conclusions:** KB707 administered by inhalation was safe and well tolerated. The MTD was not reached, and the monotherapy recommended Phase 2 dose is 10^9 PFU. Single agent anti-tumor effects were observed, including in heavily treated NSCLC patients. The study has been expanded to evaluate the combination of inhaled KB707 plus pembrolizumab, with or without chemotherapy, in advanced NSCLC pts. Enrollment in these combination expansion cohorts is ongoing. Clinical trial information: NCT06228326. Research Sponsor: Krystal Biotech Inc.

2576 **Poster Session**

A generative model for the design of novel inhibitors targeting the PD-1/PD-L1 pathway. First Author: Juan Velasco, Yale University, New Haven, CT

Background: The programmed cell death-1/programmed cell death ligand-1 (PD-1/PD-L1) signaling pathway plays a pivotal role in tumor immunosuppression. However, the design of de novo molecules with precise pharmacological and molecular properties remains a resource-intensive and financially demanding endeavor. It is hypothesized that generative models trained on molecular graph encodings can design novel inhibitors targeting the PD-1/PD-L1 pathway. Objective: This study aims to develop a generative model capable of designing novel, orally bioavailable inhibitors of the PD-1/PD-L1 pathway. **Methods:** A large language model was pre-trained on 1 million chemical structures derived from the ChEMBL database. Each structure was represented using the Simplified Molecular Input Line Entry System (SMILES) strings, which were further tokenized into discrete atomic and functional group-level tokens. The model employs an Average-Stochastic Gradient Descent Weight-Dropped Long Short-Term Memory (AWD-LSTM) architecture. Transfer learning was applied to fine-tune the pre-trained language model on the target chemical structures, enabling domain-specific adaptation for the desired application space. **Results:** The model demonstrated robust performance in generating chemically valid, unique, and novel inhibitors targeting the PD-1/PD-L1 pathway. It achieved a validity rate of 97%, a uniqueness rate of 96%, a novelty rate of 95%, and a diversity score of 76.04%. Additionally, the generated molecules exhibited favorable physicochemical properties, including a logarithm of the partition coefficient (LogP) of 4.52, atopological polar surface area (TPSA) of 113.06 Angstrom squared, an average of 9.62 rotatable bonds, 2.77 hydrogen bond donors, and 6.79 hydrogen bond acceptors. **Conclusions:** A generative model was developed to design novel, orally bioavailable inhibitors of the PD-1/PD-L1 pathway. This approach provides an efficient and automated tool for designing de novo molecules with precise molecular and pharmacological properties, potentially accelerating drug discovery in immuno-oncology. Research Sponsor: None.

2577 **Poster Session**

Completed phase 1a dose escalation study of the first oral ENPP1 inhibitor RBS2418 immunotherapy in subjects with metastatic solid tumors. First Author: Thomas Urban Marron, Division of Hematology and Medical Oncology, Tisch Cancer Institute, Icahn School of Medicine at Mount Sinai, New York, NY

Background: ENPP1 clears cGAMP and ATP in the tumor microenvironment (TME). Its expression is associated with poor prognosis in cancer and development of metastases. ENPP1 inhibition can protect cGAMP and ATP from hydrolysis and reduce adenosine levels in the TME. These immune modulators are known to activate APCs and increase T-cell infiltration, promoting anticancer immunity. RBS2418 is a potent and selective oral first-in-class inhibitor of ENPP1. In this open-label, multi-site Phase 1a/b study, safety and efficacy of RBS2418 is being evaluated as monotherapy and in combination with pembrolizumab in advanced/metastatic solid tumors. **Methods:** The phase 1a dose escalation part comprised 100, 200, 400 and 800 mg BID dose levels of RBS2418 alone or in combination with pembrolizumab (200 mg IV q3w) in patients who have failed all approved treatments including immunotherapy using a 3+3 study design. Study objectives were to evaluate safety, pharmacokinetics (PK), pharmacodynamics (PD), and clinical outcomes. Tumor and blood samples were collected to determine PK/PD and immune profiles using LC/MS, IF, IHC, TCR and RNAseq analyses. **Results:** Dose escalation is complete, andRBS2418 was safe and well tolerated at all dose levels with no DLTs (n = 24). Treatment durations range from 1 to 15 months to date, and no treatment-related grade 3 adverse effects (TRAEs) or serious AEs (SAEs) have been observed. A total of 21 grade 1 or grade 2 TRAEs were reported in 9 (37.5%) subjects; the most common TRAE was grade 1 fatigue. Median plasma concentrations of RBS2418 increased in a dose-proportional manner. Plasma and tumor concentrations of RBS2418 were maintained above the ENPP1 inhibition EC90 level in all patients and at all dose levels tested. Of 19 patients with adequate baseline tissue, pre-treatment ENPP1 and cGAS co-expression (EG+ phenotype, n = 8) in tumors correlated with RBS2418 treatment-associated immune activation and significantly improved progression-free-survival (PFS) as compared to EG- phenotype at baseline (n = 11). A switch from “cold” tumor to “hot” tumor phenotype was consistently observed in EG+ subjects. Disease control rate (DCR) was 75% (6/8) in EG+ and 9% (1/11) in EG- subjects. **Conclusions:** The Ph1a dose escalation study with oral RBS2418 alone, and with pembrolizumab has been completed. All doses were safe and well tolerated with no grade 3 TRAEs, SAEs or DLTs. RBS2418 plasma concentrations enabling full cGAMP protection was observed in all patients at all dose levels. Immune activation and clinical benefits strongly correlated with EG+ phenotype. RBS2418 achieved Phase 1a goals of safety, PK, PD, and target engagement and showed significant treatment benefits in advanced metastatic cancer patients. The results support further development of RBS2418. Phase 1b dose expansion is in progress and the first Phase 2a study has been initiated for the treatment of mCRC. Clinical trial information: NCT05270213. Research Sponsor: None.

2578 **Poster Session**

Deep learning—powered H&E whole-slide image analysis of endothelial cells to characterize tumor vascular environment and correlate treatment outcome to immunotherapy. First Author: Seungeun Lee, Lunit Inc., Seoul, South Korea

Background: Beyond their vascular function, endothelial cells (ECs) regulate tumor growth through recently described angiocrine signaling, influencing cancer progression and treatment outcomes. Here, we applied a deep learning model, which we validated using spatial transcriptomics data, to a pan-cancer dataset to analyze the EC distribution associated with the response to immuno-oncology (IO) treatments. **Methods:** An AI-powered H&E analyzer, Lunit SCOPE IO, quantifies tumor microenvironment EC density and tumor-infiltrating lymphocytes (TILs) density in cancer epithelium and stroma. We validated AI-powered cell type prediction by evaluating cell-specific gene expression through spatial transcriptomics (10x Xenium). 7,467 pan-carcinoma samples from The Cancer Genome Atlas (TCGA) were analyzed for EC distribution and overall survival (OS). From a previously described multi-center, multi-national pan-cancer cohort (Pan-IO, Shen et al JITC 2024), 1,654 patients were analyzed for IO treatment response. **Results:** We validated our AI prediction of cell types by demonstrating consistency with known cardinal gene expressions from spatial transcriptomic results, where 77.5% of AI-predicted endothelial cells (ECs) expressed VEGFR2 (compared to 6.9% in tumor cells (TCs)), while VEGFA expression was 2.8 times higher in TCs. Consistent with previous studies, EC density was highest in RCC and HCC, while lowest in pancreatic adenocarcinoma, melanoma, and cholangiocarcinoma. While EC and TIL density were not correlated pan-cancer ($r = 0.08$), exceptions were head and neck cancer ($r = 0.45$, $p < 0.001$) and pancreatic cancer ($r = 0.44$, $p < 0.001$). In the TCGA cohort, the high EC density was associated with prolonged OS (HR 0.84, $p < 0.001$). In contrast, within the Pan-IO cohort (HR 1.26, $p < 0.001$) and its lung cancer subgroup (HR 1.26, $p < 0.001$) high EC density was associated with shorter progression-free survival (PFS) on treatment with IO monotherapy. Moreover, the predictive impact of EC density varied by TIL status. In the Pan-IO cohort, EC density predicted PFS in both TIL-high (HR 1.40, $p < 0.001$) and TIL-low cancers (HR 1.33, $p < 0.001$). Among four groups divided by median values, the EC-low and TIL-high group showed the longest PFS (median PFS of EC/TIL high/low: 2.5m, high/high: 3.2m, low/low: 3.6m, low/high: 5.6m, $p < 0.001$). **Conclusions:** EC distribution varied among cancer types, and importantly high EC content strongly correlated with poor IO monotherapy response, including NSCLC. These findings support exploring immunotherapy combination strategies that include anti-endothelial approaches, which could encompass the emerging class of PD-1/VEGFR bispecifics, for tumors with high EC content. Early evidence was observed for this for HCC (Chon et al ASCO GI 2024), with a hazard ratio of 0.62 for high EC HCC for atezolizumab/bevacizumab. Research Sponsor: None.

2580 **Poster Session**

SECN-15: A novel treatment option for patients with checkpoint inhibitor–resistant tumors by targeting Neuropilin-1 with antisense oligonucleotides. First Author: André Maaske, Secarna Pharmaceuticals, Planegg-Martinsried, Germany

Background: SECN-15 is a high-affinity antisense oligonucleotide (ASO) targeting Neuropilin-1 (NRP1), a transmembrane protein that exerts a variety of protumorigenic functions by interacting with various receptors and ligands. NRP1 contributes to an immunosuppressive microenvironment, tumor growth, metastasis, and neoangiogenesis. The recent success of bispecific antibodies targeting PD-1/PD-L1 and VEGF such as ivonescimab has highlighted the potential of combining checkpoint inhibitors with anti-angiogenic approaches. Consequently, NRP1 represents a highly attractive target for treating patients with tumors that are resistant to or insufficiently responsive to checkpoint inhibitor therapies, such as gastric (GC) and breast cancer, where high NRP1 expression correlates with poor prognosis. **Methods:** NRP1-specific locked nucleic acid (LNA)-modified ASOs were identified using our OligoCreator platform. We assessed in vivo anti-tumor efficacy after systemic administration in various mouse tumor models as monotherapy and in combination with checkpoint inhibitors. Target downregulation was analyzed in tissues and in plasma by measuring soluble NRP1. Cell composition and transcriptome changes in tumors were analyzed using flow cytometry and RNA sequencing. Exaggerated pharmacology was investigated in a 28 non-GLP tolerability study in mice. In silico analyses of patient transcriptomics data were performed to prioritize indications for the upcoming Phase I/II clinical trial. **Results:** Systemic administration of NRP1-specific ASOs resulted in robust knockdown in tumors across various cell types, including macrophages and T cells. Soluble NRP1 levels were reduced in treated animals, serving as a target engagement biomarker. Tumor growth was delayed in the monotherapy setting, with several animals showing complete responses. Combining NRP1-specific ASOs with checkpoint inhibitors enhanced efficacy in models where checkpoint inhibitors alone had limited activity. Transcriptomic analysis showed upregulation of inflammatory genes and downregulation of extracellular matrix organization genes. No adverse effects were observed from persistent NRP1 downregulation in non-tumor-bearing mice. In silico analyses revealed that NRP1 expression is negatively associated with survival and increases in advanced GC stages. GC was selected as one of the priority indications for the upcoming Phase I/II clinical trial to investigate SECN-15's safety and efficacy as monotherapy and in combination with PD-1 blocking antibodies. **Conclusions:** Targeting NRP1 with ASOs is a promising therapeutic strategy for solid cancers. Combining NRP1 ASOs with ICIs significantly enhances anti-tumor efficacy, potentially overcoming current ICI therapy limitations. IND-enabling studies are underway to advance SECN-15 into clinical development. Research Sponsor: None.

2581 **Poster Session**

Utilizing targeted intra-tumoral hyperthermia as an immunotherapy in immunogenically 'cold' tumor models. First Author: Carman Giacomantonio, Dalhousie University, Halifax, NS, Canada

Background: Hyperthermia is an established adjunct in multimodal cancer treatments, with mechanisms including cell death, immune modulation, and vascular changes. Traditional hyperthermia applications are resource-intensive and often associated with patient morbidity, limiting their clinical accessibility. Gold nanorods (GNRs) offer a precise, minimally invasive alternative by leveraging near-infrared (NIR) light to deliver targeted hyperthermia therapy (THT). THT induces controlled tumor heating, promoting immunogenic cell death (ICD) and modulating the tumor microenvironment (TME) to enhance immune engagement. This study explores the synergistic potential of GNR-mediated THT with immunotherapies in immunogenically 'cold' tumors to achieve durable anti-tumor immunity. **Methods:** GNRs from Sona Nanotech Inc.™ were intratumorally injected and activated using NIR light to induce mild hyperthermia (42–48°C) for 5 minutes. Tumor responses were analyzed for cell death pathways and immune modulation. The immunogenic effects of THT were assessed alone and in combination with intratumoral interleukin-2 (i.t. IL-2) or systemic PD-1 immune checkpoint blockade. Immune cell infiltration, gene expression changes, and tumor growth kinetics were evaluated. **Results:** THT reduced tumor burden through cell death mechanisms, including upregulated ICD marked by calreticulin exposure within 48 hours. By 48 hours, CD45+ immune cell levels were increased, including increased levels of immunosuppressive M2 macrophages. While THT led to innate immune cell stimulations highlighted by gene expression upregulation in the STING cGAS pathway and enhanced M1 and dendritic cell levels, tumor regrowth was observed within six days post-treatment. To enhance THT's immunogenic effects, the therapy was combined with intratumoral interleukin-2 (i.t. IL-2) or systemic PD-1 immune checkpoint blockade. Sequential administration of i.t. IL-2 post-THT induced robust CD8+ T-cell infiltration and led to sustained tumor regression in both treated and distant tumors, accompanied by the emergence of memory T cells. However, IL-2-induced immunosuppressive T-reg populations were also sustained to tumor endpoint suggesting that therapy could be further enhanced. Additionally, PD-1 expression, which was upregulated in CD8+ T cells by THT, was targeted with systemic PD-1 inhibition, further augmenting immune engagement within the TME. **Conclusions:** These combinatory treatments demonstrated synergistic effects, promoting durable anti-tumor responses and immune memory. Collectively, GNR-mediated THT effectively reduces tumor burden and remodels the TME, potentiating systemic immunity and enhancing the impact of complementary immunotherapies. Research Sponsor: None.

2582 **Poster Session**

Employing novel pan-cancer targets for immunotherapy in leukemias and solid tumors. First Author: Ashley Varkey, Hackensack University Medical Center, Hackensack, NJ

Background: Acute myeloid leukemia (AML) and many solid tumors are difficult to treat. Tumor-associated protein targets that are the focus of cancer immunotherapy research are prone to on-target, off-tumor toxicity and antigen-negative relapse due to mutation or downregulation. Targeting cancer-specific markers less susceptible to resistance is key for safer therapies. Our research explores high mannose (Man 9) oligosaccharides and phosphatidylserine (PS) as non-protein targets. Man9 glycans are absent on healthy cells but are present in cancers like AML, breast, colon, and lung. PS, exposed during malignant transformation, is found on colon, prostate, and brain tumors. **Methods:** We have engineered trispecific T cell engagers (Man9/PS/CD3) to target Man9 and/or PS-positive cancers. We tested solid tumor cell lines (pancreatic, lung, colorectal) via flow cytometry and found that the dual affinity molecule (Man 9 x PS) had high binding to many solid tumors (Table 1). We assessed their efficacy *in vivo* and specificity using glycan microarray, and immunohistochemistry to confirm tumor specificity and predict favorable safety profiles. **Results:** Flow cytometry showed that our therapeutic molecules specifically bind to AML cells and various solid tumors while sparing healthy tissues. Glycan microarrays confirmed selective binding to abnormal glycans on cancer cells. Immunohistochemistry of FFPE tissues indicated tumor specificity and enrichment on cancer stem cells. *In vitro* studies (coculture of luciferase-transduced target cells with activated CD8+ T cells in the presence of absence of the T cell engager) demonstrated strong anti-leukemia activity against AML cell lines, with IC50 values of 5–10 pM. *In vivo* studies in human CD3 transgenic mice treated with intravenous doses of VTRU200 (Man9 x PS x CD3) showed significant therapeutic responses, based on *in vivo* bioluminescence imaging. **Conclusions:** Our data supports Man9 and PS as promising non-protein targets for pan-cancer immunotherapy. The dual targeting approach with T cell engagers reduces on-target, off-tumor toxicity and antigen-negative relapse, advancing a first-in-class Man9 x PS x CD3 trispecific T cell engager. We have also designed and validated a bispecific (Man9 x PS) chimeric antigen receptor (CAR) and research is ongoing for CAR-T therapy for pancreatic cancer. With IND-enabling studies underway, we aim to advance this breakthrough immunotherapy for AML and other cancers, targeting an IND submission within 18 months. Research Sponsor: Vitruviae; Alex's Lemonade Stand Foundation; Hyundai Hope on Wheels; National Cancer Institute.

Cell type	Man9/PS positivity (%)	Sample size
Mouse AML (cell line)	75-80	2
Human AML (cell line)	54-100	9
Human adult AML (primary)	35-98	8
Human pediatric AML (primary)	31-87	7
Human pediatric ALL (primary)	80-97	3
Human MM (cell line)	88-99.9	2
Human DLBCL (cell line)	56-93	3
Human pancreatic cancer (cell line)	46-95	3
Human colorectal cancer (cell line)	66-98	2
Human lung cancer (cell line)	82	1

2583 **Poster Session**

Prevalence of the HPV, EBV, and TTV viral RNA in the plasma of patients with solid and hematologic neoplasms and the detection of a specific immune signature. First Author: Gustavo Rivero, Tampa General Hospital, Tampa, FL

Background: Epstein—Barr virus (EBV) and human papillomavirus (HPV) are considered human oncoviruses. In contrast, the torque teno virus (TTV) is not associated with any disease but its detection in circulation is associated with the status of the immune system. In this study, we examine the prevalence of active EBV, HPV and TTV viral RNA in patients treated for solid tumors or hematologic neoplasms. In addition, we compared differential expression of selected immune and inflammatory biomarkers between Virus positive (V+) and Virus negative (V-) cases using peripheral blood cell-free RNA (cfRNA). **Methods:** cfRNA was extracted from the peripheral blood of 581patients with a diagnosis of hematologic neoplasms and 558 patients with solid tumor. cfRNA was sequenced by NGS using a targeted RNA panel of 1600 genes and the viral RNA of TTV, EBV and HPV. Two thirds of the samples were used for training and one third for testing machine learning (ML) system (Bayesian/Random Forest) and exploring the presence of specific inflammatory profiles distinguishing V+ from V- patients. **Results:** RNA testing was selected to ensure that only active and proliferating viruses were detected. We detected TTV in 52/1139 (4.6%), EBV in 251/1139 (22%), and HPV in 68/1139 (6.0%). TTV with EBV codetection was observed in 11 samples (1%), and with HPV in 4 patients (0.4%). Co-detection of EBV with HPV was observed in 13 patients (1.1%). Using 90 biomarkers in ML algorithm can reliably distinguish V+ from V- with AUC of 0.725 (CI: 0.658-0.791) in the testing set. Significantly higher levels of B-cell markers are noted in V+ patients. PD-L1 mRNA was significantly ($P < 0.001$) higher in V+ patients, which suggests that these patients may be more responsive to checkpoint immune therapy. CD70 is also detected at high level in V+ patients ($P < 0.0001$). Upon comparing between the V+ groups (TTV, EBV, and HPV), there was no statistical difference between the three groups after adjusting for multiple testing. However, some difference in cytokine levels was noted between TTV-positive patients and HPV-positive patients. CD36, IFNA2 and IL17A were higher in TTV-positive cases as compared with HPV-positive cases (P-value 0.0003, 0.005 and 0.004, respectively). **Conclusions:** Globally, detectable active viruses in plasma of patients with cancer is relatively high (29%) and this detection is associated with a specific immune/inflammatory "activation" signature characterized by transcriptomic upregulation of PD-L1 and CD70 and increase in B-cells. There is no specific signature that distinguishes between the V+ subgroups [TTV vs EBV vs HPV]. However, transcriptionally, CD36, IFNA2 and IL17A upregulation distinguished TTV+ and HPV+ cases, a phenomenon that may indicate HPV ability to initiate an immunosuppressive tumor microenvironment. Research Sponsor: None.

2584 **Poster Session**

Phase 1 trial of HCB101, a novel Fc-based anti-SIRPα-CD47 fusion protein, in subjects with advanced cancers. First Author: Lucy Yan, Hanchor Biopharma Inc., Taipei City 114, Taiwan

Background: CD47-targeting agents face challenges, including "on-target, off-tumor" toxicities affecting red blood cells, limited efficacy, and manufacturing complexities. Clinical holds and discontinued trials highlight these difficulties. These issues have constrained their therapeutic potential and broadened the need for better solutions. HCB101 is an engineered human SIRPα fused to human IgG4 crystallizable fragment (Fc) protein developed using the proprietary FBDB platform, blocks the signal of the SIRPα-CD47 pathway, enhancing macrophage-mediated phagocytosis. Preclinical studies show HCB101's potent antitumor activity across solid tumors and hematological malignancies. HCB101's safety profile in repeat-dose cynomolgus monkey toxicity studies revealed acceptable red blood cell or platelet abnormalities, supporting its potential as a best-of-the-kind SIRPα-CD47 directed immunotherapy. **Methods:** This Phase 1, open-label, dose-escalation trial evaluates HCB101's safety, tolerability, pharmacokinetics, pharmacodynamics, and preliminary antitumor activity in advanced solid tumors or non-Hodgkin lymphoma (NHL) in the US, Taiwan, and mainland China. Eligible adults have treatment-refractory cancers, an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1, and adequate organ function. The 3+3 dose-escalation Bayesian Optimal Interval (BOIN) design assesses dose-limiting toxicities (DLTs) in the first 28-day cycle. Secondary endpoints include objective response rate (ORR), duration of response, and progression-free survival. Exploratory endpoints include CD47 receptor occupancy (RO), correlating response, and immune cell infiltration (NCT05892718). **Results:** 32 participants (median age 61 years; 74% male) enrolled across 7 escalating cohorts (0.08-5.12 mg/kg, QW). Patients had a median of 4 prior regimens. 68% had solid tumors, and 32% had NHLs. HCB101 was well tolerated, only 1 DLT reported at 2.56 mg/kg dose level (G3 platelet decrease). The most common treatment related AEs were anemia (17%), all grade 1or 2, that did not require blood transfusion or other treatments. HCB101 systemic exposure increased in a dose-dependent manner. Preliminary efficacy showed 29% stable disease (6 patients) in 21 evaluable patients, with 2 patients have SD $>$ 16 wks, and 1 patient has SD $>$ 23 wks. Doses $\geq$1.28 mg/kg achieved $\geq$90% CD47 RO in peripheral T cells. **Conclusions:** HCB101 demonstrated an acceptable safety profile and preliminary antitumor activity in heavily pretreated advanced cancer patients. These findings support its further clinical development, including expansion cohorts to evaluate efficacy in specific tumor types or in combination with other agents. Clinical trial information: NCT05892718. Research Sponsor: None.

2585 **Poster Session**

Role of p57 in cGAS-STING-mediated innate sensing and immunotherapy response in hepatocellular carcinoma. First Author: Shirong Zhang, The First Affiliated Hospital of Xi'an Jiaotong University, Xi'an, ShaanXi, China

Background: Hyperactivation of cell cycle programs in cancer cells suppresses the antitumor immune response. The endogenous cyclin-dependent kinase inhibitor p57 is an important tumor suppressor and a potential therapeutic target for hepatocellular carcinoma (HCC). However, the role of p57 in modulating antitumor immunity to HCC remains unclear. **Methods:** We examined p57 expression in HCC patient samples prior to treatment with immune checkpoint inhibitors (ICIs) through immunohistochemistry (IHC). Multiple mice tumor models were constructed to explore the role of p57 on the recruitment of $CD8^+$ T cells in the tumor immune microenvironment. Through performing transcriptome sequencing, we analyzed the differential genes and activation pathways induced by p57 overexpression; through Real-Time Quantitative Polymerase Chain Reaction (RT-qPCR), western blot (WB) , Enzyme-Linked Immunosorbent Assay (ELISA), IHC, immunofluorescence (IF) , Flow Cytometry (FCM) and other molecular experimental methods, we verified the molecular mechanism of increasing $CD8^+$ T infiltration and elevating PD-L1 caused by p57 overexpression; Through constructing mice model and giving different treatments, we explored the anti-tumor efficacy of p57 overexpression combining with ICIs. **Results:** We found that patients with p57 expression had a higher disease control rate, correlating with the number of tumor infiltration $CD8^+$ T cells. Using mouse models, we discovered that p57 promoted $CD8^+$ T cells infiltration and that $CD8^+$ T cells were required for p57 to function as a tumor growth suppressor. Furthermore, through RNA-sequencing analysis and the multiplex assay *in vitro* and *in vivo*, we found that p57 induced chromosomal instability and subsequently stimulates cGAS-STING-type I IFN signaling, leading to upregulation of the chemokines CCL5 and CXCL10, which promoted $CD8^+$ T cell infiltration into the tumor microenvironment. Meanwhile, p57 also elevated the expression of PD-L1 on the surface of HCC cells. Moreover, combining p57 overexpression with anti-PD-1 treatment synergistically inhibited tumor growth *in vivo*. **Conclusions:** Our studies demonstrated that p57 may serve as a new biomarker for ICIs efficacy and that increasing p57 expression is a potential therapeutic strategy for improving the efficacy of immunotherapy in HCC patients. Research Sponsor: National Natural Science Foundation of China.

2586 **Poster Session**

Phase 1 study of LB1410, a bivalent TIM-3/PD-1 bispecific antibody, in patients with advanced solid tumors or lymphoma. First Author: Jiajian Liu, L&L Biopharma Co. Ltd., Shanghai, China

Background: LB1410 is a recombinant humanized anti-PD-1/TIM-3 bispecific antibody (BsAb) developed by L&L Biopharma Co., Ltd. for patients (pts) resistant to or refractory to PD-1/PD-L1 treatments, showing superior T/DC cell activity and in vivo anti-tumor efficacy compared to a combination of TIM-3 and PD-1 antibodies in preclinical studies. Here, we report the dose escalation and dose expansion results of LB1410 as monotherapy in patients with advanced solid tumors (Keyplus-001). **Methods:** Eligible patients were $\geq$18 years old with ECOG PS 0-1 and advanced solid tumors. Dose cohorts ranged from 0.001 mg/kg to 20 mg/kg IV Q2W: 0.001 mg/kg-1 mg/kg in an accelerated titration design, and 3 mg/kg - 20 mg/kg using a traditional 3+3 design. Selected dose levels were expanded in patients with advanced clear cell renal cell carcinoma (ccRCC) and cervical cancer (CC). The primary objective was safety, including dose-limiting toxicities (DLTs). Secondary/exploratory objectives included efficacy, pharmacokinetics (PK), and immunogenicity. **Results:** As of January 15, 2025, a total of 79 patients received LB1410 at doses ranging from 0.001 mg/kg to 20 mg/kg as of January 15, 2025. The median age was 59 years, and 70% of patients were male. All enrolled patients had multiple organ metastases or multiple metastases in a single organ and were heavily pretreated with anti-tumor therapies. Of the patients, 76.9% (60/79) had solid tumors that had failed standard therapies and were resistant or refractory to anti-PD-1/PD-L1 treatments. Treatment-related adverse events (TRAEs) occurred in 63.3% of patients. The most common TRAEs ($\geq$10%) included anemia (24.1%), proteinuria (12.7%), increased alanine aminotransferase (11.4%), increased aspartate aminotransferase (11.4%), hyponatremia (10.1%), increased blood lactate dehydrogenase (10.1%), and weight loss (10.2%). Grade 3 TRAEs occurred in 7 patients, including 3 with hypokalemia, 2 with hypertension, 1 with hyponatremia, 1 with proteinuria, and 1 with pulmonary embolism. No dose-limiting toxicities (DLTs) were observed. On- treatment scan was available for 66 patients. The observed overall response rate (ORR) per RECIST 1.1 was 3/66 (4.5%), with 3 confirmed partial responses (PRs) in patients with ccRCC and CC. The disease control rate (DCR) was 45.5% (30/66). In patients with ccRCC, the ORR was 16.7% (1/6), and the DCR was 66.7% (4/6). In patients with CC, the ORR and DCR were both 66.7% (2/3). Of the 27 patients with stable disease, 3 had stable disease for nearly 12 months, and 2 of them are still receiving ongoing treatment in the study. **Conclusions:** LB1410 has a manageable safety profile and demonstrates potential efficacy at tolerable doses in heavily pretreated patients, particularly those with immune-oncology (IO)-refractory or resistant ccRCC and CC. Clinical trial information: NCT05357651. Research Sponsor: L&L Biopharma Co., Ltd., Shanghai, China.

2587 **Poster Session**

Effect of KROS 101, a small molecule GITR ligand agonist, on T effector cells, T reg cells and intratumoral CD8 T cell cytotoxicity. First Author: John S. Yu, Cedars-Sinai Medical Center, Los Angeles, CA

Background: A small molecule was identified that stabilizes the trimerization of the glucacorticoid-induced tumor necrosis factor receptor (GITR) ligand which then leads to the trimerization of GITR and magnified signaling of GITR. GITR signaling of T cells results in T effector cell expansion and T reg reduction. An antagonist to the GITR ligand was also indentified which stabilizes the GITR ligand dimer formation preventing trimerization. **Methods:** Binding of KROS 101 to the GITR ligand was assessed and the binding region of GITR ligand to KROS was determined with targeted deletion of GITR. T cell suppression studies were performed with T cell proliferation assays and T cell cytotoxicity assays with glioblastoma target cells using patient derived PBMCs. Double humanized GITR/GITRL mice bearing B16-F10-LUC2 tumors were treated with KROS 101 or controls. Tumor-infiltrating lymphocytes were analyzed by flow cytometry and tumors assessed. **Results:** KROS 101 agonist binds to GITRL with high affinity with a K_D of 340nM by Surface Plasmon resonance. T cell suppression assay showed KROS 101 had peak proliferative induction of T effector cells at 25 uM concentration to 52% increase in proliferation, and peak proliferation induction of T effector cells with 1:1 ratio of T reg cells at 50uM concentration to 80% increase in proliferation of T effectors. KROS 101 treated T cell show enhanced effetor function and selectively target glioblastoma and cancer stem cells in vitro. KROS 101 enhances tumor immune infiltration by Increasing CD3+ T Cells, CD8+ T Cells, and M1 Macrophages While Reducing Tregs and Myeloid Cells *in vivo*. KROS 101 enhances cytotoxicity by increasing IFNγ and TNFα While Reducing TIGIT and TIM3 in CD4+ and CD8+ T Cells I*n Vivo*. **Conclusions:** KROS 101 is a GITR ligand agonist that increases T cell proliferation and increased cytotoxicity and reduces the T reg population more effectively than TRX 518 which is a therapeutic GITR antibody that was in clinical trial. Research Sponsor: None.

2588 **Poster Session**

Machine learning–driven approaches for predicting T-cell–mediated immunity and beyond. First Author: Chongming Jiang, Terasaki Institute for Biomedical Innovation, Los Angeles, CA

Background: Recognition of peptides presented by the major histocompatibility complex (MHC) through the T cell receptor (TCR-pMHC) is crucial for T cell function, influencing disease conditions such as cancer, infections, and autoimmune disorders. Despite previous attempts, predictive models of TCR-pMHC specificity remain challenging. **Methods:** Inspired by recent breakthroughs in protein structure prediction achieved by deep neural networks, we explored structural modeling using AlphaFold 3 (AF3)-based AI-enabled computation as a potential avenue for predicting TCR epitope specificity. **Results:** We show that a specialized version of the neural network predictor AlphaFold can generate models of TCR-pMHC interactions, effectively distinguishing valid peptide epitopes from invalid ones with increasing accuracy. Strongly immunogenic epitopes could be identified and selected for vaccine development through in-silico high-throughput processes. Higher-affinity and specificity T cells could also be computationally designed to achieve improved efficacy and safety profiles for T cell therapy. An accurate TCR-pMHC prediction model is expected to significantly benefit T-cell-mediated immunotherapy and facilitate advanced drug design. **Conclusions:** Overall, precise prediction of T-cell immunogenicity holds substantial therapeutic potential, enabling the identification of peptide epitopes associated with tumors, infectious agents, and autoimmune diseases. Although much work remains before these predictions could achieve widespread practical utility, deep learning-based structural modeling represents a promising path toward the generalizable predictions of TCR-pMHC interactions and beyond. Research Sponsor: None.

2589 **Poster Session**

Phase 1 study of DK2^{10} (EGFR), a tumor-targeted IL2 x IL10 dual immunocytokine, in advanced cancer patients: Dose escalation, immune activation, and safety results. First Author: Alexander I. Spira, NEXT Oncology Virginia, Fairfax, VA

Background: IL-2 induces anti-tumor immunity and toxicity, predominantly vascular leak syndrome (VLS), leading to edema, hypotension, organ toxicity, and therapy-inhibiting regulatory T cell (Treg) accumulation. DK2^{10} (EGFR) couples wild-type IL-2 to a high affinity variant of EBV IL-10 via an scFv that binds to epidermal growth factor receptors. The IL-10 component was designed to block IL-2 mediated cytokine release syndrome (CRS) and VLS while retaining T cell activation and proliferation and limiting Treg expansion. We report the clinical and pharmacodynamic results from the dose escalation in the DEKA-1 phase 1 (NCT05704985) study. **Methods:** Eligible patients (pts) had advanced/metastatic tumors known to express EGFR, progressive disease on $\geq$1 lines of systemic treatment, and ECOG $\leq$1. DK2^{10} (EGFR) (2-16 mg; 0.025-0.5 mg/kg for an 80 kg subject) was self-administered subcutaneously 3 times per week in 21-day cycles following a BOIN design. Adverse events (AEs) including serious (SAEs) were evaluated using CTCAE version 5.0. Cytokines and anti-drug antibodies were monitored during the first cycle and every 3 cycles thereafter. RECIST 1.1 tumor responses were evaluated every 9 weeks. **Results:** 35 pts (14 RCC, 6 NSCLC, 9 CRC, 5 PDAC, 1 SCC) were enrolled. Median age was 63 yrs (range 35-80). Treatment-related AEs (TRAEs; any grade) in $\geq$ 10% pts were injection site reactions (63%), fever (40%), fatigue (31%), nausea (23%), anemia (17%), chills (17%), eosinophilia (14%), CRS (14%), diarrhea (11%); the majority were G1-2. G3 TRAEs included fatigue (n = 4), anemia (n = 3), syncope (n = 3) and single events of acute kidney injury, cellulitis, hypoalbuminemia, and lymphopenia. No DLTs were observed. While MTD was not exceeded, a dose proportional induction of IFNγ was observed through 8 mg but not at 16 mg. Therefore, higher doses were not explored, and a 12 mg dose level was introduced for dose optimization. No appreciable increase in IL-6, TNF-a, or IL-1β was seen other than 1 subject at 4 mg with G2 CRS and elevated IL-6. IFNγ and IL-5 were concomitantly induced proportional to dose level and reached saturation between levels 3 and 4, consistent with pK exposure of DK2^{10} (EGFR). Sustained IL-5 associated eosinophilia was observed and correlated with drug concentration but did not require intervention. IL-2 and IL-10 induction led to sustained elevation of IL-2Ra and IL-18, respectively. 33% of evaluable patients had a best ORR of SD. **Conclusions:** DK210 (EGFR) demonstrates strong IL-2 activity shown by IL-5 driven eosinophilia, shed IL-2Ra, T and NK cell proliferation and expansion but not Treg accumulation. These effects have been decoupled from IL-2 driven toxicity, confirming the hypothesis of the balancing effect of IL-10. These data support further evaluation in combination with T cell engagers, T cell therapeutics, and kinase inhibitors. Clinical trial information: NCT05704985. Research Sponsor: Deka Biosciences.

2590 **Poster Session**

PCT1:CO-STIM TCR T-cells to overcome the hostile tumor microenvironment and target triple-negative breast cancer. First Author: Dora Hammerl, Pan Cancer T, Rotterdam, Netherlands

Background: Adoptive T-cell therapy has demonstrated impressive efficacy in hematoligical cancers but the solid tumor micro-environment presents a unique challenge. However, recently TCR-T cell therapy has shown benefit in difficult-to-treat solid tumors and selection of specific tumor targets and control of the tumor micro-environment can unlock the broader potential of T cell therapy. Triple-negative breast cancer (TNBC) is a difficult-to-treat tumor as it lacks classical targets for hormone and antibody-based therapies. It harbors a highly immune-suppressive microenvironment and rarely responds to immune-checkpoint inhibitors. We sought to identify a novel target to make TNBC amenable for adoptive T-cell therapy with T-cell receptor (TCR)–engineered cells and applied a unique next-generation gene-engineering approach to make T-cells overcome the hostile microenvironment. **Methods:** (i) Discovery of TNBC-restricted target: We applied *in silico* analyses of $>$500 TNBC samples and $>$1,500 healthy tissues and validated findings with qRT-PCR and immune stainings of $>$300 TNBC samples as well as 40 healthy tissues. (ii) Discovery and selection of PCT1 TCR: We enriched ROPN1-specific TCRs from naïve repertoires and assessed specificity, sensitivity and performed preclinical safety studies. (iii) Development of TCR:CO-STIM technology to overcome immune suppression: we designed a panel of murine TCRs harboring different intracellular co-stimulatory domains, thereby providing additional stimulation to T cells aimed to overcome immune suppression in solid cancer. We tested their ability to extend anti-tumor durability in a murine melanoma model, performed comprehensive permutations to enable stable expression of fully human *TCR:CO:STIM* and applied it to multiple TCR specificities. **Results:** For TNBC, we identified that Ropporin (ROPN1), a protein expressed homogeneously in $>$90% of TNBC and persistent across disease stages but absent from healthy tissues, as an ideal target. We identified 13 clonal TCRs directed against 9 different ROPN1 epitopes. The lead TCR, termed *PCT1 TCR*, demonstrated high sensitivity and specificity towards ROPN1$^+$/HLA-A2$^+$ cell lines and patient-derived organoids in 3D. Our *TCR:CO-STIM* technology significantly improved duration of response in a murine model and improved T cell fitness. Notably, when repeatedly challenged with ROPN1$^+$/HLA-A2$^+$ TNBC cells, *PCT1:CO-STIM*, but not *PCT1* TCR T-cells, could resist up-regulation of T-cell exhaustion markers and retained tumor-killing capacity for 3-10 extra rounds of stimulation. Importantly, *PCT1:CO-STIM* did show any signs of tonic signaling nor crossreactivity nor alloreactivity towards any major HLA-I allele. **Conclusions:** *TCR:CO-STIM* technology has shown enhanced activity of a selective and specific TCR targeted at ROPN1 and we are progressing *PCT1:CO-STIM* to the clinic for the treatment of TNBC. Research Sponsor: None.

2591 **Poster Session**

First-in-human mRNA CAR therapy: Correlative biomarker analysis from the MT-302 phase 1 study targeting TROP2 in patients with advanced epithelial tumors. First Author: Charlotte Rose Lemech, Scientia Clinical Research, Randwick, Australia

Background: Outcomes for patients with epithelial cancers, including breast, lung and gastrointestinal tumors, remain poor particularly in advanced stages. MT-302, an mRNA-based chimeric antigen receptor (CAR) therapy, seeks to address this unmet need by reprogramming myeloid cells in vivo to recognize and kill TROP2-expressing tumors, recruit immune cells into tumor and induce systemic anti-tumor responses. Its CAR construct combines an anti-TROP2 scFv with truncated CD89 and becomes functionally active only upon association with FcRγ-expressing myeloid cells, ensuring precise immune engagement. Delivered as an off-the-shelf, repeatable intravenous treatment without the need for preconditioning, MT-302 overcomes the logistical and technical challenges of traditional cell and CAR therapies. MT-302 is being evaluated in a Phase 1, multicenter, open-label dose-escalation study (NCT05969041) in adults with advanced epithelial cancers expressing TROP2. Here, we present a correlative biomarker analysis from the first-in-human MT-302 study. **Methods:** Tumor biopsies and peripheral blood samples were collected pre- and post-dose. Biomarkers were evaluated utilizing advanced technologies including immunohistochemistry (IHC), Xenium and Hyperion imaging, flow cytometry, Chromium single-cell sequencing, T cell receptor sequencing and Meso Scale Discovery (MSD). These methods assessed TROP2 expression on cancer cells, TROP2 CAR expression within immune cells, systemic pharmacodynamic effects, immune cell infiltration and tumor microenvironment changes. **Results:** Results showed robust TROP2 CAR expression in circulating myeloid cells within hours of dosing. In tumor biopsies, CAR-positive myeloid cells co-localized with TROP2-expressing cancer cells. Post-dose tumor biopsies exhibited an increase in antigen presentation markers and pro-inflammatory signaling compared to baseline. MT-302 elicited systemic interferon-driven chemokine responses and reprogrammed the tumor immune microenvironment, promoting effector T cell recruitment. T cell receptor sequencing confirmed the emergence of novel T cell clones, consistent with adaptive immunity activation. Baseline IHC confirmed high TROP2 expression in enrolled patients, correlating with pharmacodynamic activity and immune reprogramming. **Conclusions:** This Phase 1 study provides the first evidence of successful delivery of mRNA-CAR therapy in humans. These biomarker findings demonstrate that MT-302 selectively engages myeloid cells and induces robust innate and adaptive anti-tumor pharmacodynamic responses, providing support for further investigation of MT-302's potential as a transformative treatment for patients with TROP2-expressing epithelial cancers. Clinical trial information: NCT05969041. Research Sponsor: None.

2592 **Poster Session**

AI-driven biomarker prediction in oncology: Enhancing pathological image analysis with EXAONEPath. First Author: Hyung Kyung Kim, Samsung Medical Center, Seoul, South Korea

Background: Hematoxylin and eosin (H&E)-stained whole-slide images (WSIs) are fundamental in cancer diagnosis, providing critical insights into tumor morphology and the tumor microenvironment. Traditionally, biomarker assessment has relied on manual pathological evaluations, which are prone to human error and limited in scalability. Subtle biomarker expressions that evade visual detection further challenge conventional methods. **Methods:** We developed EXAONEPath, an artificial intelligence (AI) model trained on approximately 73,000 pan-cancer H&E-stained WSIs, to predict key cancer biomarkers. The model was evaluated across three major biomarker prediction tasks: Tumor Mutation Burden (TMB) Prediction in Lung Adenocarcinoma (LUAD): Using the TCGA-LUAD cohort, the model was trained (n=373), validated (n=47), and tested (n=47). Cross-institutional validation was conducted on Samsung Medical Center (SMC) (n=341) and an in-house dataset (n=254). EGFR Mutation Prediction in LUAD: The TCGA-LUAD dataset was split into training (n=382), validation (n=48), and test (n=48) sets. Additional validation was performed on the SMC LUAD cohort (n=341). Microsatellite Instability (MSI) Prediction in Colorectal Adenocarcinoma (CRC): A combined TCGA-STAD/TCGA-READ dataset was used for training (n=432), validation (n=55), and testing (n=54). The model was further validated on the SMC CRC cohort (n=974). **Results:** EXAONEPath demonstrated a strong predictive performance: TMB in LUAD: AUROC scores of 0.77 (TCGA), 0.81 (SMC), and 0.76 (in-house). EGFR Mutation in LUAD: AUROC scores of 0.78 (TCGA) and 0.84 (SMC). MSI in CRC: AUROC scores of 0.92 (TCGA) and 0.86 (SMC). **Conclusions:** EXAONEPath advances AI-driven pathological image analysis by automating biomarker prediction with high accuracy and cross-institutional robustness. Its strong performance in predicting clinically relevant biomarkers, including TMB, EGFR mutations, and MSI, highlights its potential for integration into precision oncology workflows. Future research will focus on expanding biomarker applications and enhancing cross-institutional generalizability for broader clinical impact. Research Sponsor: None.

2593 **Poster Session**

Systemic antitumor virotherapy: Pre-clinical evaluation of tumor targeting, efficacy, and safety of lead candidate (CLD-401). First Author: Duong Hoang Nguyen, Calidi Biotherapeutics, San Diego, CA

Background: Systemic antitumor virotherapies are a promising modality of cancer immunotherapy. However, challenges include quick virus clearance from the bloodstream and potential off-target toxicity. To overcome these limitations, we have developed a novel strain called RT vaccinia virus which can be enveloped by an extracellular membrane during the manufacturing process and become resistant to human-complement. Our RTNova program, using extracellular enveloped RT (envRT) vaccinia viruses, focuses on generating potent systemic virotherapies with improved survival in circulation, tumor-specific targeting and enhanced therapeutic efficacy. **Methods:** The RT virus was genetically engineered to improve tumor selectivity and increase resistance to complement-mediated inactivation. The virus's ability to kill cancer cells was tested using the NCI-60 panel. The resistance of envRT vaccinia virus against human humoral immunity and its rapid spread were assessed ex-vivo. Targeting, biodistribution, therapeutic efficacy, and safety profile of selected envRT was evaluated in multiple animal models. **Results:** Out of several genetically modified RT Vaccinia viruses, we selected the one with three knockouts (3KO): TK (Thymidine kinase), A46R (immunomodulator), and VGF (Vaccinia virus growth factor). These genetic modifications significantly improved tumor-selective amplification and safety profile while maintaining therapeutic efficacy. The 3KO RT virus demonstrated strong oncolytic activity against more than 60 different human cancer cell lines NCI-60. Additionally, the 3KO RT virus was genetically engineered with CD55-domain fused with viral envelope A33R. This chimeric protein is designed to be expressed specifically in the extracellular envelope of the viral particle to robustly protect the envRT and viral progeny from inactivation by human complement. Targeting and biodistribution studies revealed that RT virus targeted all tumors after intravenous administration followed by significant tumor-selective amplification and spreading. In multiple immunocompetent mouse models, including metastatic lung cancer, RT virus demonstrated excellent tumor killing, and expression of selected therapeutic payload. **Conclusions:** We have developed a new scalable process to manufacture extracellular enveloped antitumor virotherapies and identified the first lead candidate from RTNova Platform, designated as CLD-401. This candidate, CLD-401, demonstrates promising therapeutic efficacy and safety in preclinical models. It effectively addresses the challenge of targeting and treating metastatic lung cancer by delivering Immunotherapeutics directly to disseminated tumors. Research Sponsor: None.

2594 **Poster Session**

The predictive value of BRCA mutation on survival of cancer patients treated with immune checkpoint inhibitors: A systematic review and meta-analysis of phase III randomized clinical trials. First Author: Mus'ab Theeb Mustafa, The Hashemite University, Faculty of Medicine, Zarqa, Jordan

Background: Immune checkpoint inhibitors (ICIs) have significantly enhanced survival for various types of cancers; however, resistance has limited the number of patients who can benefit from these regimens. Therefore, additional biomarkers are necessary to hopefully overcome resistance. Currently, the role of BRCA Mutation in ICI therapy remains poorly understood and controversial. **Methods:** We systematically searched PubMed, Web of Science, and Cochrane for phase III randomized clinical trials (RCTs) comparing ICI with placebo or standard-of-care cancer treatment stratified by BRCA mutation status as wildtype or mutant type up to 19 November 2024 regardless of cancer type or stage. The included phase III trials must report at least one of the following: Progression-free survival (PFS) or overall survival (OS); the meta-analysis was conducted using RevMan 5.4 pooling hazard ratio (HR) with 95% confidence intervals (CI) with a p-value of < 0.05 considered significant. **Results:** We conducted a meta-analysis of six phase III RCTs involving 3,328 patients: three trials investigated ovarian cancer, two investigated prostate cancer, and one investigated breast cancer. The analysis revealed that ICIs significantly improved both OS and PFS for patients with BRCA mutation, with HR of 0.61 (95% CI, 0.46 – 0.81, p = 0.0008) and 0.64 (95% CI, 0.47 – 0.89, p = 0.008), respectively. Furthermore, for patients with wildtype BRCA, the analysis revealed that using ICIs significantly improves PFS with HR of 0.81 (95% CI, 0.72 – 0.90, p = 0.0001). However, ICIs did not significantly improve overall survival, with HR of 0.94 (95% CI, 0.84 – 1.06, p = 0.33). **Conclusions:** The use of ICIs in cancer patients with BRCA mutation is associated with significant improvement in PFS and OS; however, in patients with wildtype BRCA, the use of ICIs showed only significant improvement in PFS with no significant improvement in OS. Research Sponsor: None.

2595 **Poster Session**

Monotherapy of envafolimab in patients with high tumor mutational burden advanced solid tumors: Results from a phase II clinical trial. First Author: Jian Li, Department of Gastrointestinal Oncology, Key laboratory of Carcinogenesis and Translational Research (Ministry of Education), Peking University Cancer Hospital & Institute, Beijing, China

Background: Tumor mutational burden (TMB) has emerged as a predictive biomarker of immune checkpoint blockade response in cancers. Envafolimab, a humanized single-domain anti-PD-L1 antibody subcutaneous administration (s.c.), has been approved in China for the treatment of advanced solid tumors with MSI-H. The study is to explore the potential anti-tumor activity in patients with TMB-high (TMB-H) in China. **Methods:** The study consists of two parts. Part 1 is to explore the association of single agent envafolimab activity with tissue TMB (tTMB) measured by Onco500 assay in patients with advanced solid tumors. Part 2 will further evaluate the efficacy of envafolimab in advanced solid tumor patients base on the cutoff of TMB value identified from Part 1. Envafolimab is administrated s.c. at 400 mg every 4 weeks until disease progression, adverse events, or other reasons causing treatment discontinuation. Efficacy and safety are assessed in all patients who received at least one dose of envafolimab. tTMB is assessed by a central lab using SimcereDx Onco500 assay (Jiangsu Simcere Medical Device Co., Ltd, China). The primary endpoint was objective response rate (ORR) assessed by independent review committee per RECIST v1.1 criteria. **Results:** As of Nov 15, 2024, a total of 70 patients with advanced cancers (colorectal cancer [9,12.6%], cervical cancer and soft tissue sarcoma [8 each; 11.4%], and other 18 tumor types) have received envafolimab in Part 1. 30 (42.9%) patients had received $\geq$3 systemic therapies (median 2; range 1-19). Median follow-up time was 31.2 months (range: 0.6-36.8). 49 (70%) patients had at least one treatment-related adverse events (TRAEs), and 6 (8.6%) had grade 3 or 4 TRAEs. The most common TRAEs were anemia and alanine aminotransferase increased (9 each; 12.9%). Grade 2 decreased appetite was the only TRAE resulting in treatment discontinuation. No treatment-related death reported. TMB$\geq$13 mut/Mb with Onco500 panel was selected as the threshold of TMB-H based on the clinical data and previous comparison of platforms for determining TMB value in patients. Key efficacy outcomes are presented (Table). ORR and DOR were higher in patients with tTMB $\geq$13mut/Mb (33.3% and 20.2m) than patients with tTMB $<$ 13mut/Mb (4.3% and 3.8m). **Conclusions:** tTMB could be a useful predictive biomarker for response to envafolimab in patients with pre-treated advanced solid cancer. The Part 2 of this study is ongoing (NCT04891198). Clinical trial information: NCT04891198. Research Sponsor: None.

	tTMB≥13 mut/Mb (n = 24)	tTMB<13 mut/Mb (n = 46)
Objective response rate, n (%) [95% CI]	8 (33.3) [15.6-55.3]	2 (4.3) [0.5-14.8]
Complete / partial response	1 (4.2) / 7(29.2)	0 (0) / 2 (4.3)
Stable disease / progressive disease	2 (8.3) / 9 (37.5)	16 (34.8) / 24 (52.2)
Median DoR, months (95% CI)	20.2 (4.4-NE)	3.8 (NE-NE)
Median PFS, months (95% CI)	2.8 (1.8-8.7)	1.9 (1.8-3.6)
Median OS, months (95% CI)	13.2 (5.7-NE)	12.7 (7.4-18.2)

2596 **Poster Session**

A phase 1 study of fixed-dose regimens of serplulimab, an anti-PD-1 antibody, in patients with advanced solid tumors. First Author: Ching-Liang Ho, Division of Hematology and Oncology, Tri-Service General Hospital, Taipei, Taiwan

Background: Serplulimab is a recombinant humanized IgG4 monoclonal antibody targeting PD-1. A two-cohort phase 1 study was conducted to evaluate the safety of serplulimab monotherapy in patients with advanced solid tumors (NCT03468751). Findings from the dose-finding cohort has been previously reported at the 2022 ASCO Annual Meeting (No. e14560). Here we present results from the dose expansion cohort, in which fixed-dose regimens were evaluated. **Methods:** This multicenter phase 1 study enrolled patients with locally advanced or metastatic solid tumors who have failed or are intolerant to standard therapy or for whom no standard therapy is available. In the dose expansion cohort, patients received intravenous serplulimab at 200 mg Q2W, 300 mg Q3W, 400 mg Q4W, or 600 mg Q6W. The primary endpoints were adverse event profile and maximum tolerated dose (MTD). Secondary endpoints included pharmacokinetic (PK), immunogenicity, pharmacodynamics (PD), and efficacy. **Results:** As of data cut-off on Jan 5, 2024, 37 patients received at least one dose of serplulimab at 200 mg Q2W (n = 9), 300 mg Q3W (n = 9), 400 mg Q4W (n = 10), or 600 mg Q6W (n = 9). All patients were Asian, 70.3% male; median age was 60.0 yrs (range 33–88). Patients had head and neck cancer (n = 10, 27.0%), esophageal cancer (n = 6, 16.2%), colorectal cancer (n = 4, 10.8%) or other types of tumor. Most patients had metastatic disease (64.9%). All patients had prior systemic cancer treatment, including 4 (10.8%) with prior immunotherapy; 51.4% had $\geq$ 3 prior lines of therapy. All 37 patients were included in safety, PK, and PD analyses; 35 response-evaluable patients were included in efficacy analysis. No dose-limiting toxicity was reported, and MTD has not been determined. Treatment-related adverse events (TRAEs) were observed in 19 patients (51.4%), including 7 (18.9%) reporting grade $\geq$ 3 TRAE. TRAE incidence was similar across regimen groups. Following multiple infusions, the geometric mean $t_{1/2}$, ss was from 341.1–751.3 h, and geometric mean CL_{ss} was 0.006–0.009 L/h. Treatment-emergent anti-drug antibody (ADA) was detected in 7 (18.9%) patients. No difference in safety or PK was noted between ADA-positive and -negative patients. Profiles of PD-1 receptor occupancy in circulating $CD3^+$ T cells and interleukin-2 stimulation ratio were similar across dose groups, suggesting dose-independent functional blockade. Six patients (300 mg Q3W, 4; 400 mg Q4W, 2) achieved partial response, resulting in an ORR of 17.1%. Among the responders, 12-month duration of response rate was 66.7% (95% CI confidence interval, 19.5–90.4). Median progression-free survival was 2.3 months (95% CI, 1.9–5.1). **Conclusions:** Fixed-dose regimens of serplulimab showed favorable safety, PK, and PD characteristics and preliminary anti-tumor activity, supporting its further investigation. Clinical trial information: NCT03468751. Research Sponsor: Shanghai Henlius Biotech, Inc.

2597 **Poster Session**

Consolidative camrelizumab following definitive concurrent chemoradiotherapy with involved-field irradiation in locally advanced esophageal squamous cell carcinoma: A single-arm phase 2 trial. First Author: Jun Wang, Department of Radiation Oncology, the Fourth Hospital of Hebei Medical University, Shijiazhuang, China

Background: Definitive concurrent chemoradiotherapy (dCCRT) is considered the standard treatment for esophageal squamous cell carcinoma (ESCC). The PACIFIC study demonstrated that consolidation durvalumab significantly improves overall survival (OS) in patients with stage III non-small cell lung cancer (NSCLC) after dCCRT. However, the efficacy of consolidation immunotherapy in ESCC still remains unclear. We conducted a clinical trial to evaluate the efficacy of camrelizumab in patients with unresectable, locally advanced ESCC following dCCRT. **Methods:** This single-arm, phase 2 study enrolled patients with locally advanced ESCC. All participants received dCCRT with involved-field irradiation (IFI). Patients were treated with camrelizumab within 1 to 42 days after completing dCCRT. Camrelizumab was administered intravenously over 30 minutes every 2 weeks for up to 12 months. The primary endpoint was progression-free survival (PFS). Secondary endpoints included disease control rate (DCR), objective response rate (ORR), duration of response (DoR), overall survival (OS), and safety. **Results:** Thirty-five patients were enrolled between April 2020 and November 2023. Data from 32 patients were analyzed. As of December 22, 2024, the median follow-up was 25.1 months (IQR 5.5–56.8). Twelve patients experienced disease progression, and seven patients died. The DCR was 59.4%. The median PFS and OS were not reached. The 1- and 2-year PFS rates were 81.3% and 60.6%, respectively. The 1- and 2-year OS rates were 96.9% and 81.0%, respectively. The most common adverse events were grade 1-2. No grade 4 or 5 adverse events were reported. Pneumonia occurred in 31.3% of patients, all of whom experienced grade 1-2. **Conclusions:** Consolidative camrelizumab following definitive concurrent chemoradiotherapy with IFI shows promising efficacy and manageable toxicity in patients with unresectable locally advanced ESCC. Clinical trial information: NCT04286958. Research Sponsor: None.

2598 **Poster Session**

Efficacy of low-dose nivolumab in advanced cancers: A retrospective analysis from medical oncology clinic in Eastern India. First Author: Kiran Yidagur Gangadharaiah Lokesh Sr., All India Institute of Medical Sciences, Bhubaneswar, Bhubaneswar, India

Background: Immunotherapy with PD-1/PDL1 blocking monoclonal antibodies has improved survival across several malignancies at different stages of these malignancies. But in Low- & middle-income countries, only 1-3% of cancer patients can access the standard dose of Immunotherapy. In this study, we aim to assess the response to low dose (LD) of Immunotherapy (nivolumab) across a broad range of malignancies. **Methods:** The study is a retrospective descriptive study. A total of 104 patients with advanced cancers were included in the study. Patients received a lower dose of Nivolumab (20/40 mg), ones in a 2-weekly-4weekly schedule, with treatment continued until disease progression or intolerable toxicity Their demographics, clinical profile, response to therapy, and adverse events were analyzed. **Results:** Male to female ratio was 5:1. The median age of patients was 49 years (range - 15 years to 78 years) and 70% patients were ECOG-PS 1-2 30% were ECOG-PS 3-4. Overall 56 patients were diagnosed with Squamous cell carcinoma (SCC) Head&neck, 15 had Renal cell carcinoma (RCC), 14 had Malignant melanoma, 5 had lung cancer, 4 with Hepatocellular carcinoma (HCC), 2 each of Gynecological cancer, Gall bladder cancer & CUP and 1 each of stomach cancer, Urinary bladder malignancy (HGUC), & Lymphoma. The most common metastatic sites were Lungs (46%) > Bone(27%) > Liver(15%). A total of 73 patients were included for assessment (received $\geq$2 cycles of Nivolumab). The overall response rate (ORR) was 39.7% and the Disease control rate (DCR) was 54.7%. Median PFS was 4 months (range - 1month to 26months) with Median OS being 11 months (range - 3months to 30months). Grade 3-4 adverse events were seen in 21/104(20%), the most common being dermatological (8/21) followed by anemia (7/21) and endocrinal AEs (4/21). **Conclusions:** Low-dose Nivolumab showed good response rates in advanced malignancies with manageable toxicities even in poor general condition. The cost of therapy was 1/5th to 1/10th of the standard dose of Nivolumab, highlighting its potential as a cost-effective alternative in resource-limited settings. Research Sponsor: None.

Response and survival analysis.

Charectiristics	N=73
Response rates	
CR	**5**
PR	**24**
SD	11
PD	33
ORR	**39.7%**
DCR	54.7%
Survival analysis	
mPFS	4 months
mOS	11.5 months

2599 **Poster Session**

Immune related liver toxicity, management, and outcomes in ICI treated patients with advanced or metastatic cancers. First Author: Zara Izadi, Bristol Myers Squibb, Princeton, NJ

Background: The impact of hepatic immune-related adverse events (HirAEs) and their management (mgmt) on clinical outcomes in patients receiving immune checkpoint inhibitors (ICI) has not been fully examined. We aimed to evaluate the association between HirAEs, their mgmt, and overall survival (OS) in ICI-treated cancer patients. **Methods:** Data were drawn from the Flatiron Health Research Database, an EHR-based database representing 280+ U.S. community oncology practices. Adults with advanced non-small cell lung cancer (aNSCLC), advanced melanoma (aMel), or metastatic renal cell carcinoma (mRCC) who initiated ICI between 1/1/16 - 12/31/20 were included and followed from ICI initiation to death, loss to follow-up, or end of the study period (12/31/2021). CTCAE Grade 2 or higher HirAEs and mgmt actions (immunosuppression using corticosteroids or other immunosuppressants, ICI-regimen holds, ICI-regimen discontinuations) and hospitalizations were curated from unstructured data. Cox regression was used to evaluate the association between HirAEs, their mgmt (both as time-varying covariates) and OS adjusting for baseline characteristics such as line of therapy and corticosteroid use. The earliest HirAE per patient was examined in OS analysis. **Results:** The study included 529 aNSCLC, 557 aMel, and 431 mRCC patients. For aNSCLC, aMel, and mRCC, respectively, 23.4%, 41.5%, and 30.9% experienced at least one HirAE, with a median time to onset of 59, 60, and 63 days. Among all HirAEs, elevated liver enzymes were the most common (72.9% in mRCC to 76.6% in aMel), followed by hepatitis (8.3% in aNSCLC to 12.6% in aMel). Immunosuppression was used to treat HirAEs in 47.6%, 57.6%, and 38.3% of aNSCLC, aMel, and mRCC patients with HirAEs. In aNSCLC, aMel, and mRCC, respectively, median survival was 12.7, 52.2, and 25.5 months and HirAEs were associated with a higher risk of all-cause mortality than no HirAEs [HR (95%CI): 1.8 (1.3-2.2); 1.4 (1.0-1.8); 1.3 (1.0-1.8)]. In mRCC, ICI-regimen holds and discontinuations were associated with a higher risk of all-cause mortality than immunosuppression alone (HR$\geq$4.0; P$\leq$0.05). In aNSCLC, HirAEs that led to hospitalization were associated with a higher risk of all-cause mortality regardless of HirAE mgmt (HR: 6.2; $P < 0.01$). In aMel HirAE mgmt was not associated with OS. **Conclusions:** ICI-related HirAEs were associated with higher mortality in aNSCLC, aMel, and mRCC. HirAE mgmt impacted OS differently across cancer types, highlighting the need for tailored, timely, and multidisciplinary mgmt strategies in the ambulatory care setting, especially for cancers with poorer prognosis. Research Sponsor: Bristol Myers Squibb.

2600 Poster Session

Baseline autoimmune diseases and characteristics of solid tumor patients on immune checkpoint inhibitor (ICI) therapy enrolled in a prospective study of immune-related adverse events (irAEs): SWOG S2013 (I-CHECKIT). First Author: Krishna Soujanya Gunturu, Hartford HealthCare Cancer Institute, Hartford, CT

Background: I-CHECKIT is a prospective observational study whose primary objective is to develop and independently validate a risk prediction model for the development of Common Terminology Criteria for Adverse Events (CTCAE) Grade 3 or higher non-hematological irAEs in patients with solid tumors during the first year of treatment with ICI. **Methods:** Any patient initiating ICI per their treating oncologist and National Comprehensive Cancer Network guidelines was eligible to participate in this study. Eligibility criteria were unrestrictive and included participants with active autoimmune disease, decreased performance status, and any stage of cancer. One important exclusion criterion was planned receipt of ICI with chemo, biological or targeted therapy. Hormonal therapy and palliative radiation were allowed. The study is close to accrual in May 2024. Here we describe baseline participant characteristics. **Results:** Of a total of 2084 enrolled participants, 62 were ineligible. Community based NCORP sites enrolled the majority (n= 1,181, 56%) of participants. Participants were also enrolled from SWOG Latin American sites and Veteran Affairs (VA). 31% (n=656) had skin cancer (melanoma 90%, squamous 5% and Merkel cell 2.9%), 29% (n=604) had lung cancer and 12% (n=256) had kidney cancer. 17% (n=346) received combination ICI. The median age was 69.9 years. 64% were male, 90% (n=1866) were white, 8% (n=165) Hispanic/Latino, 5% (110) black, and 1% (16) Asian. 12% had performance status (PS) 2 or greater. 67% of the participants were overweight or obese. 9% (n=180) of the participants had active autoimmune disease such as rheumatoid arthritis, Type I diabetes, hypothyroidism, psoriasis, Crohn's, ulcerative colitis. 3% (n=54) had a history of autoimmune disease not currently requiring treatment. **Conclusions:** The I-CHECKIT observational study enrolled participants representative of a real-world population, as most of the participants were from community practices such as NCORP. Most participants had melanoma, resulting in a higher proportion of white participants. 9% of this population had baseline active autoimmune disease, a population excluded in initial clinical trials, highlighting the broader use of ICI in daily clinical practice. Clinical trial information: NCT04871542. Research Sponsor: NIH/NCI/NCORP grant UG1CA189974.

Baseline characteristics.

Age	All No (%)	Single ICI No (%)	Combo ICI No (%)	Skin No (%)	Lung No (%)
61-65 years	301 (14)	244 (14)	57 (16)	94 (14)	91 (15)
66+ years	1324 (64)	1119 (64)	205 (59)	372 (57)	430 (71)
PS					
0-1	1822 (88)	1523 (88)	299 (87)	607(93)	500(83)
2 and +	258 (12)	211 (12)	47 (14)	48 (7)	101 (17)
Active Autoimmune	180 (9)	153 (9)	27 (8)	54 (8)	51 (8)
Hypothyroidism	113 (9)	97 (9)	16 (8)	28 (8)	34 (8)
Type I Diabetes	15 (1)	10 (1)	5 (1)	5 (1)	4 (1)
Psoriasis	11 (1)	9 (1)	2 (1)	3 (0)	3 (0)

2601 Poster Session

Immune related kidney toxicity, management, and outcomes in ICI treated patients with advanced or metastatic cancers. First Author: Zara Izadi, Bristol Myers Squibb, Princeton, NJ

Background: The impact of kidney immune-related adverse events (KirAEs) and their management (mgmt) on clinical outcomes in patients receiving immune checkpoint inhibitors (ICI) has not been fully examined. We aimed to evaluate the association between KirAEs, their mgmt, and progression-free survival (PFS) and overall survival (OS) in ICI-treated cancer patients. **Methods:** Data were drawn from the Flatiron Health Research Database, an EHR-based database representing 280+ U.S. oncology practices. Adults with advanced non-small cell lung cancer (aNSCLC), advanced melanoma (aMel), or metastatic renal cell carcinoma (mRCC) who initiated ICI between 1/1/16 - 12/31/20 were included and followed from ICI initiation to death, loss to follow-up, or end of the study period (12/31/21). CTCAE Grade 2 or higher KirAEs and mgmt actions (immunosuppression using corticosteroids or other immunosuppressants, ICI-regimen holds, ICI-regimen discontinuations) and hospitalizations were curated from unstructured data. Cox regression was used to evaluate the association between KirAEs, their mgmt (both as time-varying covariates) and PFS and OS adjusting for baseline characteristics such as line of therapy and corticosteroid use. The earliest KirAE per patient was examined in survival analyses. **Results:** The study included 513 aNSCLC, 463 aMel, and 451 mRCC patients. For aNSCLC, aMel, and mRCC, respectively, 21.1%, 29.6%, and 33.9% experienced at least one KirAE, with a median time to onset of 70, 84, and 128 days. Nephritis ranged from 2.1% of KirAEs in aNSCLC to 4.6% in aMel. Elevated creatinine was the most common KirAE (23.6% in mRCC to 29.1% in aNSCLC), followed by acute kidney injury (20.5% in mRCC to 28.4% in aNSCLC). Immunosuppression was used to treat KirAEs in 67.6%, 80.3%, and 67.3% of aNSCLC, aMel, and mRCC patients with KirAEs. In aNSCLC, aMel, and mRCC, respectively, median OS was 17.1, 58.6, and 33.7 months, median PFS was 7.8, 8.9, and 9.5 months, and patients with KirAEs had longer PFS than those without KirAEs [HR (95%CI): 0.65 (0.51-0.83); 0.74 (0.57-0.97); 0.67 (0.53-0.84)]. In aNSCLC, KirAEs were associated with shorter OS [1.31 (0.98-1.74); P = 0.06]. In all cancers, KirAEs that occurred during hospitalization or led to hospitalization were associated with shorter OS (HR$\geq$2.84; P $<$ 0.02). KirAE mgmt was not associated with OS or PFS. **Conclusions:** Results suggest that while KirAEs might indicate an intensified immune response, their management and impact on survival vary across cancer types and call for cancer-specific strategies for early identification and management of KirAEs in the ambulatory care setting. Research Sponsor: Bristol Myers Squibb.

2602 Poster Session

Hepatotoxic adverse events with immune checkpoint inhibitors: Real world pharmacovigilance study using FAERS database. First Author: Panah Tushar Parab, Saint Vincent Hospital, Worcester, MA

Background: Immunotherapy with immune checkpoint inhibitors (ICIs) has revolutionized cancer treatment. With their increasing use, it is important to track and manage potential adverse events (AEs) . One such AE of ICI therapy is immune-mediated liver injury (ILICI). We aim to review the real-world data on ILICI using FDA Adverse Event Reporting System (FAERS) database. **Methods:** We queried FAERS using a search-by-product strategy on 22nd January 2025 and retrieved 224889 adverse events from 2013-2024. We employed 5 ICIs in the analysis (Pembrolizumab, Nivolumab, Atezolizumab, Durvalumab, and Ipilimumab). Descriptive statistics were carried out, and disproportionality analysis was done by calculating the reportable odds ratio (ROR) with 95% confidence intervals (CI). ROR was considered significant when the lower limit of the 95% CI was $>$ 1. RORs were calculated for all hepatic events in general and Autoimmune Hepatitis (AIH), Drug-induced liver injury (DILI), Vanishing bile duct syndrome (VBDS), Primary biliary cholangitis (PBC), and Venooccluisve disease (VOD). **Results:** Total AEs from all included ICIs were 224889 and Hepatobiliary AEs constitute 9.2% of all AEs across all ICIs. ROR for any hepatic event is highest with Durvalumab i.e., 17.97 (16.08,20.08) in general as compared to the rest of the ICIs. AIH was seen highest with Ipilimumab with a ROR of 48.0 (43.1, 53.5); DILI with Pembrolizumab with a ROR of 5.8 (5.3, 6.4) (Overlapping CI); VBDS and PBC with Pembrolizumab with a ROR of 7.93 (4.9, 12.8) and 7.91 (4.46,14.03) respectively. Atezolizumab showed the highest ROR of 6.15 (3.6, 10.4) for VOD. (Table) **Conclusions:** This is the largest real-world study demonstrating specific hepatotoxic AEs with ICIs. Our results show varying patterns of hepatotoxicity with ICIs. Knowing these patterns will help us make better decisions in treating patients with ICIs. Research Sponsor: None.

Baseline characteristics, hepatic AEs and outcomes.

Baseline characteristic	Pembrolizumab (n= 67603)	Nivolumab (n=79283)	Atezolizumab (n=28521)	Durvalumab (n=13303)	Ipilimumab (n= 36179)
ROR for any hepatic event (95% CI)	8.24 (7.66,8.87)	7.46 (6.95, 8.01)	7.94 (7.08, 8.89)	17.97 (16.08, 20.08)	11.47 (10.54, 12.48)
ROR for AIH	21.34 (18.9, 24.0)	27.3 (24.8, 30.1)	22.3 (18.7, 26.5)	22.3 (18.7, 26.5)	48.0 (43.1, 53.5)
ROR for DILI	5.8 (5.3, 6.4)	3.74 (3.34, 4.19)	5.3 (4.61,6.29)	5.3 (4.61, 6.29)	5.04 (4.37, 5.82)
ROR for VBDS	7.93 (4.9, 12.8)	4.37 (2.41, 7.94)	0.5 (0.03, 8.8)	1.1 (0.15, 7.86)	2.61 (0.84, 8.1)
ROR for VOD	2.22 (1.2, 3.9)	3.79 (2.5, 5.6)	6.15 (3.6, 10.4)	0.44 (0.06, 3.12)	2.08 (0.9, 4.63)
ROR for PBC	7.91 (4.46,14.03)	3.37 (1.5, 7.5)	0.78 (0.04, 12.5)	1.51 (0.21, 11.1)	2.46 (0.6, 9.8)

Hepatic AEs included in the ROR calculation with these agents are Drug-Induced Liver Injury (DILI), Autoimmune hepatitis (AIH), Vanishing bile duct syndrome (VBDS), Veno-occlusive disease (VOD), Primary biliary cholangitis (PBC).

2603 Poster Session

Impact of body mass index on immunotherapy outcomes and complications in solid tumor patients: A real-world evidence analysis. First Author: Moath Albliwi, Cleveland Clinic Foundation, Cleveland, OH

Background: Obesity alters immune function by modifying cytokine profiles and altering immune cells. Body mass index (BMI) influences cancer outcomes, including response to therapy. Several studies have shown that patients (pts) with a higher BMI respond better to immunotherapy (IT). This study assesses the impact of BMI on IT outcomes, admission risk, and major complications in pts with solid tumors. **Methods:** We utilized TriNetX, a global data platform from 104 healthcare institutions, to analyze outcomes in cancer pts on IT. Patients were categorized into two groups: BMI $<$ 25 (n = 8,460) and BMI $\geq$ 25 (n = 13,631). Propensity Score Matching balanced groups for age, sex, race, comorbidities, smoking status, and alcohol use. Pts aged 18–65 years with solid tumors who received $\geq$1 IT dose were included with a 1-year follow-up. IT regimens included PD-L1, PD-1, or CTLA-4 antibodies. Cancers analyzed: esophagus, bladder, stomach, endometrium, melanoma, lung, kidney, head and neck, and breast. Outcomes included: ICU admissions, hospital admissions, mortality, heart failure, ischemic stroke/transient ischemic attack (TIA), venous thromboembolism (VTE), myocardial infarction, polyneuropathy, pneumonitis/pneumonia, and acute kidney injury (AKI). Risks were assessed using 1-year event-free survival and survival analysis. **Results:** After 1:1 PSM, the two groups each consisted of 8,460 pts, with balanced baseline variables. Post-matching, the mean age was ~52.5 $\pm$ 9 years, 56.0% were White, and 54.7% were female. A BMI $<$ 25 was found to be a predictor of increased risk for multiple adverse outcomes. The 1-year risk-free survival was significantly lower in pts with BMI $<$ 25 compared to those with BMI $\geq$ 25 for ischemic stroke/TIA (94.6% vs. 95.9%, log-rank P $<$ 0.01), ICU admissions (83.3% vs. 89.05%, P $<$ 0.01), hospital admissions (37.5% vs. 48.1%, P $<$ 0.01), mortality (64.01% vs. 80.62%, P $<$ 0.01), heart failure (84.3% vs. 87.6%, P $<$ 0.01), and pneumonitis/pneumonia (79.1% vs. 84.9%, P $<$ 0.01). However, there was no significant difference in the incidence of VTE, myocardial infarction, polyneuropathy, or AKI (P $>$ 0.05). We performed several sensitivity analyses using different BMI cutoff groups and compared outcomes to the BMI $<$ 25 group. In these balanced comparisons, we found similar trends except for an increased incidence of polyneuropathy in BMI $\geq$ 35 compared to BMI $<$ 25 (1-year risk-free: 89.2% vs. 91.6%, P $<$ 0.01) and in BMI $\geq$ 40 compared to BMI $<$ 25 (1-year risk-free: 89.0% vs. 91.4%, P $<$ 0.01). **Conclusions:** Our study provides real-world evidence on the types of complications experienced by pts with BMI $<$ 25 when treated with IT for different types of solid tumors. It also explains, at least partly, the improved outcomes and tolerability observed in pts with higher BMI receiving IT. Based on our findings—such as the increased risk of hospital admissions and pneumonitis—we postulate that pts with low BMI may have a stronger inflammatory reaction to IT, leading to a higher incidence of complications. Research Sponsor: None.

2604 Poster Session

Final analysis of a multicenter, open-label, phase 2 study evaluating the efficacy and safety of tislelizumab (TIS) in combination with fruquintinib (F) in patients (pts) with selected solid tumors. First Author: Keun-Wook Lee, Division of Hematology and Medical Oncology, Department of Internal Medicine, Seoul National University Bundang Hospital, Seoul National University College of Medicine, Seongnam, South Korea

Background: Immunotherapy in combination with antiangiogenic agents has shown promising antitumor activity compared with either agent alone. We report efficacy and safety data from the final analysis of the phase 2 BGB-A317-Fruquintinib-201 trial evaluating the programmed cell death-1 antibody TIS combined with the selective vascular endothelial growth factor receptor (VEGFR)-1, -2, and -3 inhibitor F in pts with advanced solid tumors. **Methods:** This was an open-label, multicenter, two-part study with a safety run-in followed by dose-expansion. Eligible pts were adults with advanced or metastatic unresectable gastric cancer (GC), microsatellite stable colorectal cancer (MSS CRC), or locally advanced surgery-/radiotherapy-ineligible and programmed death ligand-1–positive (PD-L1+; defined as PD-L1 ≥1%) stage IIIB/IV non-small cell lung cancer (NSCLC). F 5 mg daily (3 weeks on, 1 week off) plus TIS (300 mg IV Q4W) was administered as second-line therapy for pts with GC, third-line therapy for pts with MSS CRC, and first-line therapy for pts with PD-L1+ NSCLC. The primary outcome measure was overall response rate (ORR) per RECIST v1.1. Secondary endpoints included other efficacy measures and safety. **Results:** The median study follow-up was 11.6 months (mo; range, 0.4-32.8). A total of 84 pts were enrolled (GC, n=31; MSS CRC, n=31; PD-L1+ NSCLC, n=22). One study treatment component-related death was reported in the GC cohort and 1 in the PD-L1+ NSCLC cohort. The recommended phase 2 dose was established at F 5 mg daily (3 weeks on, 1 week off) in combination with TIS with no observed dose-limiting toxicities. Efficacy and safety are reported in the Table. Any-grade treatment-emergent adverse events (TEAEs) occurred in 83 (98.8%) pts; proteinuria (32.1%), hypoalbuminemia (27.4%), and hypothyroidism (25.0%) were most common. 9/32 (10.7%) pts had grade ≥3 immune-mediated AEs. **Conclusions:** Despite the limited sample size, TIS+F demonstrated moderate antitumor activity in pts with advanced solid tumors, with manageable safety observed in pts with GC and MSS CRC. Further investigation of TIS+F is warranted in the GC and MSS CRC settings. Clinical trial information: NCT04716634. Research Sponsor: BeOne Ltd.

	GC (N=31)	MSS CRC (N=31)	PD-L1+ NSCLC (N=22)
ORR, n (%)	4 (12.9)	3 (9.7)	9 (40.1)
Disease control rate, n (%)	23 (74.2)	23 (74.2)	15 (68.2)
Clinical benefit rate, n (%)	10 (32.3)	12 (38.7)	13 (59.1)
Median progression-free survival, mo (95% CI)	4.6 (3.4, 7.4)	4.6 (3.6, 7.2)	15.6 (1.8, NE)
Median overall survival, mo (95% CI)	10.5 (5.2, 14.6)	10.0 (4.7, 15.2)	NR (6.0, NE)
Median duration of response, mo (95% CI)	NR (5.6, NE)	11.9 (3.7, NE)	NR (7.7, NE)
Grade ≥3 TRAE, n (%)	10 (32.3)	12 (38.7)	14 (63.6)
Serious TRAE, n (%)	3 (9.7)	3 (9.7)	9 (40.9)
TEAE leading to discontinuation of any study treatment, n (%)	5 (16.1)	3 (9.7)	7 (31.8)

CI, confidence interval; NE, not evaluable; NR, not reached.

2605 Poster Session

Effects of UCHL1 on tolerogenic DC maturation and promotion of mregDC-Treg crosstalk to nullify anti–PD-L1 therapy. First Author: Yu-Fei Zhao, Zhongshan Hospital Fudan University, Shanghai, Shanghai, China

Background: Immune-checkpoint blockade (ICB) therapies have revolutionized cancer treatment, but such immunotherapy regimens fail in a subset of patients. Dendritic cells (DCs) are a heterogeneous group of professional antigen-presenting innate immune cells that activate adaptive immunity and determine the efficacy of immunotherapies. While they can also be hijacked by tumour-mediated factors to contribute to immune tolerance and tumor progression. However, little is known about the molecular mechanisms that drive the tolerogenic maturation of DCs in the tumor microenvironment (TME). **Methods:** We enrolled 85 patients with advanced hepatocellular carcinoma (HCC) exhibiting varying response to immunotherapy, and profiled the tumor ecosystems using a single-cell transcriptomes sequencing (scRNA-seq) and mass cytometry by time of flight (CyTOF) for 10 patients, and plasma protein level quantification, conducted both pre-treatment and post-treatment across all patients. We integrated our in-house data and 6 additional published scRNA-seq cohorts of 83 donors to generate a comprehensive landscape of cellular dynamics underlying different responses to immunotherapy. We verified the prognostic value in our in-house tumor microarray (TMA) of 342 patients. **Results:** UCHL1 overexpression nullifies anti-PD-L1 therapy by driving conventional DC transformation into mature DC enriched in immunoregulatory molecule (mregDC) via tolerogenic maturation and promoting mregDC and regulatory T (Treg) cell crosstalk, thereby restrains $CD8^+$ T anti-tumor immunity. Mechanistically, UCHL1 enhances glycolysis and lactate accumulation in TME by stabilizing HIF-1α, which further promotes SREBP2 activation and nuclear translocation in DC. We verified the positive correlations of UCHL1 with HIF-1α/VEGFα/LAMP3/FOXP3 in 342 patients with HCC. Genetic ablation or pharmacological inhibition of UCHL1 all reduce the mregDC and Treg accumulation, restore the immuno-surveillance of tumour-infiltrating lymphocytes, and safeguard anti-tumour immunity and efficacy of anti-PD-L1 therapy in mouse models. **Conclusions:** UCHL1 hijacks tolerogenic DC maturation and promotes mregDC-Treg crosstalk to nullify anti-PD-L1 therapy. Genetic ablation or pharmacological inhibition of UCHL1 unleash the immuno-surveillance of tumour-infiltrating lymphocytes, and safeguard the anti-tumor immunity. Plasma level of UCHL1 predicts the efficacy of anti-PD-L1 therapy in patients with HCC. Clinical trial information: NCT04649489. Research Sponsor: None.

2606 Poster Session

A phase 1b/2, open-label study of selective Axl, Mer and CSF1R inhibitor adrixetinib (Q702) in combination with intravenous pembrolizumab in patients with selected advanced solid tumors: Results of a phase 1 study (QRNT-008). First Author: Hong Jae Chon, CHA Bundang Medical Center, CHA University, Gyeonggi-Do, Korea, Republic of

Background: Adrixetinib (Q702) is an orally administrated novel Axl/Mer/CSF1R tyrosine kinase inhibitor for which the primary mechanism of action of tumor regression is through immune-stimulating effects. The safety profile, pharmacokinetics (PK) and efficacy data for Q702 in combination with pembrolizumab are presented. **Methods:** QRNT-008 (NCT05438420) is an ongoing Phase 1b/2 multicenter, open-label, dose escalation and expansion study in patients with advanced esophageal, gastric/GEJ, hepatocellular, and cervical cancers who have progressed on prior anti-PD-1/PD-L1 treatment. The Part 1 dose escalation was guided by a mTPI design to determine the Part 2 dose of Q702 in combination with pembrolizumab. Patients received Q702 (week on/off dosing regimen) orally at 100 mg or 120 mg doses in combination with pembrolizumab (200 mg Q3W) intravenously in 42-day cycles. **Results:** As of the data cutoff (December 19th, 2024), 29 patients received Q702 plus pembrolizumab across 2 dose levels: 7 patients at 100 mg and 22 patients at 120 mg. The median number of prior lines of systemic therapy was 4 (range 1-7). Of the 29 patients (3 esophageal; 11 gastric; 2 GEJ; 9 hepatocellular; 4 cervical) who received Q702 across all doses, there were no treatment discontinuations due to the treatment-related AEs (TRAEs). Most common TRAEs ≥10% were AST increase (51.7%), ALT increase (41.3%), CPK increase (37.8%) and LDH increase (34.5%). One patient dosed at 120 mg experienced 1 DLT (G3 skin rash and G3 diarrhea). Adrixetinib PK analyses showed dose dependent increase of $AUC_{0\text{-last}}$ and C_{max}. Overall response assessment (RECIST 1.1) included 1 confirmed complete response (CR) in a patient with metastatic gastric cancer (GC) and 6 patients with stable disease (SD) across multiple tumor types. Among 6 SD patients, 1 GC and 1 hepatocellular cancer (HCC) patient continued treatment for ≥24 weeks. **Conclusions:** Preliminary data from QRNT-008 study showed that selective Axl/Mer/CSF1R inhibitor Q702 plus pembrolizumab has a manageable safety profile. The Part 2 dose of Adrixetinib is confirmed at 120 mg. Preliminary anti-tumor activity in patients previously treated with anti-PD-1 supports further development of the combination. Clinical trial information: NCT05438420. Research Sponsor: Qurient Co., Ltd.

2607 Poster Session

Outcomes of conversion surgery after immune checkpoint inhibitor-based combination therapy in initially unresectable hepatocellular carcinoma: A retrospective cohort study. First Author: Mingjian Piao, Department of Liver Surgery, State Key Laboratory of Complex Severe and Rare Diseases, Peking Union Medical College Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China

Background: Hepatocellular carcinoma (HCC) has a high incidence rate and is often asymptomatic in its early stages. Combination therapies using immune checkpoint inhibitors (ICIs) have demonstrated survival benefits and high objective response rates, offering hope for conversion surgery in patients with initially unresectable HCC. We aimed to investigate the oncological outcomes of conversion surgery compared to those with continuing systemic treatment alone in patients who responded well to ICIs-based therapy, as well as the surgical outcomes associated with conversion surgery. **Methods:** We consecutively enrolled patients diagnosed with HCC between January 1, 2019 and April 1, 2024. These patients received treatment with ICIs combined with either anti-VEGF antibodies or tyrosine kinase inhibitors. Tumor response and resectability were assessed every 2 months. Patients who responded positively and met the criteria for conversion surgery were included. **Results:** Among 613 patients with initially unresectable HCC, 136 achieved conversion and met the surgical resection criteria during combination therapy. The median follow-up time was 26.9 and 42.5 months for the surgery and non-surgery groups, respectively. The median PFS was 29.1 months in the surgery group versus 11.2 months in the non-surgery group ($P < 0.0001$, hazard ratio [HR] = 0.40 [0.25–0.63]). The median OS was 50.8 months in the surgery group, compared to 25.8 months in the non-surgery group ($P < 0.0001$, HR = 0.27 [0.15–0.47]). The median RFS was 18.7 months in the surgery group. Multivariate Cox regression analysis indicated that conversion surgery was independently associated with improved OS and PFS ($P < 0.001$), and continuing the original treatment post-surgery significantly influenced OS and RFS. **Conclusions:** Conversion surgery after meeting the surgical criteria during immunotherapy provides significant prognostic benefits for patients with initially unresectable HCC, demonstrating high safety and R0 resection rates. For those specifically selected based on their response to immunotherapy and undergoing conversion surgery, promptly resuming the original treatment after surgery is necessary. Our results emphasize the importance of continuing immunotherapy post-conversion surgery to prevent recurrence in patients who respond to immunotherapy. Research Sponsor: None.

2608 **Poster Session**

Phase I/II study of the EP4 antagonist vorbipiprant combined with anti-PD-1 immunotherapy: Safety and efficacy results in metastatic gastrointestinal non-colorectal cancers. First Author: Filippo Pietrantonio, Department of Medical Oncology, Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy

Background: Novel combination strategies are being explored to enhance the effectiveness of immune checkpoint inhibitors (ICIs). Prostaglandin E2, through its receptor 4 (EP4), is a major contributor to immunosuppression in the tumor microenvironment. In a dose-response phase I/II study, the EP4 antagonist vorbipiprant (CR6086) combined with PD-1 blockade was well tolerated and showed promising efficacy in refractory mismatch-repair-proficient/microsatellite stable metastatic colorectal cancer (CRC) (Pietrantonio et al, Clin Cancer Res 2024). Here we report the results from a study extension in non-colorectal gastrointestinal (GI) cancers with the vorbipiprant dose selected for further development in combination with immunotherapy. **Methods:** Twenty-seven adult patients (pts) with metastatic non-colorectal GI cancers, ECOG PS $\leq$1, and $\geq$1 prior treatment line were included in 3 cohorts (9 pts each): gastric cancer (GC) with PD-L1 Combined Positive Score (CPS) $\geq$5 (cohort A), GC with PD-L1 CPS $<$ 5 (cohort B), and GI cancers other than CRC and GC (cohort C). Pts receive oral vorbipiprant (90 mg twice daily) plus iv balstilimab (3 mg/kg every 2 weeks) until disease progression, unacceptable toxicity or death. Primary endpoints are safety and disease control rate (DCR) per RECIST 1.1. Secondary endpoints include objective response rate, progression-free and overall survival (ORR, PFS, OS). Exploratory endpoints include tissue and blood biomarkers. **Results:** At a cutoff date of November 20, 2024, enrolment is completed. In cohort C, we enrolled: 5 BTC, 2 pancreatic and 2 ampullary cancer patients. Overall, median age was 61 (interquartile range: 55-68) years, similar among cohorts; 70% were men, with a slightly higher prevalence in Cohort A; the median number of prior treatment lines was 3 (IQR: 2-4) overall and in gastric cohorts, and 2 (IQR: 2-3) in other GI cancers cohort. Prior ICIs were administered in 44%, 22% and 11% in Cohort A, B and C, respectively. No treatment-related serious or grade $>$ 3 adverse events were reported. Promising activity was observed. In cohort A, 3 pts had a partial response (PR), 2 of them still ongoing and 2 lasting more than 6 months; in addition, 1 pt had stable disease (SD). In cohort B, 4 pts had SD, 1 of them still ongoing and 2 lasting more than 6 months. In cohort C, 1 pt with pancreatic cancer had a PR, still ongoing for $>$ 6 months; in addition, 1 BTC patient had SD. Median PFS and OS were: 4,5 and 9,7 months in Cohort A, 1,8 and 6,8 months in Cohort B, 2,0 and 4,5 months in Cohort C. Responses occurred irrespective of MSI/MMR status and prior exposure to ICIs. **Conclusions:** Vorbipiprant combined with PD-1 blockade was well tolerated and showed signs of activity in non-colorectal GI cancers, thus confirming a broader spectrum of activity on top of the results in MSS CRC. Clinical trial information: NCT05205330. Research Sponsor: Rottapharm Biotech.

2609 **Poster Session**

Bispecific innate cell engager (ICE) AFM24 in combination with atezolizumab in patients with advanced/metastatic *EGFR*-expressing non-small cell lung cancer (NSCLC) without driver mutations: Initial results from a phase 2a study. First Author: Hye Ryun Kim, Division of Medical Oncology, Yonsei Cancer Center, Yonsei University College of Medicine, Seoul, South Korea

Background: Novel treatments are needed for patients with advanced/metastatic NSCLC without actionable driver mutations who progress after prior therapies including checkpoint inhibitors (CPI) and platinum-based chemotherapy. AFM24 is a tetravalent, bispecific ICE that binds CD16A on NK cells and macrophages and EGFR on solid tumors, redirecting and enhancing the innate and possibly the adaptive immune response. The *EGFR*-wildtype (*EGFR*-WT) NSCLC expansion cohort of the Phase 1/2a study (NCT05109442) is evaluating the combination of AFM24 and atezolizumab. **Methods:** AFM24 is given weekly at 480 mg intravenously (IV) in combination with 840 mg atezolizumab IV fortnightly to patients with advanced or metastatic *EGFR*-WT NSCLC who progressed on $\geq$1 prior line of therapy, including at least a platinum doublet and a CPI. The primary endpoint is overall response rate (ORR) by RECIST v1.1 by Investigator assessment. Secondary endpoints include safety, pharmacokinetics, and immunogenicity. Treatment is given in 28-day cycles until disease progression, intolerable toxicity, investigator discretion, or patient withdrawal of consent. **Results:** As of 15 January 2025, 43 patients received AFM24 and atezolizumab for a mean (range) duration of 19.6 (1–78) weeks. Median (range) age is 67 (40–79) years; 72% male; all patients had an ECOG performance status of 0 (14%) or 1 (86%). Median (range) number of prior lines is 2 (1–7). All patients had discontinued their previous CPI treatment due to progressive disease. The combination was well tolerated with no unexpected toxicities; infusion-related reactions, the most common adverse events (AE), were reported in 54% of patients (28 Grade 1–2, 4 Grade 3). Most common $\geq$G3 treatment-related AEs were ALT/AST elevations in 2 patients, all fully resolved. The 35 response-evaluable patients showed an ORR of 23% (8 responses: 1 complete response, 7 partial responses), tumor shrinkage in 46% (16/35) and a disease control rate (DCR) of 77%. Of the 8 responders, 6 had never achieved an objective response on prior CPIs. Preliminary median progression-free survival (PFS) is 5.5 months (95% CI 2.9–7.4), with 29% of patients still on treatment. **Conclusions:** AFM24 in combination with atezolizumab shows promising clinical efficacy in patients who failed prior treatment including platinum-based chemotherapy and CPI. Patients showed a tolerable and well-managed safety profile. A considerable DCR of 77%, with some long, sustained responses was observed. Confirmed responses were achieved in patients who had not responded to prior CPI. This combination treatment approach could offer a promising chemotherapy-free alternative to patients who have exhausted the available therapeutic options and could provide a strategy to overcome resistance to prior CPI. Clinical trial information: NCT05109442. Research Sponsor: Affimed GmbH.

2610 **Poster Session**

Combination of bispecific innate cell engager (ICE) AFM24 with atezolizumab in patients with advanced/metastatic non-small cell lung cancer (NSCLC) with *EGFR* kinase domain mutations (*EGFR*mut): Initial results from a phase 2a study. First Author: Omar Saavedra, Vall d'Hebron Institute of Oncology (VHIO), Barcelona, Spain

Background: Immune checkpoint inhibitor (ICI) monotherapy has shown limited activity against advanced *EGFR*mut NSCLC. However, combinatorial approaches may enhance the clinical outcomes and are under evaluation. AFM24 is a tetravalent, bispecific ICE that binds CD16A on NK cells and macrophages and EGFR on solid tumors, redirecting and enhancing immune responses towards EGFR-expressing tumors. Atezolizumab, an anti-PD-L1 antibody, has been approved in patients with various solid tumors. The *EGFR*mut NSCLC expansion cohort of this Phase 1/2a study explores a possible synergistic effect of AFM24 in combination with atezolizumab in heavily pretreated patients with NSCLC *EGFR*mut (NCT05109442). **Methods:** AFM24 is given weekly at 480 mg intravenously (IV) in combination with 840 mg atezolizumab IV fortnightly to patients with advanced or metastatic *EGFR*mut NSCLC who progressed on $\geq$1 prior line of therapy, including $\geq$1 prior TKI. The primary endpoint is overall response rate (ORR) by RECIST v1.1 by Investigator assessment. Secondary endpoints include safety, pharmacokinetics, and immunogenicity. Treatment is given in 28-day cycles until disease progression, intolerable toxicity, investigator discretion, or patient withdrawal of consent. **Results:** As of 15 January 2025, 28 patients received AFM24 and atezolizumab for a mean (range) duration of 21.7 (2–65) weeks. Median (range) age is 65 years (32–83); 67.9% were female. All patients had received prior *EGFR*-specific TKI, 82% had received platinum-based chemotherapy and 75% 3rd gen TKIs. Patients received a median (range) of 3 (1–8) prior lines of treatment. The combination was well tolerated with no new or unexpected toxicities observed compared to each single agent. The most common treatment-related adverse events (TRAE) were infusion-related reactions in 64% of patients (19 Grade 1–2, 1 Grade 3). 9 patients had $\geq$G3 TRAEs, the most common being neutropenia/neutrophil count decrease, with no associated infections. No other immune TRAEs were reported. The 22 response-evaluable patients achieved an ORR of 23% (1 CR, 3 PRs, 1 unconfirmed PR), a DCR of 64% and tumor shrinkage in 50% of patients. Responses were deepening over time in 3 patients. With a median follow-up of 9 months, the median PFS was 5.5 months (95% CI 1.9–not-evaluable). 6 (27%) patients have received treatment for over 10 months. **Conclusions:** AFM24 combined with atezolizumab demonstrated encouraging clinical efficacy in patients with *EGFR*mut NSCLC who had exhausted prior lines of therapy. Treatment showed a well-managed safety profile. This approach potentially offers a feasible, chemotherapy-free therapeutic option for the *EGFR*mut NSCLC patients who have progressed to prior TKIs and platinum-based chemotherapy and warrants further evaluation. Clinical trial information: NCT05109442. Research Sponsor: None.

2611 **Poster Session**

Primary efficacy and safety results of BAT1308, a PD-1 inhibitor, + chemotherapy ± bevacizumab in phase 2 trial for persistent, recurrent, or metastatic cervical cancer. First Author: QingLei Gao, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China

Background: BAT1308 is a fully humanized and high-affinity anti-PD-1 IgG4κ antibody. Previous phase 1 study demonstrated BAT1308 had a promising efficacy in patients with advanced cervical cancer. Here we present the primary safety and efficacy results in phase 2 study for BAT1308 combined with platinum-based chemotherapy ± bevacizumab as first-line therapy for PD-L1–positive persistent, recurrent, or metastatic cervical cancer. **Methods:** In this multicenter, single-arm, open-label, phase 2 study, eligible patients were $\geq$18 to $\leq$75 years of age with PD-L1 CPS $\geq$1, FIGO Stage IVB cervical cancer, who did not receive prior systemic anti-tumor therapy for persistent, recurrent or metastatic cervical cancer and not amenable to curative treatment. Patients received BAT1308 (300 mg Q3W for up to 24 months) plus platinum-based chemotherapy (paclitaxel 175 mg/m^2 + cisplatin 50 mg/ m^2 or carboplatin AUC 5) and, per investigator discretion, bevacizumab (15 mg/kg). The primary endpoint was safety. The major secondary endpoint was objective response rate assessed by investigator according to RECIST 1.1. **Results:** As of January 7, 2025, a total of 29 patients were enrolled, with a median age of 53 years (range 32-69), 20 (69.0%) patients had ECOG performance status of 1, 15 (50.7%) patients with PD-L1 CPS $\geq$ 10, 24 (82.8%) patients had squamous-cell carcinoma, 17 (58.6%) patients received previous neoadjuvant or adjuvant chemotherapy or chemoradiotherapy with a paclitaxel + platinum regimen, 7 (24.1%) patients had previous untreated metastatic disease at trial entry. Bevacizumab was used by 23 (79.3%) patients in this phase II study. All 29 subjects received combination therapy. 27 subjects completed at least one efficacy assessment. The ORR was 74.1%, with a confirmed ORR of 70.4%. The complete response rate was 11.1%, and the disease control rate was 100%. Currently, 16 subjects remain on treatment. Among those who discontinued the study, 8 withdrew informed consent, 4 experienced disease progression, and 1 died. The 6-month, 9-month, and 12 -month PFS rates were 83.4%, 78.8%, and 78.8% respectively. The median PFS has not yet been reached. The most common adverse events were anemia (82.8%), white blood cell decreased (51.7%), alopecia (51.7%), thrombocytopenia (48.3%), and neutropenia (44.8%). Grade 3 and above adverse events occurred in 72.4% of 29 patients, and $\geq$ Grade 3 irAEs observed in 3 (10.3%) patients. Serious adverse events occurred in 44.8% of the patients. **Conclusions:** BAT1308 combined with platinum-based chemotherapy ± Bevacizumab as first-line therapy showed durable anti-tumor activity and manageable safety profile for PD-L1-positive (CPS $\geq$ 1) persistent, recurrent or metastatic cervical cancer. These data are consistent with the earlier results and provide support for further studies. Clinical trial information: NCT06123884. Research Sponsor: Bio-Thera Solutions, Ltd.

2612 **Poster Session**

Neoadjuvant serplulimab with concurrent chemoradiotherapy in resectable esophagogastric junction adenocarcinoma: Phase 2 updated results. First Author: Yuping Ge, Peking Union Medical College Hospital, Beijing, Beijing, China

Background: This study evaluated the efficacy and safety of neoadjuvant Serplulimab combined with concurrent chemoradiotherapy for locally advanced resectable esophagogastric junction (EGJ) adenocarcinoma. **Methods:** Eligible patients with resectable EGJ (cT3-4 or N+M0) adenocarcinoma received neoadjuvant Serplulimab (300 mg) plus SOX (oxaliplatin 130 mg/m^2; TS1 40-60 mg) for the first cycle, followed by Serplulimab with concurrent chemoradiotherapy (oxaliplatin 100 mg/m^2, TS1 40-60 mg; radiotherapy dose 45 Gy/ 25 fractions) during the second and third cycles. Surgery was performed 6-8 weeks after chemoradiotherapy. Tissue and blood samples were collected for genetic analysis. Primary endpoints included pathological complete response (pCR) and major pathological response (MPR). **Results:** From March 2023 to November 2024, 24 patients were enrolled and 19 patients underwent radical resection. The R0 rate was 100%. pCR rate was 26.3%, MPR rate was 36.8%. T downstaging rate 78.9%, ypN0 89.5%. The median DFS was not reached. Microsatellite stable status was 100%. PD-L1 CPS expression: $<$ 1 (5.3%), 1-5 (42%), $>$ 5 (52.6%), $>$ 10 (31.6%). PD-L1 expression was associated with pathological response, with MPR rates of 57.1% for CPS $\geq$5 and 14.3% for CPS $<$ 5. Minimal residual disease positivity (MDR+) before enrollment was 68.7%, and 6 MRD+ patients converted to MRD- after neoadjuvant therapy. Grade $\geq$3 adverse events occurred in 33.3% of patients, with manageable treatment-related adverse events. **Conclusions:** Neoadjuvant Serplulimab with concurrent chemoradiotherapy showed promising efficacy for locally advanced resectable EGJ adenocarcinoma. Improved R0 and ypN0 rate may change the surgical procedure in the future. Follow-up will assess correlations between biomarkers and outcomes. Clinical trial information: NCT05918419. Research Sponsor: None.

2613 **Poster Session**

Niraparib plus PD-1 inhibitor for patients previously treated with immune checkpoint inhibitor for solid tumors with homologous recombination repair gene mutation (IMAGENE): A phase II basket study. First Author: Taigo Kato, Department of Urology, Osaka University Graduate School of Medicine, Suita, Japan

Background: Prior clinical trials have established the effectiveness of poly (ADP-ribose) polymerase (PARP) inhibitor (PARPi) or immune checkpoint inhibitor (ICI) monotherapy in patients with cancer characterized by mutations in homologous recombination repair (HRR) genes. This trial aims to evaluate the efficacy and safety of PARPi and PD-1 inhibitor in patients with HRR gene-mutated solid tumors previously treated with ICIs. **Methods:** IMAGENE is an open-label phase II basket study evaluating the efficacy and safety of niraparib and PD-1 inhibitor in patients with HRR gene-mutated cancers that have shown resistance to one or more standard therapy including ICIs. HRR mutation status was evaluated by circulating tumor DNA (ctDNA) or tumor tissue DNA. The primary endpoint was confirmed objective response rate (cORR) per investigator assessment. Patients were treated on a 21-day cycle with niraparib (200 mg orally daily) and nivolumab/pembrolizumab (240 mg/body intravenously every 2 weeks or 3 mg/kg every 3 weeks, respectively). **Results:** Of 47 enrolled patients, 22 were enrolled based on HRR gene alteration detected in ctDNA. The most common tumor type was gastric cancer (36.2%), followed by bladder cancer (BC, 25.5%), and renal cell carcinoma (RCC, 12.8%). As of data cutoff (September 30, 2024), the median duration of follow-up was 31.7 weeks. The median number of prior treatment line was 6.5 (1 to 20). In total, the cORR was 4.4% (90% CI, 0.8 to 13.3), with a disease control rate (DCR) of 55.6% (90% CI, 42.3 to 68.3). Notable DCRs were observed in patients with RCC (83.3%) and BC (80.0%). The median duration of response and progression-free survival (PFS) were 35.0 weeks (90% CI, 20.0 to 50.0) and 11.6 weeks (90% CI, 7.0 to 13.6), respectively. At data cutoff, 28 patients (62.2%) had died, with 12-month overall survival (OS) rate of 41.7% (90% CI, 29.1 to 53.8). Interestingly, *BRCA1/2*-mutated patients had significantly shorter OS compared to those with other HRR gene mutations (p = 0.0096). The three most common treatment-emergent adverse events (TEAEs) were nausea (31.1%), vomiting (31.1%), and anaemia (26.7%). Grade $\geq$3 TEAEs were reported in 18 patients (40.0%), with the most common being anaemia (17.8%). TEAEs led to treatment regimen discontinuation in one patient, and there were no deaths due to TEAEs. **Conclusions:** Niraparib combined with PD-1 inhibitor showed modest activity even in heavily pretreated patients with HRR gene-mutated cancers who progressed on ICI therapy. Furthermore, patients with specific cancer type had promising benefit from this combination therapy, warranting further investigation in specific populations. Clinical trial information: jRCT2051210120. Research Sponsor: The Japan Agency for Medical Research and Development; 21ck0106656h0001; Takeda Pharmaceutical Co., Ltd.

2614 **Poster Session**

Stereotactic radiotherapy plus immunotherapy and influence on prognosis in driver-gene–negative non-small cell lung cancer patients with brain oligometastases. First Author: Xiaomei Gong, Tongji University Affiliated Shanghai Pulmonary Hospital, Shanghai, China

Background: This study seeks to elucidate the therapeutic benefits of integrating stereotactic radiotherapy (SRT) with immunotherapy for treating brain oligo-metastases (BMs) in patients with non-small cell lung cancer (NSCLC). **Methods:** In this retrospective real-world study, patients with driver-gene-negative NSCLC and 1-3 BMs were enrolled to evaluate the therapeutic benefits of combining SRT with immune checkpoint inhibitors (ICIs) and chemotherapy. The primary endpoint was overall survival (OS). Secondary endpoints included intracranial progression-free survival (iPFS), progression-free survival (PFS), and the response of intracranial lesions. **Results:** Based on chemotherapy (CT), 65 patients underwent SRT+ICIs therapy, 47 patients underwent SRT, and 44 patients underwent ICIs. For patients with with $>$ 500 mm^3 BMs, SRT + ICIs + CT significantly improved the OS (22.1 vs. 13.5 vs. 18.5 months, p = 0.012), iPFS (17.5 vs. 7.8 vs. 11.8 months, p $<$ 0.001), PFS (11.3 vs. 7.6 vs. 5.3 months, p = 0.019), and iORR (56.3% vs. 20.3% vs 28.9%, p = 0.001) compared to SRT+CT or ICIs + CT therapy. In the sub-group of patients of symptomatic BMs, SRT + ICIs + CT significantly improved the OS (24.7 vs. 14.7 vs. 17.5 months, p = 0.012), iPFS (13.7 vs. 9.8 vs. 11.8 months, p = 0.046), and iORR (34.5% vs. 13.8% vs 23.7%, p = 0.027) compared to SRT + CT or ICIs + CT therapy as well. Concurrent SRT with ICIs (time interval $<$ 2 weeks) significantly improved the OS (28.2 vs. 15.4 months, p = 0.01), iPFS (25.8 vs. 12.1 months, p = 0.014), and iORR (63.2% vs. 37.0%, p = 0.017) when compared to sequential SRT with ICIs. Combined therapy did not increase the incidence of any grade of central nervous system and immune-related adverse events. **Conclusions:** Based on chemotherapy, the combination of concurrent SRT and ICIs improve the prognosis of driver-gene-negative NSCLC with BMs without increasing the occurrence of adverse events. Furthermore, it demonstrates increased effectiveness for treating larger and symptomatic intracranial lesions, specifically those $>$ 500 mm^3 in volume. Research Sponsor: None.

Data on patient outcomes.

	All Patients				Sub-Group in Lesions > 500 mm^3				Sub-Group in Symptomatic Brain Metastases				SRT+ICIs+CT Sub-Group		
Median, months	SRT+ICIs+CT (n=65)	SRT+CT (n=47)	ICIs+CT (n=44)	p-Value	SRT+ ICIs+CT (n=44)	SRT+CT (n=28)	ICIs+CT (n=17)	p-Value	SRT+ ICIs+CT (n=38)	SRT+CT (n=38)	ICIs+CT (n=21)	p-Value	Concurrent (n=31)	Sequential (n=34)	p-Value
OS	23.0	14.2	18.7	0.033	22.1	13.5	18.5	0.012	24.7	14.7	17.5	0.012	28.5	15.4	0.01
iPFS	15.3	8.5	13.0	0.002	17.5	7.8	11.8	$<$ 0.001	13.7	9.8	11.8	0.046	25.8	12.1	0.014
PFS	9.8	6.7	8.0	0.072	11.3	7.6	5.3	0.019	8.9	6.7	5.7	0.13	12.2	9.0	0.009
iORR	48.8%	24.5%	49.0%	0.01	56.3%	20.3%	28.9%	0.001	34.5%	13.8%	23.7%	0.027	63.2%	37.0%	0.017
iDCR	83.3%	75.5%	76.5%	0.46	85.4%	62.1%	72.2%	0.063	22.2%	17.2%	12.7%	0.61	92.1%	76.1%	0.05

SRT, stereotactic radiotherapy; ICIs, immune checkpoint inhibitors; CT, chemotherapy; OS, overall survival; iPFS, intracranial progression free survival; PFS, progression free survival; iORR, intracranial overall response rate; iDCR, intracranial disease control rate.

2615 **Poster Session**

A randomized controlled study of tislelizumab combined with concurrent chemoradiotherapy in the treatment of locally advanced cervical cancer and the predictive value of T lymphocyte subsets for efficacy. First Author: Fang Wu, Department of Radiation Oncology, the First Affiliated Hospital of Guangxi Medical University, Nanning, Guangxi, China

Background: Concurrent chemoradiotherapy (CCRT) has been the standard of care for locally advanced cervical cancer (LACC) for over 20 years. However, 30-40% of treated patients have recurrence or progression within 5 years. **Methods:** A total of 53 patients with LACC who were treated in the First Affiliated Hospital of Guangxi Medical University from May 2023 to November 2024 were prospectively collected and randomly divided into the CCRT group (N = 26) and the CCRT+T group (N = 27). The treatment plan was as follows: 200 mg of tislelizumab was intravenously infused on the first day of radiotherapy, once every 3 weeks, for 1 year or until disease progression or intolerable toxicity, whichever occurred first. Chemotherapy involved single-agent cisplatin at a dose of 40 mg/m^2. External irradiation used 6MV-X-ray intensity-modulated radiotherapy with a dose of 45-50Gy/25f. Simultaneously, peripheral blood T lymphocyte subsets were detected in the enrolled patients before and at the end of radiotherapy. The primary endpoint of the study was the objective response rate, and secondary endpoints included toxicity, PFS and OS. **Results:** Follow-up was completed by January 2025, with a median follow-up time of 13.7 months (5.2-20.5 months) in the CCRT group and 11.2 months (5.9-20.6 months) in the CCRT+T group. The CCRT+T group had higher complete response (CR) and objective response rates (ORR) compared to the CCRT group, with CR rates of 44.4% versus 19.2% (p = 0.035) and ORR rates of 100% versus 84.6% (p = 0.046). The patients with CR were subjected to logistic regression analysis. The results of univariate and multivariate analysis showed that CD4+T cell percentage (p = 0.034) and tislelizumab use (p = 0.038) were significantly associated with CR. However, no statistical difference was observed in the OS (p = 0.414) and PFS (p = 0.716) between the two groups, as shown by the Kaplan-Meier survival curves. After treatment, the CCRT+T group had increased levels of total T cell percentage, CD4+T cell percentage, CD4/CD8, double positive T lymphocyte subset percentage, absolute T lymphocyte count, absolute CD4+T lymphocyte count, and B lymphocyte (CD19) compared to the CCRT group. Notably, the double positive T lymphocyte subset percent (p = 0.025) and absolute CD4+T lymphocyte count (p = 0.047) showed significant increases. There was no significant difference in the incidence of acute adverse reactions between the two groups (P $>$ 0.05). **Conclusions:** CCRT+T demonstrated superior short-term efficacy in treating LACC compared to CCRT, although long-term efficacy necessitates further follow-up observation. The combination of tislelizumab and CCRT in the treatment of LACC can improve the levels of T cell subsets, with tolerable acute toxic and good safety. CD4+T cell percentage and tislelizumab use may be associated with CR. Research Sponsor: None.

2616 Poster Session

PD-1 inhibitors combined with radiotherapy and GM-CSF, sequentially followed by IL-2 regimen in advanced refractory solid tumors: A prospective, multicenter clinical trial. First Author: Pengfei Xing, Center for Cancer Diagnosis and Treatment, The Second Affiliated Hospital of Soochow University, Suzhou, China

Background: Low frequency of durable responses in patients treated with immune checkpoint inhibitors demands for taking complementary strategies in order to boost immune responses against cancer. Our previous PRaG1.0 trial also demonstrated that PD-1 inhibitors in combination with radiotherapy and granulocyte macrophage-colony stimulating factor (GM-CSF) could improve clinical response in patients with advanced refractory solid tumors (ChiCTR1900026175). In an effort to further enhance efficacy, we conducted this PRaG2.0 trial (ClinicalTrials.gov: NCT04892498) and optimized the PRaG1.0 regimen by incorporating interleukin-2 (IL-2). **Methods:** The PRaG 2.0 regimen was administered to patients with advanced refractory solid tumors who lacked or were unable to tolerate standard-of-care treatments. A treatment cycle consisted of radiotherapy (5 or 8Gy$\times$2-3f) delivered for one metastatic lesion, PD-1 inhibitor dosing within one week after completion of radiotherapy, GM-CSF 200μg subcutaneous (SC) injection once daily for 7 days, and then sequentially followed by IL-2 2million IU SC once daily for 7 days. PRaG 2.0 regimen was repeated every 21 days for at least 2 cycles until no appropriate lesions for irradiation or reached the tolerance dose of normal tissues. Patients who could not continue radiotherapy and had not yet developed progression disease (PD) allowed PD-1 inhibitors to be continued as maintenance therapy until PD or unacceptable toxicity but no more than one year. The endpoints were Progression-Free Survival (PFS), objective response rate (ORR) and overall survival (OS). **Results:** As of 31st October 2024, 66 patients were enrolled in the study. The median Progression-Free Survival (PFS) was 4.3 months, and the median overall survival (OS) was 10.3 months. The objective response rate (ORR) was 22.7%, and the disease control rate (DCR) was 56.1% according to RECIST version 1.1. Treatment-related adverse events (TRAE) experienced in 57 (86.4%) patients, with 6 patients (9.1%) experiencing Grade $\geq$ 3 TRAEs. We found that in the period prior to disease progression, the absolute count of Treg cells increased compared to baseline, while the percentage of CD8+PD-1+/CD8+ cells decreased compared to baseline. **Conclusions:** The PRaG 2.0 trial demonstrates that PD-1 inhibitors in combination with radiotherapy, GM-CSF, and IL-2 could be a potential treatment regimen for patients with advanced refractory solid tumors. The decrease in the CD8+PD-1+/CD8+% ratio and the increase in the absolute count of Treg cells may suggest potential tumor progression in patients. Clinical trial information: NCT04892498. Research Sponsor: None.

2617 Poster Session

Phase 1 study of recombinant interleukin 15 in combination with nivolumab and ipilimumab in subjects with refractory cancers. First Author: Jibran Ahmed, National Cancer Institute, Bethesda, MD

Background: Combining immune checkpoint inhibitors with cytokine therapies holds promise in cancer immunotherapy. Recombinant human interleukin-15 (rhIL-15) increases circulating CD8+ T cells and natural killer (NK) cells. This Phase 1 study evaluated the safety (NCI-CTCAE v5.0), tolerability, and preliminary efficacy (RECIST v1.1 and iRECIST) of rhIL-15 with nivolumab and ipilimumab. Safety data for rhIL-15/ipilimumab and rhIL-15/nivolumab doublets were reported earlier (O'Sullivan et al., AACR 2019). Here, we present updated triplet dose-escalation results and correlative analyses. **Methods:** This open-label, non-randomized Phase 1 trial employed a 3+3 dose-escalation design to determine the MTD/RP2D of rhIL-15 SQ (administered on days 1-8 and 22-29, cycles (C) 1-4 only) combined with fixed doses of nivolumab (240 mg IV on days 8, 22, 36) and ipilimumab (1 mg/kg IV on day 8) in 42-day cycles in patients with advanced, refractory cancers. Correlative analyses assessed effects on circulating T cell subsets, PD-1/PD-L1 expression, and immune cell activation in tumor tissue (using multiplex immunofluorescence, immunohistochemistry and flow cytometry). **Results:** Thirty-one patients (median age: 56 years, range: 24-81) were enrolled and evaluable for safety and response. The most prevalent cancer types were sarcoma, pancreatic, and colorectal cancers (n = 5 each). The MTD/RP2D was established at 1 μg/kg/day SQ rhIL-15, with a manageable safety profile. Common treatment-related adverse events (TRAE) included injection site reactions (74%), fever (65%), and chills (65%). Grade 3/4 lymphopenia was seen in 13% of patients (4 of 31). Confirmed partial response (cPR) was measured in 1/31 patients (3%); the patient had cholangiocarcinoma and was treated at dose level 1 (DL1, 0.5 μg/kg/day rhIL-15) and the response lasted through cycle 16. Stable disease (SD) occurred in 17/31 patients (55%, median: 2 cycles, range: 1-10), including durable SD (10 cycles at DL1) in salivary gland squamous cell carcinoma. Nine patients had progressive disease as a best response. Four patients did not have tumor measurements after C1 or did not complete C1, including 3 with clinical disease progression and one with grade 3 TRAE. NK cells and $\gamma\delta$-T cells increased in blood, but increases did not correlate with tumor infiltration measured on C1D42. CD8+ T cells increased modestly in blood and tumor without correlation to either clinical benefit, increased PD1+CD3+ lymphocytes, or PD-L1+ tumor cells on C1D42. **Conclusions:** These data suggest the addition of rhIL-15 to the combination of ipilimumab and nivolumab is safe, elicited a pharmacodynamic response from the immune system in blood but not tumor, and did not improve overall response rate. Clinical trial information: NCT03388632. Research Sponsor: U.S. National Institutes of Health.

2618 Poster Session

Effect of AdAPT-001 on checkpoint inhibitor resistance in solid tumors. First Author: Anthony Paul Conley, Department of Sarcoma Medical Oncology, The University of Texas MD Anderson Cancer Center, Houston, TX

Background: Checkpoint inhibitors (CIs) have revolutionized cancer treatment, but most patients do not respond to them because of primary or secondary resistance. Introduction or reintroduction of CIs to resistant patients is relatively contraindicated because of the likelihood of an unfavorable harm-benefit profile. An intensive search is on for therapies that sensitize resistant tumors to CI therapy. AdAPT-001 is an oncolytic adenovirus armed with a transforming growth factor beta (TGFβ) trap that eliminates the immunosuppressive cytokine, TGFβ. Clinical data demonstrate that AdAPT-001 reverses the tumor immune evasion phenotype and improves the efficacy of immune checkpoint therapy, increasing response rate and progression-free survival (PFS) in CI refractory angiosarcoma. **Methods:** Patients with CI-refractory solid cancers of any type including sarcomas, melanoma, and breast cancer who received AdAPT-001 with a concurrent checkpoint inhibitor. Response was assessed every 8 weeks using RECIST 1.1. Treatment beyond progression was allowed for patients clinically benefiting, and if progression was confirmed on the next assessment then the first assessment meeting PD criteria was considered the date of progression. PFS on AdAPT-001 + CI was compared to duration of treatment on the most recent previous regimen including a CI before study enrollment. **Results:** Among all patients who were treated with a CI in a previous line of therapy (Prior CI) before being treated with AdAPT-001 + CI, the 6-month PFS rate was 17% (3/18) with Prior CI and 33% (6/18) with AdAPT-001 + CI, and the 12-month PFS rate was 0% (0/18) with Prior CI and 17% (3/18) with AdAPT-001 + CI. Particular activity was seen in angiosarcoma, where all patients progressed within 3 months on Prior CI and 75% (3/4) had PFS $>$ 11 months with AdAPT-001 + CI. Treatment with AdAPT-001 was well tolerated and no new safety signals emerged. **Conclusions:** CI treatment is not an option for many patients because of primary or secondary resistance to them and the potential for harm without benefit. The data from this P2 clinical trial strongly suggests that AdAPT-001 circumvents resistance to CIs in multiple tumor types, improving PFS when compared to the patient's prior CI regimen. In addition, AdAPT-001 may prevent the development of CI-induced autoimmune toxicities. P3 clinical trials in sarcoma and hepatocellular carcinoma are planned. Clinical trial information: NCT04673942. Research Sponsor: None.

Duration of treatment on a previous CI regimen compared to subsequent PFS with AdAPT-001 + CI.

Subject ID	Months on prior CI regimen	PFS (months) with AdAPT-001 + CI	PFS Change (months)
1	3.0	11.4	+8.4
2	3.0	2.0	-1.0
3	1.9	13.0	+11.1
4	2.7	12.0	+9.3
Median	2.8	11.7	+8.9

2619 Poster Session

Efficacy and toxicity of nivolumab and ipilimumab in rare cancer brain metastases: A multi-center basket trial analysis (NCI/SWOG S1609). First Author: Manmeet Singh Ahluwalia, Miami Cancer Institute, Baptist Health South Florida, Miami, FL

Background: Outcomes of patients with brain metastases (BM) treated with single or dual checkpoint inhibitors have been previously evaluated, showing similar intra-cranial and extra-cranial response rates and overall survival (OS). However, prior research has primarily focused on common tumor types such as melanoma and lung cancer. We report outcomes in patients with BM from the largest basket trial for rare cancers (N=684 evaluable patients) to evaluate efficacy and toxicity. **Methods:** Patients were treated with nivolumab (NIVO, 240 mg Q2W) and ipilimumab (IPI, 1 mg/kg Q6W) in the federally funded SWOG S1609 DART trial (NCT02834013), conducted across $>$1000 sites. The protocol and consent were reviewed and approved by SWOG, the NCI, the NCI central institutional review board, and institutional review boards of participating sites. Efficacy and toxicity were assessed in patients with and without BM at enrollment. Progression-free survival (PFS), and OS were estimated using Kaplan-Meier methodology. Tumor response was evaluated per RECIST v1.1, toxicities were assessed using CTCAE v5.0. Hazard ratios (HR) with 95% confidence intervals (CI) and P-values were calculated to compare outcomes. **Results:** Similar response rates were observed in patients without BM (11%, n=707) compared to 10% in those with BM at enrollment (n=20). PFS and OS were comparable between patients with and without BM at enrollment (HR=1.29 [0.81-2.07], P=0.28; HR=1.36 [0.81-2.27], P=0.24, respectively). Grade $\geq$3 CNS treatment-related toxicity occurred in 3% of patients without BM versus 5% in those with BM (P=0.43). Similarly, Grade 5 treatment-related toxicity was observed in 2% of patients without BM compared to 5% in patients with BM (P=0.31). Among 18 patients with BM with progression, intra-cranial progression only was seen in 1 (5.5%) patient, while extra-cranial disease progression only in 12 (66.7%); 5 (27.8%) patients experienced concurrent intra- and extra-cranial disease progression. **Conclusions:** In this unique cohort of patients with rare tumors and BM receiving dual checkpoint inhibitor therapy, similar response rates and survival outcomes were observed in patients with or without BM at enrollment. No significant differences in CNS or non-CNS toxicity were noted. Funding: NIH/NCI/NCTN grants U10CA180888, U10CA180819. Clinical trial information: NCT02834013. Research Sponsor: None.

Clinical outcomes and cox regression analysis.

Outcome	No BM (n=707), n (%)	BM (n=20), n (%)	P-value
Best RECIST Response			0.76
Confirmed CR/PR	81 (11.5)	2 (10)	
Unconfirmed CR/PR	22 (3.1)	0 (0)	
Clinical benefit (SD >6 mo)	97 (13.7)	3 (15)	
SD <6 mo or censored	123 (17.4)	1 (5)	
Progression/Failure	384 (54.3)	14 (70)	
PFS, HR (95% CI)			
Univariate	1.22 (0.77-1.93)		0.39
Multivariate	1.29 (0.81-2.07)		0.28
OS, HR (95% CI)			
Univariate	1.23 (0.75-2.02)		0.41
Multivariate	1.36 (0.81-2.27)		0.24

2620 **Poster Session**

Clinical factors and prognostic outcomes of hyperthyroidism induced by immune checkpoint inhibitor therapy. First Author: Baqir Jafry, Charleston Area Medical Center, Charleston, WV

Background: Hyperthyroidism is a recognized but less frequent immune-related adverse event (iRAE) associated with Immune Checkpoint Inhibitor (ICI) use. While its occurrence has been documented, gaps remain in understanding the underlying risk factors, and its impact on patient outcomes. This study seeks to provide clarity on these aspects and guide improved management strategies. **Methods:** Data were obtained from the TriNetX research network for patients with cancers where ICI is used. Inclusion criteria encompassed patients aged 18 years or older treated with ICIs (e.g., pembrolizumab, nivolumab, atezolizumab, cemiplimab) between January 1, 2013, and December 31, 2024. Patients with a history of thyroid disorders or Levothyroxine use were excluded. Competing risk analyses evaluated the likelihood of hyperthyroidism versus death up to 12 months after ICI use and the likelihood of beta-blocker usage after diagnosis. Cox proportional hazards modeling was used to identify significant covariates associated with hyperthyroidism, including age, sex, cancer type, comorbidities, and ICI type. Backwards batchwise elimination was employed to retain only significant variables. **Results:** Among 39,749 patients receiving ICIs, 2.3% developed hyperthyroidism within 12 months after treatment. In patients with hyperthyroidism, 31.3% initiated metoprolol, 9.5% initiated propranolol, and 6.0% initiated atenolol for symptom management. The mortality rate in the group was 32.1% based on the cumulative incidence. An increased risk of hyperthyroidism was associated with endometrial cancer (HR: 1.44; 95CI: 1.23-1.69; $p < 0.0001$), non-Hodgkin lymphoma (HR: 1.42; 95CI: 1.09-1.84; p = 0.010), and kidney cancer (HR: 1.34; 95CI: 1.25-1.63; p = 0.001). Conversely, patients with colon cancer (HR: 0.74; 95CI: 0.55-0.98; p = 0.038) had a lower chance of developing hyperthyroidism. Among all ICIs, atezolizumab (OR: 1.32; 95% CI: 0.82–2.13; p = 0.25) showed the strongest trend toward hyperthyroidism, followed by durvalumab (OR: 1.24; 95% CI: 0.75–2.05; p = 0.39), pembrolizumab (OR: 1.23; 95% CI: 0.81–1.87; p = 0.34), and nivolumab (OR: 1.22; 95% CI: 0.80–1.86; p = 0.37). In contrast, cemiplimab (OR: 0.61; 95% CI: 0.17–2.16; p = 0.44) showed a lower likelihood of causing hyperthyroidism. **Conclusions:** ICI-induced hyperthyroidism, while less common, has a significant impact on patient outcomes, including mortality. Identifying high-risk cancer subtypes and implementing proactive management, including beta-blocker therapy for symptom control, are critical steps to mitigate adverse effects and improve patient care. Personalized management and early intervention, particularly for high-risk groups, are essential to improving patient outcomes. Research Sponsor: None.

2621 **Poster Session**

Quantum mechanics–based multi-tensor AI/ML discovery and validation of actionable and mechanistically interpretable whole-transcriptome predictors of survival in response to immunotherapy from real-world clinical trial data. First Author: Orly Alter, University of Utah and Prism AI Therapeutics, Inc., Salt Lake City, UT

Background: Prediction in cancer remains limited, and 90% of drugs continue to fail trials and post-market validation. The entire multi-ome affects the disease. Previously, we developed quantum mechanics-based multi-tensor AI/ML to overcome the limitations of typical AI/ML, e.g., neural networks and deep learning, in small-cohort, noisy, high-dimensional, multi-omic clinical data [doi: 10.1073/pnas.0530258100, 10.1145/3624062.3624078]. We have demonstrated the algorithms in the discovery and validation of whole-genome and -chromosome predictors of survival and response to treatment in, e.g., brain, lung, ovarian, and uterine cancers [doi: 10.1063/1.5142559, 10.1200/JCO.2024.42.16_suppl.10043]. **Methods:** Here, we use the algorithms to discover two whole-transcriptome predictors of OS in response to atezolizumab PD-L1 inhibitor immunotherapy in a 348-patient, multi-center, single-arm, bladder cancer clinical trial, and validate the predictors in the 401-patient bladder cancer cohort in the Cancer Genome Atlas (TCGA). **Results:** The algorithms discovered the two predictors in the open-source, pre-atezolizumab, locally advanced or metastatic disease profiles of the 348 patients alone. By incorporating the patient labels, both predictors were found to outperform the best indicator of response to the treatment to date, i.e., the tumor mutation burden (TMB): The Cox proportional hazards model ratios, i.e., the corresponding relative risks, of 2.7 and 1.7, and concordance indices, i.e., accuracies, of 0.70 and 0.63, of each predictor, are greater than the ratio, of 1.3, and index, of 0.61, of TMB (Wald P-values=2.0×10^{-7} and 8.2×10^{-3} vs. 2.1×10^{-5}). The maximum Kaplan-Meier median OS difference of the two predictors together, of 22 months, is greater than that of TMB, of 16 months (log-rank P-values=3.6×10^{-11} vs. 1.7×10^{-4}). One predictor is additionally correlated with the objective response rate (ORR), and the other – with the tissue of advanced or metastatic disease (Kruskal-Wallis P-values=9.8×10^{-4} and 2.2×10^{-3}). Both predictors are similarly correlated with the OS of the 401 TCGA bladder cancer patients. Both are statistically independent of the imbalanced variations in the patient demographics, e.g., race, or the tissue batches, e.g., pre- vs. post platinum-based chemotherapy. By using the transcript labels, the predictors were interpreted in terms of known and new disease mechanisms and drug targets to sensitize the tumors to the treatment. **Conclusions:** Our multi-tensor AI/ML discovered and validated two whole-transcriptome predictors of OS in response to atezolizumab that outperform TMB. This further suggests that quantum mechanics-based algorithms can be used to derive predictors that are consistent across studies and over time. Research Sponsor: None.

2622 **Poster Session**

Phase II trial of neoadjuvant nivolumab and SOX in resectable gastric/gastroesophageal junction cancer: Therapeutic response and biomarker correlations. First Author: Xiangdong Cheng, Zhejiang Cancer Hospital, Hangzhou, Zhejiang Province, China

Background: Neoadjuvant immunotherapy produces a major pathologic response (MPR) in 40% of patients with locally advanced gastric cancer (LAGC). Herein, we conducted a phase prospective clinical study to investigate markers related to the response to neoadjuvant immunotherapy. **Methods:** Patients with locally advanced gastric or gastroesophageal junction cancer (cT3-4N+M0,CY0,P0) were enrolled and received either 3 preoperative and 3 postoperative cycles of nivolumab (360 mg, IV, d1, Q21d) plus SOX regimen (oxaliplatin 130 mg/m^2, IV, d1 with oral S-1 40-60mg, bid, d1-d14, Q21d) therapy, followed by 11 cycles of nivolumab monotherapy. The primary endpoint was the pCR rate, while the mPR, 3-year-DFS and 3-year-OS as the second endpoint. This clinical trial was registered at Clinicaltrial.gov (NCT05739045). In addition, tissue samples from patients before and after preoperative therapy were performed scRNA-seq to explore the changes of tumor microenvironment during the therapy and biomarkers associated with therapy response. **Results:** Forty-six patients were enrolled from November 2022 to March 2023, with a median age of 66 years (range, 34-74), and 38 (82.60%) were male. There were 28 (60.87%) patients with PD-L1 CPS $\geq$5. The study achieved its primary endpoints, with a pCR rate of 21.74% and an MPR rate of 41.30%. Among the 46 patients who underwent D2 gastrectomy, the 1-year OS rate was 97.83% and 1-year DFS rate was 95.65%. Single-cell RNA sequencing of 131 tumor samples obtained from 46 patients with LAGC at multiple time points during neoadjuvant therapy showing that the expression of MHC-II was upregulated in malignant cells in the pre-sensitive group. In a retrospective cohort of 226 patients treated with neoadjuvant immunotherapy, MHC-II-positive patients exhibited significantly higher rates of pCR and mPR compared to MHC-II-negative patients. Furthermore, 30 MHC-II-positive GC patients were prospectively enrolled to receive neoadjuvant immunotherapy, showing pCR and mPR rates of 36.67% and 66.67%, respectively. Mechanistically, we observed that T cell-induced IFN-γ signaling predominated in the tumor microenvironment of the sensitive group before treatment. This signaling pathway induces MHC-II expression in tumor cells, thereby enhancing the T cell-mediated antitumor immune response during neoadjuvant immunotherapy. In addition, MHC-II expression in tumor cells can be detected via IHC and commercially available antibodies in standard pathology laboratories, making it a potential biomarker to guide the selection of appropriate GC patients for neoadjuvant immunotherapy. ClinicalTrials.gov registration: NCT05739045. **Conclusions:** Our study illuminates the role of MHC-II expression in tumor cells in modulating the response to immunotherapy in gastric cancer. Clinical trial information: NCT05739045. Research Sponsor: None.

2623 **Poster Session**

Delineation of immunotherapeutic predictive versus prognostic transcriptional programs to identify SLC22A5-centric carnitine metabolism-driven resistance to anti-PD-L1 treatment in advanced non–small-cell lung cancer. First Author: Yuze Wang, The First Affiliated Hospital, Sun Yat-sen University, Guangzhou, China

Background: Prognostic factors indicate the natural course of a disease regardless of treatment, whereas predictive factors determine the likelihood of response to specific therapies. Distinguishing between predictive and prognostic factors is essential for separating treatment-specific outcomes from the inherent progression of cancer, thereby guiding clinical decision-making. We aim to dissect the predictive and prognostic transcriptional programs underlying the efficacy of anti-PD-L1 versus chemotherapy in advanced non-small cell lung cancer (NSCLC) to uncover mechanisms specific to immunotherapy resistance. **Methods:** Clinical and baseline tumor transcriptomic data were collected from two randomized controlled trials comparing atezolizumab with docetaxel: OAK (n=697, discovery cohort) and POPLAR (n=192, validation cohort). Transcriptional program scores for each biological process and metabolic pathway from the Reactome database were calculated using gene set variation analysis for each patient. Cox regression and P-value for interaction tests were conducted to differentiate predictive versus prognostic effects of transcriptional programs. Tumor microenvironment and cell-cell communication underlying immunotherapy resistance were explored using bulk and single-cell transcriptomic data. **Results:** Transcriptional programs in the OAK discovery cohort were divided into four categories associated with different predictive effects specific to atezolizumab or docetaxel. Carnitine metabolism was the most prominent process contributing to atezolizumab-specific resistance, while porphyrin metabolism drove docetaxel-specific resistance. SLC22A5, the only high-affinity carnitine transporter, was upregulated in atezolizumab-resistant patients. The predictive effect of SLC22A5-centric carnitine metabolism for resistance to atezolizumab rather than docetaxel was confirmed in the POPLAR validation cohort. Integrative analyses of bulk and single-cell transcriptomes revealed that cancer cell-specific SLC22A5 expression induced M2 macrophage polarization and decreased CD8+ T cell infiltration via carnitine uptake, thus forming an immunosuppressive microenvironment. **Conclusions:** Our study elucidates the distinction between predictive and prognostic factors in advanced NSCLC from a metabolic perspective. Cancer cells uptake of carnitine via SLC22A5 mediates resistance to anti-PD-L1 treatment. Combining inhibition of SLC22A5-centric carnitine metabolism with anti-PD-L1 agents might be a promising strategy to reverse immune escape in advanced NSCLC. Keywords: Predictive, Prognostic, Non-small cell lung cancer, Carnitine metabolism, Resistance. Research Sponsor: National Natural Science Foundation of China; 82373307; Natural Science Foundation of Guangdong Province; 2024A1515013214; the China Postdoctoral Science Foundation; 2024M753780; the institutional funding of The First Affiliated Hospital of Sun Yat-sen University.

2624 **Poster Session**

Biomarkers associated with outcomes from OPTIMIZE-1: CD40 agonist mitazalimab with mFOLFIRINOX in patients with untreated metastatic pancreatic cancer. First Author: Philippe Alexandre Cassier, Centre Léon Bérard, Lyon, France

Background: Metastatic pancreatic ductal adenocarcinoma (mPDAC) has a 5-year overall survival (OS) rate of less than 5% and remains a leading cause of cancer related mortality. Mitazalimab, a human CD40 agonistic IgG1 antibody, activates CD40 signaling in myeloid cells, enhancing tumor sensitivity to chemotherapy and licensing dendritic cells to prime and activate tumor-specific T cells. The OPTIMIZE-1 Phase 1b/2 trial evaluated the safety and efficacy of mitazalimab combined with mFOLFIRINOX (mFFX) in treatment *naïve* mPDAC patients (pts) (Van Laethem 2024). This combination therapy has shown promising clinical efficacy compared to historical controls with a median OS of 14.9 months, median duration of response of 12.6 months, median progression free survival of 7.7 months, and an overall response rate of 54.4 % (42.1% confirmed) (Geboes, 2024). **Methods:** Patients received mitazalimab on day 1 (priming dose), followed by a 2-week regimen starting with mFFX on day 8 and mitazalimab on day 10. Associations between survival benefits and both baseline and on treatment biomarkers (RNAseq data from tumor biopsies and longitudinal circulating tumor KRAS (ctKRAS) data) were assessed in patients from the full analysis set (n = 57) treated with 900 μg/kg mitazalimab. **Results:** Differential gene expression analysis (DGEA) identified a fibrosis-related gene signature (including genes involved in extracellular matrix (ECM) remodeling) that correlated with improved OS (p = 0.002). Conversely, a distinct gene signature linked to chemoresistance mechanisms involved in the inactivation and secretion of mFFX components was associated with shorter OS. Comparing DGEA of three on-treatment biopsies from patients with partial response to baseline samples revealed treatment-induced tumor changes. These analyses identified upregulation of genes involved in myeloid cell biology and regulation of T cell responses, along with downregulation of immunosuppressive genes. Longitudinal data analyses revealed that ctKRAS clearance was reached by 72% of pts and was significantly associated with longer OS. Molecular response was also associated with longer OS and predicted radiological response with 76.7% accuracy (sensitivity 72.7%, specificity 81.0%). Further, molecular progression was significantly associated with OS and predicted radiological response with 62.8% accuracy (sensitivity 71.4%, specificity 58.6%). **Conclusions:** A potentially predictive fibrosis-related gene signature, directly linked to mitazalimab's mode of action, was associated with improved OS. Biomarker correlations further suggest a mitazalimab-driven contribution to clinical benefits in the OPTIMIZE-1 trial. These encouraging results will inform the planned randomized confirmatory trial of mitazalimab in combination with mFFX in mPDAC. Clinical trial information: NCT04888312. Research Sponsor: Alligator Bioscience AB.

2625 **Poster Session**

Tumor mutational burden, PD-1, negative Wnt/β-catenin regulators, and positive MHC class II antigen presentation regulators as predictors of longer survival after immune checkpoint inhibitors across cancers: A comprehensive analysis of 400 immunity biomarkers. First Author: Yu Fujiwara, Department of Medicine, Roswell Park Comprehensive Cancer Center, Buffalo, NY

Background: Immune checkpoint inhibitors (ICIs) have become a standard treatment, yet no universal biomarker consistently predicts prolonged survival across cancer types. While multiple biomarkers have been proposed, they have not been systematically compared or evaluated in a tumor-agnostic manner. This study comprehensively investigates the impact of 397 immunoregulatory transcripts and other factors on survival in patients with cancer treated with ICIs. **Methods:** The Profile-Related Evidence Determining Individualized Cancer Therapy (PREDICT, NCT02478931) study enrolled 514 patients, including 217 treated with ICIs. The study analyzed the effect of bulk tumor transcriptomic expression of 397 immunoregulatory factors plus microsatellite instability [MSI], tumor mutational burden [TMB], and PD-L1 immunohistochemistry (total = 400 biomarkers) along with cancer type on overall survival (OS) and progression-free survival (PFS) following ICI therapy. Transcriptome expression was categorized into three groups based on percentile ranks compared to 735 controls spanning 35 histologies: "High" (75–100th percentile), "Intermediate" (25–74th percentile), and "Low" (0–24th percentile). Hazard ratios (HRs) for OS and PFS were estimated using a Cox regression model. Storey's q-value correction accounted for multiple testing, and a multivariable analysis was performed to explore novel biomarkers and different TMB cutoffs (10 [mutations/mb], 16, 20, and continuous). **Results:** In the 217 ICI-treated patients (median age: 61.2 years; women: 56.2%), the most common ICI was anti-PD-1 therapy (83.4%, N = 181), and the median TMB was 5.0 mut/mb. MSI was detected in 9 patients (4.1%). In multivariable analysis adjusting for age, sex, significant markers ($q < 0.05$) and co-inhibitory checkpoints ($p < 0.1$ in univariate analysis), and TMB (with different cutoffs and as a continuous variable), high expression of CIITA, KREMEN1, and PD-1 (but not PD-L1), as well as higher TMB (≥10 mut/mb, ≥16 or ≥20 or continuous), were independently associated with longer OS ($p \leq 0.05$). In the PFS analysis, high KREMEN1 expression and higher TMB (≥16 or ≥20 or continuous but not ≥10 mut/mb) also independently correlated with longer PFS. Cancer type was not independently correlated with outcome. **Conclusions:** Our comprehensive biomarker analysis identified novel factors associated with ICI efficacy. In addition to confirming the predictive role of TMB, the study highlights CIITA, a regulator of MHC class II expression that enhances tumor antigen presentation, and KREMEN1, a suppressor of Wnt/β-catenin signaling that preserves antitumor immunity, as well as the PD-1 checkpoint, as predictive biomarkers for ICI therapy across cancers. Clinical trial information: NCT02478931. Research Sponsor: U.S. National Institutes of Health; P30 CA023100; U.S. National Institutes of Health; 5U01CA180888-08; U.S. National Institutes of Health; 5UG1CA233198-05.

2626 **Poster Session**

Impact of *Helicobacter pylori* infection on molecular alterations and immune dynamics in gastric cancer. First Author: Daisuke Takayanagi, Showa University, Tokyo, Japan

Background: *Helicobacter pylori* (HP) infection, a major risk factor for gastric cancer (GC), modulates tumor immunity. Evidence indicates that *H. pylori* infection status correlates with the efficacy of immune checkpoint inhibitors (ICI), with varying outcomes in *H. pylori*-positive (*HPP*) and -negative (*HPN*) patients. This study investigated the impact of HP infection on splicing alterations to elucidate its role in shaping immune responses and the tumor immune microenvironment (TIME), immune checkpoint molecule expression, transcriptional profiles in GC. **Methods:** Tumors and adjacent normal tissues were collected from 24 patients with GC, comprising 39 tumor samples from *HPP* patients, 27 samples from *HPN* patients, and 13 and 10 normal samples of each, respectively. RNA sequencing was performed on these tissues and whole blood RNA from six patients (four *HPP* and two *HPN*) to analyze the alternative splicing (AS) events, the transcriptional profiles, and immune-related gene expression. Differential gene expression (DGE) and enrichment analyses were conducted, and immune cell fractions were evaluated using CIBERSORTx. **Results:** DGE analysis revealed that *HPP* tumors were enriched in genes related to cell cycle regulation, whereas *HPN* tumors were enriched in immune response pathways, including those involved in leukocyte activation, chemokine signaling, and immune effector processes. Additionally, *HPN* tumors showed higher expression of immune checkpoint molecules, such as CD160 (p = 0.016), PDCD1LG2 (p = 0.0082), and BTLA (p = 0.025). Immune cell profiling demonstrated increased proportions of gamma-delta T cells (p = 0.0077), resting dendritic cells (p = 0.0002), and neutrophils (p = 0.016), reflecting enhanced immune activation and a favorable ICI response. In contrast, *HPP* tumors were enriched in cell cycle-related pathways, suggesting a proliferative phenotype. *HPP* tumors also exhibited higher levels of M0 macrophages (p = 0.0039) and CD276 expression (p = 0.0082), indicative of an immunosuppressive TIME. AS analysis identified increased intron retention (IR) events in *HPP* tumors, particularly in genes associated with RNA processing and extracellular matrix remodeling. These alterations may contribute to immune evasion and tumor progression. In the peripheral blood, *HPP* samples exhibited upregulation of tripartite motif family genes, which are implicated in immune modulation. **Conclusions:** This study demonstrated that *HP* infection significantly affects the TME and gene expression profiles of GC. *HPP* tumors are characterized by increased M0 macrophage populations, CD276 expression, and IR events that contribute to immunosuppression and tumor progression. In contrast, *HPN* tumors exhibit greater immune activation and checkpoint molecule diversity. These findings highlight the potential role of HP status in shaping the immune landscape of GC and influencing responsiveness to ICI. Research Sponsor: None.

2627 **Poster Session**

Levels of immune responses in tertiary lymphoid structures of non-small cell lung cancer (NSCLC) and association with survival. First Author: Jiangping Li, Division of Thoracic Tumor Multimodality Treatment, Cancer Center, West China Hospital, Sichuan University, Chengdu, Sichuan, China

Background: Tumor-infiltrating tertiary lymphoid structures (TLSs) are thought to have anti-tumor activity and are believed to indicate a favorable prognosis in cancer patients. However, the prognostic value of TLSs in non-small cell lung cancer (NSCLC) is unknown. **Methods:** RT-qPCR analysis of the reactive Th-cell subsets and fluorescence activated cell sorting (FACS) analysis of the cell composition in tumor and paired controls. Histological evaluation of the co-localization of tumor-associated $CD20^+$ B cells, $CD4^+$ T cells and DC-$LAMP^+$ mature dendritic cells (DCs) within TLSs, and statistically analysis of the relationship between TLSs and overall survival. **Results:** The results indicated high levels of immune responses in tumour microenvironment ofNSCLC, which that high levels of Th-CXCL13, Th1, Tfh and Treg cell immune responses were the main reactions in tumor tissue of NSCLC, followed by weak Th2 and Th17, suggesting high levels of immune responses in tumor microenvironment of NSCLC. Tumor-associated TLS is a complete and mature lymphoid follicle-like structure containing T cells, B cells and APCs in tumor of NSCLC**.** Six-color MIHC staining indicated tumor-associated TLSs were complete and mature lymphoid follicle-like structures containing T cells, B cells and antigen presenting cells (APCs), and tumor-associated TLSs. Architectural analysis showed that $CD20^+$ B cell clusters were localized in the local tumour microenvironment, and were mainly colocalized with $CD4^+$ T cells, $CD68^+$ macrophages, $CD11c^+$ DCs and DC-$LAMP^+$ mature DCs, which indicated the formation of mature TLSs. One of the primary functions of TLS is to support the survival of incoming lymphocytes. The vast majority of the evaluated tumour-associated TLSs in NPC represented mature secondary-follicle-like TLSs, as indicated by the presence of both $CD21^+$ FDC and $CD23^+$ GC-B cells. Understanding and analyzing the phenotypes of these TABs was important for interpreting the local immune response. We used six-color MIHC staining (CD10, CD20, CD38, CD138, CD27 and DAPI) to approximate six different TABs in whole tissue sections of NPC. These molecules were expressed to varying degrees in all paraffin sections, and MIHC showing that $CD38^+$ plasmablast cells and $CD138^+$ plasma cells were primarily located at the tumor interstices or margins, which indicated improved survival outcome. In conclusion, this is the first research of applying multiple complementary strategies to map the biological function and clinical relevance of those cells in the TLSs of NSCLC. **Conclusions:** Our findings provide insights into the potential role of TLSs in the adaptive anti-tumor immune response, with implications for the development of biomarkers and therapeutic targets. Research Sponsor: None.

2629 **Poster Session**

Clinical significance of the CGRP pathway gene expression in advanced solid tumors: A sub-analysis of MONSTAR-SCREEN-2. First Author: Takao Fujisawa, Department of the Promotion of Drug and Diagnostic Development, National Cancer Center East, Kashiwa, Japan

Background: Calcitonin gene-related peptide (CGRP), a neuropeptide associated with pain perception, has emerged as a therapeutic target for migraine. Recent studies have reported that the CGRP pathway is associated with suppression of anti-tumor immunity and poor prognosis in patients (pts) with solid tumors via induction of CD8+ T cell exhaustion by sensory nerves. However, clinical significance of the CGRP pathway genes in oncology including the impact for the efficacy of immune checkpoint inhibitors (ICIs) remains elusive. Herein, we evaluated the landscape of the CGRP pathway gene expression and their association with efficacy of ICIs by mRNA expression level of the CGRP pathway genes in advanced solid tumors from the SCRUM-Japan MONSTAR-SCREEN-2, a nationwide molecular profiling project. **Methods:** Pts with advanced solid tumors were enrolled; tumor tissues were profiled using whole exome/transcriptome sequencing (MI Profile, Caris Life Sciences, Phoenix, AZ, USA). The association between the expression profiles of the CGRP pathway genes (*CALCA* encoding CGRP, *CALCRL* and *RAMP1* encoding CGRP receptors) and the efficacy of ICI monotherapy was analyzed. **Results:** Among 2,768 pts enrolled as of March 2024, mRNA expression data of baseline tissue samples were available in 1,475 pts across 36 cancer subtypes: most common subtypes were colorectal adenocarcinoma (n = 352) and esophagogastric adenocarcinoma (EGAC, n = 192). mRNA expression of the CGRP pathway genes were observed across diverse cancer types. One hundred and fifty-eight pts were treated with ICI monotherapies: most common subtypes were urothelial carcinoma (UC, n = 41), EGAC (n = 30) and head and neck squamous cell carcinoma (HNSCC, n = 30). The low *RAMP*1 mRNA expression group tended to have a better objective response rate (ORR) and significantly better progression-free survival (PFS) than the high mRNA expression group (ORR: 29.3% vs 15.2%, P = 0.056, PFS: 5.1 vs 2.7 months, hazard ratio [HR]: 0.68, 95% CI: 0.47-0.98, P = 0.04). Among the patients with UC and HNSCC, the low *RAMP1* mRNA expression group tended to have a better PFS than the high mRNA expression group (UC: 3.5 vs 6.0 months, HR: 0.69, 95% CI: 0.34-1.39, P = 0.3, HNSCC: 1.5 vs 6.0 months, HR: 0.67, 95% CI: 0.30-1.51, P = 0.3). **Conclusions:** High RAMP1 mRNA levels were associated with worse therapeutic efficacy of ICI, highlighting the potential of CGRP pathway as a resistance mechanism and a treatment target. Clinical trial information: UMIN000043899. Research Sponsor: SCRUM-Japan Funds.

2630 **Poster Session**

Predication of clinical outcomes of advanced cutaneous squamous cell carcinoma to PD1 inhibition directly from histopathology slides using inferred transcriptomics. First Author: Johnathan Arnon, Sharett Institute of Oncology, Hadassah Hebrew Universty Medical Center, Jerusalem, Israel

Background: Metastatic or locally advanced cutaneous squamous cell carcinoma (CSCC) not amenable to local therapy is treated with programmed death (PD)-1 inhibitors, namely Cemiplimab . While response rates are relatively high at approximately 45%, no predictive biomarkers for PD-1 inhibition have been validated in advanced CSCC subjecting some patients, especially older, to unnecessary immune-related adverse events (irAE). We present a retrospective analysis of ENLIGHT-DP, a novel biomarker for response to PD-1 inhibition in advanced CSCC, calculated directly from histopathological slides. **Methods:** We retrospectively examined high resolution hematoxylin and eosin (H&E) slide scans from archived tumor-tissue samples of advanced CSCC patients treated with Cemiplimab to generate an individual prediction score to PD-1 inhibitors using ENLIGHT-DP. This is composed of two main steps: (I) prediction of individual mRNA expression directly from H&E slides using the digital pathology-based DeepPT algorithm (II) use these values as input to ENLIGHT, a transcriptomics-based precision oncology platform for prediction of response to cancer therapies. We then unblinded clinical outcomes and assessed the predictive values of ENLIGHT-DP. **Results:** We evaluated 39 cases of advanced CSCC (tumors from various origins) at a median age of 81 years old (range 57-100). Of them, 32 cases (82%) were initially treated with surgery or radiotherapy with curative intent, but ultimately suffered disease progression. The objective response rate (ORR) was 69%, median progression free survival (PFS) was 11 months (CI 95% 10.4-17.6) and 6 patients (15%) suffered from severe irAE necessitating treatment cessation. ENLIGHT-DP was predictive of response with ROC AUC = 0.67. Using a binary threshold for classification, calibrated on previous lung and head and neck cohorts, ENLIGHT-DP displays promising biomarker characteristics: 81.8% PPV, 66.6% sensitivity and 4.0 OR (p = 0.04) for matched vs. unmatched patients. ENLIGHT-DP successfully stratified PFS with HR 0.02 (CI 95% 0.0005-0.96, p = 0.05). Importantly, omitting cases in which ENLIGHT-DP was calculated on samples which were taken more than 6 months prior to Cemiplimab therapy (i.e., during diagnostic excisions) did not influence the results. No other patient characteristics (e.g., age, stage, co-morbidities, previous treatments) were associated with outcomes. **Conclusions:** ENLIGHT-DP demonstrates high predictive values for clinical outcomes of PD-1 inhibition in advanced CSCC, relying solely on easily accessible archived H&E slides. Research Sponsor: Pangea Biomed.

2631 **Poster Session**

Evaluation of AI-assisted PD-L1 CPS scoring in immunostained pan-organ tumor whole-slide images. First Author: Céline Bossard, Pathology Department, IHP Group, Nantes, France

Background: PD-L1 inhibitors have shown remarkable results in oncology, yet many patients fail to respond, underscoring the importance of reliable assessment of PD-L1 expression for patient selection. PD-L1 scoring, especially the Combined Positive Score (CPS), is hindered by inter-observer variability, complex staining patterns, and technical discrepancies across platforms and antibody clones. These challenges may impact therapeutic decisions. Artificial intelligence (AI) offers a solution by standardizing PD-L1 evaluation. This study evaluates Diadeep PD-L1 CPS AI solution designed to provide reproducible and robust PD-L1 scoring across diverse tumors and conditions. **Methods:** AI performance was validated on 142 formalin-fixed, paraffin-embedded samples spanning multiple tumor types (GI, head and neck, breast, uterine cervix) and sourced from four centers, reflecting diverse staining protocols (22C3 and QR001 clones; BenchMark ULTRA and Omnis/Dako platforms). The routine scores were available for these cases. A Gold Standard was established through independent retrospective scoring by three blinded senior pathologists, which allowed to compute the intraclass correlation coefficient (ICC). The scoring was followed by collegial discussions to resolve discordant cases and ensure medical consensus. After a washout period, pathologists re-evaluated the cases with the AI assistance. AI-computed scores and routine manual scores were evaluated and compared by using the Gold Standard as a reference and the organ-specific recommended cut-offs. **Results:** The AI assistance improved interobserver agreement among pathologists, with the ICC increasing from 0.62 to 0.74. This effect was particularly pronounced for challenging cases with CPS $<$ 20 (n = 91), where ICC improved from 0.19 to 0.62, underscoring the AI's value in reducing variability near clinical decision thresholds. Moreover, the AI-based scoring tool demonstrated superior accuracy (88%) compared to routine manual scoring (75%) in classifying PD-L1 expression based on clinical cutoffs. Sensitivity was significantly higher with AI (96% vs. 78%, $p < 0.001$), while the positive predictive value was comparable (88% vs. 87%), indicating an improved ability to detect true positive cases. **Conclusions:** This study highlights the potential of an AI-driven tool to enhance PD-L1 scoring by significantly improving accuracy and reducing inter-observer variability, particularly in cases near clinical decision thresholds where consistency is critical. By delivering reliable and reproducible results, the AI algorithm addresses key challenges in PD-L1 evaluation, ensuring more precise patient stratification for immunotherapy. Beyond accuracy, the integration of such tools into clinical workflows could optimize patient selection and improve therapeutic outcomes, offering oncologists greater confidence in treatment decisions. Research Sponsor: None.

2632 **Poster Session**

Validation of ENLIGHT, an AI predictor of immune checkpoint blockade (ICB) response and resistance, across the treatment span. First Author: Scott Strum, Princess Margaret Cancer Centre – University Health Network, University of Toronto, Toronto, ON, Canada

Background: Advanced computational AI algorithms, such as ENLIGHT and DeepPT (Med 2023, Nature Cancer 2024), represent a promising approach to identify predictive biomarkers for cancer therapeutics. Evaluation of ICB response prediction via these algorithms through the full span of pre-treatment, on-treatment, and at progression time points provides a dynamic perspective of response prediction abilities. **Methods:** A post-hoc analysis of two pan-cancer clinical trials was performed: i) BIO2 is a biobanking protocol of ICB-naïve patients (pts) treated with pembrolizumab (NCT02644369); and ii) The IRIS study (NCT04243720) which enrolled pts who have progressed immediately post ICB. In BIO2, complete, partial response or stable disease for $>$6 months was classified as responders (R), the rest as non-responders (NR). In IRIS, acquired and primary resistance were defined according to trial protocol. ENLIGHT matching scores were calculated using either transcriptomics from NGS (EMS-NGS), or transcriptomics imputed directly from H&E slides using DeepPT (EMS-DP). The predictive value of EMS was compared to PD-L1 IHC, tumor mutational burden (TMB) and tumor infiltrating lymphocytes (TILs) abundance by IHC, and its trajectory across timepoints was studied. **Results:** 76 pts from BIO2 (23:53, R:NR), and 37 pts from IRIS (18:19, AR:PR), comprising of 14 tumor types, were analyzed. We first established the value of ENLIGHT as a predictive biomarker using the BIO2 pre-treatment samples. EMS-NGS was a superior predictive biomarker compared with PD-L1 IHC, TMB and TIL abundance, while EMS-DP was comparable (Table). The EMS-NGS scores of responders were significantly higher than non-responders pre-treatment (medians: 0.92 vs. 0.62, p = 1.4e-4). Analyzing the trajectory of the EMS-NGS scores across two additional timepoints reveals that while the scores of non-responding patients remained low (median: 0.62, 0.69, 0.67 for pre-, on–treatment and post-progression, respectively), it is higher among responders (median: 0.92, 0.78 for pre- and on–treatment, respectively). Finally, EMS-NGS was higher among pts with acquired vs primary resistance in IRIS (medians: 0.75 vs 0.59, p = 0.17). **Conclusions:** In two pan-cancer cohorts, EMS-NGS outperformed conventional biomarkers in predicting ICB response. EMS-DP was comparable to conventional biomarkers and could be calculated directly from H&E slides in a fast, low-cost manner. EMS-NGS values were concordant with response or resistance throughout the ICB treatment course, reflecting the level of the tumor's vulnerability to ICB inhibition. Further validation of ENLIGHT in larger ICB-treated pts is warranted given these promising results. Clinical trial information: NCT02644369, NCT04243720. Research Sponsor: BMO Chair in Precision Genomics, Dr. Lillian Siu.

	ROC AUC (p)	Sensitivity	PPV (cf 30% baseline response rate)	F1 Score
EMS-NGS	0.74 (0.0003)	61	48	54
EMS-DP	0.64 (0.02)	57	45	50
PD-L1 IHC	0.7 (0.003)	70	40	51
TMB	0.64 (0.03)	39	69	50
TILs	0.6 (0.065)	39	52	44

2633 Poster Session

Effect of elevated expression of *LILRB4* and *TSC22D3* on survival in lung cancer. First Author: Borys Hrinczenko, Michigan State University, East Lansing, MI

Background: HER2/neu mutations or amplifications, present in up to 23% of non-small cell lung cancers (NSCLCs), activate STAT3, promoting inflammation and suppressing adaptive immune responses. Elevated systemic inflammation-immune index (SII) in small cell lung cancer (SCLC) correlates with reduced response to PD-1/L1 immune checkpoint inhibitors (ICIs), leading to worse overall survival (OS) and progression-free survival (PFS). These findings highlight the need to mitigate inflammation in lung cancers to enhance ICI response and improve survival. Biomarker studies can identify genes that differentiate inflammatory and immune pathways, offering therapeutic insights. **Methods:** To identify genes regulating the HER2/neu oncogene, HER2/neu-overexpressing mice were crossed with genetically Diverse Outbred (DO) mice. The resulting DO F1 offspring were monitored for HER2/neu-expressing tumor onset and growth. Tumor phenotypes were associated with mouse haplotypes to identify quantitative trait loci (QTL) on chromosomes (chr) 2, 6, and X linked with aggressive HER2/neu tumors. Of the 35 candidate genes harboring protein-coding changes, homologous genes on human chr 1, 10, and X were analyzed using Caris Life Sciences datasets of NSCLC and SCLC: 25,143 primary NSCLC; 12,365 metastatic NSCLC; 621 primary SCLC; and 971 metastatic SCLC where primary biopsies are those taken from the lung and metastatic biopsies from sites other than the lung. Patient cohorts stratified by gene expression (top vs. bottom 50%) were correlated with OS, ICI response, and time on pembrolizumab or atezolizumab treatment (TOT). **Results:** Several homologous candidate genes correlated with lung cancer survival in both NSCLC and SCLC. Notably, high expression of *LILRB4*, a macrophage-specific checkpoint molecule, was associated with improved survival (HR 0.66–0.84, $p < 0.001$) across all lung cancer types and sites. Additionally, elevated *TSC22D3*, a glucocorticoid receptor-activated gene regulating anti-inflammatory pathways, including *LILRB4* expression, was positively associated with OS in metastatic NSCLC (HR 0.82, $p < 0.00001$) and SCLC (HR 0.77, $p < 0.001$). Expression of *LILRB4* and *TSC22D3* further enhanced survival in ICI-treated patients (SCLC: HR 0.72; NSCLC: HR 0.82; $p < 0.001$). In NSCLC, high *LILRB4* expression conferred an 18% improved TOT with pembrolizumab (HR 0.858, $p < 0.0001$). **Conclusions:** *LILRB4* and *TSC22D3* are key genes linked to improved survival outcomes in both SCLC and NSCLC, likely through their roles in mitigating inflammation. Their association with enhanced ICI responses underscores their potential as therapeutic targets. Future research will evaluate the relationship between *LILRB4* and *TSC22D3* expression and HER2/neu status in NSCLC and validate protein-level correlations in positive cells. Our long-term goal is to determine the therapeutic potential of *LILRB4* and *TSC22D3* in SCLC, NSCLC and HER2/neu-positive NSCLC. Research Sponsor: U.S. National Institutes of Health; 7R01CA278818-02.

2634 Poster Session

Tertiary lymphoid structures and their association with immune checkpoint inhibitor response and survival outcomes in patients with non-small cell lung cancer. First Author: Dmitrii Grachev, BostonGene, Corp., Waltham, MA

Background: Immune checkpoint inhibitor (ICI)-based therapy is currently the first-line treatment for patients with lung adenocarcinoma (LUAD) and lung squamous cell carcinoma (LUSC) without actionable mutations. However, the commonly utilized biomarkers, including PD-L1 protein expression and tumor mutation burden, are not sufficiently accurate to predict the treatment response from ICI in this patient population. As tumor microenvironment (TME) and tertiary lymphoid structure (TLS) play a significant role in antitumor immunity, we explore these immunophenotypic factors to determine the potential biomarkers in patients with LUAD or LUSC. **Methods:** We evaluated all patients with LUAD or LUSC from three publicly available data and two novel retrospective cohorts for transcriptomic-based immune TME subtype classification (immune-hot vs. immune-cold) and TLS signature, along with associated clinical and genomic data. Those with other histological subtypes of non-small cell lung cancer or those who harbored *EGFR* mutations or *ALK* rearrangements were excluded from our study. The cellular decomposition within tumor samples was calculated using the deconvolutional Kassandra algorithm. Survival analysis was evaluated using log-rank test and multivariate Cox regression adjusted by PD-L1 status, KEAP1/STK11/KRAS/TP53 mutational status, immune TME subtype, and TLS signature. All statistical analyses were performed using Python. **Results:** A total of 514 patients were included from five cohorts, with 272 and 505 having genomic and transcriptomic data, respectively. 59% of patients with LUAD or LUSC exhibited an immune-cold phenotype, which correlated with adverse overall survival (OS) and progression-free survival (PFS) than immune-hot phenotype in LUAD. However, the ICI response rates were similar in both groups. Superior PFS and ICI response rates were observed in patients with high TLS signatures ($>$ 88th percentile) in LUAD, even after multivariate adjustments. Immune signatures that were positively associated with ICI response included the infiltration and trafficking of T and NK cells for LUAD and B-cell percentage for LUSC. In contrast, $CD8^+$ T-cell abundance did not correlate with ICI response. The presence of *KEAP1* or *STK11* mutations also did not affect the response rates but were associated with shorter OS and PFS. **Conclusions:** Transcriptomic-based immune-hot TME and high TLS signature may serve as novel predictive and prognostic biomarkers in patients with LUAD, while the presence of *KEAP1* or *STK11* mutations only offered prognostic values. Further prospective studies are warranted to expand to other treatment combinations with PD-(L)1 inhibitors. Research Sponsor: None.

2635 Poster Session

CCR8 positive Tregs and their correlation with immunotherapy response in advanced non-small cell lung cancer (NSCLC). First Author: Jean Philippe Guégan, Explicyte, Bordeaux, France

Background: Regulatory T cells (Tregs) expressing the chemokine receptor CCR8 are pivotal modulators of the tumor immune microenvironment. CCR8 has recently emerged as a promising therapeutic target due to its selective expression on activated Tregs in the tumor microenvironment and its role in promoting immunosuppression. This study investigates the prognostic and therapeutic implications of CCR8-positive Tregs in non-small cell lung cancer (NSCLC), focusing on their impact in relation to tertiary lymphoid structure (TLS) status. **Methods:** A validated 6-plex multiplex immunofluorescence (mIF) panel was used to analyze tumor samples from NSCLC patients treated with immune checkpoint blockers (ICB) in the BIP precision medicine study (ClinicalTrials.gov: NCT04389143). Markers included CD4, CD8, CD20, FoxP3, PanCK, and CCR8, alongside DAPI staining to assess immune contexture (infiltrated, excluded, desert), TLS status, and CCR8/FOXP3 double-positive Tregs. Clinical outcomes, including progression-free survival (PFS) and objective response rate (ORR), were analyzed in 50 responders and 50 non-responders. Findings were validated using transcriptomic data from the POPLAR (NCT01903993) and OAK (NCT02008227) studies, which evaluated atezolizumab versus docetaxel in advanced NSCLC. Kaplan-Meier curves, hazard ratios, and Cox regression models were used for survival analyses. **Results:** CCR8-expressing Tregs were significantly enriched in infiltrated tumors, showing a 1.5-fold increase compared to excluded tumors (p = 0.057), a 3.3-fold increase compared to desert tumors (p = 0.001), and a 1.8-fold increase in TLS-positive tumors compared to TLS-negative tumors (p = 0.003). These findings highlight that activated Tregs co-infiltrate with CD8 T cells and other immune cell types. This enrichment was confirmed in samples from the POPLAR and OAK studies using transcriptomic analyses (3-fold increase, p = 2e-16). Due to their correlation with overall immune cell infiltration, the presence of CCR8-positive Tregs was significantly associated with better survival (HR 0.45, $p < 0.001$) across the entire patient cohort. However, when stratified for TLS-positive tumors, the presence of activated Tregs was associated with diminished objective response rate and progression-free survival suggesting a negative impact of these immunosuppressive cells on response to ICB. **Conclusions:** This study provides the first evidence linking CCR8-positive Tregs with immunotherapy resistance in NSCLC, particularly in TLS-positive tumors. These findings parallel observations in TLS-positive sarcomas, where Treg abundance predicted poor outcomes (Italiano et al., *Nature Medicine*, 2022). This study supports the exploration of CCR8-targeted therapies to deplete immunosuppressive Tregs and enhance the efficacy of immunotherapy in TLS-positive NSCLC. Research Sponsor: None.

2636 Poster Session

Biological determinants of immune exclusion in non-small cell lung cancer: An analysis of the precision medicine BIP study. First Author: Jean-Philippe Guegan, ImmuSmol, Bordeaux, France

Background: Immune exclusion has been associated with resistance to immunotherapy in NSCLC. However, its biological determinants remain largely unknown. Instead of relying on preclinical models, high-throughput profiling of patient samples using spatial transcriptomics (ST) and multiplex immunofluorescence (m-IF) offers a powerful approach to dissect immune profiles and uncover key drivers of immune response and resistance. **Methods:** Tumor samples collected from NSCLC patients enrolled in the BIP precision medicine study (NCT02534649) prior to initiation of ICI therapy and divided into Discovery and Validation cohorts (n = 148 and 117, respectively). Response to treatment was assessed as per RECIST criteria. Multiplex immunohistochemistry (mIHC) with CD8 and panCK markers was used to classify tumors as desert, excluded or inflamed through pathologist assessment (PA) and image analysis ST using the NanoString GeoMx Whole Transcriptome Atlas compared gene expression profiles between inflamed and excluded tumors Spatially resolved T-cell receptor (TCR) profiling assessed clonal diversity and repertoire to evaluate T-cell functionality. m-IF was used for proteomic validation. **Results:** In both the training and validation cohorts, excluded tumors demonstrated lower objective response rates (ORR), progression-free survival (PFS), and overall survival (OS) compared to inflamed tumors (Table 1), independent of PD-L1 expression in multivariate analysis. ST identified marked overexpression of HLA-A/B (MHC class I) and CD74 (involved in MHC class II processing) in inflamed tumors versus excluded tumors, underscoring their crucial roles in antigen presentation. These results were validated by m-IF. Spatially resolved TCR profiling demonstrated higher Gini coefficients and lower Shannon entropy in excluded tumors, indicating a more oligoclonal TCR repertoire dominated by fewer T-cell clones. These findings suggest impaired antigen recognition and restricted T-cell diversity in excluded tumors. **Conclusions:** Our classification approach using mIHC and IA offers a practical, and clinically actionable biomarker for predicting response to ICI therapy. Immune exclusion, prevalent in NSCLC, is associated with resistance to ICI and characterized by reduced expression of key antigen presentation molecules such as HLA-A/B and CD74 and a restricted TCR repertoire highlighting the need for novel strategies to overcome this immune barrier. Research Sponsor: None.

	Phenotype	Objective Response Rate (ORR)	PFS (Median, Months)
Discovery	Inflamed (n=32)	**58%**	**12.8** (95% CI: 6.16-NA)
	Excluded (n=65)	**38.7%**	**4.1** (95% CI: 2.4-10.3)
	Desert (n=51)	**20%**	**2.8** (95% CI: 1.9-6.9)
Validation	Inflamed (n=40)	**57.5%**	**11.3** (95% CI: 4.6-NA)
	Excluded (n=30)	**43.3%**	**6.1** (95% CI: 3.4-14.9)
	Desert (n=47)	**31.9%**	**4.4** (95% CI: 2.3-7.2)

2637 **Poster Session**

The predictive role of TRAIL gene expression in immune checkpoint inhibitor (ICI)-treated patients (pts). First Author: Obada Ehab Ababneh, The University of Texas MD Anderson Cancer Center, Houston, TX

Background: Despite FDA-approved molecular biomarkers such as PD-L1 levels, tumor mutation burden (TMB), and microsatellite instability (MSI) status, only ~30% of matched cancer pts respond to ICI. TRAIL, a protein product of TNFSF10 gene, is a member of the TNF superfamily involved in regulating immune responses and inducing apoptosis when bound to either Death Receptor 4 or 5 (DR4/5) especially in cancer cells. While TRAIL has been studied for its prognostic roles in cancer, its predictive value for pts treated with ICI remains unclear. This study investigates the association between TRAIL expression and outcomes in ICI-treated pan-cancer pts. **Methods:** RNA expression levels of TRAIL were assessed in a cohort of 217 pan-cancer pts treated with ICIs at the University of California San Diego (UCSD) Moores Cancer Center. RNA transcripts were normalized using an internal housekeeping gene profile of 735 tumors and 35 histologies. Transcript abundances were percentile-ranked (0–100) and categorized as high ($\geq$75th percentile) or low ($<$ 75th percentile). Associations between TRAIL expression and overall survival (OS) and progression-free survival (PFS) were analyzed. Statistical significance was defined as p-value $\leq$ 0.05. **Results:** Among the 217 ICI-treated pts, the median age was 61.9 years, and 56.2% were female. The most common cancer types were colorectal (24.9%), breast (8.8%), ovarian (8.3%), pancreatic (7.4%), and lung (6.5%) cancers. FDA-approved ICI biomarkers favorable rates were PD-L1 $\geq$1% in 40.1%, TMB-high ($\geq$10 mut/Mb) in 11.5%, and MSI-high in 4.8%. Based on the ICI type used, 91.7% received anti-PD-(L)1 while 7.8% received anti-CTLA-4 with anti-PD-1. Pts with high TRAIL expression (24%) had similar PD-L1, TMB, MSI profiles ($p > 0.05$). Pts with high levels of TRAIL expression achieved better OS (HR = 0.41, 95%CI:0.25-0.69, p = 0.0004) and PFS (HR = 0.67, 95%CI:0.47-0.96, p = 0.027). After adjusting for age, sex, cancer type, PD-L1 IHC level ($\geq$1% vs. $<$ 1%), TMB ($\geq$10 mut/Mb vs. $<$ 10mut/Mb), MSI status (stable vs. unstable), KRAS, TP53 and CDKN2A/B alteration status and immune checkpoints genes expression, overall survival remained significantly associated with better survival in TRAIL high pts compared to TRAIL low pts (HR = 0.38, 95%CI:0.19-0.76, p = 0.006). However, no difference was found between both groups in regard to progression-free survival (HR = 0.68, 95%CI:0.42-1.10, p = 0.11). **Conclusions:** High TRAIL expression is associated with improved overall survival in ICI-treated pan-cancer pts, independent of cancer type or other predictive biomarkers. These findings suggest TRAIL as a potential biomarker for ICI benefit. Larger studies in diverse and real-world settings are warranted to validate these findings. Research Sponsor: None.

2638 **Poster Session**

Randomized phase II trial evaluating the combination of TG4001, an HPV16 therapeutic vaccine, and avelumab (ave) in patients (pts) with immunotherapy-naïve recurrent and/or metastatic (R/M) HPV16-positive cervical or anogenital cancer. First Author: Christophe Le Tourneau, Department of Drug Development and Innovation (D3i), Institut Curie, Paris-Saclay University, Paris, France

Background: Human papillomavirus (HPV) is a small DNA virus associated with cervical, anogenital (AG) cancers and squamous cell carcinoma of the head and neck. TG4001 is a therapeutic vaccine based on modified vaccinia virus Ankara with insertion of modified non-oncogenic HPV-16 E6 and E7 antigens and interleukin-2 as adjuvant. The phase I trial of TG4001 combined with ave showed a favorable safety profile (Borcoman E. et al, 2023). **Methods:** Pts with R/M cervical and anogenital cancer and who were checkpoint inhibitors naïve were randomized independent of PD-L1 expression between ave plus TG4001 or ave alone. Pts were required to have no more than one prior line of therapy for R/M disease and no liver involvement. Primary endpoint was PFS. Subgroup analysis (cervical, anal, other genital cancer) was preplanned in the protocol. **Results:** 90 pts were randomized between June 2021 and April 2024. 49 (54%), 27 (30%) and 14 (16%) pts had cervical, anal, and other genital cancers, respectively. Patients' demographics were well balanced between the 2 arms. Median PFS (mPFS) was 3.0 and 2.8 months (mo) in the experimental and control arm, respectively (HR=0.87 [90%CI: 0.59-1.29], p=0.28). In the cervical cancer subgroup, mPFS was 4.3 and 2.1 mo in the experimental and control arm, respectively (HR=0.58 [90%CI: 0.33-1.01], p=0.053). Overall Response Rate (ORR) in the whole population was 15.2% (7/46pts) in the experimental arm and 13.6% (6/44pts) in the control arm. In the cervical cancer subgroup ORR was 20% (5/25pts) in the experimental arm and 8.3% (2/24pts) in the control arm. There were no new safety signals. Three pts (6.5%) in the experimental arm and 2 pts (4.5%) in the control arm presented grade 3 or 4 treatment-related AEs. Translational analysis including immunogenicity results will be presented. **Conclusions:** TG4001 combined with ave did not improve PFS over ave alone in the whole patient population. Preplanned subgroup analysis in cervical cancer showed a positive efficacy signal in the combined arm. Avelumab was provided by the healthcare business of Merck KGaA, Darmstadt, Germany (CrossRef Funder ID: 10.13039/100009945). Clinical trial information: NCT03260023. Research Sponsor: None.

2639 **Poster Session**

Induction of neoantigen-specific immune responses by VB10.NEO in combination with atezolizumab in heavily pretreated patients with advanced solid tumors: Final analysis of the phase 1b VB N-02 trial. First Author: Sebastian Ochsenreither, Charité University of Medicine Berlin Comprehensive Cancer Center, Berlin, Germany

Background: VB10.NEO, a personalized DNA-based neoantigen vaccine, was evaluated with atezolizumab in a Phase 1b trial to assess safety, clinical activity, and immune responses in heavily pretreated patients with advanced solid tumors. The NeoSELECT platform enriches for clonal neoantigens by analyzing RNA and circulating tumor DNA, incorporating frameshift antigens and single nucleotide variants. **Methods:** This open-label, dose-escalation trial investigated VB10.NEO across three dose levels (3, 6 and 9 mg) combined with atezolizumab (1200 mg Q3W). Eligible patients had advanced or metastatic solid tumors, sufficient tumor material for vaccine manufacturing, at least 10 identified tumor neoantigens, and measurable disease. Immune responses were assessed using ELISpot assays (in vitro stimulation and ex vivo), T cell receptor sequencing, and flow cytometry. Endpoints included safety, immune response, and antitumor activity per RECIST v1.1. **Results:** At study completion (October 2024), 26 patients (median age 61 years, range 28–72; 62% female) received at least one dose of VB10.NEO. Median prior therapy lines for advanced disease were three (range 1–6), and 54% had prior immunotherapy, including checkpoint inhibitors. Tumor types included head and neck squamous cell carcinoma (15%), triple-negative breast cancer (15%), and others (31%; most were tumors with low tumor mutational burden). The majority (69%) of evaluable patients had low or negative PD-L1 expression. Injection site reactions (15%) and fatigue (12%), mainly Grades 1–2, were the most common adverse events. A dose-limiting Grade 3 transient blood pressure increase occurred in the 9 mg cohort. No treatment-related serious events or deaths occurred. Across all dose levels, VB10.NEO induced robust and durable neoantigen-specific immune responses. In vitro stimulated ELISpot assays detected vaccine-induced T cell responses in 85% (11/13) of evaluable patients and in 58% of evaluated neoantigens, while *ex vivo* ELISpot demonstrated responses in 22% (4/18) of patients and 5% of evaluated neoantigens. T cell receptor sequencing showed persistent T cell clone expansion in 9/11 patients, indicating durable immune responses. Putative neoantigen-specific clones were detected in 6/7 analyzed patients, with persistent expansion in 4. All patients achieving stable disease (34.8%, 8/23) exhibited neoantigen-specific immune responses. **Conclusions:** VB10.NEO combined with atezolizumab demonstrated a favorable safety profile while eliciting robust, durable immune responses across all dose levels, even in heavily pretreated patients with advanced solid tumors. The potential correlation between immunogenicity and clinical benefit supports further exploration in earlier treatment settings. Clinical trial information: NCT05018273. Research Sponsor: Nykode Therapeutics in collaboration with Roche/Genentech.

2640 **Poster Session**

An open-label single-center investigator-initiated exploratory clinical study in patients with refractory or recurrent solid tumors: R-ISV-FOLactis trial. First Author: Ruojing Lv, Comprehensive Cancer Centre of Drum Tower Hospital, Medical School of Nanjing University, Clinical Cancer Institute of Nanjing University, Nanjing, China

Background: Soft tissue sarcomas (STSs) are a highly complex group of tumors and the treatment still remains a challenge. Immunotherapy has become a powerful clinical strategy, especially the application of therapeutic tumor vaccine. Hypofractionated radiotherapy (HFRT) can serve as an in situ vaccine and provide durable local control. We also develop a bifunctional engineered Lactococcus lactis (FOLactis) which expresses an encoded fusion protein of Fms-like tyrosine kinase 3 ligand and co-stimulator OX40 ligand to conduct in situ vaccination (ISV). In this study, we establish a novel R-ISV-FOLactis strategy, which refers to the combination of HFRT, intratumoral (IT) injection of FOLactis and synergetic anti-PD-1 therapy, to further enhance efficacy and realize the activation of the whole immunity cycle. **Methods:** This study is an open-label, single-center trial aimed at patients with advanced STSs who are unresponsive or intolerable to previous standard treatment. Patients will be treated with HFRT, the IT injection of FOLactis and PD-1 inhibitors. The primary endpoint is the objective response rate (ORR) of target lesions at 3 month and 6 month. The secondary endpoint includes the disease control rate (DCR) of target lesions, progression-free survival (PFS), overall survival (OS), etc. **Results:** This study started from July 2022 and ended in December 2023, involving 30 eligible patients with solid tumors and 16 of them are patients with STSs. The ORR and DCR of all target lesions after three months are 27.6% and 93.1% respectively, and in sarcomas, the ORR and DCR are 11.1% and 88.9%. We calculate the ORR and DCR of target lesions after six months, which are 56.3% and 100% respectively, and in sarcomas, these are 41.7% and 100%. Systemic median PFS are 2.87 months. Median PFS of target lesions has not been reached. Among the evaluable target lesions, 6-month EFS is 50% in sarcomas (6/12) and 50% in all patients (8/16). We test the level of cytokines before and after the first treatment and find that the changes in the percentage of CD8+ T cells, CD103+CD8+ T cells and CD39+CD8+ T cells have significance. Moreover, in sarcomas, PFS is relevant to the level of CD103+CD8+ T cells before treatment, CD39+CD8+ T cells after treatment, NK cells before treatment and immature DC cells after treatment. The most common treatment-related adverse events (TRAEs) are fever (83.3%), lymphocytopenia (53.3%), hypocalcemia (30%), neutrophilia (26.7%) and nausea (26.7%). Grade$\geq$3 TRAEs occur in 11 patients, including lymphocytopenia (30%), fever (6.7%), leukopenia (3.3%), anemia (3.3%) and cardiac insufficiency (3.3%). **Conclusions:** The R-ISV-FOLactis strategy demonstrates its efficacy among patients with advanced STSs and induces certain anti-tumor immunity. The ISV of "FOLactis" may provide a promising option in the treatment of recurrent or refractory solid tumors. Clinical trial information: ChiCTR2200060660. Research Sponsor: None.

2641 **Poster Session**

First-in-human study of ZGGS15, a dual-specific antibody targeting LAG-3 and TIGIT, as monotherapy in patients with advanced solid tumors. First Author: Ji Zhu, Cancer Hospital of the University of Chinese Academy of Sciences (Zhejiang Cancer Hospital), Hangzhou, China

Background: ZGGS15 is a novel humanized bispecific antibody of anti LAG-3 and TIGIT. It could reverse Treg inhibition of T cells and NK cells, and kills tumor cells by restoring the function of T cells and NK cells. In non-clinical studies, ZGGS15 showed synergistic anti-tumor effects with the anti-PD-1 antibody. We conducted a Phase 1 dose escalation and expansion study to assess tolerability, safety, and efficacy of ZGGS15 as monotherapy in patients with advanced solid tumors. **Methods:** In the dose-escalation phase, a standard "3+3" design, with an accelerated titration for the starting dose. Total of 6 dose levels, from 0.3 to 30 (0.3, 1, 3, 10, 20, 30) mg/kg administered by the intravenous infusion, once every three weeks, in patients with advanced solid tumors who had failed to the available standard treatments. The first treatment cycle (21 days) was defined as the dose-limiting toxicity (DLT) observation period. The study assessments included tolerability, safety, preliminary efficacy, etc. and tumor responses were assessed by RECIST1.1 and iRECIST criteria. **Results:** As January 8 2025, a total of 22 patients (9 males and 13 females), with a median age of 59 years, participated in the dose escalation from 0.3 to 30 mg/kg and completed the DLT observation. Of the 22 patients, 11 (50.0%) received at least 3 prior lines of therapies, and eight (36.4%) had previously treated with PD-1 or PD-L1 inhibitors. No DLT events were observed. TRAEs occurred in 20 (90.1%) patients, with only one patient (4.5%) experienced a Grade 3 TRAE of lymphocyte count decreased, and no Grades 4 or 5 TRAEs were reported. Among the 17 patients who had at least one post-baseline tumor scan, six had achieved stable disease (SD) with a disease control rate (DCR) of 35.3%. In the subgroup of 8 patients with lung adenocarcinoma, 5 (62.5%) had achieved SD, including two patients who had $\geq$ 2 prior lines of treatments and maintained SD over 36 weeks. **Conclusions:** The results showed that ZGGS15 was well tolerated and had a very good safety profile. It is anticipated that when in combination with other anti-cancer therapies, e.g., an anti-PD-1 or PD-L1 antibody, for advanced solid tumors, ZGGS15 may provide synergistic anti-tumor effects and further enhance treatment benefits. Clinical trial information: NCT05864573. Research Sponsor: Suzhou Zelgen Biopharmaceuticals. Co., Ltd.

2642 **Poster Session**

Adverse events profile of novel agents targeting immune checkpoints beyond PD-1/PD-L1 and CTLA-4 in solid tumors: A meta-analysis. First Author: Yu Fujiwara, Department of Medicine, Roswell Park Comprehensive Cancer Center, Buffalo, NY

Background: PD-1, PD-L1, and CTLA-4 blockade are standard therapies in multiple solid tumors, and novel agents targeting alternative co-stimulatory and co-inhibitory immune checkpoints are under development. Immune checkpoint inhibitors are well known to cause immune-related adverse events (irAEs) and multiple studies reported the accurate incidence of irAEs from PD-1, PD-L1, and CTLA-4 blockade. With the increasing investigation and anticipated approval of novel immunotherapy agents, understanding their toxicity profiles is critical. **Methods:** We systematically searched PubMed/MEDLINE, EMBASE, and Web of Science for clinical trials published up to December 1st, 2024. Studies evaluating the safety of agents targeting co-inhibitory checkpoints (B7-H3, CD47, TIGIT, LAG-3, and TIM-3) or co-stimulatory checkpoints (OX40, 4-1BB, CD27, ICOS, GITR, CD70, and CD40) in solid tumors were included. Incidence rates of grade 1-5 (G1-5) and grade 3-5 (G3-5) treatment-related adverse events (trAEs) and irAEs were extracted. Toxicity data were derived from phase 2 and 3 trials, as well as phase 1/2 trials with safety information reported at the recommended phase 2 dose. Random-effects meta-analysis was used to pool odds ratios (ORs) from two-arm studies evaluating the addition of LAG-3 or TIGIT blockade to control-arm therapy, and proportional meta-analysis was conducted to analyze AE incidence across immunotherapy subtypes. **Results:** A systematic review identified 27 clinical trials with 40 cohorts comprising 3,946 patients and evaluating 10 immune checkpoints (B7-H3, LAG-3, TIGIT, CD47, OX40, CD137. TIM-3, CD40, CD27, CD40, ICOS). Meta-analyses showed that the addition of LAG-3 blockade to either PD-1 blockade-based therapy or placebo was associated with increased G3-5 trAEs (OR 1.79, 95% confidence interval [CI]: 1.26–2.54, p = 0.001), G3-5 adrenal insufficiency (OR 8.43, 95% CI: 1.04 - 68.37, p = 0.046), G1-5 adrenal insufficiency (OR 4.81, 95% CI: 1.81-12.78, p = 0.002) and arthralgia (OR 2.07, 95% CI: 1.29-3.30, p = 0.002). The addition of TIGIT blockade to PD-L1 blockade-based therapy was associated with increased G1-5 rash (OR 2.32, 95% CI: 1.01–5.34, p = 0.048) (other outcomes will be shown). Proportional meta-analysis revealed varying irAE patterns across agents: G5 trAEs (0.9-2.9%), G3-5 pneumonitis (0.5-5.5%, highest in TIM-3 blockade), G3-5 colitis (0.2-5.4%, highest in LAG-3 blockade), G3-5 hepatitis (1.5-5.5%, highest in TIM-3 blockade), G3-5 rash (0.8%-18.4%, highest in CD40 agonists), G3-5 adrenal insufficiency (1.7-8.4%, highest in TIGIT blockade) (details of all outcomes will be presented). **Conclusions:** This study highlights the distinct toxicity profiles of novel immunotherapy agents, providing essential safety data to support clinicians as these therapies move toward anticipated clinical approval. Research Sponsor: None.

2643 **Poster Session**

JAK inhibitor for the treatment of steroid refractory and life-threatening immune-related adverse events secondary to immune checkpoint inhibitors. First Author: Rami Habib, McGill University, Montreal, QC, Canada

Background: Immune checkpoint inhibitors (ICIs) boost anti-tumor immune responses but carry the risk of off-target effects, manifesting as immune-related adverse events (irAEs). Approximately 20% of irAEs are refractory to steroids, requiring subsequent immunosuppressive therapies, while a smaller subset presents with fulminant reactions requiring multiple agents simultaneously. Although biologics like TNF and IL-6 inhibitors are often used, their targeting of single inflammatory pathways may be insufficient to resolve irAEs in these critical scenarios. We conducted a prospective study to assess the safety and efficacy of oral JAK inhibitors, molecules capable of rapidly modulating multiple inflammatory cytokine signals, in managing steroid-refractory or life-threatening irAEs. **Methods:** The MIRAE Biobank is a prospective cohort study of cancer patients treated with ICI at the Jewish General Hospital in Montreal, Canada. Patients with steroid refractory subjects with grade $>$ 3 irAE or persistent grade 2 toxicity despite optimal therapy, as well as life-threatening irAEs in the first-line setting treated with JAK inhibitors were extracted from the database and their clinical data was summarized. Among those who survived at least 30 days post-JAK inhibitor, we compared characteristics of responders and non-responders. Responders were defined as resolution of the irAE to grade $<$ 1 and $<$ 10mg prednisone equivalents without any relapses during a 30-day period. **Results:** In this series, 29 patients were treated with JAK inhibitors for refractory or life-threatening irAEs. Mean age was 69 years, 34.5% were women, 82.8% received anti-programmed cell death protein-1 (PD-1) antibodies alone, and 13.8% patients were treated with the combination of anti-cytotoxic T lymphocyte antigen-4 and anti-PD-1 antibodies. Cancer types were primarily melanoma (10, 34.5%) and lung cancer (6, 20.7%). Primary irAEs for which JAK inhibitors were initiated included myocarditis (n=11), colitis (n=4), arthritis (n=4), hepatitis (n=4), encephalitis (n=2), pneumonitis (n=2), myasthenia gravis (n=1) and sicca (n=1). JAK inhibitors were used as second- (refractory to steroids alone), third- or fourth- or more line in 9, 11 and 9 patients, respectively. Median duration of JAK inhibitor exposure was 30.5 days. Among the 24 patients who survived at least 30 days, 17 (71%) responded after a median of 11 days from initiation of the JAK inhibitor. Interestingly, this included 6/8 patients with myocarditis, 4/4 with arthritis and 2/3 with colitis. Of those who responded to JAK inhibitor, 11/18 were steroid refractory and 6/6 were life-threatening cases requiring simultaneous treatment with steroids. **Conclusions:** This preliminary data suggests that JAK inhibitors may be effective at treating various types of steroid-refractory and life-threatening irAEs. Research Sponsor: Arthritis Society Canada; #23-313.

2644 **Poster Session**

Albumin-myosteatosis gauge as a prognostic biomarker in patients treated with immune checkpoint inhibitors. First Author: Taha Koray Sahin, Hacettepe University, Department of Medical Oncology, Ankara, Turkey

Background: Although immune checkpoint inhibitors (ICIs) have heralded a new era in cancer treatment, many patients do not respond, underscoring the need for biomarkers. The albumin-myosteatosis gauge (AMG) is a recently developed integrated measure of myosteatosis and serum albumin levels, reflecting systemic inflammation and malnutrition. Herein, we investigate the prognostic value of AMG in patients with advanced cancer treated with ICIs. **Methods:** A total of 308 patients with advanced cancer treated with ICIs were included. Skeletal muscle index (SMI) and skeletal muscle radiodensity (SMD) were measured from computed tomography images obtained at the level of the L3 vertebra. The AMG was calculated by multiplying SMD by albumin and expressed as an arbitrary unit (AU). Survival outcomes were assessed using Kaplan-Meier survival curves and Cox regression models. **Results:** The median age (interquartile range) was 63 (55-70), and 198 (64.3%) were male. Non-small cell lung cancer (NSCLC) was the most common primary cancer (28.2%), followed by renal cell carcinoma (RCC) (20.8%) and melanoma (20.2%). Regarding AMG, the cutoff values were determined to be 109.38 AU for males and 102.11 AU for females. Multivariable analyses revealed that lower AMG values were independently associated with decreased OS (HR: 1.43; 95% CI: 1.08-1.90; p=0.012) and PFS (HR: 1.39; 95% CI: 1.07-1.79; p=0.011) compared to the AMG high-group. **Conclusions:** Our findings suggest AMG, an easily accessible novel biomarker, is an independent prognostic factor for survival in patients with advanced cancer treated with ICIs. Prospective studies are required to validate these findings and evaluate the role of AMG measurement in aiding treatment choices. Research Sponsor: None.

2645 **Poster Session**

Tumor flare reactions secondary to T-cell engaging immunotherapies: A study from the French REISAMIC registry. First Author: Alexandre Xu-Vuillard, Gustave Roussy, Villejuif, France

Background: Tumour flare reactions (TFR) were recently reported in patients receiving T-cell engagers (TCE) and require further investigations. This study aims to investigate incidence, predictive factors, and outcomes of pts with TFRs related to TCE. **Methods:** This observational cohort study is nested in the French academic pharmacovigilance register, Registre des Effets Indésirables Sévères des Anticorps Monoclonaux Immunomodulateurs en Cancérologie (REISAMIC, CNIL number 2098694v0). All patients treated at Gustave Roussy (France) with TCE, for all tumor indications except acute leukemia, were included. The main objectives were to determine the incidence, predictive factors, associated clinical and biomarker profiles, as well as the outcomes of patients. TFRs were clinically defined with transient worsening of tumor symptoms including tumor pain, effusions, or compressive symptoms, mimicking tumor growth but without reflecting disease progression. Statistical analyses included log-rank tests and Cox regression models. **Results:** Overall, 222 TCE-treated patients were included, median [range] age: 53 [5 - 87] years; male-to-female ratio: 1.44, median prior lines of therapies was 3 [2-9]. Of them, 147 (66.2%) had solid tumors, including prostate cancer (n=51), high-grade serous ovarian carcinoma (n=28), and small-cell lung cancer (n=24), and 75 (33.8%) had hematologic malignancies, primarily multiple myeloma (MM, n=35) and diffuse large B-cell lymphoma (DLBCL, n=31). Common TCE targets included CD3/CD20 (n=40), CD3/KLK2 (n=36), CD3/BCMA (n=35), CD3/DLL3 (n=28), and CD3/B7-H4 (n=27). TFRs occurred in 54 pts (24.3%), with higher TFR frequency in solid tumors (34.0%) than lymphomas (12.1%) and none in MM. Median TFR onset was 1 day [1–8]. Symptoms of TFRs were pain (92.6%), compression syndrome (22.2%), and effusion (7.4%). Severity of TFRs was grade 3–4 in 68.5% of cases. No TFR-related deaths occurred. TFRs management included corticosteroids (35.2%), opioids (61.1%), paracentesis (7.4%), JJ stenting (3.7%) and tocilizumab (3.7%). TFRs correlated with transient increases of CRP (182 vs. 69 mg/L; p=0.0002) and LDH (316 vs. 225 U/L; p=0.04). Patients with TFRs were more frequently exposed to cytokine release syndrome (p=0.0001). Predictors included tumor serous localization (p=0.052) and a higher CD4+/CD8+ ratio in blood (p=0.048). In solid tumors pts; TFRs were associated with higher response rates (18.0% vs. 6.3%; p=0.013) and disease control rates (72.0% vs. 49.5%); PFS (2.83 vs. 2.76 months; p=0.865) and OS (9.92 vs. 9.72 months; p=0.539) were comparable regardless of TFRs. **Conclusions:** TFRs related to TCE are clinically significant adverse events, primarily observed in solid tumor pts. TFRs may indicate a unique pattern of antitumor response distinct from progression. Better recognition and management of TFRs should help to optimize tolerability of TCE therapies. Research Sponsor: Gustave Roussy.

2646 **Poster Session**

Evaluating the role of exercise in modulating immunity and immunotherapy outcomes in cancer: A systematic review. First Author: Samhitha Gundakaram, Joan C. Edwards School of Medicine, Marshall University, Huntington, WV

Background: Immunotherapy has become a key cancer treatment, improving survival and reducing side effects. However, its effectiveness can be influenced by immune system function, overall health, and treatment-related side effects. Exercise, known for its health benefits, may also modulate immune responses and enhance immunotherapy outcomes. Despite promising evidence, the impact of exercise on immune function and cancer treatment remains insufficiently understood. This review aims to assess the role of exercise in modulating immunity and improving immunotherapy outcomes in cancer patients. **Methods:** A systematic review was conducted following PRISMA guidelines, with a comprehensive search of PubMed, Cochrane Library, EMBASE, and ClinicalTrials.gov for studies published from 2010 to 2025. Eligible studies included randomized controlled trials (RCTs), non-randomized trials, pilot studies, and systematic reviews investigating exercise interventions on immune function and immunotherapy in cancer. Key outcomes included changes in immune markers, immune function, and quality of life. Data were extracted and analyzed using standardized protocols. **Results:** Eight studies, involving 1,172 cancer patients across various types (lymphoma, CLL, melanoma, NSCLC, breast, ovarian, prostate), were included. Exercise modalities studied included aerobic exercise, resistance training, cycling, yoga, and mind-body practices like qigong. Findings consistently showed positive effects of exercise on immune function and treatment outcomes. Two studies reported that exercise mobilized T cells and NK cells, enhancing immune responses. Another two demonstrated improved efficacy of immunotherapeutic agents such as rituximab. Additionally, three studies indicated that exercise improved physical fitness, body composition, and overall quality of life. **Conclusions:** This review provides evidence that exercise may enhance immune responses and improve outcomes in cancer immunotherapy. While exercise appears to be a beneficial adjunctive therapy, the optimal type, intensity, and duration remain unclear. Further large-scale, high-quality trials are needed to define effective exercise regimens and explore their impact on immunotherapy across various cancer types. The study is registered in PROSPERO: CRD42024627822. Research Sponsor: None.

2647 **Poster Session**

Safety, pharmacokinetics (PK), pharmacodynamics (PD), and preliminary efficacy of HLX301, a bispecific antibody targeting PD-L1 and TIGIT, in patients with advanced solid tumors. First Author: Michelle Frances Morris, Sunshine Coast University Hospital, Birtinya, Australia

Background: Immune checkpoint proteins PD-L1 and TIGIT are important components of cancer-related T cell immunosuppression. HLX301 is a humanized, bispecific IgG1 antibody targeting PD-L1 and TIGIT that showed anti-tumor activity in preclinical studies. A phase 1/2 first-in-human study was conducted to evaluate HLX301 monotherapy in patients with advanced solid tumors (NCT05102214). Here we report findings from the dose escalation part (phase 1a). **Methods:** This multicenter study enrolled patients with locally advanced or metastatic solid tumors who had failed or were intolerant to standard therapy, or for whom no standard therapy was available. Phase 1a evaluated doses of 0.25-15 mg/kg IV Q2W. Primary endpoints included safety, dose-limiting toxicity (DLT), and maximum tolerated dose (MTD). Secondary endpoints included PK, PD, and immunogenicity. **Results:** As of Oct 27, 2023, 9 patients were enrolled (0.25 mg/kg, 3; 1 mg/kg, 3; 2.5 mg/kg, 1; 5 mg/kg, 2). Patients were all White, 55.6% female, median age 72.0 yrs; 88.9% had metastatic disease; all had ECOG PS of 0 (44.4%) or 1 (55.6%). All patients had prior systemic cancer treatment, including 3 (33.3%) treated with PD-(L)1 blockade; 5 (55.6%) patients had $\geq$ 4 prior lines of therapy. All patients were included in DLT, safety, and PK analyses. Median duration of HLX301 treatment was 10.3 weeks. One patient (11.1%) in the 5 mg/kg cohort reported DLT (grade 3 cytokine release syndrome [CRS]). MTD was not determined. All patients experienced at least one treatment-emergent adverse event (TEAE). TEAEs leading to death occurred in 3 (33.3%) patients, none of these adverse events (AEs) were related to HLX301. Six (66.7%) patients experienced at least one treatment-related adverse event (TRAE). TRAE of grade $\geq$ 3 was reported in 1 patient (11.1%; grade 3 CRS), who was also the only patient for whom TRAE led to treatment discontinuation. Treatment-related immune-related AEs occurred in 4 (44.4%) patients and treatment-related infusion-related reactions (IRRs) in 2 (22.2%). TRAEs occurring in $\geq$ 2 patients included IRR (22.2%) and arthralgia (22.2%). HLX301 exhibited linear PK over 0.25-5 mg/kg after single infusion and very limited accumulation after multiple infusions. Mean PD-L1 and TIGIT receptor occupancy in peripheral $CD3^+CD8^+$ cells reached saturation at 5 mg/kg. Anti-drug antibody was detected in 7 patients (77.8%). Among 8 efficacy-evaluable patients, 1 (5 mg/kg cohort) achieved partial response and 2 achieved stable disease; objective response rate and disease control rate per RECIST 1.1 were 12.5% and 37.5%, respectively. **Conclusions:** HLX301 showed an acceptable safety profile with preliminary anti-tumor activity. These findings could support further clinical investigation. Clinical trial information: NCT05102214. Research Sponsor: Shanghai Henlius Biotech, Inc.

2648 **Poster Session**

Solid tumor–specific patterns of immune-related adverse events due to immune checkpoint inhibitor. First Author: Shabnam Eghbali, Vanderbilt University Medical Center, Nashville, TN

Background: Immune checkpoint inhibitors (ICIs) are the backbone of therapy for several solid tumors; however, they have a unique toxicity profile that may limit treatment. The objective of this systematic review was to identify differences in type and frequency of immune-related adverse events (irAEs) across solid tumors. **Methods:** Using PubMed, we identified registrational phase 2 and 3 clinical trials of ICI-based therapy (i.e., single agent immunotherapy (single I/O), single I/O plus chemotherapy, single I/O plus kinase inhibitor, double immunotherapy combination (double I/O), double I/O plus chemotherapy) for first-line and second-line unresectable disease for which irAEs (dermatologic, endocrine, gastrointestinal, hepatic, renal, pulmonary) were specified for the following tumor types: melanoma, non-small cell lung (NSCLC), esophageal, colorectal (CRC), biliary tract (BTC), hepatic (HCC), renal (RCC), urothelial, endometrial, head and neck (H&N). Odds ratio (OR) were used to analyze effect size. All analysis performed on Microsoft Excel. **Results:** 105 trials (n = 32,896 patients) were identified with the most commonly studied regimens being those that were PD-1 or PD-L1-based. While endocrinopathies were the most frequent irAE (~15-20%) with first-line single I/O, one tumor type was not more likely than the other to develop endocrinopathies. Interestingly, patients with melanoma and RCC treated with first-line single I/O were significantly more likely to develop gastrointestinal irAE compared to those with NSCLC, CRC, HCC, urothelial, and H&N with OR of 3.41 – 30.64 and 2.96 – 26.60, respectively. Second-line single I/O led to increased frequency of irAE and greater variation in the predominant irAE for a given tumor type – four tumor types (melanoma, NSCLC, gastric, H&N) had dermatologic irAE as most frequent, five (esophageal, CRC, HCC, urothelial, endometrial) had endocrine irAE, and two (BTC, RCC) had gastrointestinal irAE. Overall odds of developing irAE were greater with double I/O than with single I/O in the first-line setting and more pronounced in the second-line. For example, in melanoma, OR for endocrine irAE was 2.55 (95% CI 1.27 – 5.10) in first-line and 17.03 (95% CI 8.04 – 36.05) in second-line and for hepatic irAE was 4.41 (95% CI 1.55 – 12.50) in first-line and 7.63 (95% CI 2.45 – 23.78) in second-line. The addition of chemotherapy or kinase inhibitor did not significantly alter irAE frequency across tumor types. In fact, there were fewer irAEs in some tumor types with addition of kinase inhibitor in first-line unresectable disease compared to single I/O alone; for example, OR for dermatologic irAE with kinase inhibitor compared to single I/O alone was 0.36 (95% CI 0.18 – 0.70) for melanoma and 0.22 (95% CI 0.08 – 0.59) for RCC. **Conclusions:** irAE profiles vary across tumor type, treatment regimen, and line of therapy and do not necessarily correlate with the primary tumor site. Research Sponsor: None.

2649 Poster Session

Impact of immune checkpoint inhibitor (ICI)-associated autoimmune hemolytic anemia (AIHA) on mortality in cancer patients: A retrospective analysis. First Author: Haris Sohail, Charleston Area Medical Center, Charleston, WV

Background: Immune checkpoint inhibitors (ICIs) have revolutionized cancer treatment but can cause serious immune-related adverse events; including rare yet severe autoimmune hemolytic anemia (AIHA) . This study evaluates the impact of ICI-associated AIHA on mortality in patients with solid cancers. **Methods:** A retrospective analysis using the TriNetX database examined patients with solid cancers treated with ICIs. Patients were defined using ICD-10 codes and grouped into those who developed AIHA after ICI use and those who did not. Baseline characteristics, including cancer diagnosis, ICI medications, and comorbidities, were compared between groups using TriNetX's built-in t-tests and z-tests to calculate p-values. Confounding variables were adjusted with 1:1 propensity score matching. Primary outcomes were 30- and 60-day mortality; secondary outcomes included transfusions and hospitalizations. Outcomes were evaluated using measures of association, Kaplan-Meier log-rank tests, and a Cox proportional hazards model. **Results:** Among 106,388 ICI-treated patients, 352 developed AIHA. After matching (352 per group), the AIHA group had a significantly higher 30-day mortality (15.25% vs. 5.14%; OR 3.493, 95% CI: 1.898-5.803, $p < 0.0001$) and 60-day mortality (22.87% vs. 6.86%; OR 4.195, 95% CI: 2.479-6.54, $p < 0.001$). Transfusions (OR 4.085, 95% CI: 2.897-6.525, $p < 0.0001$) and hospitalizations (OR 1.865, 95% CI: 1.525-2.837, $p < 0.0001$) were also significantly higher in the AIHA group. Hazard ratios (HR) confirmed significant mortality risks in AIHA group at 30 days (HR: 3.16, 95% CI: 1.849-5.402, $p < 0.0001$) and 60 days (HR: 3.673, 95% CI: 2.324-5.805, $p < 0.0001$) (table 1). HRs for transfusion and hospitalization were 4.309 (95% CI: 2.975-6.241, $p < 0.0001$) and 2.049 (95% CI: 1.692-2.48, $p < 0.0001$), respectively. **Conclusions:** This study highlights the clinical impact of ICI-associated AIHA, which is linked to higher mortality at 30 and 60 days, as well as increased transfusion and hospitalization rates. Although rare, ICI-associated AIHA is a potentially fatal complication. Clinicians should maintain a high level of suspicion for AIHA in patients on ICIs, as early recognition and intervention may improve outcomes. Research Sponsor: None.

Primary Outcomes	HR	95 % Confidence Interval	P-Value
Mortality within 30-days*	3.16	(1.849,5.402)	< 0.0001
Mortality within 60-days*	3.673	(2.324,5.805)	< 0.0001
Transfusion	4.309	(2.975,6.241)	< 0.0001
Hospitalization or emergency services	2.049	(1.692,2.48)	< 0.0001

2650 Poster Session

Improved survival with sodium-glucose cotransporter-2 inhibitors and immune checkpoint inhibitors in metastatic solid tumors. First Author: Sara Young, Division of Hematology and Oncology, University of Virginia, Charlottesville, VA

Background: Immune checkpoint inhibitors (ICI) are used in the first-line setting for the treatment of many advanced solid tumor malignancies. Patients with type 2 diabetes mellitus (T2DM) have decreased response rates to ICI, and poor glycemic control is associated with worse outcomes in patients with cancer. Further adjunctive therapies increasing the efficacy of ICI in these patients are needed. Sodium-glucose cotransporter-2 inhibitors (SGLT2i) have emerged as effective antihyperglycemic medications with concomitant cardiovascular benefits. SGLT2i have been approved by the Food and Drug Administration for use in patients with DM and congestive heart failure (CHF). Pre-clinical studies have demonstrated the potential benefit of SGLT2i in slowing tumor growth in-vitro and in-vivo; however, there is a lack of clinical data regarding SGLT2i use in patients with advanced malignancy receiving ICI. **Methods:** We performed a retrospective, matched cohort study of patients with stage IV malignancy and T2DM or CHF, who were treated with ICI using the Epic Cosmos dataset (2013–2024). Ten different solid tumor types, five ICI, and three SGLT2i were analyzed. Among 4,808 patients treated with ICI, 282 had at least one overlapping cycle of ICI and SGLT2i. 1:1 propensity score matching was conducted to balance baseline covariates including cancer type, comorbidities, age at diagnosis, and sex. Kaplan-Meier curves were generated to examine survival differences and Cox proportional hazards models were used to estimate hazard ratios (HR). The primary outcome was overall survival (OS) for the entire matched cohort and sub-groups by cancer, ICI, and SGLT2i types. **Results:** Patients who received ICI and SGLT2i had significantly improved OS compared to those who received ICI alone (HR = 0.62, 95% CI: 0.49-0.79). Among cancer types, significant improvements in survival were observed in patients with renal cell carcinoma (RCC, HR = 0.48, 95% CI: 0.27–0.84) and non-small cell lung cancer (NSCLC, HR = 0.60, 95% CI: 0.37–0.96). Among ICI types, ipilimumab + nivolumab (HR = 0.35, 95% CI: 0.15–0.79) and pembrolizumab (HR = 0.49, 95% CI: 0.32-0.74) showed a significant improvement in survival when used with SGLT2i. There was no statistically significant difference in OS amongst the three SGLT2i types. **Conclusions:** In this retrospective, matched cohort study we observed encouraging improvements in OS in patients with T2DM or CHF receiving SGLT2i in addition to ICI across multiple solid tumor types. Patients with RCC and NSCLC derived the greatest benefit. Patients treated with either ipilimumab + nivolumab or pembrolizumab had the best responses to therapy. SGLT2i may be beneficial as adjunctive therapies in patients with advanced malignancy receiving ICI. However, further prospective studies to validate our observations and determine potential underlying mechanisms are needed. Research Sponsor: None.

2651 Poster Session

Prognostic value of host genetic variants determining Bifidobacterium abundance in the lactose metabolism pathway for immunotherapy efficacy. First Author: Wenhui Liu, The Second Xiangya Hospital of Central South University, Changsha, Hunan, China

Background: The potential predicative and therapeutic value of *Bifidobacterium* in immune checkpoint inhibitors (ICIs) treatment has been widely studied. However, the value of its genetic determinants on the prognosis of ICIs treatment remains unclear. **Methods:** we examined the associations of 11 single nucleotide polymorphisms (SNPs) located at host genes determining *Bifidobacterium* abundance with the outcomes of ICIs treatment in 370 eligible cancer patients. **Results:** Cox regression analysis revealed that rs3739020 TT carriers experienced significantly extended OS (*P*-value = 0.003, adjusted HR = 0.46, 95%CI = 0.27-0.77) compared with GG+TG carriers. The *LCT* haplotype analysis showed that the lactose poor metabolizers exhibited significantly poorer OS (*P*-value = 0.002, adjusted HR = 0.45, 95%CI = 0.27-0.74) than the extensive or intermediate metabolizers. In polygenic SNP analysis, the high galactose level carriers exhibited significantly prolonged OS (*P*-value = 0.007, adjusted HR = 0.32, 95%CI = 0.14-0.73) and progression-free survival (PFS, *P*-value = 0.001, adjusted HR = 0.45, 95%CI = 0.29-0.71). All the four SNPs and the *LCT* metabolic phenotype were not associated with the occurrence of overall immune-related adverse events (irAEs). Genetically predicted *Bifidobacterium* abundance was significantly associated with an increased abundance of lactose metabolism pathway (*P*-value = 0.012, Beta coefficient = 0.549). **Conclusions:** SNPs determining *Bifidobacterium* abundance in the lactose metabolism pathway have prognostic value for immunotherapy efficacy, and the lactose extensive and intermediate metabolizers exhibited better immunotherapy efficacy. Research Sponsor: National Natural Science Foundation of China; 82204534.

The details of *LCT* metabolic phenotypes and the associations of *LCT* metabolic phenotypes with overall survival.

	LCT genotypes and their risk allele					
	rs3739020G	rs56263017C	rs55809728A	rs3739022A	HR	P
Lactose extensive metabolizer (EM, no risk allele exist)	TT	TT	GG	GG	Refernces	
Lactose inermediate metabolizer (IM, risk alleles exist in 1-3 SNPs)	TG or GG	TT	GG	GG	0.58,95%CI=0.33-0.99	0.049
	TT	TC or CC	GG	GG		
	TT	TT	AA or GA	GG		
	TG or GG	TT	GG	AA or GA		
	TG or GG	TC or CC	GG	GG		
	TG or GG	TT	AA or GA	GG		
	TT	TT	GG	AA or GA		
	TT	TC or CC	AA or GA	GG		
	TT	TC or CC	GG	AA or GA		
	TG or GG	TT	AA or GA	AA or GA		
	TG or GG	TC or CC	AA or GA	GG		
	TG or GG	TC or CC	GG	AA or GA		
	TT	TT	AA or GA	AA or GA		
	TG or GG	TC or CC	AA or GA	AA or GA		
Lactose poor metabolizer (PM, risk alleles exist in 4 SNPs)	TG or GG	TC or CC	AA or GA	AA or GA	0.33,95%CI=0.18-0.62	0.001

The patients were stratified into three *LCT* metabolic phenotypes (PMs, IMs, EMs) according to the existence of the risk alleles (rs3739020 G, rs56263017 C, rs55809728 A, and rs3739022 A) in these four *LCT/MCM6* SNPs.The lactose EMs and IMs exhibited significantly extended OS than PMs.

2652 Poster Session

Early peripheral Treg expansion after SBRT combined with low-dose radiotherapy to predict subsequent immune checkpoint inhibitor responses in patients with metastatic lung or gastrointestinal cancers. First Author: Byoung Hyuck Kim, Seoul National University College of Medicine, Smg-Snu Boramae Medical Center, Seoul, South Korea

Background: This study aims to explore the potential therapeutic advantages of combining stereotactic body radiation therapy (SBRT) and low-dose radiotherapy (LDRT) prior to immune checkpoint inhibitor (ICI) treatment for metastatic lung or gastrointestinal cancers, to induce an immune-favoring tumor microenvironment. **Methods:** Patients with metastatic cancer and three or more measurable lesions scheduled for ICI therapy were enrolled in this study. Treatment consisted of three SBRT doses of 8–10 Gy to the main target lesion and LDRT (2–3 Gy) for other lesions. Patients without evidence of disease progression within 6 months after the first dose of ICI were defined as responders, while others were classified as non-responders. Peripheral blood samples obtained before SBRT/LDRT (W0), 1 week after SBRT/LDRT but prior to ICI initiation (W1), and 4 weeks after SBRT/LDRT (W4) were analyzed using multi-color flow cytometry. This trial has been registered at cris.nih.go.kr (registration number: KCT0005879). **Results:** Among the 13 enrolled patients (lung 9, gastrointestinal 4), samples from 4 responders and 7 non-responders were analyzed initially, revealing a median progression-free survival of 22.2 months for responders and 3.1 months for non-responders. The fold change in the proportion of regulatory ($Foxp3^+CD25^+$) $CD4^+$ T cells (Tregs) among total $CD4^+$ T cells at W1 compared to W0 (Treg/CD4–$FC_{W1/W0}$) was lower in responders than in non-responders (0.66 vs. 1.22; $P = 0.08$). Furthermore, the fold change in the proportion of suppressive $Foxp3^{hi}CD45RA^+$ Tregs among Tregs at W1 compared to W0 (Fr.II/Treg–$FC_{W1/W0}$) was significantly lower in responders than in non-responders (0.80 vs. 1.18; $P = 0.047$). This difference was no longer evident after one cycle of ICI, as Treg/CD4–$FC_{W4/W0}$ (1.15 vs. 0.86; $P = 0.46$) and Fr.II/Treg–$FC_{W4/W0}$ (1.06 vs. 1.33; $P = 0.18$) were not significantly different between responders and non-responders. **Conclusions:** We investigated circulating T cell modulation and its potential as a biomarker which revealed early expansion of Tregs in peripheral blood after SBRT/LDRT is associated with suboptimal response to ICIs in patients with metastatic cancers. Clinical trial information: KCT0005879. Research Sponsor: None.

2653 Poster Session

The impact of immunotherapy versus chemotherapy on mortality and adverse events in cancer patients hospitalized with septic shock. First Author: Saad Javaid, Charleston Area Medical Center, Charleston, WV

Background: Traditionally, chemotherapies have been associated with well-characterized toxicity profiles and adverse events. Meanwhile, immune checkpoint inhibitors (ICIs) have revolutionized cancer treatment, but their secondary toxicities, particularly in patients with septic shock, remain underexplored. Our study sought to evaluate the comparative risk of mortality and adverse events in patients treated with ICIs versus chemotherapy. **Methods:** Using the TriNetX Research Database, we identified cancer patients (≥18 years) diagnosed with septic shock between January 1, 2013, and December 16, 2024. Eligible cancers included malignancies of the oral cavity, pharynx, larynx, stomach, kidney, bladder, skin, head, neck, and lung. Patients treated with ICIs or chemotherapy within 6 weeks before or up to 2 weeks after septic shock diagnosis were stratified into two cohorts. Propensity score matching (1:1) adjusted for confounders. Kaplan-Meier log-rank tests analyzed outcomes. Primary outcomes were mortality at 30, 60, and 90 days. Secondary outcomes included irAEs, organ failure, and hospitalization or emergency services within 1 week to 1 month. **Results:** Through our study we identified 44,052 cancer patients diagnosed with septic shock. A total of 4,284 patients were on chemotherapy within the time of their diagnosis, while 472 patients were on ICIs. ICI use was associated with higher 30-day (HR: 1.27, 95% CI: 1.03-1.57, p = 0.02), and 90-day (HR: 1.21, 95%CI: 1.009-1.45, p = 0.03) mortality. But only a near significant difference was noted at 60-days (HR: 1.20, 95%CI: 0.99-1.45, p = 0.054). Additionally, the risk of organ failures (HR: 1.28, 95%CI: 1.11-1.48,p $<$ 0.001) and hospitalization or usage of emergency services (HR: 1.35, 95%CI: 1.16-1.56, p $<$ 0.001) was higher in patients treated with ICIs compared to chemotherapy. The frequency of irAEs was slightly higher in patients with ICIs, though these results were only near significant (HR: 1.155, 95%CI: 0.977-1.364, p = 0.0532). **Conclusions:** Cancer patients treated with ICIs with septic shock exhibited higher short-term mortality, organ failure rates, and hospitalization or emergency service usage compared to those receiving chemotherapy. These findings are unexpected, given the perceived safety profile of immunotherapy compared to traditional chemotherapy. Further research is warranted to better understand these risks and to develop strategies for mitigating adverse outcomes in this population. Research Sponsor: None.

	Log-Rank Test			
	HR	95% CI	P-Value	$\chi 2$
Primary Outcomes				
30-day Mortality	1.272	(1.032,1.569)	0.0231	0.233
60-day Mortality	1.203	(0.996,1.452)	0.054	3.714
90-day Mortality	1.212	(1.009,1.455)	0.039	4.262
Secondary Outcomes				
Frequency of irAEs	1.155	(0.977,1.364)	0.0532	3.737
Incidence of organ failure	1.285	(1.115,1.48)	$<$ 0.0001	23.556
Hospitalization or emergency services	1.349	(1.165,1.562)	$<$ 0.0001	22.937

2654 Poster Session

Gut dysbiosis as a potential guide for immunotherapy (dis)continuation after 2 years in non-small cell lung cancer: A mono-institutional, multi-omic assessment. First Author: Lorenzo Belluomini, Section of Innovation Biomedicine - Oncology Area, Department of Engineering for Innovation Medicine (DIMI), University of Verona, Verona, Italy, Italy

Background: Although most phase II and III clinical trials have set the duration of immune checkpoint blockers (ICB) for advanced non-small cell lung cancer (NSCLC) at two years, there remains uncertainty regarding the feasibility and safety of discontinuing treatment after this period. Of note, gut microbial taxonomic profiling prior to starting immunotherapy shows promise as biomarker for predicting ICB response. Here, we recommend integrating multi-omics approaches over time (24 months -mo-) to inform clinical decision-making and guide personalized treatment strategies. **Methods:** Pts completing 18 to 24 mo of ICB treatment between July 2016 and January 2023 were identified and enrolled (NCT04567446) at Gustave Roussy. Clinical factors influencing treatment (dis)continuation were assessed at 24 mo. Multi-omic analyses, including gut-based biomarkers (TOPOSCORE by whole genome sequencing), PET-FDG imaging, and ctDNA, were proposed at this timepoint. Key outcomes, including overall survival (OS) and progression-free survival (PFS) rates, were analyzed. **Results:** Among 123 advanced NSCLC pts treated for ≥18 mo, 35 (28,5%) completed 24 mo, with 31 included in the analysis (4 excluded due to PD). Of these, 68% continued ICB, while 32% stopped between 23.5 and 29.7 mo, mainly based on the physician or the patient decision. Clinical characteristics were comparable between the 2 groups (Table 1). After a median follow-up of 59.1 mo, no significant OS and PFS differences were observed between pts who discontinued and those who continued (OS p=0.9012, PFS p=0.3715). Among the multi-omic assessments performed at 24 mo, only gut-based biomarkers appeared to be conditionally associated with PFS24 rates. The proportion of long-responders (progression-free at 24 mo) was higher among those with a favorable gut composition compared to those with harmful composition (81% vs 44%, respectively, p=0.0870). **Conclusions:** Our results suggest that multi-omics approaches may help safely discontinue ICB after two years of treatment. In this context, multi-institutional validation and the implementation of a translational multi-omic algorithm, including gut-based biomarkers, could provide insight into the optimal duration of ICB therapy beyond the predefined 24-mo period. Clinical trial information: NCT04567446. Research Sponsor: None.

Clinical characteristics of the cohort (n=31).

Characteristics	Cessation group N = 10	Pursuit group N = 21	p-value*
Gender - no. (%)			
Male	5 (50)	12 (57)	0.7366
Female	5 (50)	9 (43)	
Age years - median (range)	61 (39-68)	62 (43-77)	
ECOG performance status - no. (%)			
0-1	9 (90)	15 (71)	0.2044
2	1 (10)	6 (29)	
PD-L1 expression - no. (%)			
<1%	0	2 (13)	0.5749
≥1%-<50%	3 (30)	2 (13)	
≥50%	7 (70)	11 (73)	
unknown	-	6	
Treatment regimen - no. (%)			
Chemoimmunotherapy	3 (30)	2 (10)	0.1907
Monoimmunotherapy	7 (70)	19 (90)	
Line of treatment - no. (%)			
First	7 (70)	10 (48)	0.7332
≥ Second	3 (30)	11 (52)	

*Chi-Square test.

2656 Poster Session

Validation and refinement of Society of Immunotherapy of Cancer (SITC) definitions for PD-(L)1 resistance: An analysis of more than 1,300 participants from SWOG. First Author: Megan Othus, Fred Hutchinson Cancer Center, Seattle, WA

Background: New immuno-oncology (IO) agents are commonly used in patients who previously received PD-(L)1 inhibitors. In order to facilitate clinical trial interpretation and better delineate therapeutic contributions of novel IO agents, consensus definitions of PD-(L)1 single-agent and combination immunotherapy resistance were published in 2020 (PMC7174063) and 2022 (PMC10016305) by the Society of Immunotherapy of Cancer (SITC); definitions outlined in Table. Validation of these expert-derived definitions is currently lacking. Herein we analyze two SWOG trials to evaluate the proposed definitions for the advanced and adjuvant settings. **Methods:** S1609/DART (NCT02834013) was a basket trial for patients with rare cancers treated with ipilimumab (1mg/kg intravenously [IV] every 6 weeks) plus nivolumab (240mg IV every 2 weeks). S1404 (NCT02506153) included an arm where patients with high-risk resectable Stage III melanoma received adjuvant pembrolizumab (200mg IV every 3 weeks for 1 year). In both trials, overall survival (OS) was measured from study registration to death from any cause with those last known to be alive censored. OS was evaluated with Kaplan-Meier and martingale residual plots and Cox regression models. **Results:** In S1609 (advanced setting), 733 participants were analyzed: 127 (17%) were not evaluable for primary resistance due to death or off treatment before 6 weeks. Among the 570 evaluable, 366 met the SITC primary resistance definition and 204 did not. Martingale residuals plots indicated a positive association between time to progression and OS with no evidence of a threshold. With a 6-month landmark, participants with primary resistance had significantly shorter OS compared to those who did not: hazard ratio (HR)=2.84, 95% confidence interval (CI) 2.28-3.55, p$<$0.001. In S1404 (adjuvant setting), 626 participants were analyzed with 12 (2%) meeting the definition of early recurrence/primary resistance and 138 (22%) meeting the definition of late recurrence/secondary resistance. Using a 12-month landmark, there was no significant difference in OS between early and late recurrences (HR=0.98, 95% CI:0.35-2.70, p=0.25), however late recurrences were associated with significantly shorter OS than no recurrence (HR=7.69, 95% CI:2.71-20.1,p$<$0.001). **Conclusions:** In the advanced cancer cohort, the SITC definitions were validated. In the adjuvant cohort, early recurrences were uncommon and there was no significant difference in OS between early and late recurrences suggesting a 12-month cutoff may be more appropriate than 12 weeks. Additional analyses in other patient cohorts are needed to further understand if the SITC definitions for advanced cancers validate more broadly and if data-drive refinements are needed for the adjuvant setting. Research Sponsor: US National Cancer Institute; Bristol-Myers Squibb Company.

Advanced	
Primary	Treatment $>$ 6 weeks; no response or $<$ 6 months
Secondary	Treatment $>$ 6 months; response/stable $>$ 6 months
Adjuvant	
Early/primary	$<$ 12 weeks last dose
Late/secondary	12 weeks

2657 Poster Session

PhaseX: Patient tumor avatars for evaluating anticancer therapeutics. First Author: Kanishka Fernando, National University of Singapore, Singapore, Singapore

Background: Current preclinical tumor platforms, such as in vitro 2D cell cultures and organoid models, fail to fully recapitulate the complexity of the tumor microenvironment, including critical components like the extracellular matrix and immune interactions. While humanized patient-derived xenograft models address some of these limitations, they are costly, low-throughput, artificial, and technically challenging to establish. PhaseX (Patient-derived hydrogel-assisted eXplants) presents a robust alternative, preserving the native TME, including cellular diversity, gene expression, and immune landscapes, for at least seven days. This study utilizes PhaseX to assess patient-specific responses to immune checkpoint blockade (ICB), chemotherapeutics, and targeted therapies while providing insights into their mechanisms of action. **Methods:** Fifteen fresh patient-derived tumor explants (PDTEs) from HNSCC patients were embedded in bioengineered hydrogel and treated ex vivo with pembrolizumab. Supernatants were collected at 2 and 4 days post-treatment for immunoassay analysis. Tumor explants were either dissociated for high-dimensional flow cytometry or processed into FFPE sections for immunofluorescence analysis at 2 and 5 days. Additionally, ten PDTEs representing various cancer types (peritoneal, colorectal, sarcoma, lung and ovarian) were used to evaluate dose-dependent responses to commonly used chemotherapeutics, including cisplatin, doxorubicin, and erlotinib. Six PDTEs were treated with plasminogen activator inhibitor-1 (PAI-1), and their post-treatment metabolic activity was assessed using the resazurin cell viability assay. **Results:** This study highlights the importance of capturing temporal dynamics in ex vivo tumor models to accurately predict pembrolizumab responses, achieving 100% sensitivity and specificity in HNSCC patients. Increased IFN-γ secretion and upregulation of chemokines (CXCL9, CXCL10, CXCL11) distinguished responders, alongside elevated cytotoxicity markers (perforin, granulysin, sFasL, sFas) contributing to cancer cell death. Responders exhibited reduced terminally exhausted CD8+ T cells (PD-1$^+$TIM3$^+$), allowing reinvigoration of functional CD8+ T cells, while non-responders showed elevated Tox$^+$CD38$^+$ levels, indicating resistance to PD-1 blockade. Spatial analysis revealed greater T cell infiltration in responders, facilitating tumor-cell interactions. Additionally, the PhaseX platform demonstrated its utility in evaluating dose-dependent responses across multiple tumor types (sarcoma, colorectal, lung, cervical) and identified patient-specific responses to PAI-1 inhibition. **Conclusions:** The PhaseX platform accurately predicts patient-specific responses for ICB, chemotherapeutics and targeted therapy across multiple tumor types. These findings establish PhaseX as a valuable tumor platform to evaluate anticancer therapeutics. Research Sponsor: None.

2658 Poster Session

Examining the relationship between multi-agent immunosuppressive therapy for immune-related adverse events (irAE) and infectious complications. First Author: Tristan Lee Lim, Mass General Cancer Center, Massachusetts General Hospital, Boston, MA

Background: Treatment of severe irAEs with multiple immunosuppressive therapies (ISTs) decreases the morbidity and mortality of these conditions. Nevertheless, the rates of and risk factors for infectious complications in this population are not known. **Methods:** We conducted a retrospective study of patients (pts) who received an immune checkpoint inhibitor (ICI) and experienced ≥1 irAE requiring treatment with corticosteroids along with at least two lines of steroid-sparing ISTs administered either concurrently or within 90 days of each other. We annotated all infections from ICI start until 90 days after IST. Opportunistic infections (OIs) were defined as herpesvirus (CMV, EBV, VZV, and HSV) and invasive fungal infections. Infection density was reported as number of infections per 1000 patient-days and graded as mild (not requiring treatment), moderate (requiring oral treatment), severe (requiring hospitalization or parenteral treatment), life threatening, or fatal. Risk factors were identified using univariable and multivariable Cox regression analysis adjusting for age at ICI initiation, sex, ICI regimen, ISTs, and steroid dose. **Results:** 175 pts (52% male, mean age: 66) with 238 irAEs and 417 ISTs were analyzed with a median follow-up of 367 days. The associated ICI regimens included αPD-1 (n = 81, 46%) and αPD-1/αCTLA-4 (n = 67, 38%). The most common irAEs were colitis (n = 67, 38%), hepatitis (n = 42, 24%), and myocarditis (n = 26, 15%). The most frequently used ISTs were mycophenolate mofetil (n = 92, 53%), infliximab (n = 77, 44%), and vedolizumab (n = 54, 31%). 103 pts (59%) developed 223 infections (median 2/pt, range: 1-8). 93 pts had 187 non-OIs. Of the 87 pts (50%) who had OI testing, 29 (33%) had 36 OIs, most commonly EBV DNAemia (n = 14, 16%) and CMV reactivation (n = 12, 14%). 6 pts had >1 OI, including 1 pt with CMV, EBV, and HSV. OI density significantly increased after starting ISTs for irAEs, but non-OI density was unchanged (Table 1). αCD20 use was associated with increased non-OI risk (HR: 10.58, 95% CI: 3.64-30.72, p < 0.001), while there was a trend towards increased non-OI risk with a max prednisone dose >100mg (HR: 1.74, 95% CI: 0.96-3.13, p = 0.07). In contrast, a max prednisone dose >100mg was associated with increased OI risk (HR: 2.89, 95% CI: 1.21-6.90, p = 0.017). 58 pts (33%) had severe or life-threatening infections, of whom 16 (9%) had OIs. 8 pts (5%) had fatal infections in this population. **Conclusions:** Use of multiple ISTs for severe irAEs is associated with increased rates of opportunistic infections as well as a 5% infection-related mortality rate. Patients requiring multiple lines of ISTs must be closely monitored for infectious complications, and prophylaxis should be considered when appropriate. Research Sponsor: None.

Mean OI and non-OI density per 1000 patient-days while on ICI alone vs ISTs.

	ICI	ISTs	p-value
OI	0.03	1.70	0.002
Non-OI	10.70	8.98	ns

2659 Poster Session

Incidence and outcomes of immune checkpoint inhibitor (ICI) rechallenge after ICI pneumonitis: A single-center retrospective study. First Author: MacKenzie Adams, Brown University Health, Providence, RI

Background: Limited evidence is available on the safety and efficacy of immune checkpoint inhibitor (ICI) rechallenge following an immune-related adverse event (irAE). Pneumonitis is a potentially life-threatening irAE, and minimal data is available with regards to outcomes after rechallenge. In this single-center retrospective analysis we analyzed patients who developed ICI pneumonitis and were later rechallenged with an ICI to further investigate incidence patterns and outcomes. **Methods:** We conducted a manual chart review on a cohort of 69 patients with ICI pneumonitis at our institution from 2015 to 2024. Rechallenged cases were defined as any patient who developed ICI pneumonitis and were later trialed on the same or another ICI. Patient records were reviewed to identify demographics, clinical features, treatment, and outcomes. **Results:** Of 69 patients with ICI pneumonitis, we identified 19 that were rechallenged with an ICI. Of these, 10 were women and 9 were men. The average age was 64 years (range: 42-82). Most patients had lung cancer (42%, 8/19) followed by melanoma (32%, 6/19). The treatment intent was palliative for 74% of patients (14/19). The most common therapy was nivolumab (n = 15), however, pembrolizumab, atezolizumab, and durvalumab were also used. The initial grade of ICI pneumonitis was as follows: grade 1 (n = 2), grade 2 (n = 13), grade 3 (n = 3), and grade 4 (n = 1). Many of these patients were treated with steroids, with the average time on steroids being 136 days (range: 0-488). Additionally, the only grade 4 patient was also treated with infliximab due to steroid-refractory pneumonitis. After recovery from their pneumonitis, all patients, except for two, were rechallenged with the same ICI that they had originally been treated with. The average time to rechallenge was 149 days (range: 12-714). Ultimately, 6/19 (32%) patients had recurrent ICI pneumonitis after rechallenge, but all six eventually recovered. On grading ICI toxicity after recurrence, 60% (4/6) remained grade 2, one was downgraded from grade 3 to 2, and one escalated from grade 2 to 3. Eleven percent (2/19) of patients developed an irAE other than pneumonitis (e.g. colitis, arthritis) after rechallenge. Finally, none of the 19 patients died from complications associated with ICI therapy. **Conclusions:** The recurrence rate of ICI pneumonitis after ICI rechallenge was 32%. At initial presentation, most of these patients had lower grade (grade 1: 2/19, grade 2: 13/19) ICI pneumonitis and most cases of recurrent pneumonitis remained at their initial grade 2. These results indicate that resuming ICI therapy could be considered in select patients with mild to moderate pneumonitis. Further research is needed to investigate immunotherapy rechallenge as it remains a nuanced decision that involves assessing the potential benefits of continued tumor control against the risk of a life-threatening toxicities. Research Sponsor: None.

2660 Poster Session

Clinical outcomes of patients with or without DNA repair pathway alterations by treatment type: The MD Anderson Cancer Center IMPACT 2 study. First Author: Jacopo Venturini, Investigational Cancer Therapeutics, The University of Texas MD Anderson Cancer Center, Houston, TX

Background: DNA repair deficiency is common among tumors, and emerging data suggest that genomic instability is associated with response to immuno-oncology (IO) therapies (PMID 28630051). We evaluated patients with advanced metastatic cancer across tumor types, who were treated on the IMPACT2 study (NCT02152254) and analyzed their clinical outcomes by treatment type (anti-DNA damage repair [DDR] agents, IO, or other [non-IO, non-anti-DDR]). **Methods:** Patients had tumor biopsies followed by molecular profiling in a CLIA-certified lab. All cases were discussed at Molecular Tumor Board meetings. Patients were treated on early-phase clinical trials. Progression-free survival (PFS), overall response rate (ORR), and overall survival (OS) were compared by therapy type in patients with or without DDR/MMR mutations (DDR+). **Results:** Of 829 enrolled patients, 510 had molecular profiling and received anticancer therapy: 85 were DDR+ (PS 1, 75%; med. age, 59 yrs; males 56.5%; med prior therapies 4; PDL1+ 44.9%; TMB-H 18%,) and 425 DDR- (PS 1, 88%; med. age, 60 yrs; men 47%, med. No. prior therapies 3; PDL1+ 46%; TMB-H 6.5%). Results are shown in the Table. In patients with DDR mutations, IO was associated with a higher ORR compared with "other" treatments (p=0.044); and with longer PFS compared with anti-DDR therapies (p = 0.044); no difference was noted in OS by treatment type. In the DDR-neg group, IO was associated with longer PFS (p = 0.017), and longer OS (p = 0.0004) compared with anti-DDR therapy; OS was longer in the IO group compared with "other" treatments (p = 0.029) and in the "other" treatments group compared with anti-DDR agents (p=0.006). **Conclusions:** Our data indicate the complexity of assessing outcomes in patients with various tumor types and without DDR mutations. Further work is needed to develop predictive biomarkers for IO and anti-DDR agents. Clinical trial information: NCT02152254. Research Sponsor: Steven McKenzie's Endowment for Dr Tsimberidou's personalized medicined program; Katherine Russell Dixie Distinguished Endowed Professorship for Dr Tsimberidou; Jamie's Hope for Dr Tsimberidou's personalized medicined program; NIH National Cancer Institute award number P30 CA016672 (to The University of Texas MD Anderson Cancer Center).; Tempus, Inc. for the IMPACT 2 study; Foundation Medicine, Inc for the IMPACT 2 study.

	Rx type	DDR-pos	N	Outcome	Anti-DDR vs IO	IO vs Other	Anti-DDR vs Other	DDR-neg	N	Outcome	Anti-DDR vs IO	IO vs Other	Anti-DDR vs Other
Overall response (%)	IO		34	6 (25%)	OR* 0.78; p=0.81	**OR* 20.73; p=0.044**	OR* 16.09; p=0.1		116	9 (11%)	OR* 0.34; p=0.46	OR* 2; p=0.13	OR* 0.67; p=0.79
	Anti-DDR		18	1 (16.7%)					52	0 (0%)			
	Other		33	0 (0%)					257	12 (5.9%)			
PFS, med. (95% CI)	IO		34	4.26 (2.3, 7.4)	**HR 2.01 (1.02,3.96) (p=0.044)**	HR 0.91 (0.56,1.47) p=0.69	HR 1.82 (0.95,3.49) p=0.07		116	5.42(3.02,6.61)	**HR 2.02 (1.14,3.61) p= 0.017**	HR 0.85 (0.68,1.06) p= 0.15	HR 1.71 (0.98,2.99) p=0.058
	Anti-DDR		18	2.58 (1.68, NA)					52	1.64 (1.45, NA)			
	Other		33	4.54 (3.06, 6.54)					257	3.98 (3.45, 4.57)			
OS, med. (95% CI)	IO		34	14.37 (10.22, NA)	HR 1.68 (0.82,3.42) p=0.16	HR 0.73 (0.43,1.23) p=0.24	HR 1.23 (0.62,2.42) p=0.56		116	12.46 (8.75, 20.78)	**HR 2.98 (1.62,5.48) p=0.0004**	**HR 0.76 (0.6,0.97) p=0.029**	**HR 2.27 (1.27,4.07) p=0.006**
	Anti-DDR		18	8.98 (3.48, NA)					52	4.31 (2.66, NA)			
	Other		33	10.82 (7, 16.83)					257	9.4 (8.28, 11.21)			

*OR, Odds Ratio, p values, unadjusted for multiple comparisons.

2661 Poster Session

MicroRNA-based signatures of early and late immune-related adverse events to anti-PD1 treatment. First Author: Joanne B. Weidhaas, University of California, Los Angeles, Los Angeles, CA

Background: Immune checkpoint inhibitors (ICIs) have transformed cancer treatment but are associated with toxicity in the form of immune-related adverse events (irAEs). We previously reported a genetic signature predicting anti-PD1 irAEs in a retrospective analysis of a heavily pretreated melanoma cohort, which validated in a pan-cancer cohort. Here we investigate the applicability of that signature in a prospectively collected cohort of GU, breast, and NSCLC cancer patients. We evaluated clinical and genetic differences between the original training set and this cohort and leveraged the expanded dataset to develop novel models for timing-specific anti-PD1 toxicity. **Methods:** We analyzed clinical and genetic differences in the melanoma training cohort (n=58) and the new cohort of patients, all treated with single agent anti-PD1/PDL1 therapy (n=137). Clinical and genetic differences were assessed using Fisher's exact test for categorical variables: pre-treatment, concurrent radiation, and SNP genotype across 165 loci. Kruskal-Wallis tests were used for age, toxicity timing, and severity of toxicity. Predictive genetic models were constructed using elastic net, random forest, and boosted tree algorithms and evaluated using leave-one-out cross-validation (LOOCV) metrics. Outcomes included cycle-specific toxicity (early ≤5 cycles, late ≥15 cycles). SNPs were pre-filtered for inclusion in genetic models using Fisher or Jonckheere-Terpstra p-values (<0.2) for relevance to outcomes. **Results:** The training and current cohort were different in their toxicity timing, with earlier toxicity onset in the new cohort (median 5 cycles vs. 20 cycles in melanoma, Kruskal p = 0.00018). Genetic analysis identified 12 significantly different SNP genotypes (Fisher p < 0.05) between cohorts, including mir146A rs2910164 (Fisher p = 0.0005). This SNP was associated with early toxicity overall and within data subsets. Refining our model to account for cycle-specific toxicity events significantly enhanced performance. For late toxicity (≥15 cycles), the refined model achieved a LOOCV AUC of 0.793 (genetics + clinical). A newly developed early toxicity model (≤5 cycles) using genetics alone demonstrated robust predictive accuracy with an AUC of 0.753. **Conclusions:** These findings emphasize the importance of defining clinical and genetic diversity in refining predictive models for anti-PD1/PDL1 outcomes. The development of an early toxicity model offers significant clinical utility. Next steps will be to use time to event (toxicity) versus cycle number. This study provides a foundation for the application of personalized genetic tools to predict the safety of ICIs for currently treated patient cohorts. Research Sponsor: U.S. National Institutes of Health; R01CA238998.

New LOOCV performance metrics in expanded PD1 data (n=234).

Outcome	Covariates	Sensitivity	Specificity	PPV	NPV	F1	AUC
Late Toxicity (>= 15 cycles)	SNPs + Clin	0.692	0.894	0.450	0.959	0.545	0.793
Early Toxicity (<=5 cycles)	SNPs Only	0.600	0.907	0.486	0.939	0.537	0.753

2662 Poster Session

Overall survival according to timing of immune checkpoint inhibitors administration in patients with advanced cancer: Results from a large single-centre cohort analysis. First Author: Tommaso Bosetti, The Christie NHS Foundation Trust, Manchester, UK, United Kingdom

Background: Immune checkpoint inhibitors (ICIs) have revolutionised cancer treatment but are only effective in a subset of patients. Evidence of a circadian dependence of the immune system has led to retrospective studies which suggested that the time of day of ICIs infusion influences treatment response, with better outcomes for early treatment times. Previous studies are limited by small sample size and methodological bias. We performed a retrospective study in patients with advanced solid tumours treated with ICIs at a large tertiary cancer centre. **Methods:** Patients who received regimens comprising ICIs for advanced/metastatic disease between January 2018 and December 2023 were grouped according to whether they received ≥50% ("late group") or < 50% ("early group") of cycles after the median time of all treatments. The primary endpoint was overall survival (OS). Hazard ratios (HRs) for OS after multivariable adjustments for age, sex, Eastern Cooperative Oncology Group (ECOG) performance status, cancer type and treatment were estimated using Cox models with and without time-dependent variables that allowed for group (early vs. late) assignment to change after baseline. **Results:** 2631 patients with lung cancer (45%), melanoma (23%), renal carcinoma (18%), head and neck (9%) and urothelial cancer (5%) were included. The median age was 68.2 years and 1602 (61%) were men. The median follow up was 38 months. The median infusion time was 12:49h. Median OS was 13.1 (95% confidence interval [CI] 11.8-14.4) vs. 21.4 (95% CI 19.8-24.5) months for late and early group. The late group was associated with shorter OS compared to the early group on both the standard multivariate analysis (HR 1.48, 95% CI 1.33-1.63) and the time dependent Cox model (HR 1.30, 95% CI 1.16-1.44). The association was significant for most regimens with ICIs alone (n = 1886) and for ICIs plus tyrosine kinase inhibitors (n = 163). There was no difference for regimens comprising chemotherapy (n = 582). A sensitivity analysis based on exposure at 3 months showed no difference between the groups with the standard model (HR 1.09, 95% CI 0.98-1.20) and a higher risk of death for the late group with the time dependent model (HR 1.14, 95% CI 1.02-1.26). **Conclusions:** This study suggests a benefit in OS with early administration of ICIs with a large sample size and a time-dependent Cox model which reduces the risk of immortal time bias. These findings could have a major clinical impact after small changes in the way services are provided. Exclusive morning administration for all doses in the first 3 months could be a feasible approach to minimise complexity of treatment slot allocation. Research Sponsor: None.

2663 Poster Session

The impact of lymphocyte count dynamics on the predictive value of tumor mutational burden (TMB) for immune checkpoint inhibitors (ICI) outcomes in patients (pts) with cancer. First Author: Mustafa Jamal Saleh, Dana-Farber Cancer Institute, Boston, MA

Background: TMB has become a reliable biomarker for ICI response in several cancer types, leading to the pan-cancer FDA approval of the PD-1 inhibitor pembrolizumab in tumors with a TMB ³10 mut/Mb. Lymphocyte count dynamics (lymphocyte stability LS) have been reported to be associated with both increased immune-related adverse events and improved overall survival (OS) on ICI. We aimed to investigate the role of LS as a risk stratification tool, in combination with TMB, in patients with cancer treated with ICIs. **Methods:** We identified 1215 pts from the Dana-Farber Cancer Institute, who had received ICI between 2015 and 2024. The change in relative blood lymphocyte counts was calculated between pre- (up to 30 days) and post-treatment (between 21 and 49 days). Lymphocyte counts were considered stable (LS ≥80%) if the drop in lymphocyte count did not exceed 20% after ICI-exposure. TMB was assessed from targeted panel sequencing and categorized into high and low, based on a cutoff of 10 mut/Mb. Overall survival was assessed using a multivariable Cox regression model, adjusting for several baseline characteristics. **Results:** The most prevalent cancer types were non-small cell lung cancer (n = 190), breast carcinoma (n = 160), glioma (n = 104), and melanoma (n = 100). Median TMB was 6.8 (IQR: 0–265.4). In total, 846 (69.6%) patients had LS (drop < 20%), while 369 (30.4%) did not. Higher TMB (≥10) and LS were both independently associated with better survival on ICI after adjusting for age, sex, tumor purity, line of therapy, ICI type and cancer type (HR 0.58, CI: 0.50–0.67; p < 0.001) and 0.75 (CI: 0.63–0.90; p = 0.002) respectively. Overall, patients with LS and high TMB demonstrated the longest median OS while the combination of unstable lymphocyte counts and low TMB was associated with the worst survival (Table). **Conclusions:** LS provides additional value, irrespective of TMB, in predicting response to ICI, suggesting distinct underlying immunological pathways. These findings emphasize the need for further research to validate LS and explore its integration into clinical decision-making in ICI-treated pts. Research Sponsor: None.

Results from multivariable Cox regression.

Groups	Median OS (mo)	N	HR	95% CI	P-value
Stable lymphocytes (LS ≥80%) & High TMB (Cutoff = 10)	34.27	245	Ref.	Ref.	Ref.
Stable (LS ≥80%) & Low TMB	18.99	601	1.3	1.04 - 1.63	0.019
Unstable (LS <80%) & High TMB	17.05	96	1.66	1.22 - 2.26	0.001
Unstable (LS <80%) & Low TMB	9.59	273	2.28	1.79 - 2.90	<0.001

Model is adjusted for age, sexe, tumor purity, lines of treatment, PD1/PDL1 therapy, and CTLA-4 therapy.
Abbreviations: TMB: Tumor mutational burden; LS: Lymphocyte Stability; OS: Overall Survival; mo: Months.

2664 Poster Session

Association of intestinal exfoliome and Prevotellaceae with toxicity and clinical outcome during immune-checkpoint blockade. First Author: Giacomo Vitali, MetaGenoPolis, INRAE, Paris-Saclay University, Jouy-En-Josas, France

Background: Immune-related adverse events (irAEs) are autoimmune side effects related to ICI, varying in severity, onset and organ involvement that may be hard to differentiate from non-irAEs. Some reports have demonstrated that gut microbiota (GM) plays a role in modulating the risk of AEs. In this study, we combine gut mamalian and microbial metagenomics sequencing (MGS) to explore the influence of GM on treatment response and risk of AEs. **Methods:** NCT04567446 allowed fecal MGS at baseline and longitudinally in patients (pts) with advanced non-small cell lung cancer (), renal cell carcinoma and bladder cancer treated with ICI alone (ICI cohort, n = 542pts) or in combination with chemotherapy (CT+ICI cohort, n = 122 pts) in France and Canada. Pts who experienced severe (≥ grade 3) irAEs after ICI+/-CT were compared to those who did not, using microbial MGS parameters (Shannon diversity, TOPOSCORE, PCoA and LEfSe). Multivariate Cox regression models to analyze factors influencing overall survival (OS) included microbiota composition and the host exfoliome (i.e., mammalian eukaryotic DNA read counts within stools). **Results:** Pts with severe irAEs (10%) presented a less diverse microbiome, a lower TOPOSCORE and a distinct microbial community compared to those without severe irAEs, showing an overabundance of several members of the *Prevotellaceae* family. Interestingly, CT+ICI pts who experienced severe irAEs had the most dysbiotic microbiome, characterized by a lower alpha-diversity and TOPOSCORE, dominated by oral taxa (*Ligilactobacillus salivarius)* and tolerogenic *Hungatella* spp. and *Enterocloster spp.* Among pts screened for exfoliation, 44% presented hstool mammalian DNA than healthy subjects, showed a GM enriched with pathobionts, including the *Enterocloster* genus, and exhibited worse OS (HR 1.212, p = 0.0135) in univariate and multivariate analyses (HR 1.18, p = 0.049). Although there was no significant correlation between toxicity and exfoliation, either in CT+ICI or ICI alone, pts enriched with Prevotellaceae family appeared to exhibit the highest levels of exfoliation. **Conclusions:** Host-microbial interactions influence immunity and therefore ICI prognosis and toxicity. We found Prevotellaceae members as potential biomarkers for ICI-related toxicity. The host exfoliome is an interesting parameter that may reflect gut fitness, requiring further investigation. Clinical trial information: NCT04567446. Research Sponsor: RHU IMMUNOLIFE, RHU LUMIERE.

2665 Poster Session

A Bayesian population-based framework for detecting hyperprogressive disease on cancer immunotherapies. First Author: Madison Stoddard, Fractal Therapeutics, Lexington, MA

Background: Hyperprogressive Disease (HPD), defined as an unexpected treatment-induced rapid increase in tumor growth rate relative to the tumor burden pretreatment growth rate, has been reported in 9% of patients receiving immune checkpoint inhibitor (ICI) therapies (Champiat et al, Clin Cancer Res (2017)). The definition of HPD used in that work was an increase in the on-treatment "Tumor Growth Rate" (TGR) by a factor of 2 or greater over the pre-treatment TGR as calculated from three consecutive CT scans: pre-baseline, baseline and on-treatment. This method of directly calculating TGR from slopes between successive tumor measurements, however, does not consider uncertainty in the CT-assessed sum of diameters (SoD) of target lesions (~8% per Zhao et al, Radiology (2009)), nor prior knowledge of the distribution of responses under ICI treatment. We sought to develop and test a Bayesian approach to HPD detection and compare its receiver operating characteristics (ROC) to the published TGR ratio threshold of 2-fold as well as the TGR ratio considered as a continuous classifier of HPD. **Methods:** We represented the prior distribution of exponential TGR (eTGR) pre-treatment based on population modeling of historical data of untreated NSCLC tumor dynamics. We then calibrated the on-ICI-treatment prior distribution based on reported rates of HPD and tumor regression. Next, we developed a Bayesian parameter estimation system to take three successive SoD assessments to calculate a patient's posterior probability of being in a state of HPD, attenuated tumor growth (ATG) or tumor regression (REG). We then simulated a cohort of 1000 virtual patients (VPs) with known state and tested the ability of the Bayesian method, the TGR ratio method, and the TGR ratio > 2 method to correctly classify each VP. We additionally developed a user-friendly web-based prototype tool (https://deanbot1.shinyapps.io/GRICalc/) to solicit feedback from a potential future user community. **Results:** ROC analysis estimated the area under ROC curve (AUROC) to be 0.94 for the Bayesian method, a significant improvement in classification accuracy over the TGR ratio method (AUROC = 0.77) as well as better maximal sensitivity (Se) and specificity (Sp) than the TGR ratio > 2 method (Se = 80% & Sp = 90% vs Se = 90% & Sp = 40%). **Conclusions:** We have developed a Bayesian population-based methodology and prototyped a web-based tool which under simulated conditions consistently outperformed previous methods for detecting HPD. We believe that this approach, trained on a larger patient-level dataset, can potentially support and improve clinical management and decision-making for cancer patients taking immune checkpoint inhibitor therapies. Research Sponsor: None.

2666 Poster Session

Safety outcomes of intravenous immunoglobulin (IVIG) in treatment of steroid-refractory immune-checkpoint inhibitor pneumonitis. First Author: Mary Metkus, Department of Medicine, Johns Hopkins University, Baltimore, MD

Background: Pneumonitis is a potentially severe adverse event of immune checkpoint inhibitors (ICIs). While the first line treatment for ICI pneumonitis is corticosteroids, there are subsets of patients who either fail to respond, deemed steroid-refractory, or who cannot be tapered off steroids, deemed steroid-dependent. In these patients, there is no clear consensus on the best approach to treatment. IVIG has emerged as a potentially efficacious treatment for its immunomodulatory effects. It is also less immunosuppressive than other potential therapies, which is beneficial in a population which respiratory infection could lead to rapid clinical decline. However, there are concerns about treatment safety, including volume overload, thrombosis, and renal injury, which can be devastating in a patient population with pre-existing respiratory compromise. In this study, we aimed to assess the safety of IVIG treatment in patients with steroid-refractory ICI pneumonitis. **Methods:** A retrospective review was conducted of patients with steroid-refractory ICI pneumonitis treated with IVIG at Johns Hopkins Hospital from 2018 to 2024. Patient characteristics, treatment features, disease severity, clinical outcomes, and development of adverse events post-IVIG including renal injury, volume overload, or thrombosis were evaluated. **Results:** A total of 31 patients were selected with steroid refractory pneumonitis treated with IVIG. Mean age at diagnosis was 68 (56-80). The most common primary tumor site was lung (n = 23) and majority of patients had stage IV malignancy (n = 19). 81% (25/31) had grade 3 or 4 pneumonitis at the time of IVIG therapy. In-hospital death occurred in 41% (13/31). Majority of in-hospital death was due to respiratory decompensation from pneumonitis and no deaths were directly related to complications of IVIG. Regarding adverse events, 9.68% (3/31) of patients developed a venous thromboembolism related to IVIG. 3.23% (1/31) developed acute kidney injury and 12.90% (4/31) developed hypervolemia in response to IVIG. **Conclusions:** IVIG was not associated with a high rate of toxicity when used in the treatment of steroid refractory ICI-pneumonitis. The increased in-hospital mortality indicates the severity of illness in this patient population. Despite this, IVIG-related adverse events were low overall. Although a small cohort, these results suggest a favorable safety profile and support further study to evaluate efficacy of IVIG as compared with other immunomodulatory agents. Research Sponsor: None.

IVIG treatment related adverse events.

VTE related to IVIG* (%; n)	9.68 (3)
Acute kidney injury (%; n)	3.23 (1)
Volume overload (%; n)	12.90 (4)

IVIG: intravenous immunoglobulin, VTE: venous thromboembolism.
*2 of the patients died.

2667 Poster Session

Vedolizumab or infliximab: Treatment option in immune checkpoint inhibitor–induced colitis. First Author: Shreya Shambhavi, RWJBH Rutgers Health Community Medical Center, Toms River, NJ

Background: ICI use is linked to severe gastrointestinal (GI) immune-related adverse events (irAEs), which affect morbidity and mortality and often require treatment pauses. Among these, immune-mediated colitis (IMC)—primarily associated with CTLA-4 therapy—occurs in 5.7% to 39.1% of patients receiving CTLA-4 inhibitors and 0.7% to 31.6% of those receiving PD-1/PD-L1 inhibitors; combination therapy can raise this incidence to 40.4%. IMC symptoms range from mild diarrhea to severe colitis, typically requiring urgent intervention within six to eight weeks of immunotherapy to prevent complications such as colonic perforation or sepsis. Corticosteroids are the usual first-line treatment, with TNF-alpha inhibitors (e.g., infliximab) considered when patients do not improve after three to seven days. Vedolizumab, a gut-selective $\alpha4\beta7$ integrin antagonist that targets gastrointestinal-homing T-lymphocytes, offers an alternative approach. Both infliximab and vedolizumab—referred to as Selective Immunosuppressive Therapies (SITs)—have shown promise, though their distinct mechanisms have led to a lack of standardized protocols and reliance on provider discretion. This study compares infliximab, vedolizumab, and combined SITs (infliximab plus vedolizumab) in managing IMC, focusing on remission rates, recurrence, and improved steroid tapering success. **Methods:** A systematic search was conducted across the PubMed database. The Meta-Analysis was conducted using R version 4.4.1 to calculate odds ratios (ORs) and 95% confidence intervals (CIs). **Results:** A total of eight studies were included in the final analysis. In patients with immune checkpoint inhibitor–induced colitis, vedolizumab was associated with higher rates of colitis recurrence (OR = 0.32, 95% CI = 0.19–0.53) compared to infliximab. Patients receiving vedolizumab also had lower overall corticosteroid usage (mean difference in days: -18.29, 95% CI = -21.88 to -14.71) compared to infliximab recipients. There was no significant difference in remission rates between vedolizumab and infliximab monotherapy; however, higher remission was noted with combination therapy (vedolizumab plus infliximab) (OR = 0.40, 95% CI = 0.19–0.84) compared to infliximab monotherapy. **Conclusions:** Vedolizumab was associated with a higher recurrence rate of colitis but resulted in significantly lower corticosteroid usage compared with infliximab. Although remission rates were similar for both monotherapies, combination therapy (vedolizumab plus infliximab) demonstrated higher remission rates than infliximab alone. Research Sponsor: None.

TPS2668 Poster Session

A phase 1, first-in-human study of DS-2243, an HLA-A*02/NY-ESO–directed bispecific T-cell engager, in patients with advanced solid tumors. First Author: Sandra P. D'Angelo, Memorial Sloan Kettering Cancer Center, New York, NY

Background: NY-ESO-1 and LAGE-1 are homologous proteins commonly expressed in various malignancies but not in normal tissues other than the testis and placenta. Tumor types showing prevalent NY-ESO-1 and/or LAGE-1 expression include synovial sarcoma (SS), myxoid/round cell liposarcoma (MRCLS), non-small cell lung cancer (NSCLC), and urothelial carcinoma (UC). Both NY-ESO-1 and LAGE-1 undergo intracellular proteolytic processing to generate the same highly immunogenic 9-mer NY-ESO peptide (SLLMWITQC), which is presented on the cell surface in association with HLA-A*02 major histocompatibility complex molecules. DS-2243 is a bispecific antibody and T-cell engager with an effectorless Fc region. It is designed to target HLA-A*02/NY-ESO peptide complexes on tumor cells and specific molecules on T-cells, redirecting T-cell–mediated cytotoxicity toward the tumor. **Methods:** DS2243-054(NCT06644755) is a Phase 1, first-in-human, open-label, multicenter, 2-part, dose-escalation and -expansion trial of DS-2243. Patients must be $\geq$18 years of age and have HLA-A*02-positive advanced or metastatic SS, MRCLS, squamous or adenocarcinoma NSCLC, or UC, and be unable to tolerate standard treatments, or have relapsed disease after or be refractory to such treatment. Patients with NSCLC or UC in dose escalation and all patients in dose expansion must have NY-ESO protein expression confirmed in tumor tissue by immunohistochemistry in a central laboratory. Further inclusion criteria include the presence of $\geq$1 measurable lesion per Response Evaluation Criteria in Solid Tumours, version 1.1 (RECIST 1.1) and Eastern Cooperative Oncology Group performance status of 0 or 1. The primary objective of dose escalation is to evaluate the safety and tolerability of DS-2243 and determine the maximum tolerated dose and/or recommended dose for expansion (RDE). The dose-expansion part includes 4 cohorts defined by tumor type—SS/MRCLS, squamous NSCLC, adenocarcinoma NSCLC, and UC—in which patients receive DS-2243 at the RDE. The primary objectives of dose expansion are to evaluate safety and determine the objective response rate (ORR) assessed by the investigator per RECIST 1.1. Safety endpoints include dose-limiting toxicities (dose escalation only) and treatment-emergent adverse events. Secondary outcome measures include ORR (dose escalation only), time to response, duration of response, progression-free survival (all assessed by the investigator per RECIST 1.1), and overall survival. The planned sample size is ~150 patients; enrollment is ongoing. Clinical trial information: NCT06644755. Research Sponsor: Daiichi Sankyo, Inc.

TPS2669 Poster Session

Phase 2 expansions of OR502, an antibody targeting leukocyte immunoglobulin-like receptor B2 (LILRB2) ± cemiplimab in patients with advanced solid tumors. First Author: Mohamad Adham Salkeni, Virginia Cancer Specialists, Fairfax, VA

Background: LILRB2 is an inhibitory receptor expressed on myeloid cells, including tumor-associated macrophages, which binds to HLA-class I proteins and is associated with poor outcomes in multiple cancers. OR502 is a humanized immunoglobulin G1 antibody that blocks LILRB2 binding to HLA-class I proteins. Preclinically, OR502 has demonstrated best-in-class reversal and prevention of myeloid cell-mediated immune suppression and restoration of T cell functions. Using OR502 to tackle immunosuppression and improve T cell-mediated responses in the tumor microenvironment (TME) is a rational for combination with checkpoint inhibitors. **Methods:** This is an ongoing, first-in-human, Phase 1-2 study of OR502 $\pm$ cemiplimab in patients with advanced solid tumors (NCT06090266). The primary objectives are to evaluate the safety/tolerability and identify a dose for further clinical development. Secondary objectives include assessment of pharmacokinetics (PK), immunogenicity and anti-tumor activity. We are also assessing the effects of OR502 on the TME and associations between response and pharmacodynamic (PD) markers. Dose escalation enrolled 39 patients at OR502 doses of 100–1600 mg, once every 3 weeks (Q3W) $\pm$ standard dose cemiplimab (350 mg), using a modified toxicity probability interval-2 design. As dose escalation completed, it became clear that to satisfy the FDA's Project Optimus, adaptations were needed to provide dose-response proof and identify the minimal effective dose before proceeding with development. The protocol's adaptive elements, in conjunction with Safety Committee oversight, enabled modifications without amendment. Prior to dose-response optimization, we adapted the design in order to explore the efficacy signals from phase 1, specifically in patients with melanoma and NSCLC. Based on efficacy signals and excellent safety, PK and PD results, we selected OR502 800 mg Q3W for both expansion cohorts. Two new mini-expansion cohorts are now actively recruiting 10–20 patients each: monotherapy in patients with cutaneous melanoma and combination in patients with NSCLC. The sample size was chosen pragmatically, to exclude a response rate of ~ 10%, with a target of ~ 35%. If $<$ 2 responses are seen in the first 10 patients, the cohort will be discontinued. All patients must have a histological diagnosis of measurable disease that has progressed with $\geq$ 2 lines of treatment, $\geq$ 12 weeks of prior PD-(L)1-based therapy, resolved prior toxicity with a 2–4 week washout, adequate organ function, ECOG $\leq$ 2, and no significant ascites, pleural effusion or CNS metastases, recent infections or autoimmune disease requiring steroids or immunosuppressants. Cycles 1 and 3 include serial PK sampling, while Cycles 2, 4 and beyond require only one visit on Day 1. Efficacy is assessed Q6W for 1 year, then Q6 months. Safety follow-up at end of treatment is at 120 days. Clinical trial information: NCT06090266. Research Sponsor: OncoResponse, Inc.; The Cancer Prevention and Research Institute of Texas.

TPS2670 **Poster Session**

A phase 1/2a, multicenter, first-in-human, open-label clinical trial evaluating MDX2001, a tetraspecific T cell engager-expander in patients with advanced solid tumors. First Author: Ecaterina Elena Dumbrava, Department of Investigational Cancer Therapeutics, The University of Texas MD Anderson Cancer Center, Houston, TX

Background: MDX2001 is a multispecific antibody recognizing CD3 and CD28 on T cells, and c-MET and TROP2 on tumors. Anti-CD3 provides the primary signal for T cell activation; anti-CD28 delivers the secondary signal for enhanced T cell activation, survival, and proliferation. Combinatorial targeting of c-MET and TROP2 by MDX2001, either on the same or different cancer cells, provides more effective engagement on tumor cells, and may better address tumor heterogenicity and the development of resistance due to antigen downregulation. *In vitro* and *in vivo* studies with MDX2001 demonstrate potent antitumor activity with no CD28-superagonist activity and minimal T cell activation in the absence of tumor cells. **Methods:** This Phase 1/2a, multicenter, first-in-human, open-label clinical trial explores intravenous MDX2001 in patients with advanced solid tumors (NCT06239194). The study design consists of Phase 1a dose escalation guided by a Bayesian Optimal Interval design with a target maximum tolerated dose toxicity rate of 30%, Phase 1b dose expansion, and Phase 2a indication expansion. Patients with non-small cell lung, renal cell, prostate, breast cancer and 10 other selected tumors known to have significant levels of TROP2 or c-MET expression are eligible for Phase 1a. In Phase 1b, patients will be randomized into 2 dose cohorts using a Bayesian Optimal Phase 2 (BOP2) design. Once a recommended Phase 2 dose (RP2D) is determined, Phase 2a will enroll patients in search of initial efficacy signals using a BOP2 design. The primary objectives of this study are to characterize the safety, tolerability, and anti-tumor activity of MDX2001 in patients with advanced solid tumors. Secondary endpoints include time to response, disease control rate, duration of response, pharmacokinetics, immunogenicity and evaluation of the relationship between baseline tumor target protein expression and clinical benefit. Patients will have radiologic tumor assessments every 8 weeks and will continue to receive treatment until disease progression per RECIST v1.1 (as assessed by the investigator), unacceptable toxicity, withdrawal of consent, another protocol-defined discontinuation criterion is met, or the sponsor terminates the study, whichever occurs first. The study will be conducted in United States, Europe, and Asia. Recruitment is ongoing. Clinical trial information: NCT06239194. Research Sponsor: None.

TPS2671 **Poster Session**

ARC101-P1-101: A first-in-human phase 1 study of ARC101, a next generation T cell engager (TCE), in patients with advanced solid tumors. First Author: Prachi Bhave, Peter MacCallum Cancer Centre, The University of Melbourne, Melbourne, VIC, Australia

Background: T-cell Engagers (TCEs) are emerging as a promising immuno-therapeutic modality in the treatment of solid tumors, demonstrating outstanding potency and a manageable safety profile. Claudin 6 (CLDN6) is an oncofetal protein that has recently emerged as a particularly attractive tumor-associated antigen (TAA) for TCE therapy because of its highly tumor-restricted pattern of expression. ARC101 is a bispecific antibody that targets CLDN6 on tumor cells with high specificity and selectivity, and CD3 on T cells. In pre-clinical models, ARC101 demonstrated potent cytolytic activity at low concentrations against a panel of CLDN6-expressing tumor cells in vitro and an ovarian cancer xenograft in vivo. **Methods:** First-in-human, multicenter, phase 1 study ARC101-P1-101 (NCT06672185) aims to determine the optimal dosing, safety, pharmacokinetics (PK), pharmacodynamics (PD), and preliminary antitumor efficacy of ARC101 as monotherapy in patients with locally advanced or metastatic CLDN6 expressing solid tumors. The study will be conducted according to the Bayesian Optimal Interval (BOIN) design in two parts: Part 1 (dose escalation) and Part 2 (dose expansion). Part 1 is designed to select the Maximum Tolerated Dose (MTD), Recommended-Phase 2-Dose (RP2D) and dosing schedule of ARC101. Part 1 will start with an 'Accelerated Titration Phase', with cohorts of at least one, but no more than three patients and a fixed dose, intravenous regimen. Once a single event of clinically significant toxicity of Grade $\geq$2 occurs, the 'Standard Titration Phase' will be initiated with cohorts of at least three patients per ARC101 target dose level. Once immune-related toxicity is observed, the regimen may be changed to a 'Fractionated Step-up Dosing' IV regimen. The study design allows for backfill cohorts and intra-patient dose escalations. Part 2 will further explore the safety, PK/PD characteristics, and preliminary efficacy of ARC101 administered at the RP2D and schedule identified in Part 1 in patients with testicular and ovarian cancer. Key eligibility criteria include patients with any advanced or refractory solid tumor malignancy that expresses CLDN6 and is metastatic or unresectable. Patients must be $\geq$18 years of age and have Eastern Cooperative Oncology Group (ECOG) performance status 0 or 1. Patients must have received standard therapy for advanced or metastatic disease, and disease must be measurable per Response Criteria in Solid Tumors (RECIST) v1.1 or evaluable. Mandatory requirement of a pre-study tumour sample for IHC analysis will facilitate the exploratory objective of biomarker analysis, including correlating CLDN6 expression with treatment response. The study is actively enrolling participants for the dose escalation phase. Contact clinicaltrials@thirdarcbio for additional information. Clinical trial information: NCT06672185. Research Sponsor: None.

TPS2672 **Poster Session**

EGL-121, a first-in-human phase 1/2 trial of EGL-001 in adult patients with selected advanced and/or metastatic solid tumors. First Author: Thiziri Nait Achour, EGLE Therapeutics, Suresnes, France

Background: Regulatory T cells (Tregs) play a key role in the resistance to immune checkpoint inhibitors therapy (ICI). Disarming Tregs could therefore restore/enhance anti-tumor responses and increase the number of patients benefiting from these treatments. EGL-001, a novel therapeutic agent, is designed to provide checkpoint inhibition by antagonizing the CTLA-4-CD80/86 interaction while selectively depleting intratumoral Tregs by downregulating CD25 and inhibiting IL-2 signaling specifically within these cells. This dual mechanism of action effectively unleashes potent anti-tumor immunity even in anti-PD-1 resistant models, independent of FcgR activity. In murine models, EGL-001 shows preferential distribution and persistence in the tumor until Treg get depleted/inactivated. Our data demonstrated complete anti-tumor activity of EGL-001 as a single agent across various tumor models and it overcomes resistance to anti-PD-1 treatment in many tumor models, highlighting its broad therapeutic potential. Additionally, EGL-001 effectively depletes Tregs and exhibits activity in ex-vivo human tumor samples, where other ICI showed no significant effect. In NHPs, EGL-001 was well tolerated across all tested doses, with rapid peripheral clearance preventing lymphoid tissue hyperplasia in the spleen and lymph nodes. **Methods:** A Phase I/II clinical trial (NCT06622486) is currently underway in eight sites in France and Spain to evaluate EGL-001 as monotherapy and in combination with checkpoint inhibitors in selected tumor types characterized by tumor Treg implication in induction of mechanism of resistance to ICI. The selective targeting of tumor-infiltrating Tregs could effectively improve anti-tumor immune response and limit systemic immune-related toxicities. This first-in-human, multicenter, open label Phase 1/2 study evaluates the safety, tolerability, and initial activity of EGL-001 in adult patients with selected advanced and/or metastatic solid tumors. The study consists of a Part 1 (Phase 1) dose escalation of EGL-001 administered as a single agent (from 0.3 mg/kg to 12 mg/kg), and in combination with pembrolizumab treatment, according to a BOIN design, followed by a Part 2 (Phase 2) dose expansion of EGL-001 administered at the selected doses as monotherapy and/or in combination therapy with anti-PD(L)1. Eligible patients are those who have initially benefited (secondary resistance) from an ICI treatment as monotherapy or in combination as SoC as defined by a CR, PR, or SD $\geq$3 months as best response by RECIST Version 1.1. As of January 2025, the first 3 Cohorts of EGL-001 (0.03, 0.1, 0.3 mg/kg) have been completed. EGL-001 was well tolerated with no DLTs reported. Clinical trial information: NCT06622486. Research Sponsor: None.

TPS2673 **Poster Session**

SUPRAME: A phase 3 trial comparing IMA203, an engineered T-cell receptor expressing T cell therapy (TCR-T) vs investigator's choice in patients with previously treated advanced cutaneous melanoma. First Author: Jason J. Luke, University of Pittsburgh, Pittsburgh, PA

Background: Frequent recurrence and limited long-term survival in unresected or metastatic melanoma after relapse from 1L treatment with a checkpoint inhibitor (CPI) highlight the critical need for new therapies that deliver deeper, more durable responses (Knight *Cancers* 2023; Switzer *JCO Oncol Pract* 2022). ACTengine IMA203 is an autologous T cell receptor (TCR)-engineered T cell therapy (TCR-T) targeting PRAME, an intracellular protein displayed as peptide antigen at high density on the surface of multiple solid tumors, including melanoma. IMA203 TCR-T demonstrated a favorable tolerability profile and durable objective responses in heavily-pretreated patients with different tumor types. In melanoma, IMA203 showed 54% confirmed ORR (14/26), 12.1 months mDOR and 6 months mPFS. mOS was not reached at a mFU of 8.6 months (Wermke et al., SMR, Oct 10, 2024). Based on these observations, a registration-enabling randomized phase 3 trial, SUPRAME, was initiated to evaluate IMA203 in 2L patients with advanced cutaneous melanoma after treatment with a CPI. **Methods:** SUPRAME (NCT06743126) is a phase 3, multicenter, open-label, randomized, actively controlled, parallel-group trial that will evaluate the efficacy, safety and tolerability of IMA203 compared to investigator's choice of treatment in patients with previously treated, unresectable or metastatic cutaneous melanoma (incl. acral melanoma). Eligible patients are $\geq$18yo, HLA-A*02:01-positive, with measurable disease (RECIST v1.1), ECOG PS of 0-1 and disease progression on or after at least one PD-1 inhibitor. Patients with BRAF mutation should have been treated with one prior line of BRAF-directed therapy ($\pm$ MEK inhibitor) prior to initial eligibility assessment. Patients with asymptomatic stable brain or leptomeningeal metastases will be assessed for eligibility. Patients with active brain metastases or with primary mucosal, uveal melanoma and melanoma of unknown primary are excluded. The study will randomize ~360 patients 1:1. Patients in the experimental arm will undergo leukapheresis to generate the PRAME-specific TCR-T product, IMA203. Following lymphodepletion with cyclophosphamide (500 mg/m^2 x 4 days) and fludarabine (30 mg/m^2 x 4 days), 1-10x10^9 IMA203 TCR-T cells will be administered, followed by low-dose IL-2 (1mio IU daily x5 days, twice daily x5 days). Patients in the control arm will receive approved investigator's choice of standard treatment (nivolumab/relatlimab, nivolumab, ipilimumab, pembrolizumab, lifileucel (US), chemotherapy). The primary efficacy endpoint is BICR-assessed (RECIST v1.1) PFS. Secondary endpoints include OS, ORR, safety and patient-reported outcomes (EORTC QLQ-C30, EQ-5D-5L). The trial will enroll patients in the US and Europe. Clinical trial information: NCT06743126. Research Sponsor: None.

TPS2674 **Poster Session**

Autologous tumor-infiltrating lymphocytes (HS-IT101) with low-dose lymphodepletion and IL-2 infusion for the treatment of advanced solid tumors: A phase I clinical trial. First Author: Ning Li, Department of Clinical Trial Center, National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China

Background: Adoptive cell therapy with tumor-infiltrating lymphocytes (TIL-ACT) has demonstrated great therapeutic potential in numerous solid tumors and has become an effective treatment for melanoma. However, high-dose lymphodepletion chemotherapy and IL-2 infusion during the treatment could cause serious safety risks, even death. The purpose of this study is to develop a TIL cell therapy product (HS-IT101) that requires low-dose lymphodepletion and IL-2 infusion to reduce safety risks and to improve clinical accessibility. Currently, the Phase I clinical trial (NCT06342336) for the treatment of advanced solid tumors with HS-IT101 has been initiated. **Methods:** HS-IT101 is an autologous non-genetically modified TIL-ACT product independently developed by Sino-cell Biomed. The tumor tissue of culture require is $\geq$0.05g, and the manufacture time needed is 14 days. This study is a single-arm, multi-center, open-label Phase I clinical trial of HS-IT101 for advanced solid tumors. The plan is to enroll 20 - 44 patients to explore the safety and preliminary efficacy under low-dose lymphodepletion and IL-2 infusion. Before HS-IT101 infusion, subjects will receive lymphodepletion chemotherapy consisting of cyclophosphamide (Cy) and fludarabine (Flu) for 3 - 4 days (Cy: 900/2250mg/m^2 & Flu: 90/120mg/m^2). After HS-IT101 infusion, 1/2MIU/m^2 of IL-2 will be subcutaneously injected once a day for a maximum of 3 doses. The primary endpoint is the occurrence of adverse events (AE) and serious adverse events (SAE) after HS-IT101 infusion. The secondary endpoints include the objective response rate (ORR), disease control rate (DCR), time to response (TTR), duration of response (DOR), progression-free survival (PFS), overall survival (OS) in efficacy evaluation, and changes in relevant pharmacokinetic (PK) indicators. The exploratory endpoint is the change in pharmacodynamic (PD) indicators. Clinical trial information: CTR20234065. Research Sponsor: Qingdao Sino-Cell Biomedicine Co., Ltd.

TPS2675 **Poster Session**

A phase 1/2 study of KSQ-004EX: Autologous tumor infiltrating lymphocytes, engineered to inactivate genes encoding SOCS1 and Regnase-1, in patients with select advanced solid tumors. First Author: Rodabe Navroze Amaria, The University of Texas MD Anderson Cancer Center, Melanoma Medical Oncology, Houston, TX

Background: The effectiveness and durability of TIL therapy may be limited by the immunosuppressive tumor microenvironment and baseline functionality of transferred T cells. Through KSQ Therapeutics' CRISPR^2 platform, a novel method for screening optimal combinatorial targets for enhancing T cell anti-tumor efficacy in vivo, SOCS1 and Regnase-1 were identified as the most potent gene editing combination. KSQ-004EX, an engineered TIL product with CRISPR/Cas9 mediated dual-inactivation of SOCS1 and Regnase-1, is anticipated to in enhance T cell tumor infiltration, persistence, and efficacy. This first-in-human clinical study (NCT06598371) evaluates KSQ-004EX in patients with melanoma, non-small cell lung cancer (NSCLC), head and neck squamous cell carcinoma (HNSCC), colorectal carcinoma (CRC), pancreatic cancer, and cervical cancer. **Methods:** The phase 1/2, single-arm, open-label study will assess the safety, tolerability, and efficacy of KSQ-004EX in patients with select advanced solid tumors. Patients with melanoma, NSCLC, HNSCC, CRC, pancreatic, and cervical cancer who have progressed following treatment with 1 to 3 lines of prior standard therapy including standard directed therapy (as applicable), are eligible. KSQ-004EX is manufactured from the patient's tumor, which is collected through surgical resection or core needle biopsy. All patients must have at least 1 measurable lesion following resection. Patients receive lymphodepleting chemotherapy with cyclophosphamide and fludarabine prior to KSQ-004EX infusion. Patients in the initial dose escalation cohorts do not receive dosing with IL-2; IL-2 dosing may be included in subsequent cohorts. Approximately 6 patients will be enrolled in Phase 1 dose escalation, in escalating dose levels. The primary objective of Phase 1 is to evaluate the safety and tolerability of KSQ-004EX. In Phase 2, patients will be enrolled in indication-specific cohorts. The primary objective of Phase 2 is to assess the anti-tumor activity of KSQ-004EX in patients with advanced solid tumors by ORR per RECIST v1.1. This is currently a single-institution study that is actively enrolling/recruiting patients. Clinical trial information: NCT06598371. Research Sponsor: KSQ Therapeutics, Inc.

TPS2676 **Poster Session**

A phase 1, first-in-human study of IB-T101, an OUTLAST CAR-T product for the treatment of CD70-positive clear cell renal carcinoma. First Author: Matthias Schroff, Inceptor Bio, Morrisville, NC

Background: Relapsed or treatment-resistant clear cell renal cell carcinoma (ccRCC) poses a significant, unmet medical challenge, as patients contend with scarce therapeutic alternatives and unfavorable clinical prognoses. CD70 is expressed in the majority of ccRCC and presents an attractive target for chimeric antigen receptor T cell (CAR-T) therapy. IB-T101, an autologous CAR-T expanded under OUTLAST conditioning, targets CD70 for the treatment of ccRCC. OUTLAST conditioning has been demonstrated to result in CAR-T cells that exhibit an early memory T cell phenotype, are resistant to suppressive signals from the tumor microenvironment, and exhibit increased persistence. The effects of OUTLAST conditioning are expected to lead to superior clinical outcomes for IB-T101 CAR-T cells in the ccRCC solid tumor setting. **Methods:** Here we report an in-progress phase 1, first-in-human, open label, investigator-initiated clinical trial aimed at evaluating the safety and efficacy of IB-T101 in ccRCC. Patients eligible for inclusion had previously relapsed following VEGF targeting therapies alone or in combination with an immune checkpoint inhibitor. Autologous patient T cells are transduced with a lentiviral vector encoding a CD70-targeting CAR and are CRISPR Cas9 gene edited to knock out endogenous CD70, followed by expansion under OUTLAST conditioning. Escalating doses of IB-T101 CAR-T cells (150 – 500 x 10^6) will be infused following lymphodepletion. Primary endpoints of the study will assess the safety and tolerability of IB-T101. Additional objectives of the study are to assess the anti-tumor activity and the pharmacokinetics of IB-T101. Correlative assessments will include pre-treatment biopsies to assess the level of CD70 expression in the tumor. Research Sponsor: None.

TPS2677 **Poster Session**

Logic-gated, allogeneic Tmod chimeric antigen receptor T-cell (CAR T) therapy targeting epidermal growth factor receptor (EGFR) in advanced solid tumors with human leukocyte antigen (HLA) loss of heterozygosity (LOH): DENALI-1 trial. First Author: Kedar Kirtane, Moffitt Cancer Center, Tampa, FL

Background: Despite the success in hematologic malignancies, CAR T therapies face significant challenges in solid tumors due to the lack of tumor-specific targets that distinguish cancer from normal cells. EGFR plays a critical role in oncogenesis across several cancers and is often upregulated (TCGA 2022). While monoclonal antibodies targeting EGFR have demonstrated efficacy, these approaches are often limited by on-target, off-tumor toxicities, such as skin rash, which constrains dose escalation and efficacy (Macdonald, et al. *J Am Acad Dermatol*. 2015). A2B395 is an allogeneic, logic-gated, EGFR-targeted Tmod CAR T therapy designed to address these limitations and provide a convenient and consistent off-the-shelf option. This therapy incorporates 2 CARs: an activator targeting EGFR, and a blocker targeting HLA-A*02. The activator recognizes EGFR on both tumor and normal cells, while the blocker inhibits CAR T activity against normal cells with preserved HLA expression and decreases the risk for graft-versus-host disease (Hamburger, et al. *Mol Immunol*. 2020). To address potential host-vs-graft response, an shRNA expression module targeting B2M is included in the Tmod construct, which significantly reduces major histocompatibility complex class I levels and subsequent host immune response (DiAndreth, et al. *Clin Immunol*. 2022). Importantly, the Tmod system is modular and adaptable to multiple targets. Initial data on autologous Tmod CAR T therapy suggest reduced off-tumor toxicity and encouraging clinical efficacy (Grierson, et al. SITC 2024. Abstract 588). A2B395 represents a novel approach for EGFR-expressing solid tumors with HLA-A*02 LOH. **Methods:** DENALI-1 (NCT06682793) is a phase 1/2, open-label, nonrandomized study evaluating the safety and efficacy of A2B395 in adults. Patients are enrolled through BASECAMP-1 (NCT04981119), a master pre-screening study that identifies patients with HLA LOH at any time in the course of their disease via next-generation sequencing (Tempus AI, Inc.). Key inclusion criteria include histologically confirmed recurrent unresectable, locally advanced, or metastatic cancers associated with EGFR expression, including colorectal, non-small cell lung, squamous cell head and neck, triple negative breast, and renal cell cancers. Patients must have received $\geq$1 line of prior therapy, such as a checkpoint inhibitor, molecular targeted therapy, or chemotherapy. The primary objective of phase 1 is to evaluate safety, tolerability, and the recommended phase 2 dose (RP2D) using a Bayesian optimal interval design for dose escalation. The dose-expansion phase will confirm RP2D and collect biomarker data. Phase 2 will assess overall response rate per RECIST v1.1. Clinical trial information: NCT06682793. Research Sponsor: A2 Biotherapeutics, Inc.

TPS2678 **Poster Session**

A phase I study of AFNT-211, autologous CD4$^+$ and CD8$^+$ T cells engineered to express a high avidity HLA-A*11:01-restricted, KRAS G12V-specific transgenic TCR; CD8α/β coreceptor; and FAS-41BB switch receptor in patients with advanced or metastatic solid tumors. First Author: Soumit K. Basu, Affini-T Therapeutics, Inc., Watertown, MA

Background: Activating mutations in KRAS (including KRAS G12V) are well-described oncogenic drivers in solid tumors, conferring poor prognosis to patients due to a lack of effective therapies for cancers with such KRAS driver mutations. T cell receptor (TCR)-T cell therapies targeting mutant KRAS have demonstrated proof of concept in the clinic, but duration of response remains a challenge.[1,2] AFNT-211 represents a novel strategy to address the immunosuppressive tumor microenvironment and improve response rate as well as duration of response in solid tumors. **Methods:** This ongoing Phase 1, first-in-human, multicenter, open-label study of AFNT-211evaluates safety/tolerability, as well as its clinical (antitumor) activity with the goal to identify an optimal biological dose (OBD) and recommended Phase 2 dose (RP2D) in patients with HLA 11:01 who suffer from cancers driven by the KRAS G12V mutation. The initial dose escalation part of the study follows Bayesian optimal interval Phase 1/2 (BOIN12), which quantifies the desirability of a dose in terms of toxicity-efficacy tradeoff and adaptively allocates patients to the dose with the highest estimated desirability. After determination of OBD and RP2D based on the totality of the risk/benefit assessment and the BOIN12, the study is planned to proceed to the dose expansion phase which will consist of cohorts enrolling patients with tumors with high KRAS G12V prevalence (pancreatic cancer, colorectal cancer, non small cell lung cancer) as well as a tumor agnostic arm (any other solid tumor with KRAS G12V). This study has started enrolling patients $\geq$ 18 years old positive for HLA-A*11:01-positivewithadvanced/metastatic solid tumors harboring a KRAS G12V mutation who have proven intolerant of or refractory to at least one prior standard of care systemic therapy. Patients undergo leukapheresis to collect T cells for the manufacturing of AFNT-211, and receive lymphodepleting chemotherapy prior infusion of their autologous AFNT-211 product. Following this, patients proceed into a 28-day dose-limiting toxicity observation period (during dose escalation) followed by a post-treatment follow-up period for 24 months/until disease progression. The study is open for recruitment in the United States (NCT06105021). References: 1. Cook J, Melloni G, Gulhan D, *et al*. The origins and genetic interactions of KRAS mutations are allele- and tissue-specific. *Nat Commun* 2021;12:1808. 2. Hofmann MH, Gerlach D, Misale S, *et al*. Expanding the reach of precision oncology by drugging all KRAS mutants. *Cancer Discov*. 2022;12:924–937. Clinical trial information: NCT06105021. Research Sponsor: Affini-T Therapeutics, Inc.

TPS2679 **Poster Session**

Safety and efficacy of HLA-G–targeted CAR T cells (IVS-3001) in patients with advanced HLA-G–positive solid tumors: Clinical trial in progress. First Author: Samer Ali Srour, The University of Texas MD Anderson Cancer Center, Houston, TX

Background: Immunotherapies have transformed cancer treatment, yet only a small proportion of patients experiences durable responses. IVS-3001 is an innovative autologous chimeric antigen receptor (CAR) T-cell therapy specifically targeting Human Leukocyte Antigen (HLA-G). HLA-G is an immune-modulatory checkpoint molecule expressed on various solid tumors, positioning it as an ideal a tumor-specific targeted antigen. Our third-generation CAR construct features enhanced T cell activation and persistence against HLA-G. By harnessing IVS-3001 to target HLA-G and revitalize immune cells, we aim to overcome the suppressive tumor microenvironment and improve antitumor activity, potentially leading to better outcomes for patients with advanced solid tumors who otherwise have no standard options known to confer clinical benefit. **Methods:** Study NCT05672459 is a First-in-Human, phase 1/2a, safety and efficacy study of IVS-3001 in subjects with previously treated advanced HLA-G-positive solid tumors. Phase 1 (n$\leq$24 patients) is a Bayesian Optimal Interval Design (BOIN) with primary objective to determine the safety, tolerability and the recommended phase 2 dose. The primary objective for phase 2 (n$\leq$90 patients) is to evaluate the anti-tumor activity of IVS-3001. The secondary objectives of the study are to evaluate i) pharmacokinetic profile of IVS-3001 (persistence, expansion); ii) the clinical activity of IVS-3001 in selected HLA-G+ solid tumor types; iii) assess the long-term safety of IVS-3001. Exploratory endpoints include functionality of CAR-T cells, immune biomarker changes, and relationships with clinical response. Key inclusion criteria: adults with advanced solid tumors expressing HLA-G; ECOG $<$ 2; adequate organ function. Key exclusion criteria: uncontrolled brain metastasis; prior exposure to HLA-G targeted therapy. Subjects undergo lymphodepletion with fludarabine and cyclophosphamide on days -5 to -3, followed by CAR-T cell infusion on day 0 and a 28-day monitoring period for dose limiting toxicity. Response assessment per RECIST criteria. Study is currently accruing at Dose level 3. Active recruitment and enrollment are ongoing at The University of Texas MD Anderson Cancer Center, Houston, Texas. Clinical trial information: NCT05672459. Research Sponsor: Invectys; National Cancer Institute.

TPS2680 **Poster Session**

QUILT 3.076 phase 1 study of memory-like cytokine-enriched natural killer (M-CENK) cells plus N-803 in locally advanced or metastatic solid tumors. First Author: Chaitali Singh Nangia, Chan Soon-Shiong Institute for Medicine, El Segundo, CA

Background: Lymphopenia and low levels of natural killer (NK) cells may contribute to poor prognosis and response to therapy in cancer patients, conditions that may be addressed by infusion of memory-like cytokine-enriched NK (M-CENK) cells stimulated ex vivo by IL-12, IL-18, and the IL-15 agonist N-803 (ANKTIVA). M-CENK cells express elevated IFN-γ and granzyme B compared to healthy donor NK cells, and display toxicity against multiple tumor cell lines including SCLC lines [Fousek 2023 JITC 11 ab358]. The phase 1 study QUILT-3.076 (NCT04898543) assesses the safety and preliminary efficacy of M-CENK cells plus N-803 in participants with locally advanced or metastatic solid tumors. **Methods:** In this first-in-human study, cohort 1 (up to n = 40) includes participants with newly diagnosed solid tumors who have not received prior 1st line treatment; cohort 2 (up to n = 21) includes participants with relapsed/refractory solid tumors who progressed after $\geq$ 2 prior therapies. Both cohorts undergo apheresis (part A), but only cohort 2 undergoes treatment with M-CENK cells and N-803 (part B). During M-CENK cell generation, cohort 2B participants receive oncologist-recommended therapy. Cohort 1 participants may subsequently enroll in cohort 2B if they have progressive disease (PD) after $\geq$ 2 prior therapies or within 12 months of receiving neoadjuvant/adjuvant chemotherapy. In part B, M-CENK cells are administered weekly up to 10 times and N-803 SC for up to 5 doses every 2 weeks prior to every other dose of M-CENK cells. Key inclusion criteria are age $\geq$ 18 years, ECOG performance status of 0 to 2, and histologically confirmed locally advanced or metastatic solid tumor, with at least 1 measurable lesion and/or non-measurable disease in accordance with RECIST v1.1. There are no exclusion criteria for part A (apheresis). Key exclusion criteria for part B are life expectancy $<$ 16 weeks, involuntary weight loss of $>$ 10%, serious uncontrolled concomitant disease, systemic autoimmune disease requiring medical treatment, and/or currently receiving or received antibiotics since enrollment. The primary objective is safety as assessed and recorded by TEAEs, SAEs, and clinically significant changes in laboratory tests and vital signs. Toxicities are graded using CTCAE v5.0 or a specified grading system for CRS. Secondary measures evaluate the quantity and quality of the investigational M-CENK cells (number of MNCs for manufacturing M-CENK cells, number of cryopreserved M-CENK aliquots, % NK cells, and number, phenotype, and function of M-CENK cells). Preliminary efficacy objectives in cohort 2B are objective response rate (RECIST v1.1 and iRECIST criteria) and progression-free and overall survival evaluated using Kaplan-Meier methods. As of January 27, 2025, 15 participants have been enrolled in cohort 1, 21 participants in cohort 2 have undergone apheresis, and 10 participants have been treated with study therapies. Clinical trial information: NCT04898543. Research Sponsor: ImmunityBio, Inc.

TPS2681 **Poster Session**

A phase I, multicenter, open-label study of UB-VV111 in combination with rapamycin in relapsed/refractory CD19+ B-cell malignancies. First Author: Jacob Randolph Garcia, Umoja Biopharma, Seattle, WA

Background: Autologous, ex vivo-manufactured chimeric antigen receptor (CAR) T cells directed against CD19 have demonstrated clinical activity. These products have gained approvals in the relapsed/ refractory (R/R) setting in multiple B-cell malignancies (BCMs), including large B-cell lymphoma (LBCL) and chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL). However, challenges in product availability due to limited manufacturing capacity, the need for apheresis and lymphodepletion, failure to prior ex vivo CAR T therapy, and the level of patient fitness needed to wait for and receive ex vivo autologous CAR T therapy all pose significant challenges to the field, presenting significant unmet clinical need. UB-VV111 is a third-generation, self-inactivating, replication-incompetent lentiviral vector (LVV) investigational drug product comprising an envelope with cocal virus fusion glycoprotein (cocal) and surface engineered with a membrane-bound multidomain fusion (MDF) protein. The MDF protein contains CD58, CD80, and anti-CD3 single-chain variable fragment (scFv) components that provide both T-cell tropism and activation signals thought to be critical for effective CAR T-cell generation. UB-VV111 addresses the limitations of currently available autologous CD19-directed CAR T therapies to deliver a product that would generate CD19-directed cells in the patient. UB-VV111 is to be administered by either intranodal (IN) or intravenous (IV) route of administration (ROA). Administration of UB-VV111 by either the IN or IV ROA is expected to transduce T cells to generate CAR T cells designed to bind to CD19 antigen to mediate cell killing and express the rapamycin-activated cytokine receptor (RACR) system which, in the presence of rapamycin, is designed to enhance specific enrichment and expansion of transduced cells. **Methods:** Study UB-VV111-01 (INVICTA, [NCT06528031CO]) is a first-in-human, global, multicenter, dose-finding study of UB-VV111 administered IN or IV +/- rapamycin in CAR-naïve and CAR-exposed subjects with R/R LBCL and CLL/SLL. Dose escalation will proceed independently for each ROA using a Bayesian optimal interval (BOIN) design. Confirmation of CD19 expression will be required for all subjects with prior CD19-directed therapy. Major eligibility criteria include adults with R/R LBCL/CLL/SLL following at least 2 lines of prior therapy who have standard organ function, measurable disease according to Lugano 2014 (LBCL) or iwCLL 2018 (CLL/SLL), ECOG 0 or 1, and no prior allogeneic transplant. Primary objectives include determining the safety profile, maximum tolerated/administered dose, and recommended Phase 2 dose of UB-VV111 +/- rapamycin. Secondary/exploratory objectives include measuring preliminary antitumor activity (magnitude and durability), as well as translational correlates of safety/efficacy. Clinical trial information: NCT06528301. Research Sponsor: Umoja Biopharma.

TPS2682 **Poster Session**

Phase 1 clinical trial of autologous T-cells genetically engineered with a chimeric receptor to target the follicle-stimulating hormone receptor (FSHR) in recurrent ovarian cancer (OVCA). First Author: Robert Michael Wenham, Department of Gynecologic Oncology, H. Lee Moffitt Cancer Center and Research Institute, Tampa, FL

Background: FSHR is a tissue specific antigen expressed in $>$ 55% of high-grade epithelial OVCAs with negligible FSHR expression in non-ovarian tissues. OVCA xenografts treated with FSHCER T (FSH-Chimeric Endocrine Receptor + T-Cell (CER T)) cells demonstrated cytotoxic activity against patient-derived FSHR+ ovarian carcinomas. We hypothesize targeting FSHR in women with FSHR+ OVCA will result in improved response rates due to engraftment, expansion, and survival of these adoptively transferred FSHCER T-cells and will have acceptable toxicity. **Methods:** The primary objective of this phase 1 dose-escalation study (NCT05316129) in high-grade epithelial OVCA using T-cells genetically modified to express CER targeting FSHR is to assess the safety of the intraperitoneal (IP) and intravenous (IV) infusions of FSHCER T-cells. Secondary objectives include antitumor efficacy, persistence of transferred FSHR T cells, expansion of endogenous tumor-targeted cells, and comparison of IP and IV administration routes. Patients unable to be treated in the IP arm may be treated in the IV arm in the lowest unfilled cohort for that arm. Cohorts of 3 to 6 patients will be infused with escalating doses of FSHCER T-cells to establish the maximum tolerated dose (MTD) with 6 planned dose levels from 1 x10^5 to 1 x 10^7 cells/kg with the 5^{th} level receiving lymphodepleting chemotherapy. Following MTD determination, an expansion phase will be initiated. Nine patients have been enrolled in the first three dose-level cohorts. Eight have cleared the DLT period and one patient is currently being treated. One patient received a second dose of 3 x 10^5 cells/kg after 20 months apparent stable disease. Cohorts 1 and 2 correlates are being processed. NCT05316129. Moffitt Scientific Review #21113. Advarra Institutional Review Board #00000971. Clinical trial information: 05316129. Research Sponsor: Anixa BioSciences Inc., San Jose CA, USA.

TPS2683 **Poster Session**

INVOKE: A phase 1 study of OKN4395, a first-in-class EP2/EP4/DP1 triple prostanoid receptor antagonist, in patients with advanced solid tumors. First Author: Neal Shiv Chawla, Sarcoma Oncology Center, Santa Monica, CA

Background: Immunotherapy is an established cancer therapy, although mechanisms of non-response & resistance are emerging, leaving few options post-relapse. The immunosuppressive pathway of prostaglandin E_2 (PGE_2), part of the cyclooxygenase (COX) pathway, is upregulated in certain cancers and has been implicated in tumor evasion of CD8 T, NK, and dendritic immune cells, allowing tumor growth and metastasis (Jin et al., 2023). COX2 inhibitors, aspirin and nonsteroidal anti-inflammatories (NSAIDS) have shown some survival benefit in patients with colon, lung, prostate, and endometrial cancer (Cao et al., 2016; Lim et al., 2012; Huang et al., 2014; Takiuchi et al., 2018), however results are inconsistent, likely due to toxicity limiting complete blockade of the pathway, highlighting the need for more potent but selective COX pathway inhibitors. OKN4395 is a first-in-class, highly selective, equipotent inhibitor of EP2, EP4 and DP1, downstream receptors for COX-derived PGE_2, and PGD_2, respectively. DP1 has described roles in immunosuppression and inhibition of apoptosis, supporting the therapeutic rationale (Luo et al., 2024; Peinhaupt et al., 2017). OKN4395 is hypothesized to modulate the tumor microenvironment to allow an effective immune response as monotherapy, and to potentiate the effect of immunotherapies such as checkpoint inhibitors, both of which are evaluated in INVOKE. **Methods:** INVOKE (OKN-4395-121; NCT06789172) is a Ph1a/1b, first-in-human study of OKN4395 (oral, BID) as monotherapy (mono) or in combination with pembrolizumab 200mg IV 3-weekly (combo), in patients with advanced solid tumors that have evidence of COX-associated immunosuppression. Ph1a is a Bayesian dose escalation in mono, followed by combo dose confirmation, primarily assessing safety, establishing the optimal dose for Ph1b. Using multimodal artificial intelligence (AI) drug-matching algorithms, Ph1b tumor types were selected, and response will be assessed (cohorts of n = 20 each): select sarcomas (mono), pancreatic carcinoma (mono), non-small cell lung cancer (combo), colorectal carcinoma (combo), head and neck squamous cell carcinoma (combo). Key inclusion criteria include COX-active (Ph1a) or above-listed (Ph1b) tumors, performance status 0-1, biopsy-amenable lesions, and adequate organ function. Active CNS metastases, upper GI bleed risk factors, untreated H. pylori infection, and concomitant NSAIDs/COX inhibitors/prostaglandins are exclusionary. Ph1b mono cohorts will include exploratory analyses including evaluation of the effect of food & gastric pH on OKN4395 pharmacokinetics. Trial data, paired pre- and on-treatment biopsies, and exploratory biomarkers will be used to enhance development using advanced agentic AI systems, including a synthetic digital twin control arm. Ph1a of the study is currently recruiting in the US, UK, and Australia. Clinical trial information: 06789172. Research Sponsor: Epkin.

TPS2684 **Poster Session**

An open-label, phase Ib dose-expansion study to assess the efficacy of CD137/FAP agonist BI 765179 plus pembrolizumab as a first-line treatment in metastatic or incurable, recurrent programmed cell death ligand-1 (PD-L1)-positive head and neck squamous cell carcinoma (HNSCC). First Author: Rachna T. Shroff, University of Arizona Cancer Center, Tucson, AZ

Background: HNSCC is the seventh most common cancer globally and is often associated with poor quality of life and a dismal prognosis. Median overall survival for advanced HNSCC with first-line standard-of-care pembrolizumab $\pm$ chemotherapy is approximately 13 months, highlighting the need for new therapies. Fibroblast activation protein (FAP)-positive fibroblasts are frequently present in the tumor stroma of HNSCC tumors, representing a potential therapeutic target. BI 765179 is a bispecific antibody that simultaneously binds to FAP and CD137 expressed on T-cells, leading to local activation of tumor-specific CD137-positive T-cells. The Phase Ia part of the present study (NCT04958239) determined safety and doses for dose escalated BI 765179, both as monotherapy and in combination with an anti-programmed cell death protein 1 (PD-1) antibody in patients with advanced solid tumors. Here we present the design of the Phase Ib dose-expansion part, which aims to assess the preliminary efficacy of two doses of BI 765179 in combination with pembrolizumab in patients with metastatic or incurable, recurrent HNSCC whose tumors express PD-L1. **Methods:** In the Phase Ib dose-expansion part, approximately 60 patients with a histologically or cytologically confirmed diagnosis of metastatic or incurable, recurrent HNSCC will be enrolled. Key inclusion criteria are: no prior systemic therapy administered in the metastatic or incurable recurrent setting; primary tumor locations of oropharynx, oral cavity, hypopharynx, or larynx; at least one measurable lesion outside of the central nervous system (modified RECIST v1.1); a PD-L1-positive tumor (combined positive score $\geq$1, local assessment); and Eastern Cooperative Oncology Group performance status 0–1. Patients who have previously received CD137-targeted or anti-PD-1/PD-L1 agents are not eligible. Patients will be randomized 1:1 to receive either Dose 1 or Dose 2 of BI 765179 intravenously in combination with pembrolizumab. The primary endpoint is objective response (OR), defined as best overall response of confirmed complete or partial response (RECIST v1.1). Secondary endpoints include occurrence of adverse events (AEs) and serious AEs, OR (immune-related RECIST v1.1), duration of response, progression-free survival, and overall survival. Clinical trial information: NCT04958239. Research Sponsor: Boehringer Ingelheim.

TPS2685 **Poster Session**

A phase 1, first-in-human study of CTIM-76, a claudin-6 (CLDN6)-directed bispecific antibody, in patients with recurrent ovarian cancer and other advanced solid tumors. First Author: Roisin Eilish O'Cearbhaill, Memorial Sloan Kettering Cancer Center and Weill Cornell Medical College, New York, NY

Background: CLDN6 is an oncofetal protein expressed at high levels in many solid tumors while expressed at very low levels in adult normal tissues. The high target antigen density and slow rate of internalization makes it an attractive target in cancer therapeutics. CTIM-76, a CLDN6 x CD3 T cell engager bispecific antibody is engineered to bind with high selectivity to CLDN6 and redirect the immune system's T cells to recognize and kill CLDN6-expressing cancer cells. CTIM-76 effectively inhibited tumor growth, inducing complete responses in ovarian cancer xenograft models. The first in human study of CTIM-76 in patients with advanced ovarian, endometrial, and testicular cancers (NCT06515613) is described here. **Methods:** Part 1 dose escalation exploring 9 ascending dose levels with a 3+3 design. The first two dose levels are single patient cohorts (22.5 μg starting dose), CTIM-76 delivered as weekly iv infusions, with step dosing and steroid premedication to minimize cytokine release syndrome. Approximately 40 patients with platinum resistant ovarian cancer, or endometrial or testicular cancers relapsed after standard of care will be enrolled. Tumors from patients with ovarian or endometrial cancer require prospective CLDN6 + confirmation by IHC (10% $\geq$ 1+), testicular cancer patients will not require prospective screening due to the known uniformly high prevalence of CLDN6. The primary objective is to evaluate safety and tolerability (incidence and severity of adverse events per NCI CTCAE v5.0) and establish the recommended dose for expansion. Secondary objectives include assessment of antitumor activity (RECIST v1.1, iRECIST), pharmacokinetics, and pharmacodynamic correlates of immune activation. Part 2 will evaluate two doses in approximately 30 patients with one tumor type, with efficacy and further safety as primary objectives. This multicenter study has currently five sites open for enrollment. The first patient was dosed in January 2025. Clinical trial information: NCT06515613. Research Sponsor: None.

TPS2686 **Poster Session**

A phase 1a/1b study to evaluate the safety, tolerability, pharmacokinetics, and anti-tumor activity of IMGS-001 in patients with relapsed or refractory advanced solid tumors. First Author: David S. Hong, The University of Texas MD Anderson Cancer Center, Houston, TX

Background: IMGS-001 is a fully human, dual specific immunoglobulin G1 (IgG1) monoclonal antibody (mAb) that binds both PD-L1 and PD-L2, silencing the entire PD-1 inhibitory circuit, with an engineered fragment crystallizable (Fc) region designed to induce robust antibody-dependent cell-mediated cytotoxicity (ADCC) and phagocytosis (ADCP). IMGS-001 mediated killing of PD-L1+ and PD-L2+ tumor and stromal cells can reduce the level of multi-modal immune suppression throughout the tumor microenvironment while catalyzing cross presentation of tumor antigens to the adaptive immune system. IMGS-001 also blocks binding of the T cell co-inhibitory receptor PD-1 with its ligands, restoring activation and function to tumor-specific T cells. In addition, IMGS-001 blocks binding of PD-L1 to B7-1, increasing costimulation of tumor-specific T cells. A phase 1a/1b study has been opened to investigate IMGS-001 safety, anti-tumor activity, and pharmacokinetics (PK) in solid tumor patients (Protocol IMGS-001-011; NCT06014502). **Methods:** This multi-center, first-in-human study is enrolling subjects with advanced solid tumors refractory to standard of care therapy. Phase 1a uses a Bayesian optimal interval (BOIN) dose-escalation design to investigate doses from 0.3-15 mg/kg (Q2W). Phase 1b is a two-part design in subjects with PD-L1+ expression $\geq$ 5% across 5 tumor types: triple negative breast, bladder, gastric/esophageal, colorectal, ovarian. Part 1 will enroll up to 10 subjects per cohort. Cohorts meeting prespecified efficacy criteria will proceed to Part 2 dose optimization randomly assigning 40 subjects (1:1) between two doses. The primary objective of Phase 1a is to assess IMGS-001 safety, and of Phase 1b is to define the pharmacologically optimal dose (POD). Both study phases will assess tolerability, PK, immunogenicity, and anti-tumor activity including objective response rate and progression free survival, as well as exploratory tissue and serum biomarker analyses. The study will enroll approximately 25 patients in Phase 1a and up to 250 in Phase 1b. The first two cohorts (0.3 and 1 mg/kg) have completed without any dose limiting toxicities (DLTs), and cohort 3 (3 mg/kg) is enrolling as of the submission date. Clinical trial information: NCT06014502. Research Sponsor: ImmunoGenesis; Cancer Prevention and Research Institute of Texas (CPRIT); Cancer Focus Fund.

TPS2687 **Poster Session**

Phase 2 dose expansion of START-001: A phase 1/2 study of invikafusp alfa (STAR0602), a first-in-class, selective T cell receptor (TCR)-targeting, bifunctional antibody-fusion molecule, as monotherapy in patients with antigen-rich tumors resistant to anti-PD(L)-1. First Author: Claire Frances Friedman, Memorial Sloan Kettering Cancer Center, New York, NY

Background: Many patients do not respond to anti-PD(L)-1-based therapies and most responders eventually develop resistance. Thus, the development of effective therapies for anti-PD(L)-1 resistance is a significant unmet medical need. Invikafusp, a selective, dual T cell agonist targeting Vβ6/Vβ10 T cells, is being evaluated in START-001: a multicenter Phase 1/2 monotherapy trial in patients with anti-PD(L)1-resistant, antigen-rich (TMB-H, MSI-H/dMMR, or virally associated) solid tumors. The completed Phase 1 dose escalation of intravenous invikafusp, Q2W, per 3+3 design, identified a recommended Phase 2 dose (RP2D) of 0.08 mg/kg, and demonstrated clinically meaningful single-agent anti-tumor activity in patients with anti-PD(L)-1 resistant tumors, including confirmed partial responses in TMB-H, microsatellite stable, colorectal cancer (CRC) patients with one durable response lasting ~12 months. It promoted potent and selective expansion of mainly CD8+ Vβ6/ Vβ10 T cells with a novel central memory T cell phenotype, and led to ctDNA decrease and expansion of antigen-specific T cells. Based on these results, the US FDA granted Fast Track Designation for invikafusp in TMB-H CRC. **Methods:** Study design: Using an optimal Simon's 2 stage design, Phase 2 of START-001 is a dose expansion at the RP2D, to further investigate the safety and anti-tumor activity of invikafusp in 9 cohorts of patients who have the following solid tumors: 1) tissue-agnostic, TMB-H; 2) tissue-agnostic, dMMR/MSI-H; 3) CRC (both Ras wild-type and mutant) TMB-H and/or MSI-H/dMMR); 4) virally associated tumors such as Merkel cell carcinoma, cervical, oropharyngeal, anal, penile, vaginal, and vulvar cancers, or EBV-related solid tumors; 5) metastatic triple-negative breast cancer; 6) platinum-resistant epithelial ovarian cancer; 7) metastatic castration-resistant prostate cancer; 8) primary stage IV or recurrent non-small cell lung cancer; and 9) immunogenic tumors (e.g., cSCC, melanoma and RCC). Major Eligibility criteria: $\leq$ 3 lines of prior cancer therapies [anti-PD(L)-1s allowed] for advanced or metastatic disease; intolerance to standard therapies including anti-PD(L)-1s allowed; no liver metastases or adequately treated liver metastases either locally (e.g., by surgery, radiofrequency ablation, or chemoembolization) or systemically and stable for 3 months. Primary objective: to further evaluate anti-tumor activity of invikafusp as monotherapy in each of the above-described 9 cohorts of patients with anti-PD(L)-1-resistant, unresectable, locally advanced, or metastatic solid tumors. Primary endpoint: overall response rate (ORR) per iRECIST. The enrollment to the first three cohorts has begun. Clinical trial information: NCT05592626. Research Sponsor: Marengo Therapeutics, Inc.

TPS2688 **Poster Session**

A phase 1 first-in-human study of the novel anti-LLT1 antibody (ZM008) alone and in combination with anti-PD1 antibody in patients with advanced solid tumors. First Author: Maloy Ghosh, Zumutor Biologics, Bangalore, India

Background: ZM008 is a first-in-class, fully human, IgG1 monoclonal antibody targeting the LLT1 antigen. It disrupts the interaction of LLT1-CD161, an NK-mediated innate immunity checkpoint. LLT1 expression on tumor cells has been associated with poor overall survival in multiple solid tumors. *Ex vivo* experiments with lung and bladder cancer biopsies showed significant tumor reduction and immune cell infiltration were observed with ZM008 monotherapy. Synergistic anti tumor effects were observed with ZM008 in combination with pembrolizumab. An open-label, phase 1, first-in-human study evaluating the safety, tolerability, pharmacokinetics (PKs), preliminary anti-tumor activity and the Recommended Phase 2 Dose (RP2D) of ZM008 alone and in combination with pembrolizumab in advanced solid tumors is now ongoing at 3 US sites (NCT06451497). **Methods:** The study includes a dose-escalation Part 1 and a dose-expansion Part 2. In dose escalation (part 1), ZM008 monotherapy follows 3+3 standard design starting with 0.15 mg/Kg and up to 18 mg/Kg IV Q3W. A staggered parallel arm will explore ZM008 in combination with pembrolizumab (200mg Q3W) from dose level 6. Histologically confirmed advanced or metastatic non-small cell lung, head & neck, pancreatic, biliary, prostate, colorectal, triple negative breast, urothelial, ovarian and diffuse large B cell malignancies with no standard alternative are included. Measurable disease by RECIST v1.1, adequate haematological, hepatic and renal functions are required. In Part 2, two or more doses of ZM008 will be used to select RP2D and indications of interest. Major exclusion criteria include, patients with history of uncontrolled brain metastasis, autoimmune disease, pneumonitis, active infections, and significant cardiovascular diseases. The primary objective is to determine the maximum tolerated dose (MTD) and RP2D of ZM008. Secondary objectives include PKs, incidence and severity of treatment-emergent AEs as per common terminology criteria for adverse events (CTCAE) v.5.0, immunogenicity, pharmacodynamic changes, and preliminary anti-tumor activity. Exploratory biomarkers will evaluate pharmacodynamics changes, receptor occupancy, immune and cytokine profiling, ctDNA, and transcriptomics. Paired pre- and on-treatment biopsies will be analysed using immunohistochemistry and the spatial distribution of immune and tumor cells in the tumor microenvironment. At the time of submission, enrollment of 9 subjects were completed in three dose cohorts with no reported DLTs. The study is ongoing and open for enrolment at NEXT Oncology (San Antonio and Austin sites) and Dana-Farber Cancer Institute, Boston. Clinical trial information: NCT06451497. Research Sponsor: Zumutor Biologics Inc.

TPS2689 **Poster Session**

ELEPHAS-01, ELEPHAS-02 and ELEPHAS-04: Multi-institutional observational prospective clinical trials to assess the accuracy of an ex vivo live tumor fragment platform for predicting immunotherapy response. First Author: Hinco J. Gierman, Elephas, Madison, WI

Background: Immune checkpoint inhibitors (ICIs) have revolutionized cancer treatment. However, existing FDA approved companion diagnostic biomarkers like PD-L1, dMMR/MSI-H and TMB have low accuracy in predicting response. Ex vivo cytokine profiling of live tumor samples has shown promise as an improved means of predicting response to PD-1 blockade (Voabil, et al. *Nat Med.* 2021), but this approach has been limited to tumor resections given the need for large amounts of tissue. Here we present three clinical trials that leverage a novel approach using limited tissue from a single core needle biopsy (CNB) (20 gauge or larger). A sequential ex vivo treatment strategy is used, eliminating the need for a separate control arm and addressing challenges with tumor heterogeneity, particularly in CNBs where tissue is limiting. Using a specialized instrument, CNBs are cut into live tumor fragments (LTFs) which are viable in culture and retain the native tumor microenvironment, enabling cytokine profiling in response to ICI treatment ex vivo. **Methods:** ELEPHAS-01 (NCT05478538), ELEPHAS-02 (NCT05520099) and ELEPHAS-04 (NCT06349642) are observational prospective clinical trials initiated to characterize the accuracy of this approach for predicting ICI response. Over 750 patients that are being considered for standard of care (SOC) ICI therapy in the metastatic/relapse or neoadjuvant setting will be enrolled (Table). Fresh live CNBs are collected prior to treatment start and processed within 24 hrs enabling prediction of results within 72 hrs of receipt. LTFs are treated using a strategy where control (IgG) and SOC ICI treatments are performed sequentially on the same tissue in a single well. Changes in the cytokine secretion rates are then compared between ICI and control to characterize immunotherapy response. Additionally, tissue viability and tumor content measurements are used to assess tissue quality. Clinical response is measured using pathologic response in patients receiving neoadjuvant ICI therapy, while RECIST v1.1 is used in all other patients. The primary objective of these trials is to determine the platform's ex vivo accuracy (e.g., sensitivity, specificity) for predicting clinical response to ICIs and comparing it to the accuracy of PD-L1, dMMR/MSI-H and TMB. Clinical trial information: NCT06349642, NCT05478538, NCT05520099. Research Sponsor: None.

	ELEPHAS-01 (Lung)	ELEPHAS-02 (Hoosier)	ELEPHAS-04 (Mayo)
Setting	Metastatic & recurrent	Metastatic & recurrent	Metastatic, recurrent & neoadjuvant
Tumor type	Lung	Bladder, kidney, colorectal, head and neck, lung, melanoma, endometrial	Metastatic/recurrent: lung, skin, esophageal, cervical, endometrial, colon, liver, kidney, bladder Neoadjuvant: breast–TNBC, lung
Enrollment as of 1/27/2025	26	44	20
Est. total enrollment	216	216	324
Clinical endpoints	RECIST v1.1	RECIST v1.1	RECIST v1.1 & Pathologic response at surgery

TPS2690 **Poster Session**

Phase II basket study to evaluate the tissue-agnostic efficacy of anti-PD1 in patients with advanced rare tumors: The ANTARES trial. First Author: Camila M. Venchiarutti Moniz, Instituto do Câncer do Estado de São Paulo (ICESP), Universidade de São Paulo and Instituto D'Or de Pesquisa e Ensino (IDOR), São Paulo, Brazil

Background: Rare tumors account for 25-30% of all malignancies; however, patients (pts) with these cancers are underrepresented in clinical trials. The limited evidence on sequential oncologic treatment strategies in this population leads to a poorer prognosis compared to pts with more common malignancies. The predictive role of the tissue-agnostic biomarker PD-L1 and the combined positive score (CPS) in determining the efficacy of anti-PD1 therapy remains poorly understood in this population. **Methods:** ANTARES TRIAL (NCT06638931) is a basket phase 2 single-arm multicentric study to evaluate the efficacy of anti-PD 1 in rare tumors. Key inclusion criteria are invasive neoplasia with incidence lower than 6/100.000 people-year, expressing PD-L1 with a combined positive score (CPS) ≥10, ECOG 0-1, measurable disease by RECIST v1.1, progression or intolerance to all available treatments for metastatic disease. Patients will receive nivolumab 480 mg intravenously every 4 weeks until disease progression or for a maximum duration of 12 months. The primary endpoint was the disease control rate (DCR) assessed by RECIST v1.1. Based on Simon's two-stage design (DCR under alternative hypothesis > 25%; DCR under null hypothesis ≤5%), nine patients were accrued in the first stage. If ≥1 responses are observed, the trial will accrue an additional 16 pts. The study will be considered positive if 4 or more pts achieve DCR among 25 pts in the second stage. Considering a drop-out rate of 10%, a sample size of 28 patients will be needed to attain 90% power and alpha 0.05. Secondary endpoints include progression-free survival, overall survival, response duration, and response time. Blood samples for circulating tumor DNA, microvessels, and seric immune checkpoint biomarkers will be collected at screening, at 8, 20, 32, 44 weeks, and at the final visit. Enrollment started in Brazil on June/24 at Instituto do Câncer do Estado de São Paulo (ICESP) and Instituto D'Or de Pesquisa e Ensino (IDOR); 8 sites are planned to open later in 2025. Clinical trial information: NCT06638931. Research Sponsor: FINEP - Financiadora de Estudos e Projetos, Brazil; Reference 1676/22 protocol FADDE222-E1AE-45D9-A318- 0C8477BEA1D9.

TPS2691 **Poster Session**

Phase 2 trial of TU2218, TGFβ-RI, and VEGF-R2 dual inhibitor in combination with pembrolizumab in patients with biliary tract cancer and head and neck cancer. First Author: Do-Youn Oh, Department of Internal Medicine, Seoul National University College of Medicine, Seoul, South Korea

Background: TU2218 is a low molecular weight dual kinase inhibitor highly specific to TGFβR1 and VEGFR2 and has a potential to be an efficacious therapy against cancer growth. In vitro and in vivo nonclinical studies have shown that TU2218 reduced the growth and migration/invasion of tumor cells and increased antitumor effects in combination with anti-PD-1/anti PD-L1 antibodies. To investigate safety and tolerability of TU2218 Phase 1a trial was conducted with 6 dose level escalation (30mg/day → 60mg/day → 105mg/day → 150mg/day → 195mg/day → 270mg/day) of TU2218 alone, and it was confirmed that TU2218 was safe and tolerated in all dose levels. And to explore the synergistic effect of TU2218 in combination with Pembrolizumab and to decide RP2D Phase 1b trial was conducted with 3 dose level escalation (105mg/day → 150mg/day → 195mg/day) of TU2218 in combination with Pembrolizumab in patients with advanced solid tumors. The RP2D of TU2218 was established as 195mg/day in combination with Pembrolizumab, the total 19 patients received the treatment and most frequently observed TRAE was pruritus and proteinuria, and three Grade 3 TRAEs (Pruritus, Rash Maculo-Popular, Malaise) were observed. The MTD was not identified during dose escalation period. The ORR of overall dose levels demonstrated 19%, and DCR was about 63%. In particular, 80% DCR was observed in TU2218 195mg/day in combination with Pembrolizumab. The trial was expanded to the specific cancer types, Biliary Tract Cancer and Head and Neck Cancer using the established RP2D for Phase 2 trial. **Methods:** Locally advanced unresectable or metastatic biliary tract cancer (BTC) patient whose tumor has progressed on/after first line standard anticancer therapy and anti-PD-(L)1 agent-naive metastatic or with unresectable, recurrent head and neck squamous cell carcinoma (HNSCC) patient whose tumor express PD - L1 (CPS ≥1) as determined by an FDA-approved test or recurrent or metastatic HNSCC with disease progression on or after platinum-containing chemotherapy are eligible for this non-randomized, open-label multicenter trial. All patients are administered with TU2218 195mg/day (97.5mg BID) on a 2 weeks-on/1 week-off in combination with Pembrolizumab 200mg IV Q 3 weeks and will be evaluated by investigator-assessed objective response rate (ORR) defined as the proportion of patients with a best overall response of complete response (CR) or partial response (PR) according to RECIST version 1.1. If 2 or less patients out of 22 evaluable BTC patients are observed with CR/PR and 3 or less patients out of 22 evaluable HNSCC patients are observed with CR/PR, this suggests futility and the cohort may be stopped. Up to 40 BTC patients and up to 36 HNSCC patients are planned to be enrolled and a dropout rate of up to 10% is expected. As of this abstract submission date, 14 BTC patients and 8 HNSCC patients have been enrolled. Clinical trial information: NCT05784688. Research Sponsor: TiumBio., Co., Ltd.; Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc.

TPS2692 **Poster Session**

A multi-center, single-arm, phase II study of pemigatinib combined with immune checkpoint inhibitor in FGFR1/2/3 alteration advanced solid tumor. First Author: Tao Qin, Phase I Clinical Trial Centre, Sun Yat-sen Memorial Hospital, Sun Yat-sen University, Guangzhou, China

Background: FGFR mutations are a significant genetic factor contributing to the onset and progression of various cancers. FGFRs are aberrantly activated, including single-nucleotide variants, gene fusions, and copy number amplifications in human cancer. FGFR mutation alterations are most commonly observed in urothelial carcinoma, breast cancer, endometrial cancer, squamous cell carcinoma of the lung, etc. The preliminary efficacy of FGFR inhibitors in solid tumors has been established ORR ranged from 20% to 30% [1,2,3]. However, the efficacy of FGFR inhibitors as monotherapy in treating FGFR mutations of solid tumors has not yet met the clinical needs. Evidence from preclinical research suggested that a combination of FGFR inhibition and PD-1 suppression expanded the T-cell clones and caused immunological changes in the tumor microenvironment to enhance anti-tumor immunity and survival [4]. Based on the synergistic interplay between the FGFR signaling pathway and immune mechanisms, this study aims to evaluate the safety and efficacy of combining the FGFR inhibitor pemigatinib plus PD-1 inhibitor to treat solid tumors harboring FGFR mutations. **Methods:** 1. This study is a single-arm, multicenter, prospective Phase II clinical trial. Gene testing confirms FGFR1/2/3 variants, including but not limited to mutations, fusions/rearrangements in solid tumors. 2. Patients have not previously used specific small molecule multi-target inhibitors of the FGFR pathway, as assessed by investigators, and have been treated with immune checkpoint inhibitors. 3. Patients receive pemigatinib (13.5 mg QD, orally, 2 weeks on 1 week off, 21 days per-cycle), with immune checkpoint inhibitor therapy (strictly follow instructions). Treatment should continue until disease progression or unacceptable toxicity occurs of intolerable toxicities. 4. At least one measurable lesion per RECIST v1.1 criteria. 5. The safety of the study will be assessed using the NCI-CTCAE v5.0 criteria. The primary outcome measures: objective response rate (ORR). Secondary outcome measures: disease control rate (DCR), progression-free survival (PFS); overall survival (OS); safety and quality of life. Clinical trial information: NCT06551896. Research Sponsor: None.

TPS2693 **Poster Session**

IMMUNORARE[5]: A national platform of 5 academic phase II trials coordinated by Lyon University Hospital to assess the safety and the efficacy of the immunotherapy with domvanalimab + zimberelimab combination in patients with advanced rare cancers—The Anaplastic Thyroid Carcinomas Cohort. First Author: Hélène Lasolle, Lyon 1 University, Lyon, France

Background: In patients with rare cancers, there is an unmet medical need for investigating innovative therapeutics beyond standard first-line treatment. Indeed, these diseases are rarely assessed in clinical trials. Anaplastic thyroid carcinomas (ATC) represent 2-3 % of thyroid carcinomas, but are responsible for 15-40% of thyroid cancer mortality. Most cases (> 90%) are diagnosed with advanced unresectable disease. In such patients carrying the BRAFV600 mutation (20-30%), the standard 1st-line treatment relies on dabrafenib & trametinib. In patients without BRAF mutation, the 1st line treatment is chemoradiation. There is no validated 2nd line treatment, but immunotherapy combinations seem promising. In DUTHY trial (Durvalumab + tremelimumab), the 6month-OS was 65.6% in ATC. Moreover, TIGIT expression increased during ICI treatment, suggesting potential synergistic effects by simultaneous blockade of TIGIT and PD-1. **Methods:** IMMUNORARE[5] (NCT06790706) is a platform of 5 single arm phase II trials testing the efficacy and safety of DOMVANALIMAB (anti-TIGIT) and ZIMBERELIMAB (anti PD-1) in 5 independent cohorts of rare cancers. The trial, sponsored by Lyon University Hospital, is conducted in 15 French centers, led in partnership with the corresponding French national reference centers. The ATC cohort, led in collaboration with the French network ENDOCAN-TUTHYREF (https://www.tuthyref.com/fr), will enroll 24 patients with either non-mutated BRAF tumours with persistent disease at the first evaluation after chemoradiation or disease progression/relapse after the end of chemoradiation, or with mutated B-RAF tumors in progression after a standard B-RAF inhibitor. Patients will receive intra-venous DOMVANALIMAB and ZIMBERELIMAB, every three weeks, until disease progression. The primary endpoint is the survival rate at 6 months. The secondary objectives are overall response rate and duration of the response, progression-free survival and tolerability. The trial is designed with a two-stage Simon design, with early termination for futility (5% one-sided alpha level, 80% power. The treatment would be considered interesting if the survival rate at 6 months is statistically higher than 25%; 50% is expected. Translational research projects will be developed aiming at deciphering cellular and molecular mechanisms involved in response to treatment. Moreover, data from the prospective database of the ENDOCAN-TUTHYREF network will be investigated to build a synthetic historical arm representative of the efficacy of the standard treatments in a similar population of patients. Clinical trial information: NCT06790706. Research Sponsor: None.

TPS2694 **Poster Session**

Trial in progress: A first-in-human (FIH) phase I study of PTX-912 in patients with locally advanced or metastatic solid tumors. First Author: Yan Xing, City of Hope Comprehensive Cancer Center, Duarte, CA

Background: High-dose IL-2 (HD IL-2) received FDA approval for metastatic melanoma (mM) and metastatic renal cell carcinoma (mRCC), but its use is limited by severe systemic toxicities. While PD-1 blockade has improved overall survival in 20–30% of cancer patients, resistance remains a significant challenge. Notably, HD IL-2 has shown durable anti-tumor effects in mM and mRCC patients who have progressed on anti-PD-1 therapy. Moreover, combining IL-2 with pembrolizumab in mRCC demonstrated a durable response rate of 70%, compared to objective response rates (ORR) of 20% and 33% with IL-2 and pembrolizumab monotherapy, respectively (*Chatzkel et al., Clin Genitourin Cancer(2022)*). These findings suggest that combining IL-2 receptor (IL-2R) activation with PD-1 blockade may be a promising strategy to overcome PD-1 resistance and enhance clinical outcomes. PTX-912 is a novel, first-in-class bifunctional PD-1-proIL-2v fusion protein designed to synergize PD-1 blockade with PD-1-cis-directed IL-2R agonism specifically within the tumor microenvironment (TME), reducing systemic toxicities typically associated with high dose IL-2 therapy. **Methods:** This first-in-human (FIH), multi-center Phase I study (NCT06190886) evaluates the safety, tolerability, and preliminary efficacy of PTX-912 in patients with locally advanced or metastatic solid tumors who have had disease progression on all available standard of care and/or refused available standard of care therapies that would confer clinical benefit. Eligible patients must have measurable disease per RECIST v1.1 and may have received any number of prior therapies. Key exclusions include immunodeficiency, unresolved toxicities $>$ Grade 1 per NCI CTCAE from prior therapy, active autoimmune disease, primary CNS or leptomeningeal involvement, history of transplant, recent major surgery, and significant cardiac or pulmonary dysfunction. The study includes dose escalation (Part 1a) and dose expansion (Part 1b) cohorts. In Part 1a, seven dose levels (DL1–7) will be tested, with DL1–3 following an accelerated titration design and DL4–7 using a standard 3+3 design. The primary objectives are to determine the maximum tolerated dose (MTD), optimal biological dose (OBD), and/or the recommended Phase II dose (RP2D) of PTX-912, assessed via dose-limiting toxicities (DLTs). Patients with melanoma, renal cell carcinoma (RCC), non-small cell lung cancer (NSCLC), or other populations identified based on Part 1a data will be enrolled in Part 1b. In Part 1a, patients will receive intravenous infusions of PTX-912 every two weeks (Q2W), followed by subsequent cycles with a 28-day DLT observation period. Study enrollment began in June 2024 in the United States at 3 centers. Cohorts 1 to 4 (6 patients) have been completed without DLT. Enrollment to cohort 5 is currently ongoing. Clinical trial information: NCT06190886. Research Sponsor: Proviva Therapeutics.

TPS2695 **Poster Session**

Phase 1/2 study of tiragolumab and atezolizumab in patients with relapsed or refractory SMARCB1- or SMARCA4-deficient tumors: PEPN2121. First Author: Mary Frances Wedekind, Pediatric Oncology Branch, National Cancer Institute, National Institutes of Health, Bethesda, MD

Background: The SMARCB1/A4 gene products are core subunits of the SWItch/Sucrose Non Fermentable (SWI/SNF) chromatin remodeling complex. Tumors with defects in SWI/SNF are histologically distinct aggressive cancers occurring in children and young adults. SMARCB1/A4 deficient tumors, particularly malignant rhabdoid tumor (MRT), atypical teratoid rhabdoid tumor (ATRT), poorly differentiated chordoma (PDC), epithelioid sarcoma (ES), and renal medullary carcinoma (RMC), have immune cell infiltrates and programmed death ligand 1 (PD-L1) expression. Responses to immune checkpoint inhibition (CI) have been observed in SMARCB1/A4 deficient tumors; however, responses are not durable. T cell immunoreceptor with Ig and ITIM domains (TIGIT) is a novel inhibitory receptor expressed on multiple immune cells. TIGIT inhibits T and NK cells by binding to its ligand poliovirus receptor (PVR) and Nectin2 on both tumor and antigen-presenting cells. Utilizing RNAseq data, SMARCB1/A4 deficient tumors demonstrate high expression of PVR and Nectin2. Tiragolumab is an antibody to the TIGIT receptor. The combination of tiragolumab and atezolizumab has shown promising activity in early phase studies, and phase 3 studies are ongoing in multiple adult indications. Thus, there is rationale that the addition of tiragolumab to CI may also enhance response rates in patients with SMARCB1/A4 deficient tumors. **Methods:** This is a phase 1/2 trial of tiragolumab monotherapy (300 mg if $\leq$ 15 kg; 420 mg if $>$ 15 kg to $\leq$ 40 kg; 600 mg if $>$ 40 kg or $\geq$ 18 years) and in combination with atezolizumab (15 mg/kg [max 1200 mg]) if $<$ 18 yrs or 1200 mg if $\geq$ 18 years) administered IV on Day 1 of 21-day cycles in patients $>$ 12 months of age with SMARCB1/A4 deficient tumors. Part A evaluating the safety of tiragolumab monotherapy in patients $<$ 18 years based on cycle 1 dose limiting toxicities is complete. Part B estimates the antitumor activity of tiragolumab in combination with atezolizumab in 6 histology-specific cohorts (RMC, MRT, ATRT, PDC, ES, and other SMARCB1/A4 deficient tumors) and is now open to all eligible age groups. Each cohort is conducted using a 6+4 Simon's two stage design. Enrollment for each cohort is as follows: Part A 6/6, Part B RMC 1/6, MRT 1/6, ATRT 4/6, PDC 2/6, ES 3/6, other 6/6. Radiographic imaging central response assessment for the first stage of the "other" cohort is ongoing. Cycle 1 toxicities of the combination therapy are monitored in Part B patients $<$ 12 yrs using a Bayesian Optimal INterval (BOIN) design with a target toxicity of 17%. Secondary objectives are to characterize the pharmacokinetics/anti-drug antibody development and to estimate progression free survival, overall survival, and duration of response. Enrollment is open at all Pediatric Early Phase Clinical Trial Network sites. Data cutoff: Jan 10, 2025. Clinical trial information: NCT05286801. Research Sponsor: National Cancer Institute; UM1CA22882; Cookie for Kids Foundation; Genentech, A Member of the Roche Group,; NIH, NCI Intramural research program.

TPS2696 **Poster Session**

A phase 1b study of combined treatment with dupilumab (anti-IL-4Ra) and cemiplimab (anti-PD-1) in patients with early-stage, resectable NSCLC. First Author: Fionnuala Crowley, Division of Hematology & Medical Oncology, The Tisch Cancer Institute, Icahn School of Medicine at Mount Sinai, New York, NY

Background: For resectable stage II/III non-small cell lung cancer (NSCLC), neoadjuvant chemoimmunotherapy has become standard of care. Patients with Stage I disease (as per AJCC 8) were excluded from chemoimmunotherapy studies given prior data demonstrating no survival benefit from perioperative chemotherapy. However, even patients with Stage 1A ($<$ 2cm) tumors have a 30% chance of recurrence (Altorki *et al, NEJM* 2023). Recent research has revealed that tumor-infiltrating myeloid cells express an IL-4 responsive transcriptional signature, and IL-4 signaling within monocyte-derived macrophages plays an essential role in NSCLC progression and tumor microenvironment remodeling. Dupilumab, a monoclonal antibody targeting IL-4 receptor alpha (IL-4Rα), is currently approved for treating asthma and allergic rhinitis, and preclinical studies have demonstrated that blocking IL-4 signaling can significantly reduce lung tumor burden by activating dendritic cells and effector T cells to generate a robust immune response against tumor antigens. These findings are supported by early clinical evidence from a phase 1/2 trial showing that dupilumab can work synergistically with PD-(L)1 inhibition to induce sustained tumor responses in some patients with metastatic NSCLC who had previously progressed on immunotherapy. Whether similar synergy would be seen in the pre-operative setting in patients with Stage 1 tumors, or patients not suitable for chemoimmunotherapy, is not known, though an immunotherapy-alone approach may enable much more brief preoperative treatment given that T cell changes peak at one week in the metastatic setting, and prior studies show PD-1 blockade alone can cause robust responses in some patients within only a few weeks. **Methods:** This Phase 1b/2a single-arm trial will enroll patients with early-stage ($>$ T1b), resectable NSCLC. Patients will receive one dose each of dupilumab (600mg SC) and cemiplimab (350mg IV) on day 1, followed by surgical resection within 15-21 days, with delays beyond 8 weeks considered a delay of surgery. The trial consists of a 3+3 safety run-in (Phase 1b, up to 6 patients) followed by a Simon's two-stage expansion (Phase 2a, up to 24 total patients). The primary endpoints are safety/feasibility (Phase 1b) and major pathological response rate, defined as $\leq$10% viable tumor at resection (Phase 2a). Secondary endpoints include time to surgery, pathological complete response rate, event-free survival, and overall survival. Comprehensive correlative studies will characterize the immune response through serial blood sampling (days 1, 4, 8, 15, surgery, and 30 days post-op), matched proteomic and transcriptomic tumor tissue analysis (pre-treatment and operative samples), and stool microbiome profiling to identify potential biomarkers of response. Clinical trial information: NCT06088771. Research Sponsor: Cancer Research Institute.

TPS2697 **Poster Session**

A phase 1 trial of APX-343A, NOX inhibitor targeting CAF-mediated immunosuppression, as monotherapy or in combination with pembrolizumab in patients with advanced solid tumors. First Author: Hyesung Shin, Aptabio Therapeutics, Yongin-Si, South Korea

Background: Cancer-associated fibroblasts (CAFs), a key component of tumor stroma, promote tumor growth and resistance to anticancer therapy. They contribute to immune suppression within the tumor microenvironment (TME), with evidence linking CAFs to immune checkpoint inhibitor (ICI) resistance and T-cell exclusion. Nicotinamide adenine dinucleotide phosphate (NADPH) oxidase (NOX), which is clinically upregulated by CAF in many human cancers, has been reported to be a critical effector of myofibroblast transformation during fibrosis. Inhibiting NADPH oxidases, NOX2 and NOX4, restored cluster of differentiation 8 + T-cell proliferation by reducing reactive oxygen species (ROS) generation in CAF-induced myeloidderived suppressor cells (MDSCs). A pivotal role of CAFs in regulating monocyte recruitment and differentiation demonstrated that CC-chemokine receptor 2 inhibition and ROS scavenging abrogate the CAF-MDSC axis, illuminating a potential therapeutic path to reversing the CAF-mediated immunosuppressive microenvironment. APX-343A, a selective NOX1, NOX2, and NOX4 inhibitor, has been shown to ameliorate the fibrotic and immunosuppressive properties of CAFs. In CAF-rich tumor mouse models that do not respond to ICIs, APX-343A demonstrated significant anticancer efficacy by modulating both fibrosis and immunosuppression via NOX inhibition. **Methods:** This is a Phase 1, open-label, dose-escalation study designed to assess the safety, tolerability, PK, and preliminary efficacy of APX-343A as monotherapy (Part A) and in combination with pembrolizumab (Part B) in patients with advanced solid tumors. The trial aims to determine the MTD and/or RP2D. Part A is a dose-escalation study of APX-343A monotherapy, starting at a dose of 100 mg BID (Cohort 1) and escalating up to 600 mg BID (Cohort 6) until dose-limiting toxicity (DLT) is identified. APX-343A will be administered on a continuous daily dosing schedule in 21-day cycles. Part B is a dose-escalation study of APX-343A in combination with pembrolizumab (200mg IV, Q3W). Using the BOIN design, the dose level of APX-343A will escalate from 200 up to 600 mg BID without exceeding the MTD. The BOIN design will guide dose escalation based on safety, with decisions made by the Safety Review Committee (SRC). Dose finding will be conducted independently for Parts A and B. APX-343A selective NOX inhibitor has the potential to become an effective treatment option in combination with ICIs for patients with CAF-rich solid tumors that are unresponsive to current immunotherapies. By inhibiting CAF activity in the TME and resensitizing tumors to cancer immunotherapy, APX-343A offers a promising therapeutic approach. Phase 1 results are anticipated in Q1 2026. Research Sponsor: Aptabio Therapeutics Inc.

TPS2698 **Poster Session**

A phase Ib study of a pooled synthetic long peptide mutant KRAS vaccine combined with balstilimab/botensilimab in metastatic pancreatic cancer and metastatic MMR-proficient colorectal cancer in the maintenance setting. First Author: Kai-li Liang, Department of Oncology, Johns Hopkins Sidney Kimmel Comprehensive Cancer Center, Baltimore, MD

Background: Expressed in > 90% of all patients with pancreatic ductal adenocarcinoma (PDAC) and ~40% in mismatch repair-proficient colorectal cancer (MMRp CRC), the mutated oncoprotein KRAS (mKRAS), is an attractive neoantigen vaccine target. Efforts to sensitize these immunologically 'cold' tumors to immune checkpoint inhibitors have just started to yield encouraging clinical data with novel agents. In an ongoing pilot study in patients with resected PDAC and metastatic MMRp CRC (NCT04117087), we demonstrated that a pooled synthetic long peptide (SLP) mKRAS vaccine in combination with ipilimumab and nivolumab was safe and well tolerated. This combination induced robust de novo mKRAS-specific T cells in peripheral blood associated with improved disease-free survival (Haldar *et al.,* 2023). Recently, the Fc-enhanced anti-CLTA-4 antibody, botensilimab (bot), in combination with balstilimab (bal; anti-PD-1) has been shown to demonstrate clinical activity in metastatic relapsed/refractory MMRp CRC (Bullock *et al*., 2024). Based on these encouraging data, our study combines mKRAS vaccine with dual checkpoint blockade to assess safety and early clinical efficacy in patients with metastatic PDAC and metastatic MMRp CRC in the maintenance setting. **Methods:** This is a first-in-human, single-arm, open-label phase Ib trial evaluating mKRAS vaccine with bal/bot in patients with metastatic PDAC (Cohort A, n = 21) and metastatic MMRp CRC (Cohort B, n = 21). The vaccine consists of SLPs corresponding to six common mKRAS alleles: G12D, G12V, G12R, G12C, G12A, G13D admixed with poly-ICLC adjuvant. In the priming phase (Cycle 1) the mKRAS vaccine is given on days 1, 8, 15 and 22 along with bal/bot on day 1 and bal on day 15. In the boost phase, (Cycle 2 and beyond), patients receive bal every 2 weeks and boost vaccines starting on Cycle 4 and every other cycle for a maximum of 2 years. Eligible patients must have metastatic PDAC or MMRp CRC and measurable disease per RECIST 1.1 amenable to biopsies at baseline and week 9. Patients must have one of the six KRAS mutations contained in the vaccine. Patients must have received 4-6 months of 1st line standard chemotherapy without disease progression. The primary endpoints are safety and tolerability, 4-month progression free survival (Cohort A), and objective response rate (Cohort B). Secondary endpoints include disease control rate, objective response rate (Cohort A), and progression free survival (Cohort B). Correlative studies will examine T cell receptor (TCR) clonal expansion in peripheral blood and paired tumor specimens pre- and post-vaccination by next generation TCR sequencing. Patient accrual began in October 2024 with the safety run in completed. Enrollment is currently ongoing. Study drug support provided by Agenus. Trial information: NCT06411691. Clinical trial information: NCT06411691. Research Sponsor: U.S. Department of Defense; U.S. National Institutes of Health.

TPS2699 **Poster Session**

A phase I study of a pooled synthetic long peptide mutant KRAS vaccine in patients with pancreatic cystic neoplasms at risk for developing pancreatic cancer. First Author: Kai-li Liang, Department of Oncology, Johns Hopkins Sidney Kimmel Comprehensive Cancer Center, Baltimore, MD

Background: Mutant KRAS (mKRAS) is an oncogenic driver expressed in > 90% of patients with pancreatic ductal adenocarcinoma (PDAC) and the majority of pancreatic precursors, including > 90% of intraductal papillary mucinous neoplasms (IPMNs) and pancreatic intraepithelial neoplasia (PanIN) (Kanda *et al.,* 2012). If left untreated, approximately 40-60% of high-risk IPMNs will have malignant transformation (Fonseca *et al.,* 2018). mKRAS vaccines have recently demonstrated encouraging results in generating mKRAS-specific T cell responses that correlate with clinical benefit in patients with resected PDAC. We previously reported that a mKRAS-targeted *Listeria*-based vaccine given with Treg-depleting agents results in slowing of PanIN progression to PDAC in a murine model (Keenan *et al.,* 2014). Based on these data, we have initiated a clinical trial testing this vaccine in individuals at high-risk of developing pancreatic cancer. In our first Cohort [A], we have tested this vaccine in individuals at high-risk due to a known germline mutation or familial predisposition (n = 20). Our current study [Cohort B] aims to determine the safety and immunogenicity of a pooled synthetic long peptide (SLP) mKRAS vaccine with poly-ICLC adjuvant in patients with pancreatic cystic neoplasm at risk for developing PDAC and who are scheduled to undergo surgical resection**. Methods:** This is a single-arm, open-label phase I trial evaluating mKRAS vaccine in patients with pancreatic cystic neoplasms at risk for developing PDAC and scheduled to undergo surgical resection (n = 10). The vaccine consists of SLPs corresponding to six common mKRAS mutations: G12D, G12V, G12R, G12C, G12A, G13D admixed with poly-ICLC adjuvant. A two-dose series of the mKRAS vaccine is administered at weeks 1 and 2 followed by pancreatic surgery at week 4. Peripheral blood will be collected pre-vaccination (week 1) and post-vaccination (weeks 4 and 8). Following completion of the treatment phase, patients have the option to continue annual follow-up visits until study closure. Eligible patients must have clinical, radiographic, or histologic evidence of a pancreatic cystic neoplasm with features warranting surgical resection per the discretion of the treating hepatobiliary surgeon. Co-primary endpoints include the safety profile per NCI CTCAE v5.0 and maximal percent change of mutant-KRAS-specific T cells measured by IFNg ELISPOT at weeks 4 and 8 post-vaccination compared to pre-vaccination baseline. Correlative studies of resected specimens will include characterization of the pre-malignant microenvironment and mKRAS-specific T cell trafficking post-vaccination. Methods of analyses include bulk RNA and T cell receptor (TCR) sequencing, spatial transcriptomics, and imaging mass cytometry. Patient accrual began in December 2024 and is currently ongoing. Clinical trial information: NCT05013216. Research Sponsor: Lustgarten Foundation for Pancreatic Cancer.

TPS2700 **Poster Session**

A phase 2 basket trial of tarlatamab in patients with advanced DLL3-expressing tumors: University of California Lung Cancer Consortium UCCC-01/UCLA L-10. First Author: Michael Oh, David Geffen School of Medicine at University of California, Los Angeles, Los Angeles, CA

Background: Delta-like ligand 3 (DLL3) is an inhibitory Notch ligand that is aberrantly expressed on the surface of tumor cells, in particular on those with neuroendocrine differentiation. Tarlatamab is a bispecific T cell engager that binds to DLL3 and CD3 to promote T cell killing of DLL3-expressing cells. Prior studies of tarlatamab have demonstrated encouraging antitumor activity and manageable toxicity in patients with small cell lung cancer (SCLC; DeLLphi-301) and neuroendocrine prostate cancer (NEPC; DeLLpro-300). Meanwhile, DLL3 has been reported to be highly expressed in multiple tumor types, including in many neuroendocrine neoplasms (NENs) other than SCLC and NEPC. The role of anti-DLL3 therapies in these cancers has not been established. **Methods:** This is a phase 2, multicenter, open-label, basket study designed to evaluate the efficacy of tarlatamab in patients with DLL3-expressing cancers. Key inclusion criteria include presence of advanced stage disease with progression following $\geq$1 prior line of therapy and positive tumor DLL3 expression by immunohistochemistry (Ventana SP347 assay). Patients with de novo SCLC or NEPC are excluded, but all other tumor types and NENs are eligible, including large cell neuroendocrine carcinoma and SCLC transformed from previously treated NSCLC. Tarlatamab will be administered at an initial step-up dose (1 mg on D1 and 10 mg on D8 and D15 of cycle 1) followed by 10 mg every 2 weeks. Treatment will continue until unacceptable toxicity, progressive disease, or withdrawal of consent. The study will follow a Simon's two-stage design: in Stage 1, 10 patients with tumor DLL3 expression $\geq$25% will be enrolled, and the study will be stopped if $\leq$1 patient achieves an objective response; otherwise, an additional 19 patients with tumor DLL3 expression $\geq$1% will be enrolled for Stage 2. The primary endpoint is the objective response rate. Secondary endpoints include safety, progression free survival, duration of response, and overall survival. Exploratory studies will evaluate correlation of antitumor activity with tissue and blood-based biomarkers, such as DLL3 expression on tumor and liquid biopsies. This study is currently enrolling patients through the University of California Lung Cancer Consortium (UCLCC). Clinical trial information: NCT06788938. Research Sponsor: None.

TPS2701 **Poster Session**

EXPAND-1, a phase I/II study with ANV600, a novel PD-1 targeted IL-2R-βγ agonist, in monotherapy and in combination with pembrolizumab, in patients with advanced solid tumors. First Author: Iphigenie Korakis, Inst University Du Cancer De Toulouse, Toulouse, France

Background: ANV600 is a novel PD-1 targeted, interleukin-2 receptor beta/gamma (IL-2Rβ/γ) selective agonist. This bispecific agent comprises two functionally distinct arms: a PD-1 targeting arm consisting of an anti-PD-1 antibody binding to an epitope that does not overlap with pembrolizumab or other PD-1 checkpoint inhibitors and an IL-2 receptor (IL-2R) agonistic arm, composed of an interleukin-2 (IL-2)/anti-IL-2 antibody fusion protein which selectively signals through IL-2Rβ/γ. ANV600 is expected to promote anti-tumor activity by preferentially stimulating and expanding antigen-experienced PD-1^{+} CD8^{+} T cells and be combinable with existing anti-PD-1 clinical therapies. ANV600 will be studied as single agent and in combination with pembrolizumab for the treatment of advanced solid tumors. **Methods:** Study ANV600-001 (EXPAND-1) is a global, multicenter, open-label, first-in-human Phase I/II study to characterize the safety, tolerability, pharmacokinetics (PK), pharmacodynamics (PD), immunogenicity and antitumor activity of ANV600 administered as a single agent or in combination with pembrolizumab in patients with advanced solid tumors. The Phase I will determine the maximum tolerated dose (MTD) and/or recommended phase 2 dose (RP2D) of ANV600 administered intravenously every 2 weeks (Q2W) either as single agent or in combination with pembrolizumab in previously treated advanced solid tumors. A Bayesian Optimal Interval (BOIN) design will guide the dose escalation to determine the MTD and/or RP2D. Once the RP2D has been determined, ANV600 will be further evaluated as monotherapy and in combination with pembrolizumab in the Phase II part of the study for efficacy and safety in PD-1 experienced patients with advanced melanoma, NSCLC and HNSCC. Additional cohorts may be selected based on emerging data. Tumor response will be assessed using RECIST v1.1. Enrolment began in June 2024, with 10 patients enrolled in the monotherapy arm and 4 in the combination arm. Up to 240 participants will be enrolled in 7 countries: Belgium, France, Germany, the Netherlands, Spain, Switzerland and the USA. Research Sponsor: ANAVEON AG. Clinical trial information: NCT06470763. Research Sponsor: None.

TPS2702 **Poster Session**

Fecal microbiota transplantation combined with sintilimab and SOX as first-line treatment for advanced gastric cancer (FMT-JSNO-01): A prospective, multicenter, double-blind, randomized placebo-controlled phase II trial. First Author: Wenyu Zhu, Department of Oncology, The Second People's Hospital of Changzhou, the Third Affiliated Hospital of Nanjing Medical University, Changzhou, China

Background: Chemotherapy in combination with immunotherapy has emerged as the first-line(1L) standard of care for gastric cancer (GC) patients(pts); nonetheless, the overall prognosis remains suboptimal. Fecal microbiota transplantation (FMT) holds promise in modulating the patient's gut microbiota and immune milieu, thereby augmenting the efficacy of tumor immunotherapy and enhancing long-term survival outcomes. We propose to integrate FMT into the regimen of chemotherapy plus immunotherapy, aiming to assess its efficacy and safety in pts with advanced GC (NCT06405113). **Methods:** FMT-JSNO-01 is a prospective, multicenter, randomized, double-blind, placebo-controlled phase II trial designed to enroll pts with previously untreated, unresectable advanced gastric or gastroesophageal junction adenocarcinoma (GAC/GEJAC) that is human epidermal growth factor receptor 2 (HER2) negative. The physical status score of Eastern Tumor Collaboration Group (ECOG) was 0-1.The study will be conducted in more than 15 multidisciplinary treatment centers for GC in China.The eligible pts were randomly assigned to arm A and arm B. Using a network random system, subjects are randomly assigned in a 1:1 ratio to the experimental group and control group, and competitive random enrollment is conducted at each center.Pts in arm A received fecal microbiota capsule transplantation combined with sintilimab immunotherapy plus S-1 and oxaliplatin (SOX) chemotherapy, while pts in arm B received placebo combined with sintilimab plus SOX . If there is no progression of the disease after 4-6 cycles of 1L treatment, both arms of pts will enter the 1L maintenance treatment stage: S-1 plus sintilimab, until disease progression, intolerance, or death occurs.The primary endpoint of the study is the 2-year overall survival rate (2-year OS rate), with secondary endpoints including median progression-free survival (mPFS), objective response rate (ORR), incidence of adverse events (AEs), diversity of fecal microbiota, and quality of life (QoL). Additionally, exploratory endpoints will encompass efficacy prediction markers in the gut microbiota and proteomics. This study began recruiting pts in June 2024 and is currently ongoing. Clinical trial information: NCT06405113. Research Sponsor: the 2022 Clinical Research project of Changzhou Medical Center, Nanjing Medical University; CMCC202201; 2022 Changzhou 8th Batch of Science and Technology Project (Applied Basic Research); CJ20220086; 2023 Clinical Research Project of Changzhou Medical Center,Nanjing Medical University; CMCC202307; 2023 Changzhou Health Commission Science and Technology Project; QN202320.

TPS2703 **Poster Session**

A first-in-human phase 1 clinical trial of INI-4001, a novel TLR7/8 agonist, in patients with advanced solid tumors. First Author: Shannon Marilee Miller, Inimmune Corp., Missoula, MT

Background: Inimmune has developed INI-4001, a novel TLR7/8 agonist as an immunotherapy treatment for cancer. Pre-clinically, the lead formulation of INI-4001 was able to eliminate Lewis Lung Carcinoma (LLC) flank tumors in mice after just two treatments. Moreover, INI-4001 slowed the growth of MC38 and B16F10 tumors and synergized when combined with anti-PD-1 therapy, leading to an increased cure rate in both MC38 and B16F10 flank tumors in mice when both drugs were used compared to either treatment alone. In July of 2024, we dosed our first patient in a Phase 1 clinical trial in patients with advanced solid tumors. **Methods:** INI-4001 will be evaluated in a Phase Ia/Ib, open-label, dose-escalation, and dose expansion study. This study will be conducted in two parts: Phase Ia (dose escalation) and Phase Ib (dose expansion). Phase Ia will initially seek to establish the MTD or OBD of INI-4001 administered as monotherapy. Using a BOIN design, we have planned six ascending 1-3-subject cohorts with weekly dosing on continuous 21-day cycles. Imaging shall occur after each 3 cycles, and combination therapy with a checkpoint inhibitor is allowable under certain conditions after 3 cycles of monotherapy. Combination with checkpoint inhibitor is allowed if the subject has progressed or achieved stable disease according to iRECIST criteria and has a tumor type for which a checkpoint inhibitor is approved. Following identification of the MTD or OBD, Phase 1b allows any dose level at or below the MTD to be expanded with up to 20 additional subjects to further explore the safety, PK, PD, and preliminary efficacy of INI-4001 alone or as combination therapy. Currently in Phase Ia, Cohorts 1, 2, and 3 have been completed without DLT. Enrollment to Cohort 4 will begin in February 2025. INI-4001 may continue as monotherapy or combination as long as the subject receives benefit. Following cessation of INI-4001, patients will be requested to participate in long-term follow-up to assess overall survival. Clinical trial information: NCT06302426. Research Sponsor: None.

3000 Oral Abstract Session

DB-1310, a HER3-targeted ADC, in pts with advanced solid tumors: Preliminary results from the phase 1/2a trial. First Author: Aaron Lisberg, Division of Hematology/Oncology, University of California, Los Angeles, Santa Monica, CA

Background: DB-1310 is a novel ADC comprised of a humanized anti-HER3 IgG1 monoclonal antibody, cleavable peptide linker, and DNA topoisomerase I inhibitor. Here, we report the preliminary results of the FIH trial. **Methods:** This global, multi-center, open-label Ph 1/2a trial includes dose escalation and expansion. Pts with advanced solid tumors who had failed standard therapy were enrolled. In Ph1, DB-1310 was planned to be administered at doses from 1.5 mg/kg to 6.5 mg/kg, Q3W, iv, using a 3+3 design, with additional pts enrolled to determine the RP2D. Ph 2a will include approximately 30-40 pts per cohort to optimize the RP2D and assess efficacy. **Results:** As of Jan 17, 2025, 123 pts were enrolled and treated with DB-1310 monotherapy in Ph1 (ECOG PS 1, 80.5%; White, 39.0%, Asian, 52.8%; NSCLC, 65.0%, EGFRm NSCLC, 37.4%; brain metastasis, 17.1%), median prior lines of systemic therapy was 3 (range, 1-11). Of the 42 efficacy-evaluable pts with EGFRm NSCLC, 92.9% had previously received 3rd generation EGFR TKI, 92.9% had received platinum-based chemotherapy. The unconfirmed ORR was 25.5% (95% CI, 17.63, 34.65) across all tumor types and 35.7% (95% CI, 21.55, 51.97) in EGFRm NSCLC. Median PFS was 5.4 months overall and 7.0 months for EGFRm NSCLC. 38 (30.9%) pts experienced ≥ G3 TRAEs, while 7 (5.7%) had drug-related SAEs. TRAEs led to dose reduction in 14 (11.4%) pts and discontinuation in 5 (4.1%) pts. No TRAE leading to death was reported. Most common TRAE (> 20%, any grade/≥G3) were nausea (36.6%/0.8%), anemia (35.8%/4.1%), neutrophil count decreased (34.1%/17.9%), platelet count decreased (31.7%/9.8%), white blood cell count decreased (29.3%/8.9%), decreased appetite (23.6%/0.8%), and vomiting (21.1%/0%). Interstitial lung disease occurred in 7 pts (5.7%, 6 G1 and 1 G2). PK exposure was increased through dose escalation, with low systemic payload exposure and no accumulation of DB-1310 upon repeated administration. **Conclusions:** DB-1310 showed a manageable safety profile and encouraging antitumor activity in pts with heavily pretreated advanced solid tumors, particularly EGFRm NSCLC. Clinical trial information: NCT05785741. Research Sponsor: None.

Tumor response by dose (efficacy-evaluable).

Dose (mg/kg)	1.5	3	4.5	5.0	5.5	6	Total
All tumors, n	3	10	25	53	16	3	110
uORR, n (%) (95% CI)	0 (0) (0.00, 70.76)	1(10.0) (0.25, 44.50)	8 (32.0) (14.95, 53.50)	13 (24.5) (13.76, 38.28)	6 (37.5) (15.20, 64.57)	0 (0) (0.00, 70.76)	28 (25.5) (17.63, 34.65)
DCR, n (%) (95% CI)	3 (100.0) (29.24, 100.00)	8 (80.0) (44.39, 97.48)	23 (92.0) (73.97, 99.02)	42 (79.2) (65.89, 89.16)	11 (68.8) (41.34, 88.98)	2 (66.7) (9.43, 99.16)	89 (80.9) (72.31, 87.78%)
EGFRm NSCLC, n	0	7	9	16	8	2	42
uORR, n (%) (95% CI)	-	1 (14.3) (0.36, 57.87)	4 (44.4) (13.70, 78.80)	5 (31.3) (11.02, 58.66)	5 (62.5) (24.49, 91.48)	0 (0) (0.00, 84.19)	15 (35.7) (21.55, 51.97)
DCR, n (%) (95% CI)	-	6 (85.7) (42.13, 99.64)	9 (100.0) (66.37, 100.00)	14 (87.5) (61.65, 98.45)	7 (87.5) (47.35, 99.68)	2 (100.0) (15.81, 100.00)	38 (90.5) (77.38, 97.34)

3001 Oral Abstract Session

Phase I study of iza-bren (BL-B01D1), an EGFR x HER3 bispecific antibody-drug conjugate (ADC), in patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) with driver genomic alterations (GA) outside of classic EGFR mutations. First Author: Yunpeng Yang, Department of Medical Oncology, Sun Yat-Sen University Cancer Center, Guangzhou, China

Background: iza-bren is a first-in-class ADC comprised of an EGFR x HER3 bispecific antibody conjugated to a novel topo-I inhibitor payload (Ed-04) via a stable tetrapeptide-based cleavable linker. Safety/efficacy data from the phase Ib study are presented, focusing on NSCLC patients (pts) with driver mutations outside of classic TKI-sensitizing EGFR mutations. **Methods:** Phase Ib part of this study included the expansion cohorts, each defined by a pre-specified GA, including EGFR exon 20 insertions, non-classical EGFR mutations, mutations in HER2, ALK, ROS1, BRAF (V600E and others), KRAS (G12C and others), SMARCA4, MET (Exon 14), RET, and NTRK. Pts with these GA who progressed on standard targeted therapies (if available) and no more than one prior line of chemotherapy were enrolled. iza-bren was given at 2.5 mg/kg D1D8 Q3W. **Results:** As of Dec 5, 2024, a total of 73 NSCLC pts with listed GA were enrolled. Five pts were still on treatment, but were excluded from the analysis due to insufficient follow-up for the first post-baseline scan (see table below). Among 7 pts with EGFR exon 20 insertions, 85.7% (6 out of 7) achieved cPR. Among 8 pts with KRAS G12C mutations, 3 cPR and 1 PR pending confirmation were observed. Efficacy for subgroups will be presented. The most frequent hematologic TRAEs (all grades) were anemia (87.7%), leukopenia (74.0%), thrombocytopenia (74.0%), and neutropenia (72.6%); the most frequent non-hematologic TRAEs were asthenia (42.5%), nausea (41.1%), stomatitis (37.0%), diarrhea (32.9%), and alopecia (31.5%). Grade 3 and above TRAEs which were predominantly hematologic in nature, were able to be effectively managed with standard supportive measure including dose reductions, as demonstrated by the TRAE leading to discontinuation rate of 2.7%. Only 1 case of G2 ILD was observed. Notably, no iza-bren related death was reported. No new safety signals were observed. **Conclusions:** In NSCLC pts with these GAs, iza-bren showed promising activity with a manageable safety profile, supporting further evaluation of iza-bren in these populations. Clinical trial information: NCT05194982. Research Sponsor: None.

	Total (N = 68)	EGFR mut exon20ins/non-classical (N=12)	HER2 mut (N=13)	ALK/ROS1/ RET fusion (N=19)	KRAS/BRAF/ MET mut (N=22)	SMARCA4 (N=2)
Prior lines of therapy, median (range)	1 (1-5)	1 (1-2)	1 (1-3)	3 (1-5)	1 (1-2)	1 (1-1)
BOR, n						
PR	31	9	8	5	9	0
cPR	24	8	7	3	6	0
PR pending confirmation	6	1	1	2	2	0
SD	25	3	5	10	7	0
PD	9	0	0	3	5	1
NE[1]	3	0	0	1	1	1
ORR, %	45.6	75.0	61.5	26.3	40.9	0
cORR, %	35.3	66.7	53.8	15.8	27.3	0
DCR, %	82.4	100.0	100.0	78.9	72.7	0
mDOR (mo) (95% CI)	7.0 (5.6, NR)	NR (5.6, NR)	5.7 (4.2, NR)	4.5 (2.7, NR)	NR (NR, NR)	/
mPFS (mo) (95% CI)	6.7 (4.1, 11.2)	NR (6.9, NR)	8.4 (2.1, NR)	2.8 (1.3, 4.1)	6.7 (1.5, NR)	1.4 (1.3, NR)

Note:
[1]Including pts w/o post-baseline scan.

3002 Oral Abstract Session

Phase I study of iza-bren (BL-B01D1), an EGFR x HER3 bispecific antibody-drug conjugate (ADC), in patients with locally advanced or metastatic small cell lung cancer (SCLC). First Author: Yan Huang, Department of Medical Oncology, Sun Yat-Sen University Cancer Center, Guangzhou, China

Background: iza-bren is a first-in-class ADC comprised of an EGFR x HER3 bispecific antibody conjugated to a novel topo-I inhibitor payload (Ed-04) via a stable tetrapeptide-based cleavable linker. Unlike existing ADCs targeting general tumor antigens, iza-bren uniquely targets the EGFR and HER3 pathways, which are implicated in the aggressive biology of SCLC. It has shown promising clinical activity and a manageable safety profile in patients (pts) with advanced or metastatic solid tumors. Results for safety/efficacy from this phase I study in SCLC pts are presented. **Methods:** Pts with locally advanced or metastatic SCLC who had progressed on prior systemic therapies were enrolled and treated at 2.0, 2.5 mg/kg D1D8 Q3W, or 4.5, 5.0 mg/kg D1 Q3W. Tumor scans were done every 6 weeks. Efficacy was evaluated in the overall cohort and specific subgroups, with a particular focus on pts with limited prior treatment exposure. **Results:** As of Dec 5, 2024, a total of 58 SCLC pts were enrolled. All pts who received at least one dose of iza-bren are included in the analysis. The median follow-up was 16.4 mo, ORR was 55.2%, confirmed ORR was 44.8%, median PFS was 4.0 mo, and median OS was 12.0 mo. Among the 52 pts at 2.5 mg/kg, 20 pts received only 1 prior line of PD(L)-1 and PBC combination treatment. In this subgroup, ORR was 80.0%, confirmed ORR was 75.0%, median DOR was 5.6 mo, median PFS was 6.9 mo, and median OS was 15.1 mo. The most frequent hematologic TRAEs (all grades) were anemia (84.5%), leukopenia (74.1%), thrombocytopenia (72.4%), and neutropenia (70.7%); the most frequent non-hematologic TRAEs were asthenia (41.4%), hypoalbuminemia (39.7%), stomatitis (34.5%), nausea (31.0%), and vomiting (31.0%). Grade 3 and above TRAEs which were predominantly hematologic in nature, were able to be effectively managed with standard supportive measure including dose reductions, as demonstrated by the TRAE leading to discontinuation rate of 12.1%. Two infection-related deaths (1 respiratory failure, 1 gastrointestinal infection) associated with iza-bren were reported. No ILD was observed. No new safety signals were identified. **Conclusions:** In SCLC pts, iza-bren has demonstrated an encouraging efficacy with a manageable safety profile. Notably, the high confirmed response rate of 75% in pts with limited prior treatment underscores its potential as a novel therapeutic option for SCLC, a disease with limited therapeutic advancements over decades. The phase III study of iza-bren in SCLC pts who received 1 prior line of PD(L)-1 and PBC combination treatment is ongoing (NCT06500026). Clinical trial information: NCT05194982. Research Sponsor: None.

3003 Oral Abstract Session

Safety and efficacy of TQB2102, a novel bispecific anti-HER2 antibody–drug conjugate, in patients with advanced solid tumors: Preliminary data from the first-in-human phase 1 trial. First Author: Rui-Hua Xu, Department of Medical Oncology, University Cancer Center State Key Laboratory of Oncology in South China, Collaborative Innovation Center of Cancer Medicine, Guangzhou, China

Background: TQB2102 is an antibody-drug conjugate (ADC) comprised of a recombinant, humanized anti-human epidermal growth factor receptor 2 (HER2) bispecific antibody conjugated to a topoisomerase I inhibitor via an enzyme-cleavable linker. The bispecific antibody component can target both extra-cellular domains II (pertuzumab binding site) and IV (trastuzumab binding site) of HER2. We conducted a multicenter, dose escalation and expansion first-in human (FIH) phase 1 study of TQB2102 in advanced solid tumors. **Methods:** In the dose escalation phase, eligible patients (pts) with advanced solid tumors whose disease had progressed after standard systemic treatments, were enrolled in a 3+3 dose escalation study of TQB2102(1.5, 3, 4.5, 6, 7.5 or 9 mg/kg) IV, every 3wks (Q3W). In the dose expansion phase, pts with HER2 positive cancers and HER2 low (HER2 1+ or HER2 2+ and FISH negative) metastatic breast cancer (MBC) received the selected recommended phase 2 dose (RP2D). The primary objectives were to evaluate the safety and tolerability, dose limiting toxicities (DLTs) and maximum tolerated dose (MTD) of TQB2102. **Results:** As of October 1, 2024, 181pts (41 pts in dose escalation phase and 140 pts in dose expansion phase) were enrolled from 12 centers. Most common tumor types included MBC (N = 80), Colorectal cancer (N = 37) and Gastric cancer (N = 23).Twenty-five (31%) MBC received prior anti-HER2 ADCs, including 21 pts received T-DM1, 8 pts received DS-8201.The median duration of follow-up was 8.15 months. TQB2102 was well-tolerated with no DLTs occurred and MTD was not reached. The most common (occurring in ≥5%) grade ≥3 AEs were neutrophil count decrease (21.7%), WBC count decreased (10.6%), anemia (8.9%), platelet count decreased (6.1%), diarrhea (5.0%). Only one patient had grade 2 interstitial lung disease (ILD) until the cutoff date. 6 or 7.5mg/kg was selected for dose expansion. Objective response rate (ORR) per RECIST v1.1 was 41.2% (68 partial responses [PR]) in 165 responses evaluable pts who had ≥1 response assessment. Surprisingly, 7 pts reached PR in 10 HER2+ MBC pts with brain metastases, one of whom the brain metastatic lesions reached complete response after 4 cycles of treatment. This trial is ongoing now. **Conclusions:** TQB2102 is well tolerated with promising anti-tumor activity in pts with HER2-expressing cancer. These early signs of activity support a phase 3 trial in patients with HER2-low MBC that has been initiated (NCT06561607). Clinical trial information: NCT05735496. Research Sponsor: Chia Tai Tianqing Pharmaceutical Group Co., Ltd.

6mg/kg and above	ORR(%)	DCR(%)	6-months PFS rate, (%)
HER2 positive MBC (N=39)	51.3	84.7	87.0
HER2 low MBC (N=33)	51.5	87.9	63.0
HER2 3+ colorectal cancer (N=23)	34.8	87.0	88.4
HER2 positive gastric cancer (N=10)	70.0	90.0	90.0
HER2 positive Other (N=5)	60.0	100.0	NE

3004 **Oral Abstract Session**

Efficacy and safety of the DLL3/CD3 T-cell engager obrixtamig in patients with extrapulmonary neuroendocrine carcinomas with high or low DLL3 expression: Results from an ongoing phase I trial. First Author: Jaume Capdevila, Department of Medical Oncology, Vall d'Hebron University Hospital & Vall d'Hebron Institute of Oncology, Barcelona, Spain

Background: Delta-like ligand 3 (DLL3) is highly expressed in neuroendocrine carcinomas (NEC). Obrixtamig (BI 764532) is a DLL3/CD3 IgG-like T-cell engager that targets DLL3-positive (DLL3+) tumors. NCT04429087 is an ongoing, Phase (Ph) I dose-escalation trial of obrixtamig in patients (pts) with DLL3+ pulmonary and extrapulmonary NEC (epNEC), who had failed to respond to standard treatment (Tx). This analysis examined the efficacy and safety of obrixtamig in pts with epNEC with high vs low DLL3 expression. **Methods:** Obrixtamig was given IV in 4 dose-escalation regimens (R): RA (fixed dose q3w); RB1 (fixed dose qw); RB2 (step-up dose, then qw) and RB3 (step-up dose, then qw for 3 weeks, then q3w), until disease progression or unacceptable toxicity. Efficacy was assessed through objective response rate (ORR) and disease control rate (DCR) using RECIST v1.1. Results are reported for pts who received obrixtamig RB2 or RB3, categorized as having high vs low DLL3, using a threshold of ≥50% of tumor cells stained with an investigational antibody for DLL3 (SP347, Roche Diagnostics). **Results:** As of June 21, 2024, 60 pts with epNEC were included (gastroenteropancreatic [GEP]: 45.0%, genitourinary [GU]: 30.0%, other/unknown primary site: 25.0%); 30 each DLL3-high and DLL3-low. Mean age: 63.9 years in DLL3-high; 59.1 in DLL3-low pts. Baseline characteristics were well-balanced across DLL3 groups. All pts had received prior systemic therapy; 30.0% of DLL3-high and 50.0% of DLL3-low pts had received > 2 lines of prior Tx. Efficacy data are shown in the Table. After obrixtamig Tx, pts with high DLL3 expression had greater ORR, DCR, and duration of response (DoR) than DLL3-low pts. Responses were seen most frequently amongst pts with DLL3-high GEP (50.0%) or GU (60.0%) epNECs. Seven DLL3-high pts are still receiving Tx. Most treatment-related AEs (TRAEs) were mild to moderate for both groups (Table). **Conclusions:** Analyses from this ongoing Ph I study show greater obrixtamig efficacy in patients with epNEC with high DLL3 expression compared with low DLL3 expression, with a manageable safety profile that is comparable across both groups. The ORR of 40.0% and median DoR of 7.9 months in heavily pretreated epNEC tumors with DLL3 high expression are encouraging, and support further development of obrixtamig for this subgroup. Clinical trial information: NCT04429087. Research Sponsor: Boehringer Ingelheim.

Efficacy/safety parameter	DLL3-high (n=30)	DLL3-low (n=30)
ORR, % (95% CI)	40.0 (24.6–57.7)	3.3 (0.6–16.7)
DCR, % (95% CI)	66.7 (48.8–80.8)	26.7 (14.2–44.4)
Median DoR (95% CI), months	7.9 (6.2–NC)	2.8 (NC–NC)
TRAEs, all G/G ≥3, (%)	100.0/23.3	90.0/20.0
Cytokine release syndrome, all G/G ≥3, (%)	70.0/3.3	60.0/3.3
Neurotoxicity, including immune effector cell-associated neurotoxicity syndrome*, all G/G ≥3, (%)	16.7/6.7	10.0/3.3

*Evaluated with a customised MedDRA query.
CI, confidence interval; NC, not calculable.

3005 **Oral Abstract Session**

[^{212}Pb]VMT-α-NET therapy in somatostatin receptor 2 (SSTR2) expressing neuroendocrine tumors (NETs): Dose-limiting toxicity (DLT) observation participants after 1 year follow-up and preliminary report for expansion participants. First Author: Thorvardur Ragnar Halfdanarson, Mayo Clinic Comprehensive Cancer Center, Rochester, MN

Background: [^{212}Pb]VMT-α-NET, a next generation ^{212}Pb-based, SSTR2-targeted alpha-particle radiopharmaceutical therapy (RPT), was designed to achieve superior biodistribution via optimized tumor uptake and retention and rapid renal clearance. Results reported here are from the Phase 1/2a first-in-human study [NCT05636618]. **Methods:** Safety, pharmacokinetics, dosimetry and efficacy using RECIST v1.1 were investigated in the treatment of participants with [^{212}Pb]VMT-α-NET who had SSTR2-expressing, well-differentiated adult NETs of any grade. Participants received ≥1 prior therapy. No prior peptide receptor radionuclide therapy was allowed. The trial has multiple dose cohorts including 92.5 MBq (2.5 mCi, cohort 1) and 185 MBq (5 mCi, cohort 2) of administered activity based on a Bayesian modified toxicity probability interval (mTPI-2) design. Up to 8 participants per cohort were treated with 4 doses of [^{212}Pb]VMT-α-NET for DLT observation. Cohort 2 enrollment was expanded to further define the safety and efficacy profile at this dose level. **Results:** Nine (9) gastroenteropancreatic NET participants were enrolled into cohorts 1 and 2 for DLT observation. The ninth of these participants was enrolled more than 1 year prior to presentation of these data. Among these participants at the time of abstract submission, no DLTs were observed, and there were no grade 4, 5 or serious adverse events (SAEs). Specifically, no renal insufficiency or dysphagia were observed. Hematologic AEs were low grade and few in number. No treatment discontinuations due to AE occurred. Three (3) of the 7 cohort 2 participants enrolled for DLT observation achieved investigator-assessed partial responses (PRs). Two PRs were unconfirmed at the time of abstract submission. Durable progression-free survival (PFS) was consistently observed. More than 15 additional participants were enrolled in the cohort 2 expansion. Preliminary data for these patients will be reported at the congress. **Conclusions:** [^{212}Pb]VMT-α-NET is a well-tolerated, next generation RPT showing signs of clinical activity at early dose-levels in this phase 1/2a study. Based on these clinical data, further dose-escalation and development of this promising therapy are warranted. Clinical trial information: NCT05636618. Research Sponsor: Perspective Therapeutics, Inc.

3006 **Oral Abstract Session**

Comprehensive genomic profiling of matched ctDNA and tissue from patients with less common cancers enrolled in but not eligible for a treatment arm of the NCI-MATCH trial. First Author: Biswajit Das, Frederick National Laboratory for Cancer Research, Frederick, MD

Background: During NCI-MATCH (NCT02465060) clinical trial screening, 5961 advanced cancer patients underwent next-generation sequencing to assess eligibility. About 60% of these patients had less common tumors (i.e., cancers other than colon, rectal, breast, non-small cell lung, or prostate). Most patients lacked a study eligible mutation of interest (MOI) and thus didn't receive a trial therapy. Analysis of plasma samples from these patients may illuminate circulating tumor DNA (ctDNA) profiles, potentially guiding ctDNA testing for clinically relevant mutations in less common cancer types. Here we report the molecular profiles of ctDNA and matched tumor from a subset of the NCI-MATCH screened patients. **Methods:** Comprehensive genomic profiling of ctDNA (from blood collected at enrollment) was performed using the TSO500 ctDNA v2 assay (523-genes) and sequenced on the Illumina NovaSeq 6000. Matched tumor was sequenced with the Oncomine Comprehensive Assay v2, a 143-gene panel. Positive percent agreement (PPA) between mutations of interest (MOI) identified in plasma ctDNA and tissue-based screening was calculated with tumor tissue as referent (PPA_{ref_tumor}). **Results:** We tested 2253 patients from the less common tumor cohort. 2194 samples were evaluable with 98.6% pass and 1.4% failure rates. A subset of five tumor histologies with larger representation (n > 35) in sample size were further analyzed: cholangiocarcinoma (CCA, n = 90), small cell lung cancer (SCLC, n = 59), adenocarcinoma of the esophagus (EAC, n = 37), adenocarcinoma of the pancreas (PDAC, n = 232), and salivary gland cancer (SGC, n = 47). Overall, $PPA_{ref\ tumor}$ was 83.4% (range: 76.5%-97.9%) in these five histologies. In patients with concordance < 75%, median tumor fraction (as determined by maximum somatic allele frequency) was much lower (0.37%) than for specimens with concordance > = 75% (6.49%). The most frequently mutated genes identified in CCA were *TP53*, *KRAS*, and *IDH1*; in SCLC were *TP53* and *RB1* loss; in EAC were *TP53*, *KRAS, and ERRB2* amplification; in PDAC were *TP53* and *KRAS*; and in SGC was *TP53*. Additionally, there were several clinically relevant mutations detected only in ctDNA such as *IDH1* for CCA; and *BRAF*, *TP53*, and *PIK3CA* in several histologies. Microsatellite instability, as measured only in ctDNA, was most prevalent in SCLC, followed by CCA. **Conclusions:** Concordance of rare tumors in the NCI-MATCH trial is 83.4% in the representative histologies analyzed, which is similar to concordance of clinically relevant MOIs in common cancer studies. Liquid biopsy may be a viable screening option for matching targeted therapies in clinical trials, especially when a tumor biopsy is not practical or evaluable. The detection of some mutations in ctDNA only may suggest the presence of tumor heterogeneity in multiple lesions in patients with less common cancers. Research Sponsor: National Cancer Institute, National Institutes of Health; Illumina Inc.

3007 **Oral Abstract Session**

Ultra-sensitive pan-cancer molecular residual disease assessment using whole-genome sequencing-based personalized ctDNA panel: Initial results from the MONSTAR-SCREEN-3 project. First Author: Tadayoshi Hashimoto, Department of Gastroenterology and Gastrointestinal Oncology, National Cancer Center Hospital East, Kashiwa, Japan

Background: While circulating tumor DNA (ctDNA) demonstrates promise as a molecular residual disease (MRD) biomarker, its clinical implementation has been primarily limited to tumors with favorable ctDNA shedding characteristics. We are evaluating an ultra-sensitive whole-genome sequencing (WGS)-based MRD assay in the MONSTAR-SCREEN-3 study to establish a comprehensive pan-cancer MRD platform inclusive of traditionally low-shedding tumors. **Methods:** MONSTAR-SCREEN-3, a prospective multicenter study targeting 1,100 patients with solid tumors undergoing curative-intent treatment in the definitive cohort, utilizes personalized panels constructed via Precise MRD (Myriad Genetics). These panels incorporate up to 1,000 tumor-specific alterations identified through WGS of matched tumor tissue, including both short variants and insertion-deletions. Serial plasma samples were collected at baseline, post-neoadjuvant chemotherapy (when applicable), 1-month post-surgery, quarterly in year 1, and biannually thereafter up to 2 years. The assay performance was evaluated across multiple cancer types for ctDNA detection and recurrence monitoring. **Results:** As of December 2024, 114 patients across 15 cancer types were enrolled, including colorectal (n = 33), gastric (n = 22), head and neck (n = 13), renal cell (n = 10), esophageal (n = 8), and pancreatic (n = 7) cancers. Treatment strategies included upfront surgery (n = 76) and neoadjuvant chemotherapy (n = 38). The median follow-up time was 2.4 months (range, 0.5–7.7). WGS analysis identified a median of 6,089 panel-eligible alterations per patient (range: 214-14,112), with high variants counts observed in a deficient mismatch-repair colorectal cancer, enabling comprehensive personalized panel design. Customized panel creation was successful in 69/71 patients (97.2%) across 8 cancer types, with two pancreatic cancer cases deferred to surgical specimens due to insufficient variants in FNA samples. The assay demonstrated 100% baseline sensitivity (41/41), detecting tumor fractions ranging from < 0.001% to 45.2% across all cancer types, including traditionally low-shedding tumors. Post-operative 1-month MRD assessment revealed 35.7% positivity (10/28), with tumor fractions ranging from < 0.001% to 0.27%. Two MRD-positive patients developed radiological recurrence with lead times of 2.5 and 3 months before conventional imaging detection. **Conclusions:** These interim results demonstrate successful pan-cancer implementation of WGS-based personalized ctDNA detection, achieving universal baseline sensitivity and ultra-sensitive MRD detection across tumor types, including those traditionally challenging to assess. Updated molecular and clinical outcome data will be presented. Clinical trial information: UMIN000053975. Research Sponsor: SCRUM-Japan Funds (http:// www. scrum -japan. ncc. go. jp/ index. html); Myriad Genetics.

3008 Oral Abstract Session

Circulating tumor DNA (ctDNA) in patients with stage 2/3 HR+HER2- negative breast cancer (BC) treated with neoadjuvant endocrine therapy (NET) in the I-SPY2 endocrine optimization pilot (EOP) trial. First Author: Silver Alkhafaji, University of California, San Francisco, San Francisco, CA

Background: Numerous studies have demonstrated the prognostic value of ctDNA analysis after neoadjuvant chemotherapy for early-stage high-risk breast cancer. Few studies have characterized ctDNA in pts receiving NET for early-stage hormone receptor positive (HR+)/HER2- BC that is predicted to benefit less from chemotherapy. **Methods:** Cell-free DNA (cfDNA) was isolated from 432 plasma samples from 108 pts enrolled in the I-SPY2 EOP trial. Pts had Stage 2/3 HR+/HER2-, MammaPrint low or high risk 1 BC. Pts were randomized to one of 7 neoadjuvant-based treatment arms including arms containing AI, Z-endoxifen, Lasofoxifene, vepdegestrant (ARV-471), and Abemaciclib. Pts were treated for 6 months prior to surgery. Blood was collected at baseline (T0), 3 weeks (T1), 12 weeks (T2), and 6 months (T3). A personalized ctDNA test (Signatera) was designed to detect up to 16 patient-specific mutations (from whole-exome sequencing of pretreatment tumor) in cfDNA by ultra-deep sequencing. The chi-square test was used to assess associations between categorical variables, and the Wilcoxon rank-sum test was used to evaluate differences in medians. **Results:** ctDNA information was available for 101 patients at baseline (T0) (Table 1). At T0, 36 (35.6%) patients were ctDNA-positive. 23/36 (63.9%) became ctDNA-negative and 13/36 (36.1%) remained ctDNA-positive. At T0, 65/101 patients (64.4%) were ctDNA-negative. Of these, 57 (87.7%) remained negative, while 8 (12.3%) became ctDNA-positive at T1 before reverting to ctDNA-negative. A higher percentage of ctDNA-positive patients at T0 were cN+ compared to ctDNA-negative pts (p = 0.036, 64% vs. 40%). Additionally, ctDNA-positivity at T0 was strongly associated with higher Ki67 (p = 0.03) and larger functional tumor volume by MRI at baseline (p = 0.03). T3/T4 and high-grade tumors at baseline were also associated with having ctDNA positivity at baseline, though this was not statistically significant (p = 0.34 and 0.058, respectively). **Conclusions:** In this study of pts with Stage 2/3 HR+ HER2- BC with largely MammaPrint low risk signatures, over one-third of pts had detectable ctDNA at baseline. Detectable ctDNA at baseline was associated with cN+ disease, larger FTV, and high baseline Ki67. The majority of pts with positive ctDNA at baseline cleared the ctDNA on NET. Clinical trial information: NCT01042379. Research Sponsor: NIH/NCI ctDNA/MR; Breast Cancer Research Foundation; Give Breast Cancer the Boot; Quantum Leap Healthcare Collaborative.

Clinicopathologic characteristics of EOP patients.

	All Patients (N=101)
Age at screening	55 (27-80) years*
Clinical N Stage	
Node+ (cN+)	49 (48.5%)
Node- (cN-)	52 (51.5%)
SET status	
High	84 (83.2%)
Low	14 (13.9%)
Missing	3 (2.97%)
MammaPrint (MP) risk**	
High risk 1 (H1)	15 (14.9%)
Low risk	86 (85.1%)

*Mean(min-max).
**H1: MP score between 0 and -0.57; low: MP score between 0 and 0.355.

3009 Rapid Oral Abstract Session

Initial phase 1 dose escalation data for emiltatug ledadotin (Emi-Le), a novel B7-H4-directed dolasynthen antibody-drug conjugate. First Author: Erika P. Hamilton, Breast Cancer Research Program, Sarah Cannon Research Institute, Nashville, TN

Background: B7-H4 is a transmembrane protein over-expressed in breast (BC), ovarian (OC), endometrial (EC), and adenoid cystic carcinoma type 1 (ACC-1) cancers, with limited expression in healthy tissues. Emi-Le (XMT-1660) is a B7-H4-directed Dolasynthen ADC designed with a proprietary auristatin F-HPA microtubule inhibitor payload with controlled bystander effect. **Methods:** The Phase 1 trial is investigating Emi-Le monotherapy in adult patients (pts) with advanced/metastatic TNBC, HR+/HER2- BC, OC, EC and ACC-1. In dose escalation, eligible pts received Emi-Le at doses of 7.2-115 mg/m2 per cycle, with all collected data informing the recommended doses for the expansion (EXP) portion of the trial. Tumors were evaluated retrospectively for B7-H4 expression by IHC, with the preliminary high cutoff set at TPS≥70. **Results:** As of December 13, 2024, 130 pts were dosed. Across all tumor types, median age of pts was 55; median 4.5 prior lines of therapy (range 0-15). B7-H4 status was evaluated for 103 pts, with 44% determined to be B7-H4 TPS high. Overall, Emi-Le was generally well tolerated. The most common TRAEs were transient AST increase (38%, G3 14%), proteinuria (31%, G3 9%), nausea (29%, G3 1%) and fatigue (28%, G3 0%). The only G3 TRAEs in ≥5% of pts were AST increase and proteinuria. No G4 or 5 TRAEs were reported. No observed dose-limiting treatment-related neutropenia, neuropathy, ocular toxicity, interstitial lung disease or thrombocytopenia. TRAEs leading to discontinuation were observed in 2.3% of pts. Clinical activity was correlated with both dose and B7-H4 expression. For pts treated with doses ranging from 38.1–67.4 mg/m2 per cycle (intermediate dose range), the confirmed ORR in evaluable pts with high B7-H4 expression was 23% (6/26), including a 23% (3/13) confirmed ORR in evaluable pts with TNBC, with all 13 pts having previously received at least one topoisomerase-1 inhibitor (topo-1) ADC. At doses ≥76.2 mg/m2 per cycle (high dose range), the confirmed ORR in evaluable pts with high B7-H4 expression was 22% (2/9), with 78% (7/9) having ≥30% reduction in target lesions. Of the 8 pts with confirmed responses at doses ≥38.1 mg/m2, 5 had reduction in target lesions > 60%, including 1 CR. All 4 pts with high B7-H4 expression treated at the initial EXP dose of 67.4mg/m2 Q4W had tumor reductions and were on treatment with durations of ≥16 weeks as of data cutoff. **Conclusions:** Based on the initial reported data, Emi-Le appears to have encouraging clinical activity and tolerability in a heavily pretreated population. Further clinical development is ongoing in the EXP portion of the trial at a dose of 67.4 mg/m2 Q4W in pts with advanced/metastatic TNBC who have received 1-4 prior lines of systemic therapy, including at least one topo-1 ADC. Dose exploration is ongoing to identify a potential second higher EXP dose. Clinical trial information: NCT05377996. Research Sponsor: Mersana Therapeutics.

3010 Rapid Oral Abstract Session

Sigvotatug vedotin (SV), an investigational integrin beta-6 (IB6)–directed antibody–drug conjugate (ADC), and pembrolizumab combination therapy: Initial results from an ongoing phase 1 study (SGNB6A-001). First Author: Kartik Sehgal, Dana-Farber Cancer Institute, Boston, MA

Background: IB6, a tumor-associated membrane protein, is overexpressed in many solid tumors, including non-small cell lung cancer (NSCLC) and head and neck squamous cell carcinoma (HNSCC). SV, an IB6-directed ADC, demonstrated encouraging antitumor activity and manageable safety as a monotherapy in patients (pts) with advanced NSCLC in SGNB6A-001, an ongoing phase 1 study (Peters, ASCO 2024). Due to immunogenic cell death induction and innate immune system activation, SV activity may be enhanced when combined with pembrolizumab (P; SV+P). We report initial results of SV+P in pts with advanced solid tumors. **Methods:** SGNB6A-001 (NCT04389632) is an open-label, multicenter, dose-escalation and dose-expansion phase 1 study evaluating the safety, pharmacokinetics (PK), and antitumor activity of SV. Part C is evaluating safety of SV+P in pts with advanced solid tumors; part D is currently enrolling to evaluate SV+P in treatment-naive pts with locally advanced, unresectable, or metastatic NSCLC and HNSCC. Pts receive SV 1.8 mg/kg by adjusted ideal body weight IV Q2W and P 400 mg IV Q6W. Primary endpoint is safety; secondary endpoints include efficacy and PK. Results reported here are from parts C and D. **Results:** As of Nov 26, 2024, 31 pts received ≥1 dose of SV+P in parts C and D (19 NSCLC, 11 HNSCC, and 1 esophageal); median (95% CI) follow-up was 2.9 (1.6-5.0) months, and 26 pts remain on treatment. Median (range) age was 65 (34-80) years, 61% were male, and 52% had ECOG PS 0. Of pts with NSCLC, 12 (63%) had non-squamous tumors and 11 (58%) had tumors with PD-L1 TPS ≥1. All pts with HNSCC had tumors with PD-L1 CPS ≥1. Any-grade (Gr) and Gr ≥3 treatment-emergent adverse events (TEAEs) occurred in 87% and 35% of pts, respectively. Most common TEAEs are shown in the Table. Any-Gr and Gr ≥3 immune-mediated TEAEs occurred in 61% and 10% of pts, respectively. Pneumonitis/interstitial lung disease occurred in 3 pts (9.7%), with no Gr ≥3 events. Renal TEAEs led to discontinuation of both SV and P in 2 pts (6%); 3 other pts discontinued treatment (1 progressive disease, 2 consent withdrawal). There were no treatment-related deaths. In 7 efficacy-evaluable pts with TPS≥1 NSCLC, 1 confirmed (c) complete response (CR), 1 c partial response (PR), and 2 PRs pending confirmation were observed (ORR 57%; cORR 29%). In 8 efficacy-evaluable pts with 1L HNSCC, 2 cCR and 1 cPR were observed (cORR 37.5%). **Conclusions:** SV+P demonstrated manageable safety and encouraging preliminary efficacy. These data support the ongoing phase 3 Be6A-Lung-02 study (NCT06758401) comparing SV+P vs P as first-line treatment for pts with PD-L1 high (TPS≥50) advanced NSCLC. Clinical trial information: NCT04389632. Research Sponsor: Seagen, which was acquired by Pfizer in December 2023.

	All Treated Pts (n=31)	
TEAEs	**Any Gr (>25%) n (%)**	**Gr ≥3 n (%)**
Fatigue	13 (42)	1 (3)
Decreased appetite	13 (42)	3 (10)
Nausea	12 (39)	0
Alopecia	11 (35)	0
Asthenia	9 (29)	2 (6)
Decreased weight	8 (26)	0
Dysgeusia	8 (26)	0

3011 Rapid Oral Abstract Session

BMS-986504 in patients (pts) with advanced solid tumors with homozygous *MTAP* deletion (*MTAP*-del): Clinical update and first report of pharmacokinetics (PK) and pharmacodynamic (PD) analyses from CA240-0007. First Author: Kathryn C. Arbour, Memorial Sloan Kettering Cancer Center, New York, NY

Background: BMS-986504 selectively binds to the PRMT5-MTA complex, which represents a synthetic lethal target in *MTAP*-del cancer cells, while sparing *MTAP*–wild-type cells. In the first-in-human phase 1/2 CA240-0007 study in advanced, unresectable or metastatic solid tumors with homozygous *MTAP*-del, BMS-986504 was found to be well tolerated and demonstrated antitumor activity in multiple tumors. Here, we report clinical results and the first PK and PD analyses of BMS-986504 from the dose escalation and expansion phases of CA240-0007. **Methods:** Pts with measurable/evaluable disease and no available treatment (Tx) with curative intent were enrolled; 7 doses were evaluated (50 to 800 mg) in dose escalation. Objective response rate (ORR), disease control rate (DCR), duration of response (DOR), time to response (TTR), safety, PK, PD, including plasma SDMA were assessed. **Results:** As of 2 Dec 24, 152 heavily pretreated pts were enrolled across all doses: NSCLC (n = 34), PDAC (n = 41), cholangiocarcinoma (n = 12), and mesothelioma (n = 12) were the most common tumor types. With a median f/u of 9.0 mo (95% CI 7.6–9.9), continued durable antitumor activity and deepening tumor regression were seen across tumor types and doses (ORR = 23%, DCR = 70%, median DOR = 10.5 mo, TTR = 4.6 mo). No new safety signals were identified. Most Tx-related adverse events (TRAEs) were grade (Gr) 1 or 2; 13% had Gr ≥ 3 TRAEs (Gr 3 = 12%, Gr 4 = < 1%, Gr 5 = 0). Doses from 50 to 600 mg QD were assessed for PK/PD. The $AUC_{(0\text{-}24)}$ after multiple doses was approximately dose proportional at 200 to 600 mg, and the terminal $t_{1/2}$ after a single dose was approximately 24 h (table). There were dose-dependent reductions in predicted plasma SDMA, with the 400 and 600 mg doses approaching the plateau. **Conclusions:** With longer f/u, BMS-986504 continued to show increasingly durable antitumor activity. BMS-986504 demonstrated a favorable PK/PD profile, supporting QD dosing at 400 and 600 mg. These results support further investigation of BMS-986504 at 400 and 600 mg QD as a potential first-in-class synthetic lethal Tx option in pts with advanced solid tumors with *MTAP*-del. Clinical trial information: NCT05245500. Research Sponsor: Bristol Myers Squibb.

PK and PD.

	50 mg QD	100 mg QD	200 mg QD	400 mg QD	600 mg QD
PK after multiple doses					
t^{a}_{max} (min–max), h	2.0 (2.0–4.0)	2.0 (1.0–2.0)	2.0 (0.5–6.0)	2.0 (0.5–4.0)	2.0 (1.0–6.0)
	n = 3	n = 3	n = 8	n = 10	n = 10
C_{max},[b] ng/mL	107	377	685	1240	2110
	n = 3	n = 3	n = 8	n = 10	n = 10
$AUC_{(0\text{-}24)}$,[b] h•ng/mL	948	3060	7150	11,800	26,700
	n = 3	n = 3	n = 7	n = 10	n = 9
$AUC_{(0\text{-}24)}$,[b,c] h•ng/mL/mg	19.0	30.6	35.8	29.5	44.6
	n = 3	n = 3	n = 7	n = 10	n = 9
Terminal $t_{1/2}$ after single dose,[d] h	21.7	80.7	21.5	21.7	24.1
	n = 1	n = 1	n = 14	n = 14	n = 1
PD					
Translational exposure targets (C_{avgss}), X	0.08	0.21	0.5	1.1	1.7
Predicted plasma SDMA reduction,[a] % (90% PI)	30.0 (23.2–37.8)	38.8 (27.1–47.5)	48.3 (42.0–53.0)	55.0 (50.7–57.6)	57.4 (54.3–59.0)

[a]Median. [b]Geometric mean. [c]Dose-normalized. [d]Arithmetic mean.

3012 Rapid Oral Abstract Session

Preliminary results from a first-in-human, phase I/II study of VLS-1488, an oral KIF18A inhibitor, in patients with advanced solid tumors. First Author: Ecaterina Elena Dumbrava, The University of Texas MD Anderson Cancer Center, Houston, TX

Background: VLS-1488 is an oral small molecule inhibitor of KIF18A, a mitotic kinesin protein important for successful division of cancer cells with chromosomal instability (CIN) but not required for mitosis in normal cells. Preclinical studies of VLS-1488 showed dose-dependent inhibition of tumor growth in CIN models. **Methods:** VLS-1488-2201 is a phase I/II study of patients (pts) with advanced solid tumors consisting of two parts, Dose Escalation and Dose Expansion. During Dose Escalation, a Bayesian Optimal Interval design was utilized to enroll pts to dose escalation cohorts with additional pts enrolled to backfill cohorts at dose levels (DLs) that did not meet de-escalation/elimination rules. Primary objective was to assess safety/tolerability of VLS-1488 at various DLs to determine the Maximum Tolerated Dose (MTD). Secondary objectives included evaluating preliminary efficacy and pharmacokinetics (PK). Eligible pts had exhausted standard of care treatments and had measurable disease per RECIST v1.1. Pts received VLS-1488 once daily, orally for 28-day cycles until disease progression, unacceptable toxicity or other stopping criteria. **Results:** 52 pts (ITT) were enrolled across 5 DLs including 50mg (n = 4), 100mg (n = 12), 200mg (n = 14), 400mg (n = 12) and 800mg (n = 10). Tumor types were high grade serous ovarian (HGSOC; n = 20), colorectal (n = 14), triple negative breast (n = 7), squamous lung (n = 3), endometrial (n = 3), ovarian carcinosarcoma (n = 2), esophageal (n = 2) and bladder (n = 1). The median number of prior lines was 4 (range 1-8). As of data cutoff, 52 pts (100%) received >1 dose of VLS-1488. No dose-limiting toxicities (as assessed during the first 28 days) were observed and MTD was not reached. Treatment-related AEs (TRAEs) occurred in 22 pts (42%), with fatigue (17.3%; G1 13.5%, G2 3.8%), aspartate aminotransferase increased (13.5%; G1 7.7%, G2 1.9%, G3 3.8%) and rash (11.5%; G1 3.8%, G2 1.9%, G3 5.8%) observed in >10% of pts. 6 pts (12%) experienced G3 TRAEs and no > G3 TRAEs were observed. Drug exposures exceeded preclinically defined efficacious thresholds and were approximately dose proportional at analyzed DLs. 41 pts (79%) were evaluable for response per RECIST v1.1. In the 16 HGSOC pts evaluable for response (where the median number of prior lines was 4.5; range 2-8), 3 partial responses (PRs; including 2 pts with sustained PR >24 weeks) and 6 with stable disease (SD; including 4 pts with tumor reductions) were observed across multiple DLs, with 5 pts continuing with study treatment. **Conclusions:** VLS-1488 was found to be safe and tolerable, with encouraging anti-tumor activity observed in heavily treated HGSOC pts. VLS-1488 will be evaluated further in the Dose Expansion phase of the study. Clinical trial information: NCT05902988. Research Sponsor: Volastra Therapeutics, Inc.

3013 Rapid Oral Abstract Session

A first-in-human phase I/II study of GFH375, a highly selective and potent oral KRAS G12D inhibitor in patients with KRAS G12D mutant advanced solid tumors. First Author: Xinghao Ai, Department of Medical Oncology, Shanghai Chest Hospital, School of Medicine, Shanghai Jiao Tong University, Shanghai, China

Background: Kirsten rat sarcoma (KRAS) G12D is one of the most prevalent RAS mutations in human cancers and suggests poor survival. GFH375 is an orally bioavailable, highly selective and potent KRAS G12D inhibitor targeting both "ON" (GTP-bound) and "OFF" (GDP-bound) states. Here we report the preliminary results of GFH375 in patients (pts) with advanced KRAS G12D mutant solid tumors. **Methods:** This is a Phase I/II study (NCT06500676) evaluating the safety, tolerability, pharmacokinetics and efficacy of GFH375 in pts with advanced solid tumors harboring KRAS G12D mutation. Pts with locally advanced or metastatic solid tumor failed to prior standard therapies are eligible for enrollment. Accelerated titration, plus Bayesian Optimal Interval (BOIN) and back filling design are employed in the phase I part with safety and tolerability as the primary objective, and pharmacokinetics and anti-tumor activity as the secondary objectives. **Results:** As of 03Jan2025, thirty-two pts were treated, including 11 pancreatic ductal adenocarcinoma (PDAC), 11 non-small cell lung cancer (NSCLC), 5 colorectal cancer (CRC) and 5 others (median age: 59.5 yrs; 62.5% female). No dose-limiting toxicities (DLTs) were observed at the tested dose levels of 100 mg, 200 mg, 400 mg, 600 mg, 750 mg, 900 mg once daily (QD) and 300 mg twice daily (BID). Eight pts (25%) experienced at least one G3/G4 treatment related adverse event (TRAE) and no G5 TRAEs. Five pts (15.6%) experienced at least one serious adverse event. Eight pts (25%) had treatment interruptions, and 2 (6.3%) discontinued treatment due to treatment emergent adverse events (TEAEs). No dose reduction occurred. The most common TRAEs were gastrointestinal events including diarrhea (71.9%), vomiting (71.9%) and nausea (62.5%); all were grade 1 or 2. Anti-tumor activities were observed starting from 100 mg QD. Among 22 pts who had at least one post-treatment tumor assessment, objective response rate (ORR) was 27.3% (6/22), and disease control rate (DCR) was 86.4% (19/22). Nine out of 13 pts with stable disease (SD) had tumor shrinkage. Among the 7 pts with PDAC, all exhibited tumor shrinkage with 3 partial response (PR) and 4 SD. Among the 9 pts with NSCLC, 3 achieved PR, 5 SD, and 1 progression disease (PD). GFH375 demonstrated good oral bioavailability with a T_{max} of 2~4 h and a terminal half-life of 18.5-21.6 h. **Conclusions:** According to the preliminary data from ongoing FIH study, GFH375 monotherapy has demonstrated good tolerability and promising anti-tumor activities in pts with advanced solid tumor supporting further clinical development. Clinical trial information: NCT06500676. Research Sponsor: GenFleet Therapeutics (Shanghai) Inc.

3014 Rapid Oral Abstract Session

Efficacy and safety of selumetinib in adults with neurofibromatosis type 1 (NF1) and symptomatic, inoperable plexiform neurofibroma (PN): Primary analysis of KOMET (NCT04924608), a phase 3, international, randomized, placebo-controlled study. First Author: Alice P. Chen, Developmental Therapeutics Clinic, Division of Cancer Treatment and Diagnosis, National Cancer Institute, National Institutes of Health, Bethesda, MD

Background: No globally approved therapies exist for adults with NF1 and symptomatic, inoperable PN.KOMET is evaluating the efficacy and safety of selumetinib (SELU; ARRY-142886, AZD6244) in adults. **Methods:** KOMET is an ongoingPhase 3, randomized, double-blind, placebo-controlled trial. Adults (≥18 yrs) with NF1 and symptomatic, inoperable PN were randomized 1:1 to 28-day cycles of oral SELU 25 mg/m^2 BID or placebo (PBO) with crossover to SELU at progression or the end of Cycle (C) 12. Among others, baseline (BL) PAINS-pNF target PN chronic pain intensity score (< 3 or ≥3) was a stratification factor; 70% of patients (pts) were required to have a score ≥3. Primary analyses were conducted after the last pt completed C16 (data cutoff: Aug 5, 2024). The primary endpoint was objective response rate (ORR; confirmed partial/complete response) per ICR REiNS by the end of C16. Key secondary endpoints were change from BL to C12 in PAINS-pNF chronic pain score in pts with a BL score ≥3 and PlexiQoL total score in all randomized pts (SELU vs PBO). A planned sample of 73 pts per arm with a 2-sided 5% alpha Fisher's exact test had > 99% power to detect the difference between a SELU ORR of 20% and PBO ORR of 0%. Key secondary endpoints were analyzed with a mixed model for repeated measures. **Results:** Of 145 randomized pts (SELU: 71; PBO: 74), 51.7% were male; median age was 29 yrs (range 18–60). SELU led to a rapid onset of response (median 3.7 mos), with an ORR of 19.7% (95% CI 11.2, 30.9) by C16 vs 5.4% (95% CI 1.5, 13.3) with PBO (p = 0.011). At C12, pts with a BL chronic pain score ≥3 had a greater reduction in pain score with SELU (LS mean −2.0; 95% CI −2.6, −1.4) vs PBO (LS mean −1.3; 95% CI −1.8, −0.7); and clinically meaningful improvement (meaningful score difference −2 points) vs BL, but this was not statistically significant vs PBO (p = 0.070). Reduction in chronic pain intensity was observed with SELU vs PBO in the full analysis set (all pts regardless of BL chronic pain intensity, nominal p = 0.024). Change from BL to C12 in PlexiQoL total score between treatment arms was not statistically significant (LS mean difference −0.1; 95% CI −1.2, 1.1). Adverse events (AEs) in the randomized period were consistent with the known safety profile of SELU. The most common AEs (≥10% of pts) were dermatitis acneiform (59%), increased blood creatine phosphokinase (45%), and diarrhea (42%) with SELU, and COVID-19 (20%), nausea (16%), and fatigue (14%) with PBO. Fourteen pts on SELU and 1 pt on PBO reported CTCAE Grade ≥3 treatment-related AEs; 9 SELU and 5 PBO pts discontinued due to AEs. **Conclusions:** In the first international, randomized, placebo-controlled trial in adults with NF1-PN, SELU achieved a significant ORR vs PBO (C16), meeting the primary endpoint, and a clinically meaningful reduction in PN-associated chronic pain (C12). Clinical trial information: NCT04924608. Research Sponsor: Alexion, AstraZeneca Rare Disease and Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA.

3015 Rapid Oral Abstract Session

Phase 2 evaluation of the nilotinib-paclitaxel combination in patients with rare solid tumors: Rapid analysis and response evaluation of combination anti-neoplastic agents in rare tumors trial 1 (RARE CANCER 1). First Author: Sarah Shin, Developmental Therapeutics Clinic/Early Clinical Trials Development Program, Division of Cancer Treatment and Diagnosis, National Cancer Institute, Bethesda, MD

Background: Rare tumors constitute a heterogeneous group of cancers with limited treatment options and poor outcomes. To address the need for novel therapeutic options in this challenging population, patient-derived xenograft models of rare cancers were developed to screen combinations of anticancer agents. Based on these preclinical data, the NCI Developmental Therapeutics Clinic designed a series of phase 2 clinical trials to assess promising novel combination therapies in patients (pts) with rare tumors. RARE1—the first trial in this series—evaluates the nilotinib-paclitaxel combination, for which a preceding phase 1 study (NCT02379416) recently identified the recommended phase 2 dose (RP2D) and promising clinical activity, including confirmed partial responses (PR) in 3 pts (2 adult granulosa cell ovarian tumors [AGCOT], 1 endometrial cancer) and 1 unconfirmed PR (anal cancer). Given this clinical experience and preclinical activity in rare tumor models, RARE1 (NCT04449549) aims to evaluate the response and mechanism of action of the nilotinib and paclitaxel combination in rare, refractory solid tumors. **Methods:** Pts with rare tumors meeting the RARECARE definition were treated at the RP2D: nilotinib 300 mg orally twice a day and paclitaxel 80 mg/m^2 IV on days 1, 8, and 15 in 28-day cycles. Response was assessed by RECIST v1.1. Tissue biopsies and research blood were collected at multiple timepoints for pharmacodynamic and genomic analyses. **Results:** This study enrolled 31 pts of diverse rare cancers as of the data cut-off. Of the 30 evaluable pts, 2 (7%) had confirmed PRs: 1 Ewing sarcoma and 1 ovarian clear cell cancer, completing 12 and 11 cycles (C) on study, respectively. Stable disease (SD) was the best response in 15 pts (50%), of which 5 pts (17%) had prolonged SD: 1 AGCOT (23+ C), 1 testicular embryonal rhabdomyosarcoma (22 C), 1 non-uterine leiomyosarcoma (21 C), 1 salivary gland (12 C), and 1 ampullary adenocarcinoma (6 C). Overall, the median number of cycles completed is 2 (range 0 - 23) and the median progression free survival is 3.8 months. No unexpected treatment-related adverse events have occurred. No grade 3-4 peripheral neuropathy has been observed. **Conclusions:** Preliminary clinical outcomes for the nilotinib-paclitaxel combination in patients with rare tumors showed encouraging signals of activity. To facilitate further evaluation of response and the underlying mechanism of action for this combination, enrollment now focuses on the 4 tumor types that have previously demonstrated response: Ewing sarcoma, ovarian clear cell carcinoma, AGCOT, and anal cancers. Pharmacodynamic and genomic analyses are also ongoing. This project has been funded in whole or in part with federal funds from the NCI, NIH, under contract HHSN261201500003I. Clinical trial information: NCT04449549. Research Sponsor: U.S. National Institutes of Health.

3016 Rapid Oral Abstract Session

Clinical utility of circulating tumor RNA (ctRNA) in a combined circulating tumor DNA (ctDNA) and ctRNA next-generation sequencing (NGS) pan-cancer liquid biopsy assay. First Author: Jonathan Poh, Lucence Diagnostics Pte Ltd, Singapore, Singapore

Background: Liquid biopsies are increasingly used in the real world for cancer therapy selection, disease monitoring, and early detection. Combining RNA with DNA sequencing for the detection of FDA-actionable gene fusions is already recommended as standard of care in guidelines as fusions are inherently challenging to detect by DNA-only methods. However, the clinical utility of profiling plasma ctRNA in addition to ctDNA has not yet been quantified in large studies. Here we report results from the first large real-world study establishing the clinical utility of combining ctRNA and ctDNA in a single liquid biopsy assay. **Methods:** A total of 1,007 consecutive plasma samples from 979 cancer patients across the USA and Asia underwent real-world liquid biopsy testing with a combined ctDNA and ctRNA assay (LiquidHALLMARK) in two CAP-accredited CLIA-certified laboratories from Jun 2021 to Dec 2024. The combined amplicon-based assay profiles genomic alterations in 80 genes on ctDNA and up to 37 genes on ctRNA. Only gene fusions (including *MET* exon 14 skipping) were included in this analysis. The limit of detection for gene fusions of the ctDNA and ctRNA panel were validated as 0.5% and 10 copies. **Results:** Plasma ctRNA was successfully analyzed in 99.6% (1003/1007) of samples across 30 cancer types. The top 5 cancer types (lung, prostate, breast, colorectal, and pancreas) comprised 84.2% of the clinical volume. Gene fusions were detected across 11 genes (*ALK*, *RET*, *ROS1*, *MET*, *NRG1*, *NTRK1*, *FGFR2*, *FGFR3*, *ESR1*, *ERG*, *ETV4*) in 7.8% (78/1003) of cases, primarily in prostate and lung, but also in breast, bile duct, thyroid, liver, and bladder cancers. A total of 80 fusions were detected, of which 25 were detected by both ctDNA and ctRNA, while ctDNA and ctRNA each exclusively detected 27 and 28 fusions. Among the 28 ctRNA-only fusions, 5 were not covered by the ctDNA panel (1 *ATP1B1-NRG1*, 1 *ESR1-CCDC170*, 1 *ESR1-AKAP12*, and 2 *SLC45A3-ERG* fusions). Eleven (11/28) ctRNA-only fusions were actionable; all 11 were found in lung cancer. Two of these co-occurred with another lung driver mutation, highlighting potential resistance mechanisms to targeted therapy. Of the remaining 9, 3 were treated with fusion-matched targeted therapy. Two patients had real-world response rates available; both exhibited partial response to treatment. Overall, inclusion of ctRNA analysis increased the diagnostic yield of all fusions by 53.8% and actionable fusions by 36.7%. **Conclusions:** This is the first large study showing that adding ctRNA to ctDNA liquid biopsy increases total actionable diagnostic yield by 36.7%, highlights potential resistance mechanisms, and can broaden panel coverage to include gene fusions not amenable to detection by conventional DNA-based methods. These findings support recommendations for combined DNA/RNA testing of fusions in both tissue and liquid samples. Research Sponsor: None.

3017 Rapid Oral Abstract Session

Enhancing prognostic precision in bladder cancer: AI-driven tumor microenvironment analysis from H&E images. First Author: Evelyn Ramberger, Aignostics GmbH, Berlin, Germany

Background: Bladder cancer (BC) represents a significant healthcare burden. Despite advancements in diagnostics and treatment, the survival rate remains low, underscoring the need for improved prognostic tools. The current UICC staging system often lacks precision in patient stratification. Moreover, there is a paucity of scalable methods that explore and quantify tumor microenvironment (TME) features and their influence on patient outcome. Here, we present an artificial intelligence (AI) framework that operates on routine hematoxylin & eosin-stained (H&E) slides to enable systematic TME characterization and improve prognostic accuracy. **Methods:** In a bicentric cohort of over 700 resected BC patients, we developed and validated a deep learning approach for TME analysis. The model was trained using multiplex immunofluorescence-validated annotations but operates solely on H&E-stained images, maximizing clinical applicability. Key features included tissue compartment segmentation, cell classification, and spatially resolved cell patterns. We evaluated the model's performance and integrated TME features with clinicopathological variables to improve prognostic stratification beyond UICC staging. **Results:** The model demonstrated robust tissue compartment segmentation (F1-score = 0.91) and accurately identified key immune cell populations in tissue regions. When integrating the spatially resolved cellular features with clinicopathological variables, we observed significant improvements in prognostic capabilities for overall survival. The integrated approach demonstrated a 22% relative improvement over the conventional UICC staging system alone (C-index increased from 0.59 to 0.61, $p < 0.01$), measured against the random baseline C-index of 0.5. Our integrated model displayed a hazard ratio of 1.859 (95% CI: 1.530-2.259, p = 4.390e-10), markedly stronger than traditional risk stratification which showed a hazard ratio of 1.477 for high versus low risk groups (95% CI: 1.219-1.791, p = 7.117e-05). These findings demonstrate that AI-driven analysis of the tumor microenvironment provides valuable prognostic information beyond current clinical staging methods, suggesting promising opportunities for enhancing patient risk stratification. **Conclusions:** We show that a combination of AI with UICC staging shows improved patient stratification compared to stratifying by UICC alone. This study demonstrates the feasibility of automated TME characterization from routine H&E slides in BC and suggests that incorporating TME features into prognostic models enhances accuracy and could support personalized patient management in individualized oncology. While further validation in larger, multicentric-datasets is required, our approach shows potential for facilitating systematic biomarker development and improving clinical decision-making in BC care. Research Sponsor: BMBF.

3018 Poster Session

Preliminary results from a first-in-human phase 1 dose escalation trial of ADRX-0706, a next generation Nectin-4 ADC, in subjects with advanced solid tumors. First Author: Alexandra Drakaki, Jonsson Comprehensive Cancer Center, David Geffen School of Medicine at UCLA, Los Angeles, CA

Background: ADRX-0706 is a Nectin-4 targeting ADC designed to provide an increased therapeutic window through stable conjugation of a novel microtubule inhibitor payload (AP052) to an IgG1 monoclonal antibody at a drug-to-antibody ratio of 8. Preliminary safety, anti-tumor activity, pharmacokinetic (PK) and Nectin-4 expression results are presented from the dose escalation part of the ongoing Phase 1 trial (NCT06036121). **Methods:** Eligible subjects with select advanced solid tumors (urothelial [UC], cervical [CC], breast [BC], head and neck [HNSCC], ovarian [OC], non-small cell lung [NSCLC], and pancreatic [PC]) were enrolled in cohorts of escalating dose levels (1-16 mg/kg, Q3W, IV) using a BOIN design with backfill. Nectin-4 expression was evaluated retrospectively. Primary and secondary endpoints included dose-limiting toxicities [DLTs], adverse events [AEs], laboratory value changes, PK, immunogenicity, and response per RECIST v1.1. **Results:** As of the 13Dec24 data cutoff, 53 subjects with a median age of 59 years and median of 4 (1-14) prior therapies were enrolled. One DLT (G3 stomatitis) occurred at the highest dose of 16 mg/kg. The most common treatment related AEs (TRAE ≥15%) were arthralgia (32%), fatigue (21%), rash (19%), anemia (17%), and nausea (15%). The majority of TRAEs were G1-2 in severity and manageable, including only 3 (5.7%) subjects with peripheral neuropathy and 2 (3.8%) with liver enzyme increase. The most common ≥G3 TRAE was neutropenia (11%). ADC exposure increased in a dose-proportional manner with minimal deconjugation and the ADC half-life was 15 days. There were 5 subjects who achieved objective response across different tumor types (UC, NSCLC, CC) and 9 with stable disease per RECIST among 30 response-evaluable subjects treated at doses ≥8 mg/kg (ORR 16.7%, DCR 46.7%), including 2 triple negative BC (TNBC) subjects with 27% and 29% decrease in tumor size who remain on treatment. ADRX-0706 demonstrated Nectin-4 expression-dependent anti-tumor activity with all responses observed in tumors with H-score ≥100, including a confirmed complete response (CR) in a CC subject (H-score 250). Two responses were observed after prior progression on other Nectin-4 targeting MMAE drugs and three responses remain ongoing with subjects on treatment for 9+ to 23+ weeks. Based on these data, 10 mg/kg Q3W was selected as the Phase 1b dose. **Conclusions:** ADRX-0706 demonstrated a preliminary safety profile differentiated from MMAE-conjugates and with manageable toxicities. The antibody-like PK profile together with minimal deconjugation supports Q3W dosing. Encouraging anti-tumor activity was observed in multiple heavily pretreated tumors with moderate-high Nectin-4 expression. Enrollment in Phase 1b cohorts of UC, CC, and TNBC is ongoing. Clinical trial information: NCT06036121. Research Sponsor: Adcentrx Therapeutics.

3019 Poster Session

BC3195, a novel ADC targeting cadherin-3 (CDH3): Updated results of a first-in-human phase I study in patients with advanced solid malignancies. First Author: Haiyan Tu, Guangdong Lung Cancer Institute, Guangdong Provincial People's Hospital (Guangdong Academy of Medical Sciences), Southern Medical University, Guang Zhou, Guang Dong, China

Background: Cadherin-3 (CDH3), a calcium-dependent cell-cell adhesion glycoprotein, is overexpressed on lung, breast, head and neck and other malignancies, and associated with cancer invasiveness and poor prognosis. BC3195 is known as the only antibody drug conjugate (ADC) in clinical stage, targeting CDH3 with cleavable linker and payload of monomethyl auristatin E (MMAE). **Methods:** A phase I, open-label, first in human study whose objectives were to evaluate the safety, tolerability, pharmacokinetics (PK), and preliminary antitumor activity of BC3195 is being performed in patients (pts) with advanced solid malignancies. BC3195 is administered as 1-hr IV infusion every 3 weeks (Q3W) or every week (QW). An evaluation of seven dose levels (DLs) is planned: 0.3, 0.6, 1.2, 1.8, 2.1, 2.4 mg/kg Q3W and 1.2 mg/kg QW with a BOIN design guiding dose escalation. **Results:** As of the data cut-off-date (Dec 26th, 2024), 56 pts have been enrolled. The number of pts in each DL is shown in the table. Twenty-five (44.6%) pts had received ≥3 prior lines of treatment. Stomatitis (71.4%), rash (60.7%) and anemia (53.6%) were the main adverse events (AEs). Stomatitis and rash typically occurred in the first cycle and were manageable. Twenty-one pts (37.5%) experienced Grade≥3 treatment related adverse events (TRAEs). Among the 50 pts who were evaluable for tumor response, 5 pts in 2.4 mg/kg Q3W had partial response (PR). Of the 20 NSCLC pts treated in 2.4 mg/kg, 4 pts had confirmed PR (cPR), and 14 pts had stable disease (SD) as their best response; the objective response rate (ORR) was 50% (4/8) in previously-treated EGFR-mutant NSCLC pts, and mPFS was 168 days (Table). PK results demonstrated that exposure of the ADC, total antibody (TA) and MMAE increased in a non-linear manner at dose up to 2.4 mg/kg. Median T_{max} values for ADC and TA were 1 h, and median T_{max} for free MMAE was 25-169 h. In addition, elimination $t_{1/2}$ values averaged 54 h, 78 h and 63 h for the ADC, TA, and MMAE at 2.4 mg/kg, respectively. **Conclusions:** BC3195 has a manageable safety profile and favorable PK characteristics and demonstrated impressive preliminary antitumor activity in heavily-pretreated pts with NSCLC, of which most had EGFR-mutations (ORR=50%). Dose optimization and expansion are ongoing. Clinical trial information: NCT05957471. Research Sponsor: Biocity Biopharmaceutics Co. Ltd.

Safety and efficacy data of study BC3195-101 (safety analysis set).

Efficacy and Safety	0.3 mg/kg Q3W (N = 3)	0.6 mg/kg Q3W (N = 3)	1.2 mg/kg Q3W (N = 3)	1.8 mg/kg Q3W (N = 9)	2.1 mg/kg Q3W (N = 6)	2.4 mg/kg Q3W (N =31)		All* (N=56)
All tumor types (N = 31)	EGFR-mut NSCLC (N = 8)							
ORR, n (%)	0	0	0	0	0	5 (16.1)	4 (50.0)	5 (8.9)
DCR, n (%)	1 (33.3)	2 (66.7)	1 (33.3)	3 (33.3)	2 (33.3)	22 (71.0)	7 (87.5)	32 (57.1)
mPFS, days	40	82	40	40	39	130	168	91
Grade≥3 TRAE n (%)	0	0	0	2 (22.2)	1 (16.7)	17 (54.8)	3 (37.5)	21 (37.5)

*The subject in 1.2 mg/kg QW dose level is not presented in a dedicated column in this table.

3020 **Poster Session**

A phase 2 basket trial of ado-trastuzumab emtansine for patients with *HER2* amplified cancers. First Author: Jessica Ross, Memorial Sloan Kettering Cancer Center, New York, NY

Background: The *HER2* gene is commonly amplified (amp) across a variety of tumor types. Ado-trastuzumab emtansine (TDM1) is a potent antibody-drug conjugate targeting HER2 that is approved in HER2+ breast cancer. The efficacy of TDM1 in other *HER2*-amp solid tumors is unknown. **Methods:** We conducted a single-arm, phase 2 basket trial of TDM1 in which patients (pts) were enrolled in one of 5 *HER2*-amp cohorts: non-small cell lung cancer (NSCLC), colorectal cancer, endometrial cancer, salivary gland cancer, or other solid tumor. *HER2* amp was identified through next generation sequencing by MSK-IMPACT, defined as two-fold change, or by in-situ hybridization (ISH) with *HER2*/*CEP17* ratio $\geq$2.0 in a CLIA-certified laboratory. In tumors sequenced by MSK-IMPACT, precise level of the ERBB2 amplification (i.e. integer copy number) was assessed and correlated with clinical response. All pts received TDM1 3.6mg/kg IV every 21 days. The primary endpoint was overall response rate (ORR). For each cohort, a Simon two-stage optimal design was used. In the first stage, 7 pts were accrued in each cohort; if 0/7 responses, the cohort was closed. Otherwise, up to 11 additional pts were accrued. Cohorts 1, 3, and 4 were expanded by up to 5 pts (max 23 pts) due to durable responses seen early on. Response and progression of disease was evaluated using RECIST version 1.1. Modified PERCIST was allowed if pts did not have RECIST measurable disease. Toxicity was graded as per CTCAE v4.1. Circulating tumor DNA was collected pre-, post-, and on-treatment for all pts when feasible. **Results:** 88 pts were accrued between 2016 and 2023. The ORR by cohort is listed in Table 1. The most common toxicities were decreased platelet count and elevated ALT. There was one incident of grade 5 pneumonitis in a patient in cohort 1. Median time on treatment was 2.5 months (range 0.03 – 53.7 months); in pts with salivary gland tumors, median time on treatment was 17.6 months (0.3 – 53.7). **Conclusions:** TDM1 demonstrated efficacy in multiple *HER2*-amp tumor types. The highest ORR was seen in salivary gland tumors, with a median time on treatment of about 1.5 years. More work is needed to understand the enhanced efficacy of TDM1 in these tumors. Clinical trial information: NCT02675829. Research Sponsor: Genentech.

Response rate by cohort and disease site.

Cohort	RECIST-only ORR	Combined* ORR
1: *HER2*-amp lung	4/18 (22.2%)	4/19 (21.1%)
2: *HER2*-amp colorectal	0/7 (0.0%)	0/7 (0.0%)
3: *HER2*-amp endometrial	5/23 (21.7%)	5/23 (21.7%)
4: *HER2*-amp salivary	8/10 (80.0%)	14/16 (87.5%)
5: Other *HER2*-amp solid tumors	2/23 (8.7%)	2/23 (8.7%)
Biliary	1/8 (12.5%)	1/8 (12.5%)
Bladder & urinary tract	0/5 (0.0%)	0/5 (0.0%)
Cervical	0/2 (0.0%)	0/2 (0.0%)
Ovarian	1/7 (14.3%)	1/7 (14.3%)
Pancreatic	0/1 (0.0%)	0/1 (0.0%)
TOTAL	**19/81 (23.5%)**	**25/88 (28.4%)**

ORR=overall response rate. *Combined: RECIST when available, PERCIST if non-RECIST-evaluable.

3021 **Poster Session**

The safety, tolerability, and efficacy of BRY812 in patients with advanced solid tumors: Preliminary results from the phase I clinical study. First Author: Herui Yao, Sun Yat-sen Memorial Hospital, Sun Yat-Sen University, Guangzhou, China

Background: Antibody-conjugated drugs (ADCs) have demonstrated outstanding clinical efficacy in treating a wide range of solid tumors as well as hematological tumors currently. An ongoing multicenter, open-label, phase I clinical study assessed the safety, tolerability and preliminary efficacy of BRY812, the ADC targeting transmembrane protein LIV-1 with MMAE as cytotoxic payload, in advanced solid tumors. Here we report the interim analysis results. **Methods:** In Phase Ia (dose escalation), the eligible patients with advanced solid tumors were enrolled in each of 7 dose groups (0.25, 0.5, 1.0, 2.0, 2.8, 3.6 and 4.4 mg/kg) for evaluation to determine the MTD of BRY812. An "accelerated titration" method (0.25, 0.5 mg/kg) as well as a modified toxicity probability interval-2 method (subsequent doses) was applied. Subsequently dose expansion was conducted for dose levels of 2.0, 2.8 and 3.6 mg/kg that demonstrated tolerability and relative efficacy. The patients received treatment every 3 weeks until intolerable toxicity or disease progression. The primary endpoint was to evaluate DLT and MTD to determine RP2D, other endpoints included ORR. **Results:** Overall, as data cut-off date (Dec 13, 2024), 36 patients (including 30 patients with breast cancer) with advanced solid tumors were enrolled, including 20 patients in dose escalation phase and 16 patients in dose expansion respectively. Treatment is still ongoing for 19 patients. No DLT was observed up to 3.6 mg/kg. 4.4 mg/kg was not tolerated due to DLTs (2 of 4 patients experienced DLT events). The most common grade $\geq$3 TEAE was neutropenia, and grade 4 neutropenia was observed in 3.6 mg/kg (2/12) and 4.4 mg/kg (4/4). 4 patients discontinued treatment due to AE including 2 injury corneal (each of 3.6 & 4.4 mg/kg), 1 peripheral neuropathy (2.8 mg/kg) and 1 hepatic enzyme increase (3.6 mg/kg). Among 34 patients in efficacy analysis, 8 (23.5%) patients and 7 (20.6%) patients had PR and SD, respectively, and 17 (50%) patients had PD, leading to ORR of 23.5% (95% CI: 10.7, 41.1) and DCR of 44.1% (95% CI: 27.2, 62.1). The patients with higher LIV-1 expression showed better efficacy, as among 14 patients with PS2+ enriched, ORR was 43% (6/14 in breast cancer). In addition, ADC and Total antibody clearance were similar. BRY812 showed dose-dependent decrease of clearance in the dose range of 0.25 to 2.0 mg/kg, while approximately linear clearance in the dose range of 2.0 to 4.4 mg/kg, and the half-life were ~7 days. No accumulation was observed after multiple dosing. ADA positive rate was 11.43% (4/35). **Conclusions:** BRY812 demonstrated favorable safety and tolerability profile, with promising clinical efficacy in patients with advanced solid tumors. Further dose optimization and clinical efficacy will be explored in Phase Ib. Clinical trial information: NCT06038058. Research Sponsor: BioRay Pharmaceutical (Hangzhou) Co., Ltd.

3022 **Poster Session**

A pooled analysis of JSKN003, a biparatopic anti-HER2 antibody conjugate (ADC), in patients with advanced HER2-overexpressing (IHC 3+) gastrointestinal tumors. First Author: Dan Liu, Beijing Cancer Hospital, Beijing, China

Background: JSKN003 is a biparatopic HER2-targeting ADC conjugated with a topoisomerase I inhibitor (TOP1i) payload via a dibenzocyclooctyne tetrapeptide linker. The efficacy and safety of JSKN003 in several solid tumors have been highlighted in previous reports. **Methods:** JSKN003-101 and JSKN003-102 are dose escalation and expansion studies involving Australian and Chinese patients (pts) with metastatic solid tumors. This pooled analysis of two studies was performed to assess the efficacy and safety in advanced HER2-overexpressing (IHC 3+) gastric or gastroesophageal cancer (GC/GEJC) and colorectal cancer (CRC) pts. **Results:** As of data cutoff (18 Dec 2024), 40 patients with HER2-overexpressing (IHC 3+ by local lab) gastrointestinal tumor (23 in GC/GEJC and 17 in CRC) were enrolled across 7 dose levels: 2.1 mg/kg (n = 1), 4.2 mg/kg (n = 1), 5.2 mg/kg (n = 1), 6.3 mg/kg (n = 33), 7.3 mg/kg (n = 1), 8.4 mg/kg (n = 2), 10.5 mg/kg (n = 1). The median follow-up time of two studies was 7.16 months. Most pts were heavily pretreated (37.5% had $\geq$3 lines of prior treatment; 45.0% received irinotecan; 67.5% received anti-HER2 therapy; 42.5% received IO therapy). Four of the 17 CRC pts were RAF/RAS mutations (n = 2 RAS-mut, n = 2 RAF-mut). Thirty-nine patients had at least one tumor assessment after baseline. The overall response rate (ORR) per RECIST v1.1 in HER2-overexpressing gastrointestinal tumor was 66.7% and the disease control rate (DCR) was 94.7%. Among 22 GC/GEJC pts, the ORR was 68.2% and DCR was 95.5%. The median progression-free survival (PFS) was 9.59 months (95% CI: 2.96, NE) with 66.3% (95% CI: 29.4, 87.1) PFS rate at 6 months. Among 17 CRC pts, the ORR was 64.7% (66.7% in RAF-wild pts, n = 15) and DCR was 94.1%. The mPFS was 13.77m (95% CI: 7.1, NE) with 94.1% (95% CI: 65, 99.2) PFS rate at 6 months. The median overall survival (OS) was not yet mature. Notably, one BRAF-mut patient achieved PR at first tumor assessment after baseline, two RAS-mut pts achieved PR and duration was over 48 weeks. The most common treatment-related adverse events (TRAEs) included nausea, diarrhea, neutropenia, decreased appetite, vomiting, rash, anemia and fatigue. Grade 3/4 neutropenia was observed in 2 (5.0%) pts, Grade 3/4 anemia was observed in 1 (3.0%) pts. No TEAEs led to death or treatment discontinuation. Interstitial lung disease (ILD) occurred in 3 (7.5%; n = 2 G1; n = 1 G2) pts. **Conclusions:** JSKN003 demonstrated promising efficacy in heavily pretreated pts with advanced HER2-overexpressing gastrointestinal tumors, with a manageable and predictable safety profile. Clinical trial information: NCT05494918, NCT05744427. Research Sponsor: Jiangsu Alphamab Biopharmaceuticals Co., Ltd.

3023 **Poster Session**

Initial results from a first-in-human phase 1 study of LY4170156, an ADC targeting folate receptor alpha (FRα), in advanced ovarian cancer and other solid tumors. First Author: Isabelle Laure Ray-Coquard, Centre Léon Bérard, and GINECO, Lyon, France

Background: Folate receptor alpha (FRα) is overexpressed in several solid tumors. LY4170156 is an Fc-silent, FRα specific humanized IgG1 ADC linked to exatecan, a topo-I inhibitor, via a novel cleavable polysarcosine linker at a homogenous DAR of 8. LY4170156 demonstrated *in vivo* preclinical efficacy in tumor models, across all FRα expression levels. **Methods:** This is a multicenter, open-label, first-in-human phase 1a/b study of LY4170156 in patients (pts) with advanced FRα-expressing ovarian, endometrial, cervical, and other solid tumors. Pts with prior ADCs targeting FRα with payloads other than topo-I (including mirvetuximab soravtansine-gynx [mirv]) were allowed. Dose escalation followed the mTPI-2 method. LY4170156 was administered Q3W IV (dose range of 2-6 mg/kg); dose limiting toxicity (DLT) evaluation period was 21 days. Dose escalation included a randomized dose optimization cohort in PROC. Key endpoints were safety, PK, and antitumor activity per RECIST v1.1. Efficacy evaluable pts were those who had a post baseline response assessment or discontinued treatment prior to the response assessment. **Results:** As of 27 Nov 2024, 45 pts were treated with LY4170156. Median age was 63 yrs (range, 24-85), 100% had ECOG PS 0-1, and 32 (71%) had high-grade serous ovarian cancer (HGSOC). Among the HGSOC pts (32), median lines of prior therapy was 5 (range, 1-10), 19% had received prior mirv, and 44% had FRα expression $<$ 75% by local or central testing. PK of LY4170156, total antibody, and exatecan were linear and dose-proportional within the tested dose range. Unconjugated payload release from ADC at C_{max} was $<$ 4% at 4 mg/kg; median half-life of LY4170156 was 5.7-7.0 days and exatecan was 7.2-8.6 days. Main toxicities were myelosuppression and GI-related, as expected from an exatecan payload. Across all doses, the most common treatment-emergent adverse events (TEAEs; $\geq$15%) were nausea (58%, 2% gr 3), fatigue (44%, 0% gr 3-4), anemia (33%, 24% gr 3), vomiting (27%, no gr 3-4), diarrhea (22%, 4% gr 3), and neutropenia (20%, 11% gr 3-4). Febrile neutropenia (FN) was observed in 3 pts (7%). To date, no pulmonary or ocular toxicity were noted. Two DLTs were observed (1 gr 3 FN [6 mg/kg]; 1 gr 3 anemia [2 mg/kg]); no MTD has been established to date. Among 13 efficacy evaluable HGSOC pts (6 FRα $\geq$75%; 6 $<$ 75%; 1 pending data), 9 showed reduction in target lesions; preliminary ORR was 38% (n = 5) with 1 CR, 4 PR, and 4 SD across all dose levels. Combined ORR for 4 and 6 mg/kg dose levels was 55%. All responses were unconfirmed and ongoing at the time of data cutoff. Three of 5 responders had FRa expression $<$ 75% and two $\geq$75% including 1 who was mirv refractory. **Conclusions:** LY4170156 was well-tolerated with encouraging clinical activity among HGSOC pts, including those with FRα expression $<$ 75% and those with prior mirv. Randomized dose optimization is ongoing and updated data will be presented. Clinical trial information: NCT06400472. Research Sponsor: Eli Lilly and Company.

3024 **Poster Session**

BAT8008, a TROP-2 antibody-drug conjugate (ADC), in patients with advanced solid tumor: Results from a phase 1 study. First Author: Jianli Zhao, Sun Yat-sen Memorial Hospital, Sun Yat-Sen University, Guangzhou, China

Background: BAT8008 is a monoclonal ADC that delivers exatecan to cells expressing TROP-2. TROP-2 is a cell surface glycoprotein that can be expressed in certain normal tissue but is frequently overexpressed in multiple carcinomas including cervical cancer (CC) and esophageal cancer (EC). Here we report the safety and efficacy data of BAT8008. **Methods:** BAT8008 was administered by intravenous infusion at doses of 0.8-2.7mg/kg on days 1 of each14-day cycle(the first cycle is 21-day). The study included dose escalation, dose expansion and cohort expansion which included CC, EC and other solid tumors that progressed after $>$ I systemic treatments (Tx). Primary objectives were assessment of safety and preliminary efficacy. **Results:** As of Jan 15, 2025, 170 patients (pts) were enrolled with doses ranging from 0.8 to 2.7mg/kg. 2 out of 6 pts in 2.7mg/kg group had dose limiting toxicity (1 with G3 increased lipase, 1 with G4 thrombocytopenia and G4 febrile neutropenia). The maximum tolerated dose and the RP2D was selected as 2.4mg/kg. 147 pts were enrolled at dose of 2.4mg/kg. The most common TRAEs of 2.4mg/kg dose group ($\geq$20%, all grade/$\geq$5%, $\geq$G3) were anemia (78.8%,13.7%), white blood cell count decreased (62.3%, 18.5%), nausea (59.6%,0%), stomatitis(59.6%,19.2%), neutrophil count decreased (52.7%,19.2%), platelet count decreased (38.4%,8.2%), vomiting (38.4%,0.7%), lymphocyte count decreased (35.6%,5.5%), fatigue (34.9%, 0%), body weight loss (29.5%, 0.6%), constipation (26.7%,0%), anorexia (23.3%,2.7%). 22 CC pts and 13 EC pts were enrolled at 2.4mg/kg and evaluable for tumor assessment. The obiective response rate (ORR) was 36.4% and 23.1%, respectively. Median prior lines of Tx were 2(range, 1-5). 50% CC and 93% EC pts progressed after platinum-based chemotherapy and immune checkpoint inhibitors, respectively. 23% EC had previously used topoisomerase I inhibitors. Objective responses were also observed in pts with other solid tumor types. **Conclusions:** The data indicated encouraging efficacy of BAT8008 in advanced CC and EC. The safety profile showed adequate tolerability. Clinical trial information: NCT05620017. Research Sponsor: Bio-Thera Solutions, Ltd.

Tumor Type	CC	EC
n	22	13
CR	1	1
PR	7	2
ORR,%	36.4	23.1
cORR,%	31.8	15.4
DCR,%	77.3	100
PFS, months (95% CI)	6.8 (3.4-10.2)	5.3 (3.1-7.4)

3025 **Poster Session**

A phase I clinical study to evaluate the safety, tolerability, and pharmacokinetic characteristics of HLX43 (anti-PD-L1 ADC) in patients with advanced/metastatic solid tumors. First Author: Jie Wang, Internal Medicine, Department of Medical Oncology, National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Beijing, China

Background: Antigens highly expressed in tumors such as HER2 and TROP2 have been widely investigated as antibody-drug conjugate (ADC) targets, leading to their approval for various cancers due to their promising efficacies. However, limited targets for approved ADCs and resistance to the cytotoxic agents render the imperative need for new ADCs. This study aimed to evaluate the safety, tolerability, and preliminary efficacy of HLX43, a novel anti-PD-L1 ADC in patients with advanced/metastatic solid tumors. **Methods:** This phase 1 study consisted of 2 parts. Parts 1 and 2 were dose escalation and dose expansion phases, respectively, to explore different doses of HLX43. In Part 1, patients with histologically or cytologically confirmed advanced/metastatic malignant solid tumors refractory to or not amenable to standard therapies received intravenous HLX43 at 0.5 mg/kg, 1 mg/kg, 2 mg/kg, 3 mg/kg, or 4 mg/kg, Q3W. In Part 2, patients with advanced/metastatic non-small cell lung cancer (NSCLC) refractory to standard treatment received HLX43 at 2 mg/kg, 2.5 mg/kg, or 3 mg/kg, Q3W. The primary endpoints for Part 1 were the proportion of subjects experiencing dose-limiting toxicity (DLT) in each dose group within three weeks after the first drug administration and the maximum tolerable dose (MTD) while that for Part 2 were the recommended Phase 2 dose and IRRC-assessed objective response rate (ORR). **Results:** As of 27 June 2023, 18 patients with non-small cell lung cancer (n = 12, 66.7%), head and neck squamous carcinoma, cervical squamous carcinoma, thymic squamous cell carcinoma, nasopharyngeal cancer, uterine carcinosarcoma, or small cell lung cancer (n = 1, 5.6% for each) were enrolled in Part 1 and received HLX43 at 0.5 mg/kg (n = 3), 1 mg/kg (n = 3), 2 mg/kg (n = 3), 3 mg/kg (n = 3), or 4 mg/kg (n = 6). All the patients experienced treatment-emergent adverse events (TEAEs) that were mostly grades 1-2. One patient in the 4 mg/kg dose group experienced DLTs of febrile neutropenia and decreased white blood cell count. Investigator-assessed ORR was 31.3% (95% CI 11.0-58.7). In Part 2, only data from 21 patients enrolled to receive HLX43 at 2 mg/kg is available and presented here. Among these patients, 15 (71.4%) had squamous NSCLC and 6 (28.6%) had nonsquamous NSCLC. Investigator-assessed ORR and disease control rate were 38.1% (95% CI 18.1-61.6) and 81.0% (95% CI 58.1-94.6); no complete response was achieved, and 8 patients (6 sqNSCLC and 2 nsqNSCLC) had partial response. All the patients experienced TEAEs, most of which were grades 1-2; grade $\geq$3 TEAEs occurred in 7 (33.3%) patients. **Conclusions:** HLX43 was well tolerated with no new safety signals across different dose and exhibited encouraging preliminary efficacy in patients with advanced solid tumors, including those with NSCLC, who had failed standard therapies, which warrants further investigation. Clinical trial information: NCT06115642. Research Sponsor: Shanghai Henlius Biotech, Inc.

3026 **Poster Session**

First in human phase I study of TQB2103, a Claudin18.2 (CLDN18.2) targeted antibody-drug conjugate (ADC), in patients with advanced solid tumors. First Author: Xiangdong Cheng, Zhejiang Cancer Hospital, Hangzhou, Zhejiang Province, China

Background: Claudin18.2 is a promising target for CLDN18.2-expressing cancers such as gastric and pancreatic cancers. TQB2103 is a novel ADC comprised of a humanized anti-CLDN18.2 IgG1 monoclonal antibody, a cleavable linker and topoisomerase I inhibitor, with a drug-to-antibody-ratio (DAR) of 8. **Methods:** This is a multicenter, first-in-human study of TQB2103 in patients (pts) with previously treated advanced solid tumors. This study comprised of a dose escalation part in patients regardless of Claudin18.2 expression level and a dose expansion part in patients specified by CLDN18.2 positive expression. The primary objectives were to assess safety and tolerability and determine the recommended phase 2 dose. Secondary objectives were to assess the pharmacokinetics and preliminary anti-tumor activity. **Results:** As of December 16 2024, 59 pts were enrolled to receive TQB2103 intravenously every 3 weeks at 7 dose level (range from 0.5 to 6.0mg/kg). One patient experienced dose-limiting toxicity (DLT) of grade 3 transaminase elevation at 0.5mg/kg which might also be related to the comorbidity of choledocholithiasis. Fifty-six (94.9%) patients experienced at least one treatment-related adverse event (TRAE). The most frequent TRAEs were nausea (72.9%), vomiting (64.4%), appetite decreased (57.6%), hypoalbuminemia (49.2%), anemia (49.2%), white blood cell decreased (44.1%), and asthenia (44.1%). The most frequent grade $\geq$3 TRAEs were anemia (11.9%) and neutrophil count decreased (10.2%). Most of AEs were grade 1 or grade 2 and manageable. Among the 30 response evaluable pts with CLDN18.2 expression, the ORR and DCR were 20% and 76.7%, respectively. Shrinkage of the target lesions occurred in 17(56.7%) patients. In patients with CLDN18.2 moderate to high expression, the ORR was 42.9% of gastric cancer at 5mg/kg. Surprisingly, all of 3 response-evaluable biliary tract cancer had shrinkage of the target lesions at the first assessment, and 1/3 achieved partial response. **Conclusions:** TQB2103 demonstrated encouraging anti-tumor activity in CLDN18.2 positive solid tumors, with a favorable safety profile. The findings support further development of TQB2103 monotherapy or in combination with other anti-cancer therapies. Clinical trial information: NCT05867563. Research Sponsor: Chia Tai Tianqing Pharmaceutical Group Co., Ltd.

3027 **Poster Session**

Association of genomic alterations in circulating tumor DNA (ctDNA) with clinical response to telisotuzumab vedotin (Teliso-V) in 2L+ *EGFR* wildtype (*EGFR*wt) non-squamous non-small cell lung cancer (NSCLC) patients (pts) with c-Met overexpression (OE). First Author: David Ross Camidge, University of Colorado Cancer Center, Aurora, CO

Background: Teliso-V is an antibody-drug conjugate comprising the c-Met–targeting antibody telisotuzumab linked to the microtubule inhibitor monomethyl auristatin E. In the LUMINOSITY trial (NCT03539536), Teliso-V monotherapy demonstrated efficacy in *EGFR*wt pts with c-Met OE ($\geq$25% tumor cells at 3+ intensity by IHC) (Camidge et al. JCO 2024;42: 3000-11). We used ctDNA molecular profiling to investigate baseline (BSL) and longitudinal changes in pts' tumor mutational spectrum, and to identify potential mechanisms of tumor response and drug resistance to Teliso-V. **Methods:** Pts received 1.9 mg/kg Teliso-V intravenously Q2W. In total, 83 pts with ctDNA data and evaluable tumor assessments in Stage 2 were included in the analysis. Plasma ctDNA was collected at multiple timepoints and analyzed for genomic alterations using the PGDx elio Complete NGS assay (521 genes). Variants with allele frequency (VAF) $<$ 0.3% or from putative clonal hematopoiesis of indeterminate potential genes were removed. High ctDNA levels were defined as having a mean (m)VAF $\geq$median (2.05%), and low ctDNA levels as mVAF $<$ median. Molecular response (MR) was defined as having $\geq$50% reduction in the mVAF vs BSL levels without gene amplification. Mutational profiles and their association with RECIST-defined tumor response and/or drug resistance were assessed. **Results:** Overall, pts with high BSL ctDNA levels had an ORR (28.6%, 12/42) similar to all *EGFR*wt pts with c-Met OE (28.6%, 46/161) and were not statistically different vs pts with low BSL levels. However, pts with low BSL ctDNA had longer median OS (16.3 vs 8.5 mo) and mPFS (8.1 vs 5.4 mo) vs those with high BSL levels. Although the total pts with genomic alterations (GA) in this analysis was limited, *KRAS* GA were one of the most common mutations detected at BSL (24%, 20/83 pts). ORR to Teliso-V among pts with the actionable GA (AGA) of *KRAS* G12C was 100% (5/5). Conversely, among pts with non-AGA *KRAS* G12V/D/A and Q61H/L, the ORR was 23% (3/13). Additional AGAs were found in BSL ctDNA, including 1 *BRAF* V600E, 3 *MET* ex14del, 1 *EGFR* G719C, and 2 *RET1-KIF5B* translocations; none had response to Teliso-V. Pts with a MR at week 6 had higher ORR (35% vs 23%), longer median OS (15.5 vs 12.2 mo), and median PFS (8.5 vs 5.7 mo) vs those who did not. One pt with stable disease had several new AGAs detected in circulation at week 6, including activating *EGFR* ex20ins. At week 24, clinical progression was accompanied by gene amplifications of *ERBB2, FGF4, FGFR4,* and *FGFR3*. Other types of pharmacodynamic changes in ctDNA that could predict clinical response or drug resistance will be presented. **Conclusions:** ctDNA is a promising biomarker in predicting Teliso-V activity. Confirmatory research is planned in larger pt cohorts and/or with tissue-based NGS analyses. Clinical trial information: NCT03539536. Research Sponsor: AbbVie, Inc.; n/a.

3028 **Poster Session**

First-in-human phase 1 dose escalation trial of OMTX705, a novel anti-fibroblast activation protein (FAP) antibody drug conjugate (ADC), in monotherapy and in combination with pembrolizumab in patients with solid tumors. First Author: Javier Torres-Jiménez, Hospital Universitario 12 de Octubre, Madrid, Spain

Background: Cancer Associated Fibroblasts (CAFs) are key components of tumor microenvironment and have immunosuppressive functions. FAP is expressed in a restricted fashion on CAFs. OMTX705 is a first-in-class ADC targeting FAP with a novel tubulysin payload. OMTX705 demonstrated a good safety profile in relevant toxicology models and high linker stability in plasma. We report the dose escalation phase 1 trial of OMTX705 in monotherapy and in combination with pembrolizumab (PEM). **Methods:** Patients (pts) with advanced carcinomas or sarcomas received 1-18 mg/kg of OMTX705 monotherapy and 2-10 mg/kg with standard PEM. Escalation used a classical 3+3 design with backfilling. OMTX705 schedule is Day 1, 8 every 21 days. The primary endpoint is safety and key secondary are efficacy, pharmacokinetics and biomarkers. Biopsy and blood samples were collected for biomarker analysis. **Results:** A total of 78 pts have been dosed: 31 pts in monotherapy in 9 dose cohorts and 47 in combination in 7 cohorts of 3 pts each plus 2 backfilling cohorts at 4 and 7.5 mg/kg in pancreatic adenocarcinoma (PDAC) and microsatellite stable (MSS) colorectal cancer (CRC). Median age was 60, 43% male and ECOG PS 0 in 44%. Main histologies were PDAC 33% and MSS CRC 21% with median of 2 (1 to 5) and 3 (1 to 5) prior lines of therapy, respectively. Median treatment exposure was 44 days (range 8 to 113) in monotherapy and 92 days (1 to 422) in combination. OMTX705 relative dose intensity was ~100% in all dose levels. No DLT has been observed. The most frequent related TEAEs were asthenia 35%, AST increased 14%, diarrhea 8%, anemia 8%, and nausea 8%. Grade 3 related TEAEs (pts): anemia (2), immune-mediated hepatitis (2), GGT increased (1), neutropenia (1) and asthenia (1). In monotherapy, best response was SD in 26%. In combination, PR was achieved in 4% (1 MSS CRC and 1 PDAC; DOR 11+ and 8 months, respectively), SD in 33%, PD in 51%, and NE in 13%. In 13 pts there was target lesion reduction: median -17% (-46 to -1%). Median PFS was 1.4 months (0 to 14+). In combination, 20% PDAC (4/20) and 21% CRC (3/14) pts showed PFS $>$ 4 months. 2/3 NSCLC with previous checkpoint inhibitor treatment, 2 PDAC, and 2 MSS CRC showed PFS $>$ 7 months. High FAP expression (H-score $>$ 30) was observed in 86% PDAC, 64% CRC and 50% other carcinomas. CD8+ and CD56+ immune-cell infiltration in tumor biopsies and down-regulation of immunosuppressive cytokines in plasma samples were observed in PDAC and CRC best responders. OMTX705 tubulysin payload was detected in both CAFs and tumor epithelial apoptotic regions. **Conclusions:** OMTX705 is a novel anti-FAP ADC with excellent safety profile. The combination with PEM showed disease control in some heavily pretreated PDAC, MSS CRC and NSCLC. Changes in immune infiltrates and cytokines suggest that OMTX705 may revert CAF-mediated immunosuppression. Clinical trial information: NCT05547321. Research Sponsor: Oncomatryx Biopharma.

3029 **Poster Session**

A first-in-human clinical study of 9MW2921, a novel TROP-2 antibody-drug conjugate (ADC), in patients with advanced solid tumors. First Author: Shuiping Gao, Fudan University Shanghai Cancer Center, Shanghai, China

Background: TROP-2 (trophoblast cell surface antigen 2) is commonly overexpressed in multiple solid tumors and associated with poor prognosis. 9MW2921 is a novel TROP-2 ADC developed with a site-specific linker to conjugate the class of novel camptothecin-based payload Mtoxin, with a drug-to-antibody-ratio (DAR) of 4. Here we report the safety and efficacy data of 9MW2921 in patients with advanced solid tumors in a phase 1 study. **Methods:** 9MW2921 was administered by intravenous infusion at doses of 1.0-6.0 mg/kg once every 3 weeks. Primary objectives were assessment of dose-limiting toxicity, safety and the recommended phase 2 dose/maximum dose. **Results:** As of 12 November, 2024, thirty-nine patients (pts) were enrolled and treated at dose levels of 1.0 (N = 1), 2.0 (N = 3), 2.5 (N = 12), 3.0 (N = 20) and 4.5 (N = 3) mg/kg. The average age of all patients was 55.6 (range: 37-72) years with 20.5% male and 79.5% female. The median prior therapy lines were 2 (range: 1~11); 48.7% pts treated after immunotherapy. Three patients at 4.5mg/kg experienced at least one dose limiting toxicity (DLT), and this dose level was considered intolerable. No other pts was observed DLTs at the 1.0~3.0 mg/kg groups. The most common $\geq$grade 3 ($\geq$5% pts)TRAEs were stomatitis, anemia, white blood cell (WBC) count decreased, neutropenia, lymphocyte count decreased, rash, vomiting and platelet count decreased. There were no TRAEs leading to death. 38 pts were evaluable for efficacy with at least one post-baseline tumor assessment, 12 pts achieved partial response and 16 pts maintained stable disease. The ORR of 3.0 mg/kg was 42.1% (8/19) and DCR was 84.2% (16/19). The ORR, DCR of 3.0 mg/kg in patients diagnosed with endometrial cancer (4 pts), HR+/HER2- breast cancer (4 pts), HER2- gastric cancer (4 pts) and Non-squamous non-small cell lung cancer (4 pts) were 75%, 100%; 50%, 75%; 50%, 100%; 25%, 100%, respectively. **Conclusions:** The data indicated that 9MW2921 has acceptable tolerability and promising anti-tumor activity in patients with advanced EC, HR+/HER2- BC, HER2- GC and nsq-NSCLC. Clinical trial information: NCT05990452. Research Sponsor: Mabwell (Shanghai) Bioscience Co., Ltd.

3030 **Poster Session**

Efficacy and safety results of a multi-center phase I study of utidelone capsule, a novel oral microtubule inhibitor, in advanced solid tumor patients. First Author: Judy S. Wang, Florida Cancer Specialists/Sarah Cannon Research Institute, Sarasota, FL

Background: Utidelone is a novel microtubule inhibitor, whose injectable formulation (UTD1) has been approved for advanced breast cancer in China since 2021. Attempts to develop oral microtubule inhibitor have not made significant progress; no oral microtubule inhibitors have been approved in the United States to date. Utidelone is insusceptible to P-glycoprotein-mediated efflux, thereby optimizing it for oral administration on an intermittent schedule. Utidelone capsule (UTD2) can significantly improve medication compliance and the convenience of clinical application. This is the first-in-human study of UTD2, and the trial has been completed with final results presented here. **Methods:** Eligible patients were aged $\geq$18, with an ECOG PS of 0-1, life expectancy $\geq$12weeks, pathologically confirmed advanced solid tumor refractory to prior standard therapies. Patients were treated with UTD2 monotherapy. The starting dose was 5-day 25 mg/m^2/d for 2 patients, with planned escalation to 5-day 50, 75, 100 mg/m^2/d and 7-day 70 mg/m^2/d for 2, 6, 3 and 2 patients, repectively in a 21-day cycle. The primary objective was to determine DLT and the MTD. Secondary objectives included efficacy, PK profile and RP2D. **Results:** 18 advanced solid tumor patients were enrolled (3 didn't complete DLT observation) with median age of 60.8 years (range 29.0-81.0), 9 females and 9 males. All patients had received prior treatment in advanced settings with maximal 9 lines. Two DLTs of Grade 3 and Grade 4 diarrhea occurred, one at 5-day 100 mg/m^2/d and one at 7-day 70 mg/m^2/d. Considering the total dose per cycle for both cohorts were similar, the MTD was determined to be 5-day 75 mg/m^2/d via SMC. 11 patients were evaluated for efficacy with an outcome of 1 CR (ovarian cancer), 1 PR (ovarian cancer), 7 SD (testicular Sertoli cell tumor, NSCLC*2, pancreatic adenocarcinoma*2, appendiceal adenocarcinoma and soft tissue sarcoma), with the longest DoT of 12 cycles. The ORR was 18.2% and the CBR was 81.8%. PK results showed that the characteristics of utidelone were consistent with a two-compartment model. Compared to single-dose administration, there was no accumulation of utidelone in plasma upon multi-dose. The most frequent TEAEs were Grade 1/2, including diarrhea, fatigue, nausea, peripheral sensory neuropathy, vomiting, and decreased appetite ($\geq$20% incidence rate), which recovered with supportive treatments. The $\geq$Grade 3 TRAE included diarrhea (27.8%) and fatigue (5.6%). **Conclusions:** This completed study demonstrates encouraging anti-tumor activity with manageable safety of UTD2 in patients with heavily pre-treated advanced solid tumors. The results support continuing development of UTD2 for the upcoming phase II/III studies for gastric and ovarian cancers. Clinical trial information: NCT05681000. Research Sponsor: Biostar Pharma, Inc.

3032 **Poster Session**

RC48-ADC combined with radiotherapy and immunotherapy as salvage therapy for advanced solid tumors with HER2 expression: A multicenter, phase II trial. First Author: Meiling Xu, Center for Cancer Diagnosis and Treatment, The Second Affiliated Hospital of Soochow University, Suzhou, China

Background: Antibody-drug conjugates (ADC) have demonstrated efficacy in treating tumors with HER2 over expression. However, the clinical benefits of ADCs are limited in tumors with lower HER2 expression. The combination of ADCs, radiotherapy, and immunotherapy has shown promising feasibility with HER2-expressing tumors across various cancer types. This approach can enhance spatial and physicochemical synergistic effects, resulting in a more diverse and increased release of tumor antigens. Subsequently, PD-1 inhibitors activate effector T cells, generating a robust immune response that targets and eliminates tumor cells. A single-arm, multicenter phase II trial was initiated to evaluate the clinical efficacy of RC48-ADC combined with radiotherapy and immunotherapy, in HER2-expressing advanced solid tumors. The findings from this trial may establish a new salvage treatment strategy for tumors with low HER2 expression. **Methods:** This study enrolled patients with advanced, HER2-expressing (IHC 1+, 2+, or 3+) solid tumors that had progressed following standard therapies or due to intolerance. Participants received RC48 (disitamab vedotin, 2.0 mg/kg on day 1), followed by radiotherapy every other day (2-3 fractions of 5-8 Gy), GM-CSF 200 μg on days 3-7), sequential IL-2 (2 million IU on days 8-12), and a PD-1 inhibitor administered within one week after completing radiotherapy. This regimen was repeated every three weeks. The primary endpoint was the objective response rate (ORR). **Results:** As of the cutoff date (December 31, 2024), 52 patients were enrolled, including 10 with gynecological cancers, 10 with pancreatic cancer, and 32 with various other tumor types (including breast, gastric and colorectal cancers). All participants had evaluable data. According to RECIST 1.1, the overall ORR was 36.5%, with two patients achieving a complete response (CR) that lasted nearly two years, maintaining minimal residual disease negative status. The ORRs for patients with HER2 expression of 1+, 2+, and 3+ were 29.0%, 43.4%, and 60.0%, respectively. The median progression-free survival (PFS) for all patients was 5.9 months (95% CI: 4.1–9.7 months). The median overall survival (OS) for all patients was 14.3 months (95% CI: 8.6–15.7 months).Treatment-related adverse events were predominantly mild (grade 2 or lower), including fatigue, hair loss, nausea, fever, and rash. Only three patients (5.8%) experienced grade 3 adverse events. **Conclusions:** The results indicate promising efficacy and manageable safety, with a favorable short-term tumor response rate. This suggests that the combination of RC48-ADC, radiotherapy, and immunotherapy could serve as an effective salvage therapy option for patients with HER2-expressing advanced solid tumors. The combination therapy appears to enhance the synergistic effects of radiotherapy and immunotherapy. Clinical trial information: NCT0511550. Research Sponsor: None.

3033 **Poster Session**

First-in-human study of BG-C9074, a B7-H4-targeting ADC in patients with advanced solid tumors: Preliminary results of the dose-escalation phase. First Author: Cesar Augusto Perez, Sarah Cannon Research Institute at Florida Cancer Specialists, Orlando, FL

Background: B7-H4 is a transmembrane glycoprotein in the B7 superfamily with limited expression in normal tissue but is upregulated in solid tumors including cholangiocarcinoma, breast, ovarian, and endometrial cancers. BG-C9074 is an investigational topoisomerase I inhibitor antibody-drug conjugate. This abstract presents the initial results of monotherapy dose escalation from the ongoing phase 1 study. **Methods:** BG-C9074-101 (NCT06233942) is a first-in-human, multicenter study designed to evaluate the safety, tolerability, pharmacokinetics, and preliminary antitumor activity (per RECIST v1.1) of BG-C9074 as monotherapy and in combination with tislelizumab in patients with advanced solid tumors. Patients with histologically or cytologically confirmed locally advanced, unresectable, or metastatic solid tumors, irrespective of B7-H4 expression, received BG-C9074 intravenously every 3 weeks in sequentially escalating dose cohorts ranging from 1 to 7 mg/kg. **Results:** As of January 22, 2025, 55 patients with advanced tumors (n = 25, ovarian cancer; n = 16, breast cancer; n = 10, cholangiocarcinoma; n = 4, other tumor types) received BG-C9074 monotherapy. Three patients experienced dose-limiting toxicities including fatigue (6 mg/kg), and febrile neutropenia and thrombocytopenia (7 mg/kg). Treatment-emergent adverse events (TEAEs) were reported in 48 patients (87.3%) with grade ≥3 TEAEs occurring in 27.3% of patients. The most common TEAEs were nausea (45.5%), fatigue (38.2%), and neutropenia (32.7%), with neutropenia being the most frequent grade ≥3 TEAE (16.4%). Among 39 efficacy-evaluable patients, eight (20.5%) partial responses (n = 4, confirmed; n = 4, unconfirmed) were observed. **Conclusions:** BG-C9074 showed a manageable safety/tolerability profile in patients with B7-H4 advanced solid tumors. Preliminary clinical responses were observed at multiple dose levels across various tumor types without selection for B7H4 expression. Dose-escalation and dose-level expansion are ongoing and updated clinical data will be presented at the conference. Clinical trial information: NCT06233942. Research Sponsor: BeOne Medicines Ltd.

3034 **Poster Session**

Efficacy and safety of XNW27011, a Claudin 18.2 targeting antibody drug conjugate with topoisomerase 1 inhibitor payload, in patients with Claudin 18.2 positive gastric/gastroesophageal junction cancer: Results from ongoing phase I/II study. First Author: Jinming Yu, Affiliated Hospital of Shandong First Medical University, Jinan, China

Background: CLDN18.2 is a clinically validated target for cancer treatment. XNW27011 is a CLDN18.2 targeted ADC conjugated with a novel topoisomerase 1inhibitor (topo1i). Dose-escalation study of XNW27011 demonstrated favorable safety, pharmacokinetics, and promising preliminary efficacy in advanced solid tumors. Here we report the results of XNW27011 in CLDN18.2+ GC/GEJC pts from ongoing expansion cohorts. **Methods:** Pts with CLDN18.2+ (TC≥5%, IHC ≥ 2+), advanced/metastatic solid tumors progressed on standard therapy and an ECOG PS of 0-2 are eligible to be enrolled in dose expansion cohorts. Pts received XNW27011 iv infusion Q3W at doses of 2.4, 3.0 and 3.6 mg/kg. 1st endpoint is ORR, 2nd endpoints include safety, other efficacy parameters, PK, ADA, and correlation between CLDN18.2 expression and efficacy. **Results:** As of Dec 28th, 2024, a total of 116 pts with CLDN18.2+ solid tumors including 84 GC/GEJC pts were enrolled in expansion cohorts at doses of 2.4 mg/kg, 3.0 mg/kg and 3.6 mg/kg, with median age of 59 years, median lines of prior treatment 2, 80.2% received checkpoint inhibitors and 18.6% topo1i-containing therapies. The most common any grade TEAE (≥ 20%) in all patients were nausea, vomiting, anemia, appetite ↓, WBC ↓, neutrophil ↓, asthenia, hypoalbuminemia, platelet ↓, body weight ↓, and hypokalemia. The most common ≥ G3 TEAEs (≥5%) were neutrophil ↓, WBC ↓, anemia, lymphocyte ↓, and asthenia. TEAEs leading to dose interruption at 2.4, 3.0 and 3.6 mg/kg were 15.2%, 26% and 60%, dose reduction 10.9%, 26%, and 65%, and dose discontinuation 10.9%, 8%, and 0%. 1 pt at 3.0 mg/kg experienced TEAE leading to death (pneumonia). Safety profile was consistent with that of dose escalation part. In the 84 GC/GEJC pts enrolled in dose expansion, 75 pts were evaluable with at least one post baseline scan. The BOR and DCR across dose groups were 46.7% and 88.0%, respectively. Efficacy in each dose group was summarized in the table below. The median follow up was 4.3M, 4.0M and 7.0M for 2.4, 3.0, and 3.6 mg/kg. Preliminary anti-tumor activity was also observed in pts who had prior CPI and topo 1i containing treatments, as well as in other CLDN18.2+ solid tumor pts. **Conclusions:** In the expansion cohorts,XNW27011 demonstrated promising anti-tumor activity and favorable safety profile in GC/GEJC pts with wide expression level of CLDN18.2.The results support further development of XNW27011 in CLDN18.2+ GC/GEJC. Clinical trial information: CTR20231735. Research Sponsor: Evopoint Biosciences, Co. Ltd.

	2.4 mg/kg N=27	3.0 mg/kg N=30	3.6 mg/kg N=18
BOR, n (%)	7 (25.9%)	16 (53.3%)	12 (66.7%)
PR (confirmed)	4 (14.8%)	9 (30%)	6 (33.3%)
cPR Pending	2 (7.4%)	5 (16.6%)	3 (16.7%)
DCR, n (%)	23 (85.2%)	27 (90.0%)	16 (88.9%)

3035 **Poster Session**

Results from a phase 1/2 study of 7MW3711: A novel B7-H3 antibody-drug conjugate (ADC) incorporating a topoisomerase I inhibitor in patients with advanced solid tumors. First Author: Zhiye Zhang, Department of Medical Oncology, The First Affiliated Hospital of Henan University of Science and Technology, Luoyang, China

Background: 7MW3711 is a B7-H3 targeting ADC comprised of a recombinant humanized monoclonal anti-human B7-H3 antibody conjugated to the topoisomerase I inhibitor via a protease cleavable linker. B7-H3 is upregulated in several malignant cancers, such as lung, ovarian, breast, prostate and esophageal cancer, which plays an important role in multiple processes such as tumor occurrence, development, and immune escape. Here we present the safety and efficacy data of 7MW3711 from a first-in-human phase 1/2 study. **Methods:** The study enrolled patients (pts) with advanced solid tumor across three segments: dose-escalation (D-esc), dose-expansion (D-exp) and cohort-expansion. In the D-esc and D-exp phase, 7MW3711 was administered intravenously at doses of 1.5, 3.0, 4.5, 6.0 mg/kg every three weeks (Q3W); 4.0 mg/kg every two weeks (Q2W). **Results:** As of the data cutoff on Jan 2, 2025, 43 pts were enrolled and received at least one dose of 7MW3711 (D-esc, n = 15; D-exp, n = 28). At baseline, the median of prior lines of therapy for all pts was 2 (range, 1-9). No dose-limiting toxicities (DLTs) were observed in the D-esc phase. The maximum tolerated dose (MTD) has not yet been reached. The most common Grade ≥3 TRAEs (≥5% of pts) were decreased white blood cell count, anemia, decreased neutrophil count, decreased lymphocyte count, decreased platelet count, diarrhea, and hypokalemia. Among 33 pts treated with 7MW3711 at 4.0 mg/kg or above and reaching tumor assessment, 8 partial responses (PRs) were observed. The objective response rate (ORR) and disease control rate (DCR) were 24.2% and 84.8%, respectively. 15 pts diagnosed with esophageal cancer (EC), ovarian cancer (OC) and prostate cancer (PC) were enrolled at 4.5 mg/kg or above and were evaluable for tumor assessment. All EC pts had previously progressed after receiving platinum-based chemotherapy and immune checkpoint inhibitors. All OC pts were platinum-resistant. All PC pts had previously progressed after receiving docetaxel and endocrine therapy. The ORR of EC, OC and PC was 33.3%, 60.0% and 50.0%, respectively. The DCR of EC, OC and PC was 100.0%. Objective responses were also observed in pts with other solid tumor types, such as lung adenocarcinoma and breast cancer. **Conclusions:** The data indicated encouraging efficacy of 7MW3711 in advanced EC, OC and PC. The safety profile showed adequate tolerability. The dose optimization and expansion study is continuing to establish the RP2D for 7MW3711. Clinical trial information: NCT06008366. Research Sponsor: Mabwell (Shanghai) Bioscience Co., Ltd.

3036 **Poster Session**

Results from a phase 1/2 study of 7MW3711: A novel B7-H3 antibody-drug conjugate (ADC) incorporating a topoisomerase I inhibitor in patients with lung cancer. First Author: Ziming Li, Shanghai Chest Hospital, Shanghai Lung Cancer Clinical Medical Center, Shanghai, China

Background: 7MW3711 is a B7-H3 targeting ADC comprised of a recombinant humanized monoclonal anti-human B7-H3 antibody conjugated to the topoisomerase I inhibitor via a protease cleavable linker. B7-H3 is upregulated in several malignant cancers, such as lung, ovarian, breast, prostate and esophageal cancer, which plays an important role in multiple processes such as tumor occurrence, development, and immune escape. Here we present the safety and efficacy data of 7MW3711 from a first-in-human phase 1/2 study. **Methods:** The study enrolled patients (pts) with advanced solid tumor across three segments: dose-escalation (D-esc), dose-expansion (D-exp) and cohort-expansion. In the D-esc and D-exp phase, 7MW3711 was administered intravenously at doses of 1.5, 3.0, 4.5, 5.0, 6.0 mg/kg every three weeks (Q3W). **Results:** As of the data cutoff on Jan 8, 2025, 37 pts with lung cancer were enrolled and received at least one dose of 7MW3711 (D-esc, n = 25; D-exp, n = 12), which included 16 pts with small cell lung cancer (SCLC) and 21 pts with non-small cell lung cancer (NSCLC). At baseline, the median of prior lines of therapy for all pts was one (range, 1-5). Five pts experienced dose-limiting toxicities (2 pts at 5.0 mg/kg; 3 pts at 6.0 mg/kg), including decreased platelet count, decreased neutrophil count, myelosuppression and decreased appetite. The maximum tolerated dose (MTD) has not yet been determined. The most common Grade ≥3 TRAEs (≥5% of pts) were decreased neutrophil count, decreased white blood cell count, anemia, decreased lymphocyte count, decreased platelet count, hyponatremia, hypokalemia, and myelosuppression. Among 25 pts treated with 7MW3711 at 4.5 mg/kg or above and reaching tumor assessment, 9 partial responses (PRs) were observed. The overall objective response rate (ORR) and disease control rate (DCR) were 36.0% and 96.0%, respectively. 8 pts diagnosed with SCLC were enrolled at 4.5 mg/kg and were evaluable for tumor assessment. All 8 SCLC pts had previously progressed after receiving platinum-based chemotherapy and immune checkpoint inhibitors. The ORR and DCR of them were 62.5% and 100.0%, respectively. Among pts with B7-H3 H-score > 5, the ORR and DCR of lung squamous cell carcinoma (Sq-NSCLC) at 4.5 mg/kg or above were 37.5% (3/8) and 87.5% (7/8), respectively. **Conclusions:** The data indicated encouraging efficacy of 7MW3711 in SCLC and Sq-NSCLC. The safety profile showed adequate tolerability. The dose optimization and expansion study is continuing to establish the RP2D for 7MW3711. Clinical trial information: NCT06008379. Research Sponsor: Mabwell (Shanghai) Bioscience Co., Ltd.

3037 **Poster Session**

First-in-human trial of SYS6010 combined with SYH2051 in patients with advanced gastrointestinal tumors. First Author: Rongbo Lin, Gastrointestinal Medical Oncology, Fujian Cancer Hospital, Fuzhou, China

Background: SYS6010 is an antibody-drug conjugate (ADC) composed of an EGFR-specific antibody, a cleavable linker, and JS-1, a topoisomerase I inhibitor, as its cytotoxic payload. It targets EGFR, a transmembrane receptor tyrosine kinase overexpressed in malignancies such as lung, breast, gastric, and colorectal cancers. SYS6010 induces DNA damage leading to apoptosis, while resistance may occur through ATM-mediated DNA repair. SYH2051, an ATM inhibitor, disrupts DNA repair, enhancing SYS6010-induced apoptosis. This combination is hypothesized to exert synergistic antitumor effects. **Methods:** This first-in-human clinical trial employed a single-center, open-label, non-randomized design to evaluate the safety, tolerability, and preliminary efficacy of SYS6010 combined with SYH2051. Patients with advanced gastrointestinal tumors expressing EGFR who had progressed on at least one prior line of standard therapy were enrolled. SYS6010 was administered intravenously at a dose of 3.2 mg/kg on day 1 of each 14-day cycle, while SYH2051 was given orally at doses of 40 mg or 80 mg, once daily, for five consecutive days within the same cycle. Safety was assessed using CTCAE v5.0, and efficacy was evaluated according to RECIST v1.1 criteria. **Results:** As of December 31, 2024, 25 patients were enrolled, including 18 with colorectal cancer and 7 with gastric cancer. Twelve patients had received ≥3 prior lines of therapy. Among 6 evaluable gastric cancer patients, 3 achieved partial response (PR) and 3 stable disease (SD), resulting in an objective response rate (ORR) of 50% and a disease control rate (DCR) of 100%. The median progression-free survival (PFS) was approximately 5.8 months (data not mature), and 3 patients remained on treatment. Among 18 colorectal cancer patients (9 with KRAS mutations and 9 wild-type), preliminary analysis showed a median PFS of approximately 4.2 months in wild-type KRAS patients (data not mature). Common treatment-related adverse events (TRAEs) included hematologic toxicity, gastrointestinal symptoms, and fatigue. Frequently observed TRAEs were fatigue (60%), decreased appetite (56%), leukopenia (56%), anemia (48%), neutropenia (48%), nausea (48%), thrombocytopenia (36%), and hypoalbuminemia (32%). Grade ≥3 TRAEs occurred in 12 patients (48%), including neutropenia (7 patients), anemia (6 patients), thrombocytopenia (3 patients), vomiting (3 patients), leukopenia (2 patients), interstitial lung disease (1 patient), infection (1 patient), and elevated bilirubin (1 patient). No treatment-related deaths were reported. **Conclusions:** SYS6010 combined with SYH2051 was well tolerated and demonstrated preliminary antitumor activity in advanced gastrointestinal tumors, particularly in gastric cancer. Further evaluation is ongoing. Research Sponsor: CSPC Pharmaceutical Group Limited.

3038 **Poster Session**

Precemtabart tocentecan (M9140), an anti-CEACAM5 ADC with exatecan payload, in patients with metastatic colorectal cancer (mCRC): Results from the dose optimization of the phase 1 PROCEADE CRC-01 study. First Author: Scott Kopetz, The University of Texas MD Anderson Cancer Center, Houston, TX

Background: CEACAM5 is overexpressed in ~90% of CRCs, with limited expression on healthy cells. Precemtabart tocentecan (M9140), the first anti-CEACAM5 ADC with an exatecan payload (topoisomerase 1 inhibitor), showed a predictable, manageable safety profile and promising early clinical activity in the dose escalation of the Phase 1 PROCEADE-CRC-01 study (NCT05464030) in heavily pretreated patients with mCRC. **Methods:** This global Phase 1 study in 3L adult patients with locally advanced/mCRC (ECOG PS ≤1; previous irinotecan therapy) evaluates clinical activity, safety, and tolerability of precemtabart tocentecan. Here, we report on dose optimization of precemtabart tocentecan tested at 2.8 mg/kg Q3W (Arm A1) or 2.4 mg/kg Q3W (A2; 1:1 randomization) to select the recommended phase 2 dose (RP2D). **Results:** As of Jan 2025, 60 patients (recruited Apr–Oct 2024) had been treated (A1, n = 29; A2, n = 31). Median age was 60.0 years, and 51.7% were male. In A1, 18 (62.1%) patients remained on treatment and 16 (51.6%) in A2. Treatment-emergent AEs (TEAEs) were reported in all patients; grade ≥3 in 38 (63.3%) patients (A1: n = 19 [65.5%]; A2: n = 19 [61.3%]); anemia and neutropenia (any grade; grade ≥3) were most common. Serious TEAEs were reported in 18 (30.0%) patients (A1: n = 8 [27.6%]; A2: n = 10 [32.3%]). Grade ≥3 hematologic AEs were reported in 32 (53.3%) patients: anemia (A1, n = 9; A2, n = 10), neutropenia (A1, n = 14; A2, n = 12), thrombocytopenia (n = 6 both), leukopenia (A1, n = 7; A2, n = 6), lymphopenia (A1, n = 1; A2, n = 2), febrile neutropenia (n = 3 both), and pancytopenia (A1, n = 0; A2, n = 1). Treatment was discontinued in 26 (43.3%) patients (A1: progressive disease (PD), n = 9, patient withdrawal, n = 1, other, n = 1; A2: PD, n = 14, death, n = 1). No treatment-related deaths were reported. Overall, PK profiles were consistent with previous data, with overlap attributed to high between-subject variability. Partial responses were reported in 7 (24.1%; n = 4 [13.8%] confirmed) patients in A1 and 3 (9.7%; n = 1 [3.2%] confirmed) in A2 (all responders remain on treatment), stable disease in 15 (51.7%) and 21 (67.7%), and PD in 5 (17.2%) and 6 (19.4%) patients, respectively. DCR at 12 weeks was 72.4% in A1 and 67.7% in A2. **Conclusions:** These preliminary results corroborate the encouraging efficacy and safety data from the dose escalation part of the PROCEADE CRC-01 study, with no new relevant safety findings. ORR was higher at 2.8 mg/kg, with similar tolerability at both doses. The ORR of 24.1% (13.8% confirmed) at 2.8 mg/kg compares favorably with current monotherapy SoCs (ORRs 1-2%) and recent phase 3 data with trifluridine–tipiracil + bevacizumab (ORR 6.1%) in 3L+ mCRC. These results suggest 2.8 mg/kg as the RP2D for further development in CRC, and other solid tumors (NCT06710132). More mature data, including PFS, will be presented at the congress. Clinical trial information: NCT05464030. Research Sponsor: the healthcare business of Merck KGaA, Darmstadt, Germany (CrossRef Funder ID: 10.13039/100009945).

3039 **Poster Session**

Rinatabart sesutecan (Rina-S) for patients with advanced endometrial cancer: First disclosure from dose expansion cohort B2 of the GTC1184-01 study. First Author: Ira Seth Winer, Wayne State University, Barbara Ann Karmanos Cancer Center, Detroit, MI

Background: Rina-S is an investigational antibody-drug conjugate targeting folate receptor alpha with a novel hydrophilic protease-cleavable linker and a topoisomerase I inhibitor, exatecan payload. Patients (pts) with advanced endometrial cancer (EC) who progress after programmed death-ligand 1 [PD-(L)1] inhibitor plus chemotherapy have very poor prognoses and limited, ineffective treatment options (objective response rate [ORR] < 16% and median progression-free survival < 5 months with single-agent chemotherapy); thus, there is urgent need for novel therapies. In the dose escalation cohort, single-agent Rina-S showed preliminary anti-tumor activity in pts with heavily pretreated EC. Here we first report results for single-agent Rina-S in pts with heavily pretreated EC from dose expansion cohort B2 of the phase 1/2 GCT1184-01 study (NCT05579366). **Methods:** Pts with metastatic or unresectable EC who received prior platinum-based chemotherapy and a PD-(L)1 inhibitor received either Rina-S 100 mg/m^2 or 120 mg/m^2 every 3 weeks after initial enrollment with 120 mg/m^2 only. The primary endpoint was safety and tolerability of Rina-S. Secondary endpoints included ORR and disease control rate (DCR). **Results:** As of data cutoff November 22, 2024, 64 pts with heavily pretreated EC (median 3 prior lines [range 1-8]) received Rina-S 100 mg/m^2 (n = 22) or 120 mg/m^2 (n = 42) for a median treatment duration of 15.9 weeks. Most pts had ECOG PS 1 (64.1%), approximately half (46.9%) were aged ≥70 years, and 48.4% had received prior radiotherapy. Pts primarily had endometrioid carcinoma (45.3%) followed by serous carcinoma (26.6%). The most common (> 25%) treatment-emergent adverse events (TEAEs) were similar across doses and were primarily cytopenias and grade 1-2 gastrointestinal events (nausea, vomiting, decreased appetite). Grade 3-4 cytopenia included neutropenia (48.4%), anemia (35.9%) and thrombocytopenia (21.9%). TEAEs led to Rina-S dose reductions in 15.6% of pts and discontinuation of Rina-S in 3.1% of pts; 37.5% of pts had serious TEAEs. There was 1 related (assessed by investigator) grade 5 TEAE at 120 mg/m^2 confounded by comorbidities; no fatal TEAEs occurred at 100 mg/m^2. No signals of ocular toxicity, neuropathy, or interstitial lung disease were observed. In efficacy-evaluable pts (median follow-up: 18.7 weeks), the unconfirmed ORR was 50%, including 2 complete responses, with Rina-S 100 mg/m^2 (n = 22) and 45.5% with 120 mg/m^2 (n = 33). DCR was 100% and 81.8% with 100 mg/m^2 and 120 mg/m^2, respectively. Responses were ongoing for 9 of 11 (81.8%) and 12 of 15 (80.0%) responders with 100 mg/m^2 and 120 mg/m^2, respectively. **Conclusions:** Rina-S showed encouraging anti-tumor activity in pts with heavily pretreated EC and had a manageable safety profile consistent with previous reports. Further evaluation of single-agent Rina-S in pts with advanced EC is ongoing. Clinical trial information: NCT05579366. Research Sponsor: Genmab A/S.

3040 **Poster Session**

EVEREST-2: Initial data of the logic-gated Tmod chimeric antigen receptor T-cell (CAR T) therapy A2B694 for patients with solid tumors associated with mesothelin (MSLN) expression and with human leukocyte antigen (HLA) loss of heterozygosity (LOH). First Author: Salman Rafi Punekar, Perlmutter Cancer Center, NYU Langone Health, New York, NY

Background: EVEREST-2 is a first-in-human, phase 1/2 trial to assess the safety and efficacy of A2B694, an autologous, logic-gated Tmod CAR T therapy targeted to MSLN, which is normally expressed in the mesothelium and can be upregulated in many solid tumors. A2B694 is designed to overcome challenges of on-target, off-tumor toxicity that have limited other MSLN-targeted approaches by combining a CAR-activating receptor targeting MSLN with a blocker CAR that recognizes HLA-A*02, to distinguish between normal and tumor cells (Tokatlian, et al. *J Immunother Cancer.* 2022). **Methods:** Adults with recurrent unresectable, locally advanced, or metastatic cancers with MSLN expression who have progressed after standard-of-care therapy are eligible for EVEREST-2. Enrollment to EVEREST-2 and collection of T-cells occurs through the ongoing pre-screening study BASECAMP-1 (NCT04981119). When clinically appropriate, A2B694 is manufactured from cryopreserved T cells, and patients undergo lymphodepletion before A2B694 infusion. The dose-escalation phase is evaluating the safety and tolerability of A2B694 to identify the recommended phase 2 dose (RP2D). Dose escalation was started at 1x10^8 Tmod positive cells (dose level [DL] 1) and will increase up to 14x10^8 in combination with low-dose IL-2 (DL 5). The dose-expansion phase will confirm RP2D and collect biomarker data to further characterize A2B694. **Results:** As of January 15, 2025, 5 participants (median age: 60 years; range, 50-84) have enrolled on EVEREST-2 and received A2B694 at DLs 1-2; participants had ovarian cancer (n = 3), pancreatic cancer (n = 1), and non-small cell lung cancer (n = 1) and had received a median of 4 prior lines of therapy (range, 1-7). Lymphodepleting chemotherapy was well tolerated with no significant cytopenias observed. The most common adverse events were lymphopenia (7 [14.6%]) and decreased appetite (6 [12.5%]). There were no dose-limiting toxicities, cytokine release syndrome, nor related neurotoxicity. One participant was admitted to the hospital for decreased appetite. No long-term toxicities have been noted up to 7.5 months post-infusion. Of the participants who have received A2B694, 5 were efficacy evaluable at DLs 1-2. A2B694 was detected post-infusion in the peripheral blood in all patients. Additionally, A2B694 was detected in an abdominal tumor biopsy from a patient with pancreatic cancer 42 days post-infusion. **Conclusions:** The logic-gated approach was successful at reducing toxicity seen with prior MSLN-targeted CAR T therapies, and A2B694 showed successful CAR T expansion and tumor infiltration. The maximum tolerated dose has not been reached, and results from the dose-escalation phase continue to determine the RP2D. Clinical trial information: NCT06051695. Research Sponsor: A2 Biotherapeutics, Inc.

3041 **Poster Session**

ZL-1310, a DLL3 ADC, in patients with extensive stage small cell lung cancer: Ph1 trial update. First Author: Manish R. Patel, Florida Cancer Specialists/Sarah Cannon Research Institute, Sarasota, FL

Background: Treatment options are limited for patients (pts) with extensive-stage small cell lung cancer (ES-SCLC) that progress after platinum-based chemotherapy (chemo). ZL-1310, a DLL3-targeted antibody drug conjugate (ADC) with a topoisomerase 1 inhibitor payload and cleavable linker, demonstrated promising preliminary results in pts with relapsed/refractory (r/r) ES-SCLC (Spira et al, ENA 2024). Here, we report updated data with additional pts and follow-up (NCT06179069). **Methods:** This is a two-part Phase I study of ZL-1310 administered intravenously every 3 weeks to pts with r/r SCLC who have progressed after at least one platinum-based chemo regimen. Part 1A is a monotherapy dose escalation; Part 2 is a randomized dose optimization/expansion. Study endpoints include safety parameters, objective response rate (ORR) per RECIST v1.1, duration of response (DOR), disease control rate (DCR) and pharmacokinetics (PK). Exploratory tumor biomarkers, including DLL3 expression (expressed as H-score), are examined. **Results:** As of 28 Jan 2025, 28 pts were enrolled in the dose escalation Part 1A and received ZL-1310 at dose levels ranging from 0.8 mg/kg to 2.8 mg/kg. The median time on study is 5.1 months (range 2.4-10.1+). Median age was 66 years (range 36-79); 43% were female; 75% had an ECOG performance status of 1; 93% progressed after prior anti-PD-L1 therapy; 39% had prior lung irradiation, and 36% had baseline brain metastases. Any-grade treatment-related adverse events (TRAEs) occurred in 89% of pts (Grade≥3 TRAEs, 39%). One pt (2.4 mg/kg) had dose limiting toxicities of neutropenia and thrombocytopenia; 5 pts underwent drug reduction and 5 had drug discontinued due to TRAE. Grade≥3 TRAEs occurring in more than 1 patient include anemia (6 pts), neutropenia (5), thrombocytopenia (3), WBC decreased (2), and interstitial lung disease (2). Objective responses were observed in 19 of 28 pts (68%), including one pt pending response confirmation, and a DCR of 93%. Responses were observed across all dose levels and all levels of DLL3 expression (H-score range: 0-260), including one pt with prior tarlatamab treatment. Pts with baseline brain metastases had an 80% response rate and 100% DCR. Fourteen of 19 (74%) responders remain on study. PK data from 25 pts showed dose-proportional increase of systemic ADC and payload exposure, with relatively low exposure of the payload and no significant accumulation. **Conclusions:** ZL-1310 demonstrated a tolerable safety profile and promising antitumor activity in r/r ES-SCLC, including pts with brain metastases, pt with prior tarlatamab, and in the setting of low DLL3 expression. Updated data, including patients in the randomized Part 2 dose optimization, will be presented. Clinical trial information: NCT06179069. Research Sponsor: None.

3042 **Poster Session**

First-in-human (FIH) phase 1 study of CUSP06, a cadherin-6 (CDH6)-directed antibody-drug conjugate (ADC), in patients with platinum-refractory/resistant ovarian cancer and other advanced solid tumors. First Author: Manish R. Patel, Sarah Cannon Research Institute/Florida Cancer Specialists, Sarasota, FL

Background: CDH6 is a transmembrane glycoprotein involved in cancer metastasis expressed in various tumors including ovarian cancer (OC), renal cell carcinoma (RCC), cholangiocarcinoma (CCA), and uterine cancer. CUSP06 is an ADC composed of a humanized IgG1 mAb against CDH6 conjugated with a cleavable linker to exatecan, a topoisomerase I inhibitor. In preclinical studies, CUSP06 showed CDH6-dependent cell growth inhibition in OC cell lines and tumor regression in CDH6-expressing OC, RCC, and other tumor models including those with low CDH6 expression supporting its use across various indications and CDH6 expression levels. We report here the initial results from a FIH study of CUSP06. **Methods:** CUSP06-1001 is a Phase 1a/1b, open-label, multi-center dose escalation and expansion study to evaluate safety, tolerability, pharmacokinetics, pharmacodynamics, recommended Phase 2 dose, and preliminary efficacy of CUSP06 in patients (pts) with platinum-refractory/resistant ovarian cancer (PRROC), advanced RCC and other advanced CDH6-positive solid tumors. Prescreening for CDH6 expression was required for those pts with solid tumors other than OC or RCC. CUSP06 was administered IV every 21 days. Phase 1a followed a standard 3+3 dose escalation design and included dose enrichment cohorts at doses that had demonstrated safety. Phase 1b consists of dose expansion cohorts for pts with OC, RCC, and other CDH6-positive solid tumors to assess the safety, tolerability and efficacy at the RDE. **Results:** As of 03JAN25, 26 pts were dosed with data available for 22 pts in Phase 1a (18 OC, 2 RCC, and 2 CCA) at doses from 1.6 mg/kg to 5.6 mg/kg. The median age was 60.5 yrs and the median prior therapies was 3. Of the 18 pts with OC, all pts received prior platinum and taxane, 67% received bevacizumab, and 22% received mirvetuximab (MIRV). All patients with RCC received an immune checkpoint inhibitor and a TKI. Related TEAEs occurred in 20 pts (91%). The most common related TEAEs ($>$ 20%) were anemia (50%), neutropenia (46%), thrombocytopenia (46%), fatigue (46%), nausea (36%), diarrhea (23%), and vomiting (23%). The most common related Grade $\geq$3 TEAEs were neutropenia, thrombocytopenia, and anemia. AEs led to discontinuation in 3 (14%) pts. Five of 14 GCIG-evaluable OC pts (36%) had a CA-125 response. Among the 20 RECIST-evaluable pts, 5 partial responses (4 confirmed, & 1 unconfirmed) including MIRV-pretreated pts, and 11 stable disease were observed. All PRs were in pts with platinum-resistant high grade serous OC, with an ORR of 36% (5/14). 18 pts were ongoing at the cutoff date. **Conclusions:** The preliminary data from the Phase 1a dose escalation portion of this study showed acceptable tolerability and encouraging efficacy in pts with OC, which support further evaluation of CUSP06 in the Phase 1b expansion cohorts. Clinical trial information: NCT06234423. Research Sponsor: None.

3043 **Poster Session**

Phase 1 dose-escalation trial of talazoparib in combination with belinostat in select advanced solid tumors. First Author: Monika L. Burness, University of Michigan Rogel Cancer Center, Ann Arbor, MI

Background: Inhibitors of histone deacetylase (HDACi) may synergize with poly (ADP-ribose) polymerase inhibitors (PARPi). This Phase 1 dose escalation trial tested the combination of the PARPi talazoparib and the HDACi belinostat. **Methods:** This open-label study was conducted with a combined dose escalation of talazoparib (0.75 mg-1 mg) and belinostat (500-1000 mg/m2) in subjects with advanced breast, ovarian, prostate and pancreatic cancers. Primary objectives were to identify the safety, tolerability, and recommended phase 2 dose (RP2D) of the combination. A TITE-CRM model was used for dose level assignment and identification of RP2D. **Results:** A total of 25 evaluable subjects were enrolled. Tumor types included breast cancer (10 subjects), ovarian cancer (5), prostate cancer (5), and pancreatic cancer (5). Treatment-related adverse events (AEs) included nausea (n = 8, 32%), fatigue (n = 8, 32%), thromboembolic events (n = 6, 24%), vomiting (n = 5, 25%), and anemia (n = 4, 16%). Treatment-related serious adverse events (SAEs) encompassed thromboembolic events (n = 4) and anemia (n = 1). Dose limiting toxicities (DLTs) occurred in 3 subjects including decreased white blood cell count, fatigue, anemia, and failure to thrive. Seven subjects experienced stable disease (SD), for a clinical benefit rate (CBR) of 28% (7/25); of those with SD, 6 were assigned to the highest dose (dose level 4) and 1 subject was assigned to dose level 3. Duration of enrollment ranged from 18-291 days. **Conclusions:** In subjects with select advanced solid tumors, talazoparib and belinostat combination therapy exhibits a favorable safety profile and manageable toxicity. Nausea and fatigue were the most common adverse events. Further studies are warranted to determine the efficacy of this combination. Clinical trial information: NCT04703920. Research Sponsor: Pfizer; Acrotech.

3044 **Poster Session**

Impact of stereotactic ablative radiotherapy (SABR) on detection of ctDNA in patients with early-stage lung cancer: Interim findings from the prospective SABR-DETECT trial. First Author: Saurav Verma, Verspeeten Family Cancer Centre, Schulich School of Medicine and Dentistry, Western University, London, ON, Canada

Background: Stereotactic ablative radiotherapy (SABR) is the preferred curative treatment for inoperable patients with stage I/IIA non–small-cell lung cancer (NSCLC). In cases where the tumor is inaccessible or biopsy carries a high risk of complications, SABR is offered even in the absence of a tissue diagnosis, based on a high likelihood of malignancy as calculated by validated predictive models. In these situations, a blood based liquid biopsy detecting circulating tumor DNA (ctDNA) can serve as an aide to confirm malignancy and allow molecular testing. However, low ctDNA yield in early stage NSCLC presents a challenge for diagnosis. This study hypothesizes that ctDNA detection rates will improve by combining assessment of pre- and post-SABR plasma samples. **Methods:** This is a multi-institutional study including two cohorts: 1) patients with suspected stage I/IIA NSCLC, with a pretreatment likelihood of malignancy of ≥60% on Herder or Brock models, and 2) patients with biopsy-proven NSCLC. SABR was delivered according to standard guidelines. Plasma was collected for ctDNA analysis before and 24-72 hours following the first fraction of SABR. SHIELDING ULTRA MRD panel of hotspot regions in 2365 cancer-related genes with ultra-high sensitivity was used for ctDNA analysis (mutation + fragment profile + CNV). In this pre-planned interim analysis, we report on the secondary objective: to assess the impact of SABR on detection rates of ctDNA. **Results:** Paired plasma samples (pre- and post-SABR) were tested for 69 patients. After quality control analysis, 66 paired samples were analyzed and included in this interim analysis. The median age was 76 years (range, 56-89) and 36 (54%) were male. The median concentration of circulating free DNA (ng/mL) did not increase from pre- (5.5, inter quartile range (IQR): 3.3-8.1) to post-SABR (5.7, IQR: 4.1-7.6) (P=0.82). The ctDNA detection rate in pre-SABR samples was 22.7% versus 27.3% in post-SABR samples (Table). Interestingly, in 10 patients (15.2%), ctDNA became detectable in post-SABR samples and in 7 patients (10.6%) the ctDNA was no longer detectable in the post-SABR samples. The ctDNA remained undetectable in 41 patients (62.1%). 37.9% of patients had detectable ctDNA either before or after SABR. **Conclusions:** The diagnostic yield of ctDNA for confirming malignancy in early stage NSCLC is improved by testing both the pre- and the post-SABR samples, collected within 24-72 hours after the first fraction of SABR. This approach may improve the diagnostic rates of liquid biopsies for patients with presumed NSCLC undergoing SABR, warranting further investigation of ctDNA detection before and shortly after treatment. Clinical trial information: NCT05921474. Research Sponsor: Verspeeten Family Cancer Centre Medical Oncology Research Fund (MORF); Lawson Internal Research Fund; Lung Cancer Canada Geoffrey Ogram Memorial Research Grant; 'Crush it with Bev' fundraiser.

ctDNA detection rates (N=66).

Pre-SABR	Post-SABR	n (%)
detected	detected	8 (12.1%)
not detected	detected	10 (15.2%)
detected	not detected	7 (10.6%)
not detected	not detected	41 (62.1%)

3045 **Poster Session**

Prognostic significance of preoperational circulating tumor DNA detection in early-stage NSCLC using a tissue-free blood test. First Author: Naixin Liang, Peking Union Medical College Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China

Background: There is a growing need for risk evaluation and treatment monitoring in cancer care. However, current methods, mainly imaging, can be burdensome for patients over time and prone to variability among readers. Recent research has highlighted the potential of tumor-informed circulating tumor DNA (ctDNA) testing for identifying postoperative minimal residual disease (MRD) due to its high sensitivity by tracking individualized mutations. Nevertheless, its use in early-stage patients prior to surgery is constrained by limited tissue availability and extended turnaround times. MUSETALK-Lung01 (multiomics sequencing technique application kick-start) is a prospective, longitudinal, observational study designed to evaluate the clinical utility of a tumor-naïve ctDNA assay in patients with early-stage non-small cell lung cancer (NSCLC). **Methods:** Pretreatment plasma samples were prospectively collected from participants with stage I-IIIA NSCLC. Cell-free DNA was extracted and analyzed using a blood assay that interrogates both epigenetic and genetic information. The detection status and the estimated fraction of ctDNA were reported by a machine learning classifier and an independent statistical model, respectively. The calling threshold corresponding to a 99% clinical specificity was verified in a subgroup from the THUNDER study (NCT04820868). Longitudinal data, including vital status, cancer status, and treatment, were collected for up to 5 years. The study was approved by the institutional review board and all participants were required to provide informed consent. **Results:** A total of 289 participants from the MUSETALK-Lung01 study were analyzed. Of these, 49% (141/289) reached the 5-year follow-up, with a median follow-up duration of 59 months. To assess the prognostic value of preoperative ctDNA levels, relapse-free survival (RFS) and overall survival (OS) were evaluated across different stages and pathological subtypes separately. In stage I LUAD patients (N = 179), ctDNA-positive patients (N = 20) had significantly inferior RFS compared to ctDNA-negative patients (2-year RFS: 70% [95% CI: 46%–88%] vs. 94% [95% CI: 90%–97%]; log-rank $p < 0.001$). In contrast, no association was found between preoperative ctDNA detection and RFS in stage II-IIIA LUAD or non-LUAD NSCLC, irrespective of the clinical stage. Specifically, among the 179 stage I LUAD patients, 11 relapsed within 2 years, and 6 of these had positive ctDNA test results. This rate was significantly higher than in patients who relapsed between 2 and 5 years (1/12) or never relapsed (13/156; χ^2 test, $p < 0.001$). **Conclusions:** These findings indicate that presurgical ctDNA can serve as a prognostic indicator in early-stage NSCLC. Tumor-naive ctDNA testing may enhance the standard workflow by identifying high-risk patients who could benefit from innovative treatments. Clinical trial information: NCT04820868. Research Sponsor: None.

3046 **Poster Session**

Improved detection of circulating tumor DNA in patients with leiomyosarcoma with fragment size restriction. First Author: Nensi M. Ruzgar, Dana-Farber/Boston Children's Cancer and Blood Disorders Center, Boston, MA

Background: Prior work has shown that detection of circulating tumor DNA (ctDNA) at time of diagnosis of leiomyosarcoma (LMS) is associated with lower likelihood of objective response and patients with detectable ctDNA after two cycles of chemotherapy have worse survival. However, because ctDNA exists at much lower concentrations in plasma compared to cell-free DNA of non-tumor origin, the sensitivity of these prognostic measures to tumor signals remains unclear. With increasing evidence of ctDNA fragments being shorter than the background non-tumor cell-free DNA, we sought to test whether restricting our analysis to smaller fragment sizes would improve detection of ctDNA in LMS. **Methods:** Plasma was serially collected from patients with LMS undergoing chemotherapy. Cell-free DNA extracted from these samples was profiled by ultra-low-passage whole-genome sequencing (ULPWGS). Copy number alterations were identified and used to detect ctDNA using the ichorCNA algorithm before and after restricting the dataset to fragments of 90-150bp (short). We compared detectability of ctDNA via ichorCNA between analyses using all sequencing data and those using data restricted to short fragments. **Results:** From 28 patients, 126 plasma samples were profiled. The median fragment length of cell-free DNA was 240bp (IQR 142-349) for patients with LMS, compared to 307bp (IQR 171-465, $p < 0.001$) in samples collected from healthy controls. Short fragments made up 19.48% of LMS libraries at diagnosis when ctDNA levels were highest, 15.27% of all LMS samples, and 12.96% of libraries from healthy controls. While ctDNA was detectable by ULPWGS in 17% of all samples, detection increased to 40% when analyzed using only short cell-free DNA fragments ($p < 0.0001$). The proportion of diagnostic samples with detectable ctDNA was nominally higher when analyzed by short fragments (39% vs. 64% with 90-150bp size restriction, p = 0.1078, n = 28) and was significantly higher in samples collected after two cycles of chemotherapy (5% vs. 40% with 90-150bp size restriction, p = 0.0197, n = 20). Increases in ctDNA detectability with fragment size restriction were also observed in each of localized and metastatic subgroups (metastatic: 16% without restriction, 38% with restriction, n = 97, p = 0.0012; localized: 17% vs. 45%, n = 39, p = 0.04). **Conclusions:** Our results demonstrate that detection of ctDNA is improved by analyzing short fragments of cell-free DNA in samples collected from patients with LMS. These findings represent a potential to increase the sensitivity of an affordable, low-coverage liquid biopsy assay and may enhance the prognostic value of ctDNA detection in these patients. Further study of the association between ctDNA detection and outcome is needed to fully validate the impact of fragment size restricted analysis of cell-free DNA samples in patients with LMS and is currently ongoing in a prospective study. Research Sponsor: National Cancer Institute/U.S. National Institutes of Health.

3047 **Poster Session**

Accurate differentiation of malignant and benign gastric lesions using cell-free DNA biomarkers. First Author: Hengzhen Li, Harbin Medical University Cancer Hospital, Harbin, China

Background: Early detection of gastric cancer is challenging due to the invasive nature of current diagnostic methods and the difficulty in distinguishing cancer from benign gastric conditions. Cell-free DNA (cfDNA) features have emerged as promising biomarkers for non-invasive detection. This study aims to develop and evaluate a machine learning model utilizing cfDNA features for early gastric cancer detection. **Methods:** We developed an ensemble machine learning model incorporating four cfDNA features: repeat elements, fragment-based methylation, focal copy number variation, and fragment size pattern. The model was trained using cfDNA data from 150 gastric cancer patients and 153 individuals with stomach-related conditions. The ensemble model was validated using a cohort of 149 cancer patients, 149 individuals with high-risk benign lesions, and 50 low-risk benign lesions. Risk is stratified according to the Correa's Cascade. **Results:** The ensemble machine learning model developed using four cfDNA features achieved an AUROC of 0.913 in the training cohort and 0.912 in the testing cohort for distinguishing gastric cancer patients from individuals with stomach-related complications, which outperformed individual cfDNA features. A decision threshold of 0.418, established via cross-validation, was set to ensure at least 95% sensitivity in the training cohort. This threshold enabled accurate binary classification in the validation cohort, with model scores correlating with cancer stage and tumor differentiation, supporting its potential for clinical risk stratification. Model scores effectively differentiated cancer from high-risk individuals, with significantly lower scores in non-cancer groups compared to precancerous or Stage I–III cancer cases (Non-cancer group median score = 0.35, precancer group median score = 0.48, cancer group median score = 0.61). Additionally, the model assigned significantly higher cancer prediction scores to gastric cancer cases compared to high-grade intraepithelial neoplasia (p = 0.003). In the validation dataset, sensitivities were 92.9% (95% CI: 85.3%–96.7%) for Stage I, 96.3% (95% CI: 81.7%–99.3%) for Stage II, and 100% (95% CI: 83.2%–100%) for Stage III. Sensitivities for well-, moderate, and poorly differentiated tumors were 91.7%, 92.2%, and 100%, respectively. Of note, specificity for the detection of cancer was 66% in the training cohort and 71% in the validation cohort. **Conclusions:** Our findings demonstrate the potential of cfDNA-based machine learning models as a non-invasive and accurate diagnostic tool for early gastric cancer detection. By reducing reliance on invasive procedures, this approach could enhance clinical workflow efficiency and improve patient outcomes. Further validation in larger, independent cohorts is needed to support clinical implementation. Research Sponsor: Heilongjiang Provincial Key R&D Program Projects; "Open competition mechanism" of Heilongjiang Province; "Climbing program" of Harbin Medical University Cancer Hospital.

3048 **Poster Session**

Development of a methylation-based, tissue-free test for the detection of molecular residual disease by circulating tumor DNA. First Author: John Paul Y.C. Shen, Department of Gastrointestinal Medical Oncology, The University of Texas MD Anderson Cancer Center, Houston, TX

Background: Clinical validation studies support tumor-informed molecular residual disease (MRD) as a prognostic biomarker for disease recurrence across multiple solid tumor types. However, these tests are not always feasible due to the occasional lack of tumor tissue for next-generation sequencing. Here, we discuss the design of a test for tissue-free (tf)MRD detection and its application to a cohort of patients with colorectal cancer (CRC). **Methods:** A targeted panel composed of differentially methylated regions was developed. A machine-learning model was trained on differential methylation patterns in order to classify plasma samples as MRD-positive or MRD-negative. Performance of the trained classifier was assessed in an independent cohort of 246 patients enrolled in the Bespoke CRC trial (NCT04264702). These patients had MRD results available using a tumor-informed circulating tumor DNA (ctDNA) assay (SignateraTM), of whom 163 were persistently MRD-negative without clinical progression, and 83 had MRD-positive results. Tissue-free MRD results were compared to the tumor-informed results by calculating the percent positive agreement (PPA) and negative percent agreement (NPA). Clinical outcomes (recurrence-free survival [RFS]) were evaluated based on tfMRD results in all patients and stratified based on whether the patient received adjuvant chemotherapy (ACT). **Results:** In this clinical cohort from Bespoke CRC (72% non-Hispanic White, 54% male, mean age 61.4±12.3 years), 71 (28%) patients had stage II CRC, and 146 (59%) had stage III CRC. Overall, PPA was 86% (95% CI: 77-93%) and NPA was 98% (95% CI: 95-100%). Patients with tfMRD-positive status showed inferior RFS compared to tfMRD-negative patients ($p < 0.001$). Significant benefit from ACT was observed among tfMRD-positive ($p < 0.001$) but not among tfMRD-negative patients (p = 0.19). For patients who did not receive ACT in this cohort, we observed 100% PPV and 100% specificity. **Conclusions:** This is the first study of its kind demonstrating a high concordance between a tfMRD test and a clinically validated tumor-informed ctDNA assay. Similar to recently reported data using a tumor-informed ctDNA assay, patients with tfMRD-positive results appeared to derive benefit from ACT treatment. These findings demonstrate that in cases where tissue is not available or of inadequate quality, a methylation-based tissue-free assay may serve as a potential alternative for MRD detection. Research Sponsor: None.

3049 Poster Session

Prevalence of androgen receptor ligand-binding domain mutations (AR-LBDm) in circulating tumor DNA (ctDNA) versus tissue biopsies in participants (pts) with metastatic castration-resistant prostate cancer (mCRPC) and other tumor types. First Author: Emmanuel S. Antonarakis, University of Minnesota, Masonic Cancer Center, Minneapolis, MN

Background: AR-LBDm is a common mechanism of resistance to AR-directed therapies in patients with mCRPC. However, data on the utility of ctDNA-based versus tissue-based AR-LBDm detection in mCRPC and the prevalence of AR-LBDm in nonprostate cancers are lacking. We evaluated AR-LBDm in ctDNA and tumor tissue samples from pts with advanced solid tumors enrolled in various Merck & Co., Inc. trials. **Methods:** Samples came from pts with mCRPC and 25 other tumor types (eg, bladder, colorectal, ovarian, and pancreatic cancers). AR-LBDm data were available from ctDNA via 2 fixed panel-based ctDNA NGS assays or from tumor tissue samples (mainly archival) via a fixed-panel NGS assay. Data obtained from the 3 assays were nonoverlapping. AR-LBDm prevalence was evaluated in each tumor type and by BRCAm or HRRm status in pts with mCRPC. **Results:** The analysis included 3026 samples assessed by ctDNA assay 1 (mCRPC, n = 1785; other, n = 1241), 2232 samples assessed by ctDNA assay 2 (mCRPC, n = 378; other, n = 1854), and 8181 samples from tissue biopsies (mCRPC, n = 833; other, n = 7348). AR-LBDm was detected in 21.0% of pts with mCRPC by ctDNA assay 1 and 19.8% of pts with mCRPC by ctDNA assay 2. Across all other tumor types, only 1 pt (with hepatocellular carcinoma) had an AR-LBDm in ctDNA. The prevalence of selected AR-LBDm in tissue biopsies was 5.4% (45/833) in pts with mCRPC, 0.6% (1/159) in pts with salivary cancer, and 0% in all other tumor types. AR-LBDm prevalence in pts with mCRPC increased with later-line treatments (Tx) both by tissue and ctDNA analyses and was similar regardless of BRCAm or HRRm status (table). The prevalence of the AR-LBD T878A mutation (by ctDNA) in pts with mCRPC was higher after prior Tx with abiraterone than with enzalutamide (20.9% [43/206] vs 1.7% [3/173]). AR-LBDm was observed in tissues biopsied from the mCRPC setting (prevalence, 12.8% [12/94]) and was associated with higher AR transcriptional activity than in AR-LBD–negative tissues. **Conclusions:** Similar prevalence of AR-LBDm was observed in ctDNA of pts with mCRPC by 2 different ctDNA assays; AR-LBDm prevalence in archival tissue samples was lower than by ctDNA analysis, likely due to the Tx-emergent nature of AR-LBDm. AR-LBDm prevalence was similar regardless of BRCAm or HRRm status in mCRPC, although prevalence of certain AR-LBDm is impacted by the specific prior AR-directed Tx. These data support ctDNA-based (rather than tissue-based) AR-LBDm testing in pts with mCRPC. Research Sponsor: Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA.

AR-LBDm prevalence, % (n/N)	Frontline Tx	Later-line Tx
ctDNA assay 1	16.6 (122/734)	23.8 (252/1059)
ctDNA assay 2	Not available	19.8 (75/378)
Tissue biopsy	0.6 (3/535)	4.1 (147/3625)
	AR-LBDm +ve*	**AR-LBDm -ve***
BRCA		
Mut	26.5 (9/34)	73.5 (25/34)
WT	27.5 (95/345)	72.5 (250/345)
HRR		
Mut	28.8 (30/104)	71.2 (74/104)
WT	26.9 (74/275)	73.1 (201/275)

*Per ctDNA assay 1.

3050 Poster Session

A high-performance blood-based DNA methylation test for early detection of gastrointestinal cancers. First Author: Xiaosheng He, The Sixth Affiliated Hospital, Sun Yat-sen University, Guangzhou, China

Background: Early detection of gastrointestinal cancers (GICs), including esophageal cancer (EC), gastric cancer (GC), and colorectal cancer (CRC), remains suboptimal in China due to low screening adherence and limited access to endoscopic procedures. Multi-cancer early detection (MCED) tests present a convenient alternative, yet the efficacy in detecting early-stage GICs has been inadequate. Accurate tumor localization, particularly differentiating between upper and lower GICs, is crucial for determining subsequent diagnostic procedures. In this study, we report the performance of an MCED assay utilizing targeted DNA methylation sequencing to detect GICs. **Methods:** This multicenter, case-control study prospectively enrolled a cohort of 667 GIC patients (203 EC, 263 GC, 201 CRC; stages: I 20.8%, II 26.7%, III 35.7%, IV 16.8%) and 667 non-cancer participants. Plasma cell-free DNA was sequenced using a panel targeting tumor-specific hyper- and hypo-methylation markers. A total of 5120 GIC-specific methylation features were captured. The GIC model was trained using a gradient-boosted tree model, and nested cross-validation was implemented to determine the optimal parameters and evaluate the model's performance of cancer detection. To predict the tissue of origin (TOO), the top 256 features were first selected based on pairwise mutual information for each cancer type. An XGBoost classifier combined with Synthetic Minority Over-Sampling Technique (SMOTE) was trained to determine the TOO. **Results:** The GIC model exhibited robust performance, achieving an area under the curve (AUC) of 0.959 (95% CI: 0.949-0.970), with an overall sensitivity of 86.4% (83.5%-88.8%) at a specificity of 96.0% (94.2%-97.2%). Notably, for stage I-III GICs, which accounted for 83.2% of cases (a proportion consistent with that seen in prospective observational cohort studies of MCED, such as the SYMPLIFY study), the sensitivity reached 84.1% (80.9%-87.0%). The sensitivities for EC, GC, and CRC were 87.2%, 82.9%, and 90.0% respectively. For stage I CRC, the sensitivity of the GIC model reached 79.1% (64.8%-88.6%), comparable to that of multitarget stool DNA tests, and outperformed fecal immunochemical tests (FIT). Regarding tumor localization, the accuracy of TOO across all positive cases was 89.8% (87.0%-92.0%). For stage I-III GICs, the model maintained a high accuracy of 88.7% (85.5%-91.2%) in predicting TOO. Moreover, the model demonstrated exceptional accuracy in distinguishing between upper and lower GICs, with an accuracy of 95.5% (93.5%-96.9%). **Conclusions:** This study demonstrated the high performance of the MCED test for early detection of GICs in a large-scale, prospective cohort enriched with early-stage cancers. These findings highlight the potential of the GIC model to enhance early detection and precise localization of GICs, thus improving the efficiency of subsequent diagnostic procedures. Research Sponsor: None.

3051 Poster Session

A novel magnetic bead-based cfDNA extraction method for advanced ctDNA marker discovery and methylation profiling. First Author: Zhuoran Jiang, Shanghai Xiaohe Medical Laboratory Co., Ltd., Shanghai, China

Background: Cell-free DNA (cfDNA) extraction and circulating tumor DNA (ctDNA) enrichment are critical for liquid biopsy-based cancer diagnostics. However, the QIAamp Circulating Nucleic Acid Kit (QIA), despite its widespread use, has limitations, including a labor-intensive manual workflow and suboptimal performance in ctDNA marker enrichment and contaminant removal, potentially affecting downstream methylation analyses. To overcome these limitations, we developed a novel, automatable magnetic bead-based cfDNA extraction method to improve ctDNA enrichment and biomarker discovery. **Methods:** The optimized extraction protocol incorporates refinements in pre-treatment, lysis, and binding steps to enhance cfDNA purity and ctDNA enrichment. Plasma samples from 8 lung adenocarcinoma (LUAD) patients, 10 healthy donors, and five simulated plasma samples spiked with varying proportions of fragmented genomic DNA from H838 (cancer) and NA12878 (healthy) cells were processed using both our optimized assay and the QIA kit. **Results:** The optimized method achieved cfDNA yields comparable to the QIA kit in LUAD and healthy samples but exhibited significantly higher extraction yields in simulated samples (39.91 ng vs. 31.17 ng, $p < 0.05$). Digital PCR demonstrated superior enrichment of 136 bp and 400 bp cfDNA fragments, while library preparation showed a 1-fold and 1.46-fold increase in pre-library yield and a 16.55% and 6.45% increase in mapped ratios for LUAD and healthy donors, respectively. These results demonstrate that our method achieves superior cfDNA enrichment efficiency compared to QIA, making it better suited for NGS-based workflows. Library complexity rose from 24.07% to 31.24% in LUAD samples and from 29.71% to 35.04% in healthy donors, with coverage depth of target regions improving by 56.13% and 22.88%, respectively. This enabled the detection of more CpG sites at equivalent sequencing depths. Simulated sample analysis confirmed that our optimized method better preserved methylation accuracy, achieving higher consistency between extracted and unextracted DNA. Furthermore, the optimized method identified significantly more cancer-specific haplotypes across 1,517 LUAD markers, improving ctDNA detection sensitivity, particularly in low tumor burden samples. **Conclusions:** Our automatable magnetic bead-based cfDNA extraction method outperforms QIA in library quality, complexity, and methylation accuracy while enabling enhanced ctDNA enrichment and biomarker detection. This approach provides a robust and scalable solution for advancing liquid biopsy-based cancer diagnostics. Research Sponsor: None.

	Technique	Protocol	Throughput	Handling time per run (min)	Cost ($)	Beta bias with unextracted DNA	Unmethylated marker counts median	Methylated marker counts median
QIAamp (QIA)	Vacuum-column	Manual	24	180~240	25	0.01319	382	526
Our assay	Magnetic bead	Automatic	24	30	1	0.00365	590	734

3052 Poster Session

Liquid biopsy-informed precision oncology clinical trial to evaluate the utility of ctDNA genomic profiling in patients with advanced or metastatic solid tumors. First Author: Amna Jamali, Sidney Kimmel Comprehensive Cancer Center, Johns Hopkins School of Medicine, Baltimore, MD

Background: Genomic profiling through liquid biopsies (LB) has enabled precision oncology decision making, however a key challenge lies in critically interpreting LB data to optimize patient care. **Methods:** We report results from the first planned interim analysis of an observational biomarker trial, designed to evaluate the clinical utility of serial LB in patients with advanced/metastatic solid tumors (NCT05585684). Primary endpoints were to determine feasibility, prevalence of actionable alterations in LB and the fraction of patients with enacted genotype-matched therapies. Secondary endpoints included progression-free (PFS) and overall survival (OS), time to subsequent therapy and concordance between LB and tumor next generation sequencing (NGS). Exploratory endpoints included correlation of ctDNA dynamics with survival. Serial LBs were obtained at baseline, 1-3 weeks on therapy and at progression using a CAP/CLIA validated NGS panel (Labcorp, MD). Patient-matched white blood cell (WBC) NGS was utilized to identify clonal hematopoiesis (CH)-derived variants. Actionability of genomic alterations was assessed by an ensemble multi-resource programmatic approach; results were reviewed at the Johns Hopkins Molecular Tumor Board (JH MTB). **Results:** Between March 2023 and July 2024, 51 patients with NSCLC, SCLC and esophageal cancer were enrolled, with 45 evaluable baseline and 12 progression LBs reviewed at JH MTB. Median turnaround time from baseline and progression LB to MTB recommendation was 14 and 13 days respectively. Patient-matched analyses of baseline WBC samples revealed 30.1% (n = 22) CH-derived alterations. The frequency of actionable variants was 28.8% (n = 21) at baseline, 23.3% (n = 7) on therapy and 21.7% (n = 5) at progression. Of the 45 patients reviewed at baseline, 33 received a recommendation for genotype-matched therapies; 48.5% (n = 16) based on tumor molecular profiling, 15.2% (n = 5) based on LB alone and 36.3% (n = 12) based on LB and tissue NGS. Thirteen patients were treated according to MTB recommendations. Patients who were treated with genotype-matched MTB recommended therapies had longer OS and PFS compared to those who received alternate therapies (not reached-NR vs. 14.8 months, log-rank p = 0.028 and NR vs 6.2 months, log-rank p = 0.21 respectively). Among the 12 patients reviewed at progression, 5 received an MTB recommendation for genotype-tailored therapies based on LB alone (n = 3) or in combination with tissue NGS (n = 2). Early on-therapy ctDNA clearance was associated with longer PFS and OS (log rank p = 0.02 and p = 0.06). **Conclusions:** Our findings highlight the value of a multidisciplinary MTB when supported by comprehensive liquid biopsy molecular information to inform therapy selection and improve patient outcomes. Clinical trial information: NCT05585684. Research Sponsor: LabCorp; National Cancer Institute; 1U01CA274631-01A1; Oncology Center of Excellence, Food and Drug Administration (FDA); U01FD0005042.

3053 **Poster Session**

Real-time clinical validation of a blood cell-free, mRNA-based GeneVerify test for screening and early diagnosis of prostate cancer. First Author: Sudhir K. Rawal, Rajiv Gandhi Cancer Institute and Research Centre, New Delhi, India

Background: Prostate cancer screening methods, including prostate-specific antigen (PSA) testing, radiological imaging, and pathological assessments, often fail to achieve reliable early detection. Despite advancements, gene-based diagnostic tests tailored for early detection of prostate cancer remain underdeveloped. To bridge this gap, we evaluated the clinical utility and diagnostic accuracy of the plasma cell-free mRNA-based GeneVerify test. This cutting-edge diagnostic approach aims to deliver faster and more precise results while avoiding the risks and complications associated with surgical biopsies. **Methods:** Blood samples were prospectively collected from patients suspected of prostate cancer who presented with urinary symptoms, persistently elevated PSA levels ($>$4 ng/mL), and PIRADS 4-5 lesions. All patients were recommended for a transperineal biopsy. Plasma cell-free RNA was isolated and analyzed for 25 prostate cancer-specific genes using the GeneVerify real-time PCR kit (Hayward, USA). The log2 fold change in gene expression for each gene was calculated, and a genetic risk score (GeneVerify Dx) was assigned to each patient. The transperineal biopsy results served as the reference standard. The diagnostic performance of the test in distinguishing between benign and cancerous cases was assessed and ROC (receiver operating characteristic) curve was plotted. **Results:** We tested a total of 45 subjects, comprising 35 suspected prostate cancer cases and 10 healthy controls. The median age of the cases was 66 years (range: 45–85), while the controls had a median age of 41.5 years (range: 39–47). The genetic risk score effectively differentiated prostate cancer patients from benign cases. The Area Under the Curve (AUC) was 0.83 $\pm$ 0.07 (P = 0.002; 95% CI: 0.70–0.96), demonstrating the test's strong discriminatory ability. Using a risk score cut-off value of 10, the test achieved a sensitivity of 72% and a specificity of 90%. Additionally, patients with higher Gleason grades and those experiencing chronic inflammation exhibited elevated gene expression levels and higher risk scores compared to benign subjects. **Conclusions:** In summary, this prospective study is the first to validate a blood cell-free RNA-based GeneVerify test for real-time screening and early detection of prostate cancer. The test exhibits high precision in identifying early-stage prostate cancer, with strong concordance to biopsy results. Research Sponsor: None.

3054 **Poster Session**

Molecular profiling of body fluid cfDNA: Advancing diagnostics and therapeutic decisions. First Author: Aditya V. Shreenivas, City of Hope National Medical Center, Duarte, CA

Background: Effusions in cancer patients pose several critical challenges for clinicians. In known cancer patients, an effusion may signal recurrence, whereas in newly diagnosed, seemingly localized cases, it indicates a more advanced stage. In many patients the effusion may be secondary to complications of treatment or comorbidities, rather than malignant. Diagnosing malignant involvement of body fluids remains a challenge due to the limitations of conventional cytology. This study explores the potential of molecular profiling of body fluids to identify actionable molecular alterations and its role in diagnosing malignant effusions. **Methods:** We analyzed cfDNA from body fluids—ascitic fluid (N=26), cerebrospinal fluid (N=7), pleural fluid (N=11), and pericardial fluid (N=1), collected from 45 patients with solid tumors, including lung (N=12), breast (N=9), ovarian (N=9), pancreas (N=4), gastrointestinal cancers (N=4), cervix (N=2), and one each of CNS, endometrial cancer, HCC, liposarcoma, and melanoma. In a subset, results from fluid samples were compared with tissue and plasma samples to assess concordance across different sample types. **Results:** Pathogenic alterations were identified in 89% (40/45) of fluid samples. The most frequently mutated genes were *TP53* (53%), *EGFR* (20%), *KRAS* (18%), *PIK3CA* (9%), *CTNNB1* (7%), *FGFR3* (7%), *GNAS* (7%), *MYC* (7%), and *ESR1* (4%). Simultaneous analysis of body fluid and tissue samples (n=11) revealed that 7 patients (64%) had at least one concordant pathogenic alteration. Similarly, analysis of body fluid and plasma samples (n=16) showed that 8 patients (50%) had at least one concordant pathogenic alteration. Body fluid analysis identified acquired resistance alterations, such as *EGFR T790M* and *ALK C1156Y*, which influenced therapy decisions. Among the alterations detected exclusively in fluid samples were *ERBB2* amplification and *ESR1 D538G* mutation in two breast cancer patients. In evaluating molecular profiling against cytology for detecting malignant effusions, 17 of 25 samples were positive by both methods, while 4 of 5 cytology-negative samples were ctDNA-positive. Notably, 3 of 4 ctDNA-negative cases were cytology-positive. These results emphasize the potential role of molecular profiling for diagnosis when cytology is inconclusive. **Conclusions:** This study highlights the importance of body fluid ctDNA profiling (ascites, pleural, pericardial, CSF) in identifying actionable mutations, including unique druggable alterations not found tissue or liquid biopsies. The ability to detect ctDNA in cytology-negative samples underscores the potential of body fluid ctDNA as a valuable complement to fluid cytology for diagnosing malignant involvement. Research Sponsor: None.

ESCAT classification of pathogenic variants identified in body fluids from 45 patients.

Tier Level	Incidence (%)	Number of unique patients
IA	28.9%	13
IIA	0%	0
IIIA	35.6%	16
IIIB	4.4%	2
IVA	55.6%	25
IVB	2.2%	1
X	22.2%	10

3055 **Poster Session**

Circulating tumor DNA and late recurrence in high-risk, hormone receptor-positive, HER2-negative breast cancer: An updated analysis of the CHiRP study. First Author: Tae-Kyung Robyn Yoo, Dana-Farber Cancer Institute, Boston, MA

Background: Risk of recurrence for patients (pts) with HR+/HER2- breast cancer persists for decades. Most distant recurrences occur in the 'late' adjuvant setting, $>$ 5 years (yrs) from diagnosis. In CHiRP (ASCO 2022), we showed that minimal residual disease (MRD) was detectable in the late adjuvant setting: ctDNA was detected in 8/83 (9.6%) pts in the cohort and 6/8 (75%) pts with positive ctDNA (+ctDNA) had developed distant recurrence when initially reported (median follow-up 2 years from first plasma sample collected on study). Here, we report updated clinical outcomes and investigate the meaning of a ctDNA test result during surveillance with longer follow-up. **Methods:** In CHiRP, pts with stage II-III HR+/HER2- breast cancer at high risk of recurrence diagnosed $>$ 5 yrs prior with no evidence of recurrence were prospectively identified. All pts provided informed consent for prospective plasma collection every 6-12 months at routine follow-up visits for batched, retrospective ctDNA testing using RaDaR, a tumor-informed whole exome sequencing-based assay. Pts were followed at the discretion of the clinical provider without any routine surveillance imaging, as per guideline-concordant care. See CHiRP ASCO 2022 presentation for additional methods. **Results:** Of 83 pts in the analytic cohort, 57 (68.7%) pts had stage III disease, and most (n = 75, 90.4%) underwent (neo)adjuvant chemotherapy. All pts received endocrine therapy. In this update, median follow-up from first sample collection was 4.4 yrs (interquartile range 4.0, 4.9). 214 plasma samples were collected prior to any known recurrences and included in this analysis. 8/83 (9.6%) pts had +ctDNA at any timepoint including 4/83 (4.8%) with +ctDNA on first study plasma sample. In pts initially ctDNA-negative (-ctDNA; n = 4), median time from first sample collection to MRD detection was 1.29 yrs (range, 0.72 – 3.05). During follow-up, 8 (9.6%) pts developed distant recurrence and 1 (1.2%) pt had a local recurrence. With additional follow-up included in this update, all 8/8(100%) pts with +ctDNA developed distant recurrence with a median lead time of 1.39 years (range 0.01 – 4.24). Among -ctDNA plasma samples with $>$ 2 yrs of follow-up (n = 185), the negative predictive value (NPV) of a -ctDNA test for lack of clinical recurrence for $>$ 2 yrs post-test was 98.4% (3/185). The NPV indicating freedom from recurrence $>$ 1 and $>$ 3 yrs was 100% (0/196) and 96.6% (5/147), respectively. **Conclusions:** In pts with high-risk HR+/HER2- breast cancer in the late adjuvant setting, all pts with +ctDNA developed distant metastasis. A -ctDNA test was strongly associated with lack of recurrence over a 3 yr follow-up period. Future studies are needed to determine if ctDNA-guided intervention can impact clinical outcomes for early-stage breast cancer and to determine the optimal role of MRD surveillance during follow-up. Research Sponsor: None.

3056 **Poster Session**

A plasma proteomics-based model for predicting response to neoadjuvant chemotherapy in ovarian cancer. First Author: Coren Lahav, Oncohost Ltd, Binyamina, Israel

Background: Neoadjuvant chemotherapy (NACT) is a standard treatment option for advanced high-grade serious ovarian cancer (HGSOC). Following interval debulking surgery, pathologists assess tumor response to initial chemotherapy using a standardized chemotherapy response score (CRS) corresponding with patient survival. We sought to determine the feasibility of developing a proteomic-based biomarker to predict response to NACT based on pre-treatment plasma samples. **Methods:** Pre-treatment samples were collected from 71 HGSOC patients receiving platinum-taxane combination NACT. Deep plasma proteomic profiling was performed using SomaLogic's 7K aptamer-based technology. Based on the proteomic profiles, a computational model was developed to predict CRS, focusing on differentiating between poor CRS (CRS1) versus partial or near-complete CRS (CRS2/3). The model counted the number of response-associated proteins per patient. Patient scores were derived by resampling into training and test sets, averaging test set results. Patients were stratified into groups (i.e., 'Chemo-responsive' or 'Chemo-resistant') based on median score. Bioinformatic analysis of the HGSOC-specific proteomic biomarkers was performed to gain insight into the potential mechanisms driving NACT therapeutic benefit and resistance. **Results:** Our proteomics-based predictive model differentiated between patients with CRS1 versus CRS2/3 (ROC AUC = 0.67, p = 0.008). CRS association with disease-free survival (DFS) and overall survival (OS) in this cohort was consistent with a previous meta-analysis, though not reaching statistical significance (CRS3 versus CRS1/2, HR = 0.62, 95% CI: 0.27-1.42, p = 0.25 for DFS; HR = 0.67, 95% CI: 0.21-2.09, p = 0.48 for OS). Hazard ratios for patient classification as 'Chemo-responsive' versus 'Chemo-resistant' trended in the same direction (HR = 0.70, 95% CI: 0.37-1.30, p = 0.25 for DFS; HR = 0.65, 95% CI: 0.25-1.72, p =0.39 for OS). The predictive model incorporated 62 proteins. Of these, 27 were elevated in the plasma of patients with poor CRS compared to those with partial or near-complete CRS. These proteins were notably enriched in pathways related to cell death resistance. Moreover, several of these elevated proteins have previously been linked to HGSOC, particularly in the context of chemotherapy resistance. Conversely, patients with partial or near-complete CRS showed significant enrichment of proteins associated with genome instability and mutation. **Conclusions:** This study demonstrates the feasibility of CRS prediction using plasma proteomics at baseline, potentially complementing existing imaging approaches. While current treatment options limit immediate clinical utility, these findings provide novel insights into biological determinants of chemotherapy response and may become predictive biomarkers for novel treatment protocols. Research Sponsor: OncoHost; Israel Science Foundation (ISF); 2972/21; Israel Cancer Research Fund (ICRF); 21-302-MI.

3057 **Poster Session**

NeoCircle: Investigating circulating tumor DNA dynamics as a predictor of survival in primary breast cancer. First Author: Anthony M George, Lund University, Lund, Sweden

Background: Persistent circulating tumor DNA (ctDNA) detection during neoadjuvant treatment (NAT) of early-breast cancer (EBC) indicates high-risk disease. Following surgical resection, ctDNA-positivity indicates molecular residual disease (MRD) and heralds occult metastatic disease relapse. To incorporate ctDNA into EBC management, scalable and widely accessible diagnostic methods are necessary. Here we apply an ultrasensitive, personalized tumor-informed approach to ctDNA analysis leveraging structural variant (SV) detection using a novel multiplex digital PCR (dPCR) technology. **Methods:** 116 patients with stage I-III EBC (31.0% TNBC, 43.1% HR+/HER2- and 24.1% HER2+) and eligible for NAT were recruited through the prospective SCAN-B study (NCT02306096, substudy NeoCircle) between December 2014 and March 2019 and have been analyzed for ctDNA. Whole genome sequencing was performed on tumor material and personalized multiplex dPCR assays tracking up to 16 SVs were used for ctDNA monitoring. Plasma samples were collected at baseline, during NAT, pre- and post-surgery and at 6-monthly intervals during follow up. **Results:** High baseline detection was observed across all stages and subtypes (90.5% overall), and ctDNA-positivity at end-of-NAT (end-NAT) was a significant predictor of eventual disease relapse and death (relapse-free interval, RFI, hazard ratio, HR, 3.7, 95% CI 1.4-9.7; overall survival HR 7.7, 95% CI 2.2-26.6). A significant association was observed between end-NAT ctDNA clearance and pathological complete response (pCR), whereas non-pCR by itself was not a significant predictor of relapse or death in this cohort. At one or more post-operative timepoints, MRD+ was detected in 10 patients who experienced distant recurrence, with lead times up to 4 years (median 13.9 months, range 1.8-47.7 months). Similarly, ctDNA was detected in 3 of 4 patients with local recurrences and 1 of 2 patients with CNS-only recurrences. For 2 patients without presentation of clinical recurrence to date, ctDNA was detected post-operatively, with subsequent clearance during follow-up. Post-operative MRD associated with poor RFI (HR 45.5, 95% CI 13.0-159.8) and OS (HR 15.3, 95% CI 4.5-52.9). **Conclusions:** In this analysis of 116 patients from a prospective study in patients with EBC receiving NAT, we monitored ctDNA using an ultrasensitive tumor-informed dPCR assay tracking patient-specific SVs. ctDNA detection post-NAT and prior to surgery was associated with high-risk of disease relapse and death, outperforming pCR. Moreover, post-operative ctDNA detection was also significantly associated with disease relapse and death, with long lead-times over standard-of-care clinical assessments. These findings further validate the feasibility of SVs as an MRD analyte and support the clinical use of this approach in EBC. Research Sponsor: None.

3058 **Poster Session**

Monitoring populations of tumor-macrophage fusion cells in blood prognosticates PFS and OS in pan-metastatic cancers over 2 years. First Author: Sonia Muthuraj, Rutgers University, New Brunswick, NJ

Background: Tumor associated macrophages are known to fuse with cancer cells in the blood through a dysfunctional CD47 phagocytic immune pathway resulting in the formation of tumor- macrophage fusion cells (TMFCs) which are observed as heterokaryon (incomplete fusion), synkaryon (full fusion) or hetero-to-synkaryon transition (partial fusion). Previous studies in lung and breast cancer demonstrated that subtypes of TMFCs in blood may correlate with highly aggressive disease unlikely to respond to certain systemic therapies (i.e. chemotherapy). We initiated a prospective study to evaluate the blood of n = 100 metastatic pan-cancer patients (pts) receiving systemic therapy for the presence of full, partial, and incomplete TMFCs to compare their progression-free survival (PFS) and overall survival (OS). **Methods:** We conducted a prospective pilot study of n = 100 pathologically confirmed metastatic cancer pts with breast (n = 23), prostate (n = 21), pancreas (n = 17), colon (n = 19), or lung (20) with active progressive disease, prior to the induction of new systemic therapies, i.e. chemotherapy (n = 39), PD-L1 immunotherapy (n = 27), hormone therapy (n = 20), or targeted therapy (n = 23). TMFCs were isolated from 7.5ml peripheral blood using CellSieve microfiltration and identified by their enlarged multinucleated structure ($>$ 30 μm), which was categorized into 3 distinct subtypes: full fusion marked by a single multinucleated nuclei, partial fusion marked by 2 contacting nuclei, incomplete fusion marked by 2 distinct non-contacting nuclei. TMFC subtypes were compared to pts' PFS and OS by cox proportional univariate and multivariate analysis over 24 months. **Results:** We identified TMFCs in 78% of all pts (n = 78/100), averaging 10 per pt. 37% of pts were found to have more than one TMFC subtype in their sample, with 70 pts having full fusion, 23 partial fusion, and 28 incomplete fusion. At 24 months, pts with incomplete fusion TMFCs had significantly worse PFS (HR, 2.9; 95% CI, 1.5 to 5.7; P = 0.0023) and OS (HR, 2.5; 95% CI, 1.2 to 5.3; P = 0.0202). Interestingly, pts with incomplete fusion and treated with systemic targeted therapy (n = 7) were found to have significantly improved PFS (HR, 4.8; 95% CI, 1.8 to 13.0; p = 0.0052), but not OS (HR, 3.0; 95% CI, 1.0-9.2; p = 0.0999) versus other therapy types. There was no significant PFS differences in pts without incomplete fusion TMFCs being treated with targeted therapies. **Conclusions:** In a pan metastatic cancer setting, we found that incomplete fusion in circulating TMFCs associates with poorer outcomes at 24 months. Further, it appears that pts with incomplete TMFCs may have had better outcomes when treated with targeted therapies compared to other therapy types. These preliminary findings suggest the need for larger scale prospective studies to further evaluate relationships between TMFCs and therapeutic responses in specific disease populations. Research Sponsor: Creatv MicroTech.

3059 **Poster Session**

Whole-genome bisulfite sequencing of cell-free DNA to investigate molecular contributors to racial survival differences in advanced-stage triple-negative breast cancer. First Author: Chun Wang, Thomas Jefferson University - Department of Medical Oncology, Philadelphia, PA

Background: Black women are twice as likely to be diagnosed with triple-negative breast cancer (TNBC), a highly aggressive and difficult-to-treat subtype with poor survival outcomes. While well-defined factors such as socioeconomic status have been recognized, the impact of genomic and molecular factors on the racial disparity in TNBC survival remains understudied. Liquid biopsy, a non-invasive and real-time method for studying the molecular landscape of tumors, has yet to be explored in the context of racial survival disparities in TNBC. **Methods:** Ten Black TNBC patients were matched with ten White TNBC patients based on age, family history, tumor stage, grade, and inflammatory breast cancer (IBC) status. Baseline blood samples were collected prior to the initiation of a new therapy. Cell-free DNA (cfDNA) was extracted from plasma, bisulfite-converted, and analyzed through whole-genome bisulfite sequencing (WGBS). After quality control, ichorCNA was used to identify copy number alterations (CNAs), and MethylKit was applied for methylome analysis. Associations between CNAs, differentially methylated regions (DMRs), and progression-free survival (PFS) were evaluated and compared between Black and White patients. **Results:** The Black-White pairs were well-matched across key clinical variables, including age (P = 0.99), family history (P = 1.00), tumor stage (P = 1.00), grade (P = 1.00), and IBC status (P = 0.37). Black TNBC patients had poorer PFS compared to their White counterparts. Significant CNAs were identified on chromosome 1 (chr1:20400000-23900000_p36.12 and chr1:7200000-9200000_p36.23), regions associated with known breast cancer prognosis genes such as *EPHB2* and *E2F2*. Thirteen DMRs were found to be significantly associated with the racial differences in PFS, with key genes such as *CDH13* and *TMEM132C* identified in these regions. Notably, the methylation status of the *CDH13* promoter has previously been associated with breast cancer risk. The predictive power for PFS was significantly enhanced in a model combining these 13 DMRs with race (Concordance Index [C-index] = 0.96), compared to a model using race alone (C-index = 0.75). **Conclusions:** In this pilot study utilizing WGBS of cfDNA, we identified significant CNAs and DMRs associated with the racial disparity in survival outcomes among advanced-stage TNBC patients. These findings provide insight into the genomic and molecular contributors to this disparity and highlight the potential of liquid biopsy for future studies. Larger studies are needed to validate these results and further investigate the underlying mechanisms. Research Sponsor: National Cancer Institute/U.S. National Institutes of Health; R01CA207468; Sidney Kimmel Comprehensive Cancer Center.

3060 **Poster Session**

Beyond tumor-shed markers: AI driven tumor-educated polymorphonuclear granulocytes monitoring for multi-cancer early detection. First Author: Rajan Datar, Datar Cancer Genetics, Nashik, India

Background: Tumor educated Polymorphonuclear Granulocytes (tPMNG) are a distinct phenotypic set of Neutrophils (N2) with corrupted programmed death pathways resulting in apoptosis resistance. The presence of tPMNGs in the peripheral blood indicates up-regulation of pro-tumoral factors and resistance to apoptotic signals. Our platform leverages this unique anti-apoptotic characteristic of tPMNGs through a proprietary culture process and AI-based digital imaging analysis to detect cancer in its early stages. This approach represents a paradigm shift from detecting rare tumor-shed analytes such as ctDNA and CTCs to monitoring relatively abundant tPMNGs, whose numbers typically exceed conventional analytes by 3-4 orders of magnitude. We studied detection of tPMNGs in a case-control study to evaluate their suitability for a multi-cancer early detection test (MCED). **Methods:** We collected 10 ml of peripheral blood in EDTA tubes from 892 asymptomatic healthy volunteers above 18 years of age [463, 52% male; 429, 48% females with mean age of 48 (20 to 89) years], 24 individuals diagnosed with non-malignant conditions including prostatitis, polycystic ovarian disease and acute pancreatitis, and 90 individuals recently diagnosed with surgically resectable early stage cancers (Stage 1/ 2) comprising Head and Neck (N=32, 36%), Breast (N=20, 22%), Colorectal (N=14, 16%), others (N=24, 27%). Nucleated cells were isolated from the samples after RBC lysis and centrifugation. These cells were seeded in six well culture plates and subjected to controlled apoptotic stress under serum-free, hypoxic conditions with specific growth factor supplementation for 5 days. Surviving cells were set on imaging slides and stained with H&E. 60X images were obtained and analyzed using a convolutional neural network (CNN) based AI algorithm to detect tPMNGs per ml. **Results:** The mPMNG detection method demonstrated 84% sensitivity (95% CI: 84.44%) across multiple cancer types. The platform demonstrated 97% specificity (95% CI: 97.40%) among healthy asymptomatic cohort. In samples from individuals from individuals with non-malignant conditions, specificity was 96% (95% CI: 95.83%). **Conclusions:** This first-in-class immune cell-based MCED approach offers several advantages over tumor-shed analyte detection: 1. Leverages amplified host response rather than rare tumor products. 2. Provides robust detection across cancer types and stages. 3. Utilizes existing laboratory infrastructure and a scalable protocol. 4. Demonstrates potential for screening, diagnosis, and monitoring applications. The high sensitivity and specificity, combined with practical advantages, suggest potential for clinical implementation in cancer screening and monitoring programs either using tPMNG alone or in conjunction with CTCs / cfDNA evaluation. Research Sponsor: None.

3061 **Poster Session**

Next-generation U-Net Encoder: Decoder for accurate, automated CTC detection from images of peripheral blood nucleated cells stained with EPCAM and DAPI. First Author: Tim Crook, Cromwell Hospital, London, United Kingdom

Background: Direct circulating tumor cell (CTC) detection is a promising biomarker for early cancer detection and monitoring. Traditional fluorescence microscopy and AI-driven methods have limitations such as subjectivity and labor-intensiveness. We developed a deep-learning pipeline using a U-Net–type encoder–decoder architecture for precise pixel-level CTC discrimination in peripheral blood nucleated cells (PBNCs). This method preserves morphological and fluorescence details, overcoming convolutional neural network (CNN) limitations by maintaining fine features through skip connections for better discrimination. We present specificity and sensitivity data from a case-control study. **Methods:** We collected 5 ml of peripheral blood in EDTA tubes from 1383 asymptomatic healthy volunteers (744, 54% male; 639, 46% females with mean age of 49 [(20 to 93) yrs], 38 individuals diagnosed with non-malignant conditions including prostatitis, PCOD and acute pancreatitis, and 143 individuals recently diagnosed with surgically resectable early stage cancers (Stage 1/ 2) - Head and Neck (N=50, 35%), Breast (N=31, 22%), Colorectal (N=17, 12%), Pancreas (N=8, 6%), Prostate (N=8, 6%), Lung (N=5, 3%), Ovary (N=5, 3%) others (N=19, 13%). Nucleated cells were isolated from the samples after RBC lysis and centrifugation and stained with EPCAM and DAPI and set on imaging slides. 60X images were obtained and processed by AI utilizing U-Net–Based Encoder–Decoder Architecture and context discrimination to detect CTCs. The customized U-Net pipeline encodes spatial information through successive convolutional and pooling layers, generating a highly compressed representation of cells in the bottleneck. By employing transposed convolutions in the decoder stage—and incorporating skip connections from the encoder layers—the AI model reconstructs a pixel-wise segmentation mask to identify potential CTCs with cell diameter >10 microns. This approach aims to surpass existing methods that rely on bounding-box–based detection by offering enhanced sensitivity and specificity through end-to-end learned feature extraction. Ground truth annotations were established via expert cytopathology review, and training procedures involved cross-validation to ensure generalizable performance. **Results:** Analysis of total 1564 samples showed that our U-Net–based model achieved a sensitivity of 89% (95% CI: 88.81) and specificity of 97% (95% CI: 97.98) for detecting CTCs. Performance remained consistent across solid tumors, highlighting the flexibility and adaptability of the architecture in various fluorescence staining conditions. **Conclusions:** Our U-Net pipeline uses pixel-level segmentation and skip connections to enhance CTC detection accuracy. Integrating fluorescence and morphology, it can streamline cancer screening and disease monitoring. Research Sponsor: None.

3062 **Poster Session**

Clinical outcomes of a prospective multicenter study evaluating a combined circulating tumor DNA (ctDNA) and RNA (ctRNA) liquid biopsy assay in metastatic non-small cell lung cancer (NSCLC). First Author: Richa Dawar, University of Miami Sylvester Comprehensive Cancer Center, Miami, FL

Background: Genomic profiling of metastatic NSCLC to inform targeted therapy selection is endorsed by numerous guidelines. While tissue biopsy is the mainstay of molecular profiling, liquid biopsy offers a practical real-world approach to non-invasively identify guideline-recommended biomarkers. LIQUIK was a prospective, multicenter, observational cohort study to evaluate the performance of a combined ctDNA and ctRNA liquid biopsy assay, LiquidHALLMARK (LHM ctDNA and ctRNA) in comparison to the ctDNA-only liquid biopsy Guardant360 (G360 ctDNA) and tissue next-generation sequencing (NGS) for biomarker detection in metastatic NSCLC. Diagnostic performance of the primary cohort has been previously presented. Here, we report clinical outcomes after 1-year follow-up of the cohort. **Methods:** LIQUIK (NCT04703153) enrolled 151 non-squamous NSCLC patients across the USA and Singapore from Apr 2021 to Dec 2022. Enrolled patients were genotyped using tissue NGS, LHM ctDNA and ctRNA, and G360 ctDNA for 9 biomarkers (*EGFR, ALK, RET, ROS1, BRAF, KRAS, MET, ERBB2, NTRK1/2/3*). Patients were treated according to their physician's choice of first-line therapy following biomarker testing. Tumor assessments were performed at baseline and within 6 months (mo) of treatment initiation. Overall response rate (ORR), progression-free survival (PFS), and the clinical utility of ctRNA were investigated. **Results:** Among the 151 patients, 129 were subsequently treated in the first-line setting (49.6% on targeted therapy, 41.1% on chemotherapy, and 30.2% on immunotherapy), with 27 on combination therapy. Of the 64 patients on targeted therapy, 47 had matched biomarker findings from tissue NGS, 47 from LHM ctDNA and ctRNA, and 43 from G360 ctDNA. ORRs of patients on targeted therapy and chemo/immunotherapy were 40.4% and 16.1% respectively. Among patients treated with targeted therapy, ORR was similar between patients with biomarker-matched findings from tissue NGS (45.2%), LHM ctDNA and ctRNA (40.5%), and G360 ctDNA (36.8%). PFS of patients on targeted therapy (median 23.6 mo) was significantly longer than those not on targeted therapy (median 3.8 mo; HR = 0.26; $p < 0.001$). Median PFS was similar between patients with biomarker-matched findings from tissue NGS (23.6 mo), LHM ctDNA and ctRNA (18.6 mo), and G360 ctRNA (20.1 mo). Overall, incorporation of ctRNA into LHM identified 2 additional biomarker-positive patients. Both ctRNA-exclusive biomarkers were confirmed by tissue NGS, and both patients were treated with biomarker-matched targeted therapy. While one patient was lost to follow-up, the second patient had a partial response to treatment. **Conclusions:** Treatment outcomes based on liquid and tissue biopsies are comparable. The inclusion of ctRNA in liquid biopsy increases its diagnostic yield of actionable biomarkers. Clinical trial information: NCT04703153. Research Sponsor: None.

3063 **Poster Session**

Microbial metabolic pathways to abrogate immunotherapy toxicity and promote anti-tumor response in metastatic renal cell cancer. First Author: Shahla Bari, Duke Cancer Institute Center for Prostate and Urologic Cancers, Duke University School of Medicine, Durham, NC

Background: Metastatic RCC has a poor prognosis. Despite improvement in treatment outcomes with ICB and targeted therapy, many patients fail to respond to first line therapy and immune mediated adverse events(irAE) remains a major challenge, often leading to treatment discontinuation. Therefore, mitigating irAE without compromising antitumor immunity is a critical unmet need. Tryptophan microbial metabolic pathway is known to play a major role in immune homeostasis through its action on Aryl hydrocarbon receptor (AhR) balancing immune suppresser with immune effector responses. We hypothesize that microbial metabolism of tryptophan to indole metabolites may play a role in ICB resistance as well in irAE, identification of which may help us predict patients most likely to respond, without life threatening toxicity. **Methods:** We prospectively collected paired stool and blood samples of treatment naïve metastatic RCC patients, treated with ICB +/- Tyrosine kinase inhibitors (TKI) at treatment initiation and at time of first response assessment (12+/-3 weeks). We evaluated stool metagenomics and untargeted stool and plasma metabolomics among responders (R) and non-responders (NR). We focused on kynurenine/tryptophan and indoles/tryptophan ratio to evaluate differential host and microbial metabolism of tryptophan. A responder was classified as progression free survival (PFS) greater than 6 months while patients with grade 3 or higher irAE was classified as serious IrAE. **Results:** Among 120 patients accrued, 49 were treated with combination ICB, while 71 patients were treated with ICB + TKI. Median follow up was 27 months. 28 patients (23%) had a Grade 3 or higher irAE. 3 patients died from complications attributable to irAE. The median duration to development of any irAE was 3.5 months. Using negative binomial regression model evaluating baseline relative abundance of microbial tryptophan metabolites that were associated both with response as well as serious irAE, we noted significant higher abundance of Indole acetic acid (IAA), indole acetonitrile(ACN), indole acetyl phenylalanine (IAAP)and IAA/kynurenine (Kyn) and lower abundance of tryptophol, indole 3 pyruvic (IPA), (coefficient of 6.4, 1.8, 7.15, 4.6, 0.04, 0.46, with adj p value < 0.05) with serious irAE as well as ICB resistance (Coefficient-5.42, 1.83, 6.15, 4.05, 0.03, 0.4, $p < 0.05$). **Conclusions:** This is one of the first studies evaluating microbial metabolic pathways that may play a role in predicting patients who are more likely to respond with lower likelihood of serious irAE in RCC, thus helping to identify strategies to decouple tumor immunity from autoimmunity to improve ICB outcomes. Further the results can be extrapolated to many other solid tumor treated with immunotherapy, as tryptophan metabolism plays a immune homeostatic role across cancers. Research Sponsor: Conquer Cancer foundation-ASCO YIA.

3064 **Poster Session**

Tumor-educated platelets as a source of potential biomarkers for colorectal cancer. First Author: Rodnei Macambira, Oncológica do Brasil Cancer Center, Belém, Pará, Brazil

Background: Colorectal cancer (CRC) is the third most common cancer and the second leading cause of cancer-related death worldwide. Current diagnostic methods rely on invasive procedures and serum markers with limited sensitivity, highlighting the need for novel, minimally invasive biomarkers. Tumor-educated platelets (TEPs) have emerged as a promising source, as malignant cells reprogram platelets through molecular alterations. This study aimed to identify differentially expressed genes in TEPs from patients with CRC that could serve as potential diagnostic biomarkers. **Methods:** We downloaded gene expression data from platelets from the Gene Expression Omnibus (GEO; GSE183635), tissue gene expression data from TCGA-COAD and TCGA-READ, and vesicle data from Vesiclepedia. The data were preprocessed to remove low-quality reads, and high-quality reads were aligned to the human reference genome GRCh38.p13. We performed differential expression analysis through DESeq2 ($|\log2FoldChange| > 1$, adjusted p-value < 0.05). Gene ontology (GO) enrichment analysis (p-value < 0.05) was conducted, and shared genes between TEPs, tumor tissues, and vesicles were identified. ROC curves (AUC > 0.75) assessed diagnostic potential. **Results:** A total of 3,211 differentially expressed genes were identified in TEPs, with 55 upregulated and 3,156 downregulated. Six genes (*TLN1, IGF2, IFITM3, DKK1, MYL9, TNNC2*) were consistently upregulated in TEPs, tumor tissues, and observed in microvesicles. These genes exhibited AUC values ranging from 0.76 to 0.83, indicating high sensitivity for distinguishing CRC patients from healthy controls. **Conclusions:** Our study identified six DEGs in TEPs with elevated expression in CRC tissue, highlighting their potential as minimally invasive biomarkers for CRC diagnosis. These findings pave the way for developing more precise diagnostic tools to improve early detection and patient outcomes. Research Sponsor: Conselho Nacional de Desenvolvimento Científico e Tecnológico.

Potential biomarker genes in TEPs for CRC, ranked by Log2FC.

Gene	Log2FoldChange	P-adjusted	AUC
DKK1	2.011554	$1{,}50\times10^{-3}$	0.78
IGF2	1.5006689	$3{,}56\times10^{-9}$	0.81
IFITM3	1.102034	$3{,}01\times10^{-9}$	0.81
TLN1	1.098185	$1{,}24\times10^{-5}$	0.83
MYL9	1.060944	$1{,}91\times10^{-15}$	0.77
TNNC2	1.023068	$7{,}22\times10^{-8}$	0.76

AUC: Area Under the Curve.

3065 **Poster Session**

Molecular landscape and therapeutic vulnerability of RRAS- and RRAS2-mutant solid tumors. First Author: Alexander James Pfeil, Memorial Sloan Kettering Cancer Center, New York, NY

Background: The RRAS subfamily of small GTPases shares considerable sequence homology with the canonical RAS oncoproteins KRAS, NRAS, and HRAS. Mutations in *RRAS* and *RRAS2* that are homologous to *KRAS* hotspot mutations promote transformation *in vitro*. Most diagnostic sequencing panels do not profile the RRAS subfamily, and therefore, the prevalence and clinical relevance of these mutations and their treatment have not been fully established. **Methods:** Based on a clinical targeted DNA sequencing assay (MSK-IMPACT), an institutional cohort of 51,040 solid tumor cases prospectively sequenced between 2016-2024 was analyzed to identify *RRAS*/*RRAS2* mutations. Lung cancers were excluded and analyzed in a separate study. Hotspot mutations in *RRAS*/*RRAS2* were determined based on homology to KRAS hotspot mutations and/or previous literature demonstrating potential oncogenicity (hotspot *RRAS*: G38, G39 and Q87; hotspot *RRAS2*: G23, G24, A70T, Q72 and in-frame insertions in G23/G24). The sensitivity of cells harboring *RRAS* and *RRAS2*-mutations to the clinically active pan-RAS inhibitor RMC6236 was examined *in vitro* and *in vivo*. Western blotting was utilized to determine changes in protein expression and activation. **Results:** Among the 51,040 cases analyzed, hotspot *RRAS* and *RRAS2* mutations were detected in 6 (0.01%) and 270 (0.5%) patients, respectively. Hotspot *RRAS* mutations were seen in various cancer types, and most had other mitogenic drivers (4/6). Amongst tumors with hotspot *RRAS2* mutations, the most common cancer types included endometrial (n = 172), ovarian (n = 27), and germ cell tumors (n = 26); these variants were seen in 5%, 0.9%, and 5% of these respective patient populations. Most endometrial, ovarian, and germ cell tumors lacked other *K/H/NRAS* mutations (83%, 89%, 85%, respectively). Other tumor types with hotspot *RRAS2* mutations included esophagogastric cancers (n = 9), cholangiocarcinomas (n = 5), and breast cancers (n = 5, 2 of which were triple negative). Treatment with RMC-6236 reduced ERK and P90 RSK phosphorylation in CAL-51 (human triple-negative breast cancer line) and A2780 cells (human ovarian carcinoma cell line), both harboring the $RRAS2^{Q72L}$ mutation. Treatment of mice bearing CAL-51 xenograft tumors with RMC-6236 (50 mg/kg, once daily) significantly reduced tumor growth. Growth of cells harboring *RRAS* and *RRAS2* mutations was also blocked by MEK1/2 and ERK1/2 inhibitors. **Conclusions:** Hotspot *RRAS2* mutations are rare but recurrently found in endometrial, ovarian, and germ cell tumors. These mutations are predominantly mutually exclusive with other canonical *RAS* mutations, although co-mutations with *RAS* do occur in a subset. $RRAS2^{Q72L}$-mutant cancer cells are sensitive to inhibition of the MAPK pathway including pan-RAS inhibition both *in vitro* and *in vivo*. These preliminary findings may inform future therapeutic strategies for patients with *RRAS2*-mutated solid tumors. Research Sponsor: Memorial Sloan Kettering Cancer Center Department of Pathology and Lab Medicine.

3066 **Poster Session**

Larotrectinib resistance in TRK fusion cancers: Analysis of a tumor-agnostic, global clinical trial dataset. First Author: Alexander E. Drilon, Memorial Sloan Kettering Cancer Center and Weill Cornell Medical College, New York, NY

Background: Larotrectinib (laro) is the first-in-class, highly selective, TRK inhibitor approved for tumor- and age-agnostic use in TRK fusion cancers. This is the seminal report of primary and secondary laro resistance based on an analysis of the regulatory dataset that supported drug approval across multiple countries. **Methods:** Genomic data from patients (pts) with non-primary CNS TRK fusion cancer enrolled in a global, prospective, multicenter database of three laro clinical trials including adult and pediatric pts were analyzed. Tumor DNA (Illumina TruSight Oncology [TSO] Comprehensive, TSO 500, or FoundationOne CDx) or circulating tumor DNA (Guardant360 or GuardantOMNI) NGS was performed pre-laro (baseline; BL) and post-laro initiation. On-target *NTRK* (solvent front [SF], gatekeeper [GK], xDFG) mutations and COSMIC-classified tier 1/2 off-target alterations were identified. Primary laro resistance analysis set included pts with no meaningful clinical benefit (PD/SD $<$ 4 months). Secondary (acquired) laro resistance analysis set included pts who developed resistance after meaningful clinical benefit (CR/PR/SD $\geq$4 months). Data cutoff: July 20, 2024. **Results:** Of 304 adult and pediatric pts enrolled, 216 had BL genomic data. Primary laro resistance was observed in 24 pts. Only 1 pt had an on-target mutation (*NTRK3* G623R), likely attributable to prior crizotinib; 9 pts (38%) had off-target alterations involving *AKT, BRAF, FGFR1, GNAS, KRAS, NRAS,* and *PIK3CA*. Secondary laro resistance was observed in 55 pts with valid post-BL ctDNA (the most common of these TRK fusion cancers were infantile fibrosarcoma [22%], other soft tissue sarcoma [18%], thyroid [11%], lung and salivary gland [9% each]); acquired alterations were identified in 16 of these pts. On-target resistance alone was observed in 5 of 16 pts (31%) and were mainly SF or GK single or double mutation-mediated (*NTRK1* F589L, *NTRK1* G595R, *NTRK3* G623R [n = 2], *NTRK3* G623R/G696A). One xDFG mutation was identified. Off-target resistance alone was observed in 7 of 16 pts (44%) and included hotspot *KRAS* G12D/A/S/V or G13D, *PIK3CA* E545K or E542A, *BRAF* V600E, and *GNAS* R844H/C mutations. Complex, combined on-target and off-target resistance was observed in 4 of 16 pts (25%): on-target SF or GK alterations (*NTRK1* G595R, *NTRK1* F589L/G595R, *NTRK3* G623R, *NTRK3* G623R/F617L) co-occurred with *KRAS* G12D or G12D/G13D, and *NRAS* G12D or Q61H. An analysis of resistance profiles by cancer type and age will be presented. **Conclusions:** In this analysis, on-target resistance to laro, including potential double *NTRK* resistance mutations, was commonly observed. Off-target, largely MAPK or PI3K/AKT pathway reactivating resistance, also occurred. In select cases, complex and likely polyclonal resistance including both on-target and off-target alterations were identified. These observations impact novel therapy development for TRK fusion cancers. Clinical trial information: NCT02637687, NCT02576431, NCT02122913. Research Sponsor: Bayer HealthCare Pharmaceuticals, Inc.

3067 **Poster Session**

Non-invasive PD-L1 prediction in NSCLC patients using 3D self-supervised deep learning and radiomics. First Author: Xavier Rafael-Palou, Quantitative Imaging Biomarkers (Quibim), Valencia, Spain

Background: Non-small cell lung cancer (NSCLC) is the most common subtype of lung cancer for ~85% of all cases. Despite therapeutic advances, prognosis remains poor, especially in advanced stages. Immunotherapy has revolutionized NSCLC treatment, with immune checkpoint inhibitors (ICIs) targeting the programmed death-ligand 1 (PD-L1) pathway. While PD-L1 expression is typically measured via immunohistochemistry (IHC), predictive modeling using CT images could offer a non-invasive alternative to enhance patient stratification and treatment planning in hard-to-biopsy cases and tumor follow-up of clonal resistance. We propose a solution for non-invasive prediction of PD-L1 expression leveraging radiomics and AI. **Methods:** This multicentric retrospective study included NSCLC patients from five real-world data sources who underwent CT and biopsy. CT scans were quality-checked and annotated by imaging experts supervised by radiologists ($>$ 5 years' experience) to delineate primary tumors. PD-L1 levels were obtained via IHC. The cohort was randomly split into training and test sets (80/20%), with 5-fold cross validation for model building and fine-tuning. Three methods—radiomics, deep learning, and deep radiomics—were proposed for binary PD-L1 prediction (cut-off $>$ 1%) based on 3D lesion-centered patches. The radiomics pipeline included 3D feature extraction, standardization, dimensionality reduction and classifier selection. The deep learning approach used a self-supervised 3D network, pretrained on 2420 lung lesion patches from 751 CTs by minimizing dissimilarity between augmented pairs and then fine-tuned on the training set to predict PD-L1 expression. The deep radiomics method fused both methods via weighted averaging of predicted probabilities. **Results:** A total of 324 patients (41% women, 63 $\pm$ 10 years) with varying PD-L1 expression (63% with levels $>$ 1%), were included. The deep radiomics approach achieved the highest performance, with AUCs of 75.9% $\pm$ 5.3% and 70.1%, and F1-scores of 78.1% $\pm$ 1.2% and 76.7% on the validation and test sets, respectively, with a per-instance processing time of 1.2 $\pm$ 1.3 seconds. Compared to the radiomics method, it improved AUC by 2.6% and 1.2%, and F1-score by 2.7% and 3% on the validation and test sets, respectively. Compared to the deep learning approach, it showed AUC gains of 0.3% and 2%, and F1-score gains of 11.3% and 18.4% on the validation and test sets, respectively. **Conclusions:** This study demonstrates the effectiveness of a novel 3D image-based approach combining radiomics and 3D self-supervised learning to predict PD-L1 expression in a heterogeneous NSCLC cohort using real-world data. The model executes in seconds and could be regulatory cleared and deployed in clinical practice as a medical device performing non-invasive PD-L1 expression identification from CT scans. Research Sponsor: None.

3068 **Poster Session**

Development and implementation of molecular oncology test e-consult at the VA North Texas Health Care System (VANTHCS). First Author: Lucas Jiaxue Wang, UT Southwestern Medical Center, Dallas, TX

Background: The VA National Precision Oncology Program (NPOP), launched in 2016 as part of the White House's Cancer Moonshot Initiative, aimed to revolutionize cancer care through precision medicine for Veterans. Oncologists at the VANTXHCS utilized molecular testing to identify potentially actionable mutations to tailor treatment strategies more accurately. This study aims to evaluate the impact of the identification and impact of potentially actionable mutations with treatment decisions and overall survival. **Methods:** We conducted a retrospective chart review of Veterans with molecular oncology testing (MOT) at VANTXHCS from August 2019 to May 2024 to assess cancer type, prevalence of potentially actionable mutations, treatment decisions, targeted therapy utilization, and overall survival (OS). Potential actionable mutations were determined based on AMP/ASCO/CAP Variant Categorization mapped to the OncoKB FDA-Recognized Human Genetic Variant Database at the time of review. **Results:** 570 Veterans, almost exclusively male (N = 523, 92%) with solid tumors had MOT during the study period. Lung (N = 211, 37%), GI (N = 105, 21%), prostate (N = 49, 9%), pancreatobiliary (N = 46, 8%), head and neck cancers (N = 35, 6%) and GU (N = 30, 5%) were most common with a median overall survival (OS) of 15.93 months. Potential actionable mutations were present in 107 (18.7%) tumors, however only 41 (38%) of the mutations were associated with an FDA approved targeted therapy at the time of testing. Six Veterans (5.6%) received targeted therapy. Reasons for not receiving targeted therapy included secondary mutations (*i.e.*, KRAS), ECOG performance status, hospice or community care and death. Veterans with potentially actionable mutations had significantly worse. **Conclusions:** In the VANTXHCS Veteran population males with lung cancer represents the main tumor type with molecular oncology testing. We observe actionable mutations in nearly 20% of patients tested, with only a minor subset receiving targeted therapy. Our data showed that patients with a potentially actionable mutation have worse overall survival than those that do not. However, treatment with a targeted therapy can significantly improve survival. In conclusion, these findings underscore the need for further research to identify barriers to increase appropriate use of targeted therapies in a timely fashion to improve patient outcomes and advance precision oncology practices. Research Sponsor: None.

3069 **Poster Session**

Phase 2 multicenter clinical trial to evaluate the safety and efficacy of abenacianine for injection (VGT-309), a tumor-targeted, intraoperative molecular imaging agent, for patients undergoing surgery for cancer in the lung. First Author: Sunil Singhal, University of Pennsylvania Perelman School of Medicine, Philadelphia, PA

Background: Molecular targeted agents have revolutionized cancer diagnosis and treatment. Intraoperative molecular imaging (IMI) is a novel technique that entails performing real-time, in vivo optical imaging during surgery to ensure cancer clearance. A multicenter clinical trial was conducted using abenacianine, a cathepsin targeted near-infrared (NIR) IMI agent to visualize pulmonary nodules during surgery. The primary objective was to assess the efficacy of abenacianine in localizing pulmonary lesions, evaluating surgical margin, and identifying unsuspected disease. **Methods:** Participants scheduled to undergo surgery for known or suspected cancer in the lung received abenacianine (0.32 mg/kg intravenous) preoperatively 12 to 36 hours before surgery. During a standard-of-care surgery, the lung underwent IMI and additional disease not identified by conventional methods were identified and analyzed. Efficacy was measured by frequency of clinically significant events (CSEs) defined as localization of lesions not found by standard surgical techniques, identification of additional cancers, identification of positive surgical margins confirmed by histology, and detection of cancerous lymph nodes. **Results:** 89 participants were included in the study. The mean age was 67 years and 57 (64%) were female. Of 89 participants administered abenacianine who underwent standard of care surgical resection for known or suspected cancer in the lung, 40 (45%) had at least one CSE. Abenacianine with NIR imaging identified lesions that were not found by standard surgical methods in 34 (38%) participants, synchronous and occult cancers that were not found by pre-operative imaging in 2 (2%), margins within 10 mm of the closest staple line in 8 (9%), and lymph nodes determined to be cancerous in 1 (1%) participant. Tumors visualized by IMI with abenacianine included non-small cell lung cancers (adenocarcinoma, squamous cell carcinoma, neuroendocrine tumor) and cancers that metastasized to the lung (breast, colorectal, prostate, thymoma, renal cell, sarcoma). Abenacianine was safe and well tolerated in this study; there were no drug-related serious adverse events. **Conclusions:** This Phase 2 multicenter study demonstrated that using IMI with abenacianine during standard-of-care lung cancer surgery markedly improved clinical outcomes. Abenacianine localized tumors intraoperatively, identified synchronous and occult lesions, helped assess negative margin status, and identified cancerous lymph nodes enabling a more complete oncologic resection. Clinical trial information: NCT06145048. Research Sponsor: Vergent Bioscience, Inc.; Vergent Bioscience Australia Pty Ltd.

3070 **Poster Session**

Analysing the impact of size of NGS panel in defining first line therapeutic strategies in NSCLC. First Author: Kshitij Joshi, MOC Cancer Care & Research Centre, Mumbai, India

Background: NCCN recommends the analysis of 8 genes (EGFR, ALK, ROS1, BRAF, KRAS, MET, RET, ERBB2, and NTRK1/2/3) for NSCLC patients to identify efficacious target therapies. Concerned with the rising incidence of sub-optimal response to first-line therapy and rather early progression of disease we performed retrospective analysis in a subset of patients treated at our hospital in order to streamline molecular evaluation strategies. **Methods:** In this study, we retrospectively evaluated the impact of NGS panel sizes in therapy-naïve NSCLC patients. 242 therapy naïve patients evaluated for molecular genetic profiling were stratified into three groups based on gene panel size: a) Small panel ($<$20 genes): Focused on NCCN-recommended genes, b) Medium panel (50–100 genes): Included organ agnostic genes, c) Comprehensive panel ($>$100 genes): Included genomic signatures like TMB, MSI & HRD scores. **Results:** Of 242 therapy-naïve NSCLC patients, 60% (145/242) were evaluated using a small panel of which 13% (19/145) had no detectable genetic alterations while 37% (54/145) had 1st line targetable mutations, 31% (45/145) exhibited both targetable and resistance causing mutations, and 19% (28/145) showed only resistance causing mutations. In the 50–100 genes Panel, comprising 29% (70/242) of patients, 10% (7/70) had no genetic alterations, while 26% (18/70) had 1st line targetable mutations, 30% (21/70) demonstrated both targetable and resistance mutations, and 34% (24/70) harboured only resistance causing mutations. Finally, in the comprehensive NGS group ($>$100 genes), which accounted for 11% (25/242) of cases, only 4% (1/25) lacked detectable genetic alterations; while, 12% (3/25) had 1st line targetable mutations, 32% (8/25) exhibited both targetable and resistance causing mutations, and 52% (13/25) showed only resistance causing mutations. **Conclusions:** a. Increase in gene panel size results in reduction of true negatives. Hence smaller panels may not necessarily capture resistance causing mutations. b. As the gene panel size increases, the detection of actionable driver mutations (e.g., EGFR, ALK) remains consistent; however, there is a notable shift in the mutation profile, with a decrease in cases harbouring only targetable mutations and an increase in those exhibiting both actionable and resistance causing mutations. Hence opting for comprehensive NGS profiling at baseline may increase diagnostic costs marginally, but will have significant impact in designing more effective 1st line therapeutic strategies. Research Sponsor: None.

3071 **Poster Session**

Evaluation of ^{68}Ga-FAPI PET/CT and ^{18}F-FDG PET/CT for the primary staging of non-small cell lung cancer (NSCLC). First Author: Daniel Udayan C, P K Das Institute of Medical Science, Palakkad, India

Background: Fibroblast activation protein inhibitor (FAPI) radiolabeled with Gallium-68 or Fluorine-18 have emerged as promising tracers for targeting cancer-associated fibroblasts (CAFs) within the tumor microenvironment. Previous studies in lung cancer demonstrated that FAPI PET/CT is more sensitive in detecting metastases in the brain, lymph nodes, pleura, and bone. This study aimed to evaluate the clinical utility of FAPI PET/CT compared to FDG PET/CT for the primary staging of newly diagnosed NSCLC patients. **Methods:** This prospective study was done at Amrita Institute of Medical Sciences, Kochi between August 2022 to December 2023 among patients with newly diagnosed NSCLC who consented to undergo both scanning i.e. FDG as well as FAPI PET CT before initiating any treatment. This study was approved by institutional review board. Kolmogorov Smirnov one sample test was used to check the normality of data. To test the statistical significance of the difference in the average values of tumor volume, standardized uptake value (SUV), target to background ratio (TBR) and background uptake between FAPI and FDG, paired sample t test was used for normality and Wilcoxon signed rank test was used for non-normality. **Results:** In this study, 42 patients with newly diagnosed NSCLC (32 with adenocarcinoma (AC) and 10 with squamous cell carcinoma (SCC)) were included. Comparison of the results between FAPI and FDG PET in parameters like TBR, SUVmax and background value in metastatic lesions, FAPI performed better. In case of lymph nodes FAPI vs FDG, mean TBR was (5.06 $\pm$ 4.19 v/s 3.02 $\pm$ 2.89) p value=0.002 and in SUVmax value was (9.07 $\pm$ 5.1 v/s 6.59 $\pm$ 4.2) p value=0.01. Similar benefits were seen in TBR and SUVmax with FAPI on metastatic site like pleura and bone. In the primary lung lesion, mean tumour volume (MTV) was larger with FAPI but there was no difference in SUVmax, TBR and back ground uptake value. If we compare AC vs SCC cases, there was no advantage for SCC with FAPI in metastatic lesions as well as primary lesions. Driver mutated AC cases performed extremely well with FAPI. In brain, mean SUV max with FAPI was 4.52 $\pm$ 0.89 compared to 8.45 $\pm$ 3.31 with FDG. But the brain lesions identified with FAPI were higher than FDG due to higher TBR. In liver, SUV max was similar between FAPI and FDG but higher TBR was seen with FAPI. **Conclusions:** ^{68}Ga-FAPI PET/CT performed better than ^{18}F-FDG PET/CT in the primary staging of NSCLC. FAPI PET may be considered instead of FDG PET in staging of NSCLC. Patient compliance was also better because fasting and glycemic control was not required prior to FAPI. This is the only study where histology (AC and SCC) has been directly compared with both FAPI/PET vs FDG/PET – it shows FAPI/PET performs better with AC, and this South East Asian study showed FAPI/PET performs better with driver mutated NSCLC. Research Sponsor: None.

3072 **Poster Session**

Clinical utility of comprehensive transcriptome testing in advanced solid tumors. First Author: Fei Su, University of Texas MD Anderson Cancer Center, Houston, TX

Background: Despite breakthroughs in genomically-matched therapies, many patients lack actionable genomic alterations. Consequently, innovative new strategies to identify targets for effective therapies are imperative. To assess the potential of comprehensive whole transcriptomic sequencing (WTS) in clinical decision-making, we conducted a prospective trial to perform WTS in patients with metastatic or advanced solid tumors who had prior DNA-based panel testing ($\geq$100 genes) with no reported AMP/ASCO/CAP Tier 1 actionable genomic alterations; along with whole exome sequencing (WES) to compare RNA expression to copy number alterations. We also developed an informed actionability classification scheme to determine actionability of transcriptomics findings. **Methods:** Between August 2022 and December 2024, 100 patients at MD Anderson Cancer Center with advanced cancers were enrolled and underwent comprehensive profiling. Alterations in RNA expression of 147 genes were considered as potentially actionable if the gene's protein product is the direct target of a clinically available therapy (including cell surface targets of antibody-drug conjugates (ADCs)) and/or CNAs of the gene are predictive of response or resistance to a clinically available therapy. A clinical trial was considered a match if RNA expression was an enrollment criterion, or the gene alteration can be directly or indirectly targeted with a therapy utilized within the trial. **Results:** Actionable RNA expressions (AREs) were detected in all patients (100%). In total, 2,216 AREs were detected from 17,800 selected-reported RNA expressions; a median of 22 ARE changes were reported per patient [interquartile range (IQR), 17.0-26.0]. The majority (86.0%) of AREs were RNA overexpressions, defined as the distribution of *tpm* values of the gene expression $>$ 83% of the pan-cancer reference cohort. A median of 13 RNA expression-matched trials were identified per patient [IQR, 10.0-16.0]. The most frequent drug class of actionable RNA overexpressions were ADCs, with a median of 10 ADC targets per patient. Out of 11 distinct genes of which at least 1 amplification is reported, a concordance rate of 61.5% and a Concordance Correlation Coefficient (CCC) value of 0.70 (95% CI, 0.56-0.84) between the actionable gene amplifications (n = 13) and the actionable RNA overexpressions detected in the same patient sample from the tumor profile, indicates a substantial concordance by transcriptional profiling with copy number gain. **Conclusions:** WTS identified actionable RNA expressions in all patients– including for novel ADC targets. These results underscore the utility of comprehensive transcriptional profiling to identify additional actionable targets beyond DNA-based comprehensive profiling. Clinical trial information: MDACC 2021-1049. Research Sponsor: Strategic Alliance: BostonGene—MD Anderson Cancer Center Feasibility and Clinical Utility of Combined Genomics/ Transcriptomics with Systems Biology for Personalized Cancer Therapy; MD Anderson Cancer Center Support grant; Center for Clinical and Translational Science.

3073 **Poster Session**

Application of an epigenomic-based classifier to identify cancer signal of origin on liquid biopsy in cancer of unknown primary cases. First Author: Elmira Forouzmand, Guardant Health, San Diego, CA

Background: Cancer of unknown primary (CUP) lacking resolution to a cancer type (Cancer Signal Origin; CSO) leads to suboptimal outcomes. While several approaches currently exist for identifying a cancer type for CUP samples, they rely on clinical approaches that often require tissue biopsies for immunohistochemistry (IHC), and even still they often fail to resolve a CSO (reported to occur in 50-80% clinical cases). This requirement for tissue, and typically lengthy diagnostic journey, create a large unmet need for CSO identification in CUP individuals. Here, we present feasibility data from a high accuracy Liquid Biopsy method for CSO identification in CUP, bypassing the need for a tissue biopsy and quickly returning a CSO to individuals with CUP. **Methods:** We developed a CSO prediction algorithm on Guardant360 utilizing DNA methylation signatures across thousands of cancer-specific differentially methylated regions for 14 cancer types. We applied the CSO classifier to 1,128 CUP samples in which circulating tumor DNA was detected. Accuracy was assessed by comparing CSO predictions to suspected diagnoses based on clinicopathologic and molecular findings. **Results:** The CSO prediction algorithm was evaluated on 1,128 CUP samples; lung (285/1128, 25.3%) and bile duct (166/1128, 14.7%) were the most common predicted CSOs, aligning with reported prevalence in the literature. Of the 1,128 samples, 12 had a suspected clinical diagnosis. These 12 spanned 8 tumor types. The top CSO prediction aligned with suspected diagnosis in 91.6% (11/12) of cases. The CSO algorithm also provides confidence scores to quantify the confidence of CSO prediction. Out of the total 12 cases, 7 CSOs had high confidence, 3 had moderate confidence, and 2 had low confidence. 7/7 high, 2/3 moderate, and 2/2 low confidence predictions were correct. The single incorrect moderate sample was diagnosed as CRC but predicted to be lung. **Conclusions:** These findings show the feasibility of using plasma-based epigenomic profiling to assign CSO with acceptable accuracy. While interventional clinical studies are necessary to demonstrate clinical utility, this has significant potential for guiding treatment decisions and improving outcomes in CUP patients without ready access to tissue. Research Sponsor: Guardant Health, Inc.

3074 **Poster Session**

HRD status prediction in patients with advanced breast, prostate, ovarian and pancreatic cancers in a liquid biopsy assay. First Author: Pegah Safabakhsh, Guardant Health, Palo Alto, CA

Background: Homologous recombination and repair (HRR) deficiency (HRD) is characterized by genomic instability associated with mutations in BRCA1/2 or other HRR genes. HRD can also be detected by copy number variant (CNV) features, indels, and SNVs (HRD signature). Patients with canonical BRCA-associated cancers harboring an HRD signature with or without HRR mutations derive clinical benefit from PARPi therapy. Here, we present a method of predicting HRD status using Guardant Infinity in patients with these advanced cancers. **Methods:** We developed an ensemble logistic regression model to predict HRD status, inferred from genome-wide somatic SNV and CNV signatures indicative of deficiency in HRR genes, including ploidy-adjusted large-scale state transitions (LST), whole-genome tumor loss of heterozygosity (LOH) and telomeric allelic imbalance (TAI). The model was trained on clinical samples processed on Guardant Infinity, a next-generation platform evaluating both genomics and epigenomics, to assess the sensitivity and accuracy of detecting biallelic loss-of-function in BRCA1/2. The aggregated model was tested on an independent pan-tumor clinical cohort and pre-treatment samples from a subset of patients enrolled in TRITON2, a phase 2 single arm study evaluating rucaparib in metastatic castration resistant prostate cancer (mCRPC) patients with HRR mutations. HRD status association with radiographic progression free survival (rPFS) was evaluated with Cox-proportional hazards model. **Results:** Our model demonstrated high sensitivity in patients with BRCA1/2 biallelic loss and high specificity in HRR-wildtype patients, with an AUC of 0.95 in a pan-tumor cohort with tumor fraction (TF) >10%. In an independent cohort of breast prostate ovarian and pancreatic samples, HRD detection ranged from 79-100% in samples with BRCA1/2 biallelic loss and >10% TF. In breast (n = 703) and prostate (n = 655) cancers, HRD was detected in 14.9% and 13.5% of samples with > 10% TF (3.6% and 3.7% in all TF), with 5.5% and 6.2% attributed to samples not harboring deleterious mutations in HRR genes, respectively, potentially reflecting non-genomic drivers of HRD. In a pilot cohort (n = 15) from TRITON2, HRD was detected in 100% of patients enrolled with either BRCA1/2, or PALB2 mutations (n = 10), where rucaparib demonstrated meaningful activity as measured by independent radiology review objective response rate. HRD was not detected in patients with mutations in CDK12, FANCA, or NBN (n= 5). HRD detected status was associated with prolonged rPFS (HR = 0.07, p = 0.03). **Conclusions:** Guardant Infinity can predict HRD status in patients with advanced canonical BRCA-associated cancers, with preliminary results indicating potential for predicting PARPi benefit in mCRPC. Further studies are warranted to determine PARPi response for breast, prostate, ovarian, and pancreatic cancers with detected HRD status. Research Sponsor: None.

3075 **Poster Session**

Efficacy and safety of distinct regimens for individuals with advanced EGFR-mutated non-small-cell lung cancer who progressed on EGFR tyrosine-kinase inhibitors: A systematic review and network meta-analysis. First Author: Zhang Wengang, Shanghai Pulmonary Hospital, Shanghai, China

Background: Targeted therapy with EGFR tyrosine-kinase inhibitors (TKIs) is the preferred first-line treatment for EGFR-mutated advanced non-small cell lung cancer (NSCLC), but acquired resistance inevitably occurs in almost all responding individuals. We aimed to comprehensively review the literature to investigate the efficacy and safety of distinct regimens in the subsequent-line setting, thereby identifying the optimal regimen for these TKI-resistant NSCLC patients. **Methods:** The PubMed, Embase, Cochrane Library databases, and abstracts of ASCO, ESMO, and WCLC were searched from database inception to 3 November 2024, to identify eligible randomized controlled trials (RCTs) that assessed distinct regimens for individuals with advanced EGFR-mutated NSCLC who progressed on TKIs. The outcomes of progression-free survival (PFS), overall survival (OS), objective response rate (ORR), disease control rate (DCR), and grade 3 or higher adverse events (≥3AEs) were compared and ranked in overall patients and various subgroups among 8 regimens by network meta-analysis and the surface under the cumulative ranking curve, respectively. The protocol is registered with PROSPERO, CRD42024601619. **Results:** 14 RCTs, involving 3177 participants and 8 treatment regimens (chemotherapy plus ivonescimab (PD-1/VEGF inhibitor) [CT+IVO]; CT+amivantamab+lazertinib [CT+AMI+LAZ], CT+immunotherapy+bevacizumab [CT+IO+BEV], CT+AMI, CT+BEV, CT+IO, CT, and IO), were included. In overall patients, the most pronounced PFS benefit was observed with the CT+IVO, followed by CT+AMI+LAZ, CT+IO+BEV, and CT+AMI, ranked second, third, and fourth, respectively. In terms of OS, the regimen of CT+AMI ranked the best, followed by CT+IVO. However, the comparisons of OS among different regimens did not reach statistical significance, possibly due to immature data. The results for ORR and DCR were similar to those for OS, with CT+AMI topping the rankings, followed by CT+AMI+LAZ. In terms of safety, the incidence of ≥3AEs was highest in CT+AMI+LAZ, followed by CT+AMI. In subgroup analysis, CT+IVO demonstrates stable PFS benefits across clinicopathological characteristics, ranking first in most subgroups. Due to the unavailability of OS subgroup data in most RCTs, many regimens were missing in the OS subgroup analysis. **Conclusions:** Integrating the results of different clinical outcomes and subgroup analyses, we conclude that CT+IVO is the optimal treatment option with an acceptable safety profile for patients with advanced EGFR-mutated NSCLC who have progressed on TKIs. CT+AMI+LAZ and CT+AMI are alternative subsequent line options as well, with superior efficacy compared to immunotherapy-based or chemotherapy regimens, yet elevated toxicity profiles requiring vigilant management. Research Sponsor: None.

3076 **Poster Session**

Preliminary results of a first-in-human phase 1b (aCCeleR8-001) study of S-531011, a humanized anti-CCR8 monoclonal antibody, in patients with advanced solid tumors. First Author: Toshihiko Doi, National Cancer Center Hospital East, Chiba, Japan

Background: C-C motif chemokine receptor 8 (CCR8) is selectively upregulated in tumor-infiltrating regulatory T cells (TI-Tregs) in multiple cancers, inhibiting anti-tumor activity of the host immune system. S-531011, a humanized IgG1 monoclonal antibody, is anticipated to deplete CCR8-positive TI-Tregs, restoring anti-tumor immunity without inducing autoimmunity. **Methods:** An aCCeleR8-001 study is a Phase 1b/2, multicenter, open-label study of S-531011 which consists of Phase 1b Dose Escalation part (Parts A-1 and A-2) and Phase 2 Dose Expansion part. The safety/tolerability, pharmacokinetic (PK), pharmacodynamic, and anti-tumor activity of S-531011 as monotherapy and in combination with pembrolizumab (Merck & Co., Inc.) were evaluated in patients with various types of locally advanced or metastatic solid tumors. S-531011 monotherapy was administered at 8, 24, 80, 240, 800, or 1600 mg/kg intravenously every 3 weeks (Q3W) in Part A-1, whereas patients in Part A-2 received S-531011 at 80, 240, 800, or 1600 mg/kg in combination with pembrolizumab 200 mg/kg Q3W. The data were analyzed when all patients in Dose Escalation cohorts completed the dose-limiting toxicity (DLT) observation period. **Results:** As of the data cutoff date (30 Sep 2024), 40 and 35 patients were enrolled in Parts A-1 and A-2, respectively. No DLTs were reported at any dose level and the maximum administered dose of S-531011 was 1600 mg in both parts. One patient reported an infusion-related reaction in Part A. Immune-related adverse events (irAEs) were reported in two patients (5.0%; Grade 1/2 only) in Part A-1, whereas 15 irAEs were reported in 10 patients (28.6%; including four Grade 3 irAEs in four patients) in Part A-2. PK of S-531011 was approximately dose proportional with a terminal elimination half-life of 10 to 12 days regardless of dose level. CCR8 receptors in PBMCs were occupied at doses of 80 mg or higher. PK/CCR8 receptor occupancy modeling analysis indicated that > 90% of receptors in tumor tissues were occupied in the range of 80 to 800 mg. Multiplex immunohistochemistry analysis demonstrated proof of mechanism as evidenced by CCR8-positive Treg depletion in tumor tissue at doses of 24 mg or higher. Among 62 evaluable patients dosed at 80 to 1600 mg in Part A, four patients (6.5%) had confirmed partial response, three of whom had colorectal cancer (CRC). Twenty patients (32.3%) had disease control for ≥ 6 weeks. Response rate was not correlated with dose (80 to 1600 mg). Following a comprehensive data review, tentative recommended Phase 2 doses were determined to be 80 to 800 mg in both parts. **Conclusions:** S-531011 was well tolerated up to 1600 mg as monotherapy and in combination with pembrolizumab. A higher response rate in patients with CRC warrants further exploration of this tumor type in Phase 2 Dose Expansion part. Phase 2 CRC cohorts are currently ongoing. Clinical trial information: NCT05101070. Research Sponsor: Shionogi & Co., Ltd.

3077 **Poster Session**

First report of ROR2 directed therapy with a conditionally active antibody drug conjugate in advanced melanoma. First Author: Jacob Keeling, Sarah Cannon Research Institute at HealthONE, Denver, CO

Background: The receptor tyrosine-kinase like orphan receptors (ROR) are mediators of non-canonical WNT signaling and tissue patterning. ROR2 upregulation is observed in malignancy and has been implicated in metastasis. Development of ROR2 directed conditionally active antibodies with enhanced affinity in the tumor microenvironment is a promising treatment strategy. Here we report our institution's experience treating 5 patients with advanced cutaneous or uveal melanoma treated with the anti-ROR2 antibody drug conjugate ozuriftamab vedotin (MMAE) on the first in human phase 1 trial. (NCT03504488). **Methods:** Adults with advanced solid tumors naïve to vinca binding site therapies who had failed all standard of care therapy were eligible. The charts of all 5 patients with advanced melanoma treated at our institution were reviewed. Patients were treated with ozuriftamab vedotin at concentrations of 1.8 mg/kg or 3.0 mg/kg IV Q2W. Safety and efficacy data were collected. Patient samples were evaluated for pharmacokinetics and clinical correlates. **Results:** 4 out of the 5 patients achieved an objective response in target lesions, per RECIST v1.1 (Table 1). Two of these patients have maintained disease control, including one patient in complete remission (CR) >5 years and the other responding >1 year after starting treatment. Adverse events requiring dose reduction or interruption included neuropathy and neutropenia, both of which recovered with reduced dosing and/or colony stimulating factor. No patients discontinued therapy for adverse drug reactions. Pharmacokinetics showed predictable plasma concentrations of both drug and free MMAE. Anti-drug antibodies were not identified. Biopsies were assessed by IHC for ROR2. The biopsy belonging to the patient who achieved CR was strongly positive for ROR2. All other biopsies showed low/negative ROR2 staining of malignant cells. **Conclusions:** Ozuriftamab vedotin showed early promising antitumor activity in this first report describing ROR2 directed treatment in refractory advanced cutaneous and uveal melanoma. Clinical trial information: NCT03504488. Research Sponsor: None.

Efficacy and safety of ozuriftamab vedotin.

	Case 1	Case 2	Case 3	Case 4	Case 5
Melanoma Subtype	Uveal	Uveal	Cutaneous	Cutaneous	Cutaneous
Initial Dose (mg/kg)	1.8	1.8	3.0	1.8	1.8
Final Dose (mg/kg)	1.5	1.5	1.8	1.8	1.8
Best Target Lesion Response	10% increase	31.9% decrease (PR)	89% decrease (CR, w/ lymph nodes < 5 mm)	38.2% decrease (PR)	43.7% decrease (PR)
Time to Progressive Disease (days)	35	+475*	+2079*	127	84
Major Adverse Events	G3 Neutropenia	G2 Neuropathy	G2 Neuropathy, G4 Neutropenia	None	None
Other Adverse Events	G2 Transaminitis, G2 Myalgia, G2 Arthralgia	None	G1 Salivary Inflammation, G1 Alopecia	G2 Neuropathy	G2 Neuropathy

*Patient has not developed progressive disease since starting treatment.

3078 **Poster Session**

Glutaminase isoform expression in cancer: Implications for metabolic adaptation and therapy. First Author: Mohammed Osama Ahamd Bader, University of Khartoum Faculty of Medicine, Khartoum, Sudan

Background: Glutamine is a critical amino acid involved in various metabolic pathways, particularly in cancers where its importation is significantly elevated via multiple transporters. Glutaminase, the enzyme catalyzing the deamination of glutamine to glutamate, has two isoforms: kidney-glutaminase 1 (GLS1) and liver-glutaminase 2 (GLS2). This study investigates the expression of glutaminase isoforms in cancers originating from tissues with high glutaminase activity—namely, clear renal cell carcinoma (KIRC), chromophobe renal carcinoma (KICH), papillary renal carcinoma (KIRP), hepatocellular carcinoma (LIHC), and glioblastoma (GBM)—to understand the fate of the imported glutamine. **Methods:** The Cancer Genome Atlas (TCGA), Tumor Immune Estimation Resource ([TIMER] 2.0), Gene Expression Profiling Interactive Analysis ([GEPIA] 2.0), and the University of Alabama at Birmingham Cancer Data Analysis ([UALCAN]) Portal were used to investigate GLS1 and GLS2 expression. TIMER 2.0 analyzed 533 KIRC (72 normal), 66 KICH (25 normal), 290 KIRP (32 normal), 153 GBM (5 normal), and 371 LIHC (50 normal) samples. GEPIA 2.0 analyzed 523 KIRC (100 normal), 66 KICH (53 normal), 286 KIRP (60 normal), 163 GBM (207 normal), and 369 LIHC (160 normal). UALCAN analyzed 533 KIRC (72 normal), 66 KICH (25 normal), 290 KIRP (32 normal), 153 GBM (5 normal), and 371 LIHC (50 normal) samples. Additionally, datasets from NCBI GEO were used, including GSE15641 (23 normal, 32 KIRC, 6 KICH, and 12 KIRP), GSE7696 (4 normal, 40 GBM), and GSE41804 (20 normal, 20 LIHC). These platforms detected GLS1 expression in KIRC, KICH, KIRP, and GBM and GLS2 in LIHC by comparing tumor and normal samples. **Results:** GLS1 was significantly downregulated in KIRC, KICH, KIRP, and GBM across TIMER 2.0, GEPIA 2.0, and UALCAN ($P < 0.05$). GLS2 was also significantly downregulated in LIHC ($P < 0.05$). NCBI GEO datasets (GSE15641 for kidney cancers, GSE7696 for GBM, and GSE41804 for LIHC) supported these results, showing consistent GLS1 downregulation in KIRC, KICH, KIRP, and GBM, and GLS2 downregulation in LIHC (adjusted $P < 0.05$; $|Log2FC| > 1$). **Conclusions:** The tissue-specific downregulation of glutaminase isoforms—GLS1 in kidney and brain cancers, GLS2 in liver cancer—highlights an adaptive mechanism in cancer cells to limit glutamine deamination and preserve imported glutamine for other metabolic needs. Enhancing the deamination process could deprive cancer cells of essential precursors for nucleotide synthesis, disrupting their growth and survival. These isoforms represent potential diagnostic markers and therapeutic targets. Research Sponsor: None.

3079 **Poster Session**

A phase 1 study of PARP inhibitor (niraparib) plus HSP90 inhibitor (pimitespib) in solid tumors: Dose-expansion results from the NiraPim (EPOC2102) study. First Author: Yasuyuki Kawamoto, Cancer Center, Hokkaido University Hospital, Sapporo, Japan

Background: Heat shock protein 90 (HSP90) inhibitors have shown potential in destabilizing homologous recombination repair (HRR) proteins, thereby inducing homologous recombination deficiency and enhancing PARP inhibitor efficacy. The NiraPim (EPOC2102) study is a phase 1 study to evaluate this combination therapy in humans, investigating the safety and efficacy of combining niraparib, a PARP inhibitor, with pimitespib, a novel HSP90 inhibitor, in patients with advanced solid tumors. Following establishing the recommended dose (RD) in the dose-escalation part, we present primary analysis results from the dose-expansion part. **Methods:** In the dose-expansion part, patients received pimitespib 80 mg (5-day on/2-day off) combined with niraparib 200 mg daily. Cohort A included patients with BRCA-associated cancers (breast, ovarian, prostate, and pancreatic) harboring *BRCA* pathogenic variants and immediately after progression to prior PARP inhibitors. Cohort B included patients with breast/pancreatic cancer without g*BRCA,* prostate cancer without t*BRCA*, and other solid tumors (excluding ovarian cancer) not previously treated with PARP inhibitors. **Results:** As of August 2024, 30 patients were enrolled: 14 in cohort A and 16 in cohort B. Cohort A included breast (n=6), ovarian (n=5), prostate (n=2), and pancreatic (n=1) cancers. Cohort B included breast (n=3), prostate (n=4), pancreatic (n=4), and other tumors (n=5). The median follow-up period was 6.0 months. The median treatment cycle was 2 (range 1–18). Treatment-related adverse events ≥Grade 3 occurred in 33.3%. Common adverse events (≥20.0%) included nausea (73.3%), diarrhea (40.0%), anorexia (23.3%), vomiting (20.0%), fatigue (20.0%), and decreased platelet count (20.0%). No treatment-related deaths occurred during the study period. The objective response rate was 10.0% (95% CI: 2.1, 26.5), with disease control rate of 36.7% (19.9, 56.1) and 3-month PFS of 27.7%. In cohort A, one patient with hormone receptor-positive breast cancer achieved partial response post-olaparib progression. In cohort B, two patients (leiomyosarcoma and urothelial carcinoma) with *BRCA* pathogenic variants achieved partial response, and one prostate cancer patient with *CDK12* pathogenic variant maintained stable disease ≥3 months. **Conclusions:** The dose-expansion part demonstrated a manageable safety profile and potential efficacy at the recommended dose of niraparib plus pimitespib. Clinical benefit was observed in both BRCA-associated cancers resistant to PARP inhibitors and PARP inhibitor-naive non-BRCA associated cancers, supporting further investigation in biomarker-selected populations. Clinical trial information: jRCT2031220179. Research Sponsor: Takeda Pharmaceutical Co., Ltd.; Taiho Pharmaceutical Co., Ltd.

3080 **Poster Session**

Development and validation of an AI-enabled prediction of prostate cancer (PCa) using urine-based liquid biopsy. First Author: Marvin S. Hausman, Genetics Institute of America, Delray Beach, FL

Background: Prostate cancer (PCa) remains a major cause of malignancy-related mortality among men. Current diagnostic techniques, including PSA testing, lack accurate early detection capabilities, while global barriers include limited access to specialized facilities and cultural sensitivities around transrectal biopsy and digital rectal examination. This study evaluates a non-invasive, urine-based liquid biopsy assay for diagnosing PCa through disease-specific biochemical profiles using an artificial intelligence pipeline. **Methods:** We collected urine from men scheduled for prostate biopsy (biopsy-positive PCa n=197) and healthy controls (n=84). Samples were processed using NUTEC slides, underwent heat cycling, and were converted to digital images for AI analysis. Using 5x2 cross-validation with a random forest classifier, we evaluated cancer detection performance and analyzed cohorts with specific Gleason scores (Gle): Gle 6 (n=70), Gle 7 (3+4) (n=55), Gle 7 (4+3) (n=34), and Gle 8,9,10 (n=38). **Results:** Our classifier demonstrated strong overall performance in distinguishing cancer versus non-cancer subjects (F1=0.843) with notably high recall (R=0.967). Importantly, performance remained robust across Gleason score cohorts (F1=0.799-0.838), maintaining high recall (R>0.89) while preserving clinically relevant precision. The classifier showed particular strength in detecting intermediate- (Gle 7 (3+4): F1=0.838) and low- (Gle 6: F1=0.822) Gleason grade cancers. **Conclusions:** AI-enabled prediction of PCa using urine-based liquid biopsy demonstrates accurate, rapid, and accessible early cancer detection, with consistent performance across disease grades. This non-invasive approach addresses both clinical and cultural barriers to prostate cancer diagnostics. Research Sponsor: None.

TASK	F1	P	R	AUC	ACC
Cancer v. Controls	0.843	0.748	0.967	0.768	0.748
Gle6 v. Controls	0.822	0.770	0.893	0.776	0.746
Gle347 v. Controls	0.838	0.757	0.940	0.752	0.754
Gle437 v. Controls	0.800	0.715	0.913	0.695	0.691
Gle8910 v. Controls	0.799	0.722	0.900	0.695	0.698

AI-enabled prediction of PCa using urine-based liquid biopsy demonstrates accurate, rapid, and accessible early cancer detection, with consistent performance across disease grades. This non-invasive approach addresses both clinical and cultural barriers to prostate cancer screening.

3081 Poster Session

Genomic landscape of 5'methylthioadenosine phosphorylase (*MTAP*) deleted (*MTAP* loss) non-squamous carcinoma of unknown primary site (nsCUP). First Author: Parth J. Sampat, SUNY Upstate Medical University, Syracuse, NY

Background: *MTAP*, a key enzyme in the polyamine pathway breaks down 5'Deoxy-5-Methylthioadenosine (*MTA*) into methionine and adenine. *MTAP* loss reduces adenine and accumulates MTA, which inhibits protein arginine methyltransferase 5 (*PRMT5*). This suggests *MTAP* loss cancers may respond to *PRMT5* inhibition. Methionine adenosyl transferase 2α (*MAT-2A*) is a primary producer of donor S-adenosylmethionine (*SAM*) and the depletion of *MAT-2A* has antiproliferative effect in cancers with *MTAP* loss. Based on the synthetic lethality concept, *MTAP* loss is being used as a biomarker for accrual in multiple trials with *PRMT5* and *MAT-2A* inhibitors. We queried the genomic landscape of *MTAP* loss in patients with nsCUP. **Methods:** DNA extracted from formalin-fixed paraffin-embedded (FFPE) tissue of 7,440 nsCUP cases from 2020 to 2024 underwent hybrid capture-based comprehensive genomic profiling (CGP) to assess all classes of genomic alterations (GA). All cases underwent central pathology review to confirm that at the time of sequencing, a primary site for the cases was not established. Microsatellite instability (MSI) status and tumor mutational burden (TMB) were derived from the CGP data. Programmed death-ligand 1 (PD-L1) was determined by immunohistochemistry (IHC) using the DAKO 22C3 system. **Results:** 853 (11.5%) of nsCUP cases had either complete or partial *MTAP* loss with 0.7% 1 exon, 1.2% 2 exons, 2.9% 3 exons, 5.1% 4 exons, 0.5% 5 exons, 2.5% 6 exons, 32.8% 7 exons and 54.3% 8 exons lost. The median age of the *MTAP* loss patients was higher (68 vs 65; p<.0001) and the gender distributions were similar (52% to 54% female; not significant (NS)). Cyclin-dependent kinase inhibitor 2A (CDKN2A) loss co-occurred in 99.8% in patients with *MTAP* loss. MSI-high status was uncommon in both *MTAP* loss vs *MTAP* wildtype (0.4% vs 0.7%; NS). The *MTAP* wildtype group had higher tumor mutational burden (TMB) > 10 mutations/mb (15.7% vs 11.1%; p=.0004) and TMB >20 mutations/Mb (5.4% vs 3.5%; p=.017) rates. *MTAP* loss nsCUPs had higher frequencies of *KRAS* GA and *KRAS* G12C, whereas *MTAP* wildtype cases had greater frequencies of *ERBB2*, *PTEN*, *MET* and *EGFR* GA (Table). GA in *BRCA1/2* and *FGFR2* were similar in both groups. GA in *ALK*, *RET*, *ROS1*, *RET* and *TRK* were extremely uncommon in both groups (all less than 1%). **Conclusions:** At 11.5%, nsCUP features a relatively high frequency of *MTAP* loss, with the vast majority involving either all (8 of 8) or nearly all (7 of 8) exons. *MTAP* loss patients are slightly older and have reduced TMB levels which may impact their responsiveness to immunotherapy-based combination regimens with *PRMT5/MAT-2A* inhibitors. Clinical trials for the development of targeted therapies to use *PRMT5* inhibition and *MAT-2A* in nsCUP are warranted. Research Sponsor: None.

	nsCUP *MTAP* Loss (N=853)	nsCUP *MTAP* wildtype (N=6,587)	P value
***KRAS* all/G12C**	45.9%/7.6%	31.2%/4.2%	<.0001/<.0001
***ERBB2* all/amp only**	6.7%/4.3%	10.9%/8.1%	<.0001/<.0001
PIK3CA	6.2%	7.1%	NS
BRAF	6.0%	5.0%	NS
FGFR2	4.3%	4.0%	NS
PTEN	4.1%	6.1%	.02
BRCA1/2	1.8%/2.3%	2.1%/2.4%	NS/NS
MET	2.1%	4.6%	.0004
EGFR	2.6%	4.1%	.031

3082 Poster Session

Preliminary efficacy results from an ongoing phase I/II trial of CTS2190, a PRMT1 inhibitor, in patients with advanced/metastatic solid tumors. First Author: Jianan Jin, Oncology Department/Phase I Clinical Center, Zhejiang Cancer Hospital, Hangzhou, Zhejiang, China

Background: Epigenetic gene regulation, including arginine methylation holds significant promise in immunomodulation and long survival outcomes. It represents a potential clinical approach to address the highly unmet needs of patients (pts) with advanced solid tumors who failed PD-(L)1 immune checkpoint inhibitors (ICIs) or standard of cares (SoCs) therapies. CTS2190, the orally available, first-in-class small molecule, specifically inhibits arginine methyltransferase 1 (PRMT1) with significant reduction of intra-tumor asymmetric dimethylarginine (ADMA) level, DNA damage response (DDR), androgen receptor (AR) level, and oncogenic proliferation through epigenetic modulation in various solid tumors. Here we present clinical data from an ongoing Phase I/II study of CTS2190 (NCT06224387). **Methods:** Eligible pts in the dose-escalation stage received 60~300 mg of CTS2190 orally, while pts in the dose-expansion stage were treated with 180 or 240 mg until disease progression or intolerable toxicity. Efficacy, safety, PK, PD and biomarker profiles were evaluated. **Results:** As of January 24, 2025, 38 pts had received CTS2190 treatment, 32 of them were response-evaluable. In the PD-(L)1 primarily resistant group, the objective response rate (ORR) and disease control rate (DCR) were 18.2% (2/11) and 72.7% (8/11), respectively. In addition, in PD-(L)1 primarily resistant non-small cell lung cancer (NSCLC) subgroup, the ORR and DCR were 28.6% (2/7) and 71.4% (5/7), respectively, with significantly prolonged median progression-free survival (PFS) (summarized in the table below). Among 2 response-evaluable pts with metastatic castration-resistant prostate cancer (mCRPC), one achieved partial response (PR) while the other exhibited stable disease (SD) with tumor shrinkage. Most treatment-related adverse events (TRAEs) were grade 1/2 and manageable. The only TRAE ≥ grade 3 with an incident rate > 15% was platelet count decreased (31.6%). No TRAEs led to treatment discontinuation or death. CTS2190 exposure increased proportionally with escalating doses, and a PK-PD-efficacy model demonstrated a relationship between CTS2190 exposure, efficacy and PD marker changes. The correlation between clinical efficacy and intratumor PRMT1 expression, as detected by immunohistochemistry (IHC), is under investigation. **Conclusions:** CTS2190 demonstrated a favorable safety profile and promising efficacy in heavily pretreated pts with advanced solid tumors, particularly in immunologically cold mCRPC and PD-(L)1 primarily resistant NSCLC. These results position CTS2190 as a promising therapeutic option to fulfil unmet medical needs following ICIs therapies. Clinical trial information: NCT06224387. Research Sponsor: CytosinLab Therapeutics Co., Ltd.

PFS of pts with PD-(L)1 primary resistance.

	Patients, n	≥ 3 prior lines of therapy, n (%)	Event	Median PFS (weeks)
All comers	11	7 (63.6%)	7	12.7 (95% CI: 8.0~35.3)
NSCLC	7	4 (57.1%)	5	24.9 (95% CI: 8.0~35.3)

3083 Poster Session

The first-in-human phase 1/2 study of TSN1611, a highly selective KRAS G12D inhibitor, in patients with advanced solid tumors. First Author: Siqing Fu, The University of Texas MD Anderson Cancer Center, Houston, TX

Background: TSN1611 is a novel small molecule KRAS G12D inhibitor targeting both active (GTP-bound) and inactive (GDP-bound) forms of KRAS G12D protein. TSN1611 showed high potency and selectivity against KRAS G12D mutant tumor cells in vitro and effectively inhibited tumor growth in several pancreatic ductal carcinoma (PDAC), colorectal cancer (CRC) and non-small cell lung cancer models (NSCLC) in vivo. **Methods:** A phase 1/2 study of TSN1611 was developed to enroll patients (pts) with advanced solid tumors harboring KRAS G12D mutation. The study comprised a phase 1a dose escalation part following a BOIN design with accelerated titration to determine the maximum tolerated dose (MTD), recommended phase 2 dose and pharmacokinetics (PK), followed by a phase 1b part for dose optimization to compare different recommended doses and a phase 2 part to evaluate the efficacy of TSN1611 across various tumor types. Alternative dose levels or regimens could be explored based on the emerging data. Pts received oral TSN1611 twice daily (BID), until disease progression, unacceptable toxicity, or patient withdrawal. Here we report the preliminary data from phase 1a part. **Results:** As of Jan 05, 2025, 18 pts received TSN1611 from 50 to 600 mg BID (9 with CRC, 5 PDAC, 2 NSCLC, and 1 each with ampullary cancer and gallbladder cancer, all with pre-identified KRAS G12D mutation). Median age was 61 years (range 36-81). The median prior lines of systemic therapy were 3 (range 1-6). No dose-limiting toxicity was reported and MTD was not reached. The most common (≥ 10%) treatment related adverse events (TRAEs) were grade 1 or 2 vomiting (44.4%), nausea and diarrhea (38.9% each), fatigue (16.7%), ALT increased, blood CPK increased, hyperkalemia and hyperuricemia (11.1% each). No treatment related grade 3 or higher AE or SAE was reported. Four (30.8%) out of the 13 evaluable pts demonstrated stable disease per RECIST v1.1. Tumor reductions were observed in 3 pts (CRC, PDAC, and NSCLC, n = 1 each) at 200 or 400 mg BID, with treatment ongoing. Serial assessment of plasma ctDNA revealed declines in KRAS G12D variation allele frequency at 200 mg BID and above, echoing that the exposure at 200 mg BID reached that of ED_{90} in the CRC GP2D model. TSN1611 was rapidly absorbed with T_{max} around 2 hours and half-life around 15 hours. The PK profile indicated a general dose proportionality in exposure across the evaluated dose ranges and low to moderate accumulation after multiple BID dosing. Dose escalation is ongoing, and more data will be available at the conference presentation. **Conclusions:** TSN1611 was well tolerated, demonstrating acceptable PK characteristics as predicted, with preliminary tumor shrinkage observed in pts with refractory KRAS G12D mutant tumors. Phase 1b/2 studies are planned to evaluate TSN1611 both as a monotherapy and in combination with standard of care and/or novel agents treating cancer. Clinical trial information: NCT06385925. Research Sponsor: Tyligand Pharmaceuticals (Suzhou) Limited.

3084 Poster Session

Artificial intelligence (AI)-powered evaluation of protein drug-targetability through subcellular-level expression profiling from immunohistochemistry (IHC) images. First Author: Sukjun Kim, Lunit Inc., Seoul, South Korea

Background: As a standardized methodology for quantifying the targetability of proteins in drug development has yet to be established, we developed an AI-powered analyzer capable of scalably measuring cellular and subcellular-level expression to assess 74 membrane-specific targets in development. **Methods:** A total of 160K cancer and normal IHC images from Human Protein Atlas (HPA) were analyzed, including 47,591 on 74 target genes. The AI model trained on pathologist-annotated histology images, took the IHC images as input to predict cell types and subcellular compartments (nucleus, cytoplasm, and membrane) along with intensity scores. Target genes were evaluated by 1) Tumor cell specificity (TCS): normalized ratio of positive tumor cells to the total positives, 2) Inverse normal score (INS): inverse ratio of positive normal cells to the total normal cells, 3) Membrane intensity score (MIS) and 4) Membrane specificity (MBS): ratio of MIS to the intensity scores from 3 subcellular compartments. Finally, the targetability score (T score) was calculated as $Z_{TCS}x2 + Z_{INS}x2 + Z_{MIS}x0.5 + Z_{MBS}x0.5$. Also, Tumor infiltrating lymphocytes (TIL) were compared between Tumor Proportion Score (TPS)≥1 and TPS<1 groups in each target. **Results:** The IHC analyzer assessed 528M cells including 147M cancer cells. In 34 cancer types, the average T score for the 74 targets was 0.62, which was higher than -0.07 observed for the other 699 targets that have never been explored as drugs. The average T score of the top 10 targets in pan-cancer was 4.27, which was significantly higher than the average (0.0). Among the top 10 targets in pan-cancer (Table), MUC16 was ranked high in non-squamous lung, ovary, uterine, cervical cancers; and CEACAM5 and TACSTD2 were ranked high in 7 and 10 cancer types, respectively. Most targets showed an association with lower TILs and higher TPS, whereas CEACAM5 demonstrated significantly higher TILs (x1.39) in the TPS≥1 group in bladder cancer. **Conclusions:** We developed a pipeline leveraging AI-powered and big-data-driven approaches to assess the cancer and membrane-specific expression of target proteins in IHC images. The current pipeline reproduces the targetability of developed targets as well as novel targets with a potential synergy with immuno-oncology agents. Research Sponsor: None.

Top 10 targets and their association with TILs.

Targets	T score	Top 5 ranked cancer types	TIL fold change
MUC16	5.82	LUAD, OV, UCEC, CESC	0.37
SEZ6	5.14	CESC, PAAD, Skin, Brain, UCEC	0.33
CLDN4	4.67	PAAD, BLCA, CRAD, PRAD, STAD, UCEC, THCA	0.21
DLK1	4.49	LN, HCC, LUAD, UCEC, RCC, Brain	0.60
TM4SF4	4.27	BLCA, LUSC, BRCA, HNSC, PRAD, CESC, THCA, PAAD	0.26
CLDN1	4.11	STAD, HNSC	0.22
CLDN3	3.77	RCC, UCEC	0.08
CEACAM5	3.76	STAD, CRAD, LUSC, BRCA, HNSC, LUAD, CESC	0.40 1.39 (BLCA)
NECTIN4	3.42	HNSC, BLCA, THCA	0.39
TACSTD2	3.27	BLCA, LUSC, BRCA, HNSC, PRAD, CESC, THCA, PAAD	0.31

3085 Poster Session

Seizure-related homolog 6 (SEZ6) expression and ctDNA methylation profiles in patients with high-grade neuroendocrine carcinomas (NECs)/ neuroendocrine tumors (NETs) from a phase 1 study of ABBV-706 in advanced solid tumors. First Author: Song Wang, AbbVie, Inc., North Chicago, IL

Background: SEZ6 is a transmembrane protein with overexpression in small cell lung cancer (SCLC) and other neuroendocrine neoplasms (NENs) and minimal expression in normal tissues, making it a promising therapeutic target for these NENs that have a significant unmet need for treatments. ABBV-706 is a novel SEZ6-targeting antibody-drug conjugate with a potent topoisomerase 1 inhibitor payload and is being evaluated in a phase 1 study (NCT05599984) in patients (pts) with advanced solid tumors. Preliminary data from ABBV-706 monotherapy dose escalation demonstrated a manageable safety profile and promising efficacy in pts with SCLC and NECs/NETs (*JCO* 2024;42[suppl 16]: abs 3001). Herein, we describe SEZ6 expression at the protein and mRNA levels in tumor tissues of pts with NENs outside of SCLC, as well as detection of high-grade NEN cancer signal of origin (CSO) among these pts by investigating ctDNA methylation prior to ABBV-706 treatment. **Methods:** This phase 1, open-label study enrolled pts (≥18 yr) with relapsed/refractory high-grade NECs/NETs (well-differentiated grade 3 NETs and poorly differentiated NECs), atypical lung carcinoid, and medullary thyroid cancer (MTC) in dose-escalation and -expansion cohorts. Pts received ABBV-706 monotherapy IV at 1.3–3.5 mg/kg Q3W. FFPE tumor tissues of these pts, when available, were subjected to a proprietary IHC assay for SEZ6 and RNAseq analysis. ctDNA samples collected prior to ABBV-706 treatment were subjected to the Cancer Research Solution (RUO; GRAIL, Inc.). ctDNA abundance and CSO were assessed by examining cancer-specific methylation patterns of ctDNA. **Results:** As of Aug 27, 2024, in the NEC/NET cohort of 64 pts, median age was 63 yr (range 33–86) and the median number of prior therapies was 3 (range 1–8). High prevalence of moderate to strong SEZ6 expression (SEZ6 cytomembrane IHC H-score ≥100) was observed across NEC/NET histologies: 78% of extrapulmonary small cell NEC of diverse anatomic sites (n = 9); 80% of neuroendocrine prostate carcinoma (n = 5); 43% of large cell NEC of diverse anatomic sites (n = 14); 50% of MTC (n = 4); 40% of gastroenteropancreatic NENs (n = 10); 50% of atypical lung carcinoid (n = 6). *SEZ6* mRNA levels were highly correlative with SEZ6 IHC scores. ctDNA positivity rate was 95% from baseline plasma samples of the NEC/NET cohort (n = 60); 67% of ctDNA-positive samples (n = 57) were predicted to have high-grade NEN as their primary CSO. **Conclusions:** Robust SEZ6 expression was observed with some heterogeneity across histologies of the NEC/NET monotherapy cohort. High ctDNA detection rate at baseline indicates the feasibility of monitoring molecular response longitudinally without an invasive procedure and identifying predictive biomarker(s) for ABBV-706. Clinical trial information: NCT05599984. Research Sponsor: AbbVie, Inc.; n/a.

3086 Poster Session

EphA2 siRNA in DOPC nanoliposomes (EPHARNA): A phase I clinical trial in patients with solid tumors. First Author: Ravali Annam Reddy, The University of Texas MD Anderson Cancer Center, Houston, TX

Background: EphA2 overexpression is common in human cancers and has an important role in promoting tumor growth and metastasis. Further, EphA2 has kinase-dependent and independent functions, making it ideal for RNAi-based targeting. EphA2 siRNA incorporated in DOPC nanoliposomes (EPHARNA) was effective in reducing EphA2 protein levels and reducing tumor growth in preclinical studies. This is a first-in-human phase I clinical trial of EPHARNA in patients with solid tumors. **Methods:** Adult patients with advanced solid tumors received escalating doses of intravenous EPHARNA twice weekly in 3-week cycles. A total of 8 dose levels were explored under a BOIN design (Table 1). Study objectives included evaluation of safety, tolerability, maximal tolerated dose, and efficacy. Adverse events were assessed per NCI CTCAE Version 4.03 and efficacy per RECIST v1.1. Patients were evaluable for response if they completed at least 2 cycles. Clinical benefit was defined as objective response or stable disease for 4 or more cycles. **Results:** A total of 48 patients were treated. Most common diagnoses were colorectal (29.2%) and ovarian cancer (12.5%). 20.8% of treated patients were Black and 8.3% were Hispanic. Median age was 60.3 years (range 24.5-78.8). Median number of prior therapies was 4 (range 0-12). Among treated patients, 36 (75%) experienced an AE. Most common AEs (≥20%) were fever (33.3%), infusion-related reaction (25%), and chills (20.8%). 5 (10.4%) treated patients experienced Grade 3 AEs that were dose-limiting toxicities including chills (2.1%), dyspnea (2.1%), hypertension (2.1%), infusion-related reaction (2.1%), and nausea/vomiting (2.1%). No Grade 4 AEs were noted. Of the 25 patients evaluable for response, disease control rate was 44% (95% CI: 24.5-63.5%) with 11 patients demonstrating stable disease for at least 2 cycles. No patients demonstrated partial or complete response. Clinical benefit was observed in 4 (16%, 95% CI: 1.6-30.4%) patients who demonstrated stable disease for at least 4 cycles. One patient received 16 cycles with stable disease before withdrawing consent and discontinuing the trial due to desire for a treatment break. The study was closed to enrollment prior to confirmation of the MTD due to unavailability of the drug. **Conclusions:** EPHARNA demonstrated an acceptable safety profile with manageable adverse events in patients with advanced solid tumors. Further investigation of this novel therapeutic approach is warranted to fully elucidate efficacy and optimal dosing strategy. Clinical trial information: NCT01591356. Research Sponsor: University of Texas MD Anderson Cancer Center; National Cancer Institute; P30CA016672; Gateway for Cancer Research; G-18-300; U.S. National Institutes of Health; 5P50CA098258; T32 Institutional Training Grant; T32CA101642.

Dose levels, patients treated, and DLTs.

Dose Level	EphA2 siRNA-DOPC Dose ($\mu g/m^2$)	Number of Patients Treated	Number of Patients Experiencing DLTs	DLTs
1	450	14	2	G3 chills G3 nausea G3 vomiting
2	675	6	1	G3 hypertension
3	1012.5	5	0	N/A
4	1518.75	5	0	N/A
5	2278.13	7	0	N/A
6	3417.2	2	2	G3 infusion-related reaction G3 dyspnea
7	3600	3	0	N/A
8	7200	6	0	N/A

3087 Poster Session

A phase 2 study of olaparib in IDH1 and IDH2 mutant advanced chondrosarcomas and other solid tumors. First Author: Philippos Apolinario Costa, Yale Cancer Center, New Haven, CT

Background: Pre-clinical data have shown that mutations in isocitrate dehydrogenase (IDH) 1 and 2 can lead to a "BRCAness" phenotype by impairing homologous recombination (HR) repair. Olaparib, a PARP inhibitor effective in BRCA-mutated cancers such as ovarian, prostate, pancreas and breast cancer, may also be effective in IDH1/2 mutant solid tumors. IDH1/2 mutations are frequently present in gliomas and cholangiocarcinomas but also in other solid tumors, such as chondrosarcomas, and melanomas. This study evaluated the efficacy of olaparib in treating advanced IDH1/2 mutated solid tumors other than cholangiocarcinoma and gliomas. **Methods:** NCI 10129 was a 3-arm, open-label Phase II clinical trial performed in the NCIExperimental Therapeutics Clinical Trials Network (ETCTN) evaluating olaparib 300 mg twice daily for IDH mutated solid tumors refractory to standard treatment. Patients with solid tumors, excluding cholangiocarcinoma and glioblastoma, were enrolled in cohort 3 of the Phase II trial. The primary endpoint was the overall response rate (ORR), and the secondary endpoints were progression-free survival (PFS) and overall survival (OS). **Results:** From March 2019 until January 2024, a total of 26 patients with IDH1/IDH2-mutant tumors were enrolled in the study across 10 sites. Of these, 14 (53%) had chondrosarcomas, with 5 (35%) being dedifferentiated. Following, the most prevalent histologies were gastrointestinal adenocarcinomas (4, 15%), other sarcomas (3, 12%) and other tumors (5, 19%). Most tumors had IDH1 mutations (n = 20, 77%), with R132C (n = 12, 60%) being the most common substitution. The median age was 62 years (range 43-78), and 18 (69%) participants were male. Patients had received a median of 1.5 prior line of therapy (0-9). After a mean follow-up time of 8.6 months (0.8-62.6), no objective responses were seen, leading to the closure of enrollment. The median PFS was 2 months (95% CI 1.8-2.2), and the median OS was 7.5 months (95% CI 1.3-13). Only two patients had a clinical benefit, defined as PFS > 6 months. Olaparib was tolerable, with most adverse events scored as grades 1-2. **Conclusions:** Olaparib did not demonstrate activity in IDH-mutant chondrosarcomas and other solid tumors. This study underscores the remarkably poor outcome associated with IDH mutant tumors, emphasizing the urgent need for additional therapeutic options. Further evaluation of the correlative data, including assessment of HR proficiency, is required to elucidate why pre-clinical evidence suggesting potential efficacy did not translate into clinical benefit in IDH mutant solid tumors. Clinical trial information: NCT03212274. Research Sponsor: National Cancer Institute; NCI-2017-01182.

3088 Poster Session

The effect of HIFU treatment on liver metastasis of colorectal cancer in mice and its impact on immunity. First Author: Shasha Wang, Department of Medical Oncology, Affiliated Hospital of Qingdao University, Qingdao, China

Background: The liver represents the predominant site for metastasis in colorectal cancer, with over 85% of cases exhibiting the microsatellite stable (MSS) phenotype, which typically shows limited response to immunotherapy. High-Intensity Focused Ultrasound (HIFU) not only facilitates direct destruction of tumor tissues but also has the potential to remodel the tumor immune microenvironment, thereby enhancing systemic anti-tumor immunity. This study aimed to explore the effects of HIFU on liver metastasis in a murine model and its subsequent impact on immune modulation. **Methods:** A BALB/c mice model of colorectal cancer liver metastasis was established and validated. The animals were treated with HIFU, followed by transcriptomic profiling and immunohistochemical staining to assess immune-related markers (CD8, F4/80, FOXP3, PD-L1, IL-6) in the liver metastasis tissues. **Results:** Transcriptomic sequencing performed on liver metastatic tissues collected seven days after HIFU treatment revealed a notable upregulation of CXCL14 expression, which was corroborated by protein immunoblotting. Immunohistochemical analysis demonstrated an increased infiltration of cytotoxic T cells (CD8+), a reduction in macrophage populations (F4/80), and a significant decrease in T regulatory cells (FOXP3 expression). Additionally, both PD-L1 and IL-6 levels were substantially reduced in the treated tissues. **Conclusions:** Seven days post-HIFU treatment, significant immune modulation was observed in liver metastatic tumor tissues, including enhanced infiltration of cytotoxic T cells, a reduction in immune-suppressive cell populations such as macrophages and Tregs, and the attenuation of inflammatory cytokines. These findings suggest that HIFU not only enhances the anti-tumor immune response but also facilitates the transition of liver metastases from an immune "cold" to a "hot" tumor microenvironment, potentially improving the efficacy of subsequent immunotherapeutic strategies. Research Sponsor: None.

3089 **Poster Session**

A phase 2 study of the olaparib and AZD6738, an ATM/ATR inhibitor, in isocitrate dehydrogenase (IDH) mutant solid tumors. First Author: Philippos Apolinario Costa, Yale Cancer Center, New Haven, CT

Background: Pre-clinical data has shown that mutations in isocitrate dehydrogenase (IDH) 1 and 2 can lead to impaired homologous recombination repair. IDH1/2 mutations are frequently present in gliomas and cholangiocarcinomas but also in other solid tumors, such as chondrosarcomas. AZD6738 is an ATR inhibitor, and Olaparib is a PARP inhibitor. Preclinical evidence showed a synergistic effect of this combination in models with DNA damage repair effects. This study aims to evaluate the efficacy of Olaparib and AZD6738 in treating advanced IDH1/2 mutated solid. **Methods:** NCI 10222 is an open-label Phase II clinical trial performed in the NCI National Clinical Trials Network evaluating olaparib 300 mg twice daily with AZD6738 160 mg daily for IDH mutated solid tumors refractory to standard treatment. The primary endpoint was the overall response rate (ORR), and the secondary endpoints were progression-free survival (PFS) and overall survival (OS). **Results:** From January 2020 until March 2023, a total of 24 patients with IDH1/IDH2 mutant tumors were enrolled in the study across 8 sites. Of these, 14 (58%) had cholangiocarcinoma, 4 (17%) had chondrosarcomas, and 6 (25%) had other tumors. Most tumors had IDH1 mutations (n = 16, 70%). The median age was 59 years (range 29-83), and 15 (63%) participants were male. Patients had received a median of 3 prior lines of therapy (0-6). After a mean follow-up time of 3 months (0.2-ongoing), no objective responses were seen, leading to the closure of enrollment. The median PFS was 2 months (95% CI 2-4), and the median OS was 7 months (95% CI 3-NE). Only three patients had a clinical benefit, defined as PFS $>$ 6 months, with one patient diagnosed with G1 chondrosarcoma still on treatment with stable disease. Combination of Olaparib with AZD6738 resulted in G3 AE in 9 (38%) patients, leading to 4 (17%) discontinuations. **Conclusions:** Olaparib with AZD6738 did not demonstrate activity in IDH mutant solid tumors. However, the stability seen in the patient with low-grade tumors could suggest that the effect is restricted to lower-grade tumors, still dependent on IDH mutations. Further evaluation of the correlative data is required to elucidate why pre-clinical evidence suggesting potential efficacy did not translate into clinical benefit in IDH mutant solid tumors. Clinical trial information: NCT03878095. Research Sponsor: None.

3090 **Poster Session**

Effect of extrachromosomal DNA (ecDNA) on *MYCN* amplified neuroblastoma and patient outcomes. First Author: Mihika Sonalkar, UCSD, La Jolla, CA

Background: Recurrent cytogenetic abnormalities represent candidate therapeutic targets for children with neuroblastoma (NB). *MYCN* oncogene amplification is associated with significantly worse survival rates for children with NB and remains one of the primary predictors of patient prognosis. *MYCN* amplifications in NB can be found both within the linear genome and on circular extrachromosomal DNA (ecDNA), and therapeutic targeting of the mechanisms underlying *MYCN* amplification represents a novel and promising strategy in NB. However, the molecular features and clinical and biological significance of these amplifications in NB tumors are not sufficiently understood. **Methods:** Whole genome and RNA sequencing data were analyzed for NB cell lines and NCI TARGET NB samples using AmpliconSuite software for ecDNA identification and characterization. GISTIC was used for identification of recurrently amplified regions. Gene expression levels were determined using StringTie, and gene clustering heatmaps were generated using FeatureCounts software. For differential gene expression analyses, samples were divided into ecDNA**+** and ecDNA**-**, and genes contained on ecDNA were compared to the same regions on linear DNA across samples using DESeq2. Associations between ecDNA quantity, content, and patient survival were performed using multivariate Cox regression survival analysis. Associations of gene expression with patient survival were performed using the R2 Platform. The efficacy of targeting ecDNA-associated gene products was assessed using live cell imaging and cell viability assays. **Results:** WGS analysis confirmed 7/20 NB patient tumors from the TARGET database to be ecDNA amplified with 1-5 independent ecDNA elements and *MYCN* gene expression correlated with the ecDNA copy number. ecDNAs in *MYCN*-amplified neuroblastoma cell lines contained distinct gene combinations and possessed unique structures. MYCN overexpression in NB cells has been shown to be associated with replication stress (RS), and tumor cells containing ecDNA are hyper-reliant on the DNA damage response (DDR) kinase CHK1 to manage heightened replication stress. Expression of the *CHK1* gene was associated with neuroblastoma patient outcomes and neuroblastoma was most significantly associated with *CHK1* RNA dependency. We further validated CHK1i as a promising therapeutic strategy in *MYCN* amplified NB, as CHK1 inhibition with the novel inhibitor BBI-2779 was most effective against ecDNA+, *MYCN*-amplified neuroblastoma cell lines. **Conclusions:** Our results emphasize the critical role of ecDNA in NB. We identify a synthetic lethality axis shaped by ecDNA *MYCN* amplification and CHK1 dependence. We further demonstrate the feasibility of targeting this vulnerability through CHK1 inhibition, thus offering new avenues for treatment in *MYCN* amplified tumors. Research Sponsor: Curebound Foundation; Boundless Bio, Inc.

3091 **Poster Session**

AI-driven design of novel PARP inhibitors. First Author: Juan Velasco, Yale University, New Haven, CT

Background: Inhibitors of the Poly (ADP-ribose) polymerase (PARP) family play a role in treating HER2-negative locally advanced or metastatic breast cancer with germline BRCA1/2 (gBRCA) mutations, as well as in the maintenance treatment of gBRCA-associated metastatic pancreatic ductal adenocarcinoma. However, the design of de novo small molecules targeting proteins like PARP remains time consuming and resource intensive. It is hypothesized that generative models trained on molecular graph encodings could accelerate the design of novel PARP inhibitors. Objective:This study aims to develop a generative model capable of designing novel, orally bioavailable PARP inhibitors. **Methods:** A large language model was pre-trained on 1 million chemical structures sourced from the ChEMBL database. Each structure was represented as a Simplified Molecular Input Line Entry System (SMILES) string, which was tokenized into discrete atomic and functional group-level tokens. The model leverages an Average-Stochastic Gradient Descent Weight-Dropped Long Short-Term Memory (AWD-LSTM) architecture. Transfer learning was applied to adapt the pre-trained model to specific target chemical structures, enabling domain-specific fine-tuning for the de novo design of PARP inhibitors. **Results:** The model demonstrated robust performance in generating chemically valid, unique, novel, and diverse PARP inhibitors. It achieved a validity rate, uniqueness rate, and novelty rate of 100%, along with a diversity score of 81.53%. Furthermore, the generated molecules exhibited favorable physicochemical properties, including a molecular weight of 417.52 Da, a logarithm of the partition coefficient (LogP) of 2.58, a topological polar surface area (TPSA) of 93.21 Angstrom squared, an average of 4.05 rotatable bonds, 1.84 hydrogen bond donors, and 5.14 hydrogen bond acceptors. **Conclusions:** A generative model was developed to design novel, orally bioavailable PARP inhibitors. It provides an efficient and automated tool for de novo small molecule design with tailored molecular and pharmacological properties, potentially accelerating the development of PARP inhibitors. Research Sponsor: None.

3092 **Poster Session**

A first-in-class KIF11 degrader antibody conjugate (DAC) as a potential therapy targeting a broad spectrum of cancers. First Author: Yan Feng, Accutar Biotechnology, Cranbury, NJ

Background: Kinesin family member 11 (KIF11) plays a critical role in mitotic spindle formation and centrosome separation during cell division, making it an attractive anti-cancer target. Despite its promise, the clinical success of KIF11 inhibitors has been hindered by a narrow therapeutic window, largely due to on-target toxicities, such as myelosuppression. Antibody-drug conjugates present a promising strategy to overcome this limitation by enhancing the therapeutic window of KIF11-targeting therapies. However, creating a KIF11-targeting inhibitor payload with sub-nanomolar potency remains a significant challenge. Using Accutar's chimeric degrader platform, we developed dKIF976, a first-in-class KIF11 degrader with sub-nanomolar potency. This degrader was further used as payload to create DACs demonstrating potent cell growth inhibition coupled with KIF11 degradation, thereby providing a robust foundation for further in vivo evaluation of novel KIF11-targeting therapy. **Methods:** dKIF976, a CRBN-based KIF11 degrader, was designed via Accutar's chimeric degrader platform. Western blot analysis was used to evaluate KIF11 degradation and mitotic arrest, as indicated by Histone H3 phosphorylation, in cancer cell lines. Cell growth inhibition was assessed using ATP-based assays. Mechanism and selectivity of dKIF976 were confirmed through specific cellular assays and proteomic analyses. Cell surface antigen-dependent activity of dKIF976 DACs were evaluated in cell lines with different levels of antigen expression. **Results:** dKIF976 demonstrated rapid, dose-dependent KIF11 degradation and significant upregulation of p-Histone H3 across all tested cell lines, achieving sub-nanomolar potency. In side-by-side comparisons, dKIF976 displayed significantly greater cell growth inhibition than multiple published KIF11 inhibitors. KIF11 degradation and the resulting cell growth inhibition induced by dKIF976 were confirmed to be dependent on the E3 ligase CRBN and the proteasome. Proteomic analysis via mass spectrometry validated the selective degradation of KIF11. When conjugated to antibodies, dKIF976 DACs exhibited antigen-dependent KIF11 degradation and cell growth inhibition, with enhanced potency observed in cell lines with high target expression. **Conclusions:** dKIF976 achieves specific and potent KIF11 degradation, inducing mitotic arrest and robust cancer cell growth inhibition. Its superior efficacy and unique mechanism of action establish it as a highly promising payload for antibody conjugates. dKIF976 DACs demonstrated strong antigen-dependent KIF11 degradation and cell growth inhibition. This innovation highlights the potential of using chimeric degraders as payloads for antibody conjugates, offering a promising strategy to enhance the therapeutic window of KIF11-targeted therapies and pave the way for their future success. Research Sponsor: None.

3093 **Poster Session**

Comparative analysis of fibroblast activation protein Inhibitor (FAPI) O4 PET/CT versus flurodeoxyglucose (FDG) PET/CT in staging gastrointestinal tumours. First Author: S.P. Somashekhar, Aster International Institute of Oncology, Bangalore, India

Background: FAPI 04 PET/CT has emerged as a promising alternative to FDG PET/CT, offering potential advantages in sensitivity, specificity, and patient comfort due to its unique targeting of fibroblast activation protein (FAP), which is up regulated in the stromal cells of many cancers. This study aims to evaluate the diagnostic performance of FAPI 04 PET/CT compared to FDG PET/CT for staging gastrointestinal (GI) tumours. **Methods:** 55 patients with suspected or confirmed GI malignancies underwent both FDG PET/CT and FAPI 04 PET/CT scans within a 7-day window. A total of 115 lesions were identified across the cohort, including colorectal, gastric, pancreatic, and oesophageal cancers. Tumor localization, lesion size, and uptake characteristics were compared between the two imaging modalities. Sensitivity, specificity, and diagnostic accuracy were calculated using histopathology as the gold standard. **Results:** Of the 55 patients, 31 were male and 24 female, with a median age of 58 years (range: 42–78). FAPI 04 PET/CT demonstrated superior sensitivity (92%) compared to FDG PET/CT (84%) for the detection of GI tumours, particularly in pancreatic and colorectal cancers, where stromal fibrosis is prevalent and metabolic activity may be low. Specificity of FAPI 04 PET/CT was also higher (95%) compared to FDG PET/CT (88%), reflecting the lower background activity in non-tumor tissues. Lesion detection rates were significantly improved with FAPI 04 PET/CT, with 112 out of 115 lesions identified, while FDG PET/CT detected 98 lesions ($p = 0.02$). The accuracy of FAPI 04 PET/CT was 94%, whereas FDG PET/CT had an accuracy of 86%. Notably, FAPI 04 PET/CT showed a higher diagnostic yield in detecting metastases in liver, peritoneum, and lymph nodes compared to FDG PET/CT. The average scan time for FAPI 04 PET/CT was 30 minutes, significantly shorter than FDG PET/CT (1 hour 15 minutes). **Conclusions:** FAPI 04 PET/CT outperforms FDG PET/CT in terms of sensitivity, specificity, and diagnostic accuracy for staging gastrointestinal tumours, particularly in cases with abundant stromal involvement. The reduced background activity and higher lesion detection rate enhance the utility of FAPI 04 PET/CT in clinical practice. Additionally, the walk-in basis for FAPI 04 PET/CT with shorter fasting and scan time offers significant improvements in patient comfort and convenience. Given these advantages, FAPI 04 PET/CT represents a promising alternative to FDG PET/CT for staging GI cancers, with potential implications for improved treatment planning and monitoring. Research Sponsor: None.

3094 **Poster Session**

Role of Lu177 FAPI-09 therapy in combination with chemotherapy or immunotherapy for chemo-resistant progressive cancers: Early clinical experience. First Author: Prathap H. J, Aster International Institute of Oncology, Aster Hospitals Whitefield, Bangalore, India

Background: Chemo resistant progressive tumours represent a major challenge in oncology. These tumours often adapt and develop resistance mechanisms that limit the efficacy of standard treatments. Lu177 FAPI-09 therapy, which targets fibroblast activation protein (FAP) expressed on cancer-associated fibroblasts (CAFs) within the tumor microenvironment, has emerged as a promising treatment option. By binding to FAP, Lu177 FAPI-09 selectively delivers radiation to the tumor stroma, potentially altering the tumor environment and making it more susceptible to subsequent therapies. This study aimed to evaluate the safety, feasibility, and effectiveness of combining Lu177 FAPI-09 therapy with chemotherapy or immunotherapy in patients with advanced chemoresistant cancers. **Methods:** Eighteen patients with advanced progressive and chemo resistant malignancies were included in this study. All underwent Ga-68 FAPI-09 PET/CT scans prior to treatment to confirm FAP expression in their tumors, ensuring that Lu177 FAPI-09 therapy would be beneficial. The patient group consisted of GI(7), ovarian (11). Prior to Lu177 FAPI-09 therapy, all patients had demonstrated resistance to one or more prior lines of chemotherapy or immunotherapy. Following the administration of Lu177 FAPI-09 therapy, patients received chemotherapy or immunotherapy 5 days later, tailored to their specific tumor type. Disease responses were assessed two months after the combined treatment. **Results:** After receiving Lu177 FAPI-09 therapy, 80% of patients showed either stable disease or a positive response to the subsequent chemotherapy or immunotherapy. The safety profile of Lu177 FAPI-09 therapy was favourable, with no major grade 3 or 4 adverse events reported. The most common side effects were mild reductions in blood counts, including neutropenia or anaemia. Overall, Lu177 FAPI-09 therapy in combination with chemotherapy or immunotherapy was well-tolerated by the majority of patients. **Conclusions:** Lu177 FAPI-09 therapy, when used in combination with chemotherapy or immunotherapy, shows promise in enhancing treatment responses in patients with chemo resistant progressive cancers with minimal side effects and no major toxicities. The use of Ga-68 FAPI-09 PET/CT scans to identify patients with tumors expressing FAP ensures appropriate patient selection, optimizing the likelihood of a positive outcome. These findings suggest that Lu177 FAPI-09 therapy could be an effective approach to overcome resistance and improve treatment outcomes in patients with advanced malignancies. Research Sponsor: None.

3095 **Poster Session**

Dosing tolerability and adverse events (AEs) in dihydropyrimidine dehydrogenase (*DPYD*) variant carriers receiving genotyping-guided fluoropyrimidine (FP) dosing. First Author: Grace Nguyen, Atrium Health Levine Cancer Institute, Charlotte, NC

Background: We previously showed that *DPYD* genotype-guided FP (5-FU, capecitabine) dosing reduces severe AEs and hospitalizations in variant carriers. However, optimal dose reduction and tolerability for individual *DPYD* variants are not well understood. This study aims to evaluate dosing tolerability and AEs among *DPYD* variant carriers. **Methods:** This is a retrospective cohort study of patients (pts) receiving FP-based chemotherapy at a multisite cancer center who underwent routine in-house *DPYD* genotyping covering 5 variants (Table). Test results and dose recommendations were provided to oncologists per Clinical Pharmacogenetics Implementation Consortium guidelines (i.e., 50% dose reduction in *DPYD* heterozygous carriers and slow titrations in subsequent cycles based on AEs). Clinicodemographics were collected via chart review, and AEs were graded using Common Terminology Criteria for Adverse Events criteria version 5.0. Data was collected for 3 months of FP treatment unless discontinued early. **Results:** From March 2020-October 2024, 1,645 pts were genotyped with 85 (5.2%) identified as heterozygous *DPYD* variant carriers. This analysis included 49 carriers who were tested pretreatment and started FP chemotherapy (median age 65, 35% male, 67% White, 27% Black, 71% gastrointestinal cancers, 53% 5-FU, 47% capecitabine). All pts started on dose-reduced FP at cycle 1 (Table). Of 49 carriers, 18 (37%) had at least one dose escalation, most occurring in cycles 2 or 3. Of these, 5 were eventually escalated to full dose, 5 had AEs preventing further escalation, 5 had subsequent dose reduction due to AEs, 2 completed therapy while escalating, and 1 had one dose escalation with no documented AE. Dose escalation was not performed in 31 (63%) pts due to the following reasons: any-grade AE (n = 27, of which 5 had further dose reductions due to AEs), poor performance status (n = 1), early discontinuation (n = 2, 1 disease progression, 1 declined further therapy), treatment completion (n = 1). **Conclusions:** This is the largest retrospective cohort study evaluating dosing tolerability and toxicity in *DPYD* carriers using real world data. There is interindividual variability in tolerability within each *DPYD* variant, particularly with decreased function variants. Findings will help inform prospective studies and clinical guidelines on variant-specific dosing strategies. Research Sponsor: None.

Variant	N, %	Median (range) first dose intensity, %	Median (range) final dose intensity, %	Grade 3+ AE	AE related hospitalization	AE related discontinuation
All	49	50 (40-81)	50 (27-100)	13 (27%)	9 (18%)	11 (22%)
c.1236G>A[a]	27 (55%)	50 (40-75)	54 (33-100)	6	3	6
c.557A>G[a]	12 (25%)	50 (40-81)	60 (40-100)	2	1	3
c.2846A>T[a]	6 (12%)	50 (47-54)	50 (47-54)	2	3	2
c.1905+1G>A[b]	3 (6%)	51 (45-54)	38 (27-45)	2	1	0
c.1679T>G[b]	1 (2%)	50	45	1	1	0

[a]Decreased function variant.
[b]No function variant.

3096 **Poster Session**

Monocentric pilot trial of trametinib in severe extracranial arteriovenous malformations. First Author: Emmanuel Seront, Institut Roi Albert II, Department of Medical Oncology, Saint Luc University Hospital, Brussels, Belgium

Background: The Mitogen Activated Protein Kinase (MAPK) pathway is crucial for cell growth, proliferation, and survival. Overactivation of MAPK is observed in many cancers leading to evaluation of targeted therapies such as MEK inhibitors. Vascular malformations, including arteriovenous malformation (AVM) share many oncogenic mutations with cancer. For example, AVM present KRAS, RASA1, MAP2K1 mutation that result in excessive activity of the RAS-RAF-MEK cascade. This trial aimed to assess trametinib safety and efficacy in adult patients with stage III AVM refractory to conventional therapy, causing deformities, pain, bleeding, or ulceration. This is the first trial to evaluate targeted therapies in AVM. **Methods:** We conducted a prospective Phase II trial on ten adult AVM patients. Trametinib was administered orally for 12 months, with initial dosage escalation based on patient tolerance. Clinical and radiological outcomes were assessed at baseline, during treatment, and at follow-up. Primary outcomes included safety and clinical efficacy (pain reduction, ulceration healing, thrill and deformation improvement). Secondary outcomes included radiological responses assessed via MRI, Doppler ultrasound, and angiography. **Results:** Of the ten patients (6 female, 4 male), eight had facial AVM, one auricular, and one foot AVM. All experienced deformities, with seven reporting severe pain, five ulceration, and two bleeding. Trametinib was initiated at 2mg daily for three patients but, due to skin toxicities, subsequent patients started at lower doses, with only three reaching the target dose. Trametinib led to clinical improvement in 80% of patients. Pain alleviation occurred in all symptomatic patients (VAS 5–7 to 0–5), deformation improved in 55%, and ulceration healed in 20%. Radiological assessment showed a reduction in vessel size in one patient and nidus disappearance in two. Acneiform rash was the most frequent toxicity (100%), including two cases of grade 3, requiring early drug discontinuation. Severe mucosal bleeding led to premature cessation in two patients with mucosal AVMs. Correlations with genomic-alteration will be presented at congress. **Conclusions:** Trametinib demonstrated clinical benefit in refractory AVMs, supporting MAPK inhibition as a therapeutic approach. Skin and mucosal toxicities necessitate dose adjustment, dermatological co-management, and cautious use in mucosal AVMs. Further studies are warranted to optimize therapeutic regimens and assess long-term outcomes. Clinical trial information: 2019-003573-26. Research Sponsor: None.

3097 Poster Session

Cost analysis of pre-treatment dihydropyrimidine dehydrogenase (*DPYD*) genotyping to reduce hospitalizations at a cancer center in the United States (U.S.). First Author: Sarah Morris, Atrium Health Levine Cancer Institute, Charlotte, NC

Background: Patients with certain *DPYD* variants are at increased risk of fluoropyrimidine (FP) related adverse events (AEs) and mortality at standard doses. We previously showed pre-treatment *DPYD* testing and genotype-guided FP dosing reduced severe AEs and hospitalizations in variant carriers (PMID 38935897), but testing cost remains a barrier to widespread adoption in the U.S. Herein, we performed a cost analysis of pre-treatment *DPYD* genotyping. **Methods:** Variant carrier rates, hospitalization rates, and AEs were derived retrospectively from our institutional cohort (n=442) of patients with no observed variant, dose reduced variant carriers, and standard dose variant carriers (identified reactively) receiving FP primarily for gastrointestinal cancers. All patients were genotyped and followed for three months for FP-related AEs and hospitalizations. Hospitalization cost was the weighted average cost of treating the most expensive AE experienced by the hospitalized patient. Input parameters (Table 1) were modeled using a decision tree to compare the cost of pre-treatment testing (no variant and dose reduced variant carriers) to no pre-treatment testing (no variant and standard dose variant carriers) from a health-system perspective with a three-month time horizon. The model accounted for hospitalization and genotype test costs only. **Results:** Pre-treatment testing resulted in a cost savings of $36.98 per patient compared to no pre-treatment testing (average per patient cost = $1,655.81 and $1,692.79, respectively). Cost savings increase to $124.39 per patient if half of those tested have insurance that reimburses the test cost. Additional savings are expected if costs for outpatient management of AEs and use of uridine triacetate in the inpatient setting are included in the model. **Conclusions:** Pre-treatment *DPYD* genotyping led to cost savings by reducing AE related hospitalizations among variant carriers. Cancer centers should adopt pre-treatment *DPYD* genotyping to reduce severe AEs, hospitalizations, and costs. Research Sponsor: None.

Model inputs.

Parameter	Value	Source
No variant population prevalence	94%	Institutional cohort
Variant carrier population prevalence	6%	Institutional cohort
No variant hospitalization rate	11%	Institutional cohort
Dose reduced variant carrier hospitalization rate	25%	Institutional cohort
Standard dose variant carrier hospitalization rate	64%	Institutional cohort
No variant hospitalization cost	$12930.67	HCUP NC Inpatient Database 2021
Dose reduced variant carrier hospitalization cost	$8858	HCUP NC Inpatient Database 2021
Standard dose variant carrier hospitalization cost	$8928.29	HCUP NC Inpatient Database 2021
Genotype test cost	$174.81	CMS clinical laboratory fee schedule 2023

HCUP; Healthcare Cost and Utilization Project, NC, North Carolina; CMS, Centers for Medicare and Medicaid Services.

3098 Poster Session

Predicting immunotherapy response in advanced solid tumors using quantitative imaging features from CD8 PET/CT exams. First Author: Michael A. Postow, Memorial Sloan Kettering Cancer Center, New York, NY; Weill Cornell Medical College, New York, NY

Background: CD8-PET/CT imaging with ^{89}Zr crefmirlimab berdoxam (ImaginAb, Inc), which targets CD8-expressing T-lymphocytes, is being explored as an imaging tool to predict responses and monitor immune checkpoint inhibitors (ICI) in patients with advanced solid malignancies. Here we explore how quantitative imaging features from CD8 PET/CT may predict ICI responses. **Methods:** We studied quantitative imaging features (PET parameters and radiomics) in 45 patients from the ImaginAb IAB-CD8-201 phase II trial (NCT03802123). Tumoral lesions, peritumoral ring (ring shaped margin extending 0.5 cm inwards and outwards from the segmented tumor surface), healthy tissue, benign and pathological lymph nodes were segmented from baseline and first on-treatment (4-6 weeks after standard of care treatment including ICI blockade). Imaging features from CD8-PET/CT scans were extracted. Predictive models for best overall response (BOR) according to RECIST 1.1 were developed. Models' performance was evaluated by the ability to distinguish responders (complete or partial response, n = 13) from non-responders (stable or progressive disease, n = 32). A survival random forest analysis was also conducted to estimate time to BOR. **Results:** Significantly greater delta values were identified in the tumor and peritumoral ring compared to healthy tissues, suggesting the tumor and peritumoral ring may reveal early treatment-induced changes important for predicting response. Eighteen predictive models were developed, with models using imaging features from the peritumoral ring showing comparable performance to those using features from lesions and pathological lymph nodes. The simplest BOR predictive model, which yielded the highest performance, used delta values extracted from the peritumoral ring (AUCs = 0.895, sensitivity = 0.900, specificity = 0.615). The inclusion of clinical variables (including age, sex, body mass index, cancer type, received treatments, number of lines of received treatment, white blood cell count) did not significantly enhance model accuracy, emphasizing the robustness of the imaging data alone. A final model integrating key imaging features from multiple regions successfully predicted time to BOR with a C-index, a generalizable AUC that considers censored data, of 0.86. **Conclusions:** This study highlights the potential of quantitative imaging analysis of CD8-PET/CT scans as a tool for predicting responses to cancer immunotherapy. Results suggest the effectiveness of delta imaging features from the peritumoral ring as a potential indicator of patient's ability to respond to ICI treatment, simplifying the analysis without sacrificing accuracy. Further validation in trials with more homogeneous populations and treatment regimens (eg. NCT05013099) is warranted, with the potential to advance personalized cancer care. Research Sponsor: ImaginAb.

3099 Poster Session

Interim safety and efficacy data of [^{212}Pb]VMT01 in MC1R expressing melanoma. First Author: Zachary Scott Morris, University of Wisconsin School of Medicine and Public Health, Madison, WI

Background: Immune checkpoint inhibitors (ICI) are effective in melanoma, but many patients experience progression on or after approved ICI +/- MAPK inhibitor therapy. Melanocortin-1 receptor (MC1R) is a novel target for radiopharmaceutical therapy (RPT) and is highly expressed on melanoma tumor cells. VMT01 is an MC1R-targeted RPT that can be radiolabeled with either ^{203}Pb (patient selection and dosimetry assessments) or ^{212}Pb (alpha particle therapy). Here, we present data on the first in-human evaluation of [^{203}Pb/^{212}Pb]VMT01 in patients with metastatic melanoma. FDA granted Fast Track Designation to the product on the bases of preclinical experiments combining [^{212}Pb]VMT01 with immunotherapy. **Methods:** This is a first-in-human dose-finding study to determine the safety, pharmacokinetics, dosimetry and preliminary efficacy of [^{212}Pb]VMT01 in subjects with MC1R-positive metastatic melanoma who progressed on at least 1 approved first-line therapy (NCT05655312). Phase 1 of the trial includes escalating dose cohorts. The first two cohorts incorporate dosimetry evaluations (reported separately) with the imaging surrogate [^{203}Pb]VMT01 prior to receiving up to 3 treatment cycles of [^{212}Pb]VMT01 therapy (injected activity of 111 MBq (3 mCi) or 185 MBq (5 mCi) for Cohort 1 and 2, respectively). Participants are evaluated for any DLT for the first 6 weeks after cycle one. Efficacy is assessed by RECIST 1.1 criteria by the investigator. Following the start of the study the anticipated combination arm with nivolumab was opened as an amendment. **Results:** Cohort 1 (DCO 04Sep24) was completed with 3 enrolled participants who received 3 treatment cycles without any DLTs or SAEs. Cohort 1 participants showed prolonged stabilization of disease from start of treatment (mean: 11.1 months); one participant developed a confirmed objective response (PR) after completion of all three [^{212}Pb]VMT01 administrations and is still on trial after 13.1 months from start of treatment. Cohort 2 has completed with 7 enrolled participants. No DLTs or related SAEs have been observed. All participants in this Cohort progressed after either the first cycle (3 participants) or the second cycle (4 participants).Based on these preliminary results showing anti-tumor effect at the lower dose, additional cohorts for both monotherapy and in combination with nivolumab were introduced at a de-escalated dose of 55.5 MBq (1.5 mCi). Both cohorts are now open for enrollment. Updated safety and efficacy data will be analyzed and presented at ASCO. **Conclusions:** At 111 MBq and 185 MBq activity levels, [^{212}Pb]VMT01 was safe and well-tolerated. An objective response and prolonged stabilization of disease were observed at the 111 MBq activity level while no effect was seen at 185 MBq. The study will continue to explore potentially immunostimulating lower doses of administered activity of [^{212}Pb]VMT01 either as a monotherapy or in combination with nivolumab. Clinical trial information: NCT05655312. Research Sponsor: Perspective Therapeutics.

3100 Poster Session

SPYK04, a novel RAF-MEK molecular glue: Dose escalation (DE) in first-in-human study for MAPK pathway-altered solid tumors. First Author: Sarina A. Piha-Paul, Department of Investigational Cancer Therapeutics, The University of Texas MD Anderson Cancer Center, Houston, TX

Background: SPYK04 is a novel MEK1/2 inhibitor designed to enhance RAF-MEK binding and potentially inhibit feedback activation of MEK1/2. This approach was developed to address the limited efficacy of conventional MEK inhibitors in RAS-mutated cancers, which is thought to be due to feedback activation of the MAPK pathway. **Methods:** This first-in human study of SPYK04 is conducted in the US and Japan (NCT04511845). Patients with locally advanced or metastatic solid tumors harboring MAPK pathway alterations were eligible in its DE part. The primary endpoints included assessment of pharmacokinetics, adverse events (AEs) and dose-limiting toxicities (DLTs); the secondary endpoint was objective response rate (ORR). SPYK04 was administered orally once daily in continuous 28-day cycles. **Results:** A total of 23 patients were enrolled in DE. SPYK04 was evaluated at doses ranging from 0.1 to 1.3 mg/day. An accelerated titration design was employed for doses of 0.1, 0.2, and 0.4 mg/day, followed by a transition to a 3+3 design starting from 0.8 mg/day. Over the dose range of 0.1 to 1.3 mg/day, systemic exposure demonstrated a dose-dependent increase. Grade 3 or higher treatment-related adverse events (TRAEs) were observed in 30.4% of patients. TRAEs observed in >= 20% of patients were: dermatitis acneiform and blood creatinine phosphokinase increased (60.9% each); AST increased (30.4%); nausea and stomatitis (26.1%, each). DLTs were observed in one patient each at dose levels of 0.8, 1.0 and 1.3 mg/day. All DLTs were due to receiving <75% of the planned dose. A decision was made to not escalate beyond 1.3 mg/day. The ORR was 8.7% (n = 2 of 23), with both partial responses (PRs) occurring amongst the 5 enrolled ovarian cancer patients. The disease control rate (DCR; PR+SD) was 52.2% (n = 12 of 23). **Conclusions:** SPYK04 was tolerated at doses up to 1.3 mg/day in patients with advanced solid tumors. PRs were observed in two patients with ovarian cancer. Further evaluation of safety and efficacy will occur in the expansion part of this study. Clinical trial information: NCT04511845. Research Sponsor: Chugai Pharmaceutical Co., Ltd. (Contact Person: Satoe Kawakami, email: kawakamiste@chugai-pharm.co.jp).

SPYK04 dose, mg/day	0.1	0.2	0.4	0.8	1	1.3
Patients, n	1	1	1	8	6	6
Safety, n (%)						
TRAE	0	1 (100.0)	1 (100.0)	8 (100.0)	6 (100.0)	6 (100.0)
Grade 3 or higher TRAE	0	0	0	1 (12.5)	4 (66.7)	2 (33.3)
TRAE leading to discontinuation of study treatment	0	0	0	0	1 (16.7)	0
Confirmed best response, n (%)						
Responders	0	0	0	1 (12.5)	1 (16.7)	0
Partial Response	0	0	0	1 (12.5)	1 (16.7)	0
Stable Disease	0	0	1 (100.0)	2 (25.0)	3 (50.0)	4 (66.7)

3101 Poster Session

Zanzalintinib (zanza) + nivolumab (nivo) ± relatlimab (rela) in patients (pts) with advanced solid tumors: Results from two dose-escalation cohorts of the phase 1b STELLAR 002 study. First Author: Benjamin Garmezy, Sarah Cannon Research Institute, Nashville, TN

Background: Zanza (XL092) is a novel, multi-targeted tyrosine kinase inhibitor (TKI) that inhibits VEGFR, MET, and TAM kinases. In tumor models, zanza showed antitumor activity alone and in combination with an anti-PD-1 immune checkpoint inhibitor (ICI). The addition of a VEGFR-TKI to ICI combinations of anti-PD-1 + anti-LAG-3 may enhance clinical activity. STELLAR-002 (NCT05176483) is a phase 1b, open-label, dose escalation and expansion study evaluating the safety and efficacy of zanza as monotherapy and in combination with ICIs in pts with advanced solid tumors. Data from dose escalation cohorts treated with zanza + nivo and zanza + nivo/rela are presented. **Methods:** Adults with advanced/metastatic solid tumors were enrolled. Starting doses were zanza 100 mg po qd + nivo 360 mg IV q3w (zanza + nivo cohort), and zanza 60 mg po qd + nivo/rela 480/480 mg IV q4w (zanza + nivo/rela cohort). Pts were enrolled in a rolling six design. Sparse pharmacokinetic (PK) samples were collected. The primary endpoint was safety. Exploratory endpoints included investigator-assessed ORR per RECIST 1.1 and PK. **Results:** Among 19 pts in the zanza 100 mg + nivo cohort, the most common tumor types were prostate cancer (26%) and colorectal cancer (26%). Median number of prior therapies was 6 (range: 2–16). No dose-limiting toxicities (DLTs) were observed in the first 11 DLT-evaluable pts; zanza 100 mg is the recommended dose (RD). The most common treatment-emergent adverse events (TEAEs) were fatigue (68%) and diarrhea (58%). The most common grade (G) 3/4 TEAEs were fatigue (26%) and hypertension (16%). Palmar-plantar erythrodysesthesia (PPE) occurred in 11% of pts (all G1/2). No responses were observed; the disease control rate (DCR: CR+PR+SD) was 42%. In the zanza + nivo/rela cohort, 24 pts received zanza 60 mg + nivo/rela and 25 pts received zanza 100 mg + nivo/rela. One DLT was observed in the first 6 DLT-evaluable pts at zanza 60 mg (G3 ALT increase) and none in the first 5 DLT-evaluable pts at zanza 100 mg. Zanza 100 mg is the RD with nivo/rela. In zanza 100 mg-treated pts, the most common tumor type was renal cell carcinoma (RCC; 56%). Median number of prior therapies was 4 (range: 0–15). The most common TEAEs were diarrhea (68%) and fatigue (56%). The most common G3/4 TEAE was fatigue (20%). PPE occurred in 28% (4% G3/4). ORR was 28% and DCR was 80%; these rates were 36% and 86% in pts with RCC (n = 14). Plasma zanza concentrations 2 hrs after the first dose (C_{max}, mean ± SD) were 595 ± 353 and 838 ± 689 ng/mL for the 60-mg and 100-mg dose levels, respectively. **Conclusions:** The tolerability of zanza + nivo and zanza + nivo/rela was manageable and consistent with each monotherapy agent. Preliminary safety, PK, and response data support selection of the 100-mg zanza dose in combination with nivo or nivo/rela for further investigation. Expansion cohorts are ongoing in various tumor types. Clinical trial information: NCT05176483. Research Sponsor: Exelixis, Inc.

3102 Poster Session

Phase II dose optimization update with EZH2/EZH1 inhibitor tulmimetostat in patients with *ARID1A*-mutated ovarian clear cell carcinoma or endometrial carcinoma. First Author: Linda R. Duska, University of Virginia Health System, Charlottesville, VA

Background: EZH2 inhibition antitumor activity occurs through various mechanistic pathways in multiple tumor types, including via synthetic lethality in advanced *ARID1A*-mutated ovarian clear cell carcinoma (OCCC) and endometrial carcinoma (EC). Oral, next-generation, dual EZH2/EZH1 inhibitor tulmimetostat is in Phase II evaluation in multiple disease cohorts (NCT04104776; Oaknin et al. ASCO 2024, ESMO 2024). We report updated efficacy and safety data from the *ARID1A*-mutated OCCC/EC cohorts, including dose optimization and expansion arms. **Methods:** Phase II Stage 1 evaluated tulmimetostat 350 mg once daily (QD). Stage 2 dose-optimization design randomizes further patients with OCCC (M2) or EC (M3) to 200 mg or 300 mg tulmimetostat QD in Stage 2a, with an efficacy gateway for each arm to open Stage 2b. Primary endpoint is objective response rate (complete response [CR] + partial response [PR]), and secondary objectives include safety. **Results:** As of October 15, 2024, enrollment into the M2/M3 200 mg, 300 mg, and 350 mg arms included 20/10, 21/21 and 14/11 patients, respectively. A total of 56.4% M2 and 61.9% M3 patients received ≥3 prior lines of therapy. Most responses were seen in the M2 200 mg arm and in the M3 350 mg arm (n=4 each; Table). The safety profile across arms was consistent with the EZH1/2 drug class. In M2/M3 cohorts, treatment-emergent adverse events (TEAEs) leading to dose modifications were reported in 55.0%/60.0%, 71.4%/85.7%, and 92.9%/90.9% of patients at 200 mg, 300 mg, and 350 mg, respectively. TEAEs leading to treatment discontinuation were reported in 5.0%/20.0%, 4.8%/4.8%, and 14.3%/9.1%, respectively. Serious TEAEs considered at least possibly related (TRAEs) to tulmimetostat treatment were reported in 5.0%/0%, 9.5%/14.3%, and 21.4%/27.3%, respectively. Grade ≥3 TRAEs were mainly hematologic (Table); no TRAEs leading to death were reported. **Conclusions:** Tulmimetostat showed an improved and acceptable safety profile in OCCC and EC at 200 mg and 300 mg doses (versus 350 mg) with promising antitumor activity, supporting further clinical investigation. Clinical trial information: NCT04104776. Research Sponsor: MorphoSys GmbH.

Best confirmed responses and most common grade ≥3 related TEAEs.

	Cohort	M2: OCCC			M3: EC		
	Dose, mg	**200**	**300**	**350**	**200**	**300**	**350**
	Efficacy evaluable*, N	**20**	**20**	**14**	**10**	**15**	**11**
Best confirmed response†, n	CR	0	0	0	0	1	0
	PR	4	2	1	0	1	4
	Stable disease	10	10	7	8	5	2
	Progressive disease	5	7	6	1	7	4
	No post-baseline response assessment	1	1	0	1	1	1
	Safety evaluable, N	**20**	**21**	**14**	**10**	**21**	**11**
Grade ≥3 related TEAEs‡, n (%)	Thrombocytopenia	1 (5)	3 (14)	4 (29)	0	4 (19)	2 (18)
	Anemia	3 (15)	0	7 (50)	0	5 (24)	1 (9)
	Neutropenia	0	0	2 (14)	0	0	4 (36)
	Diarrhea	0	4 (19)	0	0	0	2 (18)

Data cut off: October 15, 2024.
*Patients who received ≥1 dose, had ≥1 post-baseline response assessment, or discontinued treatment prior to first post-baseline assessment for any reason.
†RECIST 1.1.
‡>10% in any M2/M3 arm.

3103 Poster Session

OMX-0407: A novel spectrum-selective small molecule kinase inhibitor in advanced/metastatic solid tumors. First Author: Valentina Boni, NEXT Madrid Universitary Hospital Quironsalud Madrid, Pozuelo De Alarcon, Spain

Background: OMX-0407 is an orally available spectrum-selective kinase inhibitor that targets key oncology-relevant tyrosine kinases and salt-inducible kinases and is being developed as a first-in-class treatment for solid tumor indications. Preclinical investigations indicate a dual mode of action by sensitizing tumor cells to immune cell induced apoptotic cell death as well as direct inhibition of tumor growth promoting kinases. **Methods:** This is a phase Ia/Ib dose escalation and expansion study of OMX-0407 (NCT05826600). Eligible patients for the phase Ia dose escalation part had advanced solid tumors and exhausted available therapies. **Results:** As of the 30th of October 2024, 24 patients have been treated at dose levels 10 through 140 mg p. o. BID and the phase Ia part has been completed. Solid tumor histologies included melanoma, non-small cell lung cancer, sarcoma and colorectal cancer. OMX-0407 was generally well tolerated, adverse reactions were mainly gastrointestinal. Two dose limiting toxicities were observed: One case of facial swelling secondary to drug allergy at the 90 mg BID dose, and one case of fatigue at the 140 mg BID dose. One durable complete response in a patient with cutaneous angiosarcoma secondary to radiotherapy, resistant to two prior lines of chemotherapy treatment, was observed at 30 mg BID which is ongoing at 16 months (at the time of data cutoff). Pharmacodynamic analyses demonstrated phosphorylation inhibition of target kinases. A recommended phase II dose of 100 mg BID was identified. **Conclusions:** OMX-0407 has been well tolerated at pharmacologically and therapeutically active dose levels. One very durable response has been observed in an angiosarcoma patient at a low dose level. The phase Ib expansion part at the recommended phase II dose is currently recruiting patients with angiosarcoma and clear cell renal cell carcinoma. Clinical trial information: NCT05826600. Research Sponsor: iOmx Therapeutics AG.

3104 Poster Session

AI molecular search engine paired with RNA sequencing analysis to develop potent and selective VEGFR-3 inhibitors. First Author: Maxim Sorokin, OmicsWay Corp., San Mateo, CA

Background: Tumor angiogenesis (TA) is driven by several VEGF factors and corresponding receptors (VEGFRs). Targeting TA inhibits tumor growth, however there are no selective small molecule TA inhibitors on the market yet. Here we report development of a selective VEGFR-3 inhibitor with potential anti-tumor activity in multiple cancers. **Methods:** The Bioptic virtual screening pipeline employs two models. The first is a SMILES-based LLM fine-tuned on binding affinity data of contrastive molecular pairs. The screening was performed on the ultra-large 40-billion-compound virtual library Enamine REAL. For selectivity, the top-ranked molecules were re-scored using a secondary model, a GNN specifically designed for this task and trained to differentiate activity across similar kinases. The Oncobox algorithm was used to select cancer types with the highest sensitivity to VEGFR1-3 inhibitors based on VEGF(R)s expression and TA pathways activation. It was applied to RNA-seq profiles from TCGA (11428 profiles from 33 primary sites) and the internal relevant RWD cohort (1056 profiles from 89 cancer types). **Results:** Compounds with IC50 < 10 μM in Eurofins VEGFRs KinaseProfiler were considered active. Among 110 tested compounds, 1 was active against VEGFR-1, 1 - against VEGFR-2, and 4 - against VEGFR-3. One compound was active against all VEGFRs, and 3 - against a single VEGFR. One VEGFR-3 active showed $>$ 45-fold selectivity against both VEGFR1 & 2, while no compound was specific to VEGFR-1 or VEGFR-2. All 3 selective VEGFR-3 inhibitors showed minimal activities ($<$ 50% at 10 μM) against the 12 off-target kinases including B-Raf, c-Raf, c-Kit, FGFR1, FGFR2, FGFR3, FGFR4, Flt3, Met, PDGFR-a, PDGFR-b, Ret. In order to select cancer types for further pre-clinical validation, Oncobox algorithm was used to simulate predicted efficiency of a VEGFR-3 inhibitor in multiple cancer types from TCGA and internal RWD cohort. The highest response rate is expected for papillary thyroid cancer, followed by clear-cell renal, pancreatic, ovarian cancers, and sarcomas. A selective VEGFR-3 inhibitor may be beneficial when compared to already developed pan-VEGFR inhibitors due to lower toxicity. Finally, identification of potential responders to selective anti-VEGFR-3 therapy via RNA-seq analysis may enable patient enrichment in further clinical trials and development of a companion diagnostic for the drug. **Conclusions:** Our results suggest that Bioptic's molecular search engine significantly enhances identification of potent and selective inhibitors for a specific target, and, paired with the Oncobox algorithm, may facilitate development of novel anti-cancer drugs. Research Sponsor: None.

3105 **Poster Session**

Efficacy and safety of alectinib in pediatric and adult patients with ALK altered advanced solid tumors: Results from the TACKLE phase II trial, a MASTER KEY substudy (NCCH1712/MK003). First Author: Hitomi Sumiyoshi Okuma, Department of International Clinical Development, National Cancer Center Hospital, Tokyo, Japan

Background: Alectinib is an orally administered tyrosine kinase inhibitor that targets anaplastic lymphoma kinase (ALK) and is approved in ALK-positive non-small cell lung cancers and anaplastic large cell lyphomas in Japan. Beyond these, there is a rare population carrying the same ALK alteration regardless of cancer type, often referred to as "ALKomas". Treatment options are limited for these ALK altered solid tumors. **Methods:** This open-label phase II study evaluated alectinib for ALK altered locally advanced or metastatic cancer. Patients received alectinib as either a capsule or a suspension. Primary endpoint was central-assessed confirmed objective response rate (ORR) according to RECIST v1.1. A Bayesian approach was used to evaluate eligible patients in the main cohort, which were patients able to ingest capsules. Expected ORR was set at 40% and a threshold at 10%. Secondary endpoints included safety, disease control rate (DCR), progression-free survival (PFS), and overall survival (OS). **Results:** 26 patients, aged from 8 months to 78 years, across 11 tumor types received treatment. The most common tumor type was soft tissue sarcoma (STS) (n = 11) followed by embryonal neoplasm (n = 5). Alterations included fusion/rearrangements (n = 19), mutations (n = 5), and amplifications (n = 2). The median follow-up was 15.0 months. In the evaluable patients of the main cohort (n = 16), the central-assessed ORR was 43.8% (95% CI, 19.8 to 70.1), meeting the decision criteria of the Bayesian design for the primary endpoint. For the entire evaluable patients (n = 24), the central-assessed ORR was 54.2% (32.8 to 74.4), the DCR was 70.8% (48.9 to 87.4); the median PFS was 24.9 months (3.9 to not estimable); and the median OS was 38.8 months (13.9 to not estimable). In patients with ALK fusions/rearrangements (n = 17), the ORR was 76.5 % (50.1 to 93.2), DCR 82.4% (56.6 to 96.2) and the median PFS and OS were both not reached. All patients with inflammatory myofibroblastic tumor showed a response (ORR 100%, n = 8/8). In pediatric patients aged 15 and under (n = 11), the ORR was 63.6% (30.8 to 89.1) with a DCR of 100.0% (71.5 to 100.0). Although no responses were observed in the patients with ALK mutations or amplifications, a clinically meaningful stable disease was observed in 3 of 5 ALK mutated patients. Grade ≥3 drug-related adverse events were observed in 15.4% (n = 4) among all treated patients (n = 26), with no drug related deaths. **Conclusions:** Our study showed that patients with ALK alterations treated with alectinib achieved sustained clinical benefit, meaningful survival outcomes, and safety consistent with previous data. Greatest benefit was observed for the ALK fusion population including pediatric patients. These data support the potential role of alectinib as a tumor-agnostic therapy for both pediatric and adult patients with ALK altered solid tumors. Clinical trial information: jRCT2091220364. Research Sponsor: None.

3106 **Poster Session**

Phase 1 study of TT-00973-MS, a highly selective and potent AXL inhibitor, in patients with advanced solid tumors. First Author: Bo Yang, The First Affiliated Hospital of Bengbu Medical University, Bengbu, China

Background: AXL is a member of the TAM family activated by the high-affinity ligand Gas6. The Gas6/AXL signaling pathway plays a critical role in drug resistance, tumor proliferation, metastasis, invasion, epithelial-mesenchymal transition and immune regulation, implicating AXL as an important target in cancer treatment. TT-00973-MS is a highly selective and potent AXL inhibitor which exhibited significant anti-tumor activities in both SK-OV-3 and H1299 derived CDX model with AXL over-expression. Here is first time to present the first-in-human study of TT-00973-MS. **Methods:** Dose escalation is performed using"3+3"design. Adverse events (AE) are evaluated per CTCAE v5.0 criteria. Tumor responses are evaluated per RECIST 1.1. Pts receive TT-00973-MS once daily continuously for 28-day cycles. The primary endpoint is to evaluate dose limiting toxicity (DLT) and identify the maximum tolerated dose (MTD) and/or recommended phase II dose (RP2D). **Results:** As of the data cut-off date on December 24, 2024, 18 pts have received TT-00973-MS treatment in 2 mg (n = 1), 5 mg (n = 3), 10 mg (n = 3), 17 mg (n = 7), 25 mg (n = 4) at QD dose levels. Median age was 56.5 (37~69), 8 (44.4%) were males, all had ECOG PS ≤1. 66.6% of pts had Stage III/IV disease. 50% had ≥3 prior lines of systemic therapies. 66.7% had prior immunotherapies. One DLT was observed in a subject at 17 mg QD dose level (Grade 3 peripheral motor nerve disorder). The MTD was not reached. Treatment-related AEs (TRAEs) were reported in all pts, grade 3 in 6 (33.3%), and no grade 4 or 5. The most common TRAE (≥30%) included increased blood lactate dehydrogenase (83.3%), increased aspartate aminotransferase (72.2%), increased alanine aminotransferase (66.7%), hypercholesterolaemia (55.6%), hypoalbuminaemia (38.9%), hypertriglyceridemia (33.3%) and proteinuria (33.3%). Fourteen pts were efficacy evaluable. Two confirmed partial remission (PR) were achieved in pts with renal pelvis cancer (n = 1) and ovarian cancer (n = 1). TT-00973-MS is slowly eliminated from body, with a half-life of about 55 h. After multiple dosing (QD), steady state was reached within 15 days, and the mean accumulation factor of $AUC_{0\text{-}24h}$ was approximately 6. Preliminary PK analysis showed a linear increase on exposure. Plasma levels of soluble AXL (sAXL) increased to approximately 1.7 times (range: 0.9~2.8) the baseline levels at C1D28. **Conclusions:** The preliminary findings from this phase I study demonstratedthat the AXL inhibitor TT-00973-MS monotherapy exhibits a well-tolerable safety profile, promising pharmacodynamic activity, with early signs of efficacy in pts with heavily pre-treated advanced solid tumors. Further studies are warranted to comprehensively evaluate the efficacy and safety of TT-00973-MS in large patient populations and specific tumor types. Clinical trial information: NCT05673538. Research Sponsor: None.

3107 **Poster Session**

A phase 1 dose escalation study of LNP7457 (PRMT5 inhibitor) in patients with advanced or metastatic solid tumors. First Author: Shashank Deoghare, Lupin Limited, Pune, India

Background: Protein arginine transferase 5 (PRMT5) overexpression plays an important role in pathogenesis of several cancers. LNP7457 is an investigational, orally active, highly potent, S-adenosylmethionine (SAM) competitive PRMT5 inhibitor with wider therapeutic window compared to other investigational PRMT5 inhibitors. Here, we report results of dose escalation (DE) and food-effect (FE) sub-studies of LNP7457 from a Phase 1 study in patients with advanced or metastatic solid tumors. **Methods:** This is first-in-human, multicenter, open-label study in patients with advanced or metastatic solid tumors with failed prior standard therapies or for whom no standard therapy exists. DE followed initial modified acceleration followed by 3+3 design. LNP7457 was administered orally in 21-day cycles [first 16 days (on-period) and last 5 days (off-period)] at escalating doses (1 to 4mg QD). Primary objective was to determine maximum tolerated dose (MTD) assessed by dose-limiting toxicities (DLT) in cycle 1; secondary objectives included safety, pharmacokinetics, pharmacodynamics and preliminary antitumor activity measured by RECIST v1.1. FE study was conducted as a single-dose cross over study at MTD to assess impact of food on PK of LNP7457. **Results:** 17 patients (9 male & 8 females) in DE received LNP745 at doses of 1mg (n = 1), 2mg (n = 8), 4mg (n = 2), 1.5mg (n = 6); median age 51.0 (range 23 - 76) years; Diagnosis included head and neck cancer (n = 9), cervix cancer (n = 2), breast cancer (n = 1), ovarian cancer (n = 1), pancreatic cancer (n = 1), gall bladder cancer (n = 1), prostate cancer (n = 1) and uterine cancer (n = 1). Sixteen patients discontinued treatment; progressive disease (n = 8); consent withdrawal (n = 4); AE (N = 2); death (n = 1) and lost to follow up (n = 1). One patient is ongoing at data cut-off of 31-Oct-2024. A total of 16 (94.1%) patients had at least 1 treatment emergent adverse event (TEAE). The majority of TEAEs were unrelated to LNP7457 (76.4%). Anemia (47.1%) and thrombocytopenia (23.5%) were the most common TEAEs. A total of 6 (35.3%) patients had serious TEAEs, thrombocytopenia (11.8%) being the most common serious TEAE. One patient in 4mg cohort had DLT of thrombocytopenia during cycle 1. None of the patients in 2mg cohort had DLT in cycle 1, hence 2 mg was determined as MTD. After single and multiple dosing in DE study, peak plasma concentrations of LNP7457 were observed between 2-4 hrs. A single-dose cross over FE study (n = 6) at 2mg dose showed no impact of food on PK of LNP7457. Target engagement based on reduction in plasma SDMA levels was observed at all dose levels in DE study. Preliminary efficacy in the form of stable disease was observed in 8 (66.7%) patients across 8 different tumor types. **Conclusions:** LNP7457 was well tolerated with desirable safety, PK/PD and preliminary efficacy profile. Clinical trial information: CTRI/2023/07/054753. Research Sponsor: Lupin Limited, India.

3108 **Poster Session**

An open-label phase 1 dose-escalation and dose-expansion trial to evaluate the safety, tolerability, and efficacy of TQ-B3234 in adults with neurofibromatosis type 1 (NF1). First Author: Jun Liu, Neurofibromatosis Type 1 Center and Laboratory for Neurofibromatosis Type 1 Research, Shanghai Ninth People's Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai, China

Background: NF1 is an autosomal-dominant genetic disease that can manifest as neurofibromas, including cutaneous neurofibromas (cNFs) affecting almost all NF1 patients (pts), and plexiform neurofibromas (PNs, up to 50%), which are benign nerve sheath tumors. However, PNs can cause substantial pain, disfigurement and impairment in pts and are at risk of transforming into malignant peripheral nerve sheath tumors (MPNSTs). Currently, there is no medical cure for adult pts with NF1-related PN (NF1-PN), and fewer options for adult pts with cNFs. TQ-B3234 is a highly selective MEK1/2 inhibitor. A phase 1 dose-escalation and dose-expansion trial (NCT05107037) evaluated the safety and efficacy of TQ-B3234 in adult pts with inoperable NF1-PN, MPNSTs or cNFs. **Methods:** Eligible adult pts with inoperable NF1-PN, MPNSTs or cNFs were included in the dose-escalation phase using a 3+3 design, while only NF1-PN pts proceeded to the dose-expansion phase. TQ-B3234 was administered as a capsule, with doses ranging from 5 mg to 100 mg, once daily in 28-day cycles during the dose-escalation phase. A dose of 50mg was chosen for the dose-expansion phase. The primary endpoints were safety and objective response rate (ORR). ORR was assessed by investigators using REiNS for NF1- PN pts, RECIST 1.1 for MPNSTs pts, and paper frames for the cNF population. **Results:** As of September 30, 2024, 40 adult pts (31 pts of PNs, 7 pts of cNFs, and 2 MPNSTs) were enrolled. The distribution of doses was as follows: 4 pts at 5 mg, 1 at 10 mg, 3 at 15 mg, 24 at 50 mg, 5 at 70 mg, and 3 at 100 mg. One patient, a cNF case, experienced dose-limiting toxicity (DLT), in the form of G3 diarrhea (16.7%) at the 100 mg dose during the dose-escalation phase. After a median follow-up of 12 months, treatment-emergent adverse events (TEAEs) were observed in 39 pts (97.5%), with the majority were grade 1 or 2. Grade 3 TEAEs were reported in 17.5% of pts; the principal reasons for dose reductions (15.0%) TEAEs included rash acneiform (5.0%), diarrhea (2.5%), and edema (2.5%). No death occurred during the study. Among the 30 pts with NF1-PN who had at least one tumor assessment, 29 pts (96.7%) experienced tumor size reduction, and 11 (36.7%) achieved partial response (PR) based on REiNS criteria. The largest reduction in tumor size was 37.7%. For the 6 cNF pts who had at least one tumor assessment using paper frames, all 6 pts (100%) experienced reduced tumor size, with the largest reduction being 85.2%. **Conclusions:** TQ-B3234 demonstrated manageable safety and a significant ORR in adult NF1- PN pts. These results support the potential of TQ-B3234 to become a new treatment option for NF1- PN pts. Additionally, TQ-B3234 showed deep and durable volume reduction in adult cNF pts, as assessed by paper frames. This method could serve as a valuable tool in clinical research for achieving accurate quantitative phenotype for NF1. Clinical trial information: NCT05107037. Research Sponsor: None.

3109 **Poster Session**

A phase 1, multicenter, open-label study of HSK42360, a brain-penetrant BRAF inhibitor, in patients with BRAF V600-mutated solid tumors. First Author: Jian Li, Beijing Cancer Hospital, Beijing, China

Background: Limitations of approved BRAF V600E inhibitors include toxicity from paradoxical activation of RAF dimerization as well as limited brain penetration. In contrast to approved agents, investigational pan-RAF inhibitors both inhibit mutant RAF proteins and wild-type (wt) RAF proteins, leading to a narrow therapeutic index. HSK42360 is a next-generation, small-molecule BRAF paradox breaker with high brain penetration. It displays significantly less paradoxical activation than approved BRAF inhibitors and spares wtBRAF-containing RAF dimers. Treatment with HSK42360 results in excellent and durable anti-tumor effect in BRAF Class I and II mutant CDX or PDX models. Here we report the interim results from a Phase 1 study of HSK42360 in patients (pts) with BRAF V600 mutations (NCT06536400). **Methods:** This multicenter, open-label, two-part study enrolled adult pts with advanced BRAF V600-mutated solid tumors, including those with recurrent or metastatic solid tumors or primary CNS tumors. Previous BRAF±MEK inhibitor treatment is permitted. In the dose-escalation (Part 1), HSK42360 (200-3600 mg/day) monotherapy was given orally. Escalation followed a "3+3 design" with dose-limiting toxicities assessed during Cycle 1. Part 2 was cohort expansion. Primary objectives were maximum tolerated dose and recommended phase 2 dose of HSK42360. Secondary objectives included safety, tolerability, pharmacokinetics, pharmacodynamics and preliminary efficacy. **Results:** As of January 15, 2025, 17 pts (47.1% male; median age 57.0 years) have been treated with HSK42360 monotherapy across five dose levels (200-3600 mg/day). Of these, 64.7% pts experienced adverse events (TEAEs), most frequently increased ALT (23.5%) and increased AST (23.5%). Most (89.7%) of TEAEs were grade 1. Two pts had drug-related grade 3 AEs (increased creatinine and increased ALT) and one had drug-related serious AEs (SAEs) (increased creatinine). There were no DLT, grade 4 TEAEs, treatment-related discontinuations, or treatment-related deaths. Among 11 efficacy evaluable pts, the ORR was 18.2%. Two (1 CRC and 1 ganglioglioma) had a partial response (PR) and three had stable disease (SD) with shrinkage (per RECIST or RANO). This trial is ongoing. **Conclusions:** HSK42360 monotherapy was well tolerated without unexpected safety issues. Preliminary efficacy data demonstrate favorable activity of HSK42360 in pts with BRAF V600-mutated solid tumors, including primary CNS tumors. Clinical trial information: NCT06536400. Research Sponsor: Haisco Pharmaceutical Group Co., Ltd.

3110 **Poster Session**

Anti-tumor activity of BH-30643, a novel macrocyclic kinase inhibitor, in *EGFR*-mutant lung cancer models. First Author: Wei Deng, BlossomHill Therapeutics, Inc., San Diego, CA

Background: Outcomes on tyrosine kinase inhibitor (TKI) treatment in *EGFR*-mutant non-small cell lung cancer (NSCLC) fall short of the durable benefit observed with next-generation targeted therapies in *ALK* and *ROS1*-driven NSCLC. Novel targeted therapies are needed to address treatment resistance and offer prolonged patient benefit with reduced toxicity. We recently described (AACR 2025) the design and discovery of BH-30643, a first-in-class macrocyclic reversible TKI targeting the active conformation of mutant EGFR and offering potent, mutant-selective EGFR inhibition across classical and non-classical *EGFR* mutations. Here we study diverse preclinical models to assess the breadth of activity from this novel approach. **Methods:** Anti-tumor activity of BH-30643 was evaluated in cell-derived xenograft (CDX) or patient-derived xenograft (PDX) tumor models carrying classical or atypical EGFR mutations. CNS activity of BH-30643 was investigated in an intracranial xenograft model. BH-30643 was administered twice daily via oral gavage; osimertinib when used as a comparator was dosed daily. Studies were done with $n \geq 5$. The activity of BH-30643 against diverse *EGFR* exon 20 insertions (ex20ins) was evaluated in 34 engineered Ba/F3 cell lines in cell proliferation assays in vitro. **Results:** In the PC-9 (exon 19 del) CDX model, BH-30643 led to deep tumor regressions, similar to what was observed with osimertinib at the 25 mg/kg dose level. Similarly deep responses with BH-30643 were observed in double mutant CDX models including those derived from H1975 cells (cis L858R / T790M) and Ba/F3 cells engineered with exon 19 del / T790M. In a triple-mutant PDX model (cis exon 19 del / T790M / C797S) and a Ba/F3 triple-mutant CDX model (cis L858R / T790M / C797S), deep responses were observed with BH-30643 while osimertinib demonstrated no anti-tumor effect. BH-30643 activity was also evident in the HCC827-luc (exon 19 del) intracranial xenograft model with 90% tumor reduction. In two Ba/F3 CDX models carrying atypical mutations (cis G719A / S768I and cis G719A /L861Q), BH-30643 maintained strong anti-tumor activity. Finally, we explored the activities of BH-30643 against 34 different *EGFR* ex20ins in engineered Ba/F3 cell lines and BH-30643 showed anti-cell proliferation activity with a median IC_{50} value of 6.06 nM. **Conclusions:** These preclinical studies demonstrate broad activity of BH-30643 against classical and atypical *EGFR* activating mutations, *EGFR* ex20ins, as well as acquired resistance *EGFR* mutations. Such an "OMNI-EGFR" inhibitor may be able to overcome some of the limitations of earlier agents. Supported by favorable ADME and preclinical safety profiles, BH-30643 is now being assessed in a first-in-human study in locally advanced or metastatic NSCLC harboring *EGFR* and/or *HER2* mutations (NCT06706076, SOLARA). Research Sponsor: BlossomHill Therapeutics, Inc.

3111 **Poster Session**

Phase II trial of trametinib in patients with advanced solid tumors harboring genomic alterations in the MAPK pathway: Results from the BELIEVE trial (NCCH1901). First Author: Hideyuki Hayashi, Center for Cancer Genomics, Keio University Hospital, Shinjuku-Ku, Japan

Background: The MAPK pathway is one of the most mutated oncogenic pathways in solid tumors. However, effective treatments targeting this pathway have not been well-established. The BELIEVE trial aimed to evaluate the efficacy of trametinib, a selective MEK inhibitor, in patients with solid tumors harboring genomic alterations in the MAPK pathway. **Methods:** The BELIEVE trial is a multi-cohort, tumor agnostic phase II trial. Eligibility criteria included patients with solid tumors for which no standard treatment was available or those who had shown resistance or intolerance to standard therapies. In the trametinib arm, participants received 2 mg/day of trametinib continuously until disease progression or intolerable toxicity occurred. The primary endpoint was the objective response rate (ORR) within 16 weeks, and secondary endpoints were overall survival (OS), progression-free survival (PFS), disease control rate (DCR), and safety. The clinical hypothesis was that patients would respond to the genotype-matched drugs. Bayesian analysis was performed using a prior distribution with an expected response rate of 30% [Beta (0.6, 1.4)]. **Results:** Between October 2019 and October 2023, 60 patients with measurable disease and 9 without measurable disease were enrolled. The top three primary tumor sites were the central nervous system (n=20), pancreas (n=7), and ovary (n=6). The targeted genes for trametinib included non-*BRAF* V600 (n=26), *NF1* (n=18), *MAP2K1* (n=10), *NRAS* (n=6), *KRAS* (n=5), and *RAF1* (n=4). Among the full analysis set of 49 patients with measurable disease, the confirmed ORR was 12.2% (95% CI, 4.6% to 24.8%), and the expected value of posterior distribution [Beta (6.6, 44.4)] was 12.9%. Partial responses were observed in patients with genomic alterations in non *BRAF* V600 (n=3), *KRAS* (n=2), and *NF1* (n=1). However, the confirmed ORR of 12.2% fell below the prespecified threshold of 20%, therefore the primary endpoint was not achieved. The median OS was 11.9 months (95% CI, 8.5 to 22.9 months), and median PFS was 3.9 months (95% CI, 2.4 to 44 months). The DCR was 46.9% (95% CI, 32.5% to 61.7%). Among 59 patients in the safety analysis, severe adverse events (Grade ≥3) were observed in 55.9% of patients. The most frequent adverse effects were acneiform dermatitis (22%), blood creatine phosphokinase increased (20%), and stomatitis (15%). **Conclusions:** The BELIEVE trial demonstrated limited efficacy of trametinib in patients with advanced solid tumors harboring genomic alterations in the MAPK pathway. While the confirmed ORR did not meet the primary endpoint, the outcomes for OS, PFS, and DCR were consistent with the clinical hypothesis, suggesting potential benefit in a subset of patients. Clinical trial information: jRCTs031190104. Research Sponsor: Japan Agency for Medical Research and Development; Health and Labour Sciences Research Grant.

3112 **Poster Session**

Updated efficacy and safety of zurlectrectinib in adult patients (pts) with locally advanced or metastatic NTRK fusion–positive (NTRK+) solid tumors. First Author: Dan-yun Ruan, Department of Clinical Research, Sun Yat-Sen University Cancer Center, State Key Laboratory of Oncology in South China, Guangzhou, China

Background: NTRK gene fusion is one of the most defined driving factors of carcinogenesis, which occurs in various adult tumor types. Zurlectrectinib, a highly selective next-generation TRK tyrosine kinase inhibitor, previously demonstrated encouraging efficacy and manageable toxicity in pts with NTRK+ tumors in a phase I/II clinical trial (NCT04685226). The pivotal phase II clinical trial (NCT05745623) is currently ongoing. Here we present the integrated results of adult pts from both trials. **Methods:** Pts with locally advanced or metastatic solid tumors, who failed from clinical standard of care or for whom there was currently no effective therapy, were enrolled in this study. The primary endpoint was confirmed objective response rate (ORR) per independent review committee (IRC). Tumor responses were assessed by IRC and investigators per RECSIT1.1 and RANO (BM) criteria. Treatment-emergent adverse events were evaluated and graded according to CTCAE v5.0. **Results:** As of 23 Nov 2024, a total of 229 adult pts were enrolled in the two trials. Forty-nine TRK inhibitor naïve adult pts were evaluable for efficacy representing 12 different solid tumor types. Among the efficacy population, the distribution of NTRK1, NTRK2 and NTRK3 fusions was 53.1%, 2.0% and 44.9% respectively. The median age was 51.0 years (range: 18-77). Pts had received a median of two prior lines of systemic therapies, with ECOG performance status between 0-1. Median follow-up was 11.7 months. The confirmed ORR by IRC was 83.7% (95% CI: 70.3, 92.7), 5 pts (10.2%) with complete response. Median duration of response (DOR) and median progression-free survival (PFS) by IRC were not reached. The DOR rate and PFS rate by IRC at 12 months was 92.0% and 90.5%, respectively. Two of the three pts (66.7%) who had brain metastasis at the baseline achieved intracerebral ORR, which is consistent with the good brain penetration and strong intracranial activity of zurlectrectinib. In the safety population of adults (N = 229), treatment-related adverse events (TRAEs) were predominantly grade 1 or 2. The most common TRAEs (≥20%) were anemia (28.4%), increased alanine transferase (27.9%) and increased aspartate transferase (25.8%). Grade ≥3 TRAEs (≥2%) were weight gain (3.5%) and dizziness (2.2%). No Serious TRAEs occurred in ≥2% pts. TRAEs led to dose interruption, reduction and discontinuation in 9.2%, 3.9% and 0.4% of safety population, respectively. **Conclusions:** In line with previously reported results, zurlectrectinib continued to demonstrate a deep and durable responses in adult pts with NTRK+ advanced solid tumors with or without brain metastasis. Zurlectrectinib was also well-tolerated and showed favorable safety profile in adult pts with various tumor types. Clinical trial information: NCT05745623. Research Sponsor: None.

3113 **Poster Session**

Discovery of potent degraders of pan-KRAS based on a novel KRAS binder. First Author: Wei Sun, Global Drug R&D Center, Huadong Medicine Company Limited, Hangzhou, China

Background: As the most frequently mutated oncogene, KRAS alteration occurring in approximately 25% of all malignancies. Despite extensive efforts, targeting KRAS has proven to be challenging due to its structure and complex function. Recently, direct $KRAS^{G12C}$ inhibitors, such as Sotorasib and Adagrasib have occurred first successes. However, therapeutic approaches targeting other variants beyond G12C are under significant unmet needs. Recent developments in protein degradation technologies, such as Proteolysis-Targeting Chimeras (PROTACs), bring new hope for targeting pan KRAS. Based on our novel warheads, potent pan-KRAS degraders were designed and synthesized. **Methods:** The ability of compounds to degrade KRAS protein was evaluated using western blotting. The anti-tumor efficacy was assessed *in vitro* through different mutant cell lines. As a proof of concept study *in vivo*, an experiment in subcutaneous xenograft mouse model was performed. Pharmacokinetic studies were conducted in mice, with serial blood samples analyzed by (LC−MS)/MS. **Results:** A novel series of warheads exhibiting exceptional enzymatic and cellular activity against pan-KRAS has been successfully obtained. Based on these warheads, more than 100 degraders were meticulously designed and synthesized incorporating a diverse array of linkers and E3 ligands. Through a comprehensive evaluation, two series of compounds have demonstrated a remarkable KRAS degradation property and downstream inhibition at concentrations below 10 nM in $SW620^{G12V}$ and $GP2D^{G12D}$ cells. Cell proliferation assay demonstrated that the IC_{50} values of these degraders are ranging from 0.01 to 30 nM in the MIA $PaCa\text{-}2^{G12C}$, $GP2D^{G12D}$ $SW620^{G12V}$ and $LOVO^{G13D}$ cell lines, without affecting the viability of KRAS-independent cell lines (selectivity $>$ 500-fold). These compounds also possess favorable PK properties in mice (clearance $<$ 10 mL/min/kg; IV, 2 mpk, AUC $>$ 5000 ng·hr/mL) and good safety profile (hERG IC_{50} $>$ 30 μM). Moreover, these compounds showed strong antitumor activity in xenograft mouse model *in vivo*. **Conclusions:** The innovative linker elongation and branching, coupled with modifications of KRAS binder portion significantly contributed to potent pan-KRAS degraders, which demonstrate excellent pharmacokinetics and exhibit remarkable efficacy both in vitro and in vivo. The IND-enabling studies are being conducted and the regulatory IND filing will be completed in 2025. Research Sponsor: None.

3114 **Poster Session**

Development and validation of a biology-based novel therapeutic agent targeting the LIN28/*let-7* pathway in cancer. First Author: Patrick Sipila, University of Calgary, Calgary, AB, Canada

Background: Currently, brain tumors that are diagnosed in infants and young children carry an exceptionally high risk for treatment resistance and toxicities. The LIN28 family of RNA-binding proteins regulate stem cell biology and pluripotency. In addition to embryonic development, they have also been implicated in oncogenesis through interaction with the tumor suppressor micro-RNA (miRNA), *let-7*. In cancer, LIN28 expression leads to *let-7* loss-of-function, oncogenic activation, and tumorigenesis. Importantly, LIN28 expression has been associated with stemness and subsequent tumor aggressiveness and poor survival in early childhood brain tumors. Thus, LIN28 may offer an effective therapeutic strategy to prevent relapse by specifically targeting cancer stem cells. In this study, we describe a novel therapeutic inhibitor of LIN28 in cancer. **Methods:** Using an *in silico* approach, we designed and synthesized a panel of novel compounds predicted to bind and inhibit the critical molecular interaction between LIN28 and *let-7*. Cytotoxicity was evaluated by alamar blue viability assay in a panel of LIN28-positive cancer cell lines derived from atypical teratoid rhabdoid tumor (ATRT), embryonal tumor with multilayered rosettes (ETMR), and germ cell tumor. LIN28-negative cells were used as control. LIN28 protein expression and *let-7* miRNA levels were determined by immunoblot and reverse transcription quantitative polymerase chain reaction (RT-qPCR), respectively. Self-renewal capacity was analyzed by sphere formation assay. Mice carrying xenografts were treated to investigate LIN28 inhibition *in vivo*. **Results:** Preliminary screening of small molecule inhibitors identified a lead compound, designated THNB-3, that induces cell death at micromolar concentrations in LIN28-positive cell lines established from various tumors, without affecting LIN28-negative controls. Treatment with THNB-3 increased the level of *let-7* tumor suppressor, confirming effective inhibition of LIN28. In addition to cytotoxicity, THNB-3 significantly inhibited sphere formation in brain tumor cells, reducing self-renewal and multipotency of cancer stem cells. Lastly, the anticancer activity of THNB-3 was validated *in vivo* against LIN28-positive xenografts and the drug also demonstrated systemic tolerability in mice. **Conclusions:** Our studies provide the first evidence for an effective, targeted therapeutic agent against the LIN28/*let-7* pathway for the treatment of cancer in the future. THNB-3 selectively induces cytotoxicity in LIN28-positive cancers by restoring *let-7* miRNA, confirming effective target modulation. Further, LIN28 inhibition by THNB-3 may reduce self-renewal and multipotency of cancer stem cells. Together, our preclinical data supports further development of THNB-3 for the treatment of high-risk LIN28-positive tumors. Research Sponsor: Kids Cancer Care Foundation of Alberta.

3115 **Poster Session**

A first-in-human, phase 1a/b, dose-escalation/expansion study of BG-68501, a selective CDK2 inhibitor, as monotherapy or in combination with fulvestrant for patients with HR+/HER2- breast cancer and other advanced solid tumors: First disclosure of clinical data. First Author: Rohit Joshi, Cancer Research SA, Adelaide, Australia

Background: CDK2 inhibition could represent a novel treatment (tx) option for patients (pts) with resistance to CDK4/6 inhibitors (CDK4/6i) and/or increased cyclin E1 activity. BG-68501 is a highly potent CDK2 inhibitor with high CDK2 selectivity (~100x) vs other CDK family members. We present dose-escalation data of BG-68501 as monotherapy or in combination with fulvestrant in pts with HR+/HER2- metastatic breast cancer (BC) and advanced solid tumors (NCT06257264). **Methods:** This is the dose-escalation phase of a first-in-human, phase 1a/b, open-label, multicenter study to evaluate the safety/tolerability, pharmacokinetic (PK), and pharmacodynamic (PD) profiles, and preliminary antitumor activity of BG-68501 in pts with advanced, nonresectable, or metastatic solid tumors, including HR+/HER2− BC. During dose escalation, sequential cohorts received increasing doses of BG-68501 as monotherapy or in combination with fulvestrant. Eligible pts are ≥18 yrs, with histologically or cytologically confirmed advanced or metastatic solid tumors associated with CDK2 dependency who have received ≥1 line of tx for advanced or metastatic disease and prior endocrine therapy and a CDK4/6i in either the adjuvant or advanced or metastatic setting for HR+/HER2− BC, or prior standard of care for all other advanced solid tumors. **Results:** As of Jan 22, 2025, 41 pts (median age 63 yrs) have been enrolled. Eleven pts had BC (all received prior CDK4/6i), 12 had ovarian cancer (OC), 7 had endometrial cancer, and the remaining 11 pts had other tumor types. To date, 6 dose levels (DLs) of BG-68501 monotherapy and 1 DL in combination with fulvestrant have been assessed. The median duration of exposure is 1.5 months. Treatment-emergent adverse events occurred in 39 pts (95.1%; grade ≥3, 26.8%), with the most common being nausea (56.1%; grade ≥3, 0%), vomiting (48.8%; grade ≥3, 0%), and fatigue (24.4%; grade ≥3, 0%); no DLTs have been observed. BG-68501 demonstrated a linear PK profile with clinical characteristics consistent with preclinical predictions; signs of TK1 reductions have been observed across DLs tested, including in heavily pretreated pts. Of the 24 efficacy-evaluable pts, 1 extensively pretreated HR+/HER2− BC pt experienced PR and 10 pts showed SD. Dose escalation is ongoing for both monotherapy as well as in combination with fulvestrant. **Conclusions:** BG-68501 demonstrates a favorable safety/tolerability profile, with no DLTs observed to date during dose escalation. Extensively pretreated patients achieving PR and SD with monotherapy, coupled with signs of PD responses and a favorable safety profile, support continued assessment of BG-68501; updated clinical data will be presented at the time of the conference. Clinical trial information: NCT06257264. Research Sponsor: BeiGene, Ltd.

3116 **Poster Session**

Efficacy and safety of pralsetinib in *RET* fusion-positive solid tumors: Final data from the ARROW trial. First Author: Vivek Subbiah, University of Texas MD Anderson Cancer Center and Sarah Cannon Research Institute, Nashville, TN

Background: Pralsetinib is an oral tyrosine kinase inhibitor that selectively and potently targets oncogenic RET fusion and mutation proteins. *RET* fusions or mutations are present in various tumor types. We report the final results from the phase 2 portion of ARROW, a phase 1/2, open-label, multicohort, dose-expansion study evaluating the efficacy and safety of pralsetinib (NCT03037385) in patients with *RET* fusion-positive solid tumors other than non-small-cell lung cancer (NSCLC) and thyroid cancer. **Methods:** Eligible pts were ≥18 years of age with a pathologically documented, definitively diagnosed advanced solid tumor with an oncogenic *RET* fusion or mutation, had previously received standard of care appropriate for their tumor type, and were not eligible for any other study groups. Overall response rate (ORR) and safety were primary endpoints of the study. Key secondary endpoints included duration of response (DOR), progression-free survival (PFS), and overall survival (OS). The final database lock was May 20, 2024. **Results:** Twenty-nine patients were enrolled with 11 different solid tumor histologies. Twenty-six (90%) received prior systemic therapy. Median age was 58 years (range 25-75); 59% were female. Twenty-eight patients were included in the efficacy analysis. ORR (by RECIST) was 46.4% (13/28); 10.7% (3/28) achieved complete response (pancreatic cancer, n=2; cancer of unknown primary, n=1) and 35.7% (10/28) achieved partial response. Median PFS was 7 months (95% CI: 3.9, 12.8). Median DOR was 11.1 months (95% CI: 5.5, 25.1). Median OS was 10.3 months (95% CI: 6.8, 25.2). Twenty-five (86%) patients experienced treatment-related adverse events (TRAEs); 19/29 (66%) reported TRAEs ≥grade 3. The most common TRAEs included increased aspartate aminotransferase (11/29; 38%), increased alanine aminotransferase (10/29; 35%), and anemia (9/29; 31%). Four (13.8%) patients experienced hypertension, and 1 (3.4%) patient had ≥grade 3 hypertension. No new safety risks were identified; AEs remained manageable with supportive care and/or dose modifications. **Conclusions:** In the phase 2 portion of this trial, responses were observed in many tumor types (Table). Pralsetinib demonstrated robust and durable anti-tumor activity with an ORR of 46.4%. These data validate *RET* fusions as a tissue-agnostic target with sensitivity to RET inhibition and activity beyond NSCLC and thyroid cancer, further supporting the promising potential of pralsetinib to address the unmet medical need in these patients. Clinical trial information: NCT03037385. Research Sponsor: Blueprint Medicines; Genentech/Roche; Rigel Pharmaceuticals, Inc.

Overall response rate by tumor type.

Cancer Type (patient n)	ORR n (%)
Pancreatic (5)	5 (100)
Cancer of unknown primary (1)	1 (100)
Neuroendocrine (3)	2 (67)
Sarcoma (3)	2 (67)
Head and neck (2)	1 (50)
Small cell lung (2)	1 (50)
Hepatobiliary (4)	1 (25)
Colorectal (5), gastric (1), ovarian (1), thymic (1)	0

3117 **Poster Session**

Exploring the efficacy and mechanism of action of combined pan-Raf and MEK inhibition in halting the growth of non-V600 BRAF mutated tumors. First Author: Islam E. Elkholi, Lady Davis Institute, Sir Mortimer B. Davis Jewish General Hospital, Montreal, QC, Canada

Background: Class 2 & 3 non-V600 BRAF mutations mediate RAF dimerization to hyperactivate the MAPK signaling pathway. Encorafenib (Enco; BRAF monomer inhibitor) + Binimetinib (Bini; MEK inhibitor) elicit responses in $<$15% of patients with non-V600E BRAF mutations (NCT03839342). We hypothesized that Belvarafenib (Belva), a novel pan-RAF dimer inhibitor, is more potent than Enco in inhibiting the growth of Class 2 & 3 non-V600 BRAF mutated tumors. **Methods:** We performed *in vitro* colonogenic assays to compare the growth inhibitory effect of 5 independent doses of individual inhibitors (Bini, Belva, or Enco) in parallel to 25 different combinations of either Belva+Bini or Enco+Bini in 6 non-V600 BRAF mutated melanoma (WM3629, HMV-II), colorectal (CRC) (NCI-H508, HT55), and lung (NCI-H1666, NCI-H2087) cancer cells. Low nanomolar doses (10-1000 nM) were used to investigate the synergistic potential of either combination using the SynergyFinder tool. Belva+Bini (15 mg/kg each) and Enco+Bini (75 mg/kg + 15 mg/kg) combinations were assessed in 4 non-V600 BRAF (3 Class 3, 1 Class 2) metastatic CRC patient-derived xenograft (PDX) models. The inhibitory effect of Belva and Enco on MAPK activity in the outlined 6 cell lines was assessed by immunoblotting. Transcriptomic (RNA-Seq) analysis was performed on PDXs. **Results:** Belva+Bini was 2-6-fold more effective than Enco+Bini in inhibiting the growth of the 6 cell lines. Belva+Bini achieved overall higher synergy scores in the 6 cell lines and was synergistic in 5/6 cell lines (synergy score $>$ 10) vs. Enco+Bini that was synergistic in 1/6 cell lines. In the 6 cell lines, Belva inhibited MAPK activity more robustly than Enco (assessed by pERK levels). *In vivo*, Belva+Bini was significantly more effective than vehicle or Enco+Bini in halting the growth of 3 out of 4 PDXs. Both Belva+Bini and Enco+Bini significantly inhibited MAPK activity vs. vehicle (as assessed by the transcriptional MAPK Pathway Activity Score). However, there was no statistically significant difference between both combinations. Gene Set Enrichment Analysis revealed that Belva+Bini significantly downregulated genes mediating the interconnected mTORC1 pathway activity and cholesterol metabolism dynamics in the 3 PDXs where Belva+Bini had anti-growth effect. Specifically, among the top downregulated genes by Belva+Bini was *PCSK9*, a druggable key regulator of cholesterol metabolism. **Conclusions:** These results from 10 preclinical models, tested so far, put forward combined Pan-Raf and MEK inhibition as a potential effective treatment choice for patients with non-V600 BRAF mutated tumors to be investigated in clinical trials. In parallel, they unravel novel insights into the mechanism of action of this therapeutic approach and in return the druggable vulnerabilities of the non-V600 BRAF mutated tumors, a notion we are further investigating in the outlined models. Research Sponsor: Canadian Cancer Society; 707457; Conquer Cancer, the ASCO Foundation; Canadian Cancer Society; 708442.

3118 **Poster Session**

Atropisomeric pyrrolopyrimidine inhibitor as a targeted approach for RET tyrosine kinase in neuroblastoma. First Author: Ananya Bharathwaj, UCSD, La Jolla, CA

Background: Increased RET expression is associated with poor prognosis in children with solid tumors such as neuroblastoma (NB), prompting an interest in RET inhibition. A number of kinase inhibitors currently in use for cancer patients have RET inhibitory activity, but these inhibitors also display activity against other kinases, resulting in unwanted side effects and limiting their safety and efficacy. However, developing more specific RET inhibitors remains a drug design challenge due to high levels of conservation between kinase binding pockets. Using novel chiral chemistry leveraging atropisomerism to convert a promiscuous, rapidly interconverting pyrrolopyrimidine compound into an atropisomerically stable analog, we have developed a new atropisomerically stable, highly selective and specific RET inhibitor, getretinib, with similar potency and improved selectivity to that of other next generation RET inhibitors but with half the molecular weight and significantly improved ligand efficiencies towards RET. **Methods:** Associations of gene expression with patient survival and prognostic features were performed on available neuroblastoma tumor databases using the R2 Genomics Analysis and Visualization Platform. The efficacy of RET inhibition was assessed against a panel of NB cell lines using live cell imaging and cell viability assays, comparing results with the active and selective RET kinase inhibitor, (R)-getretinib to results with the inactive atropisomer, (S)-getretinib. Mechanisms of cell death and impacts on RET signaling in cells treated with (R)- and (S)-getretinib were evaluated by Western blots. **Results:** (R)-getretinib reduced NB cell confluence in a dose-dependent manner, while (S)-getretinib had no significant effect on cell confluence over time. R-getretinib treatment of NB cells resulted in reduced phosphorylation of RET in a dose-dependent manner, while treatment with (S)-getretinib resulted in paradoxical increase in RET phosphorylation. **Conclusions:** We present (R)-getretinib as an atropisomerically stable and potent inhibitor of RET and have shown its efficacy in *in vitro* models of NB. The high selectivity of (R)-getretinib towards RET has the potential to minimize unwanted side effects caused by off-target kinase binding, thereby increasing its potential for clinical utility. Research Sponsor: None.

3119 **Poster Session**

Combined RAF- and MEK-inhibition in solid cancers with kinase-impaired BRAF mutations (SORATRAM phase I trial). First Author: Anna Lena Illert, Center for Personalized Medicine (ZPM) Technical University of Munich (TUM) and Department of Medicine III, TUM University Hospital, Technical University of Munich (TUM) and German Cancer Consortium (DKTK), Munich Partner Site, Munich, Germany

Background: *BRAF* is a frequently mutated gene in cancer, with most mutations (mut) at the activating hotspot V600 codon. Recently, kinase-inactive class III *BRAF* mut emerged as oncogenic driver and potential therapeutic target, as they lead to paradoxical cross-activation of RAF1- and RAS-dependent downstream signaling. Here we report the Phase I toxicity results of combinatory inhibition of RAF kinases by sorafenib (S), a multi-kinase inhibitor (e.g. RAF1, BRAF, c-KIT, FLT-3) and MEK/ERK signaling by trametinib (T) in patients (pts) with inactivating *BRAF* mut. **Methods:** SORATRAM is a prospective, molecularly stratified, multicenter phase I trial. Primary objective is to determine the maximal tolerated dose (MTD) of T combined with S and the recommended phase II dose (RP2D). Adult pts with metastatic malignancies, confirmed or known impaired kinase *BRAF* mut (according to *in vitro* testing), ECOG $\leq$ 2 and no available therapy options were eligible. S was given in the approved dose (800 mg) from day (d)1 cycle (c)1, combined with T on c1d8 for max 12c or until progression or unacceptable toxicity. Dose levels (DL) are defined by T dose (0.5mg DL1, 1.0mg DL2 and 1.5mg DL3) and escalated in a conventional 3 + 3 design. MTD is defined as highest dose at which 0/3 pts or $<$ 2/6 pts experience a dose limiting toxicity (DLT) during c1. DLT is defined as toxicity related to S+T combination, unrelated to disease progression, intercurrent illness or concomitant medications, that requires dose reduction or drug withdrawal. **Results:** Since 2020, 236 cases from 9 sites were classified for mutational SORATRAM eligibility with 42% being kinase impaired (e.g. D594G, N581I, G466E), 21% known intermediate/high activity (excluding V600E/K) (e.g. L597V, K601E) and 36% with novel/unclear/unknown kinase activity (e.g. G469I, W531S). Eligible pts with inactivating *BRAF* mut proceeded to SORATRAM screening. 15 pts received dose finding treatment: 3 in DL1 and DL2 and 9 in DL3. Median age was 57 years (34-75) with 12f/3m pts. Included entities were colorectal cancer (60%), duodenal carcinoma/carcinoma of papilla vateri (20%), lung adenoid cystic carcinoma (6.7%), bone sarcoma (6.7%) and ovarian cancer (6.7%). 3/3 pts in DL1 and DL2 and 6/9 pts at DL3 fulfilled the minimum safety evaluation requirements ($\geq$ 80% of S+T doses in c1; 28ds observation). No DLT was observed in DL1 and DL2. 1/6 pts in DL3 developed a DLT (reduction of left ventricular ejection fraction (LVEF)). 5/15 pts (33.3%) experienced grade 3 adverse events (AEs) during c1: Hypertension (13.3%), gastrointestinal bleeding (6.7%; rated as SAE), anemia (6.7%), LVEF reduction (6.7%), diarrhea (6.7%) and fatigue (6.7%). 79 AEs grade 1/2 were reported in c1. **Conclusions:** Combination of sorafenib/ trametinib is feasible and can be safely administered to pts. MTD was determined as DL3 (800mg S + 1.5mg T), RP2D as DL2 (800mg S + 1mg T). Dose expansion part of SORATRAM is open for enrollment. Clinical trial information: EU – CT No. 2024-512887-77-00. Research Sponsor: German Cancer Consortium (DKTK); German Cancer Consortium (DKTK) Freiburg site; Sorafenib was kindly supplied by Bayer.

3120 **Poster Session**

Safety and efficacy of a small-molecule c-Myc degrader WBC100 in solid tumors: A first-in-human, phase I trial. First Author: Qi Zhang, Department of Hepatobiliary and Pancreatic Surgery, The First Affiliated Hospital, Zhejiang University School of Medicine, Hangzhou, China

Background: *c-Myc* amplification or overexpression is involved in the development and progression of many human cancers, and is often associated with poor outcomes. It is an extraordinarily desirable target, but is also considered undruggable. WBC100 is an oral active molecule glue that selectively degrades c-Myc protein. **Methods:** This is a first-in-human, dose-escalation study conducted in China. Patients with solid tumors that have progressed or relapsed after standard systemic therapy were enrolled. WBC100 was orally administered every other day (QOD) according to 3+3 design. The primary endpoints were safety, dose-limiting toxicity (DLT) and maximal tolerated dose (MTD). **Results:** As of Dec 9, 2024, 28 patients were enrolled in seven dose levels (DLs) from 0.5 to 3.5 mg. The median age was 59 (range, 45-71) years, comprising 15 males and 13 females. Three (11%) patients had an ECOG PS score of 0, while the remaining 25 (89%) had a score of 1. The median number of prior systemic therapy lines was 3 (range, 1 to 6). One DLT of prolonged QT interval was observed in DL7, and MTD has not been reached. Six patients (21%) experienced grade 3 or higher treatment-related adverse events, including five (17.9%) neutropenia and two (7.1%) leukopenia and one (3.6%) prolonged QT interval. Increased aspartate aminotransferase, thrombocytopenia, proteinuria, increased alanine aminotransferase, fatigue, nausea, anemia, and hypoalbuminemia were the most commonly reported grade 1 or 2 adverse events. Nineteen patients were evaluable for efficacy, one (5.3%) showed partial regression (PR), and six (31.6%) showed stable disease (SD), including two patients with hepatocellular carcinoma, one with duodenal adenocarcinoma, and three with pancreatic cancer. Notably, we enrolled eight patients with pancreatic cancer at DL6 and DL7, and six of them were evaluable for efficacy, with one (16.7%) PR and two (33.3%) SD. **Conclusions:** WBC100 showed a tolerable safety profile and preliminary anti-tumor activity in advanced solid tumors especially in PDAC. Dose escalation is ongoing and expected to proceed to dose expansion soon. To our knowledge, this is the first study of a small-molecule c-Myc degrader for further clinical development in cancer. Clinical trial information: NCT05100251. Research Sponsor: Weben Pharma.

3121 **Poster Session**

In vitro efficacy of CDK9 inhibitor tambiciclib (SLS009) in ASXL1 mutated colorectal cancer cell lines. First Author: Dragan Cicic, Sellas Life Sciences Group, New York, NY

Background: ASXL1 (Additional sex combs-like 1) gene encodes ASXL1 protein thought to disrupt chromatin, enhancing transcription of certain genes while repressing the transcription of others. ASXL1 mutations occur in ~20% of acute myeloid leukemia (AML) patients and ~50% of ASXL1 AML mutations are frameshift or nonsense mutations generating a truncated ASXL1 form with oncogenic gain of function in AML. Recently ASXL1 mutated AML patients were treated with a CDK9 inhibitor tambiciclib (SLS009) with promising results. ASXL1 mutations were also reported in 55% of Colorectal Carcinoma with High Microsatelite Instability (CRC MSI-H) cell lines, but it is not known whether those mutations are similar to ASXL1 mutations observed in AML and whether CDK9 inhibitors have enhanced cytotoxic effect in CRC MSI-H cells with those mutations. **Methods:** Twelve CRC MSI-H cell lines were treated with SLS009 at various concentrations. Staurosporin was used as positive control. Cytotoxicity analysis was performed by CellTiter-Glo 2.0 assay. Data analyses were performed using GraphPad Prism 9. NGS was used to determine mutations in studied cell lines. The experiment was designed to compare ASXL1 mutations in CRC MSI-H cell lines to those observed in AML and determine efficacy of SLS009 cytotoxicity in CRC MSI-H cells with and without ASXL1 mutations. Highly effective concentrations in this experiment were considered those with IC50 values below 100 nM. **Results:** Among the 12 tested cell lines, 8 (67%) had non-synonymous ASXL1 mutations of any kind, similar to the literature reported 55% ASXL1 mutations rate in CRC MSI-H. Among cell lines with ASXL1 mutations, 4 (50%) had high impact frameshift mutations, similar to estimated rate of high impact frameshift mutations in AML (~50%). Among cell lines with high impact frameshift mutations, all had mutations in protein position regions 581-582 and 642-643. Three out four had in addition high impact frameshift mutations in the region of protein position 637-638. Protein positions of these frameshift ASXL1 mutations were similar to those observed in AML (591 – 592 and 635 – 646). Among the cell lines with any ASXL1 mutation, 4/8 (50%) had IC50 values for SLS009 below 100 nM (highly efficacious) vs 0/4 (0%) among cell lines without ASXL1 mutations. Among cell lines with ASXL1 frameshift mutations, SLS009 was highly efficacious in 3/4 (75%) cell lines vs 1/8 (12.5%) in cell lines without ASXL1 frameshift mutations. High efficacy was observed in all cell lines (3/3, 100%) with frameshift mutations in the protein position region 637-638. Presence of high impact TP53 mutations did not appear to significantly affect SLS009 efficacy. **Conclusions:** Results indicate that ASXL1 mutations may be oncogenic drivers in some solid tumors, like CRC MSI-H, similar to those in AML and that efficacy of CDK9 inhibition with SLS009 may be similar in some solid tumors to the efficacy observed in AML. Research Sponsor: None.

3122 **Poster Session**

Safety and efficacy of EIK1003, a selective PARP1 inhibitor, as monotherapy in participants with advanced solid tumors. First Author: Guru P. Sonpavde, AdventHealth Cancer Institute, Orlando, FL

Background: PARP inhibitors (PARPi) selectively kill tumor cells with genetic mutations in critical DNA repair genes (eg, BRCA1/2). While approved nonselective PARPi may provide antitumor activity, they are associated with hematologic toxicities. Drugs inhibiting PARP1 but not PARP2 may improve the risk-benefit profile by retaining antitumor activity while avoiding PARP2-related toxicities. EIK1003 (IMP1734) is a potent PARP1-selective inhibitor that may widen the therapeutic index in susceptible tumors. **Methods:** EIK1003-001 (IMP1734-101) is an ongoing global, multi-center, Phase 1/2 study evaluating the safety and efficacy of EIK1003 (once daily oral) as monotherapy or in combination with anticancer agents in participants (pts) with advanced solid tumors (NCT#06253130). Pts must be $\geq$ 18 yrs with deleterious or suspected deleterious mutations in select homologous recombination repair genes. This abstract reports the interim safety and efficacy from Part 1 monotherapy (dose escalation). **Results:** At the data cut (10 Jan 2025), 32 pts were treated in the first 4 completed dose levels (DLs; n = 3 to 15 per DL, including backfill) of monotherapy dose escalation. There were no dose-limiting toxicities and a maximum tolerated dose has not been reached. The majority (29/32) of pts were female. Pts had a median age of 60 years (31 to 76), and cancers represented included ovarian (n = 15), HER2-negative breast (n = 10), pancreatic (n = 3), fallopian tube (n = 2), and prostate cancer (n = 1). Pts received a median of 3 (range 1 to 11) prior lines of therapy for metastatic disease with 50% receiving prior PARPi. To date, EIK1003 demonstrated a tolerable safety profile. All pts experienced at least one treatment-emergent adverse event (TEAE), and 13/32 experienced at least one $\geq$ Grade 3 TEAE. 27/32 pts experienced a treatment-related AE (TRAE), 6 of which experienced a $\geq$ Grade 3 TRAE. Hematologic toxicities (Grade 3) included neutropenia (3/32) and anemia (1/32). 7/32 experienced a serious adverse event (including one related case of Grade 3 vomiting). There were no Grade 4 AEs or deaths due to AE, and no trends in AEs by DL were observed. EIK1003 PK was linear, with a half-life $>$ 24 hours. Of the 13 ovarian cancer patients with post-treatment scan assessments, 3 experienced partial response (PR; one each at DL2, DL3, and DL4) and 3 experienced stable disease (SD; one at DL1 and two at DL3) by RECIST v1.1. For these 3 PRs, all had a CA125 response. Of the 6 breast cancer patients with post-treatment scan assessments, there was 1 PR (DL3) and 1 SD (DL1) via RECIST v1.1. **Conclusions:** To date, EIK1001 has demonstrated tolerable safety and encouraging preliminary efficacy. Dose escalation is ongoing. Updated safety and efficacy data will be reported at the time of presentation. Clinical trial information: 06253130. Research Sponsor: None.

3123 **Poster Session**

A first-in-human phase I/Ib study of ATG-037 monotherapy and combination therapy with pembrolizumab in patients with advanced solid tumors: STAMINA-01. First Author: Janine Margaret Lombard, Calvary Mater Hospital Newcastle, Newcastle, NSW, Australia

Background: ATG-037 is a highly potent oral small molecule inhibitor of CD73. STAMINA-01 is an open-label, first-in-human, phase 1/1b study (NCT05205109) designed to evaluate the safety, pharmacokinetics, and optimal dosing of ATG-037 as monotherapy and in combination with pembrolizumab in patients with refractory/relapsed solid tumors. **Methods:** The study successfully completed enrollment of dose escalation of ATG-037 with optional addition of pembrolizumab following two cycles of monotherapy in May 2024. The primary objectives were to evaluate the safety and define the optimal biological dose of ATG-037 as monotherapy and combination treatment. As of 20 January 2025, 43 patients were enrolled across the following doses - 20mg BID (n=3), 60mg BID (n=6), 120mg BID (n=10), 240mg BID (n=6), 400mg BID (n=12) and 600mg BID (n=6). The trial is currently recruiting the second part of the study for dose optimization of upfront combination therapy at two dose levels (120mg BID and 400mg BID). **Results:** *Efficacy:* As of the data cut-off (20 Jan 2025), 43 patients were enrolled on study and received monotherapy. While on ATG-037 monotherapy, 21 patients had a best response of stable disease (SD) with a disease control rate (DCR) of 49%. Twenty-eight patients with a history of acquired checkpoint inhibitor resistance received combination therapy; 7 of which (5 melanoma and 2 NSCLC patients) achieved a confirmed partial response (PR) with an overall response rate (ORR) of 25% (95% CI: [51.33, 86.78]). Additionally, 15 patients had a best response of SD with a DCR of 79% (95% CI: [8.30, 40.95]). Of the 11 enrolled melanoma patients who received combination, 5 achieved a PR for an ORR of 45% and 6 achieved SD for an DCR of 100%. Of the 9 enrolled NSCLC patients who received combination, 2 achieved a PR for an ORR of 22% and 4 achieved SD for an DCR of 67%. *Safety:* While on monotherapy, 24/43 (56%) patients reported treatment-related adverse events (TRAEs). While on combination therapy, 17/28 (61%) patients reported TRAEs. The majority of TRAEs were grades 1-2. The only dose limiting toxicity was a grade 3 rash which occurred at the monotherapy 400mg BID dose. Only one serious TRAE (grade 3 immune mediated hepatitis) was reported at the data cut-off. **Conclusions:** In relapsed/refractory solid tumor patients, ATG-037 appears to be well tolerated as monotherapy and in combination with pembrolizumab. The preliminary efficacy data is encouraging and suggests that the combination regimen may provide a new therapeutic option for CPI resistant NSCLC and melanoma patients. Clinical trial information: NCT05205109. Research Sponsor: None.

3124 **Poster Session**

Phase 1 study of zavondemstat (TACH101), a first-in-class KDM4 inhibitor, in patients with advanced solid tumors: Results on safety, pharmacokinetics, and anti-tumor activity. First Author: Apostolia Maria Tsimberidou, University of Texas MD Anderson Cancer Center, Houston, TX

Background: Zavondemstat is an epigenetic targeting inhibitor of KDM4 histone demethylase. Dysregulation of KDM4 enzymes (isoforms A-D) has been implicated in various cancers where they drive oncogenesis and resistance pathways by regulating gene transcription. Preclinical studies of zavondemstat demonstrated robust anti-proliferative effects and significant inhibition of tumor growth across numerous xenograft and PDX models. Targeting KDM4 offers the potential to reprogram the epigenetic dysfunction of cancer cells and inhibit drivers of tumor dedifferentiation and proliferation leading to apoptotic cell death. This is the first clinical evaluation of a pan-isoform KDM4 inhibitor. **Methods:** TACH101-CS-0001 (NCT05076552) was an open-label Phase 1 study assessing zavondemstat's safety, tolerability, pharmacokinetics (PK), and recommended Phase 2 dose (RP2D) in patients (pts) with advanced solid tumors. Pts received zavondemstat orally on a weekly schedule in 28-day cycles. Dose escalation followed a Bayesian optimal interval (BOIN) design and explored both intermittent and continuous dosing. Inclusion criteria included heavily pre-treated advanced/metastatic solid tumors that progressed or were non-responsive to available therapies and for which no standard therapy exists. Pts must have measurable disease according to RECIST (v1.1) and ECOG score of 0 to 1. Exclusion criteria included severe hematologic, hepatic, or renal insufficiency. Primary endpoints included safety/tolerability, MTD and RP2D. Secondary endpoints included PK and radiographic response per RECIST v1.1. **Results:** Thirty patients were enrolled across 6 dose cohorts. MTD was not reached; RP2D was not determined. The most common treatment-related adverse events (TRAEs) were diarrhea (12%), fatigue (7%), decreased appetite (7%), nausea (7%), and hyponatremia (7%). All TRAEs were Grade 1 or 2 (no TRAEs $\geq$ Grade 3 were reported). No treatment-related serious adverse events (SAEs) or dose limiting toxicities (DLTs) were reported. In 23 response-evaluable patients, 10 patients (44%) achieved stable disease (SD) across dosing cohorts. Two patients (9%) had SD $\geq$ 6 months, including a patient with castration-resistant prostate cancer (CRPC) and a patient with leiomyosarcoma. Another patient with leiomyosarcoma is continuing to receive zavondemstat under compassionate use, demonstrating SD for a total of 6 months at time of abstract submission. Zavondemstat demonstrated a dose-proportional exposure profile with a short half-life of about 1.5 hours. There was no to minimal drug accumulation observed. **Conclusions:** Zavondemstat was very well tolerated and showed encouraging preliminary signals of clinical benefit in very heavily pre-treated metastatic cancer patients. Continued evaluation of zavondemstat is warranted. Clinical trial information: NCT05076552. Research Sponsor: Tachyon Therapeutics; California Institute for Regenerative Medicine (CIRM).

3125 **Poster Session**

Phase I dose-escalation study of the safety and pharmacokinetics of PAS-004, a macrocyclic MEK inhibitor, for the treatment of patients with MAPK pathway–driven advanced solid tumors. First Author: Tiago Reis Marques, Pasithea Therapeutics Corp, Miami, FL

Background: PAS-004 is a small molecule allosteric inhibitor of MEK 1/2 and the first macrocyclic structure MEK inhibitor in clinical development. Macrocycles are large cyclic molecules that can bring increased potency, metabolic stability, and oral bioavailability. PAS-004 was developed to reduce metabolic liabilities and overcome the limited exposure and stability of known MEK inhibitors. We report initial results of an ongoing Phase I dose escalation, multicenter study of PAS-004 in monotherapy in patients with advanced refractory solid tumors. **Methods:** The Phase 1 clinical trial is a multi-center, open-label, dose escalation 3+3 study design to evaluate the safety, tolerability, pharmacokinetic (PK), pharmacodynamic (PD), and preliminary efficacy of PAS-004 in patients with MAPK pathway driven advanced solid tumors with a documented RAS, NF1 or RAF mutation, or patients who have failed BRAF/MEK inhibition (NCT06299839).Eligible pts, $\geq$18 years with MAPK-driven advanced solid tumors, are being enrolled in dose escalation at 8 different dose cohorts in monotherapy. **Results:** As of 3 Jan 2025, a total of 9 patients have been enrolled in dose escalation in 3 dose cohorts (2mg, 4mg, and 8mg). 55.6% of the patients were female with a median age of 60 years. Most common tumor types included colorectal (n = 5, 55.56%), pancreatic (n = 2, 22.22%), gastroesophageal (n = 1, 11.11%), and of unknown type (n = 1, 11.11%). Treatment Related Adverse Events (TRAE) were reported in 44.44% of patients. TRAEs were all low grade (n = 7, 100% were Grade 1-2). No Grade 3, 4 or 5 TRAEs were reported. The most common TRAEs were gastrointestinal disorders (n = 4, 57.14%), dehydration (14.29%), arthralgia (14.29%) and urinary incontinence (14.29%). No rash was observed in any dose cohort. No dose limiting toxicities were detected, and the MTD has not been reached. Preliminary PAS-004 PK analysis suggests linear PK with estimated t1/2 of 70h, Cmax/Cmin ratio of 1.4 at steady state, achieving potentially sufficient exposures for target engagement at the highest dose tested. In the efficacy evaluable population (n = 6), early response evaluation reveals stable disease (SD) by RECIST 1.1 was observed in 2 patients, with progression free survival of up to 159 days and overall survival of up to 253 days. **Conclusions:** To date, PAS-004 is shown to be a safe and well-tolerated novel MEK inhibitor, with dose-dependent PK profile and preliminary clinical activity in monotherapy in patients with heavily pre-treated refractory solid tumors. PAS-004 has the potential to achieve prolonged target inhibition and once-daily dosing (QD) due to its long half-life and low Cmax to Cmin ratio. These findings provide a compelling rationale to continue to test PAS-004 into clinical trials for the treatment of MAPK-driven opportunities. Clinical trial information: NCT06299839. Research Sponsor: Pasithea Therapeutics.

3126 **Poster Session**

Pertuzumab plus trastuzumab (P+T) in patients (pts) with bladder (BC) and ovarian cancer (OC) with *ERBB2/3* alterations (alt): Results from the Targeted Agent and Profiling Utilization Registry (TAPUR) study. First Author: John K. Chan, Sutter Cancer Research Consortium, San Francisco, CA

Background: TAPUR is a phase II basket study evaluating antitumor activity of commercially available targeted agents in pts with advanced cancers with genomic alt. Results of two cohorts of pts with BC or OC with *ERBB2/3* alt treated with P+T are reported. **Methods:** Eligible pts had measurable disease, ECOG performance status (PS) 0-2, adequate organ function, and no standard treatment (tx) options. Genomic testing was performed in CLIA-certified, CAP-accredited site selected labs. Recommended dosing was P at an initial dose of 840 mg intravenously (IV), then 420 mg IV every 3 weeks (wks) and T at an initial dose of 8 mg/kg IV, then 6 mg/kg IV every 3 wks until disease progression. Primary endpoint was disease control (DC) per investigator defined as complete (CR) or partial (PR) response per RECIST v.1.1, or stable disease (SD) of at least 16 wks duration (SD16+). CR was based on radiographic assessment. For both cohorts, Simon 2-stage design was based on a null DC rate of 15% vs. 35% (power = 0.85; α = 0.10). If $\geq$2 of 10 pts in stage I had DC, 18 more pts were enrolled; otherwise, the cohort was closed. If $\geq$7 of 28 pts had DC, the null DC rate was rejected. Secondary endpoints were objective response (OR), progression-free survival (PFS), overall survival (OS), duration of response and SD, and safety. **Results:** 28 pts with *ERBB2/3* alt were enrolled in each cohort. The table shows demographics and outcomes. For the BC cohort, 2 CRs (*ERBB2* amplification [amp, n=1] and *ERBB2* amp and *ERBB3* mutation [mut, n=1]), 5 PRs (*ERBB2* amp [n=3], *ERBB2* amp and mut [n=1], and *ERBB2* mut [n=1]) and 3 SD16+ (*ERBB2* mut [n=3]) were observed for DC rate of 37% (90% CI, 24 to 100) and OR rate of 25% (95% CI, 11 to 45). The null DC rate was rejected (p=0.005). For the OC cohort, 2 PRs (*ERBB2* amp [n=1] and *ERBB2* mut [n=1]) and 3 SD16+ (*ERBB2* amp [n=2] and *ERBB2* amp and mut [n=1]) were observed for DC rate of 25% (90% CI, 10 to 100) and OR rate of 7% (95% CI, 1 to 24). The null DC rate was not rejected (p=0.29). Across both cohorts, 4 pts had 6 tx-related serious adverse events (SAE) including: infusion-related reaction, confusion, diarrhea, and fever, and 2 pts had 1 grade 3 tx-related adverse event (AE) each including: GGT increase and lymphopenia. No pts had grade 5 SAEs. **Conclusions:** P+T met prespecified criteria to declare clinical activity in pts with BC with *ERBB2* alt, but not in pts with OC. Additional study is warranted to confirm the efficacy of P+T in pts with BC with *ERBB2* alt. Clinical trial information: NCT02693535. Research Sponsor: Genentech; Astrazeneca, Bayer, Boehringer Ingelheim, Bristol Myers Squibb, Eli Lilly and Company, Merck, Pfizer, Seagen (now a wholly owned subsidiary of Pfizer Inc.), Taiho Oncology.

Demographics and efficacy outcomes.

			BC (N=28)		OC (N=28)
ECOG PS, N (%)	0	6	(21)	11	(39)
	1	17	(61)	16	(57)
	2	5	(18)	1	(4)
Prior systemic regimens, N (%)	1-2	6	(21)	13	(46)
	$\geq$3	22	(79)	15	(54)
DC (OR plus SD16+) rate, % (90% CI), p-value		37	(24, 100), p=0.005	25	(10, 100), p=0.29
OR rate, % (95% CI)		25	(11, 45)	7	(1, 24)
Median PFS, wks (95% CI)		13	(7, 22)	8	(8, 16)
Median OS, wks (95% CI)		32	(17, 54)	44	(26, 89)

3127 **Poster Session**

Digital spatial profiling of advanced solid tumors and lymphomas from a phase 1 trial of copanlisib and nivolumab. First Author: Sayak Ghatak, Frederick National Laboratory for Cancer Research, Frederick, MD

Background: Digital spatial profiling (DSP) is an innovative technique that facilitates spatially resolved proteotranscriptomic analysis within tissue sections, providing essential insights into the tumor microenvironment (TME). As part of the exploratory objectives in the Phase 1B trial (NCT03502733) evaluating adult patients(pts) with solid tumors and lymphomas copanisib (C), nivolumab (N) + ipilumumab (I), we employed the NanoString-Bruker GeoMx DSP platform to evaluate spatial heterogeneity in differentially regulated biomarkers. **Methods:** The study analyzed samples from pts in the trial's doublet treatment arm, which included C + N. Pts receive C on days 1 and 15 or days 1, 8, and 15 of each cycle and nivolumab on day 1 or days 1 and 15 of each cycle. Core biopsies collected from 8 pts at cycle 1 day 1 pre-dose (C1D1, baseline), cycle 1 day 8 post-dose (C1D8, C only) and cycle 2 day 15 post-dose (C2D15, C+N) were selected for GeoMx analysis. Tissue sections (5-μm) from archival FFPE blocks were prepared on glass slides and hybridized with photocleavable tag-conjugated antibodies (targeting 85 proteins) and oligonucleotide probes (whole transcriptome- WTA) for protein and WTA analyses respectively. Tissue imaging was performed via high-resolution fluorescent microscopy using morphology markers (cytokeratin AE1/AE3, CD45, CD3, CD20, Syto-13 nuclear marker). At least three rectangular (660 x 784 μm) regions of interest (ROI) per timepoint were analyzed using NanoString nCounter for proteomics and NGS for WTA. Data quality control and analysis were conducted using the GeoMx DSP Control Center (V-3.0) with a significance threshold of α = 0.05. **Results:** In two lymphoma pts with stable disease (SD) or partial response (PR), PI3K downstream signaling showed downregulation at C1D8 due to C-mediated PI3K-AKT signaling inhibition, possibly through PIK3IP1 overexpression. This signaling returned to baseline by C2D15, likely due to C's elimination half-life. In a follicular lymphoma case (#18, PR), FOXP3 expression decreased at both C1D8 and C2D15, while CD4 and CD8 levels remained constant. Immune marker expression (PD-L1, PD-1, CTLA-4, CD80) progressively declined. However, in diffuse large B-cell lymphoma (#14, SD), no changes in T-cell markers were observed. Solid tumor cases (#12, #24, SD) showed PI3K-AKT signaling downregulation at C2D15, along with CD3+/CD8+ T-cell infiltration into the tumor. FOXP3 levels slightly decreased in tumor and immune compartments. Progressive disease cases showed no change in T-cell markers. **Conclusions:** GeoMx DSP demonstrated its capability to investigate phospho-signaling and immune profiles in tumor and stromal compartments of small biopsies, highlighting its potential to enhance the understanding of TMEs in clinical studies. Further applications may provide critical insights for clinical cancer trials. Clinical trial information: NCT03502733. Research Sponsor: None.

3128 **Poster Session**

Long non-coding RNA (lncRNA) SNHG11 as a prognostic and predictive biomarker in metastatic colorectal cancer (mCRC): Insights from CALGB (Alliance)/SWOG 80405. First Author: Michela Bartolini, Division of Medical Oncology, Norris Comprehensive Cancer Center, Keck School of Medicine, University of Southern California, Los Angeles, CA

Background: LncRNAs have emerged as key regulators of cancer progression and therapeutic responses. In CRC, several lncRNAs have been implicated in modulating tumor growth, metastasis and treatment resistance by interacting with critical tumorigenic pathways. Here, we investigate the potential prognostic and predictive value of lncRNA expression in patients (pts) with mCRC enrolled in CALGB/SWOG 80405 (NCT00265850) trial. **Methods:** We analyzed 433 mCRC pts treated with either bevacizumab (bev, n = 226) or cetuximab (cet, n = 207) plus first-line chemotherapy. Tumor RNA expression (Illumina HiSeq 2500) of 13 candidate lncRNAs (SNHG11, HOTAIR, FGF14-AS2, H19, YWHAE, NEAT1, MIR100HG, UCA1, LINC00973, SLCO4A1-AS1, POU5F1P4, MALAT1, HCG18) was explored. Median overall survival (mOS) and progression-free survival (mPFS) in months (mo) were compared between pts grouped by tertiles (low [L] vs medium [M] vs high [H]) of gene expression. Likelihood ratio tests, hazard ratios and 95% confidence intervals were computed from multivariable Cox proportional hazards models, adjusting for age, sex, ECOG PS, tumor location, number of metastatic sites, *KRAS*, Consensus Molecular Subtypes (CMS), and treatment. **Results:** Overall, SNHG11 was strongly associated with OS and PFS after adjusting for multiple tests (Benjamini-Hochberg False Discovery Rate $<$ 0.05). High SNHG11 expression (H group, n = 144) was associated with improved mPFS (H: 14.3 vs M: 11.2 vs L: 8.3 mo; p = 0.038) and mOS (H: 39.6 vs M: 31.1 vs L: 20.5 mo; p = 0.033) in the combined treatment analysis. Among cet-treated pts, SNHG11-H showed a numerically longer mPFS (H: 14.2 vs M: 11.1 vs L: 7.6 mo; p = 0.19) and significantly longer mOS (H: 41.1 vs M: 32.4 vs L: 14.3 mo; p = 0.012). In contrast, no statistically significant OS or PFS differences were observed in bev-treated pts. SNHG11-H tumors had a significant OS benefit from cet compared to bev (mOS 41.1 vs 36.5 mo, respectively; p = 0.016), with a nominally significant treatment interaction observed for OS (p = 0.030). No significant differences were observed in the L or M expression groups. Additional analyses showed that SNHG11 expression was high in the CMS2 (canonical) subtype and substantially lower in CMS1 (immune). **Conclusions:** LncRNA SNHG11 plays a significant role in CRC progression and metastasis via tumorigenic pathways, including c-Myc and HIF-1α. Moreover, elevated circulating SNHG11 levels show promise as a non-invasive biomarker for early CRC detection. In CALGB/SWOG 80405, high SNHG11 expression correlated with improved PFS and OS, particularly in cet-treated pts, supporting its role as a prognostic and predictive biomarker. Its strong association with CMS2 aligns with its reported involvement in c-Myc-driven pathways. Further validation is needed to confirm the clinical utility of this biomarker and elucidate underlying mechanisms. Research Sponsor: National Cancer Institute; P30CA014089, U10CA180821, U10CA180882, U10CA180888; Genentech; https://acknowledgments.alliancefound.org.

3129 **Poster Session**

Using single-cell sequencing to identify endothelial expression of immune checkpoint ligands in advanced hepatocellular carcinoma, pre- and post-atezolizumab plus bevacizumab in the phase II INTEGRATE study. First Author: Florence T.H. Wu, Clinician Investigator Program, University of British Columbia, Vancouver, BC & Princess Margaret-UHN, Toronto, ON, Canada

Background: Atezolizumab (atezo; anti-PD-L1) plus bevacizumab (bev; anti-VEGF-A) became a standard treatment for advanced hepatocellular carcinoma (HCC) after demonstrating an overall survival advantage over sorafenib (inhibitor of VEGFR2 & other kinases) in the phase III clinical trial, IMbrave150. However, the mechanisms of primary and acquired resistance to atezo-bev are poorly understood. VEGFR2$^+$ endothelial cells (ECs) are potential cellular targets of bev and may play a key immunomodulatory role in response to atezo-bev. In this study, we utilized single-cell sequencing to identify potential mediators of resistance within EC subsets. **Methods:** Eight patients with unresectable HCC were enrolled on the INTEGRATE study, treated with atezo-bev, and underwent intensive biospecimen collection (NCT04563338). Serial tumor biopsies were collected and viably cryopreserved including pre-treatment (n=6), 21-28 days after first dose (n=6), and at disease progression (n=2). Single-cell analysis via cellular indexing of transcriptomes and epitopes (CITEseq) has been performed and data from four patients have been analysed to date. Aggregating their nine biopsies, 8,569 hepatocytes (ALB$^+$ FABP1$^+$ FGB$^+$), 29,072 immune cells (CD45$^+$), and 8,028 ECs (CD31$^+$ vWF$^+$ KDR$^+$) were annotated. The differential expression of VEGFR2, PD-L1, and other immune checkpoint ligands by tumor vs. immune vs. endothelial cellswere interrogated (Table). **Results:** VEGFR2 (receptor for VEGF-A) is predominantly expressed by ECs, at high prevalence & intensity. PD-L1 and PD-L2 (ligands of PD-1) are expressed by ECs at low prevalence & intensity. Galectin3 (LAG3 ligand) is widely expressed by hepatocytes, immune cells and ECs; while L-SECtin (LAG3 ligand) is predominantly expressed by ECs but at low prevalence & intensity. ECs had the highest prevalence of galectin9 (TIM3 ligand) expression. Nectin2 (TIGIT ligand) is expressed by both hepatocytes and ECs at high prevalence & intensity. **Conclusions:** Liver ECs express a broad array of immune checkpoint ligands, which are more frequent than previously anticipated. These EC subsets may potentially drive resistance by contributing to exhaustion of T cell subsets entering the tumor microenvironment. Complete CITEseq, TCR sequencing, and correlative studies from the full cohort are underway. Clinical trial information: NCT04563338. Research Sponsor: This research was a collaborative effort made possible through support from F. Hoffmann-La Rohce for the imCORE Network.

	Hepatocytes	Immune cells	ECs
VEGFR2 (KDR)	0.06% (<0.01)	0.05% (<0.01)	66% (0.8)
PD-L1 (CD274)	0.2% (<0.01)	4% (0.03)	2% (0.01)
PD-L2 (PDCD1LG2)	0.02% (<0.01)	2% (0.02)	3% (0.02)
L-SECtin (CLEC4G)	0%	0.1% (<0.01)	3% (0.05)
Galectin-3 (LGALS3)	68% (0.8)	39% (0.5)	43% (0.5)
Galectin-9 (LGALS9)	5% (0.04)	28% (0.3)	34% (0.3)
PVR (CD155)	14% (0.1)	1% (<0.01)	18% (0.1)
Nectin2 (CD112)	60% (0.5)	5% (0.04)	44% (0.4)

% = proportion of cells with positive expression. ( ) = normalized mean expression.

3130 **Poster Session**

Assessment of homologous recombination deficiency and BRCA status in ovarian cancer: Analytical performance and relevance of a decentralized NGS assay for comprehensive genomic profiling. First Author: Mohit Gupta, Thermo Fisher Scientific, South San Francisco, CA

Background: Homologous recombination deficiency (HRD) is a complex biomarker with predictive value in ovarian cancer. Understanding both the causes of HRD, such as pathogenic alterations in homologous recombination repair (HRR) genes, and its consequences, like genomic instability (GI), is crucial for exploring various therapeutic strategies, including the potential use of poly (ADP-ribose) polymerase inhibitors (PARPi). This study evaluates the analytical performance and clinical research relevance of the Oncomine™ Comprehensive Assay Plus (OCA Plus), a distributable next-generation sequencing (NGS) research use assay that offers in a single workflow comprehensive genomic profiling, including HRD evaluation. **Methods:** The OCA Plus panel was used for comprehensive genomic profiling of a series of 299 ovarian cancer research samples from the PAOLA-1 trial, part of the ARCAGY biorepository. Research samples were analyzed to assess agreement with orthogonal method, specifically for *BRCA1* and *BRCA2* mutational status, GI status and overall HRD status which combined BRCA1/2 mutational status and GI status. GI status was determined using Genomic Instability Metric (GIM), a quantitative method that characterizes unbalanced copy number changes. Progression-free survival (PFS) was retrospectively studied to determine future clinical relevance. **Results:** The success rate for DNA sequencing was 100%, starting from a minimal sample input of 20ng of genomic DNA isolated from FFPE tissue blocks. The OCA Plus panel provided a detailed genomic profile in a single workflow, achieving high success rates across all biomarkers tested, including single nucleotide variants/indels and HRD (100%). Overall percent agreement (OPA) for HRD status with orthogonal method was 87%. OPA for *BRCA1/2* variants was 98%, while OPA for GI status was 80%. PFS analysis demonstrated a significantly better hazard ratio (HR: 0.51, $p < .005$) for the cases positive for OCA Plus HRD solution compared to the cases negative for the OCA Plus HRD solution (HR: 0.84, p = 0.43). **Conclusions:** The OCA Plus solution enables robust and reliable comprehensive genomic profiling with high OPA for *BRCA1/2* and HRD status compared to commonly used orthogonal method. Albeit additional studies are due, overall, the reported data suggests its future clinical utility in predicting treatment outcomes in ovarian cancer. Research Sponsor: None.

3131 **Poster Session**

Cost-effectiveness of NTRK testing strategies for detecting NTRK fusions in solid tumors in China. First Author: Jian Wang, Fudan University Shanghai Cancer Center; Shanghai Medical College, Fudan University, Shanghai, China

Background: Neurotrophic tyrosine receptor kinase (NTRK) gene fusions are oncogenic drivers in many solid tumors. With the inclusion of the targeted drug Entrectinib in China's national reimbursement drug list, the demand for NTRK testing has also increased. This study evaluates the cost-effectiveness of a two-step testing strategy (initial pan-TRK IHC testing followed by next-generation sequencing (NGS) confirmation for positive results) compared to directly conducting NGS testing, with treatment of positive cases using Entrectinib. **Methods:** A decision tree model was established from a health system perspective, based on clinical practices in China. The study included 17 cancer types as reported in the latest clinical trial of Entrectinib (n = 194). Diagnostic performance data were sourced from literature and validated by pathologists and clinicians. Clinical efficacy, treatment phase costs, and utility for progression-free survival (PFS) were obtained from open databases and literature. Turnaround time and costs for testing was gathered from expert interviews. The time horizon was set to include the duration of NTRK testing and the period of PFS associated with the medication. A one-way sensitivity analysis was conducted to assess the model's robustness. **Results:** In China, the NGS testing alone produced 0.55507 life years (LY) and 0.42646 quality-adjusted life years (QALY) at a total cost of $5932.57 , whereas the pan-TRK IHC + NGS testing strategy yielded 0.55530 LY and 0.42665 QALY at a total cost of $4176.67. The pan-TRK IHC+NGS testing strategy was dominant, offering higher QALY at lower costs than NGS testing alone. Additionally, the average wait time for pan-TRK IHC + NGS testing was reduced by 10 days. The robustness of the base case results was confirmed through sensitivity analysis. **Conclusions:** Initial pan-TRK IHC testing, followed by NGS confirmation for positive results, is the optimal strategy for NTRK fusion detection in patients with locally advanced or metastatic solid tumors in China, providing superior cost-effectiveness compared to NGS testing alone. Research Sponsor: None.

Cost-effectiveness analysis results.

Testing	Total Cost(USD$)	Effectiveness (LYs)	Effectiveness (QALY)	Incremental cost ($)	Incremental QALYs	ICER (Cost/QALY)
NGS	$5932.57	0.55507	0.42646			pan-TRK IHC +NGS was dominant
pan-TRK IHC+NGS	$4176.67	0.55530	0.42665	-$1755.90	0.000187	

ICER: Incremental cost-effectiveness ratio.

3132 **Poster Session**

Impact of sample characteristics on RNA-based next-generation sequencing (NGS) for fusion gene detection in non-small cell lung cancer (NSCLC). First Author: Jun Liu Jr., First People's Hospital, the Second Affiliated Hospital of South China University of Technology, Guangzhou, China

Background: RNA-based next-generation sequencing (NGS) has been widely employed for detecting fusion genes in NSCLC, due to its superior sensitivity and simplified design compared to DNA-based NGS. However, the impact of sample quality on fusion variant detection using RNA-based NGS remains unclear. **Methods:** The study analyzed 5,386 and 5,538 NSCLC samples using DNA- or RNA-based NGS to detect common fusion genes (ALK, RET, ROS1, NTRK, NRG1, MET exon 14 skipping, and FGFR). NGS libraries were constructed using capture-based or amplicon-based methods for DNA and RNA samples, respectively, focusing on pathogenic mutations. **Results:** RNA-based NGS detected 2.44% more fusions than DNA-based NGS [9.50% (526/5538) vs. 7.06% (380/5386)], with notable advantages for NTRK (0.13% vs. 0.02%), NRG1 (0.25% vs. 0.06%), MET exon 14 skipping (2.15% vs. 1.36%), and FGFR fusions (0.40% vs. 0.02%). Tumor cell content analysis showed no significant impact on fusion detection rates within the 20%-90% range for either method. However, higher tumor cell content ($\geq$80%) significantly increased RNA-based NGS detection rates compared to DNA-based NGS, nearly doubling the total detection rate (17.3% vs. 8.88%), primarily due to increased ALK fusion detection (8.97% vs. 5.02%). The type of sampling (surgical, biopsy, or others) did not significantly affect overall fusion detection rates for either method ($p > 0.05$). However, gene-specific analyses showed significantly higher detection rates for ROS1, MET, and RET using RNA-based NGS in biopsy samples compared to DNA-based methods (ROS1: 11.83% vs. 1.18%, MET exon 14 skipping: 2.87% vs. 1.62%, RET: 1.24% vs. 0.79%). Conversely, RNA-based detection of ALK and NRG1 fusions was higher in surgical samples (ALK: 4.00% vs. 3.25%, NRG1: 0.34% vs. 0.08%) compared to DNA-based methods. Regarding sample types, pleural/peritoneal effusions showed higher detection rates than FFPE samples, though not statistically significant. RNA-based NGS consistently showed superior detection rates for ALK and MET exon 14 skipping in all sample types compared to DNA-based methods, with the most substantial increase for MET exon 14 skipping in pleural/peritoneal effusions (2.14% vs. 0.98%). Conversely, RNA-based NGS for NRG1 and ROS1 fusions showed a greater relative increase in detection rate in 10% neutral formalin-fixed tissue/FFPE sections/unstained slides compared to pleural/peritoneal effusions. **Conclusions:** Sample characteristics did not significantly impact the overall detection rate of RNA-based fusion assays. However, detection rates for specific fusions like ALK, NRG1, and MET exon 14 skipping varied with sample type, sampling method, and tumor cell content. Optimizing testing strategies and sample handling is crucial to improving diagnostic accuracy in NSCLC. Research Sponsor: Medical Scientific Research Foundation of Guangdong Province, China; A2022519.

3133 **Poster Session**

Effect of irradiation on the killing effect of NK cells in colon cancer through MYB/TIM3 axis. First Author: Xiuli Guo, Zhongnan Hospital of Wuhan University, Wuhan, HuBei, China

Background: Natural killer (NK) cells play a crucial role in tumor progression and anti-tumor immunity. However, they often exhibit an exhausted phenotype within the tumor microenvironment (TME), limiting their full cytotoxic potential. T-cell immunoglobulin and mucin-domain containing-3 (TIM-3) has emerged as a novel immune checkpoint that is highly expressed on NK cells and suppresses their cytotoxic function. TIM-3 is closely associated with immune evasion and anti-tumor immune tolerance. This study aims to investigate the effects and mechanisms by which radiation modulates NK cell function, providing a foundation for developing strategies that specifically target TIM-3 on NK cells. **Methods:** First, mRNA high-throughput sequencing, RT-qPCR, and Western blot experiments were used to analyze changes in the expression of related genes in NK92 cells after radiotherapy. The LDH release assay was employed to evaluate the effect of radiation on the viability of NK92 cells. ELISA was conducted to detect changes in the release levels of tumor necrosis factor TNF-α and other factors after radiotherapy. Dual-luciferase reporter assays and chromatin immunoprecipitation (ChIP) experiments confirmed that the transcription factor MYB mediates radiation-induced regulation of NK cell activation by targeting and binding to the TIM-3 promoter region. A non-contact co-culture system was established, and flow cytometry demonstrated that radiation combined with MYB overexpression enhanced the cytotoxicity of NK cells against tumor cells. A colon cancer mouse model was constructed to evaluate the anti-tumor effect of combining anti-TIM-3 antibodies with radiotherapy. **Results:** We found that radiation can activate NK92 cells in vitro and enhance TIM-3 expression,promoting the secretion of granzyme B, perforin, TNF-α, IFN-γ, and other cytokines and chemokines that modulate the TME and enhance anti-tumor immune responses. Moreover, the transcription factor MYB inhibits TIM-3 expression by directly binding to the TIM-3 promoter region, mediating the effects of radiation on the TME through NK cell activation. In vivo, the combination of radiotherapy and anti-TIM-3 antibodies effectively controlled the growth of subcutaneously transplanted colon cancer tumors in C57BL/6 mice. However, this combined treatment effect was significantly diminished after NK cells were depleted by the anti-NK1.1 antibody. **Conclusions:** This study elucidates a novel mechanism by which radiation activates NK cells in the tumor microenvironment through the MYB/TIM-3 pathway. It provides new insights for enhancing the efficacy of radiotherapy and offers a theoretical basis for the potential clinical application of these cells in future research. Research Sponsor: None.

3134 **Poster Session**

Combined prognostic value of post-surgery circulating tumor DNA and tumor-stroma ratio in patients with stage III colon cancer treated with adjuvant chemotherapy. First Author: Ingrid Franken, University Medical Center Utrecht, Department of Medical Oncology, Utrecht, Netherlands

Background: Patients with stage III colon cancer (CC) are routinely treated with resection followed by adjuvant chemotherapy (ACT). About half of patients are cured by surgery and hence overtreated with ACT, yet another ~30% experience recurrence and are currently undertreated. Only ~20% of patients are cured by ACT and we are unable to identify these patients. Prognostic value of circulating tumor DNA (ctDNA) and the tumor-stroma ratio (TSR) has been shown in separate studies. This study aimed to integrate these biomarkers with pTNM substage to better predict outcome in stage III CC patients treated with ACT. **Methods:** Patients with stage III CC who received radical resection followed by ACT were selected from the Prospective Dutch ColoRectal Cancer cohort (PLCRC) substudy PROVENC3 (Rubio-Alarcon AACR 2024). Blood was collected between surgery and ACT, to determine ctDNA status using Labcorp Plasma Detect. Based on a diagnostic H&E slide from the CC resection, the TSR was determined by a trained observer according to the United study (Polack ESMO open 2024). A stroma content of $\leq$50% was considered low and $>$50% high. The primary outcome was recurrence risk (RR), calculated from date of resection. **Results:** In the overall cohort (N = 207), the 3-year RR was 23.4% [17.3-29.1]. In total, 88 patients (43%) were stroma-high and had a higher recurrence risk (3-year RR 33.1% [22.5-42.3]) than the 119 stroma-low patients (3-year RR 16.0% [8.9-22.5]; HR 2.7 [1.6-4.6]). CtDNA was detectable after surgery in 28 patients (13.5%; HR 5.8 [3.3-10]), of whom 11 (39%) were stroma-high. T4/N2 stage was observed in 82 patients (HR 2.9 [1.7-5.0]), of whom 46 (56%) were stroma-high. TSR (HR 2.6 [1.5-4.6]) had added prognostic value to ctDNA (HR 7.6 [4.3-13]) and pTNM substage (HR 2.9 [1.7-5.0]) in a multivariable cox model (LRT p$<$0.001). Patients with no detectable ctDNA and stroma-low T1-3N1 CC were at low recurrence risk (N = 71; 3-year RR 2.9% [0-6.8]). In comparison, patients with no detectable ctDNA and a tumor that was either stroma-high or T4/N2 were considered intermediate risk (N = 68; 3-year RR 17.2% [7.4-26.0]; HR 5.4 [1.5-19]). Patients with detectable ctDNA and/or stroma-high T4/N2 CC had a high risk (N = 68; 3-year RR 50.2% [36.7-60.8]; HR 19 [5.9-62]). **Conclusions:** The tumor-stroma ratio has added value to post-surgery ctDNA and pTNM substage in predicting outcome in stage III CC patients treated with ACT. The recurrence risk in the third of patients with no detectable ctDNA and stroma-low T1-3N1 CC was only 3%. It is of interest to investigate whether this low risk would persist in a cohort treated with surgery only, to suggest whether these patients could be spared ACT in the future. The third of patients with detectable ctDNA, and/or stroma-high T4/N2 CC, had a 50% recurrence risk despite ACT, highlighting the need for alternative adjuvant treatment options for these patients. Research Sponsor: None.

3135 **Poster Session**

Regorafenib response prediction in metastatic colorectal cancer by a novel genomic and transcriptomic model. First Author: Andreas Seeber, Department of Hematology and Oncology, Comprehensive Cancer Center Innsbruck, Medical University of Innsbruck, Innsbruck, Austria

Background: The multi-kinase inhibitor regorafenib (Rego) is approved for the treatment of refractory metastatic colorectal cancer (CRC). However, its efficacy is limited, and its use is frequently associated with substantial toxicities. Identifying biomarkers predicting Rego-response could improve therapeutic outcomes and reduce unnecessary treatment-related adverse effects in non-responders. **Methods:** A predictive model for Rego-response was developed based on transcriptomic and genetic data from 41 CRC cell lines. Cell lines were classified into Rego-sensitive *versus* -resistant groups based on drug sensitivity data from the CTRP2 database. Several machine-learning algorithms were evaluated, with the Generalized Linear Model via Elastic Net (GLMNET) achieving the highest predictive performance. Model accuracy was assessed using leave-one-out cross-validation. Further validation was performed using transcriptomic (WTS) data from 24,384 real-world CRC patients assessed by Caris Life Sciences, which included 720 patients treated with Rego. **Results:** The predictive model identified key cell line features associated with Rego-response, including gene expression signatures (e.g., *ZNF441, CCDC82, ZFP69*) and specific mutations (e.g., *RALGAPA1, MORC1*). Transcriptome profiling showed that Rego responders exhibited enrichment in cell-cycle regulation and DNA-repair mechanisms, while non-responders showed a stroma-rich microenvironment with significant endothelial and fibroblast infiltration. External validation using WTS data from real-world Rego-treated CRC patients revealed that predicted responders had a prolonged time-on-treatment (p = 0.02, HR = 0.79) and median overall survival (p = 0.01, HR = 0.76) compared to predicted non-responders. This association was specific to Rego-response, as there was no survival difference between predicted responders and non-responders among patients not treated with Rego (p = 0.72, HR = 1.0). **Conclusions:** This novel predictive model successfully identified and validated molecular features associated with Rego-response in CRC. The transcriptomic and genetic signature holds significant potential for improving personalized treatment strategies by identifying patients most likely to benefit from Rego and prevents unnecessary Rego-associated toxicities in non-responders. Research Sponsor: None.

3136 **Poster Session**

Relationship between FOLR1 expression and pan-cancer subgroup of tumors with specific transcriptomic profile. First Author: Andrew Ip, John Theurer Cancer Center, Hackensack University Medical Center, Hackensack, NJ

Background: Mirvetuximab soravtansine is an antibody–drug conjugate currently approved for the treatment of advanced platinum-resistant ovarian cancer. The efficacy of this therapy is correlated with high expression of folate receptor alpha (FRα), encoded by the FOLR1 gene. Treatment requires $\geq$ 75% of tumor cells to be stained positively for FRα by immunohistochemistry (IHC). Here we defined the FOLR1 RNA level that distinguishes ovarian cancers with very high FRα ($\geq$ 75% by IHC), then compared the transcriptomic profile of these cases (FOLR1-H) with the transcriptomic profile of cases with very low FRα expression (FOLR1-L). We further explored the presence similar FOLR1-H signature in various types of cancers. **Methods:** RNA was extracted from 1450 solid tumor FFPE samples and sequenced using a targeted RNA panel of 1600 genes. The RNA expression levels of various genes were quantified and expressed as transcript per million (TPM). IHC for FRα protein was performed on ovarian cancers (N = 49) using VENTANA FOLR1 RxDx assay. **Results:** Based on comparing IHC with RNA expression of FOLR1, FOLR1-H samples were defined with RNA $\geq$ 300 TPM while FOLR1 mRNA $<$ 100 was correlated with very low FRα by IHC and classified as FOLR1-L. Of the 312 ovarian cancers, 21% were classified as FOLR1-H and showed significantly (Log10FDR $<$ -2) higher expression in 39 genes as compared with FOLR1-L. The Log10FDR was $<$ -10 in 19 genes. The top highly expressed genes in FOLR1-H cases were TROP2, NECTIN4, ROR1, ROR2, ACVRL1, and NTHL1. In breast cases (N = 199) FOLR1-H was detected in 14.6% of cases and the most highly expressed genes were ACVRL1, NECTIN4, ROR1, and ACVRL1 (Log10FDR $<$ -5). Of the 932 cases of lung cancer, 21.5% classified as FOLR1-H and had significantly (Log10FDR $<$ -2) high expression of 137 genes, but similar to ovarian cancer TROP2, NECTIN4, ROR1, ROR2, ACVRL1, and NTHL1 were top expressed genes. Of the 174 pancreatic cancers 9.8% were FOLR1-H and top expressed genes were NECTIN4, ROR1, and ACVRL1. In sarcoma (N = 166), 8.4% had FOLR1-H and only three genes (NECTIN4, NTHL1 and SLC47A1) were significantly high. Of the 327 colorectal cancers, 8% met the criteria for FOLR1-H and 16 genes were significantly higher in FOLR1-H including NECTIN4, NTHL1, ACVRL1, ROR1/2. In 64 esophageal cancers 10.9% were FOLR1-H, but only 3 genes (GALNT12, ACVRL1 and NECTIN4) were significantly higher. **Conclusions:** This data suggests that cancers with significantly high expression of FOLR1 mRNA are a special subtype of tumors characterized by the expression of embryonic cell surface markers (FOLR1, TROP2, NECTIN4, ROR1/2). The pan-cancer marked overexpression of these genes suggests that cancers with FOLR1-H represent a subtype of cancers with similar biology. This subtype may benefit from combination therapy targeting more than one of these markers (e.g. anti-FOLR1 with anti-TROP2, or anti-NECTIN4) and clinical trial with such combination may be justified. Research Sponsor: None.

3137 Poster Session

Multi-omics cohort-based prediction model for early relapse of hepatocellular carcinoma post-surgery. First Author: Penghong Song, The First Affiliated Hospital, School of Medicine, Zhejiang University, Hangzhou, China

Background: Postoperative early relapse (PER) of hepatocellular carcinoma (HCC) presents significant challenges in clinical management. Identifying reliable predictive markers and therapeutic strategies for PER is crucial for improving patient outcomes. **Methods:** We constructed a predictive model for PER using multi-omics data from 177 HCC patients with follow-up information. Transcriptomic and proteomic profiling of HCC tissues was performed, followed by differential expression analysis and Weighted Gene Co-expression Network Analysis (WGCNA) to identify molecular markers associated with PER. Univariate, LASSO, and multivariate Cox regression analyses were employed to refine the marker set, resulting in a three-gene signature. The model's accuracy was validated using a proteomic cohort and The Cancer Genome Atlas (TCGA) database. Functional enrichment, drug sensitivity, and immune infiltration analyses were conducted to explore the biological characteristics and therapeutic implications of high-PER risk patients. Patient-derived organoid (PDO) models were used for further validation. **Results:** We identified 31 molecular markers associated with PER, which were narrowed down to a robust three-gene signature (MIK67, GPD1, and MBL2) with an area under the curve (AUC) of 0.868 for predicting early relapse. Functional enrichment analysis revealed that high-PER risk patients exhibited enhanced DNA damage repair and cell cycle pathways. Drug sensitivity analysis suggested potential benefits from gemcitabine and paclitaxel, which were validated using PDO models. Immune infiltration analysis showed reduced NK cell and M2 macrophage infiltration in high-PER risk patients, confirmed by single-cell sequencing and immunohistochemical validation. **Conclusions:** This study provides a novel multi-omics-based predictive model for early recurrence in HCC, highlighting potential therapeutic options for high-risk patients. The findings underscore the importance of DNA damage repair and cell cycle pathways in PER and suggest targeted therapies that could improve clinical outcomes for high-PER risk patients. Research Sponsor: None.

3138 Poster Session

Comprehensive clinicogenomic profiling of signet ring cell carcinoma across multiple organ sites. First Author: Lawrence Wen Wu, Columbia University Irving Medical Center, New York, NY

Background: Signet ring cell carcinoma (SRCC) is a rare, aggressive histological subtype of adenocarcinoma that is associated with earlier age of onset and poor prognosis. It most commonly arises from the stomach but can originate elsewhere. Few studies have compared molecular alterations in SRCC across various primary sites. Utilizing the American Association for Cancer Research (AACR) Project Genomics Evidence Neoplasia Information Exchange (GENIE) v17.0, we performed a comprehensive analysis of clinicogenomic variables in SRCC across different primary sites. **Methods:** The AACR GENIE v17.0 database was used to select tumor samples classified as SRCC by the Oncotree Code. We excluded primary SRCC sites with $<$ 10 tumor samples. Samples were analyzed for clinicogenomic characteristics including gender, race, ethnicity, age at sequencing, and oncogenic molecular alterations by OncoKB classification (somatic mutations, structural variants, copy number alterations). We classified "early onset" SRCC as age of sequencing $<$ 50. Chi-square testing was used to compare categorical variables, and Benjamini-Hochberg procedure was used to control the false discovery rate (statistical significance for $q < 0.05$). **Results:** From 355 patients with SRCC, 358 tumor samples were analyzed, with the following distribution among primary sites: stomach (n = 168), colon/rectum (n = 125), appendix (n = 38), and bladder (n = 27). There were high rates of early onset SRCC in the stomach (29.2%), colon/rectum (47.2%), and appendix (36.8%). Female gender was numerically higher in stomach (56.9%) and appendix (55.3%) SRCC cases compared to colon/rectum (47.2%) and bladder (33.3%) SRCC cases. The most prevalent altered genes included *TP53* (45.0%), *CDH1* (19.4%), *ARID1A* (14.8%), *KRAS* (12.9%), and *SMAD4* (12.3%). There was differential enrichment of molecular alterations across various sites in *TP53*, *CDH1*, *KRAS*, *SMAD4*, *TERT*, *APC*, and *BRAF* ($q <$ 0.05). **Conclusions:** To our knowledge, this study represents the largest molecular analysis of SRCC across multiple organ sites, revealing high rates of early onset SRCC and distinctive molecular alteration patterns. These findings underscore the further need to investigate functional implications and potential therapeutic targets for site-specific molecular alterations in SRCC. Research Sponsor: U.S. National Institutes of Health; 5T32CA203703-09.

Highlighted clinicogenomic features.

Clinical Variable/ Alteration	Total	Stomach	Colon/ Rectum	Appendix	Bladder	q-value
Age of Sequencing <50 (%)	34.4%	29.2%	47.2%	36.8%	3.7%	<0.001
Female Gender (%)	51.5%	56.9%	47.2%	55.3%	33.3%	0.24
TP53	45.0%	40.5%	48%	31.6%	77.8%	0.011
CDH1*	19.4%	26.2%	3.4%	7.9%	63%	<0.001
KRAS	12.9%	8.3%	17.6%	26.3%	0%	0.0055
SMAD4*	12.3%	3.6%	20.3%	21.0%	11.1%	<0.001
TERT*	8.7%	1.5%	7.1%	0%	66.7%	<0.001
APC	5.7%	1.2%	15.3%	0%	0%	<0.001
BRAF	3.9%	1.2%	8.8%	2.6%	0%	0.017

*Not all samples profiled for specific alteration; % reflects percentage of samples with alterations of those profiled.

3139 Poster Session

Comparative analysis of T-cell subsets and vessel features in matched primary colorectal tumors and corresponding resected liver metastases. First Author: Pia J. Osterlund, Tampere University Hospital and Tampere Univeristy, Tampere, Finland

Background: Outcome after liver resection for colorectal cancer metastases (CRLM) is partly determined by factors such as the number, size, and vitality of the metastases, as well as the T- and N-stage of the primary tumor. The tumor microenvironment—particularly immune cell infiltration and vascular features—also influences outcome. Data on how these factors compare between paired primary colorectal tumors and matched CRLM are limited. **Methods:** We used TMAs from matched primary tumors and CRLM samples of 50 patients, of which 15 were untreated and 35 had received neoadjuvant therapy (cytotoxic $\pm$ VEGF-/EGFR-targeted agents) before liver resection. Each tumor consisted of 1–3 tissue cores (1 mm) from both the tumor center and the invasive margin. Multiplex immunofluorescence was performed to assess T-cell (e.g., CD3, CD4, CD8, PD1, FOXP3, TIM3, Ki67), and vessel (claudin-5, αSMA, PDGFRβ) markers. Nonparametric Wilcoxon signed rank and Spearman correlations were used for cell density comparisons. Cox regression for continuous variables was used for disease-free survival (DFS) associations. **Results:** We observed significantly lower densities of CD3+CD8+Ki67+, CD3+CD4+Ki67+, and CD3+CD4+FOXP3+ cells in CRLM than in paired primary (all $p <$ .006) in both untreated and pretreated cohorts. The αSMA+PDGFR$\beta-$ vessel subset was more prevalent in CRLM compared with the primary tumor in the untreated cohort ($p <$ .001). In the untreated cohort, larger vessel size in CRLM (but not in the primary tumor) showed a positive correlation with CD3+CD8+PD1+, CD3+CD4+PD1+, and CD3+CD4+FOXP3+ densities (Spearman r = .54–.60, p = .02–.04). In the pretreated cohort, higher tumor vitality and/or CDX2+ expression in CRLM (indicative of poor treatment response) were each negatively correlated with cytotoxic (CD3+CD8+) and helper T-cell (CD3+CD4+) subsets (r = -.42 to -.63, $p <$ .01). DFS after metastasectomy was associated with vessel and T-cell features. Regarding vessel metrics in the small untreated cohort, αSMA–PDGFR$\beta-$ vessel subset in primary showed a negative trend (p = .06) as did smaller vessel size in CRLM (p = .06). CD3–CD4+TIM3+ in CRLM was negatively associated with DFS in pretreated (p = .04), with a trend also in untreated (p = .10). **Conclusions:** Densities of certain T-cell subsets are significantly lower in matched CRLM than in primary tumors indicating immune desert phenotype. Vessel subset profiling suggests differences between primary tumors and CRLM, possibly relevant for treatment response. Poor pretreatment effect, i.e., high vitality and CDX2+ density in CRLM, was negatively correlated with several T-cell subsets, a correlation not seen in untreated. The poor prognosis association of CD3–CD4+TIM3+ cells in CRLM merits further investigation. Research Sponsor: Finska Läkaresällskapet; Sigrid Juselius Stiftelse; Medicinska understödsföreningen Liv & Hälsa; The Finnish Cancer Foundation; The Competitive State Research Financing of the Expert Responsibility Area of Tampere and Helsinki; Tampere University Hospital Fund; Mary and Georg C. Ehrnrooth Foundation; Radiumhemmets fonder; Cancerfonden; Suomen onkologiayhdistys.

3140 Poster Session

Characterisation of ductal carcinoma in situ (DCIS) using mass spectrometry imaging towards near realtime margin assessment. First Author: Hemali Chauhan, Imperial College, London, London, United Kingdom

Background: Imprecision in breast-conserving surgery leads to high national average high rates of reoperative intervention. In line with updated margin guidelines, accurate differentiation between non-invasive and invasive breast cancer is essential. This study aimed to assess whether mass spectrometry can distinguish between normal breast tissue, benign, non-invasive and invasive disease towards the development of an intraoperative margin assessment tool. **Methods:** Breast tissue samples were collected from patients undergoing mastectomy. Samples were flash-frozen, sectioned, and analysed using a Xevo G2-XS QTof mass spectrometer (Waters Corp.). Selected sections were ionised using a pulsed optical parametric oscillator laser (OpoletteTM 2731/3034, OPOTEK) which operated at 2940 nm wavelength and 20 Hz repetition rate. The laser focused on the tissue through a 20 mm focal distance convex lens generating aerosol which was aspirated into the spectrometer. The data was combined using spatial distribution and chemical information from characteristic ions to generate 2D chemical images and labelled using consecutive H&E-stained sections annotated by a Consultant Histopathologist for ground truth cross-validation. **Results:** Over 1 million mass spectra were collected from imaging 52 breast tissue sections. This includes 720 mass spectra from 31 DCIS breast tissue sections, compared to 6 spectra from 2 DCIS breast tissue samples in previous work. A pixel size of 50 μm and scan rate was 250 μm/s was utilised. An ex-vivo classification model was built using n=6,796 and achieved $>$99% sensitivity for tumour detection (DCIS and IBC) and 100% specificity for identifying normal tissue. Principal Component Analysis demonstrated accurate separation of IBC, DCIS, benign breast disease, and normal breast tissue. Six possible metabolites were identified following Recursive Feature Elimination (RFE) was used to identify the most significant features which differentiate the tissue types, these were annotated using the Lipid Maps database (http://www.lipidmaps.org/) (Table 1). Cancerous tissue showed higher levels of structural lipids (600-900 Da), while normal/benign breast tissue had higher levels of small metabolites (50-300 Da) and fatty acids (200-400 Da). **Conclusions:** Mass spectrometry imaging enables accurate differentiation of IBC, DCIS, benign breast disease, and normal breast tissue. Research Sponsor: NIHR Imperial Biomedical Research Centre.

Biological features identified from the most significant RFE selected features.

m/z value	Annotation	Delta	Theoretical m/z	Ion	Class
255.2324	Palmitic acid	0.0006	255.2330	M-H	Fatty acid
297.2751	FA 19:0	0.0037	297.2799	M-H	Fatty acid
307.2019	FA 16:0	0.0026	307.2046	M+Cl	Fatty acid
766.5392	PE 38:4	0	766.5392	M-H	PE
843.5053	PI 35:4	0.0025	843.5029	M-H	PI
891.7444	TG 52:3	0.0003	891.7447	M+Cl	TG

3141 **Poster Session**

A minimal comprehensive somatic panel to aid clinical decision making in a low cost setting. First Author: Urvashi Bahadur, Strand Life Sciences, Bengaluru, India

Background: Large next-generation sequencing (NGS) panels (> 300 genes) offer multiple potential therapeutic options for patients with metastatic cancer. However a large portion of the population in developing countries is unable to avail the benefits of such testing due to limited availability of many drugs or suitable clinical trials, coupled with the high cost of these tests. There is an urgent need to offer a compact, affordable and robust testing solution which can offer expanded but feasible therapeutic options. Hence we decided to develop a custom mid-sized panel to fulfil these unmet requirements. **Methods:** A targeted solid tumor (DNA + RNA) panel comprising 74 genes (SA74) was designed to cover all genes with a Tier 1 drug recommendation for therapy, evaluating single nucleotide variants (SNV), indels, copy number variants (CNV) and gene fusions (GF). We also included certain Tier2 genes for prognosis or added clinical impact. GFs were evaluated by RNA. Inferior sample quality often results in poor quality data, so we added a DNA component for tiling select intronic regions to identify GF which to be used when RNA could not be analyzed. The analytical sensitivity was > 99% for SNV/Indels with a 5% limit of detection, > 99% for CNV and GF. The clinical sensitivity was 100% for SNV, 95% for indels, 84.2% for CNV, 100% for RNA GF and 70% for DNA GF. **Results:** 239 formalin-fixed paraffin embedded tumor samples were evaluated using SA74 and the data was scored for actionability across tumor types. This was compared with data from 706 samples across multiple cancers analyzed using the Illumina TSO500 panel. The average number of actionable alterations was 1.1 in SA74 and 1.6 in TSO500. The overall actionability (cases with at least one Tier1 or Tier2 actionable variant) of SA74 was 63.4%; while that of TSO500 was 78.3%. Of this, the overlap with SA74 was 73.7%. The actionability in the remainder was due to Tier2 genes with lesser evidence altering the same pathway as an approved drug target or targeting investigational drugs. The actionability for each cancer type was calculated and found to be: colon (34.1%; n = 44), non-small cell lung (NSCLC) (78.4%; n = 37), breast (91.7%; n = 24), carcinoma of unknown primary (CUP) (45%; n = 20), uterine (53.3%; n = 15), gallbladder (75%; n = 12) and sarcoma (40%; n = 10), among others. Smaller panels often do not include CNV and GF. Addition of these variant types increased actionability across cancers. The lack of CNV and GF would have decreased total actionability from 62.9% to 54.5%. NSCLC and CUP were most impacted with a difference in actionability of 16.2% and 15% respectively. GF increased actionability mainly in NSCLC, while CNV contributed to increases across all cancers. **Conclusions:** SA74 demonstrated high actionability across cancers. It therefore presents a practical alternative to large panel testing by optimizing actionability and affordability, useful in a cost-sensitive setting. Research Sponsor: None.

3142 **Poster Session**

Clinical performance of Signatera Genome assay in a cohort of patients (pts) with solid tumors. First Author: Mridula Annette George, Rutgers Cancer Institute of New Jersey, New Brunswick, NJ

Background: Circulating tumor DNA (ctDNA) has emerged as a powerful, minimally invasive biomarker of treatment response and pt prognosis. Signatera, a tumor-informed, mPCR-NGS ctDNA assay, offers high sensitivity and specificity for detecting molecular residual disease (MRD). Signatera (exome) uses its proprietary approach to select a highly curated set of tumor variants, followed by deep sequencing of plasma libraries at >100,000x per variant. Signatera Genome uses the same proven technology and may provide an advantage over exome in certain cases. However, beyond analytical improvements, it remains unclear if Signatera Genome provides superior performance and utility compared to the clinically validated exome-based version in the clinical setting. In this study, we assessed the clinical performance of the Signatera Genome assay in a cohort of pts with solid tumors. **Methods:** We performed a retrospective analysis of clinically annotated residual pt samples from commercial ctDNA testing (Signatera, exome-based, 16-plex mPCR-NGS assay). Adjuvant treatment decisions and ctDNA-cadence of testing were at the provider's discretion. Signatera Genome assays were designed, consisting of 64 high-quality variants, from the respective pts' matched tumor and normal whole genome sequencing data. These assays were used to detect ctDNA in the associated pts' plasma utilizing a sample calling strategy that combined the target confidences and sample-level noise into a final confidence score. ctDNA concentration was measured in mean tumor molecules per mL of plasma (MTM/mL). Longitudinal plasma samples represented postoperative time points until recurrence/end of follow-up. The correlation between any time postsurgical ctDNA positivity and recurrence-free survival (RFS) was assessed using Cox regression analysis. **Results:** The Signatera Genome assay achieved a high analytical sample-level specificity of 99.8% (healthy subjects). Clinical performance was assessed in a real-world cohort of >300 pts with several cancer types, including breast cancer, non-small cell lung cancer (NSCLC), melanoma, and renal cell carcinoma (RCC). Among pts with relapse, the Signatera Genome assay detected ctDNA ahead of clinical recurrence as confirmed by imaging. Pts with postsurgical ctDNA-positivity demonstrated significantly inferior RFS compared to ctDNA-negative pts. This trend was consistent across all cancer types investigated. Multivariate analysis adjusted for tumor type and stage revealed ctDNA-positivity to be the most significant prognostic factor associated with RFS. Performance metrics by cancer type will be presented. **Conclusions:** Here we report the largest Signatera Genome ctDNA study to date across multiple solid tumor histologies. The data indicate robust performance and concordance with Signatera Exome. Prospective clinical trials are underway evaluating clinical utility. Research Sponsor: None.

3143 **Poster Session**

Landscape of genomic alterations in genes implicated in the regulation of hypoxia inducible factor (HIF) signaling: A pooled analysis of two pan-cancer cohorts. First Author: Wassim Daoud Khatoun, Dana-Farber Cancer Institute, Boston, MA

Background: HIF2 alpha inhibitors (HIF2i) have been recently approved for VHL-related tumors, especially clear cell renal cell carcinoma (ccRCC). Alterations in genes that regulate HIF signaling may modulate response to HIF2i and may help identify tumor types that could benefit from new therapeutic approaches targeting HIF activity. Here, we describe the landscape of these alterations across different cancer types. **Methods:** This study included patients (pts) from the TCGA PanCancer Atlas and GENIE Cohort v17.0, across all cancer types. All pts underwent Next Generation Sequencing or OncoPanel analysis of their tumors. Alterations in genes related to the HIF pathway (*VHL*, *EPAS1*, *EGLN1*, and *EGLN2*) and citric acid cycle (*SDHA*, *SDHB*, *SDHC*, *SDHD*, *SDHAF1*, *FH*, *IDH1*, *IDH2*, and *MDH2*) were screened, and only driver mutations, identified by OncoKB, CIViC Variants, My Cancer Genome, and the available literature, were included. Pts with a mutation in at least one gene were included. Mutation frequencies across different cancer types were analyzed for each cohort, then pooled together. **Results:** We identified a total of 10,953 and 167,073 pts on TCGA and GENIE, respectively. Mutation frequencies for different cancer types are shown in the Table. Among the mutated cases, *IDH1* was the most altered gene in glioma (90.20% [95% Confidence Interval (CI): 90.19; 90.21]), hepatobiliary cancers (75.48% [75.40; 75.56]) and melanoma (55.75% [55.57; 55.92]), and the second most common in leukemia (39.86% [39.68; 40.04]), while *IDH2* was the most altered in leukemia (57.52% [57.34; 57.70]), and the second most common in glioma (5.25% [5.24; 5.25]), and hepatobiliary cancers (19.10% [19.04; 19.17]). *SDHA* was the second most altered gene in melanoma (12.95% [12.87; 13.03]). In RCC, *VHL* was the most mutated gene (92.79% [92.78; 92.79]), followed by *FH* (2.41% [2.40; 2.41]). *EPAS1* was mutated in 64.19% of cases with driver mutations in miscellaneous neuroepithelial tumors (MNET) ([57.07; 71.31]), but not in RCC. Among the altered cases in pheochromocytoma, *SDHB* was the most commonly altered gene (39.71% [35.31; 44.11], followed by *VHL* (18.41% [15.92; 20.91]). *SDHB* was also the second most common gene to be mutated in MNET (23.12% [19.37; 26.86]). **Conclusions:** In this analysis, mutations in HIF-regulating genes were detected in multiple cancers, and were not limited to those studied in the context of HIF inhibitors. Further research is required to elucidate whether these gene alterations sensitize tumors to HIF inhibition. Research Sponsor: None.

Pooled mutation frequencies for all considered genes in different cancer types.

Cancer Type	N	% Pooled Mutation Frequency of any gene	95% CI
RCC	3662	39.76	39.74; 39.77
Glioma	12657	23.67	23.67; 23.67
Leukemia	1857	15.49	15.47; 15.50
Hepatobiliary Cancer	4234	11.18	11.18; 11.19
MNET	253	8.61	8.54; 8.68
Pheochromocytoma	198	5.63	5.56; 5.69
Melanoma	6589	4.34	4.34; 4.34

3144 **Poster Session**

Analytical validation of EPISEEK, an epigenomic blood-based assay for multicancer detection. First Author: Thi Hanh Pham, Precision Epigenomics Inc, Tucson, AZ

Background: Early cancer detection significantly improves treatment outcomes and survival rates. However, cancer screening faces key challenges: (1) current tests detect only 14% of new cases and cover a limited range of cancers, (2) each cancer requires its own costly and complex screening process, (3) limited patient awareness of suitable screenings, and (4) poor adoption among marginalized and underinsured groups. EPISEEK was developed for multicancer detection using minimal cell-free DNA from plasma. Here, we present validation study results assessing its robustness and accuracy across 20+ cancer types and stages. **Methods:** EPISEEK is a cfDNA-based methylation assay optimized for 20 ng of cfDNA input from plasma. Plasma cfDNA underwent bisulfite conversion followed by methylation-specific quantitative PCR targeting 10 cancer biomarkers and 3 internal control markers. 251 plasma samples from four cancer stages across 25 cancer types, and 57 samples from individuals over 40 with no known cancer history, were used to establish reference ranges and assess assay specificity and sensitivity. Additional contrived and clinical samples were used to determine the assay's analytical LOD, reproducibility and stability. **Results:** 57 non-cancer samples were used to train the classifier, achieving 99% specificity at a 95% confidence level. Accuracy testing included 251 cancer samples representing > 20 primary cancer sites, including lung, colon, cervix, esophagus, head and neck, kidney, liver, breast, bladder, skin, testis, thyroid, ovary, pancreas, prostate, stomach, brain, bone marrow, and others. The cancer samples spanned all stages: I (29%), II (13%), III (29%), IV (22%), and cases with missing stage data (6.7%). Sensitivity increased with advancing stage, with observed sensitivity rate of 52%. By stage, observed sensitivity was stage I: 42%, stage II: 46%, stage III: 57%, and stage IV: 64%. Due to the limited and non-representative sample distribution for a typical multicancer screening population, SEER data were utilized to estimate EPISEEK's real-world performance by adjusting tumor incidence and stage when estimating positive predictive value and negative predictive value. At 99% specificity and based on adjusted performance, EPISEEK achieved a positive predictive value (PPV) of 40% and a negative predictive value (NPV) of 99%. Seven markers were detectable with < 0.1 ng DNA, while the remaining three markers had an LOD95 of 0.1–0.37 ng. Comparing Ct values of each cancer target both intra and inter runs, EPISEEK demonstrated high reproducibility with standard deviation of 0.383 (high positive), 0.232 (low positive) and 1.063 (negative samples). **Conclusions:** EPISEEK is a sensitive, specific, accurate, and reproducible multicancer detection test. Compared to comprehensive genomic profiling techniques, it offers an affordable testing option for broader populations with a fast turnaround time. Research Sponsor: None.

3145 **Poster Session**

Small nucleolar RNAs (snoRNAs) expression and effects on patient (pt) outcomes in metastatic colorectal cancer (mCRC): Data from CALGB (Alliance)/SWOG 80405. First Author: Francesca Battaglin, Division of Medical Oncology, Norris Comprehensive Cancer Center, Keck School of Medicine, University of Southern California, Los Angeles, CA

Background: SnoRNAs are non-coding RNAs that primarily guide the chemical modification of ribosomal RNA. Emerging evidence suggests snoRNAs play critical roles in cancer, including CRC, by regulating cell proliferation, apoptosis and tumor progression. Aberrant snoRNA expression has been linked to CRC development and poor prognosis, offering potential as diagnostic biomarkers and therapeutic targets. We investigated whether the tumor expression levels of 3 types of snoRNAs (SCARNA, SNORA, SNORD) affect treatment response in pts enrolled in CALGB/SWOG 80405 (NCT00265850). **Methods:** 433 mCRC pts treated with bevacizumab (bev, n = 226) or cetuximab (cet, n = 207) in combination with first-line chemotherapy were analyzed. RNA was isolated from FFPE tumor samples and sequenced on the HiSeq 2500 (Illumina). 422 snoRNAs were evaluated (23 SCARNA, 140 SNORA, 259 SNORD). Overall survival (OS) and progression-free survival (PFS) were compared across tertiles of gene expression (high [H], medium [M], low [L]) by multivariable Cox proportional hazards models adjusted for age, sex, ECOG performance status, tumor side, number of metastatic sites, *KRAS*, CMS subtypes, and treatment. Interaction tests for the predictive effect (bev vs cet) were performed. *P*-values were corrected for multiple testing using the Benjamini-Hochberg approach ($q < 0.05$). **Results:** Only SCARNA21 achieved statistical significance for OS after false discovery rate (FDR) adjustment. Tumors with H levels of SCARNA21 had shorter survival compared to tumors with M or L expression (median OS 24.4 vs 32.4 vs 33.9 months, respectively; $P = 0.0015$, $q = 0.033$), independent of treatment. No snoRNAs achieved FDR significance for PFS. However, several snoRNAs showed significant treatment interactions with biologic agents. SCARNA6-H and SCARNA5-H tumors had longer PFS and OS when treated with cet, but shorter PFS and OS when treated with bev, compared to the M and L expression groups (PFS interaction $q = 0.0067$ and 0.045, respectively; OS interaction $q = 0.022$ and 0.034, respectively). SCARNA7 also showed significant treatment interaction for OS, favoring cet in the H expression group ($q = 0.018$); the opposite was observed for SNORA63B, SNORA63D, SNORA35B, and SNORA36C ($q = 0.027$, 0.027, 0.027 and 0.047, respectively). No significant results were observed for any of the tested SNORDs. **Conclusions:** SnoRNAs dysregulation affects key pathways such as cell cycle control and immune evasion, making them promising players in CRC biology. Our study highlights the prognostic and predictive potential of specific snoRNAs in mCRC. Notably, high SCARNA21 expression was linked to shorter OS, while SCARNA5 and 6 showed predictive value for treatment response, indicating their potential for guiding treatment decisions. Further validation is needed to confirm these findings, and mechanistic studies are warranted. Research Sponsor: National Cancer Institute; Genentech; https://acknowledgments.alliancefound.org.

3146 **Poster Session**

Impact of MGMT methylation on overall survival in solid tumors: A systematic review and meta-analysis. First Author: Abdulla Alzibdeh, King Hussein Cancer Center, Amman, Jordan

Background: The protein O6-alkylguanine-DNA-alkyltransferase (AGT), encoded by the MGMT gene, plays a crucial role in DNA repair by singularly removing alkyl lesions from the O6 position of guanine, maintaining genomic stability. Loss of MGMT expression, often due to promoter methylation, is linked to enhanced sensitivity to chemotherapy. While MGMT methylation has been observed in various cancers, its impact on overall survival (OS) in solid tumors remains uncertain. **Methods:** According to PRISMA guidelines, we selected studies from PubMed that examined the impact of MGMT methylation on OS in adult patients with solid tumors. Data were extracted where MGMT methylation status was clearly defined, and OS was reported through hazard ratios (HR) from either uni- or multivariable analyses. We employed R version 4.4.2 and the 'meta' package for our meta-analysis, using both fixed-effects (Mantel-Haenszel method) and random-effects (DerSimonian and Laird's method) models based on the I^2 statistic for heterogeneity. Subgroup analyses were conducted by cancer type, and publication bias was assessed through funnel plot inspection and Egger's regression. Statistical significance was set at $p < 0.05$. **Results:** The meta-analysis included 23 studies, with a total of 3,410 participants across all studies. The studies included an array of cancers, the most common being colorectal (n = 7), then head and neck (n = 6), and lesser-represented groups like pancreatic neuroendocrine (n = 2) and others. The pooled analysis using a random-effects model demonstrated that MGMT methylation status was not significantly related with OS (HR of 1.1967; 95% CI: 0.9004 to 1.5904; p = 0.2040). Subgroup analysis revealed that the impact of MGMT methylation on survival varied significantly across different types of cancer. No significant association was yielded between MGMT methylation and OS for colorectal cancer (HR of 0.9496; 95% CI: 0.6252 to 1.4422), head and neck cancer (HR of 1.1520; 95% CI: 0.8223 to 1.6137), NSCLC (HR of 1.0479; 95% CI: 0.3343 to 3.2841) and pancreatic neuroendocrine cancer (HR of 1.5541; 95% CI: 0.6493 to 3.7195). Conversely, a significant association was yielded for less common cancers, including melanoma, biliary and cervical cancers. The funnel plot and Egger's test for publication bias (t = -0.3999, p = 0.6933) suggested no significant asymmetry, indicating minimal publication bias within this meta-analysis. **Conclusions:** Our findings indicate that MGMT methylation does not universally predict OS across all solid tumors. The variability in survival impact across different cancer types suggests that the prognostic significance of MGMT methylation may be context-dependent, emphasizing the need for tumor-specific studies. Research Sponsor: None.

3147 **Poster Session**

A phase II basket trial evaluating the efficacy of tasurgratinib (E7090) in patients with advanced solid tumors with fibroblast growth factor receptor (FGFR) gene alteration: FORTUNE study. First Author: Junichi Matsubara, Department of Clinical Oncology, Kyoto University Hospital, Kyoto, Japan

Background: Tasurgratinib is an orally available selective inhibitor of FGFR1-3 tyrosine kinase and is approved in Japan for biliary tract cancer with *FGFR2* fusions or rearrangements based on a global phase 2 study. We previously identified *FGFR* gene alterations that are highly sensitive to tasurgratinib using a high-throughput functional evaluation method (MANO method) (npj Precision Oncology [2021] 5:66). We conducted a single-arm, investigator-initiated multicenter phase 2 basket trial to evaluate the efficacy and safety of tasurgratinib in patients (pts) with advanced solid tumors harboring *FGFR* gene alterations, including alterations identified by MANO method. **Methods:** Pts with advanced solid tumors with *FGFR* gene alterations detected by next-generation sequencing assays received tasurgratinib 140 mg QD. Pts were allocated to each Group based on *FGFR* gene alteration (Group A: *FGFR1-3* fusion, Group B: *FGFR1-3* sensitive mutations to tasurgratinib determined by MANO methods, Group C: *FGFR1-3* activating mutation not applicable to group B or *FGFR1, 2* gene amplification, Group D: cholangiocarcinoma with *FGFR2* fusion and previous treatment with a FGFR inhibitor except for tasurgratinib). The primary endpoint for Groups A, B, and C was objective response rate (ORR) by independent central review (ICR). Group D was an exploratory cohort, and ICR was not performed. The secondary endpoints included ORR by investigator assessment (IA), progression-free survival (PFS), overall survival, and safety. The threshold and expected response rates were 5% and 30%, respectively. With the one-sided significance level of 5%, the target enrolments were 10 (62% power), 15 (87%), and 15 pts (87%) in Groups A, B, and C, respectively. Group D's target number was 1 to 5 pts without a statistical hypothesis. **Results:** From June 2021 to December 2022, 46 pts were registered. The full analysis set includes 41 pts (10, 15, 15, and 1 in Groups A, B, C, and D, respectively). The most common primary sites were brain in 4 pts (40.0%) in Group A, biliary tract in 4 pts (26.7%) in Group B, and esophagus/stomach in 4 pts (26.7%) in Group C. ORRs by ICR in Group A, B and C were 20.0% (90% CI: 3.7-50.7, p = 0.0861), 20.0% (90% CI: 5.7-44.0, p = 0.0362), 6.7% (90% CI: 0.3-27.9, p = 0.5367), respectively. ORRs by IA in Group A, B, C, and D were 20.0% (95% CI: 2.5-55.6), 40.0% (95% CI: 16.3-67.7), 13.3% (95% CI: 1.7-40.5) and 0.0% (95% CI: 0.0-97.5), respectively. Median PFS by IA in Groups A, B, C, and D were 2.5 (95% CI: 1.4-5.7), 7.2 (95% CI: 1.7-8.2), 2.2 (95% CI: 1.9-3.7) and 5.7 months (95% CI: not evaluable), respectively. There was no new safety signal compared to previous reports. **Conclusions:** In Group B, the primary endpoint was met. Tasurgratinib demonstrated clinical activity in pts with selected FGFR-mutated tumors. Further study is needed to validate these findings. Clinical trial information: NCT04962867. Research Sponsor: Eisai; Japan Agency for Medical Research and Development; 20lk1403036h0001.

3148 **Poster Session**

Efficacy and safety of larotrectinib in patients with non-primary central nervous system TRK fusion cancer: An updated analysis. First Author: Rui-Hua Xu, Sun Yat-sen University Cancer Center, Guangzhou, China

Background: *NTRK* gene fusions are oncogenic drivers in various tumor types. Larotrectinib (laro) is the first-in-class, highly selective, central nervous system (CNS)-active TRK inhibitor approved for tumor-agnostic use in patients (pts) with TRK fusion cancer based on a robust and durable objective response rate in pts with various cancers. Here, we report updated long-term efficacy and safety data in adult and pediatric pts with non-primary CNS TRK fusion cancer treated with laro. **Methods:** Pts with TRK fusion cancer enrolled in 3 laro clinical trials (NCT02637687 [SCOUT], NCT02576431 [NAVIGATE], NCT02122913) were included. Laro was administered at 100 mg twice daily (BID) and 100 mg/m^2 BID in most adult and pediatric pts, respectively. Responses were independent review committee (IRC)-assessed per RECIST v1.1. Pts enrolled in SCOUT were permitted to stop laro in the absence of on-treatment progression ("wait-and-see"). The data cutoff was July 20, 2024. **Results:** At data cutoff,304 pts were eligible for efficacy assessment by IRC; 25 pts had known CNS metastases at baseline. Median age was 45 years (range 0–90). There were 28 different tumor types, including soft tissue sarcoma (24%), infantile fibrosarcoma (16%), lung (11%), and thyroid (10%). A total of 101 pts (33%) received no prior systemic therapies in the metastatic/unresectable setting; 115 (38%) received 2 or more. *NTRK* gene fusions were detected by next-generation sequencing (NGS) in 267 (88%) pts. The overall response rate was 65% (95% confidence interval [CI] 59–70): 66 (22%) complete responses (CR), 20 (7%) pathological CR, 112 (37%) partial responses, 56 (18%) stable disease, 32 (11%) progressive disease, and 18 (6%) not evaluable/undefined. Median time to response was 1.8 months (mo; range 0.9–22.9). Median duration of response (DoR), progression-free survival (PFS), and overall survival (OS) were 43 mo (95% CI 34–not estimable), 28 mo (95% CI 22–38), and not reached, respectively, at median follow-ups of 45, 42, and 57 mo. The 4-year rates for DoR, PFS, and OS were 48% (95% CI 40–57), 39% (95% CI 32–46), and 63% (95% CI 57–68), respectively. Median duration of treatment was 19 mo (range 0–100+). Fifty-five of 99 pediatric pts in SCOUT had participated in "wait-and-see"; the median duration of the first "wait-and-see" period was 33 mo (range 1–72). At data cutoff, 83 pts (27%) remained on trial (either on treatment or in "wait-and-see"). Treatment-related adverse events (TRAEs) were mainly Grade 1/2 (n = 189; 62%). Grade 3/4 TRAEs occurred in 71 (23%) pts. Five (2%) pts discontinued due to TRAEs. **Conclusions:** Laro continues to demonstrate rapid and durable responses, extended survival, clinical benefit, and a favorable safety profile in pts with TRK fusion cancer. This data supports the wider adoption of NGS panels that include *NTRK* gene fusions to identify pts who may benefit from treatment with TRK inhibitors. Clinical trial information: NCT02637687, NCT02576431, NCT02122913. Research Sponsor: Bayer HealthCare Pharmaceuticals, Inc.

3149 **Poster Session**

Early prediction of prognosis in advanced solid tumor patients using tumor growth rates with *g* score in early phase clinical trials. First Author: Kana Kurokawa, Department of Advanced Medical Development, The Cancer Institute Hospital of Japanese Foundation for Cancer Research, Tokyo, Japan

Background: The primary objective of early phase clinical trials is to evaluate the safety of investigational drugs, which requires participants to have sufficient expected survival durations. Tumor growth rate using *g* scores, calculated using radiographic measurements and timing after treatment, is gaining attention as a potential tool for treatment efficacy assessment. This study aims to assess the utility of *g* scores before and after treatment in predicting prognosis, and explore suitable trial candidates for accelerating drug development in early phase clinical trials. **Methods:** We retrospectively reviewed patients who participated in early phase clinical trials after standard treatment at the Department of Advanced Medical Development, The Cancer Institute Hospital of Japanese Foundation for Cancer Research between January 2020 to December 2023. A mathematical exponential growth model was applied to estimate tumor growth rates (*g*) based on radiographic tumor measurements and interval time: $f(t) = \exp(g \cdot t)$, with pre-*g* scores derived from measurements before the clinical trial and post-*g* scores from measurements after trial initiation. Pre-*g* scores were calculated using trial baseline computed tomography (CT)s and the most recent CTs before trial enrollment, while post-*g* scores were calculated using baseline CTs and the first evaluated CTs after treatment. We defined dichotomized *g* score levels (high/low) using the time-dependent ROC curve procedure. We evaluated independent predictors for survival outcomes according to each *g* score and patient characteristics. **Results:** Of the 173 cases who participated in early phase clinical trials after standard treatment, 162 cases with evaluable CT scans before and after the clinical trial were included in this study. Median time to pre-trial CT was 29 days (range, 5–202), and median time to first post-treatment evaluation was 49.5 days (range, 16–87). Log-rank testing showed both high pre-. and post-. scores correlated to shorter overall survival (OS) compared to low-score groups (HR 2.16; 95% CI 1.22-3.81; P = 0.0067, HR 2.68; 95%CI 1.84-3.90; $P < 0.001$). Multivariate analysis showed both high pre-*g* and post-*g* scores were independent predictors of shorter OS (HR 2.06, 95% CI 1.13-3.75; P = 0.019, HR 3.80, 95% CI 2.44-5.90; $P < 0.001$). **Conclusions:** This study is the first to incorporate pre-. scores as an independent prognostic factor and may serve as a valuable reference for patient enrollment in early phase clinical trials under late-line settings. Additionally, post-. scores were also identified as an independent prognostic factor across multiple cancer types in early phase clinical trials. These results indicate their potential use as surrogate endpoints to, which may help facilitate drug development. Research Sponsor: None.

3150 **Poster Session**

Picking needles in a haystack: Exploring rare variants of a pan-cancer target in the RET landscape from 229,453 adult cancer patients. First Author: Niamh Coleman, Trinity St. James's Cancer Institute, Dublin, Ireland

Background: Advances in precision oncology have led to the approval of tumor-agnostic therapies, and RET, due to its role as a driver of oncogenesis across multiple tumor types, is increasingly recognized as a pan-cancer target. RET alterations, including mutations and fusions, are relatively rare events, however, potent and selective RET inhibitors such as selpercatinib and pralsetinib have demonstrated remarkable efficacy and changed clinical practice in RET-driven NSCLC, thyroid cancer and other cancers. Here, we present a comprehensive analysis of RET alterations in pan-cancer adult malignancies. **Methods:** 229,453 samples from 196,244 patients available from AACR Project GENIE v.17 database were analyzed for the prevalence of RET mutations, fusions and copy number alterations in a range of cancer types. **Results:** A total of 7011 separate RET alterations were identified in 6690 separate pts (3%), including 660 fusions (9.4%), 5553 missense mutations (79.2%), 373 splice site mutations (5.3%), 339 truncating mutations (4.8%), 86 in-frame mutations (1.2%). Most frequent tumor types included NSCLC, colorectal cancer, melanoma, thyroid cancer, endometrial cancer and glioma (23%, 12.2%, 9.5%, 6.6%, 6.4%, 5.3% identified RET alterations, respectively). RET fusions were observed in 0.3% of tumor samples, most identified in NSCLC, thyroid and colorectal cancer (53%, 24% and 4% of identified *RET* fusions). Most fusions were considered driver events using OncoKB database (632, 96%);frequent fusion gene partners included *KIF5B, CCDC6, NCOA4*, and intragenic events (34%, 25%, 9.7%, 8% of 660 fusion samples). Of the 5553 missense mutations, most (89%) were considered variants of uncertain significance; 605 (11%) were considered oncogenic or likely oncogenic. Oncogenic missense mutations occurred across codons, most frequently involving codon 918 (n = 215, 36%; M918M/K/T/V), 648 (n = 41, 6.8%; V648I/A), 886 (n = 28, 4.6%; R886W/Q/L), 630 (n = 21, 3.5%; C630G/R/S/F/Y/W), 891 (n = 31, 5%, S891A/L/W). Documented on-target drivers of multi-kinase RET inhibitor resistance gatekeeper mutations (V804M/L), and selective RET inhibitor resistance mutations were noted in 61 samples, including G810C/S substitutions, solvent-front mutations K809R/N, activation loop mutations Y806C/N (33%, 53%, 3%, 3% of identified samples); most were classified as oncogenic or likely oncogenic (85%). **Conclusions:** RET fusions are rare events across cancers; however, most are characterized as oncogenic. RET missense mutations occur in 2.4% of malignancies, and while most RET missense variants are described as variants of uncertain significance, oncogenic RET variants are diverse, occurring across codons. We confirm multiple documented oncogenic drivers of on-target resistance, and their distinct and diverse mechanisms underline the urgent need to develop next generation RET inhibitors. Research Sponsor: None.

3151 **Poster Session**

LODESTAR: A single-arm phase II study of rucaparib in solid tumors with pathogenic germline or somatic variants in homologous recombination repair genes. First Author: Sriram Anbil, University of Pennsylvania Health System, Philadelphia, PA

Background: To explore PARP inhibitor (PARPi) utility across solid tumors and identify biomarkers that predict sensitivity. **Methods:** This single-arm phase II study assessed rucaparib monotherapy in patients with solid tumors and pathogenic variants (PVs) in *BRCA1, BRCA2, PALB2, RAD51C, RAD51D* (Cohort A) or *BARD1, BRIP1, FANCA, NBN, RAD51B* (Cohort B). The primary endpoint was ORR in Cohort A. Secondary endpoints included DCR, PFS, OS and safety. A scar-based HRD signature (HRDsig) and platinum sensitivity status were explored post-hoc. **Results:** Fifty-one patients in Cohort A and 12 in Cohort B were evaluable for efficacy. ORR of cohort A was 18% (95% CI 10-30%). A significantly higher ORR was observed with HRDsig+ tumors compared to HRDsig- tumors (32%, 95% CI 15-54, vs. 0%, 95% CI 0-14%, $p < 0.01$). In the entire study population: DCR of 65% (95% CI 53-76%), mPFS of 5.5 mo (95% CI 3.68-7.82), and mOS of 12.1 mo (95% CI 10.6 – inf). PFS and OS were significantly longer for platinum sensitive tumors (mPFS: 7.8 mo vs. 3.5 mo, p = 0.02; mOS: NR vs 5.45mo, p = 0.01). Tumor histology was not independently predictive of outcome. Tumors with PVs in Cohort A genes were more likely to be HRDsig+ than tumors with PVs in Cohort B genes. Analysis of a large commercial database showed that in non-canonical tumors with *BRCA* PVs, 30.2% were HRDsig+. **Conclusions:** Rucaparib has activity in HRDsig+ solid tumors with PVs in HRR genes, regardless of histology. Platinum sensitivity correlated with improved outcomes. Clinical trial information: NCT04171700. Research Sponsor: Clovis Pharmaceuticals.

3152 **Poster Session**

A multicenter, randomized controlled trial of intrapleural drug-loaded vesicle perfusion combined with systemic therapy for malignant pleural effusion. First Author: Jiani Wang, Department of Medical Oncology, National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China

Background: This study aimed to evaluate the efficacy and safety of drug-loaded vesicle (DLV) intrapleural perfusion combined with systemic therapy in patients with lung or breast cancer and malignant pleural effusion (MPE). **Methods:** This multicenter, randomized, controlled, open-label clinical trial included patients with pathologically confirmed lung or breast cancer and MPE requiring thoracentesis. In total, 96 patients were randomised 1:1 to arm 1 receiving DLV intrapleural perfusion (50 mL daily for four consecutive days) plus systemic therapy (ST) or arm 2 receiving interleukin-2 (IL-2) intrapleural perfusion (50 mL every three days for three sessions) with ST.The primary endpoint was the objective response rate (ORR) of pleural effusion at 4 weeks post-perfusion, while secondary endpoints included overall survival (OS) and treatment-related toxicity.The difference in ORR between the two cohorts was analyzed using the Chi-square test. Kaplan-Meier survival analysis was performed for OS comparison between the two cohorts. **Results:** A total of 91 patients were evaluated for efficacy (50 in arm 1 and 41 in arm 2). The DLV+ST arm 1 showed a significantly higher ORR for pleural effusion than the IL-2+ST arm 2 (74.0% vs. 53.7%, P = 0.043). In the survival analysis of 83 evaluable patients, median OS was 15.0 months (95% CI: 9.2–26.9) in arm 1 and 6.9 months (95% CI: 5.3–15.8) in arm 2, without a statistically significant difference (HR = 0.75; 95% CI: 0.46–1.24; P = 0.266). The 1-, 2-, and 3-year OS rates for arm 1 were 83.0% (95% CI: 72.9–94.4%), 59.6% (95% CI: 47.1–75.4%), and 51.1% (95% CI: 38.6–67.6%), compared to arm 2's 69.4% (95% CI: 55.9–86.2%), 41.7% (95% CI: 28.3–61.3%), and 33.3% (95% CI: 21.0–52.9%). Both arms had similar safety profiles, with chemotherapy-induced toxicities, including leukopenia, gastrointestinal reactions, and liver dysfunction, being the most common treatment-related adverse events. **Conclusions:** Drug-loaded vesicle intrapleural perfusion combined with systemic therapy is a safe and effective treatment option for malignant pleural effusion in patients with lung or breast cancer. This approach represents a promising treatment strategy for MPE and warrants further clinical investigation and consideration in clinical practice. Clinical trial information: ChiCTR1800017104. Research Sponsor: None.

3153 **Poster Session**

The efficacy and safety of a selective PARP1 inhibitor ACE-86225106 in patients with advanced solid tumors: Preliminary results from a first-in-human phase 1/2 study. First Author: Jiongjie Chen, Acerand Therapeutics (Hong Kong) Limited, Shanghai, China

Background: ACE-86225106 is a highly selective PARP1 inhibitor, exhibiting high potency in enzymatic and DNA-trapping assays of PARP1, while maintaining significant selectivity over PARP2. Pre-clinical studies with ACE-86225106 have demonstrated strong anti-cancer activities in *in vivo* CDX models, with excellent tolerability. Here we report the preliminary clinical data of ACE-86225106 from the ongoing first-in-human study (NCT06380660). **Methods:** This is a multicenter, open-label, phase1/2 study of ACE-86225106 in adult patients with locally advanced (unresectable) or metastatic solid tumors. Phase 1 includes a typical "3+3" dose escalation and backfill module, followed by a dose expansion module in phase 2. The primary objective is to assess safety, tolerability, PK/PD profile, and pre-liminary efficacy of ACE-86225106 as a monotherapy. **Results:** As the data cut-off (23 Jan 2025), 10 patients received ACE-86225106 at a dose of 5mg, 10mg or 20mg QD, and 5 patients backfilled at a dose of 10mg QD. Median number of prior therapy lines was 3 (range 2-12). Two patients (squamous lung cancer and breast cancer each) did not complete the DLT evaluation period due to disease progression and were replaced. No DLTs were reported as of data cut-off. Among total fifteen patients (10 patients) who received at least one dose of ACE-86225106, no Grade 3 or higher treatment-related adverse events (TRAEs) were reported. There were no treatment discontinuations or dose reductions due to TRAE. The compound exhibited a relatively flat PK curve with mild accumulation after multiple dosing. The steady-state C_{trough} was approximately 5 fold, 24 fold and 36 fold above target effective concentration at dose level of 5mg, 10mg, 20mg respectively. The PARylation inhibition was $>$ 90% confirming target engagement. Of seven patients having post-treatment tumor assessment and being considered efficacy-evaluable, two patients (one fallopian tube cancer patient with BRCA mutation and one prostate cancer patient with BRCA wild type) achieved PR per RECIST1.1. **Conclusions:** Preliminary data indicate that ACE-86225106 is well tolerated and shows promising efficacy in heavily pre-treated advanced solid tumors. Clinical trial information: NCT06380660. Research Sponsor: Acerand Therapeutics (Hong Kong) Limited.

3154 **Poster Session**

Effect of biopsy requirement on patient enrollment to phase I trials in cancer. First Author: Marisa Palmeri, Rutgers Robert Wood Johnson Medical School, New Brunswick, NJ

Background: The need for safer and more effective drugs for patients with cancer is a constant unmet need. Given their narrow therapeutic index, determination of dose and toxicity through phase I clinical trials is confined to patients with cancer. Recently, there has been a trend towards a greater demand for fresh tumor biopsies (Bx) from patients to better understand the pharmacodynamic and target effect of the drugs. We sought to determine whether the requirement for Bx among this vulnerable population had any detrimental effect. **Methods:** The study population included patients who enrolled to phase I trials between June 2022 (new EMR system) through January 2025 at a single NCI-designated comprehensive cancer center. All charts were reviewed and data collected included sex, race, age, diagnosis, and dates of consent, treatment start, last dose of study drug, off treatment, last contact/death; Bx site/approach/complications. Images were reviewed by an interventional radiologist to assess safety, with targets deemed appropriate biopsied under image guidance. For lung lesions or those $<$ 1 cm, 20g core needle was used, while 18g core needle was used for others. Outcomes were analyzed by Mantel–Cox test using Prism GraphPad v 10. **Results:** 146 patients [male (n = 63, 43.2%), age 62, 23-82(median, range), NHW-81 (55.5%), NHB-23 (15.8%), Hispanic-24 (16.4%), and Asian-18 (12.3%)] consented to 25 clinical trials. Of these, 8 mandated paired tumor Bx, 15 were mandatory or optional Bx depending on cohort, and 2 did not require Bx. The most common diagnoses were colorectal (37, 25.3%), other GI (21, 14.4%), pancreas (18, 12.3%), lung (11, 7.5%), breast (6, 4.1%), prostate (3, 2.1%) and others (50, 34.2%). Bx samples were to be collected prior to the first dose of study drug (pre-dose) and repeated after the first 1-2 cycles (on-study). Image guidance included ultrasound (50, 57.5%), CT scans (34, 39.1%), and others (3, 3.4%). Overall, 62 patients (42.4%) provided 87 Bx samples; 25 paired Bx, 20 only pre-dose Bx, and 17 only on-study Bx. Five patients (3.4%) did not undergo Bx because it was deemed unsafe or high risk. The sites of Bx included liver (45, 51.7%), lung (9, 10.3%), lymph node (8, 9.2%), peritoneum (4, 4.6%), and others (21, 24.1%). Two patients experienced pneumothorax and recovered without sequelae. The median (mean) duration from consent to start of study treatment was 20 (20) days among Bx patients vs. 14 (16) among non Bx patients (p = 0.003). The median (mean) duration of time on study was 77 (91) days among Bx patients vs. 77 (125) among non Bx patients (p = 0.046). **Conclusions:** Over 40% of patients entering phase I trials underwent study specific Bx. The patients who underwent a Bx had a median delay of 6 days in receiving the first dose of study medication. Further in-depth review of medical records will help identify variables that may have led to shorter time on study for patients undergoing clinical trial related biopsies. Research Sponsor: None.

3155 **Poster Session**

Rapid analysis and response evaluation of combination anti-neoplastic agents in rare tumors (RARE CANCER) trial: RARE 2 talazoparib and temozolomide. First Author: Jibran Ahmed, National Cancer Institute, Bethesda, MD

Background: Preclinical data generated from NIH/NCI Patient-Derived Models Repository (PDMR) demonstrated significant synergistic activity of talazoparib (a PARP inhibitor) combined with temozolomide (an alkylating agent) in patient-derived xenograft models of rare adult and pediatric cancers. This clinical trial aimed to evaluate the objective response (OR) rate of this combination in patients with advanced rare cancers in exploratory fashion. Correlatives include genomic and transcriptomic profiling of tumor tissue, circulating tumor DNA (ctDNA), circulating tumor cells, and assessments of apoptosis and epithelial-mesenchymal transition in relation to treatment activity. **Methods:** This open-label, non-randomized, phase 2 trial used a Simon two-stage design. Patients aged $\geq$18 years with advanced rare cancers received temozolomide (37.5 mg/m² orally, days 2–6) and talazoparib (750 mcg orally, daily) in 28-day cycles. Tumor response was assessed per RECIST v1.1, and adverse events (AEs) assessed using CTCAE v5.0. In the first stage, if 0/14 (across all histologies) responses are observed, the trial will be closed for futility. Otherwise, additional 16 patients were planned to be enrolled. There are no selection criteria based aside from rare tumor to allow for exploration of activity. **Results:** Fourteen patients were enrolled, all evaluable for response and toxicity. Median age was 57 years; 11 were female, and all had ECOG 0–1. Tumor histologies included uterine sarcoma (N = 3), cholangiocarcinoma (N = 2), and one each of adrenocortical carcinoma, adenoid cystic carcinoma, clear cell salivary carcinoma, MPNST, angiosarcoma, carcinoma of unknown primary, squamous urothelial carcinoma, small cell neuroendocrine carcinoma, and SDHB deficient renal cell carcinoma. Best responses included stable disease (N = 6), progressive disease (N = 5), and clinical progression (N = 3). One patient with clear cell salivary cancer and another with cholangiocarcinoma remained on treatment for 8 and 6 cycles, respectively. The median progression free survival is 3.81 months. The most common treatment related AEs (TRAEs) overall as well as $\geq$Grade 3 were hematologic including thrombocytopenia (13; $\geq$Grade 3 = 10), anemia (total12; $\geq$Grade 3 = 10), lymphopenia (total 12; $\geq$Grade 3 = 5), neutropenia (total 11; $\geq$Grade 3 = 6), and leukopenia (total 10, $\geq$Grade 3 = 4). No Grade 5 TRAEs were reported. Although none of the patients discontinued treatment due to TRAEs, planned dose reductions were needed for 7 patients. **Conclusions:** Despite promising preclinical activity, this tumor agnostic exploratory trial did not meet strict goal more design for single histology. Future efforts will focus on correlative analyses, exploring histology-specific expansion cohorts informed by pre-clinical response data, and optimizing dosing schedules to reduce overlapping toxicities. Clinical trial information: NCT05142241. Research Sponsor: U.S. National Institutes of Health.

3156 **Poster Session**

Body composition modulations during cyclic fasting-mimicking diet in patients with advanced solid cancers. First Author: Caterina Sposetti, Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA

Background: Fasting-mimicking diets (FMD) can induce favorable immune-metabolic changes in humans and preclinical data suggest potential antitumor activity. Cyclic FMD impact on muscle mass and adiposity in patients (pts) is unclear. Here we evaluate body composition changes in pts with advanced solid cancers undergoing FMD in the context of a phase Ib trial (NCT03340935). **Methods:** NCT03340935 study evaluated safety and biological effects of a cyclic FMD consisting of a 5-day, calorie-restricted, plant-based diet repeated every 21-28 days for a maximum of 8 cycles, conducted in oncologic patients receiving concomitant therapies. Here we included pts with advanced solid cancers and Computed Tomography (CT) exams at baseline (BL), FMD end and disease progression (PD). Body composition parameters, i.e. Skeletal Muscle Index (SMI) and Visceral (VAT), Subcutaneous (SAT), Intermuscular (IMAT) Adipose Tissues, were assessed via axial CT scan at 3rd lumbar vertebra using SliceOmatic software. Pts with advanced triple negative breast cancer (TNBC) receiving chemotherapy (ChT) without FMD, having CT scans at BL and PD, were selected as control cohort. Wilcoxon tests were used for comparisons. **Results:** In the FMD cohort (n=36), 61% had BC, 39% had TNBC, 78% received ChT; median age was 54 (IQR 51-65), median completed FMD cycles was 5 (IQR 3-8), median time from FMD end to PD was 3.5 months (IQR 1.0-16.0); 8 pts met criteria for sarcopenia (SMI $<$38.5 cm^2/m^2) at BL, 6 of whom had TNBC. In the control TNBC cohort (n=17), median age was 54 (IQR 42-68), 6 pts were sarcopenic at BL. In the FMD cohort, between BL and FMD end there was a significant reduction of VAT, SAT and SMI, but no change in IMAT; between BL and PD only SMI was significantly decreased (Table). At FMD end and PD, 12 pts were sarcopenic in the FMD cohort, 7 having TNBC. In the control TNBC cohort (n=17), IMAT was significantly increased between BL and PD, with no changes in other parameters (Table); 8 pts were sarcopenic at PD. **Conclusions:** In advanced cancers pts, cyclic FMD reduces adiposity as well as muscle mass. Tumor/therapy-related factors contribute to sarcopenia in advanced cancer pts, thus future trials involving FMD intervention should detect pts at risk and include supportive measures to preserve muscle mass. Support: Italian Association for Cancer Research (AIRC): AIRC-Bonadonna fellowship (C Sposetti), AIRC fellowship (F Ligorio), AIRC IG 2024 ID 30499 (PI: C Vernieri); Giuliani Foundation. Clinical trial information: NCT03340935. Research Sponsor: Italian Association for Cancer Research (AIRC) / Gianni Bonadonna Foundation; Italian Association for Cancer Research (AIRC); Italian Association for Cancer Research (AIRC); Giuliani Foundation.

	Visceral Adipose Tissue change - % median	*p value*	Subcutaneous Adipose Tissue change - % median	*p value*	Intermuscular Adipose Tissue change - % median	*p value*	Skeletal Muscle Index change - % median	*p value*
FMD end vs BL								
FMD cohort, n=36	-12.4	*0.002*	-11.9	*<0.001*	+0.9	*0.55*	-4.2	*0.014*
PD vs BL								
FMD cohort, n=36	-6.2	*0.25*	-5.5	*0.083*	+1.2	*0.5*	-5.1	*<0.001*
TNBC subset, n=14	-3.2	*0.24*	-5.0	*0.042*	+0.2	*0.9*	-4.7	*0.025*
Control TNBC cohort, n=17	-1.3	*0.64*	-11.0	*0.16*	+11.7	*0.023*	-0.9	*0.24*

TPS3157 **Poster Session**

IDeate-PanTumor02: A phase 1b/2 study to evaluate the efficacy and safety of ifinatamab deruxtecan (I-DXd) in patients (pts) with recurrent or metastatic solid tumors. First Author: Takahiro Kogawa, Department of Advanced Medical Development, The Cancer Institute Hospital of JFCR, Tokyo, Japan

Background: B7-H3 is highly expressed in many solid tumors but has limited expression in normal tissues; high B7-H3 expression is associated with shorter overall survival (OS) in several tumor types. I-DXd is a B7-H3–directed antibody–drug conjugate (anti−B7-H3 mAb covalently linked to a topoisomerase I inhibitor cytotoxic payload [DXd] via an enzymatically cleavable peptide-based linker). It showed promising efficacy in pts with advanced solid tumors in the Phase 1/2 IDeate-PanTumor01 study, with objective responses in 6 of the 7 tumor types with ≥5 pts (small cell lung cancer [SCLC], esophageal squamous cell carcinoma, metastatic castration-resistant prostate cancer, squamous non-small cell lung cancer, head and neck squamous cell carcinoma [HNSCC], and endometrial cancer). I-DXd also showed encouraging antitumor activity in 88 pretreated pts with extensive-stage SCLC in the Phase 2 IDeate-Lung01 study, with greater efficacy at the 12-mg/kg than the 8-mg/kg dose (objective response rates [ORRs] of 54.8% [95% CI, 38.7–70.2] and 26.1% [95% CI, 14.3–41.1], respectively). I-DXd has demonstrated a manageable and tolerable safety profile across tumor types. We describe a study investigating the efficacy and safety of I-DXd in pts with advanced solid tumors with substantial unmet medical needs. **Methods:** IDeate-PanTumor02 (NCT06330064) is a global, multicenter, open-label, single-arm, parallel-cohort, Phase 1b/2 study in ~520 adults with recurrent or metastatic solid tumors (endometrial cancer; HNSCC; pancreatic ductal adenocarcinoma; colorectal cancer; hepatocellular carcinoma [HCC]; esophageal/gastroesophageal/gastric adenocarcinoma; urothelial carcinoma; ovarian cancer; cervical cancer; biliary tract cancer; HER2-low breast cancer [BC]; HER2-negative BC; and cutaneous melanoma). Eligible pts will have received ≥1 systemic therapy for the selected tumor type and have an ECOG PS of ≤1. The study will be divided into 2 parts: Stage 1 and Stage 2 (n≈20 per stage per cohort). Each cohort starts with Stage 1 and may continue to Stage 2 if sufficient safety and efficacy data are observed. All cohorts except the HCC cohort will receive I-DXd 12 mg/kg every 3 weeks (Q3W). The HCC cohort includes a safety run-in part to assess tolerability and the potential need for dose adjustment; the planned starting dose is 8 mg/kg Q3W, which may be escalated. Primary endpoints are ORR per investigator (all cohorts) and safety (HCC safety run-in only). Secondary endpoints are safety, duration of response, progression-free survival, OS, disease control rate, pharmacokinetics, and immunogenicity. The Kaplan–Meier method will be used to estimate time-to-event endpoints, the Brookmeyer and Crowley method for median event times, and the Clopper–Pearson exact method to summarize descriptively endpoints with proportion. Enrollment is ongoing. Clinical trial information: NCT06330064. Research Sponsor: Daiichi Sankyo, Inc., Merck, Inc.

TPS3158 **Poster Session**

REJOICE-PanTumor01: A phase 2 signal-seeking study of raludotatug deruxtecan (R-DXd) in patients with advanced or metastatic gynecologic or genitourinary tumors. First Author: Laurence Albiges, Gustave Roussy, Paris Saclay University, Paris, France

Background: Cadherin-6 (CDH6), a transmembrane protein involved in cell–cell adhesion and epithelial–mesenchymal transition, is overexpressed in many cancer types. R-DXd is an anti-CDH6 antibody–drug conjugate composed of a humanized CDH6 antibody covalently linked to a potent topoisomerase I inhibitor payload (DXd) via a plasma-stable linker. In an ongoing Phase 1 study (NCT04707248), a subgroup of patients with heavily pretreated ovarian cancer (OC) who received R-DXd 4.8–6.4 mg/kg, had an objective response rate (ORR) of 48.6% (95% confidence interval [CI], 31.9–65.6); median duration of response (DOR) was 11.2 months (95% CI, 3.1–not estimable), and progression-free survival (PFS) was 8.1 months (95% CI, 5.3–not estimable), irrespective of CDH6 expression level (data cut-off: July 14, 2023). The safety profile of R-DXd was manageable. In total, 11.1% of patients discontinued R-DXd due to treatment-emergent adverse events. These promising data warranted further investigation of R-DXd in REJOICE-Ovarian01 (NCT06161025), a Phase 2/3 study in patients with platinum-resistant high-grade serous OC (HGSOC), and in the REJOICE-PanTumor01 Phase 2 study, which is described here. **Methods:** REJOICE-PanTumor01 (NCT06660654) is a global, open-label Phase 2 study in patients with locally advanced or metastatic gynecologic (endometrial cancer [EC], cervical cancer, or non-HGSOC) or genitourinary (urothelial cancer [UC] or clear cell renal cell carcinoma [ccRCC]) tumors. Cohorts are tumor type–specific; patients in all cohorts must have relapsed or progressive disease after receiving ≥1 prior line (and ≤3 prior lines in the EC, UC, and ccRCC cohorts only) of standard treatment. Adult patients with ECOG performance status 0–1 are eligible; there is no selection for tumor CDH6 expression. Approximately 40 patients will be enrolled into each cohort to receive R-DXd 5.6 mg/kg IV every 3 weeks until disease progression per RECIST 1.1, unacceptable toxicity, death, or other reason per protocol. In each cohort, a nonbinding futility interim analysis will be conducted after 20 patients complete a minimum of 12 weeks of follow-up, the results of which may determine whether the remaining (~20) patients will be treated. Primary endpoints are ORR for the gynecological and UC cohorts, disease control rate (DCR) for the ccRCC cohort (both investigator-assessed), and safety and tolerability for all cohorts. Secondary endpoints are ORR (ccRCC cohort only), DCR (except ccRCC cohort), PFS, DOR, time to response (all investigator-assessed per RECIST 1.1), pharmacokinetics, and immunogenicity. No formal hypothesis testing will be performed; ORR and DCR will be analyzed using a Clopper–Pearson method to determine 95% CI. PFS and DOR will be analyzed using the Kaplan–Meier method (2-sided 95% CI). Study enrollment began in January 2025. Clinical trial information: NCT06660654. Research Sponsor: Daiichi Sankyo, Inc., Merck Inc.

TPS3159 **Poster Session**

A phase 1, open-label, multi-center study of the safety, tolerability, and efficacy of IPH4502 as a single agent in advanced solid tumors. First Author: Shiraj Sen, NEXT Oncology, Dallas, TX

Background: Nectin-4 is a cell adhesion molecule frequently overexpressed across multiple solid tumor types, including urothelial carcinoma (UC), esophageal cancer, non-small cell lung cancer, and triple-negative breast cancer. It plays a significant role in carcinogenesis and cancer progression and is associated with poor survival in several tumor indications. Targeting Nectin-4 with enfortumab vedotin (EV), an antibody-drug conjugate (ADC) with a monomethyl auristatin E (MMAE) payload, demonstrated clinical benefit in UC, which exhibits the highest Nectin-4 expression among all solid tumor types. EV is now approved for the treatment of UC. IPH4502 is a differentiated Nectin-4 ADC conjugated with exatecan, a topoisomerase-1 inhibitor payload with a drug-to-antibody ratio of 8 via a cleavable hydrophilic linker. IPH4502 has been developed to address the unmet medical need of UC patients who have progressed on, or are ineligible for EV, as well as to treat tumor types with lower Nectin-4 expression beyond UC. In preclinical models, internalization capability and bystander effect of IPH4502 enable an efficient antitumor activity in Nectin-4 expressing tumor models, independent of Nectin-4 expression level, as well as in models resistant to EV. Finally, IPH4502 shows antitumor activity in patient-derived xenograft models from UC and other tumor types. **Methods:** This is a first-in-human, open-label, multicenter, single-arm Phase 1 study to assess the safety profile (DLTs and MTD), tolerability according to NCI-CTCAE v5.0, and RP2D of IPH4502 in patients with advanced solid tumors. Secondary objectives aim to characterize the pharmacokinetic profile and evaluate the immunogenicity and preliminary efficacy of IPH4502. The study is being conducted in participants aged ≥18 years withhistologically confirmed, unresectable, locally advanced, or metastatic solid tumors known to express Nectin-4, including, but not limited to non-small cell lung, triple-negative breast, ovarian, esophageal, gastric, and colorectal cancers, as well as UC. Part 1 (Dose Escalation) will use a Bayesian Optimal Interval Design (BOIN) with backfilling of safety-cleared dose levels. This approach will guide dose escalation and help establish the MTD/MAD. Part 2 (Dose Optimization)will begin after identifying the MTD/MAD, to select the RP2D. It will enroll participants with selected tumor indications (up to 2), for whom a clinical benefit was observed in Part 1. Participants will be randomized at a 1:1 ratio to 2 dose levels, to determine the RP2D. A maximum of 105 participants will receive treatment with IPH4502 in France and the US. Clinical trial information: NCT06781983. Research Sponsor: None.

TPS3160 **Poster Session**

Design of a first-in-human multicenter open-label study of ZW171, a mesothelin x CD3 targeting bispecific T-cell engager, in participants with advanced solid tumors: ZWI-ZW171-101. First Author: Melissa Lynne Johnson, Sarah Cannon Research Institute, Nashville, TN

Background: Mesothelin (MSLN) is a membrane glycoprotein overexpressed in several solid tumors, making it a promising target for cancer treatments, including T cell engagers (TCEs). ZW171 is a humanized trivalent bispecific TCE antibody that targets a threshold level of MSLN expression with 2 binding sites and CD3e receptor on T cells with 1 binding site. Preclinical studies of ZW171 demonstrated favorable pharmacology, pharmacokinetics (PK), and toxicology, showing it preferentially kills MSLN-overexpressing cells, activates T cells without significant toxicity, inhibits tumor growth, and is well tolerated in cynomolgus monkeys, suggesting its potential for treating MSLN-expressing tumors[1] while sparing healthy tissues with low levels of expression. This first-in-human, phase 1, ongoing study (ZWI-ZW171-101) evaluates safety, tolerability, PK, and anti-tumor activity of ZW171 in participants with advanced solid tumors. **Methods:** This 2-part study enrolls eligible adult participants with unresectable MSLN-expressing ovarian cancer (OC), non-small cell lung cancer (NSCLC), or other MSLN-expressing cancers, with measurable disease per RECIST v1.1, ECOG PS score of 0 to 1, adequate organ function, and a minimum life expectancy of 12 weeks. Participants with additional progressing malignancies, recent transplants, clinically significant ongoing toxicity, uncontrolled renal, pancreatic or liver disease, or active autoimmune diseases requiring high-dose corticosteroids or immunosuppressive drugs are excluded. Part 1 evaluates the safety and tolerability of ZW171 and Part 2 evaluates the anti-tumor activity while continuing to evaluate safety and tolerability. Part 1 is dose escalation to identify maximum tolerated dose (using modified toxicity probability interval [mTPI-2] design, n=40) among participants with OC or NSCLC receiving subcutaneous ZW171 monotherapy on days 1, 8, and 15 of 3-week (21-day) cycles. Approximately 6 dose levels will be explored based on safety and tolerability. Step-up dosing will be used for cycle 1. Dose level 1, determined by QSP-based MABEL approach[2], is administered at 4.2 μg (day 1), 12.6 μg (day 8), and 38.0 μg (day 15). Part 2 is dose expansion in participants with OC, NSCLC, and other MSLN-expressing cancers (MSLN expression evaluated retrospectively). Primary objectives are to evaluate safety and tolerability of ZW171 and determine the maximum tolerated dose. Key secondary objectives are to assess PK, anti-drug antibodies, and anti-tumor activity. This is a global study with sites in North America, Europe, and Asia; and actively enrolling participants into Part 1. References: 1. Afacan N, et al. Presented at AACR Annual Meeting 2023; abstract 2942. 2. Afacan N, et al. Presented at SITC Annual Meeting 2024; abstract 1062. Clinical trial information: NCT06523803. Research Sponsor: Zymeworks BC Inc.

TPS3161 Poster Session

A phase 1, first-in-human study of AMT-676, an anti-CDH17 antibody-drug conjugate, in patients with advanced gastrointestinal tumors. First Author: Charlotte Rose Lemech, Scientia Clinical Research, Randwick, Australia

Background: Cadherin-17 (CDH17), also known as liver-intestine-cadherin, is a transmembrane protein that is highly expressed in a variety of gastrointestinal cancers, including colorectal, gastric, esophageal adenocarcinoma, cholangiocarcinoma, pancreatic ductal, and gastrointestinal neuroendocrine tumors. The overexpression of CDH17 is associated with tumor metastasis and progression to advanced tumor stages. AMT-676 is a novel antibody-drug conjugate (ADC) that targets CDH17. It is comprised of a humanized IgG1 monoclonal antibody specific to CDH17, conjugated to the potent topoisomerase I inhibitor exatecan, with a drug-to-antibody ratio of 4, linked through a proprietary T-moiety technology. Preclinical studies have demonstrated significant antitumor activity of AMT-676 across multiple gastrointestinal cancer models and great tolerability in safety studies, highlighting its potential as a therapeutic agent for CDH17-expressing malignancies. **Methods:** This phase 1, open-label, multicenter study aims to determine the Maximum Tolerated Dose (MTD) and the Recommended Phase 2 Dose (RP2D) of AMT-676, as well as to assess its safety, tolerability, anti-drug activity, pharmacokinetics, pharmacodynamics, immunogenicity and preliminary efficacy in patients with advanced solid tumors. Tumor types that express CDH17 including gastrointestinal cancers, treated with or with no standard therapeutic options are to be enrolled. AMT-676 will be administered intravenously on a 21-day cycle. The dose escalation will be guided by the Bayesian Optimal Interval (BOIN) design, incorporating an accelerated titration approach to evaluate 6 cohorts: 1.6, 3.2, 4.8, 6.4, 8, and 10 mg/kg. Three backfilling cohorts at doses that have demonstrated safety will also be included, each enrolling up to 18 patients, to gather additional data on safety, pharmacokinetics, pharmacodynamics, and preliminary efficacy, thereby supporting the selection of an optimized dose for expansion. Mandatory pre-study biopsy sample collection for retrospective immunohistochemistry (IHC) analysis will facilitate a comprehensive exploratory biomarker plan, potentially correlating CDH17 levels with treatment responses. The study is actively enrolling participants for the dose escalation phase. Cohorts 1-4 have been completed DLT evaluation and enrollment of cohort 5 began in December 2024. Clinical trial information: NCT06400485. Research Sponsor: Multitude therapeutics Inc.

TPS3162 Poster Session

Phase I multicenter, open-label, dose escalation study of T-1201, a small molecule drug conjugate, to assess safety, pharmacokinetics, and antitumor activity in advanced solid tumors. First Author: Hui-Ching Wang, Division of Hematology and Oncology, Department of Internal Medicine, Kaohsiung Medical University Hospital, Kaohsiung, Taiwan

Background: Phosphatidylserine (PS) is a phospholipid critical for maintaining cell membrane integrity and functionality. In rapidly proliferating cancer cells, PS translocates to the outer leaflet of the membrane, making it a promising biomarker and therapeutic target for cancer treatment. The investigational drug T-1201 is a proprietary small molecule drug conjugate combining a bioactive topoisomerase I inhibitor, SN-38, with Zn-DPA complexes, which exhibit high affinity for PS. Preclinical studies have demonstrated T-1201's in-vivo antitumor activity across multiple human tumor xenograft models. This study represents the first clinical evaluation of T-1201 in humans. **Methods:** The primary objectives of this phase I study are to evaluate the safety profile of T-1201, determine dose-limiting toxicities (DLTs), establish the maximum tolerated dose (MTD), and identify the recommended phase II dose (RP2D). Secondary objectives include characterization of pharmacokinetics (PK) and assessment of antitumor activity for T-1201. The study comprises three dose-escalation parts. In Part A, T-1201 is administered intravenously once every four weeks (Q4W), starting at 18 mg/m^2 during Cycle 1. From Cycle 2 onward, the dosing interval can be adjusted to once every two weeks (Q2W) at the investigator's discretion, subject to agreement with the Sponsor. When switching to the Q2W schedule, the dose level is halved compared to the Q4W dose. Each treatment cycle spans four weeks, with dose escalation proceeding via a single-patient cohort design (100% dose increments) initially, transitioning to a modified 3+3 design (40% dose increments) based on DLTs observed in Cycle 1. In Part B, T-1201 is administered intravenously Q2W in a 28-day treatment cycle, starting at 100 mg/m^2, which represents half of the MTD identified in Part A. In Part C, each treatment cycle is reduced to 21 days, with the starting dose not exceeding the highest dose level deemed safe by the Safety Review Committee (SRC) in Part B. Eligible patients are ≥18 years of age, have an Eastern Cooperative Oncology Group (ECOG) performance status of 0–1, and possess radiographically or clinically evaluable tumors. As of now, 27 patients have been enrolled in the Part A dose-escalation stage. This study is registered with ClinicalTrials.gov (NCT04866641). Clinical trial information: NCT04866641. Research Sponsor: Taivex Therapeutics corporation.

Dose escalation/de-escalation rule for the BOIN design.

Number of subjects treated at the current dose*	3	4	5	6	7	8	9
Escalate if # of DLT ≤	0	1	1	1	1	2	2
Stay at current dose if # of DLT =	1	NA	NA	2	2	3	3
De-escalate if # of DLT ≥	2	2	2	3	3	4	4
Eliminate if # of DLT ≥	3	3	4	4	5	5	6

*The enrollment may stop when one of the following criteria is met: The planned sample size has been reached; at least 9 subjects have been treated and evaluable for DLT at one dose level; or all doses explored appear to be overly toxic, and the MTD cannot be determined.

TPS3163 Poster Session

A phase 1 study to evaluate the safety and tolerability of the antibody–drug conjugate (ADC) MesoC2 (PF-08052666) in patients with advanced solid tumors. First Author: Amita Patnaik, START San Antonio, San Antonio, TX

Background: MesoC2 (PF-08052666) is an ADC that targets mesothelin (MSLN), a cell-surface glycoprotein overexpressed in solid tumors including mesothelioma, ovarian cancer, pancreatic cancer, non-small cell lung cancer (NSCLC), endometrial cancer (EC), and colorectal cancer (CRC), but with limited expression in normal tissues. MesoC2 is constructed from a recombinant human IgG1 anti-MSLN monoclonal antibody conjugated to a cleavable tripeptide linker that carries a topoisomerase 1 inhibitor (TOP1) payload. The average number of TOP1 molecules per antibody is 8. Following high-affinity binding to MSLN on the cell surface, MesoC2 is internalized, the linker is cleaved, and the released payload inhibits DNA religation during amplification, leading to cell cycle arrest and cell death. MesoC2 has shown potent antitumor efficacy in in vitro assays and xenograft models and an acceptable safety profile in cynomolgus monkeys. The aim of this first-in-human study is to explore the safety, tolerability, and preliminary efficacy of MesoC2 in patients with certain advanced solid tumors. **Methods:** In this phase 1, open-label study, up to 365 patients with mesothelioma, platinum-resistant ovarian cancer (PROC), pancreatic ductal adenocarcinoma (PDAC), NSCLC, EC, or CRC will receive intravenous infusion of MesoC2 in dose escalation (n=45), dose and schedule optimization (n=40), and disease-specific dose expansion cohorts (n=280; includes a biology cohort to evaluate exploratory biomarkers). Key inclusion criteria are histologically or cytologically confirmed metastatic or locally advanced mesothelioma, PROC, PDAC, NSCLC, EC, or CRC who have relapsed or progressed following standard therapies; aged ≥18 years; ECOG performance status score of 0 or 1; and available archival tumor tissue (a fresh biopsy is required if unavailable). Key exclusion criteria include prior or current treatment with systemic anticancer therapy or focal radiotherapy within 4 weeks prior to first dose of MesoC2, prior anti-MSLN therapies, and any unresolved toxicities from prior therapy greater than G1 at the time of starting study treatment, except alopecia. Primary endpoints include type, incidence, and severity of adverse events (AEs), frequency of dose modifications due to AEs, incidence of dose-limiting toxicities, cumulative safety, pharmacokinetics, pharmacodynamics, and preliminary antitumor activity. Key additional endpoints include objective and best response rates per Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST v1.1), duration of response, progression-free survival, overall survival, MSLN expression in blood and tissue, and changes in tumor-specific biomarkers. Enrollment is ongoing; clinical trial information: NCT06466187. A genAI tool (01/06/25; Pfizer; GPT-4o) developed the 1st draft; authors assume content responsibility. Clinical trial information: NCT06466187. Research Sponsor: Pfizer Inc.

TPS3164 Poster Session

TUB-030, a novel ADC targeting 5T4: A phase I/IIa multi-center, first-in-human clinical trial (5-STAR 1-01) in patients with advanced solid tumors. First Author: Shiraj Sen, NEXT Oncology, Dallas, TX

Background: TUB-030 is a novel antibody-drug conjugate (ADC) targeting 5T4, an oncofetal antigen expressed in various solid tumors with limited expression in healthy tissues. TUB-030 leverages optimized biophysical properties, an effector-silenced antibody, and an exatecan payload to maximize the therapeutic index and minimize off-target toxicities. Preclinical studies demonstrated potent anti-tumor activity, including long-lasting tumor regression at doses as low as 1 mg/kg and durable responses even in tumors with low 5T4 expression. **Methods:** 5-STAR 1-01 is a multicenter, first-in-human dose escalation and dose optimization Phase I/IIa clinical trial designed to investigate safety, tolerability, pharmacokinetics (PK), and efficacy of the anti-5T4 ADC TUB-030 in patients with advanced and metastatic solid tumors. Eligible patients have one of the following tumor types: head and neck squamous cell carcinomas (HNSCC), non-small-cell lung cancer (NSCLC), small cell lung cancer, pleural mesothelioma, triple-negative breast cancer, HR+/HER2- breast cancer, esophageal cancer, gastric cancer, pancreatic adenocarcinoma, colorectal cancer, bladder cancer, prostate cancer, cervical cancer, osteosarcoma, or soft tissue sarcomas and must have exhausted available standard-of-care therapies. Phase I is an open-label, single-arm dose escalation trial, with administration every 21 days. Dose escalation follows an accelerated titration design (ATD) transitioning to Bayesian optimal interval (BOIN) upon predefined toxicity thresholds. Backfill cohorts are planned in NSCLC and HNSCC to further evaluate the safety and efficacy profile at, or near, the maximum tolerated dose (MTD). Primary endpoints include safety and tolerability of TUB-030 as monotherapy, determination of the MTD and the recommended phase II doses; secondary endpoints assess pharmacokinetics, immunogenicity, and preliminary clinical activity using RECIST v1.1 criteria. Exploratory endpoints include analysis of circulating tumor DNA. In phase IIa, dose-optimization will evaluate two dose levels in select indications in order to identify the optimal dose for further development. Enrollment of approximately 130 patients across the US and Canada is planned, with dose escalation currently underway. This study investigates TUB-030, a novel 5T4 targeted ADC as a therapy for advanced/metastatic solid tumors. Clinical trial information: NCT06657222. Research Sponsor: None.

TPS3165 Poster Session

PROCEADE PanTumor: A phase 1b/2, multicenter study of precemtabart tocentecan (M9140), an anti-CEACAM5 antibody-drug conjugate (ADC) with exatecan payload, in patients with advanced solid tumors. First Author: Zev A. Wainberg, University of California, Los Angeles, Medical Center, Los Angeles, CA

Background: CEACAM5 is a cell surface glycoprotein that is overexpressed in various carcinomas, notably in gastric cancer (GC), non-small cell lung cancer (NSCLC), pancreatic adenocarcinoma (PDAC), and colorectal cancer (CRC), but shows limited expression on healthy adult cells. Precemtabart tocentecan is an investigational anti-CEACAM5 ADC (drug-to-antibody ratio: 8) that utilizes a unique linker–payload combination to selectively deliver the topoisomerase 1 inhibitor, exatecan, to CEACAM5 overexpressing tumor cells. Preliminary clinical data from the dose-escalation part of the first-in-human study of precemtabart tocentecan in patients with metastatic CRC (PROCEADE CRC-01) demonstrated a manageable and predictable safety profile and promising preliminary efficacy in 40 heavily pretreated patients. The PROCEADE PanTumor study is a Phase 1b/2, multicenter, open-label study that aims to investigate the clinical activity of precemtabart tocentecan, either as monotherapy or in combination with other anticancer agents, in patients with advanced GC, advanced NSCLC and advanced PDAC. **Methods:** The study was designed as a matrix study with a master protocol (applicable to all substudies) and three substudy protocols (GC; NSCLC; PDAC). Based on the master protocol, patients aged ≥18 years, with an Eastern Cooperative Oncology Group performance status ≤1, adequate baseline hematological, renal, and hepatic function, ≥1 lesion that is measurable using RECIST v1.1, who have received ≥1 prior line of treatment are eligible. Patients must have an archival formalin-fixed paraffin-embedded tumor tissue or a fresh biopsy. In the respective substudies, patients with advanced or metastatic, HER2-negative GC or gastroesophageal junction adenocarcinoma; patients with advanced (Stage III; ineligible for resection/curative radiation) or metastatic NSCLC; or patients with advanced or metastatic PDAC will be included. Patient selection will be based on CEACAM5 expression level (both high and low in GC, only high in NSCLC and PDAC [CEACAM5^{high}: ≥50% tumor cells with immunohistochemistry [IHC] ≥2+ staining; CEACAM5^{low}: <50% tumor cells with IHC ≥2+ staining]), and in patients with NSCLC, *EGFR* mutation status (*EGFR*-wt and *EGFR* mut+). The primary endpoint is objective response (proportion of patients with confirmed complete/partial response [CR/PR] per RECIST v1.1, assessed by investigator). Secondary endpoints include adverse events, duration of response (RECIST v1.1), disease control (CR, PR, stable disease, or non-CR/non-progressive disease [PD] at Week 12), time to response, progression-free survival, and pharmacokinetic assessments. The study is planned to be initiated at multiple sites globally, with an estimated enrollment of 250 patients. Clinical trial information: NCT06710132. Research Sponsor: the healthcare business of Merck KGaA, Darmstadt, Germany (CrossRef Funder ID: 10.13039/100009945).

TPS3166 Poster Session

A dose escalation and cohort expansion phase I/IIa study of ACR246, an innovative 5T4- antibody drug conjugate (ADC), in patients (pts) with advanced solid tumors. First Author: Panpan Zhang, Key laboratory of Carcinogenesis and Translational Research (Ministry of Education/Beijing), Department of Early Drug Development Centre, Peking University Cancer Hospital & Institute, Beijing, China

Background: The oncofetal antigen 5T4 is overexpressed in many solid tumors with limited expression in normal adult tissues. Overexpression of 5T4 is associated with poor prognosis. 5T4 on tumor cell surface is rapidly internalized when bound to antibody and is thus an ideal target for the development of ADC drugs. ACR246 is the first next- generation 5T4-ADC consisting of a fully human monoclonal antibody that is site-specifically conjugated to a novel DNA topoisomerase I inhibitor D2102, via a stable and cleavable linker, with a drug-to-antibody ratio (DAR) of 8. ACR246 was carefully designed to improve the safety and efficacy in treating 5T4 positive solid tumors. In preclinical studies, ACR246 demonstrated robust anti-tumor activity, superior to a Dxd-5T4 ADC (as a reference) both in CDX and PDX models, including but limited to NSCLC, gastric cancer, pancreatic cancer and Esophageal cancer, and excellent tolerability, supporting further development for clinical use. **Methods:** This is an ongoing, phase I/IIa, open-label, multicenter, dose escalation and cohort expansion study of ACR246 to be injected intravenously to adult pts with advanced solid tumors. For phase I study, a Bayesian optimal interval design is adopted to assess dose levels of ACR246, 0.6, 1.2, 2.4, 3.6 and 4.5 mg/kg, administered every 3 weeks on a 21-day cycle , and intermediate dose levels of 3.0, 4.0 and 5.0 mg/kg may be evaluated based on emergent safety or pharmacologic data. The primary objectives are to evaluate safety and tolerability and determine the maximum tolerated dose (MTD) and the recommended phase 2 dose (RP2D); the second objectives include PK, immunogenicity and preliminary clinical efficacy. Dose limiting toxicity (DLT) will be assessed at each dose level. The DLT evaluation period will be 21 days. Once the RP2D is determined, phase IIa study will be conducted to further evaluate the safety, tolerability, efficacy, PK and immunogenicity of ACR246 in 5T4-positive advanced solid tumor pts (esophageal cancer, NSCLC, ovarian cancer, prostate cancer and other types of tumors) under RP2D. Approximately 77 pts ≥ 18 years of age with advanced solid tumors that have histologically or cytologically been diagnosed recurrent or metastatic unresectable advanced disease and have failed or are intolerant of systemic standard therapy or standard therapy is not available, and having adequate ECOG performance status (0-1), hematologic function, and end organ function are planned to be enrolled, with 37 pts in phase I study and approximately 40 pts in phase IIa study. 5T4 expression is not required for enrollment for phase I, but will be assessed retrospectively. The toxicity will be assessed by Common Terminology Criteria for Adverse Events v5.0 and the tumor response will be determined per RECIST v1.1. Dose levels of 0.6 mg/kg and 1.2mg/kg has completed enrollment with no DLT. Clinical trial information: NCT06238401. Research Sponsor: Hangzhou Adcoris Biopharma Co., Ltd.

TPS3167 Poster Session

A phase 1 dose escalation and dose expansion study for LNCB74, a B7-H4 targeted antibody drug conjugate, as monotherapy in participants with advanced solid tumors. First Author: Michael M Song, NEXT Oncology, San Antonio, TX

Background: B7-H4 is a transmembrane receptor of the B7-family of immunomodulatory proteins whose expression correlates with poor clinical outcomes for ovarian and breast cancers. High expression in multiple tumor types and limited expression in normal tissues makes B7-H4 an attractive target for antibody drug conjugate (ADC) therapeutics. LNCB74 is a B7-H4 targeted ADC in which a humanized IgG1κ antibody is conjugated to the microtubule disrupting payload monomethyl auristatin E (MMAE) with a drug-to-antibody ratio of 4 (DAR4). LNCB74 is designed to maximize therapeutic index through three key elements. First, site specific ConjuAll conjugation results in a homogeneous DAR to drive uniform PK. Second, our proprietary glucuronidase-cleavable linker reduces both on- and off-target toxicity. Third, the antibody Fc was "LALA"-mutated to reduce Fc mediated uptake into Fc receptor expressing cells such as immune and endothelial cells. Compared to other B7-H4 targeted ADCs in clinical development, LNCB74 has demonstrated a superior safety profile in nonhuman primate toxicity studies and potent anti-tumor activity in multiple cell line- and patient-derived xenograft in vivo models, making it a promising ADC therapy for B7-H4-expressing solid tumors. **Methods:** LNCB74-01 is a phase 1, open-label, first-in-human study that will include dose escalation, safety, and biomarker backfills (Part 1) and randomized dose expansion/optimization (Part 2). The objectives of the study will be to determine safety and tolerability, define the maximum tolerated dose and/or recommended phase 2 dose, characterize the pharmacokinetics (PK) and pharmacodynamics (PD), and to assess the preliminary efficacy in participants with metastatic solid tumors treated with LNCB74. The tumor types include ovarian, breast, endometrial, biliary tract cancer, and squamous NSCLC. Key eligibility criteria include measurable disease based on RECIST v1.1 and the ability to provide tissue samples to test B7-H4 expression by CLIA-certified immunohistochemistry assay in a central laboratory. Participants will receive LNCB74 on Day 1 of each 21-day cycle. Dose escalation will follow a Bayesian optimal interval (BOIN) design. Dose expansion will occur in up to two tumor types. In each tumor specific dose expansion, participants will be randomized to two dose levels stratifying for prior lines of therapy (1-3 vs ≥4) and B7-H4 expression (intermediate vs high). The PK profile, immunogenicity, preliminary anti-tumor activity per RECIST v1.1, and correlation of baseline B7-H4 expression to anti-tumor activity of LNCB74 will be evaluated as secondary endpoints. Biomarkers will be assessed in peripheral blood and tumor tissue. Enrollment is ongoing in the United States. Clinical trial information: NCT06774963. Research Sponsor: NextCure Inc.

TPS3168 Poster Session

The EQUAL study: Utilizing plasma EGFR cfDNA detection as an accessible screening tool for lung cancer in underserved patients ineligible for routine screening. First Author: Narjust Florez, Lowe Center for Thoracic Oncology, Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA

Background: Lung cancer (LC) among non-tobacco-users is increasing in the United States, with no routine screening available. Among those patients, EGFR mutations (EGFRm) are common, with the highest prevalence seen in East Asian and Hispanic women. Delays in diagnosis and treatment are exacerbated in these marginalized groups and women, negatively impacting their cancer outcomes. At Dana-Farber Cancer Institute's (DFCI) Belfer Center for Applied Science, we developed a novel droplet digital PCR ctDNA assay to detect EGFR del19 and L858R mutations, which comprise 85-90% of total EGFRm in LC. Here, we report the methodology of EQUAL, a study assessing the feasibility of a diagnostic assay among non-tobacco using, historically marginalized East Asian and Hispanic populations at high risk for EGFRm-LC. **Methods:** To assess the feasibility of our ctDNA screening tool, the EQUAL study is recruiting two cohorts of participants. Cohort 1 (n=500) includes 50–80-year-olds who self-identify as East Asian or Hispanic from the general population, while Cohort 2 (n=500) includes 40–80-year-olds of the same backgrounds with an additional risk factor for LC, with a focus on direct family members of patients with EGFRm-LC. Recruitment is beginning with these family members of patients with EGFRm-LC at DFCI main campus, Beth Israel Deaconess Medical Center, Massachusetts General Hospital, DFCI Merrimack Valley, DFCI regional campuses, and will expand to primary care clinics and community events. Blood samples are collected in clinics or at home via mobile phlebotomy. Positive results are verified in a government-certified CLIA laboratory; a complementary chest CT will be arranged for those with positive assay results, and patients will receive navigation until resolution. Patients with a positive assay but negative chest CT will be followed for 12 months and will receive a second annual chest CT. Recognizing how cultural beliefs and tobacco's association with LC may hinder screening participation, EQUAL includes an optional survey and focus groups to explore perceptions and barriers surrounding LC screening with our tool for future optimization efforts. The study is available in 8 languages including Spanish, Portuguese, Korean, Vietnamese, Japanese, Chinese (simplified and traditional), and Creole. EQUAL is the first study to implement EGFRm-LC blood-based screening for historically marginalized populations who are not eligible for LC screening, thereby allowing for LC identification that can be effectively treated with targeted therapy approved for stages IB-IV. This pilot study seeks to lay the groundwork for future sensitivity and specificity trials that will confirm the value of the assay and expand the scope of current screening guidelines to reduce health disparities and delays in LC diagnosis. Clinical trial information: NCT06716580. Research Sponsor: Dana-Farber Cancer Institute Philanthropic Funds.

TPS3169 **Poster Session**

A phase 1/2 study of FOG-001, a first-in-class direct β-catenin: TCF inhibitor, in patients with colorectal cancer (CRC) and other locally advanced or metastatic solid tumors. First Author: Kyriakos P. Papadopoulos, START-San Antonio, San Antonio, TX

Background: Activation of the Wnt/β-catenin pathway, often as truncal APC mutations, in 80–90% of CRCs and other solid tumors, is known to be a key driver of cancer progression and has been associated with immune exclusion and resistance to immunotherapy. Development of agents targeting this pathway at the key β-catenin: T-cell factor (TCF) node has eluded the pharmaceutical industry to date. FOG-001 is a Helicon peptide that competitively inhibits interaction between β-catenin and TCF transcription factors. Helicon peptides are hyperstabilized α-helices that can be tuned for picomolar binding affinities, robust cell penetration, broad tissue distribution, no immune recognition, and long *in vivo* half-lives. In studies in a wide range of patient-derived xenograft (PDX) CRC and HCC models, FOG-001 inhibited tumor growth and promoted tumor regression as monotherapy. Combinations with immune checkpoint inhibitors or standard-of-care therapies, including bevacizumab and 5-FU, showed strong additivity/synergy in PDX CRC models. **Methods:** This first-in-human, phase 1/2, multicenter, open-label, dose-escalation (part 1) and dose-expansion (part 2) study evaluates the safety/tolerability, pharmacokinetics (PK), pharmacodynamics (PD), and anti-tumor effects of FOG-001 monotherapy and combined with other anti-cancer therapies in patients with microsatellite stable (MSS) CRC or advanced/metastatic solid tumors known to harbor a Wnt pathway-activating mutation (WPAM). Eligible patients must have received at least one prior systemic anti-cancer therapy and either progressed on, not responded to, or be unfit for available therapies. In Part 1, FOG-001 is administered intravenously every week, at escalating dose levels evaluated sequentially in a standard 3+3 design as monotherapy in patients with MSS CRC or any solid tumor with documented WPAM. PD effects are evaluated in a separate cohort of approximately six patients with MSS CRC. Combination cohorts will evaluate FOG-001 + FOLFOX/bevacizumab (1L MSS CRC), FOG-001 + nivolumab (3L MSS CRC or anti-PD-1/PD-L1-resistant CRC and solid tumors), and FOG-001 + trifluridine/tipiracil + bevacizumab (3L MSS CRC). Part 2 dose expansion will evaluate FOG-001 monotherapy in patients with MSS CRC and other solid WPAM+ tumors. Combination dose expansion will evaluate combinations initially studied in Part 1. Primary endpoints are safety/tolerability of FOG-001 alone or in combination. Secondary endpoints are PK, PD, recommended phase 2 dose and schedule, and preliminary anti-tumor activity (e.g., ctDNA changes, overall response rate, best objective response, duration of response, and progression-free survival). 156 patients are planned to be enrolled in Part 1, which is currently enrolling in the USA. Clinical trial information: NCT05919264. Research Sponsor: Parabilis Medicines.

TPS3170 **Poster Session**

SCRUM-Japan MONSTAR-SCREEN-3: Comprehensive tumor microenvironment analysis via multi-omics in a large-scale prospective study. First Author: Mitsuho Imai, Translational Research Supporting Office, National Cancer Center Hospital East, Kashiwa, Japan

Background: SCRUM-Japan is a multi-institutional, industry-academia collaborative cancer genome screening project launched in 2015, consisting of LC-SCRUM-Asia for lung cancer and SCRUM-MONSTAR for other malignancies. The project has successfully implemented organ-agnostic liquid biopsy-based precision oncology and molecular residual disease (MRD)-guided therapeutic development, resulting in multiple regulatory approvals of therapeutic agents and diagnostics. In 2024, MONSTAR-SCREEN-3 was launched to expand the scope of multi-omics analysis beyond advanced solid tumors to include resectable solid tumors and hematologic malignancies, aiming for a comprehensive understanding of tumor microenvironment (TME) dynamics. The project integrates a multi-omics platform, including spatial transcriptomics, ctDNA analysis, and proteomics, to advance personalized medicine and accelerate drug development. **Methods:** MONSTAR-SCREEN-3 (UMIN000053975) is a large-scale, multi-institutional prospective study involving 55 centers across Japan, aiming to enroll 3,200 patients across three cohorts: Cohort A: Advanced solid tumors undergoing systemic therapy (n=1,700); Cohort B: Resectable solid tumors receiving perioperative treatment (n=1,100); Cohort C: Hematologic malignancies (n=400). Our analysis platform combines spatial transcriptomics with circulating tumor DNA/RNA sequencing, bulk tissue whole exome/transcriptome sequencing, plasma proteomics, and microbiome analyses. For resectable cases, standardized longitudinal monitoring with whole genome sequencing-based MRD analysis is implemented, while disease-specific MRD approaches are applied to hematologic malignancies. Following SCRUM-Japan's quality assurance system, standardized monitoring collects regulatory-grade clinical data, including key indicators such as response rate, progression-free survival, and overall survival. MONSTAR-SCREEN-3 applies standardized protocols for tissue preservation and data acquisition across all centers, ensuring high-quality data. The project leverages the VAPOR CONE supercomputing infrastructure for real-time data integration and AI-driven analysis to identify biomarkers, elucidate resistance mechanisms, and deepen the understanding of tumor-immune interactions. The study aims to establish a framework for next-generation precision oncology. The latest enrollment status and initial operational results will be reported at the ASCO meeting. MONSTAR-SCREEN-3 is expected to contribute to new therapies, cross-cancer MRD assays, and the resolution of drug lags in hematologic malignancies, driving advancements in personalized cancer treatment. Clinical trial information: UMIN000053975. Research Sponsor: None.

TPS3171 **Poster Session**

A first-in-human multi-center phase 1/2 study of a selective FGFR2/3 inhibitor, CGT4859, in patients with intrahepatic cholangiocarcinomas or other advanced solid tumors. First Author: Lipika Goyal, Stanford Cancer Center, Stanford School of Medicine, Stanford, CA

Background: Genetic alterations in fibroblast growth factor receptors 2 and 3 (*FGFR2/3*) occur in nearly all cancer types. *FGFR2* fusions and rearrangements occur in up to 10-15% of intrahepatic cholangiocarcinomas (iCCA) and alterations in *FGFR3* occur in 15-30% of urothelial cancers. The clinical benefit from currently approved FGFR inhibitors (FGFRi) is often curtailed by development of acquired resistance, which may arise through on-target mutations in the *FGFR2/3* kinase domain. Additionally, off-tumor effects on FGFR1 by pan-FGFRi can lead to hyperphosphatemia and consequently to dose reductions or dose holds. Thus, there is an unmet clinical need for a selective FGFR2/3 inhibitor that has clinical efficacy against activating alterations and resistance mutations without causing FGFR1-mediated hyperphosphatemia. CGT4859 is an orally bioavailable, ATP-competitive, reversible inhibitor of FGFR2/3, with potency against clinically relevant *FGFR2/3* kinase domain mutations. In addition, CGT4859 demonstrates >140 fold selectivity over FGFR1, and shows robust efficacy in target altered *in vivo* tumor models without increases in serum phosphorus. Nonclinical pharmacokinetics (PK) and safety data support evaluating CGT4859 in a first-in-human, open-label, dose-escalation and signal-seeking Phase I/II study (NCT06777316). Safety, tolerability, PK, pharmacodynamics, and antitumor activity of CGT4859 will be assessed in adults with histologically confirmed unresectable or metastatic iCCA or other solid tumors with *FGFR2/3* alterations. **Methods:** CGT4859 will be administered orally continuously in 28-day cycles to patients (N=~50) at a starting dose of 1 mg QD, and dose escalation will not exceed 40 mg QD as determined using a Bayesian optimal interval design with backfill (BF-BOIN). This approach will be used to guide dose escalation and establish the maximum tolerated dose (MTD) and recommended Phase 2 Dose (RP2D). BF-BOIN enables backfilling of participants to doses that are cleared for safety during the dose escalation, generating additional data on safety and tolerability below the MTD. Objective response rate (ORR) and disease control rate will be determined based on investigator assessment using RECIST v1.1. Phase II will enroll up to 4 cohorts, each enrolling ~15 patients. Proposed cohorts will include participants who have iCCA and are either FGFRi-naïve or FGFRi-exposed. Two additional cohorts with other advanced solid tumors harboring *FGFR2/3* alterations may be included based on signals detected in dose escalation. The primary efficacy endpoint for Phase II is ORR per RECIST v1.1. The preclinical data support the study of CGT4859 in this patient population with solid tumors harboring *FGFR2* and/or *FGFR3* genetic alterations. The phase I dose escalation study is currently enrolling at sites in the United States. Clinical trial information: NCT06777316. Research Sponsor: Cogent Biosciences.

TPS3172 **Poster Session**

Phase IB/II study to evaluate safety and preliminary efficacy of the WEE1 inhibitor Debio 0123 in combination with sacituzumab govitecan (SG) in triple-negative or hormone receptor–positive (HR+)/HER2-negative (HER2–) advanced breast cancer (ABC): The WIN-B study. First Author: Timothy J. Robinson, University of Bristol, Bristol, CT, United Kingdom

Background: SG is a Trop-2 directed antibody drug conjugate that has shown an overall survival benefit for patients (pts) with HER2- ABC in two phase III trials. Unfortunately, most pts become refractory to this treatment, highlighting a critical need for strategies to overcome resistance to SG and improve therapeutic outcomes. WEE1 is a cyclin-dependent kinase 1 regulator, which delays the G2/M transition and maintains genomic stability during the cell cycle. Debio 0123, a highly selective and brain penetrant WEE1 inhibitor, has demonstrated synergistic activity in breast cancer preclinical models with SG. The aim of the WIN-B study is to evaluate the safety and preliminary efficacy of combining the WEE1 inhibitor Debio 0123 with SG in pts with previously treated HER2-ABC. **Methods:** WIN-B (NCT06612203) is an international, multicenter, open-label, single-arm phase Ib/II trial. In phase Ib, 12-24 pts will be assigned to different Debio 0123 dose cohorts (200, 300, 400, or 520 mg orally once daily on days 1-3 and 8-10) plus standard doses of SG (10 mg/kg intravenously on days 1 and 8) given in 3-week cycles. In phase II, 52 pts will be divided into cohorts A (triple-negative breast cancer [TNBC], n = 26) and B (HR+/HER2– tumors, n = 26), and will be treated with the recommended doses determined during phase Ib. Key inclusion criteria are: pts aged ≥18 with TNBC or HR+/HER2- tumors who have experienced disease progression after 1 or 2 lines of systemic therapy for ABC, ECOG performance status of 0-1, with evaluable (for phase Ib) or measurable (for phase II) disease as per RECIST v.1.1. Pts will receive study treatment until progression, death, unacceptable toxicity, or study discontinuation. Primary objectives are: in phase Ib, to establish the recommended phase 2 dose of the combination of Debio 0123 plus SG and, in phase 2, to assess the objective response rate (ORR) as per RECIST v.1.1. Key secondary endpoints are progression-free survival and overall survival, safety and toxicity. In phase Ib, dose escalation will be performed using a Bayesian Logistic Regression Model with overdose control. In phase 2, A'Hern one-stage design will be set at one-sided type I binomial exact test of 5% to attain 80% power. The primary analyses will estimate ORR (H0: ORR≤29% for TNBC and ORR≤19% for HR+/HER2- tumors vs H1: ORR≥55% for TNBC and ORR≥41% for HR+/HER2- tumors). The phase 2 part of the study will be deemed positive if at least 12 (46.2%) and nine (34.6%) pts with TNBC and HR+/HER2- tumors, respectively, achieve an objective response. Clinical trial information: NCT06612203. Research Sponsor: Debiopharm. Gilead will provide the supply of SG.

TPS3173 **Poster Session**

Trial in progress: First-in-human study of PFL-721/STX-721 in participants with locally advanced or metastatic non-small cell lung cancer harboring EGFR exon 20 insertion mutations. First Author: Anas Gazzah, Gustave Roussy, Villejuif, France

Background: Mutations in exon 20 of the *EGFR* gene account for approximately 4% to 10% of all EGFR mutations in Non-Small Cell Lung Cancer (NSCLC). Most of these mutations are insertions (EGFR ex20ins) that reduce the binding of first, second, and third generation tyrosine kinase inhibitors (TKI) to the ATP-binding pocket of the EGFR. Amivantamab, a bispecific anti-EGFR/c-MET-receptor antibody, is approved for the treatment of NSCLC with EGFR ex20ins mutations. However, there is significant unmet need for new oral agents that lack the limitations of intravenous administration and associated infusion-related toxicities and possess improved target engagement, mutant selectivity, and tolerability. PFL-721/STX-721 is an orally bioavailable, irreversible small-molecule inhibitor targeting a broad range of EGFR- and HER2-activating ex20ins mutations. PFL-721/STX-721 is highly selective for EGFR ex20ins mutations compared to wild type EGFR and exhibits greater selectivity compared to other EGFR mutant inhibitors. In addition, PFL-721/STX-721 has demonstrated superior anti-proliferation and antitumor effects compared to other investigational anti-EGFR ex20ins agents in relevant tumor models *in vitro* and *in vivo*. These observations suggest a more robust clinical risk-to-benefit profile and support further clinical investigation of PFL-721/STX-721. **Methods:** PFL-721/STX-721-101 (NCT06043817) is an open-label, first-in-human (FIH), Phase 1/2 study evaluating the safety, tolerability, pharmacokinetic (PK) exposure, and preliminary antitumor activity of PFL-721/STX-721 in participants with locally advanced or metastatic NSCLC harboring EGFR/HER2 ex20ins mutations. It consists of 3 parts: Part 1 Dose Escalation, Part 2 Recommended Phase 2 Dose (RP2D) selection, and Part 3 Dose Expansion. In Part 1, participants with NSCLC harboring EGFR or HER2 ex20ins mutations will be enrolled into sequential cohorts to receive ascending oral doses of PFL-721/STX-721 administered daily in 28-day treatment cycles. The main goal is to identify the maximum tolerated dose (MTD) and optimal biological dose (OBD) of PFL-721/STX-721. In Part 2, participants with NSCLC harboring EGFR ex20ins mutations who have received 1 to 2 prior lines of treatment, including a platinum-containing chemotherapy regimen and excluding EGFR targeted therapies with the exception of amivantamab, will be randomized 1:1 to receive PFL-721/STX-721 at the MTD or OBD in order to determine the optimal RP2D. Finally, Part 3 will further test the anticancer efficacy of PFL-721/STX-721 is administered at the RP2D. PFL-721/STX-721-101 is actively enrolling at 18 sites in 7 countries globally. Clinical trial information: NCT06043817. Research Sponsor: Scorpion Therapeutics, Inc.

TPS3174 **Poster Session**

A phase 1/2 dose escalation study of the oral DNA polymerase theta inhibitor (POLQi) GSK4524101 ± niraparib in adults with advanced or metastatic solid tumors. First Author: Vivek Samnotra, GSK, Waltham, MA

Background: In homologous recombination-deficient (HRd) tumors, use of a PARP inhibitor (PARPi) leads to generation of DNA breaks that cannot be effectively repaired, thus selectively killing cancer cells via synthetic lethality. An alternative DNA repair mechanism, microhomology-mediated end joining, is mediated by DNA polymerase theta (encoded by *POLQ*). In preclinical studies, POLQi + PARPi demonstrated superior efficacy vs PARPi alone in preventing HRd tumor growth. To evaluate the clinical potential of this combination, this first-in-human study investigates treatment with GSK4524101, an investigational POLQi, and niraparib, a PARPi, in patients with solid tumors. **Methods:** This open-label, phase 1/2, multicenter study opened in October 2023 and includes a phase 1a/b, dose-escalation portion (part 1; potential enrollment to n≈75). Sites in the US and Canada are enrolling patients for part 1, which aims to assess the maximum tolerated dose, pharmacokinetics (PK), and safety of oral GSK4524101 ± oral niraparib. Eligibility criteria include age ≥18 years, Eastern Cooperative Oncology Group performance status of 0–2, life expectancy ≥3 months, and diagnosis of advanced or metastatic solid tumor with all standard-of-care treatment options exhausted. Exclusion criteria include unresolved chemotherapy-induced adverse events (AEs) or symptomatic uncontrolled brain or leptomeningeal metastases, uncontrolled hypertension, history of myelodysplastic syndrome or acute myeloid leukemia, or another malignancy that has progressed or required active treatment in the past 2 years. Outcome measures include dose-limiting toxicity (DLT) incidence during the DLT observation periods (up to 28 days; primary); treatment-emergent AEs (TEAEs) and serious AEs (SAEs); percentage of patients receiving all planned doses; and percentage of patients requiring AE-related dose interruptions, reductions, and discontinuations in the DLT observation period. Secondary endpoints include the PK of niraparib and the metabolite of GSK4524101 and incidence and duration of TEAEs and SAEs beyond the DLT observation period. The study is currently recruiting, with 17 patients having received doses across 9 sites in 2 countries as of January 10, 2025. Clinical trial information: NCT06077877. Research Sponsor: GSK.

TPS3175 **Poster Session**

A phase 1 study to evaluate the safety, pharmacokinetics, and efficacy of the first-in-class cyclin A/B RxL inhibitor CID-078, an orally bioavailable, cell-permeable macrocycle. First Author: Nehal J. Lakhani, The START Center for Cancer Research, Grand Rapids, MI

Background: The cyclin-dependent kinase (CDK)-RB-E2F axis forms the core transcriptional machinery driving cell cycle progression. Alterations in *RB1* or other key components occur in many cancers, resulting in heightened oncogenic E2F activity. E2F activation relies on the interaction between the cyclin's conserved hydrophobic patch (HP) and the RxL motif found on E2F and other cyclin/CDK substrates. Disrupting this cyclin A/E2F RxL interaction leads to hyperactivation of E2F and synthetic lethality in E2F-driven tumors. CID-078 is a novel, orally bioavailable, passively cell-permeable, potent and selective macrocycle that binds to the HP of cyclins A and B, blocking the RxL motif-mediated binding of E2F1 to cyclin A2-CDK2 and Myt1 to cyclin B1-CDK1. Consequently, CID-078 induces cell cycle arrest at the G2/M phase, leading to apoptotic tumor cell death. In preclinical studies including small cell lung cancer (SCLC) and triple negative breast cancer (TNBC) tumor types, CDX and PDX models with high E2F target pathway scores and high E2F1 expression demonstrated tumor regression following single-agent CID-078 treatment. Pre-clinical species demonstrate a well-tolerated safety profile and 20% oral bioavailability. Preclinical to clinical predictions maintain a 20% bioavailability. **Methods:** This is a phase 1, first-in-human, open-label, multicenter, dose escalation and dose expansion study to evaluate the safety, tolerability, pharmacokinetics (PK) pharmacodynamics (PD) and preliminary anti-tumor efficacy of CID-078 in patients (pts) with locally advanced or metastatic solid tumor malignancies (NCT06577987). Pts previously treated with standard of care therapy and for whom no available curative therapy exists are eligible. CID-078 will be administered orally, twice-daily in repeating 21-day cycles and treatment will continue until disease progression, death, unacceptable toxicity or withdrawal from study. Part I dose escalation will be guided by a Backfill-Bayesian Optimal Interval Design (BF-BOIN) based on the incidence of dose-limiting toxicities (DLTs) and all available safety and PK data. Under the BF-BOIN design, additional pts may be enrolled to expand previous cohorts to better characterize the safety, PK, PD and preliminary efficacy activity to support a recommended dose for expansion. A pilot food effect cohort is planned as well. In Part II dose expansion, pts will be enrolled to one or more cohorts defined by histologic tumor type or molecular alteration at the recommended doses of expansion. Based on preclinical data generated to date, the study plans to include patients with SCLC, TNBC, and RB1-mutated tumors with additional tumor types expanded based on observed efficacy. Dose escalation is ongoing with no DLT reported in the initial 3 dose cohorts evaluated. Clinical trial information: NCT06577987. Research Sponsor: None.

TPS3176 **Poster Session**

First in human phase 1 dose escalation and expansion clinical trial to evaluate the safety, pharmacokinetics and antitumor activity of intravenous AROG4-01 in patients with advanced solid tumors. First Author: Sonia Macia, Applied Research using OMIC Sciences, Barcelona, Spain

Background: AROG4-01 is a synthetic compound with a first-in-class mechanism of action, targeting complex secondary structural elements in mRNA, including G-quadruplexes(G4s). These secondary nucleic acid structures, characterized by Hoogsteen base pairing, play pivotal roles in gene regulation and are abundant in cancer cells due totheir high proliferation rates and dysregulated gene expression patterns. By binding to G4s present in untranslated regions, AROG4-01 modulates gene expression atthe post-transcriptional level, reducing tumor growth and survival. Preclinical studies have demonstrated that AROG4-01 achieves significant antitumor activity,inhibiting cancer cell proliferation, with a strong effect of the compound on inhibit colony formation, evidencing the capacity of AROG4-01 to prevent the long-termsurvival and proliferation of cancer cells. This activity has been validated in vivo across multiple solid cancer models. **Methods:** This study (NCT06652529,EudraCT2024-517569-18) is an open label, Phase 1 dose escalation trial with two expansion cohorts to investigate the safety, tolerability, pharmacokinetics,pharmacodynamics and preliminary antitumor activity of AROG4-01. The study consists of two parts. Part A is a dose escalation that will include 8-20 patients withadvanced solid tumors, covering up to 6 dose levels with the primary objective of determining the safety and tolerability of AROG4-01 and defining an appropriaterecommended phase 2 dose (RP2D) for further evaluation in part B. The study will start with an accelerated-titration dose escalation scheme enrolling one evaluablepatient per cohort for the first 2 dose levels followed by a classic 3+3 design. Part B is a dose expansion, with two cohorts of ten patients: one cohort of patients withadvanced mesothelioma (cohort 1) and a second cohort of patients with other solid tumors (cohort 2). Serum samples collected from patients enrolled in part A whenreceiving the first IMP dose during the first treatment cycle will be used to assess the PK of AROG4-01. Three sites in Spain are expected to participate. Clinical trial information: NCT06652529. Research Sponsor: Applied Research using Omic Sciences.

TPS3177 **Poster Session**

IMMUNONET: A multicenter, open-label, proof-of-concept phase II trial evaluating NP137 as add-on therapy in advanced/metastatic solid tumors treated with standard immunotherapies. First Author: Jérôme Fayette, Centre Léon Bérard, Lyon, France

Background: PD-1/PD-L1 blockade has transformed oncology by offering durable responses in various cancers. However, many patients develop resistance, highlighting the need for novel therapeutic strategies. Epithelial-to-Mesenchymal Transition (EMT) plays a pivotal role in immune checkpoint inhibitor efficacy, with epithelial tumors exhibiting greater immunoreactivity than mesenchymal ones. NP137, a first-in-class anti-Netrin-1 monoclonal antibody, has shown in phase I study the ability to inhibit EMT, potentially overcoming resistance (Cassier et al., *Nature*, 2023). This phase I data demonstrated NP137's ability to shift tumors toward an epithelial phenotype, supporting its combination with immune checkpoint inhibitor to sensitize tumors and alleviate resistance. The goal of IMMUNONET study (NCT05605496) is to evaluate NP137's ability to re-sensitize advanced solid tumors to anti-PD-1/PD-L1 therapy. **Methods:** This proof-of-concept study assess NP137 (14 mg/kg, IV, Q3W) as add-on therapy to standard PD-1/PD-L1 inhibitors across three independent cohorts of patients with advanced/metastatic solid tumors of any histological types: Cohort 1 (Stable Disease [SD]): Radiological SD after $\geq$12 weeks of anti-PD-1/PD-L1 therapy. Cohort 2 (Primary Refractory): Radiological progressive disease (PD) and no response under anti-PD-1/PD-L1 therapy. Cohort 3 (Secondary Refractory): Radiological PD following initial response under anti-PD-1/PD-L1 therapy. Treatment continues until progression, unacceptable toxicity, or consent withdrawal. The primary endpoint is clinical activity: objective response rate (ORR)-12W for cohort 1 and progression-free rate (PFR)-12W for cohorts 2 and 3. Secondary endpoints include ORR-12W (cohorts 2 and 3), Time to Objective Response (ToR), Duration of Response (DoR) and safety for all cohorts. Evolution of EMT, Netrin-1, and receptor expression will be analysed and correlated with clinical outcomes. An adaptive 2-stage design is being used for this study (Lin and Shih, Biometrics 2004). The target levels of clinical activity are set at 20% (relevant) and 25% (high). In stage 1, 18 patients will be enrolled at 1-sided alpha of 5%. Depending on the observed success rate, additional 11 patients (if 1 or 2 successes) or 5 patients (if $>$ 2 successes) could be recruited into stage 2. Null hypotheses will be rejected if $\geq$4 successes are observed in 29 [test p_0 = 0.05 vs. 0.20, 80% power] or 23 patients [test p_0 = 0.05 vs. 0.25, 90% power], respectively. Current Status: Cohort 1 has been closed due to non-feasibility. Prespecified goals for the first stage were met, stage 2 enrolment is underway. Cohort 2 has enrolled 21 patients, and cohort 3 has enrolled 19 of 23 planned evaluable patients. Clinical trial information: NCT05605496. Research Sponsor: European Innovation Council.

TPS3178 **Poster Session**

Trial in progress: Phase 1 study of the selective protein degrader ASP4396 in patients with locally advanced or metastatic solid tumors with *KRAS G12D* mutations. First Author: Shiraj Sen, NEXT Oncology, Dallas, TX

Background: *KRAS G12D* is the most common *KRAS* mutation at codon 12 found in solid tumors and is difficult to target. There are no approved therapies directly targeting *KRAS G12D*. Targeted protein degradation is emerging as a promising therapeutic approach for undruggable targets. ASP4396, a novel protein degrader, targets KRAS G12D-mutated protein for degradation via the ubiquitin-proteasome system. This mode of action may offer higher efficacy and safety compared with inhibitors by blocking both enzymatic and scaffolding functions of proteins and by higher target selectivity. This first-in-human study aims to evaluate the safety and efficacy of ASP4396 in patients with advanced solid tumors with *KRAS G12D* mutations (NCT06364696). **Methods:** This Phase 1, open-label, multicenter, dose-escalation and dose-expansion study of ASP4396 is enrolling adult patients with locally advanced (unresectable) or metastatic solid tumors with documented *KRAS G12D* mutations who have $\geq$ 1 measurable lesion per Response Evaluation Criteria in Solid Tumors (RECIST) version (v)1.1, ECOG performance status of 0 or 1, adequate organ function, and who did not respond or who are ineligible for standard therapies. Tumor-specific dose expansion cohorts may be enrolled at the maximum tolerated dose (MTD) and/or candidate recommended phase 2 dose (RP2D). Patients who received prior treatment targeting KRAS G12D will be excluded. Primary endpoints are safety and tolerability (assessed by dose-limiting toxicities [DLTs], adverse events, laboratory and other standard tests), and RP2D and/or MTD of ASP4396. Secondary endpoints are antitumor activity (objective response rate, duration of response, disease control rate, and progression-free survival per RECIST v1.1 by investigator assessment; and overall survival), and pharmacokinetic/ pharmacodynamic assessments. In the dose escalation cohort, patients will receive increasing doses of ASP4396 intravenously in a 21-day cycle. The target enrollment for each dose level is set at 1 DLT-evaluable patient for dose levels 1–3 and $\geq$ 3 DLT-evaluable patients for each subsequent dose level. The study will consist of 3 periods: screening (up to 28 days), treatment (every 21-day cycle until treatment discontinuation criteria are met), and follow-up. Data will be summarized descriptively (mean, standard deviation, median) for continuous endpoints, and by counts and percentages for categorical endpoints. Study enrollment is ongoing. Clinical trial information: NCT06364696. Research Sponsor: Astellas Pharma Inc.

TPS3180 **Poster Session**

Phase 1 first-in-human clinical trial of AG01, a recombinant monoclonal antibody to progranulin/glycoprotein 88 (PGRN/GP88), to determine the safety, tolerability, pharmacokinetics, and preliminary anti-tumor response in subjects with advanced solid tumor malignancies. First Author: Katherine H. R. Tkaczuk, University of Maryland Greenebaum Comprehensive Cancer Center, Baltimore, MD

Background: GP88/PGRN is the largest member of the granulin/epithelin family. We demonstrated GP88's role as an autocrine growth & survival factor in breast cancer (BC): in ER+BC cells, GP88 stimulates proliferation & confers resistance to anti-estrogen therapy & aromatase inhibitors;GP88 is expressed in 80% of invasive ductal carcinomas & is negative in normal mammary tissue; GP88 tumor expression is a prognostic indicator of recurrence & death in BC pts; Elevated GP88 serum level in metastatic BC patients (pts) is associated with disease progression. PGRN/GP88 is overexpressed in several other solid tumors (non-small cell lung carcinoma, colorectal, bladder, ovarian, prostate & brain). In advanced NSCLC & prostate pts, elevated serum PGRN/GP88 have been found. These results make GP88/PGRN an ideal therapeutic & diagnostic target in BC and other solid tumors. An anti-human PGRN/GP88 monoclonal antibody (AG01) inhibiting PGRN/GP88 action was developed & expressed as recombinant antibody in CHO cells. Pharmacology, GMP manufacturing, formulation, stability studies & GLP toxicology studies in non-human primates were done. The IND application was cleared by the FDA to proceed with the first-in-human (FIH) AG01 study in adult subjects with advanced solid tumors. **Methods:** This IRB approved FIH study, will be conducted in 2 stages, dose escalation (1A) and dose expansion (1B). The 1A part is ongoing, with the 1 + (3+3) design. In the 1A part the AG01 is administered intravenously (IV) over 90 min. every 14 days +/- 1 day, 1 cycle = 28days, DLT assessments occur in the first 28 days of treatment. Five dose levels of AG01 & a -1 level are planned (level -1-0.5mg/kg, & 1mg/kg, 2mg/kg, 4mg/kg, 6mg/kg, 8 mg/kg). In 1A part of the study, initially an accelerated titration design (1pt/dose level) was utilized to guide dose progression & estimation of the maximum tolerated and/or administered dose (MTD/MAD). Eligibility criteria for 1A part include pts with advanced relapsed/refractory solid tumor malignancies who failed 1 or more standard of care (SOC) therapies or for whom no SOC treatment exists or is not tolerated, at least 1 RECIST1.1 measurable lesion, ECOG $<$ = 2, Life expectancy $>$ = 12wks, adequate organ & bone marrow function, willing to sign informed consent & follow study procedures. Primary objective (1A) is to determine the MTD and/or MAD of AG01. Secondary objectives: to determine the recommended phase 2 dose (RP2D), safety, tolerability, the PKs, immunogenicity & the preliminary anti-tumor activity of AG01. Exploratory objectives:todetermine PGRN/GP88 expression in tumor tissue & PGRN/ GP88 blood levels (A&G's IHC & ELISA test). This study is registered at NCT05627960. The study is supported by NCI grants NCI R44 CA224718 & CA162629. Clinical trial information: NCT05627960. Research Sponsor: National Cancer Institute; National Cancer Institute.

TPS3181 **Poster Session**

Trial in progress: First-in-human study of ATX-559, an oral inhibitor of DHX9, in patients with advanced or metastatic solid tumors, and molecularly defined cancers. First Author: Meredith Pelster, Sarah Cannon Research Institute, Nashville, TN

Background: DHX9 is a multifunctional RNA helicase that is involved in the maintenance of genomic stability by resolving DNA/RNA secondary structures that may lead to DNA replication stress and DNA damage. High expression of DHX9 is evident in multiple cancer types. ATX-559, an oral inhibitor of DHX9, has been shown preclinically to induce robust anti-tumor activity of a variety of different solid tumors with genomic instability, including models with BReast CAncer gene 1 and/or 2 alterations or deficiency (BRCA deficient) and microsatellite instability-high (MSI-H) and/or deficient mismatch repair (dMMR). **Methods:** This is a first-in-human, Phase 1, open-label, single-arm, dose-escalation and expansion study to evaluate the safety profile of ATX-559 and to determine the recommended phase 2 dose (RP2D). In dose-escalation, patients with locally-advanced or metastatic solid tumors, and molecularly-defined cancers will be enrolled for safety assessment, guided by a model-assisted dose escalation design (Yuan, 2019) to identify an acceptable dose. To assess evidence of preliminary antitumor activity in the expansion study, participants with (1) BRCA deficient, HER2-negative, metastatic breast cancer, and (2) dMMR/MSI-H solid tumors will be enrolled using a Simon 2-stage design (Simon, 1989). Primary endpoints include identification of the RP2D dose that is deemed acceptable per the model-assisted dose escalation design and to evaluate safety and tolerability as noted by the frequency and severity of adverse events (AEs). Secondary endpoints will evaluate pharmacokinetics (PK), pharmacodynamics (PD) peripherally and in a biopsy sub-study, and preliminary anti-tumor activity per RECIST v1.1. Exploratory objectives will explore potential biomarkers in relationship to ATX-559 exposure, as well as those that may correlate with treatment outcomes. A randomized cohort has also been included during dose expansion in recognition of Project Optimus. The study is open and enrollment is ongoing. Clinical trial information: NCT06625515. Research Sponsor: Accent Therapeutics.

TPS3182 **Poster Session**

A phase 1/2 study of JK06, a 5T4 antibody drug conjugate, in patients with unresectable locally advanced or metastatic cancer. First Author: Nuria Kotecki, Université libre de Bruxelles (ULB), Hôpital Universitaire de Bruxelles (H.U.B), Institut Jules Bordet, Brussels, Belgium

Background: 5T4, a Type I transmembrane glycoprotein, plays a pivotal role in neonatal development, but its expression in normal adult tissues is limited. In contrast, 5T4 emerges prominently in a broad spectrum of solid tumors, including but not limited to NSCLC, breast, ovarian, endometrial, bladder, pancreatic, esophageal, gastric and colorectal cancers. Furthermore, the expression of 5T4 is confirmed to be associated with advanced disease and worse clinical outcomes in multiple solid tumors. These features make 5T4 an attractive, but as of yet unexploited, target for cancer therapeutics. JK06 is an antibody-drug-conjugate (ADC) targeting 5T4-expressing cancer cells. The antibody moiety of JK06 has a high-affinity tetravalent binding capacity, compensating for generally low 5T4 expression levels. Further, the JK06 binding specificity is biparatopic, targeting two non-overlapping epitopes on 5T4 antigens. In this way, JK06 cross-links 5T4 on the surface of cancer cells, which enhances internalization and increases intracellular release of the cytotoxic payload. The cytotoxic payload of JK06 is the clinically proven microtubule-disrupting agent, MMAE, that inhibits cell division by preventing the polymerization of tubulin, leading to cell cycle arrest and apoptosis. JK06 mediates cytotoxicity in vitro, in a 5T4 receptor density dependent manner, and anti-tumor activity has been demonstrated in several murine xenograft models. JK06 has been shown to bind to recombinant human and cynomolgus 5T4, supporting the translation of pre-clinical toxicology studies. Preclinical toxicology studies showed no toxicity with JK06 at dose levels up to 17 mg/kg single dose and 9 mg/kg repeat dose. Toxicokinetic analysis and PK modeling suggest that a Q3W dosing regimen should provide adequately sustained exposure in clinical studies. In summary, preclinical studies support clinical development of JK06 for the treatment of multiple 5T4 expressing solid tumors. **Methods:** The Phase 1/2 study of JK06 will enroll patients with advanced relapsed/refractory solid tumors. The study will employ a 3+3 escalation design to explore the safety, PK and preliminary anti-tumor activity of JK06. Back-fill enrollment at specific dose levels is permitted but mandates fresh tumor biopsy. Patients will receive treatment with JK06 intravenously once every three weeks until confirmed disease progression or intolerable toxicity. Tumor specific expansion cohorts will be initiated once dose and schedule are established from dose escalation; fresh tumor biopsies will also be collected from patients enrolled in expansion cohorts. Response will be assessed every 9 weeks per RECIST v1.1. Clinical trial information: NCT06667960. Research Sponsor: None.

TPS3183 **Poster Session**

A phase I/Ib study of olaparib and ASTX727 in BRCA 1/2- and HRD-mutated tumors. First Author: Pamela N. Munster, UCSF Helen Diller Family Comprehensive Cancer Center, San Francisco, CA

Background: Patients with germline or somatic HRR pathway mutations often develop resistance despite initial response. Overlapping toxicities hinder combination strategies in breast, ovarian, prostate, and pancreatic cancers, creating a need for safer and more effective approaches. Preclinical studies have shown that DNMT inhibition enhances PARP inhibitor efficacy by promoting PARP trapping on DNA. This phase I study aims to assess the safety and tolerability of olaparib and AST727 in HRR-mutated patients and establish the RP2D for a phase II trial, to be supported by the NCI ComboMatch program. Correlative studies include the creation of PDX and organoid models for ex vivo analysis of therapy response. **Methods:** Further studies include cfDNA and tumor tissue assessment to elucidate mechanisms of resistance (reversion mutations, epigenetic markers) and PD markers of HR pathway modulation. Rad51 foci will be measured to determine DNA repair function and CHIP assays (clonal hematopoiesis of indeterminate potential) to study the differential rate of CHIP as an early event in the evolution of AML/MDS. Trial Design: This is a single center phase I/Ib clinical trial evaluating the combination of olaparib and ASTX727 (an oral formulation of decitabine with cedazuridine, a cytidine deaminase inhibitor that allows for oral administration). All participant enrollment and study participation will be conducted at UCSF as single site trial with collaboration from other centers for correlative/exploratory objectives. The phase I dose escalation portion will follow a standard 3+3 design for enrollment and will include adults with advanced/metastatic solid tumor malignancies with germline or somatic mutations in the HRR pathway (i.e., BRCA1/2, PALB2, ATM, and/or CHEK2 mutations). Patients will be treated in 2 escalating cohorts with a 12 patient phase Ib dose expansion in the same population. At least 6 of 12 expansion patients must have germline HRD mutations. Key Eligibility: The participant must have histologically confirmed advanced solid tumors with a germline and/or somatic mutation in one or more of the following genes: BRCA1/2, PALB2, ATM, and/or CHEK2. Patients must have adequate organ function and recovered from prior treatment associated toxicities. Prior treatment with PARP inhibitors is allowed if the participant has not required dose reductions or delays due to toxicity. Participants with treated brain metastases are eligible if follow-up brain imaging shows no evidence of progression for at least 4 weeks. Individuals with a prior or concurrent malignancy are eligible, however participants diagnosed with MDS or AML are excluded from the study. Trial Status: The study is ongoing and 4 patients have been enrolled to date. Clinical trial information: NCT06177171. Research Sponsor: National Cancer Institute/U.S. National Institutes of Health.

TPS3184 **Poster Session**

RYZ101 (^{225}Ac-DOTATATE) in patients with estrogen receptor-positive, human epidermal growth factor receptor 2–negative, locally advanced and unresectable, or metastatic breast cancer progressing after prior therapy: The phase 1b/2 TRACY-1 study. First Author: Erica L. Mayer, Medical Oncology, Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA

Background: RYZ101 (actinium-225 [^{225}Ac]-DOTATATE) is a radiolabeled somatostatin analog (SSA) for the treatment of patients with solid tumors expressing somatostatin receptor-type 2 (SSTR2). RYZ101 is composed of the alpha-emitting radioisotope ^{225}Ac, the chemical chelator DOTA (tetraxetan), and SSA octreotate (TATE). RYZ101 binds with high affinity to SSTR2 on the cell surface and is internalized, whereupon the alpha-particle emission of ^{225}Ac results in lethal double-strand DNA breaks. Although SSTR-directed therapy is widely used in patients with well-differentiated gastroenteropancreatic neuroendocrine tumors (GEP-NETs), its relevance in non-GEP-NET SSTR-expressing neoplasms is still emerging. Clinical positron emission tomography (PET) imaging studies have reported SSTR expression in estrogen receptor (ER)-positive breast cancer. Available data support investigating the efficacy of RYZ101 in patients with ER-positive, HER2-negative, locally advanced and unresectable or metastatic breast cancer. **Methods:** TRACY-1 (NCT06590857) is a global, multicenter, open-label, two-part (dose escalation and expansion) phase 1b/2 study. Key inclusion criteria are: age ≥18 years; histologically confirmed, ER-positive, HER2-negative locally advanced and unresectable or metastatic breast cancer not amenable to curative-intent treatment; endocrine-refractory disease; documented progression (per RECIST v1.1) after ≥2 and ≤4 prior lines of chemotherapy and/or ADC (≥1 must be ADC if the patient is a candidate for ADCs and treatment is available); ≥1 RECIST-measurable SSTR−PET-positive lesion and ≥80% of RECIST-measurable lesions being SSTR−PET-positive on screening scan. Key exclusion criteria are: prior radiopharmaceutical therapy; prior anticancer therapy or external beam radiotherapy in past 4 weeks; anticancer hormonal treatments in past 2 weeks. Primary objectives are to determine the recommended phase 2 dose (R2PD) of RYZ101 (dose escalation; anticipated 6−24 patients), and the efficacy of RYZ101 at the RP2D defined as ORR as determined by BICR (dose expansion; approximately 100 patients). During dose escalation, patients will receive RYZ101 by IV infusion every 6 weeks for up to 6 cycles at a starting dose of 6.5 MBq (dose level [DL] 1), with escalation to DL 2 (8.3 MBq) and DL 3 (10.2 MBq), or dose de-escalation to 4.6 MBq if DL 1 is not tolerated, based on dose-limiting toxicity rates. In the expansion phase, patients will receive RYZ101 at the RP2D. Concomitant amino acid IV infusions (containing L-arginine and L-lysine) will be co-infused with RYZ101 for renal protection. The study is ongoing and enrolling patients in the USA. Clinical trial information: NCT06590857. Research Sponsor: RayzeBio.

TPS3185 **Poster Session**

panSOHO: Phase II trial of BAY 2927088 in patients with unresectable or metastatic solid tumors other than NSCLC with *HER2*-activating mutations. First Author: Vivek Subbiah, Sarah Cannon Research Institute, Nashville, TN

Background: Human epidermal growth factor receptor 2 (*HER2*) gene mutations occur in approximately 3.5% of solid tumors, with a frequency varying from less than 1% to 9%, depending on the tumor type. BAY 2927088 is an oral, reversible tyrosine kinase inhibitor that potently inhibits HER2 and mutant epidermal growth factor receptor and has shown clinical benefit based on preliminary evidence from the Phase I/II SOHO-01 trial in patients with *HER2*-mutant non-small cell lung cancer (NSCLC; PL04.03 presented at IASLC 2024 World Conference on Lung Cancer), an indication for which the FDA has granted Breakthrough Designation. Here we introduce the panSOHO trial evaluating the efficacy and safety of BAY 2927088 in patients with unresectable, locally advanced or metastatic solid tumors with *HER2*-activating mutations. **Methods:** panSOHO is a Phase II, open-label, multicenter, multinational, single-arm basket trial of BAY 2927088 in patients with unresectable or metastatic solid tumors with *HER2*-activating mutations (NCT06760819), and will be conducted in the USA, Europe, and the Asia-Pacific region. Eligibility criteria include patients aged ≥18 years with: documented histologically or cytologically confirmed, locally advanced or metastatic solid tumor cancer (colorectal, biliary tract, bladder and urothelial tract, cervical, endometrial, or other solid tumor); documented activating HER2 mutation; ≥1 measurable lesion per RECIST v1.1; and previous standard therapy or no satisfactory alternative treatment options. Key exclusion criteria include primary diagnosis of NSCLC, treatment with a HER2 tyrosine kinase inhibitor, untreated active brain metastases, and leptomeningeal disease. Overall, 111 eligible patients will receive BAY 2927088 p.o. 20 mg twice daily in 3-week cycles until disease progression, unacceptable toxicity, or study withdrawal. The primary outcome is BAY 2927088 efficacy on objective response rate per RECIST v1.1 as assessed by blinded independent central review (BICR). Secondary outcomes include BAY 2927088 efficacy on time to response, duration of response, disease control rate, and progression-free survival per RECIST v1.1 by BICR, and overall survival, and BAY 2927088 safety and tolerability. Impact of BAY 2927088 on patient quality of life will be evaluated by EORTC QLQ-C30. Enrollment is open. Clinical trial information: NCT06760819. Research Sponsor: Bayer AG.

TPS3186 Poster Session

Molecular residual disease (MRD) in solid tumors. First Author: Majd T. Ghanim, Flatiron Health, New York, NY

Background: Pragmatically designed clinical studies facilitate rapid accrual of representative populations by aligning research with routine care and enabling study execution in community practice settings. In addition, the implementation of technologies to streamline patient ascertainment and data collection further reduce site burden and improve efficiency. Herein we describe the initial cohort under a platform study designed with pragmatic elements initiated within a technology-enabled community oncology research network. This substudy establishes a prospective observational registry that collects routinely documented clinical data plus intentionally collected biomarker samples, including blood, for the purpose of isolating circulating tumor DNA at specified intervals to enable exploration of MRD in patients with early stage solid tumors. **Methods:** This is a prospective, multicenter, observational, biospecimen collection study in participants (pts) diagnosed with early stage cancers in select solid tumors who have planned curative-intent surgery. The scientific objective is to collect tumor tissue, longitudinal blood samples, and associated clinical data to explore applications of blood and/or tissue-based cancer biomarkers for cancer detection, prognosis, therapy selection, surveillance, and therapy response. Approximately 1350 pts will be enrolled across ~30 Flatiron Research Network community oncology sites. Participants are grouped by tumor site of origin and histology into 7 cohorts (Table). Patients provide informed consent and are enrolled before starting neoadjuvant or adjuvant therapy. Study visits correspond with routine care. Research tissue and blood samples are obtained upon enrollment and at study-specified intervals up to 5.5 years or until disease recurrence for analysis by Exact Sciences laboratories. Technology enablement includes near real-time, AI-assisted, centralized patient ascertainment and integrated electronic health record-to-electronic data capture system data transfer. Under the parent protocol mechanism, the study was IRB approved 65 days from commencement of protocol writing. Target enrollments are based on the number needed to enroll to observe at least 30 events in 3 years. Clinical trial information: NCT06605404. Research Sponsor: None.

Study cohorts.

Tumor type	Disease stage	Target enrollment
Muscle invasive urothelial carcinoma	II-III	200
Esophageal	I-III	150
Gastric & gastroesophageal junction	I-III	150
Melanoma	II-III	300
Non–small cell lung cancer	I-III	200
Exocrine pancreatic cancer	I-III	150
Other solid tumors (excluding central nervous system, colorectal, breast, skin squamous and basal cell, gastrointestinal stromal tumors, thyroid, uveal melanoma, and low or intermediate grade neuroendocrine tumors)	II-III	200

TPS3187 Poster Session

Beamion PANTUMOR-1: A phase II, multicenter, multicohort, open-label trial to evaluate the efficacy and safety of the oral HER2-selective tyrosine kinase inhibitor zongertinib for the treatment of *HER2*-mutated or overexpressed/amplified solid tumors. First Author: Alison M. Schram, Memorial Sloan Kettering Cancer Center, New York, NY

Background: While it is well known that HER2 overexpression, amplification, and mutation drives various tumors, there remains an unmet need for effective, oral, HER2-targeted therapies. Zongertinib is an irreversible tyrosine kinase inhibitor (TKI) that selectively inhibits HER2 while sparing EGFR, thereby limiting associated toxicities. In the ongoing Phase Ia/Ib trial (NCT04886804), zongertinib showed manageable safety and confirmed responses in patients (pts) with HER2-overexpressed/amplified and *HER2*-mutant tumors (Wilding et al, *Cancer Discov.* 2024). Based on these encouraging data, the Beamion PANTUMOR-1 basket trial (NCT06581432) is evaluating the efficacy and safety of zongertinib monotherapy in pts with *HER2*-mutant or HER2-overexpressed/amplified solid tumors. **Methods:** In this global Phase II basket trial, ~200 pts with HER2-driven (*HER2*-mutant or HER2-overexpressed/amplified) tumors will be enrolled at ~60 sites in 13 countries. Pts will be enrolled to 10 cohorts: 8 cohorts of specific tumor types and 2 tumor-agnostic cohorts (see Table). The specific tumor type cohorts will initially recruit 10 pts, with potential for expansion to up to 20 pts after an interim analysis. In the tumor-agnostic cohorts, 20 pts will be recruited directly without an interim analysis. Pts will receive 120 mg zongertinib until disease progression, unacceptable toxicity, or withdrawal. Patients must be ≥18 years old, have documented HER2-positive (HER2-overexpressed/amplified) status or a *HER2* mutation (established by local testing), ≥1 measurable lesion outside the central nervous system, an ECOG performance score of 0 or 1, and have progressed following prior treatment or have no alternative treatment options. Exclusion criteria include *HER2*-mutant non-small cell lung cancer (NSCLC) and previous/concomitant malignancies. Primary endpoint is objective response, as assessed by central independent review according to RECIST v1.1. Secondary endpoints include duration of response, progression-free survival, disease control, occurrence of treatment-emergent adverse events, and health-related quality of life. Enrollment is ongoing. Clinical trial information: NCT06581432. Research Sponsor: Boehringer Ingelheim.

HER2 overexpression/ amplification cohorts	Tumor type	*HER2* mutation cohorts	Tumor type
Cohort 1	Urothelial cancer	Cohort 7	Urothelial cancer
Cohort 2	Biliary tract cancer	Cohort 8	Breast cancer
Cohort 3	Uterine cancer	Cohort 9	Gastroesophageal cancer
Cohort 4	Cervical cancer	Cohort 10	Other *HER2*-mutant solid tumors†
Cohort 5	Non-squamous NSCLC		
Cohort 6	Other *HER2* overexpressed/ amplified solid tumors*		

*Except breast cancer, gastric, gastroesophageal junction, or esophageal adenocarcinoma.
†Except NSCLC.

TPS3188 Poster Session

Perfume trial: Phase II trial of binimetinib in patients with *BRAF* fusion-positive low-grade glioma or pancreatic cancer. First Author: Tomoyuki Satake, Department of Hepatobiliary and Pancreatic Oncology, National Cancer Center Hospital East, Kashiwa, Japan

Background: *BRAF* fusion was reported to be a rare mutation found in 0.3% of all solid tumors, but a high percentage of BRAF fusion has been reported in pilocytic astrocytoma (30-77%) and pancreatic acinar cell carcinoma (24-67%). Although treatment for *BRAF* V600 mutations has been developed, treatment for *BRAF* fusion has not yet been established. Recently, tovorafenib has been granted accelerated approval by the FDA for pediatric low-grade glioma (LGG) with *BRAF* alteration (including *BRAF* fusion). Still, it is not yet approved in Japan, and an unmet need exists. In *BRAF* fusion-positive solid tumors, the constitutively activated BRAF kinase domain forms dimers that cause activation of the MAPK pathway. MEK inhibitors have been reported to show anti-tumor effects against *BRAF* fusion-positive cell lines. Phase I/II trials with selumetinib or binimetinib have shown efficacy in patients with *BRAF* fusion-positive LGG. **Methods:** Perfume trial (NCCH2101/MK011) is an open-label, parallel, 2-cohort, multicenter, phase II, investigator-initiated registration-directed clinical trial to evaluate the efficacy and safety of binimetinib in patients with advanced or recurrent LGG or pancreatic cancer (PC) harboring *BRAF*fusion/rearrangement. Sample sizes of 16 and 11 patients are needed for LGG and PC at a one-sided significant level of 5% to achieve 85% and 70% power, respectively. Key eligibility criteria for LGG (grade 1 and grade 2 tumors according to WHO classification) include age≧12 (body weight ≧40 kg in 12-17 year old) and KPS/LPS≧70, regardless of history of cancer drug therapy. Key eligibility criteria for PC include age≧12 (body weight ≧40 kg in 12-17 year old); ECOG PS 0-1; refractory or intolerant to at least one prior cancer drug therapy. Enrolled patients receive binimetinib 45mgadministered orally twice daily. The primary endpoint is the objective response rate (ORR) using RECIST 1.1 by independent central review. The secondary endpoints include ORR by investigators' assessment, ORR by RANO in LGG, progression-free and overall survivals, disease control rate, duration of response, and safety. This study implemented a decentralized clinical trial system for patients living in remote areas to reduce their time and economic burden. Enrollment started in March 2023 and is ongoing at 6 facilities in Japan. As of Dec 2024, 6 patients with LGG and 3 patients with PC were enrolled. Clinical trial information: jRCT2031230007, NCT06159478. Research Sponsor: None.

LBA3500 **Oral Abstract Session**

First-line encorafenib + cetuximab + mFOLFOX6 in BRAF V600E-mutant metastatic colorectal cancer (BREAKWATER): Progression-free survival and updated overall survival analyses. First Author: Elena Elez, Department of Medical Oncology, Vall d'Hebron University Hospital (HUVH), Vall d'Hebron Institute of Oncology (VHIO), IOB-Quiron, UVic-UCC, Barcelona, Spain

The full, final text of this abstract will be available at meetings.asco.org on the day of presentation and in the online supplement to the June 10, 2025, issue of the *Journal of Clinical Oncology*.

3501 **Oral Abstract Session**

Nivolumab (NIVO) plus ipilimumab (IPI) vs chemotherapy (chemo) or NIVO monotherapy for microsatellite instability-high/mismatch repair-deficient (MSI-H/dMMR) metastatic colorectal cancer (mCRC): Expanded analyses from CheckMate 8HW. First Author: Heinz-Josef Lenz, University of Southern California Norris Comprehensive Cancer Center, Los Angeles, CA

Background: In the phase 3 CheckMate 8HW study (NCT04008030), both dual primary endpoints of progression-free survival (PFS) for first-line (1L) NIVO + IPI vs chemo (HR 0.21; $P < 0.0001$) and NIVO + IPI vs NIVO across all lines (HR 0.62; $P = 0.0003$) in patients (pts) with centrally confirmed MSI-H/dMMR mCRC were met. We report expanded analyses of NIVO + IPI vs NIVO (all lines) and longer follow-up results for NIVO + IPI vs chemo (1L). **Methods:** The study design was described previously. Pts with MSI-H/dMMR per local testing were enrolled. After randomization, IHC and PCR based tests were used for central confirmation. PFS2 (time from randomization to progression after subsequent systemic therapy, start of second subsequent systemic therapy, or death) was a key exploratory endpoint. **Results:** In all randomized pts (all lines), 296 of 354 (84%) in the NIVO + IPI arm, 286 of 353 (81%) in the NIVO arm, and 113 of 132 (86%) in the chemo arm had centrally confirmed MSI-H/dMMR. In all randomized 1L pts, 171 of 202 (85%) in the NIVO + IPI arm and 84 of 101 (83%) in the chemo arm had centrally confirmed MSI-H/dMMR. Median follow-up was 47.0 mo (range 16.7–60.5). 1L NIVO + IPI continued to show PFS benefit vs chemo (Table). Subsequent systemic therapy was received by 27 (16%) and 61 (73%) pts after 1L NIVO + IPI and chemo, respectively; 10 (6%) and 21 (25%) received subsequent non-study immunotherapy. In the 1L chemo arm, 39 (46%) pts crossed over to NIVO + IPI on study. PFS2 continued to favor 1L NIVO + IPI vs chemo (Table). Across all lines, NIVO + IPI demonstrated superior PFS vs NIVO (Table). Subsequent systemic therapy was received by 54 (18%) pts in the NIVO + IPI arm and 83 (29%) in the NIVO arm; 20 (7%) and 31 (11%) received subsequent non-study immunotherapy. PFS2 favored NIVO + IPI vs NIVO across all lines of therapy (Table). In all treated pts, grade 3/4 treatment-related adverse events occurred in 78 (22%) and 50 (14%) pts in the NIVO + IPI and NIVO arms, respectively. Additional analyses will be presented. **Conclusions:** NIVO + IPI demonstrated sustained clinical benefit vs chemo (1L) and NIVO (all lines) despite use of subsequent therapy, as shown by improved PFS2 in pts with centrally confirmed MSI-H/dMMR mCRC. No new safety signals were observed. These results support NIVO + IPI as a standard of care treatment for MSI-H/dMMR mCRC. Clinical trial information: NCT04008030. Research Sponsor: Bristol Myers Squibb.

Centrally confirmed MSI-H/dMMR (1L)	NIVO + IPI (n = 171)	Chemo (n = 84)
Median PFS (95% CI), mo	54.1 (54.1–NE)	5.9 (4.4–7.8)
HR (95% CI)	0.21 (0.14–0.31)	
Median PFS2 (95% CI), mo	NR (NE–NE)	30.3 (15.2–NE)
HR (95% CI)	0.28 (0.18–0.44)	

Centrally confirmed MSI-H/dMMR (all lines)	NIVO + IPI (n = 296)	NIVO (n = 286)
Median PFS (95% CI), mo	NR (53.8–NE)	39.3 (22.1–NE)
HR (95% CI)	0.62 (0.48-0.81); $P = 0.0003$	
Median PFS2 (95% CI), mo	NR (NE–NE)	NR (NE–NE)
HR (95% CI)	0.57 (0.42–0.78)	

NE, not evaluable; NR, not reached.

LBA3502 **Oral Abstract Session**

Anlotinib versus bevacizumab added to standard first-line chemotherapy among patients with RAS/BRAF wild-type, unresectable metastatic colorectal cancer: A multicenter, prospective, randomised, phase 3 clinical trial (ANCHOR trial). First Author: Ke-Feng Ding, Department of Colorectal Surgery and Oncology, Key Laboratory of Cancer Prevention and Intervention, Ministry of Education, The Second Affiliated Hospital, Zhejiang University School of Medicine, Hangzhou, China

The full, final text of this abstract will be available at meetings.asco.org on the day of presentation and in the online supplement to the June 10, 2025, issue of the *Journal of Clinical Oncology*.

3503 **Oral Abstract Session**

ctDNA-guided adjuvant chemotherapy escalation in stage III colon cancer: Primary analysis of the ctDNA-positive cohort from the randomized AGITG dynamic-III trial (intergroup study of AGITG and CCTG). First Author: Jeanne Tie, Department of Medical Oncology, Peter MacCallum Cancer Centre and Personalised Oncology Division, Walter and Eliza Hall Institute of Medical Research, Melbourne, Australia

Background: Despite adjuvant chemotherapy (ACT) a proportion of patients (pts) with stage III colon cancer (CC) will recur. Most at risk are those with detectable ctDNA, whereas those with undetectable ctDNA have a reduced recurrence risk. The DYNAMIC-III study explored the impact of ACT de-escalation or escalation as informed by post-surgery ctDNA results. Here, we report the primary analysis on the impact of treatment escalation in ctDNA-positive pts. Outcome data for treatment de-escalation in ctDNA-negative pts is immature. **Methods:** DYNAMIC-III is a multicenter, randomized, phase II/III trial. Eligible pts had resected stage III CC and were fit for ACT. Pts were randomly assigned 1:1 to ctDNA-informed or standard of care (SOC) management. Clinicians nominated the selected SOC ACT regimen prior to randomization. For ctDNA-informed management, a ctDNA-positive result at 5-6 weeks after surgery with a tumor-informed assay prompted an escalation ACT strategy (from single agent fluoropyrimidine [FP] to oxaliplatin-based doublet, from 3 months doublet to 6 months doublet or FOLFOXIRI [clinician choice], or from 6 months doublet to FOLFOXIRI). The primary efficacy endpoint for the ctDNA-positive cohort was 2-year RFS. The target sample size of 250 provided 80% power with 90% confidence to confirm superiority of ctDNA-informed treatment escalation compared to SOC with a HR of 0.746. **Results:** Of 961 eligible pts randomized between Oct 2017 and Apr 2023, 259 (27%) were ctDNA-positive. Of these, 113 (44%) had clinical low risk disease (non-N2 + non-T4). Median follow-up was 42.2 months (range 0.78 – 63.0). 115 (89%) of 129 ctDNA-informed pts received ACT escalation, with 65 (56%) receiving FOLFOXIRI. Of 130 SOC pts, 14 (11%) and 112 (86%) received single agent FP and oxaliplatin doublet, respectively. 2-year RFS for ctDNA-informed treatment escalation was 52% (90% CI: 44 - 59%) vs 61% (90% CI: 54 - 68%) for SOC (HR 1.11, 90% CI: 0.83 - 1.48; P = 0.6). The 3-year RFS for ctDNA-positive pts receiving FOLFOXIRI and FOLFOX/CAPOX was similar (47% vs 51%, HR 1.09, 90% CI 0.78 to 1.53; P = 0.7). In a pre-specified correlative analysis of all ctDNA positive pts, recurrence risk increased with ctDNA burden, with 3-year RFS of 78%, 63%, 36% and 22% for tumor-derived mutant molecules/mL quartiles < 0.06, 0.06 – 0.17, 0.18 – 1.31, and > 1.31, respectively ($P < 0.01$). Treatment-related hospitalisation was similar for escalated and SOC pts (OR 1.21, P = 0.58). Analysis of post-ACT ctDNA is underway. **Conclusions:** In this first randomised study of ctDNA-informed management in stage III CC, we confirm the prognostic significance of detectable ctDNA, with the novel finding of recurrence risk increasing markedly with ctDNA burden. Treatment escalation, including to FOLFOXIRI, did not improve RFS. Future studies in ctDNA positive pts should explore other escalation strategies. Clinical trial information: ACTRN12617001566325. Research Sponsor: Marcus Foundation; NHMRC; U.S. National Institutes of Health.

3504 **Oral Abstract Session**

Tissue-free circulating tumor DNA assay and patient outcome in a phase III trial of FOLFOX-based adjuvant chemotherapy (Alliance N0147). First Author: Frank A. Sinicrope, Mayo Clinic Rochester, Rochester, MN

Background: Among patients with resected node-positive colon cancer, nearly 30% will relapse despite standard adjuvant chemotherapy. Analysis of molecular residual disease (MRD) using circulating tumor DNA (ctDNA) may enable risk stratification for tumor recurrence and inform adjuvant treatment decisions. **Methods:** Postsurgical ctDNA was analyzed in patients with stage III colon carcinoma who participated in a phase 3 trial of adjuvant FOLFOX alone or combined with cetuximab (n = 3084) [NCCTG N0147]. We utilized a tissue-free epigenomic assay for ctDNA detection (Guardant Reveal) with sampling prior to start of adjuvant therapy. Among ctDNA positives, epigenomic tumor fraction (TF) was estimated and ctDNA genotyping was done with Guardant360 (panel of 739 genes). Median follow-up was 6.1 years (yr). Study endpoints included time-to-recurrence (TTR), disease-free survival (DFS) and overall survival (OS) analyzed by Kaplan–Meier method. Multivariable Cox proportional hazards models were used to assess prognostic utility of ctDNA status adjusting for confounders. Interaction between ctDNA and clinicopathological features were assessed. **Results:** Among 2260 patients with evaluable ctDNA data, 461 (20.4%) were ctDNA positive.Tumors were significantly associated with higher T, N stage, $BRAF^{V600E}$, high grade, obstruction/perforation, and worse performance status. Positive vs negative ctDNA was significantly associated with shorter TTR (hazard ratio [HR] 4.33, 95% confidence interval [CI] 3.65-5.13, $P < 0.0001$), poorer DFS (HR 3.74, CI 3.18-4.39, $P < 0.0001$] and OS (HR 3.17, CI 2.63-3.83, $P < 0.0001$), adjusting for covariates and tissue MMR, *KRAS* and $BRAF^{V600E}$. ctDNA positive vs negative patients had 3y DFS of 36.4% (95%CI 32.2-41.2%) vs 82.5% (95% CI 80.0-84.4%), respectively. Adverse prognosis was consistent across subgroups (all $P < 0.05$), with stronger detrimental effects for positive ctDNA in N1 (vs. N2), T1/2 (vs T3 or 4), and mismatch repair deficient tumors [interaction P = 0.0002 to 0.041). Among patients with positive ctDNA, TF in those who recurred/died within 3 yr was double of those who remained recurrence-free ($P = 0.0001$). High vs. low ctDNA TF ($>$ vs $\leq$ median) further stratified TTR (HR 1.48, CI 1.17-1.88, $P = 0.0011$), DFS (HR 1.52, CI 1.21-1.92, $P = 0.0004$) and OS (HR 1.58, CI 1.21-2.07, $P = 0.0009$), adjusting for confounders. ctDNA positive cases, . Analyses of ctDNA detection by site of recurrence, ctDNA clearance, and genomic variant detection are ongoing. **Conclusions:** In the largest study evaluating tissue-free epigenomic-based MRD detection, we demonstrate a robust prognostic utility of postsurgical ctDNA. Tumor fraction provided further patient stratification and analysis is ongoing to identify a subgroup based on TF that may be unlikely to clear ctDNA despite adjuvant chemotherapy. Research Sponsor: National Cancer Institute; U10CA180882.

3505 **Oral Abstract Session**

Perioperative systemic therapy for resectable colorectal peritoneal metastases: A multicenter randomized phase 3 trial (CAIRO6). First Author: Koen Rovers, Catharina Cancer Institute, Eindhoven, Netherlands

Background: In patients with resectable colorectal peritoneal metastases who qualify for cytoreductive surgery with hyperthermic intraperitoneal chemotherapy (CRS-HIPEC), there is no prospective data comparing the efficacy of perioperative systemic therapy with CRS-HIPEC alone. **Methods:** In this multicenter phase 3 superiority trial, patients with resectable colorectal peritoneal metastases without extraperitoneal metastases who did not receive systemic therapy within six months prior to enrollment were randomly assigned (1:1) to receive perioperative CAPOX, FOLFOX, or FOLFIRI with neoadjuvant addition of bevacizumab (perioperative systemic therapy group) or CRS-HIPEC alone (surgery alone group). The primary outcome was overall survival. Key secondary outcomes were progression-free survival and 90-day major postoperative morbidity and mortality. The trial needed 179 patients in each arm to detect a superior 3-year overall survival of 65% in the perioperative systemic therapy group versus 50% in the surgery alone group (corresponding hazard ratio [HR] for death 0.62) with 80% power, 5% drop-out, and a two-sided log rank test of $p<0.05$. The primary overall survival analysis was done after 171 events (88% power). **Results:** Of 358 randomized patients, 351 were eligible for primary analysis: 173 in the perioperative systemic therapy group and 178 in the surgery alone group. At a median follow-up of 41 months, median and 3-year overall survival were 44 months and 54% in the perioperative systemic therapy group and 39 months and 53% in the surgery alone group, respectively (HR for death 0.85, 95% CI 0.62-1.15, p=0.28). Median and 3-year progression-free survival were 13.5 months and 20% in the perioperative systemic therapy group and 7.0 months and 5% in the surgery alone group, respectively (HR for progression or death 0.51, 95% CI 0.41-0.65). In the per-protocol population of 292 patients who underwent macroscopic complete CRS-HIPEC, median and 3-year overall survival were 54 months and 64% in the perioperative systemic therapy group (138 patients) and 45 months and 59% in the surgery alone group (154 patients), respectively (HR for death 0.73, 95% CI 0.51-1.05). Ninety-day major postoperative morbidity rates were 36% in the perioperative systemic therapy group and 26% in the surgery alone group, with a 90-day postoperative mortality of 1% in both groups. **Conclusions:** Among patients with resectable colorectal peritoneal metastases, perioperative systemic therapy did not result in superior overall survival as compared to CRS-HIPEC alone. Clinical trial information: NCT02758951. Research Sponsor: Dutch Cancer Society; F. Hoffmann-La Roche.

3506 **Oral Abstract Session**

Long-term safety and efficacy of sotorasib plus panitumumab and FOLFIRI for previously treated *KRAS* G12C-mutated metastatic colorectal cancer (mCRC): CodeBreaK 101 (phase 1b). First Author: John H. Strickler, Duke University Medical Center, Durham, NC

Background: In the phase 3 CodeBreaK 300 trial (NCT05198934), the combination of sotorasib ($KRAS^{G12C}$ inhibitor) and panitumumab (monoclonal anti-EGFR antibody) improved clinical outcomes in patients with chemorefractory *KRAS* G12C-mutated mCRC. CodeBreaK 101 is a phase 1b trial where FOLFIRI was added to sotorasib and panitumumab in previously treated patients with *KRAS* G12C-mutated mCRC. For the first time, we report mature overall survival (OS) and progression-free survival (PFS), as well as updated safety and response data. **Methods:** Patients with *KRAS* G12C-mutated mCRC who received $\geq$1 prior systemic treatment but were $KRAS^{G12C}$ inhibitor-naïve, were enrolled into the expansion cohort of the CodeBreak 101 subprotocol H (NCT04185883) phase 1b trial. As defined from dose exploration cohort, patients received the recommended phase 2 dose (RP2D) of sotorasib (960 mg orally daily) plus panitumumab (6 mg/kg intravenous every 2 weeks [Q2W]) and standard dose FOLFIRI (intravenous Q2W). The primary endpoint was safety and secondary endpoints included confirmed response, OS, and PFS, assessed by investigator per Response Evaluation Criteria in Solid Tumors (RECIST) v1.1. **Results:** By November 2024, 40 patients were enrolled (female: 47.5%; median age: 56.0 years; median [range] prior lines of systemic therapy: 2 [1-6]). The most common treatment-related adverse events (TRAEs) were dermatitis acneiform and dry skin (n = 27 [67.5%] each), decreased neutrophil count (n = 20 [50.0%]), and stomatitis (n = 17 [42.5%]). Grade $\geq$3 TRAEs occurred in 20 (50.0%) patients with no new safety signals. Discontinuation of sotorasib, panitumumab, or FOLFIRI (5-FU, irinotecan, or leucovorin/levoleucovorin) due to AEs was observed in 1 (2.5%), 1 (2.5%), and 16 (40.0%) patients, respectively. A total of 7 patients are still continuing the study, of whom 5 are off-treatment and under follow-up. Updated objective response rate (95% CI) was 57.5% (40.9, 73.0) and disease control rate (95% CI) was 92.5% (79.6, 98.4). Median time to response was 1.6 months and duration of response was 6.6 months. After a median follow-up of 29.2 months, the median (95% CI) PFS was 8.2 (7.0, 10.8) months and median OS was 17.9 (12.9, 25.1) months. **Conclusions:** Sotorasib plus panitumumab and FOLFIRI showed promising long-term safety and efficacy in pretreated *KRAS* G12C-mutated mCRC. AEs were consistent with the safety profile of the drugs administered. The ongoing phase 3 study, CodeBreaK 301 (NCT06252649), aims to evaluate this combination against standard of care in first-line patients with *KRAS* G12C-mutated mCRC. Clinical trial information: NCT05198934. Research Sponsor: Amgen Inc.

3507 **Oral Abstract Session**

Efficacy and safety of olomorasib, a second-generation KRAS G12C inhibitor, plus cetuximab in *KRAS* G12C-mutant advanced colorectal cancer. First Author: Antoine Hollebecque, Institut Gustave Roussy, Villejuif, France

Background: Olomorasib, a potent and selective second-generation KRAS G12C inhibitor (G12Ci), has demonstrated promising efficacy and a favorable safety profile in *KRAS* G12C-mutant cancers. Based on emerging nonclinical and clinical data, combining a KRAS G12Ci with cetuximab offers a compelling opportunity to improve outcomes in patients (pts) with *KRAS* G12C-mutant colorectal cancer (CRC). Here we report updated results from a phase 1/2 study (NCT04956640) on the safety, tolerability and optimal dose of olomorasib + cetuximab in pts with *KRAS* G12C-mutant CRC. **Methods:** Pts with advanced *KRAS* G12C-mutant CRC (tissue or plasma) previously treated with $\geq$1 prior oxaliplatin- or irinotecan-containing regimen were eligible and enrolled into dose escalation/expansion or optimization at 2 doses of olomorasib (100 and 150 mg, orally BID). Dose escalation of olomorasib + cetuximab followed a mTPI-2 method. Key objectives were safety and to determine the optimal dose of olomorasib + cetuximab. Antitumor activity per RECIST v1.1 was studied in pts with $\geq$1 post-baseline response assessment or who discontinued before a first response assessment. **Results:** As of 13 November 2024, 93 pts received olomorasib + cetuximab in dose escalation/expansion (n=49) or optimization (n=44). Median age was 58 yrs (range, 35-82) and median number of prior therapies was 3 (range, 1-8). All grade TRAEs in $\geq$20% of pts were dermatitis acneiform (58%), diarrhea (38%), dry skin (31%), paronychia (28%), hypomagnesemia (26%), and rash (26%). The majority of TRAEs were grade 1-2, with grade $\geq$3 observed in 24% of pts. The most common TRAEs grade $\geq$3 were diarrhea, hypokalemia, and rash, each occurring in 2 pts. TRAEs led to olomorasib dose reduction in 2% of pts, olomorasib dose hold in 22% of pts, and cetuximab dose hold in 16% of pts. Of the 61 pts who discontinued treatment, 57 were due to PD. Two pts discontinued cetuximab due to TRAEs and continued on olomorasib. The AE profile was similar between doses. Median time on combination treatment was 6.5 mo (range, 0.8-24.1) and 32 pts remained on treatment. See Table 1 for efficacy data. Biomarker analysis will be reported. **Conclusions:** Olomorasib + cetuximab demonstrated similar antitumor activity and favorable safety at both dose levels in pts with *KRAS* G12C-mutant CRC, with the optimal dose of olomorasib + cetuximab determined as 100 mg BID. These results further support combining second-generation KRAS G12Ci with other anticancer therapies to improve outcomes in previously treated pts with *KRAS* G12C-mutant CRC. Clinical trial information: NCT04956640. Research Sponsor: Eli Lilly and Company.

Endpoint	Olomorasib (100 mg BID) + Cetuximab N=64	Olomorasib (150 mg BID) + CetuximabN=29	Total N=93
ORR, % (n/N)	44% (28/64)	38% (11/29)	42% (39/93)
BOR, n (%)			
PR	28 (44)	11 (38)	39 (42)
SD	31 (48)	16 (55)	47 (51)
PD	5 (8)	2 (7)	7 (8)
mDOR, mo (95% CI)	8.3 (5.6-12.7)	6.2 (2.8-NE)	7.6 (6.0-12.2)
mPFS, mo (95% CI)	7.5 (6.7-9.7)	6.6 (4.2-7.6)	7.5 (6.6-8.8)

3508 **Oral Abstract Session**

The KRAS G12C inhibitor MK-1084 for *KRAS* G12C–mutated advanced colorectal cancer (CRC): Results from KANDLELIT-001. First Author: Iwona A. Lugowska, Maria Sklodowska-Curie National Research Institute and Oncology Centre, Warsaw, Poland

Background: Preliminary data from the phase 1 KANDLELIT-001 trial (NCT05067283) showed a manageable safety profile and preliminary antitumor activity for MK-1084, a next-generation, selective KRAS G12C-GDP covalent inhibitor, in participants (pts) with previously treated, *KRAS* G12C-mutant solid tumors, including non–small-cell lung cancer and CRC. Here, we report data for MK-1084 monotherapy, MK-1084 + cetuximab, and MK-1084 + cetuximab + mFOLFOX6 in pts with advanced *KRAS* G12C-mutant CRC. **Methods:** KANDLELIT-001 enrolled pts with confirmed *KRAS* G12C mutation, RECIST-measurable disease, and ECOG PS 0-1. Pts with any advanced solid tumor and ≥1 prior systemic therapy received MK-1084 monotherapy PO QD or BID (total daily dose, 25-800 mg) in arms 1 and 3. Pts with advanced CRC and 1-2 prior systemic therapies received MK-1084 QD (total daily dose, 25-200 mg) plus cetuximab 500 mg/m^2 IV Q2W in arm 5. Pts with advanced CRC and 0-1 prior systemic therapies received MK-1084 QD (total daily dose, 25-100 mg) plus cetuximab 500 mg/m^2 Q2W and mFOLFOX6 in arm 6. The primary endpoints were dose-limiting toxicities (DLTs), AEs, and AEs leading to discontinuation. Secondary endpoints included ORR per RECIST v1.1 by investigator review. ORR was assessed in all pts who received their first MK-1084 dose ≥5 wk before the data cutoff date of August 12, 2024, for arms 1 and 3 and November 6, 2024, for arms 5 and 6. **Results:** In arms 1+3, 99 pts, including 53 (54%) with CRC, received MK-1084 alone. In arm 5, 34 pts, including 23 (68%) who had ≥2 prior lines of therapy, received MK-1084 + cetuximab. In arm 6, 20 pts, including 10 (50%) who had no prior therapy, received MK-1084 + cetuximab + mFOLFOX6. Median (range) study follow-up was 14.8 mo (0.2-30.8) in arms 1+3, 5.3 mo (2.6-11.5) in arm 5, and 1.9 mo (0.1-5.4) in arm 6. One pt in arm 6 experienced a DLT (grade 3 febrile neutropenia); there were no DLTs in arms 1, 3, or 5. Treatment-related AEs occurred in 62% of pts in arms 1+3, 97% of pts in arm 5, and 90% of pts in arm 6, were grade ≥3 in 9%, 18%, and 25%, respectively, and led to discontinuation of any drug in 1%, 3%, and 15%, respectively. There were no treatment-related deaths. The two most common treatment-related AEs in each arm were increased AST (17%) and nausea (17%) in arms 1+3, dermatitis acneiform (47%) and rash (24%) in arm 5, and nausea (55%) and rash (50%) in arm 6. ORR (95% CI) was 36% (23-50) in pts with CRC in arms 1+3 (n = 53), 50% (32-68) in arm 5 (n = 34), and 14% (2-43) in arm 6 (n = 14); all responses were partial responses. **Conclusions:** Preliminary data suggest that MK-1084 monotherapy, MK-1084 + cetuximab, and MK-1084 + cetuximab + mFOLFOX6 have manageable safety profiles and show evidence of antitumor activity in pts with advanced, *KRAS* G12C-mutated CRC. Pts continue to be followed, and enrollment continues. Clinical trial information: NCT05067283. Research Sponsor: Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA.

LBA3509 **Clinical Science Symposium**

Association between empirical dietary inflammatory pattern (EDIP) and survival in patients with stage III colon cancer: Findings from CALGB/SWOG 80702 (Alliance). First Author: Sara K. Char, Department of Medical Oncology, Dana-Farber Cancer Institute, Boston, MA

The full, final text of this abstract will be available at meetings.asco.org on the day of presentation and in the online supplement to the June 10, 2025, issue of the *Journal of Clinical Oncology*.

LBA3510 **Clinical Science Symposium**

A randomized phase III trial of the impact of a structured exercise program on disease-free survival (DFS) in stage 3 or high-risk stage 2 colon cancer: Canadian Cancer Trials Group (CCTG) CO.21 (CHALLENGE). First Author: Christopher M. Booth, Queen's University, Kingston, ON, Canada

The full, final text of this abstract will be available at meetings.asco.org on the day of presentation and in the online supplement to the June 10, 2025, issue of the *Journal of Clinical Oncology*.

LBA3511 **Clinical Science Symposium**

Aspirin as secondary prevention for colorectal cancer liver metastases (ASAC): A multicenter, randomized, double-blind, placebo-controlled, phase 3 trial. First Author: Sheraz Yaqub, Department of Hepato-Pancreato-Biliary Surgery, Oslo University Hospital and University of Oslo, Institute of Clinical Medicine, Oslo, Norway

The full, final text of this abstract will be available at meetings.asco.org on the day of presentation and in the online supplement to the June 10, 2025, issue of the *Journal of Clinical Oncology*.

3512 **Rapid Oral Abstract Session**

Upfront modified FOLFOXIRI plus panitumumab (pan) versus FOLFOX/pan for unresectable *RAS* and *BRAF* wild-type (wt) metastatic colorectal cancer (mCRC) patients: Overall survival (OS) results from the phase III TRIPLETE study by GONO. First Author: Veronica Conca, Department of Translational Research and New Technologies in Medicine and Surgery, University of Pisa & Unit of Medical Oncology 2, Azienda Ospedaliera Universitaria Pisana, Pisa, Italy

Background: TRIPLETE (NCT03231722) is a phase III trial where unresectable *RAS/BRAF* wt mCRC patients (pts) were randomized 1:1 to first-line FOLFOX/pan (Arm A) or modified FOLFOXIRI/pan (Arm B). The study failed to demonstrate an improved overall response rate, primary endpoint of the study, in Arm B, and did not show any benefit from the intensification of the chemotherapy also in terms of progression-free survival (PFS), early tumor shrinkage, depth of response, R0 resection rate at the price of increased gastrointestinal toxicity. Here we report OS results. **Methods:** Eligible pts were stratified according to ECOG PS (0-1 vs 2), primary tumor location (right vs left), and liver-only metastases (yes vs no). OS was assessed from randomization to death from any cause. Survival curves were calculated using the Kaplan–Meier method and compared with the log-rank test stratified by the same factors as per randomization. Hazard ratios (HR) with 95% confidence interval (CI) were estimated using Cox regression models. **Results:** 435 pts (A/B: 217/218) were enrolled. Main pts' characteristics were median age 59/59 years, ECOG PS 0 80%/84%, synchronous metastases 88%/86%, liver-only disease 38%/39%, left-sided primary tumour 88%/88%; deficient MMR tumours 1%/3%. At a median follow up of 60.2 months (mos), 292 (67%, arm A/B: 71%/63%) OS events were collected. Significantly longer OS was observed in Arm B with a median OS of 41.1 vs 33.3 mos in Arm A (HR: 0.79; 95%CI: 0.63-0.99; p = 0.049). No molecular or clinical groups of interest emerged from the subgroup analyses. While no significant difference in PFS was confirmed (median PFS Arm A/B: 12.4/12.7 mos, p = 0.606), longer post progression survival (PPS) was reported in Arm B (HR: 0.73; 95%CI: 0.57-0.93; p = 0.012). The proportion of pts receiving subsequent lines of therapy was similar between arms (2^{nd}-line Arm A/B: 73%/71%, 3^{rd}-line: 52%/50%, 4^{th}-line: 33%/33%), and no differences were evident in the exposure to anti-EGFRs (Arm A/B 35%/38%) and oxaliplatin (26%/33%) after PD, while higher percentages of pts in ARM A received anti-angiogenics (59%/45%) and irinotecan (66%/56%). Similar percentages of pts received locoregional treatments with radical intent after PD (Arm A/B 16%/15%). **Conclusions:** Upfront modified FOLFOXIRI/pan provides a statistically significant and clinically meaningful survival advantage compared to standard FOLFOX/pan in pts with *RAS/BRAF* wt mCRC, with a 7.8 mos difference in median values, though in the absence of any significant difference in treatment activity and PFS. Clinical trial information: NCT03231722. Research Sponsor: GONO Foundation; Amgen.

3513 **Rapid Oral Abstract Session**

FIRE-4 (AIO KRK-0114): Randomized study evaluating the efficacy of cetuximab re-challenge in patients with metastatic RAS wild-type colorectal cancer responding to first-line treatment with FOLFIRI plus cetuximab. First Author: Lena Weiss, Department of Medicine III, University Hospital Munich LMU, Munich, Germany

Background: Several smaller studies performed in later lines of treatment have suggested a potential benefit from anti-EGFR re-challenge on survival of RAS wild-type (RAS WT) metastatic colorectal cancer (mCRC). FIRE-4 is a randomized phase-III study that prospectively evaluates re-challenge with chemotherapy plus cetuximab as compared to physician's choice. **Methods:** The FIRE-4 study was performed with two steps of randomisation. Within the first randomisation, pts were either attributed to induction therapy with FOLFIRI plus cetuximab continued until disease progression (PD) or intolerable toxicity (arm A) or to a switch maintenance using 5-FU plus bevacizumab (arm B). After first PD, an anti-EGFR-free "window therapy" was recommended. After diagnosis of second PD, RAS WT pts (again selected by liquid- or tumor-biopsy), who had responded to cetuximab-based induction therapy within FIRE-4 (entry 1) or outside of the study (entry 2), could then proceed to 2^{nd} randomization attributing pts either to re-challenge with cetuximab or to physician's choice. Overall survival (OS) after 2^{nd} randomization was evaluated as primary endpoint. **Results:** From August 2015 to February 2021, 672 pts were randomized and 657 pts were assigned to treatment in 120 German and 10 Austrian centers. Within the 2^{nd} randomization, 87 pts (entry 1: N = 62; entry 2: N = 25) were attributed either to physician's choice (A2: N = 42) or (FOLF)IRI plus cetuximab (Arm B2: n = 45). Baseline characteristics were comparable between groups without significant differences regarding parameters such as age, sex, ECOG performance status, or primary tumor sidedness. All pts were RAS WT at the time of randomization. No statistically significant difference between arm A2 and B2 was observed regarding OS (15.1 months vs. 17.6 months; HR 0.84; P = 0.48) or PFS (4.6 months vs. 5.8 months; HR 0.91; P = 0.64). ORR was greater in the experimental arm (11.9% vs. 28.9%; OR 0.33; P = 0.07), while disease control rate was nearly identical (59.5% vs. 60.0%; OR 0.98; P $>$ 0.99). **Conclusions:** FIRE-4 did not meet its primary endpoint. While the control arm using physician's choice exceeded expectations, re-challenge with anti-EGFR therapy in RAS WT pts obtained comparable results in terms of OS. Clinical trial information: NCT02934529. Research Sponsor: MERCK Serono.

3514 **Rapid Oral Abstract Session**

Longitudinal ctDNA monitoring and prediction of anti-EGFR rechallenge outcomes in RAS/BRAF wild-type metastatic colorectal cancer (mCRC): The REMARRY & PURSUIT trials. First Author: Yoshinori Kagawa, Department of Gastroenterological Surgery, Osaka International Cancer Institute, Osaka, Japan

Background: Anti-EGFR monoclonal antibody (mAb) rechallenge involves re-administering EGFR blockade after a treatment-free interval to exploit clonal evolution. Recent evidence suggests that circulating tumor DNA (ctDNA)–based selection may improve outcomes; however, the predictive value of longitudinal ctDNA monitoring remains uncertain. **Methods:** The REMARRY study evaluated plasma *RAS* (p*RAS*) dynamics in patients with *RAS/BRAF* V600E wild-type metastatic colorectal cancer (mCRC), ECOG PS 0–1, who had previously responded to anti-EGFR therapy and experienced progression within two months of the last dose. p*RAS* status was assessed at progression on prior anti-EGFR, before rechallenge, at cycle 3, and at discontinuation using BEAMing digital PCR. Patients meeting additional criteria—namely, p*RAS*-negative, refractory or intolerance to standard chemotherapies, and an anti-EGFR–free interval of at least 4 months—were enrolled in the phase II PURSUIT trial, which administered panitumumab (6 mg/kg) plus irinotecan (150 mg/m²) biweekly. The primary endpoint was confirmed objective response rate (ORR) per RECIST v1.1. In parallel, participants underwent next-generation sequencing (NGS) of ctDNA in the GOZILA trial at corresponding time points to identify resistance alterations in genes including *RAS, BRAF, EGFR*-ECD, *MAP2K*, ERBB2, and MET. **Results:** Between May 2019 and May 2021, 183 patients were enrolled in REMARRY, and 50 p*RAS*-negative patients before rechallenge were included in PURSUIT. The confirmed ORR was 14.0% (90% CI, 7.0–23.0%), with a median progression-free survival (PFS) of 3.6 months and a median overall survival (OS) of 12.0 months. Although all patients were p*RAS*-negative at baseline, 10.0% converted to p*RAS*-positive by cycle 3 and 36.0% by discontinuation. Patients who were p*RAS*-positive immediately after prior anti-EGFR had higher conversion rates at cycle 3 (42.9% vs. 6.3%, p = 0.010) and at discontinuation (85.7% vs. 32.3%, p $<$ 0.001) compared with those initially negative. The ORR was 23.8% in patients remaining p*RAS*-negative versus 0% in those converting to p*RAS*-positive (p = 0.254). Moreover, NGS-detected resistance alterations after prior anti-EGFR were associated with no responses (0/13) compared to a 27.8% response rate (5/23) in patients without such alterations (p = 0.038), and correlated with shorter PFS (HR 3.297, p = 0.002) and OS (HR 4.569, p $<$ 0.001). In 86% (7/8) of patients who were p*RAS*-positive post–anti-EGFR, the identical p*RAS* codons re-emerged during rechallenge, consistent with NGS findings. **Conclusions:** ctDNA status immediately after progression on prior anti-EGFR therapy predicts subsequent response, thereby supporting clinical decision-making and personalized therapy. Trial Registration: PURSUIT (jRCTs031190096), REMARRY (UMIN000036424), GOZILA (UMIN000029315). Clinical trial information: jRCTs031190096. Research Sponsor: None.

LBA3515 **Rapid Oral Abstract Session**

Panitumumab retreatment followed by regorafenib versus the reverse sequence in chemorefractory metastatic colorectal cancer patients with *RAS* and *BRAF* wild-type circulating tumor DNA (ctDNA): Results of the phase II randomized PARERE trial by GONO. First Author: Chiara Cremolini, Unit of Medical Oncology 2, Azienda Ospedaliera Universitaria Pisana and Department of Translational Research and New Technologies in Medicine and Surgery, University of Pisa, Pisa, Italy

The full, final text of this abstract will be available at meetings.asco.org on the day of presentation and in the online supplement to the June 10, 2025, issue of the *Journal of Clinical Oncology*.

LBA3516 **Rapid Oral Abstract Session**

JMT101 in combination with irinotecan and SG001 versus regorafenib in patients with metastatic colorectal adenocarcinoma (mCRC): Results of a randomized, controlled, open-label, phase II study. First Author: Jianmin Xu, Department of Colorectal Surgery, Zhongshan Hospital Fudan University, Shanghai, China

The full, final text of this abstract will be available at meetings.asco.org on the day of presentation and in the online supplement to the June 10, 2025, issue of the *Journal of Clinical Oncology*.

3517 **Rapid Oral Abstract Session**

Phase 2 dose expansion study of DSP107, a first-in-class bi-specific 4-1BB T-cell engager, with and without atezolizumab in metastatic MSS colorectal cancer patients. First Author: Anwaar Saeed, University of Pittsburgh Medical Center (UPMC) and UPMC Hillman Cancer Center, Pittsburgh, PA

Background: DSP107 is a bi-specific fusion protein composed of sequences from the extracellular domain of SIRPα and 4-1BBL. The SIRPα arm selectively targets CD47 overexpressed on tumor cells, while simultaneously anchoring trimeric 4-1BBL to the tumor, to engage and co-stimulate 4-1BB on activated immune cells in the tumor microenvironment. This results in tumor-localized, conditional activation of innate and adaptive immune responses. Phase 1 data demonstrated an excellent safety profile with no RBC binding and no hematological, hepatic or other dose limiting toxicities (DLTs). Here we describe safety and efficacy data from a Phase 2 microsatellite stable (MSS) colorectal (CRC) expansion cohort in which patients were treated with DSP107 alone or with atezolizumab (NCT04440735). **Methods:** Metastatic/unresectable MSS CRC patients who progressed following 2 lines of therapy including standard chemotherapy $\pm$ targeted antibodies (n = 50), were randomized to receive weekly IV DSP107 infusions (10 mg/kg/dose) alone or with atezolizumab (1200 mg) Q3W during 3-week treatment cycles. The majority (76%) had liver metastases. Study objectives were safety, tolerability and preliminary efficacy. Restaging imaging was performed every 2 months and evaluated by RECIST v1.1 criteria. **Results:** DSP107 monotherapy and with atezolizumab was well tolerated with no DLTs. The most frequent TRAEs were infusion-related reactions (IRR; 38% Grade 1 or 2, 4% Grade 3), fatigue (12% Grade 1 or 2, 4% Grade 3), Grade 1 or 2 nausea (14%) and Grade 1 or 2 anemia (10%). IRRs were managed during subsequent infusions by reducing the infusion rate and administering IV fluids. The median OS from the efficacy-evaluable patients who received DSP107 monotherapy (n = 19) and combination therapy with atezolizumab (n = 21) has not been reached but currently (Dec 2024 cutoff) stands at 7.6 and 14.6 months, respectively. Disease control was demonstrated in 26% (monotherapy) and 62% (combination) of evaluable patients including a patient who achieved complete response ($>$ 2.5 years) and a patient with a deep (86% target lesion reduction) and durable ($>$ 16 months) confirmed partial response and disappearance of pulmonary and hepatic metastases. Immunofluorescence analysis of baseline tumor biopsies (n = 16) demonstrated moderate to high levels of CD47 expression in 15/16 biopsies ($>$ 120 H-Score), and very high levels of CD47 expression ($>$ 170 H-Score) in all 7 samples collected from liver metastases. **Conclusions:** These data suggest that the combination of DSP107 with PD(L)1 blockade has anti-tumor activity and provides clinical benefit in third line metastatic MSS CRC including in patients with liver metastases. Updated survival data will be presented at the conference. A Phase 2 randomized controlled study is currently in planning to confirm this preliminary efficacy signal. Clinical trial information: NCT04440735. Research Sponsor: KAHR Medical LTD.

3518 **Rapid Oral Abstract Session**

Circulating tumor DNA as an early response indicator in anal squamous cell carcinoma treated with chemoradiation. First Author: Aron Bercz, Memorial Sloan Kettering Cancer Center, New York, NY

Background: Definitive chemoradiation (CRT) is a highly effective, organ-preserving treatment for localized anal squamous cell carcinoma (ASCC). However, a subset of patients experience locoregional failure, leading to unfavorable oncologic outcomes despite salvage surgery. Circulating tumor DNA (ctDNA) has emerged as a promising tool for monitoring treatment efficacy and predicting prognosis; however, there is a paucity of studies evaluating the baseline detectability and kinetics of tumor-informed ctDNA assays in ASCC. **Methods:** Patients with ASCC (*N*=88) undergoing definitive CRT provided prospective consent for longitudinal ctDNA monitoring using a personalized, tumor-informed ctDNA assay (Signatera, Natera, Inc.). ctDNA testing was assessed at three key time points: pre-treatment (any time before CRT to within 5 days after initiation), mid-treatment (from $>$5 days after initiation to $<$7 days before completion), and post-treatment ($>$7 days before completion to 42 days after CRT). Surveillance testing continued every three months. Changes in ctDNA levels were analyzed in relation to clinical outcomes. Locoregional failure (LRF) was assessed using competing risk regression, stratified by ctDNA status (positive vs. negative). ctDNA results were also correlated with progression-free survival (PFS). **Results:** Pre-treatment ctDNA was detected in 79% of patients, with 92% achieving ctDNA-negativity at post-treatment (Table 1). Over a median follow-up of 18 months (IQR 11–26), 7 patients experienced LRF, and 5 experienced distant failure. The cumulative LRF incidence was 0% among patients with ctDNA negativity by mid-treatment. Conversely, 26% of patients with ctDNA positivity at mid-treatment and 61% of patients with ctDNA positivity at post-treatment experienced LRF, respectively. Estimated one-year PFS was 100% for patients who achieved ctDNA negativity by mid-treatment. In contrast, patients who remained ctDNA-positive at mid-treatment and post-treatment had estimated one-year PFS rates of 81% and 44%, respectively, from the date of the corresponding ctDNA test. Among patients who achieved ctDNA negativity but subsequently developed molecular recurrence during the surveillance period (*N*=7), all developed disease recurrence. Molecular recurrence predated clinical or radiographic evidence of recurrence in all instances. **Conclusions:** This tumor-informed ctDNA assay demonstrates high baseline detectability and rapid clearance during CRT, with molecular clearance correlating with favorable outcomes in ASCC. Notably, ctDNA-based detection of molecular recurrence consistently precedes conventional clinical and radiographic indicators of disease recurrence. Further validation in large, prospective cohorts is warranted. Research Sponsor: National Institutes of Health/National Cancer Institute (NIH/NCI); R37 CA248289; National Institutes of Health/National Cancer Institute (NIH/NCI); K08 CA255574; National Institutes of Health/National Cancer Institute (NIH/NCI); 5T32 CA 9501-34; National Institutes of Health/National Cancer Institute (NIH/NCI) Memorial Sloan Kettering Cancer Center (MSK) Support Grant; P30 CA008748.

	Pre-Treatment	*Mid*-Treatment	*Post*-Treatment
Positive	61 (79%)	29 (47%)	6 (8%)
Negative	16 (21%)	33 (53%)	67 (92%)
Unknown	11	26	15

3519 **Rapid Oral Abstract Session**

Short-course radiotherapy followed by sintilimab and CAPOX as total neoadjuvant treatment in locally advanced rectal cancer: A prospective, randomized controlled trial (SPRING-01). First Author: Feng Tian, Shandong Provincial Hospital Affiliated to Shandong First Medical University, Jinan, NA, China

Background: Neoadjuvant short-course radiotherapy (SCRT) combined with chemotherapy as total neoadjuvant therapy (TNT) increases the pathological complete response (pCR) rate for locally advanced rectal cancer (LARC). The potential synergistic effects of combining radiotherapy and immunotherapy might benefit patients with LARC. This study aimed to compare the efficacy and safety of SCRT followed by 6 cycles of CAPOX chemotherapy with or without immunotherapy as TNT in LARC patients. **Methods:** In this randomized controlled trial, patients with T3-4, N+, EMVI(+), MRF(+) or lateral lymph node(+) rectal adenocarcinoma were randomly assigned to receive SCRT followed by 6 cycles of CAPOX chemotherapy with or without sintilimab. Total mesorectal excision (TME) was performed 2-3 weeks after the completion of TNT. The primary study endpoint was the pCR rate. **Results:** In this randomized controlled trial, patients with T3-4, N+, EMVI(+), MRF(+) or lateral lymph node(+) rectal adenocarcinoma were randomly assigned to receive SCRT followed by 6 cycles of CAPOX chemotherapy with or without sintilimab. Total mesorectal excision (TME) was performed 2-3 weeks after the completion of TNT. The primary study endpoint was the pCR rate. **Conclusions:** In LARC patients, SCRT combined with sintilimab and CAPOX as a TNT significantly increases the pCR rate while maintaining manageable safety in patients with LARC. SCRT followed by sintilimab and CAPOX can be recommended as a superior neoadjuvant treatment option for these patients. Clinical trial information: ChiCTR2100052288. Research Sponsor: National Natural Science Foundation of China; Special Foundation for Taishan Scholars Program of Shandong Province; Key Research and Development Program of Shandong Province; China Postdoctoral Science Foundation.

The efficacy of SIN+CAPOX and surgical and pathological results.

Intention-to-treat (ITT) population	SIN+CAPOX (N = 49)	CAPOX (N = 49)
Pathological complete response (ypT0N0, ITT population) — no. (%)	29 (59.2)	16 (32.7)
(% [95% CI])	(45.4, 72.9)	(19.5, 45.8)
Complete response	30 (61.2)	16 (32.7)
Surgical population	SIN+CAPOX (N = 45)	CAPOX (N = 44)
Tumor regression grading (AJCC 8th edition) — no. (%)		
0	29 (64.4)	16 (36.4)
1	7 (15.6)	7 (15.9)
2	5 (11.1)	13 (29.5)
3	4 (8.9)	8 (18.2)

Abbreviations: IQR, interquartile range; N, regional nodal category; T, primary tumor category; yp, pathologic.

3520 Rapid Oral Abstract Session

Proposed changes to the pathologic staging for colon cancer (CC): AJCC Colon Cancer Expert Panel (AJCCCCEP). First Author: Qian Shi, Department of Quantitative Science Research, Mayo Clinic Rochester, Rochester, MN

Background: Recent analyses highlight nonhierarchical outcomes using the 8th Edition AJCC staging system for CC. For instance, the 5-year survival rate for stages I and IIIa patients (pts) closely align. Additionally, tumor deposits (TDs) have been established as significant prognostic indicators. The AJCCCCEP commissioned this study to develop an updated pathological staging system for CC focused specifically on pts without distant metastasis (M0), while retaining the existing stage IV classification. **Methods:** Individual patient data (IPD) from pts diagnosed with cc (2010- 2017) in the NCDB were divided into training (70%) and internal validation (30%) datasets. External validation used IPD from clinical trials. The primary endpoint was overall survival (OS). Risk classification development for M0 pts incorporated ungrouped data on pathologic T categories, the number of involved regional lymph nodes (LN+), and TD counts. Recursive partitioning and regression tree analyses were applied to construct hierarchical staging levels. Pre-specified criteria required survival probabilities to be consecutive and show clear separations using Kaplan-Meier (KM) estimates with pairwise log-rank test P of $<$ 0.005 for the training and $<$ 0.05 for validation analyses. **Results:** Data from 281,997 pts (median age 67 years, 50% male, 81% white, 55% T3, 19% T4, 44% N+, 26% M+, and 11% with $\geq$1 TD) were analyzed, with a median follow-up of 7.3 years. The updated staging system (Table) met pre-specified criteria, with all observed pairwise P $<$ 0.0001 in the development and internal validation sets. KM OS curves displayed a hierarchical separation across all sub-levels after the 1st year of diagnosis. Consistent results were seen in pts treated with adjuvant chemotherapy in 4 trials (all pair-wise P $<$ 0.0001). **Conclusions:** The proposed pathological staging system for M0 pts fulfills pre-specified criteria for hierarchical risk stratification, validated both internally and externally, and provides an evidence-based update. Pending review process, the AJCCCCEP will recommend that these changes be made to the Version 9 staging protocol for colon cancer to improve prognostication for CC pts. Research Sponsor: None.

Stage	T, # of LN+, # of TD	M	% of pts	1y OS (CI), %	3y OS (CI), %	5y OS (CI), %
I	T1, 0, 0	0	5	96 (95-97)	91 (90-92)	84 (83-86)
IIa	T2, 0, 0	0	10	95 (94-95)	88 (88-89)	80 (79-81)
IIb	T1, 0, 1+ T1, 1+, 0 T2, 0, 1+ T2, 1-4, 0 T3, 0, 0	0	27	93 (92-93)	84 (84-85)	75 (75-76)
IIIa	T1, 1+, 1+ T2, 1-4, 1+ T2, 5+, 0 T3, 0, 1+ T3, 1-4, 0	0	14	92 (91-92)	80 (80-81)	71 (70-72)
IIIb	T2, 5+, 1+ T3, 1-4, 1+ T3, 5+, 0 T4a, 0-4, 0 T4b, 0-2, 0	0	13	86 (86-87)	69 (68-70)	58 (57-59)
IIIc	T3, 5+, 1+ T4a, 0-4, 1+ T4a, 5+, any T4b, 0-2, 1+ T4b, 3+, any	0	5	78 (77-80)	53 (51-54)	40 (38-41)
IVa	Any	1a	19	59 (58-60)	28 (28-29)	17 (16-18)
IVb	Any	1b	7	43 (42-44)	14 (13-14)	6 (6-7)

CI: 95% confidence internal; Peritoneum involvement data were not available before 2018 in NCDB. Thus, IVa/b were based on 7th Edition.

3521 Poster Session

Experience of patients with HIV and squamous cell carcinoma of the anal canal (SCAC) treated with retifanlimab. First Author: Jean-Philippe Spano, Department of Medical Oncology, Groupe Hospitalier Pitie-Salpetriere, Paris, France

Background: People living with HIV (PLHIV) usually have more advanced cancer at diagnosis and a higher cancer-related mortality, posing a significant burden on health care. However, clinical studies often exclude cancer patients with HIV, thereby limiting access to therapies for this patient population. PLHIV have a 25- to 35-fold higher chance of being diagnosed with SCAC than individuals who are HIV negative. We therefore evaluated safety and efficacy of retifanlimab in PLHIV with SCAC. **Methods:** The study designs for POD1UM-202 (NCT03597295) and POD1UM-303/InterAACT-2 (NCT04472429) have previously been described. Both trials permitted PLHIV to enroll if CD4+ count was $\geq$200/μL with an undetectable viral load per standard of care assay, and who did not experience any HIV-related opportunistic infection for $\geq$4 weeks prior to study enrollment. Patients continued to receive antiretroviral therapy (ART/HAART) without interruption or dose reduction. HIV viral load and CD4+ cell count was assessed every 8 weeks during the studies and could be reduced to every 6 months during safety and disease follow-up. **Results:** Patient and disease characteristics were similar among PLHIV and the overall study populations. Among the 20 patients with HIV enrolled in these SCAC trials, median age was 58 years, 70% (n = 14) were male, and 80% (n = 16) were White. Forty-five percent (n = 9) of patients received retifanlimab and 30% (n = 6) received retifanlimab with platinum-based chemotherapy, whereas the remaining 5 patients were assigned to placebo plus chemotherapy. During these studies, no patient experienced a sustained drop in CD4+ T-cell counts or increase in HIV viral load of clinical significance. No treatment-emergent opportunistic infections were recorded. Immune-related adverse events (irAEs) and grade $\geq$3 irAEs were consistent with the non-HIV population. Objective response rates were 22% (2/9) with retifanlimab in second-line and 67% (4/6) with retifanlimab and chemotherapy in first-line (previously untreated). Patient-reported outcomes showed no negative impact and based on Quality-of-Life Questionnaire for Anal Cancer, good scores for bowel function, sexual, and symptom domains were maintained. Retifanlimab pharmacokinetics was independent of HIV status and not impacted by the HAART required for ongoing HIV management. **Conclusions:** Among PLHIV and advanced SCAC who received treatment, retifanlimab showed significant clinical activity with efficacy qualitatively similar to patients without HIV and no excess toxicity or reduced HIV control. The analysis indicates that retifanlimab is generally safe for PLHIV and SCAC and also supports inclusion of HIV-positive patients in other immunotherapy trials. The favorable outcomes in PLHIV are encouraging because infection with HIV is among the most important risk factors for SCAC. Clinical trial information: NCT03597295 and NCT04472429. Research Sponsor: Incyte Corporation.

3522 Poster Session

Investigating the immunogenomic profile of anal HPV driven disease for novel therapeutic discovery. First Author: Micol Lupi, Imperial College London, London, United Kingdom

Background: Anal squamous cell carcinoma (ASCC) is driven by Human Papilloma Virus and arises from high-grade squamous intraepithelial lesions (HSIL) which, when treated, reduces the risk of cancer progression. However, current treatment options for anal HSIL are limited with considerable morbidity. Although a proportion of patients with localised ASCC can be successfully treated with pelvic chemoradiotherapy, there are significant associated side effects. Given the stepwise evolution of disease, there is an opportunity for the identification of novel therapeutic approaches for cancer prevention. **Methods:** This study investigates the mutational and immune landscape of matched fresh frozen anal cancer and HSIL samples as well as blood samples from 8 patients using multi-omic analysis (WES, RNAseq and FUME-TCRseq). We compared candidate driver mutations and pathways (including known immune escape mechanisms), copy number alterations (CNAs), differential gene expression, predicted neoantigen profiles (using NeoPredPipe) and TCR repertoire composition and diversity. In addition, digital cell classification of H&E stained sections was used to characterise the distribution of 4 immune cell types. **Results:** There was considerable copy number profile overlap between anal HSIL and cancer with 79.2% CNA concordance. Samples clustered by patient rather than pathology on gene expression and few differentially expressed genes were identified. There was no difference in predicted neoantigen burden (p= 0.11) nor the proportion of unique or common neoantigens (p = 0.64), illustrating shared immunogenicity between anal cancers with corresponding pre-cancerous lesions. However, we observed a shift in TCR repertoire composition between HSIL and cancer in all patients, with HSIL regions containing larger clusters of related TCR clonotypes (p = 0.02). Driver mutations in *PIK3CA*, *KMT2C*, *PBRM1*, *KLF5, STK11* and *CUL1* were shared between matched samples. Enriched GO terms, Kegg pathways and Reactome pathways shared by 2 or more samples included ubiquitination, lipid metabolism and glycosylation. There was higher *PD-L1* and *CTLA4* expression in anal cancer compared with HSIL, suggestive of immune escape at the transition to invasive cancer. Pathogenic mutations in the Endoplasmic reticulum aminopeptidase 1 (*ERAP1*) gene, responsible for modulating the peptide repertoire presented by MHC class I molecules, were found in one HSIL sample and two cancer samples. **Conclusions:** For the first time, this study demonstrates compelling overlap in the immunogenomic profiles of advanced anal HSIL and neighbouring invasive cancer. The shared neoantigen burden and overall immunogenicity supports future vaccine development in the treatment of anal HSIL and subsequent anal cancer prevention. Furthermore, the evidence for immune escape at the transition to invasion could motivate the use of immunotherapy in this setting. Research Sponsor: NIHR Biomedical Research Centre at the Royal Marsden Hospital and Institute of Cancer Research; The Syncona Foundation; The Royal Marsden Cancer Charity.

3523 Poster Session

Immunotherapy combined with hypofractionated radiotherapy and chemotherapy for locally recurrent rectal cancer (TORCH-R): A prospective, single-arm, two-cohort, phase II trial. First Author: Ruiyan Wu, Department of Radiation Oncology, Fudan University Shanghai Cancer Center, Shanghai, China

Background: To assess whether the integration of PD-1 inhibitor with hypofractionated radiotherapy and chemotherapy therapy can lead to an improvement in objective responses in patients with proficient mismatch repair or microsatellite stable (pMMR/MSS) locally recurrence rectal cancer (LRRC). **Methods:** We did a prospective, single-arm, two-cohort, phase 2 trial in LRRC patients without or with oligometastases. Eligible patients with previously untreated (cohort A) or progressive disease after first line therapy (cohort B), were assigned received 25-40 Gy/5 Fx irradiation or 15–30 Gy/5 Fx reirradiation for pelvic recurrence, followdd by 18 weeks of chemotherapy, toripalimab, and stereotactic ablative radiotherapy (SABR) for all metastatic lesions between chemoimmunotherapy cycles. The primary endpoint was confirmed local recurrence objective response rate (ORR). The study is registered with ClinicalTrials.gov, NCT05628038. **Results:** Between Oct 15, 2022, and Aug 31, 2024, We enrolled 67 patients: 41 in cohort A and 26 in cohort B. Median follow-up duration was 10.5 months (IQR 7.3-15.5 months). The local recurrence ORR was achieved at 82.9% (34 of 41 patients) in cohort A and 65.4% (17 of 26 patients) in cohort B. Six patients (14.7%) underwent radical resections (R0) in cohort A and two patients (7.7%) in cohort B. The CR rate was 34.1% (12 cCR patients + 2 pCR patients) in cohort A and 11.5% (2 cCR patients + 1 pCR patients) in cohort B. The most frequent grade 3-4 toxicities were neutropenia (10.8% in cohort A and 25.0% in cohort B) and diarrhea (16.2% in cohort A and 20.8% in cohort B). **Conclusions:** The PD-1 inhibitor remarkably improved ORR in pMMR/MSS LRRC compared with historical benchmark with acceptable toxicity. Up-front immunochemotherapy combined with hypofractionated radiotherapy was selected for future definitive study. Clinical trial information: NCT05628038. Research Sponsor: None.

3524 **Poster Session**

Harnessing transcriptome signatures and CD103+CD8+ immune infiltration for prognosis and treatment outcomes in anal squamous cell carcinoma. First Author: Ilma Soledad Iseas, Medical Oncology Department, Paris-St Joseph Hospital, Paris,, France

Background: Anal squamous cell carcinoma (ASCC) is a rare malignancy linked to high-risk HPV, with rising incidence among younger adults. While immunotherapy advances have improved outcomes in metastatic ASCC, treatment for localized disease has remained unchanged for decades, with high recurrence rates. This study investigates molecular biomarkers and immune mechanisms predictive of chemoradiotherapy outcomes in non-metastatic ASCC. **Methods:** This retrospective study analyzed 94 stage I-III non-metastatic anal squamous cell carcinoma (ASCC) patients treated with curative chemoradiotherapy (CRT) at Hôpital Paris Saint Joseph (2010–2017) in France. Treatment response (CR) was assessed at 24 weeks by RECIST v1.1. Molecular analyses included whole-exome and RNA sequencing on FFPE samples to evaluate somatic mutations, tumor mutational burden (TMB), and gene expression profiles. Immunohistochemistry assessed immune markers (CD8, CD103). Statistical analyses identified predictors of CR, progression-free (DFS), and overall survival (OS). **Results:** Complete response (CR) was achieved in 71% of cases, with no significant differences between treatment regimens ($p > 0.05$). Mutational analysis identified 172 alterations in novel (SLAMF7 and GOLGA6L9) and previously described cancer driver genes (KMT2C, KMT2D, and PIK3CA), with higher mutational burdens showing a non-significant trend toward CR. Transcriptomic profiling revealed 350 differentially expressed genes among CR vs. NCR patients (p-value < 0.01; FC > 2). CR was associated with modulation of immune-related pathways, including TNFα/NFkB signaling ($p < 0.01$). Immune infiltrate analysis showed enrichment of CD8+ central memory T cells (p = 0.008) and CD4+ resting memory B cells (p = 0.01) in CR cases, correlating with improved OS (p = 0.0026) and DFS (p = 0.0098). CD103+CD8+ tumor-infiltrating lymphocytes emerged as the strongest predictor of survival (OS: p = 0.011; DFS: p = 0.003), underscoring their potential as prognostic biomarkers and therapeutic targets in ASCC. **Conclusions:** These findings underscore the potential of integrating molecular and immune markers into clinical practice to better predict treatment response and guide personalized therapies for CRT efficacy for ASCC patients. Further validation in independent cohorts is necessary to confirm the clinical relevance of these biomarkers and their application in therapeutic decision-making. Research Sponsor: None.

3525 **Poster Session**

POD1UM-303/INTERAACT2 subgroup analyses and impact of delayed retifanlimab treatment on outcomes in patients with squamous cell carcinoma of the anal canal (SCAC). First Author: Marwan Fakih, City of Hope National Medical Center, Duarte, CA

Background: SCAC is a rare cancer with high unmet medical need and no FDA-approved treatment options. POD1UM-303 is the only phase 3 study of systemic therapy completed to date in advanced SCAC. The study met its primary endpoint of progression-free survival (PFS; 9.3 mo in the retifanlimab group vs 7.4 mo in the placebo group [HR, 0.63; 95% CI, 0.47, 0.84; *P*= 0.0006]) (Rao S, et al. *Ann Oncol*. 2024;35:S1217). Based on these results, retifanlimab combined with carboplatin-paclitaxel represents a new standard of care (SOC) for inoperable locally recurrent/metastatic SCAC. Here, we present outcomes for predefined subgroups of interest in POD1UM-303 and exploratory analyses in patients who received open-label retifanlimab in the crossover phase of the study. **Methods:** The POD1UM-303 study design and methods were previously presented at ESMO 2024. PFS comparisons for predefined subgroups, including PD-L1 expression, region of enrollment, presence of liver metastases, extent of disease, as well as HPV and HIV status, were performed. Exploratory analyses of investigator-assessed response to retifanlimab, overall survival (OS), and safety during crossover treatment were also performed. **Results:** A total of 308 patients were enrolled (1:1) to receive retifanlimab or placebo with chemotherapy; 69 (45%) from the placebo + chemotherapy group received crossover treatment with retifanlimab monotherapy upon confirmed progression. A consistent PFS benefit in favor of retifanlimab + chemotherapy was observed for all predefined subgroups, including tumors with PD-L1 expression $< 1\%$, patients with liver metastases, and regardless of HPV or HIV status. Median PFS in the retifanlimab + chemotherapy group was higher in the PD-L1 $\geq 1\%$ vs PD-L1 $< 1\%$ groups (9.3 mo; HR, 0.64 vs 7.5 mo; HR, 0.53) but was not impacted by presence of liver metastases. During crossover, investigator-assessed overall response rate was qualitatively similar to that seen in the POD1UM-202 study, which enrolled a similar platinum-refractory population. Median OS for patients receiving crossover treatment with retifanlimab was 24.3 mo, compared with 29.2 mo for patients who were assigned to retifanlimab + chemotherapy at randomization. Safety during crossover was consistent with earlier observations and comparable with experience in POD1UM-202. **Conclusions:** The benefits of retifanlimab combined with carboplatin-paclitaxel extend to the broad population of SCAC, including those with tumors not expressing PD-L1 and liver metastases. Response rate and safety profile of retifanlimab monotherapy in the crossover period were consistent with the previous POD1UM-202 experience; however, exploratory analysis of survival in crossover patients suggests first-line retifanlimab with SOC chemotherapy is preferable to sequential treatment after progression on chemotherapy. Clinical trial information: NCT04472429. Research Sponsor: None.

3526 **Poster Session**

Genomic characterization of anal canal squamous cell carcinoma (ASCC) and outcomes on matched targeted therapy. First Author: Maliha Nusrat, Memorial Sloan Kettering Cancer Center, New York, NY

Background: Anal canal squamous cell carcinoma (ASCC) is uncommon but increasing in incidence. 5-year survival of patients (pts) with metastatic ASCC is only 36%; new therapies are an unmet medical need. Genomic alterations (GA) in phosphoinositol-3-kinase (PI3K) signaling pathway have been reported in small datasets of ASCC. Data on clinical outcomes with therapies targeting these GA in pts with ASCC are lacking. **Methods:** Tumor genomic data of pts with ASCC at Memorial Sloan Kettering Cancer Center (MSK) were obtained using a targeted next generation sequencing assay (MSK IMPACT) from cBioPortal database. GA were annotated for biological significance using the OncoKB database, and only GA with known oncogenic potential were included. GA were categorized as mutations (mut), amplifications (amp), deletions (del) and fusions (fus). Clinical annotations were abstracted from electronic health records and outcomes of pts who participated in clinical trials were assessed. Data were summarized using descriptive statistics and survivals were estimated using Kaplan-Meier method. **Results:** Of 92,711 pts in cBioPortal, 218 (0.2%) pts had ASCC (male n = 65, 30%). Of these 218 pts, 179 (82%) had at least 1 oncogenic GA. Oncogenic GA were most frequently identified in *PIK3CA* 40% (87 pts; mut 67, amp 36, with overlap), *KMT2D* 19% (mut 42), *BCL6* 17% (amp 37), *PTEN* 12% (mut 18, del 9), *EP300* 11% (mut 24), *KMT2C* 11% (mut 20, del 3), and *FBXW7* 10% (mut 20, del 1). Oncogenic GA were most frequent in the PI3K-AKT-mTOR signaling pathway (121 pts, 55%). Amps were also seen in *FGF3*, *FGF4, FGF19* and *CCND1* in 4% pts each. Thirteen pts with metastatic treatment refractory ASCC participated in early phase clinical trials; 3 pts enrolled in > 1 studies (total 18 trial participations). GA-matched targeted therapy was administered to 8 pts: oncogene inhibitors in 6 pts (targeting PIK3CA E545K in 3, PIK3CA Q546K in 1, HER2 I767M in 1, FGFR2 amp in 1), and drugs selected for tumor suppressor gene GA in 3 pts (PTCH1 loss in 1, TP53-wild in 1, FBXW7 in 1). Six pts received immunotherapy and 3 pts were treated with antivirals drugs targeting Human Papillomavirus. Out of 4 pts treated with PI3K signaling inhibitors, 1 had partial response and 2 had stable disease, with median progression free survival of 3.6 (95% CI 0-8.6) months and median overall survival of 9.1 (95% CI 5.7-12.5) months. Two out of four pts treated with PI3K pathway inhibitors were on treatment for > 6 months. No response was seen in pts treated with drugs targeting GA other than PIK3CA or with immunotherapy; and one of three pts treated with anti-viral agents had best response of stable disease. **Conclusions:** This is the largest characterization of GA with known oncogenic potential in ASCC. The PI3K signaling pathway is altered in over half of ASCC, and PI3K-AKT-MTOR inhibitors have the potential for further investigation in pts with activating GA in *PIK3CA* gene. Research Sponsor: Robert A. Winn Career Development Award.

3527 **Poster Session**

Monitoring botensilimab- and balstilimab-induced T-cell dynamics in refractory mismatch repair proficient metastatic colorectal cancer. First Author: Gertjan Rasschaert, Gastrointestinal Oncology Department, University Hospitals Leuven, Leuven, Belgium

Background: Mismatch repair proficient (pMMR) metastatic colorectal cancer (mCRC) responds poorly to immune checkpoint inhibition (ICI). A better understanding of local and systemic immune cell activities is critical for improving ICI treatment efficacy. T cells elicit anti-tumor specificity through their T cell receptors (TCR) and dynamic changes in the TCR repertoire are associated with clinical outcomes. Circulating T cells in the blood provide an accessible liquid biomarker to quantify and track T cell activity at systems level and longitudinally. Here, we present temporal T cell tracking as a correlate of ICI efficacy in refractory pMMR mCRC patients treated with botensilimab (BOT; Fc-enhanced anti-CTLA-4 antibody) with or without balstilimab (BAL; anti-PD-1 antibody). **Methods:** 10 patients from the open-label, phase 2 study (NCT05608044) with BOT in refractory pMMR CRC (without metastatic liver disease) were included. In this trial patients were randomized into BOT (75mg or 150mg Q6W, 4x) monotherapy or in combination with BAL (240mg Q2W, for 2 years), versus standard of care (regorafenib or trifluridine/tipiracil). TCR dynamics were longitudinally assessed (0,2,4,6,12 weeks) from circulating T cells, based on deep TCR sequencing (OS-TCR, Omniscope) and quantified using functional clustering. **Results:** 2 mCRC patients out of 10 (20%) showed partial response (PR) while 8 (80%) had progressive disease (PD), however at variable timepoints. However circulating T cells showed significant expansion of both pre-existing and novel clonotypes in all patients, detectable at conserved frequencies at sequential time points. The magnitude of induced T cell clonotypes varied across treatment cycles, with repeated boosting effects observed in responders. Scoring T cell activity based on quantitative and qualitative TCR repertoire metrics, allowed to rank patients by their response. Intriguingly, TCR repertoire dynamics strongly correlated with clinical outcomes, establishing its potential as a quantitative biomarker for monitoring treatment efficacy. **Conclusions:** Deep T cell repertoire profiling detected dynamics of circulating T cells with quantitative and qualitative difference related to ICI response. Immune cell tracking from liquid biopsies is a powerful tool to quantify ICI efficacy in real time. Research Sponsor: None.

3528 Poster Session

Predictive role of circulating tumor DNA in pMMR locally advanced rectal cancer patients receiving neoadjuvant chemoradiotherapy combined with sintilimab. First Author: Xiao-bin Zheng, The Sixth Affiliated Hospital, Sun Yat-sen University, Guangzhou, Guangdong, China

Background: Circulating tumor DNA (ctDNA) has emerged as a potential biomarker for various solid tumors, including colorectal cancer (CRC). It offers the advantage of longitudinal and dynamic surveillance of the tumor-specific genetic characteristics, eliminating the need for repeated invasive biopsies. However, the predictive role of ctDNA in patients with proficient mismatch repair (pMMR) locally advanced rectal cancer (LARC) receiving neoadjuvant chemoradiotherapy (CRT) combined with immunotherapy remains to be explored. **Methods:** In this prospective single-arm, phase II trial, pMMR LARC patients ($cT_{3\text{-}4}N_0M_0$ and $cT_{1\text{-}4}N_{1\text{-}2}M_0$) with an intermediate or high immunoscore (IS_B) were enrolled (NCT05450029). Treatment-naïve patients received radiotherapy (50 Gy/25 f) and 6 cycles of mFOLFOX6 plus 5 cycles of sintilimab, followed by total mesorectal excision (TME) 6-8 weeks post-radiotherapy. Baseline tumor tissue DNA and serial ctDNA dynamic changes were evaluated using next-generation sequencing. Baseline (T0) maximal somatic variant allelic frequency (maxVAF) as well as its changes at the first (T1, two cycles after therapy) and the second clinical evaluation (T2, four cycles after therapy) were assessed. **Results:** Tumor somatic mutations and aligned ctDNA analyses were conducted in 43 patients. The most frequently mutated genes in tumor tissue samples were APC (67%, n = 29), TP53 (65%, n = 28), KRAS (47%, n = 20), and FBXW7 (28%, n = 12), which were also observed in plasma. Pathway analysis indicated that mutations in SWI_SNF were more likely to be detected in patients achieving pathological complete response (pCR) (P = 0.02 for tumor tissue, P = 0.08 for plasma), suggesting a potential sensitization to sintilimab combined with CRT. For the dynamic ctDNA analysis, 37 patients were assessed using a 950-gene panel relevant to cancer. A significant decline in maxVAF from T0 to T1 was observed in the pCR group. An optimal cut-off of 0.11 for the maxVAF ratio (T1/T0) was identified to discriminate complete responders from other patients (AUC = 0.768; sensitivity 83.3%; specificity 72.0%; $P < 0.001$; 95% confidence interval [CI] 0.597-939). Patients with a low maxVAF ratio (< 0.11) were more likely to achieve pCR following CRT plus sintilimab therapy (OR = 12.86; 95% CI: 2.23-74.08; P = 0.004). **Conclusions:** ctDNA may serve as a potential biomarker of the response to CRT combined with immunotherapy in pMMR LARC. Further validation is warranted to confirm the predictive value of maxVAF and to identify additional biomarkers with potential predictive significance in pMMR LARC. Clinical trial information: NCT05450029. Research Sponsor: National Natural Science Foundation of China; 82470696 and 82103273; Guangdong Basic and Applied Basic Research Foundation; 2022A1515012498 and 2024A1515010956; the program of Guangdong Provincial Clinical Research Center for Digestive Diseases; 2020B1111170004; Guangzhou Science and Technology Program; 2024A04J6400; Sun Yat-sen University Clinical Research 5010 Program; 2016005.

3529 Poster Session

Risk factors associated with de novo metastatic colorectal cancer in early onset colorectal cancer. First Author: Emma Schatoff, Memorial Sloan Kettering Cancer Center, New York, NY

Background: Early onset colorectal cancer (EO CRC) is rising worldwide. Epidemiologic studies have shown that diets high in sugar and/or processed foods and limited exercise are associated with EO CRC when compared to healthy controls. However, risk factors associated with *de novo* metastatic disease are less well established. Identifying such risk factors may provide insight into modifiable lifestyle variables. **Methods:** All eligible EO CRC patients were enrolled in MSK's Center for Young Onset Colorectal and Gastrointestinal Cancer and completed a risk factor questionnaire (MSK-approved IRB #20-315). We analyzed questionnaire responses and compared risk factors between patients with *de novo* metastatic disease vs localized disease using Wilcoxon rank sum test or Fisher's exact test. Clinical outcomes, including overall survival (OS) from diagnosis and progression free survival (PFS) from 1st-line chemotherapy, were estimated using Kaplan-Meier methods. The Cox regression model was used to assess association between risk factors and survival outcomes. Tumors from a subset of patients (n = 206) were sequenced using MSK-IMPACT (MSK-approved IRB #12-245) and underwent genomic analyses. **Results:** 303 patients completed the questionnaire (median age at diagnosis 42; 51% Female; 88% left-sided tumors). 112 had *de novo* stage IV disease and 191 had stage I-III disease. Patients with *de novo* metastatic disease were younger, 40.9 [95%CI: 36.8 - 44.8] vs. 43.0 [95%CI: 38.4 - 46.4] (*P*-value *0.037*). Analysis of dietary factors showed no association with fruit, vegetable, fish, poultry, red meat, processed meat, or dairy intake. However, high sugar diets were significantly associated with *de novo* metastatic disease, with 30 (45%) vs. 37 (29%) (*P*-value, 0.004) patients reporting daily consumption of high sugar foods. Daily consumption of high calorie foods was also frequently reported in patients with metastatic disease (*P*-value, 0.057). 3-year OS in the metastatic population was 72% [95%CI: 62% - 84%] vs. 99% [95%CI: 98% - 100%]. Within the metastatic group, no association was observed between daily high sugar consumption and non-daily consumption in terms of PFS or OS. 3-year OS in the daily high sugar group was 79 % [95%CI: 62%-100%] vs 74% [95%CI: 57%-95%]. For early stage patients who later progressed (n = 27), median time to progression was not significantly shorter among patients who reported daily high sugar consumption (18 vs. 19 months, *P*-value 0.5). Genomic analyses revealed no significant differences in tumor mutational burden, fraction genome altered, frequency of oncogenic or signaling pathway alterations in *de novo* metastatic vs. non-metastatic patients. **Conclusions:** In a single center study, in EO CRC patients, high sugar diets may be associated with *de novo*metastatic disease. There were no significant genomic differences detected in patients with *de novo* metastatic vs. early stage disease. Research Sponsor: None.

3530 Poster Session

Survival impact of Neo*RAS* wild-type metastatic colorectal cancer: A SCRUM-Japan GOZILA substudy. First Author: Hiroki Osumi, Department of Gastroenterological Chemotherapy, Cancer Institute Hospital, Japanese Foundation for Cancer Research, Tokyo, Japan

Background: The "Neo*RAS*" phenomenon refers to *KRAS* or *NRAS* mutant (MT) metastatic colorectal cancer (mCRC) that becomes *RAS* wild-type (WT) following treatment and may represent a novel indication for anti-epidermal growth factor receptor monoclonal antibodies. We previously described the incidence and clinicopathological characteristics of Neo*RAS* WT mCRC (Osumi et al. *Nat Commun* 2024); here we share the impact of Neo*RAS* WT on survival for patients with mCRC. **Methods:** Patients enrolled in the large-scale nationwide screening platform SCRUM-Japan GOZILA who had mCRC, tumor tissue tested for *RAS* and *BRAF* V600E (MEBGEN RASKET-B), and received systemic therapy were included. Prior to subsequent treatment, all patients underwent next-generation sequencing of circulating tumor DNA (ctDNA) (Guardant360) and were classified into cohorts according to original tissue and subsequent ctDNA genotypes: persistent *RAS/BRAF* V600 WT (*RAS* WT), persistent *RAS* MT, change from *RAS* MT to *RAS* WT (Neo*RAS*WT, including ctDNA not detected), change from *RAS* WT to *RAS* MT (acquired *RAS* MT), persistent *BRAF* V600E (*BRAF* MT). *BRAF* MT outside V600 were not considered. We evaluated the clinicopathological characteristics and overall survival (OS) of patients in each cohort. OS was measured from time of first-line treatment initiation to the date of death. **Results:** The 1,352 patients (median age 61 years) included *RAS* WT: 526 (38.9%), *RAS* MT: 387 (28.7%), acquired *RAS* MT: 223 (16.5%), Neo*RAS* WT: 91 (6.7%), and *BRAF* MT: 125 (9.2%).Median number of therapy lines from tissue assessment to ctDNA testing was 2 (range 1-13). Neo*RAS* WT had low prevalence of liver (23.1%, $P < 0.001$), lymph node (16.5%, $P < 0.001$) and multi-organ metastasis (42.9%, $P < 0.001$), whereas lung (56.0%, $P < 0.001$) and peritoneal metastases (41.8%, P = 0.004) were more common in other groups. Left-sided primary tumors were more common with *RAS* WT (80.2%) followed by Neo*RAS* WT (70.3%) and *RAS* MT (67.7%), ($P < 0.001$). Patients with *BRAF* MT had significantly shorter median OS (28.1 months) compared to others ($P_{Log\text{-}rank} < 0.001$, hazard ratio (HR), 1.91; 95% confidence interval (CI), 1.52-2.40). Patients with Neo*RAS* WT had median OS (45.6 months) that was between *RAS* WT (51.9 months) and *RAS* MT (41.0 months) ($P_{Log\text{-}rank} < 0.001$). On the other hand, patients with acquired *RAS* MT had a significantly shorter median OS (43.3 months) compared to *RAS* WT ($P_{Log\text{-}rank} < 0.001$). In multivariate analysis, *BRAF* MT (HR: 2.06, 95%CI, 1.62-2.61, $P < 0.001$), ctDNA fraction (≥1.0%, HR: 1.41, 95%CI, 1.17-1.71, P = 0.00035), *RAS* MT (HR: 1.37, 95%CI, 1.17-1.62, P = 0.0001), and lymph node metastasis (HR: 0.85, 95%CI, 0.72-0.99, P = 0.046) were independent factors associated with shorter OS. **Conclusions:** Patients with Neo*RAS* WT mCRC exhibited distinct characteristics, and intermediate survival between the *RAS* WT and *RAS* MT groups. Research Sponsor: None.

3531 Poster Session

Revisiting the relevance of sidedness in colonic tumor molecular profiling. First Author: Ashok K. Vaid, Medanta, The Medicity, Gurugram, India

Background: Colorectal cancer (CRC) is a heterogeneous disease with distinct molecular and clinical differences between right- and left-sided tumors. This study analyzes these variations to understand their impact on tumor behavior and treatment strategies. **Methods:** A total of 445 colonic tumor samples (132 right-sided, 313 left-sided) were profiled to assess mutations, amplifications, and fusions in key cancer-related genes along with targeted transcriptome analysis of 20,802 genes in a subset using semiconductor based next-generation sequencing (NGS) platform at Datar Cancer Genetics. Immunotherapy biomarkers (TMB, MSI, and PD-L1 22C3 TPS) were analyzed in a subset. **Results:** Right-sided and left-sided colon cancers exhibit substantial molecular heterogeneity, driven by distinct genetic and epigenetic alterations (Table 1). Right-sided tumors were more frequently associated with MSI and had statistically significant higher incidence of *BRAF* mutations. *KRAS* mutations were frequently observed in both right-sided and left-sided tumors at equal rates. *ERBB2* amplifications were exclusive to left side tumors, whereas oncogenic *ERBB2* mutations were equally distributed. Located around *ERBB2, PGAP3* gene co-amplification too was exclusive to left sided tumors. *TFE3* alterations were absent from left sided tumors and common on right side. *TP53* mutations, though more common in left-sided tumors, the difference was not statistically significant. Gene expression profiling of a subset, including 103 left-sided and 41 right-sided colon tumors, revealed activation of the *Wnt/β-catenin* signalling pathway, *RAS/MAPK* pathway, *TGF-β* signalling pathway, and immune-related pathways, though these differences were not statistically significant, suggesting that while specific drivers may differ—such as the predominance of *APC* mutations in left-sided tumors (56.8% vs 37.9%) leading to *WNT* activation and the higher incidence of *RSPO2/3* fusions (7.1% vs 1.7%) in right-sided tumors -eventually some pathways are commonly implicated in colorectal cancer biology. **Conclusions:** Existing therapies like ICIs, *HER2* inhibitors, and emerging molecules such as *RSPO2/RSPO3* inhibitors could have differing impact based on tumor sidedness. Integrating these distinctions into drug development and clinical trials holds potential to optimize treatment outcomes. Research Sponsor: None.

Molecular profiles of right- and left-sided colon tumors.

Gene	Right (%)	Left (%)	p-Value (Chi-square test)
TP53	64.5%	73.2%	0.075644
APC	37.9%	56.8%	0.001354
KRAS	50.0%	43.6%	0.220194
BRAF	18.8%	3.0%	0.00001
TFE3	9.5%	0%	0.109087
***ERBB2* mutation**	2.3%	2.0%	0.80941
***ERBB2* amplification**	0%	5.9%	0.023006
***PGAP3* amplification**	0%	7.1%	0.673427
***RSPO2/3* fusion**	7.1%	1.7%	0.827207
Immunotherapy Biomarkers			
TMB 10-14	24.7%	29.3%	0.458066
TMB ³15	15.6%	7.6%	0.059925
MSI-High	8.1%	3.4%	0.066213
PD-L1 Positive	15%	5.6%	0.012571

3532 **Poster Session**

Predicting pathologic complete response in colorectal cancer patients after immunotherapy based on endoscopic biopsy and deep learning approach. First Author: Chaoyuan Xiao, Colorectal Cancer Center, Department of General Surgery, West China Hospital, Sichuan University, Chengdu, China

Background: Immune checkpoint inhibitors (ICIs) have emerged as effective treatments for microsatellite instability-high (MSI-H)/deficient mismatch repair(dMMR) tumors in a select subset of colorectal cancer (CRC) patients. Patients sensitive to preoperative immunotherapy may have the opportunity to be exempted from surgery, while those insensitive may avoid unnecessary treatment. Tumor pathology provides rich biological insights. Several studies have indicated that deep learning algorithms can predict the efficacy of immunotherapy directly from digitized hematoxylin-eosin (H&E) stained Whole Slide Images (WSIs). However, their potential application in CRC immunotherapy remains underexplored. Based on WSIs of endoscopic biopsy, this study aims to construct a predictive model using deep learning approach to identify potential pathological complete response (pCR) in CRC patients after preoperative immunotherapy. **Methods:** This study enrolled CRC patients who received preoperative immunotherapy at West China Hospital, Sichuan University. Stratified randomization based on pathological outcomes was performed, assigning enrolled patients to the training set (70%) and the validation set (30%). WSIs of endoscopic biopsy were used for analysis. A predictive model was developed based on the Swin Transformer architecture, integrating convolutional neural networks (CNNs) with a self-attention mechanism. Pre-trained weights were employed for feature extraction, and the CLAM (Clustering-constrained Attention Multiple Instance Learning) framework was utilized to optimize pathological image analysis. The model's performance was assessed in the validation cohort using the Receiver Operating Characteristic Curve (ROC) and Area Under the Curve (AUC) was calculated. Attention-based visualization analysis was further performed to identify the top patches that contributes to the determination of tumor response to preoperative immunotherapy. **Results:** 96 CRC patients treated with preoperative immunotherapy were included, with 67 in the training set and 29 in the validation set. A total of 278,901 512×512-pixel patches were generated by preprocessing 144 WSIs. A predictive model were established based on the training set and verified in the validation set. The model achieved an AUC of 0.82. Attention-based visualization analysis recognized the top 5% patches contributing to the determination of tumor response to preoperative immunotherapy, with 62.66% identified as tumor tissues and 37.34% identified as non-tumor tissues. **Conclusions:** Endoscopic biopsy based deep learning model, with distinct attention to tumor and non-tumor regions, may provide a novel and effective tool for predicting pCR after preoperative immunotherapy in CRC patients. Research Sponsor: National Natural Science Foundation of China.

3533 **Poster Session**

Metastatic site pattern as predictor of outcome of first-line alternating oxaliplatin-based chemotherapy and nivolumab for patients with microsatellite-stable (MSS) colorectal cancer (CRC). First Author: Anne Hansen Ree, Akershus University Hospital, University of Oslo, Oslo, Norway

Background: The randomized METIMMOX trial evaluated short-course oxaliplatin-based chemotherapy (FLOX) alternating with nivolumab for previously untreated, unresectable abdominal metastases (mets) from MSS CRC. A subgroup of patients assigned to this experimental (exp) treatment had remarkably extended progression-free survival (PFS) compared to the control group patients given standard FLOX chemotherapy with median PFS 9.3 months. We explored if the extent of involved organs might be decisive for responsiveness to the METIMMOX regimen. **Methods:** Patients with measurable infradiaphragmatic (liver, peritoneal, nodal) mets were randomly assigned to the control group of FLOX (oxaliplatin, 5-fluorouracil, folinic acid) Q2W or the exp group of alternating 2 cycles each of FLOX Q2W and nivolumab Q2W, with prespecified break periods. Radiologic response assessment was done every 8 weeks with PFS as the primary endpoint. For this *post hoc* analysis, at baseline, the principal metastatic site was defined by the 2 largest mets (main lesions) of the dominant infradiaphragmatic organ and the global metastatic pattern by the main and subsidiary lesions of all involved organs. Patients without adverse events leading to treatment discontinuation, thus with conclusive end of treatment (EoT) tumor data, were categorized into discrete outcome groups. **Results:** Of 36 exp group patients reaching the first radiologic reassessment, enabling formal evaluation, 31 proceeded to EoT tumor data. Of these, 6 patients (3 of 25 with liver main lesions, 3 of 4 with lymph node main lesions) had complete response (CR), including 3 of 3 *BRAF*-V600E cases. The remaining 3 CR cases had tumor mutational burden (TMB) 9.4-11.8. Of all 25 patients with liver mets, 13 (52%) had objective response and 5 (20%) stable disease. All 16 patients with objective response had improved PFS (median 15.5 months, 95% CI 12.4-18.5; $p < 0.001$, log-rank test). None of main or subsidiary lesions in peritoneum or lungs responded to the treatment. The 3 outcome groups comprised 7 patients with PFS 19.8-41.6 months (longer than twice the median), 8 with PFS 9.9-16.4 months (above median), and 16 with PFS 1.9-9.2 months (below median). At baseline, the best outcome group cases would have been predicted by the combination of right-sided primary, small main lesions (sum of diameters 42 mm or less), and all mets confined to the liver and/or lymph nodes; the mid group cases by left-sided or rectal primary along with peritoneal or lung subsidiary lesions; and the poor outcome cases by extended organ mets. **Conclusions:** Alternating short-course oxaliplatin-based chemotherapy and nivolumab was particularly efficient in treating unresectable liver or lymph node mets from right-sided MSS CRC with intermediate TMB or the *BRAF* driver mutation, but inefficient at peritoneal and lung mets. Clinical trial information: NCT03388190. Research Sponsor: Norwegian Cancer Society; Bristol-Myers Squibb.

3534 **Poster Session**

Open-label phase Ib/II study of cetuximab (CET) plus LY3214996 with or without abemaciclib in patients (pts) with anti-EGFR-refractory metastatic colorectal cancer (mCRC). First Author: Guglielmo Vetere, Department of Gastrointestinal Medical Oncology, The University of Texas MD Anderson Cancer Center, Houston, TX

Background: Acquired resistance limits the efficacy of anti-EGFR (EGFRi) therapy in RAS wild-type (WT) mCRC, often through MAPK reactivation driven by secondary RAS mutations or other genomic alterations. Preclinical studies on EGFRi-refractory models led by our group showed that LY3214996, a potent ERK1/2 inhibitor, combined with CET suppresses MAPK signaling and reduces tumor growth, while the addition of Abemaciclib further enhances anti-tumor activity by synergistically inhibiting cell cycle and survival pathways. **Methods:** In this open-label, phase Ib/II study, RAS/BRAF/EGFR/MEK1 WT mCRC pts who progressed on prior EGFRi-based therapy and ≥1 chemotherapy were treated with CET + LY3214996 (Arm A) or CET + LY3214996 + Abemaciclib (Arm B). Phase Ib employed a 3 + 3 design to determine the maximum tolerated dose (MTD) and recommended phase 2 dose (RP2D). Phase II followed a two-stage design with cohort expansion to assess ORR by RECIST v1.1 as the primary endpoint. Secondary endpoints included PFS and OS. **Results:** Of 44 pts treated on trial, 2 did not meet inclusion criteria; 39 were evaluable for activity, and 34 for efficacy. The RP2D was 200 mg LY3214996 p.o. daily + 500 mg/m² CET i.v. biweekly in Arm A with the addition of 150 mg Abemaciclib p.o. twice daily in Arm B. Median age was 53.0 years (IQR 47.0 – 63.8), and 59.1% (26/44) were male. Most pts (95.5%, 42/44) had a left-sided or rectal primary, and all were pMMR/MSS. Prior EGFRi-based rechallenge, retreatment/reintroduction, or both were noted in 9.1% (4/44), 25.0% (11/44), and 4.5% (2/44), respectively. ORR, DCR, median PFS and OS were 5.3% (1/19), 36.8% (7/19), 1.8 months (95% CI 1.5 – 4.8) and 7.0 months (95% CI 5.0 – 22.0) for the doublet and 15.0% (3/20), 65.0% (13/20), 3.6 months (95% CI 2.5 – 4.5), and 14.0 months (95% CI 5.9 – 21.0) for the triplet, respectively. Longer time elapsed from last EGFRi was associated with higher predicted probability of response after adjustment for trial regimen (OR 1.35, 95% CI 1.06 – 1.94, p = 0.038). Baseline ctDNA profiling drawn prior to rechallenge revealed acquired RAS mutations in two responders, one per arm. Grade 3 TRAEs occurred in 31.8% (14/44), with acneiform rash (9.1%, 4/44), diarrhea (9.1%, 4/44), thrombocytopenia (6.8%, 3/44), fatigue (4.5%, 2/44), and anemia (4.5%, 2/44) being the most frequent while one Grade 4 TRAE (thrombocytopenia, 2.3%) was reported. **Conclusions:** CET + LY3214996 ± Abemaciclib had a manageable safety profile with no unexpected adverse events. Although activity was modest, this study is the first to report objective responses to an EGFRi-based regimen in pts harboring acquired RAS mutations in pre-rechallenge ctDNA. Translational efforts are ongoing. Clinical trial information: NCT04616183. Research Sponsor: MD Anderson Cancer Center; Jack T. and Lillian S. Clift Fellowship; Andrew Sabin Family Fellowship; NIH GI SPORE; Mr. and Mrs. Jack Lee.

3535 **Poster Session**

COPEC trial: Early determination of pathological tumor response to neoadjuvant chemotherapy in low/intermediate risk stage II/II rectal cancer—A multicenter, non-inferiority phase III randomized trial. First Author: Mingtian Wei, West China Hospital (China), Chengdu, China

Background: Multiple large-scale prospective studies have confirmed that neoadjuvant chemotherapy (NCT) alone can achieve optimal distant and local control in locally advanced rectal cancers (LARC) without high risks. However, due to the potentially lower overall response rate compared to chemo-radiotherapy, it is rational to discontinue ineffective NCT in chemo-resistant patients. In our phase II study, we applied 4 cycles of Capox in LARC patients with low to intermediate risks, observing a considerable pathoclinical response rate and an accuracy of 0.89 in predicting non-responders using MRI features after two cycles of Capox. To determine the optimal number of NCT cycles and prevent unnecessary prolonged treatment, we conducted this phase III trial to assess the non-inferiority of two cycles of NCT compared to four cycles with respect to the final pathological tumor response grade (pTRG) of 3. **Methods:** This multicenter, non-inferiority, phase III randomized controlled trial was conducted at 14 centers across China. Eligible patients with low- to intermediate-risk stage II/III rectal cancer were randomized to receive either 2 or 4 cycles of CAPOX, followed by total mesorectal excision (TME) surgery. The primary endpoint was the proportion of patients with a poor pathological response to NCT (pTRG 3). Secondary outcomes included the accuracy of MRI in predicting tumor response, treatment-related adverse events, and 3-year survival outcomes. **Results:** From August 6, 2021, to May 27, 2024, a total of 573 patients were enrolled. Ultimately, 527 patients (2-cycle group, 266 vs. 4-cycle group, 261) were included in the primary analysis. The pTRG 3 rate in the 2-cycle group (27.8%, 74/266) was non-inferior to that in the 4-cycle group (26.4%, 69/261, p = 0.722). Better lymph node response was observed in the 4-cycle group (pN negative: 83.1%, 217/261 vs. 72.5%, 193/266, p = 0.011). The incidence of major adverse events (grade ≥3, according to CTCAE 5.0) was comparable between the two groups (37.9% vs. 44.8%, p = 0.094). A tumor longitudinal length reduction rate (TLLR) of less than 30% on MRI predicted pathological poor responders with a high positive predictive value of 0.918 after two cycles of NCT in the two-cycle group, 0.864 after two cycles of NCT in the four-cycle group, and 0.841 after four cycles of NCT in the four-cycle group. **Conclusions:** Four cycles of NCT do not result in a greater reduction in poor pathological response compared to two cycles, highlighting the importance of early response assessment. MRI evaluation of tumor response after 2 cycles predict the final pathological results with considerable accuracy. These findings lay the groundwork for future studies exploring response-guided treatment approaches in rectal cancer. Clinical trial information: NCT04922853. Research Sponsor: None.

3536 Poster Session

Survival of patients (pts) with microsatellite stable/mismatch repair proficient (MSS/pMMR) metastatic colorectal carcinoma (mCRC) treated with EO4010 + nivolumab (EO/N). First Author: Arvind Dasari, Department of Gastrointestinal Medical Oncology, The University of Texas MD Anderson Cancer Center, Houston, TX

Background: EO is designed to expand pre-existing memory CD8 T cells cross-reacting with tumor associated antigens (TAAs). EO is composed of microbial-derived sequences mimicking CD8 T cell HLA-A2 epitopes on 5 TAAs, BIRC5, FOXM1, UBE2C, CDC20 and KIF2C, upregulated in mCRC, and the CD4 peptide UCP2. **Methods:** Pts had MSS/pMMR mCRC, treated with FU, oxaliplatin, irinotecan and anti-VEGF/EGFR. Cohort (C)1 safety lead-in followed by expansion C2; pts received EO (300 μg/peptide in Montanide ISA 51 VG) q2 weeks (w) x4 then q4w + N (240 mg q2w x 3 then 480 mg q4w; C1 omitted 2 first N doses). **Results:** 20 pts (C1 = 3, C2 = 17), 55% female, 70%/30% ECOG 0/1, median age 58 (45-80) years, started EO + N June 2023 to March 2024. Primary tumor right sided 35%/left 35%/rectal 30%, median 2 (1-4) tumor involved organs, 55% liver mets, 65% KRAS mutated, and median 3 (1-5) prior lines of treatments. Any grade related AEs in $>$ 2 pts: local administration site reactions (85%), asthenia (15%), and fatigue (15%); 1 related Gr 3, local administration site ulceration; 1 related SAE, N infusion related reaction. CD8 T cells (EO/TAA peptide specific tetramers staining of PBMC ex vivo) against EO found in 10/11 tested pts, cross-reactivity against TAAs in all 10 positive pts. Best response (RECIST 1.1): 1 partial response (liver mets -47%, lung mets -34%; CEA normalized), 1 stable disease (SD) (lung mets -7%; CEA -68%, CA19-9 -55%; pat died w 17 non-related myocardial infarction), and 1 SD until w 18 (withdrawn consent); 6 (30%) pts had target SD, and unequivocal progression of non-target lesions; 11 pts (55%) had progressive disease. Median PFS 1.8 months (mo) (range 1.4-10.5). 14 pts (70%) received post-study anti-cancer treatment. After a median follow-up of 14.7 mo, median overall survival (OS) 11.2 mo; 80% 6- and 39% 12-mo survival. Immune response assessed using a composite score of EO4010-specific T cell responses, measured by ex vivo tetramer assays weeks 5 to 9 of treatment (best response used), with pts stratified into high and low responders based on median score. Kaplan-Meier analysis with log-rank test showed trend towards better OS in high responders (p = 0.065). Median OS low responders 9.6 mo and not reached for high responders. Immune response magnitude showed no correlation with baseline T cell activation potential (by anti-CD3 stimulation/ELISPOT); independence indicates that EO4010-induced CD8 T cell expansion occurs irrespective of baseline T cell status. **Conclusions:** EO4010 + nivolumab promotes expansion of TAA specific CD8 T cells and shows good safety and interesting survival in previously treated MSS/pMMR mCRC. Data suggests a potential survival benefit associated with stronger EO4010-induced immune responses. Continued evaluation of EO is warranted; further immune testing data, and results of addition of bevacizumab to EO + N in a separate cohort are awaited. Clinical trial information: NCT05589597. Research Sponsor: Enterome.

3537 Poster Session

The prognostic and predictive role of HER2 amplification/overexpression and *HER2* mutations in metastatic colorectal cancer treated with first-line chemotherapy plus bevacizumab/anti-EGFRs: An individual patient data pooled analysis of eight randomized trials. First Author: Marco Maria Germani, Department of Translational Research and New Technologies in Medicine and Surgery, University of Pisa, Pisa, Italy

Background: HER2 amplification/overxpression (HER2-pos) is detected in the 5% of *RAS/BRAF* wild-type (wt) metastatic colorectal cancers (mCRC) and is associated with poor efficacy of EGFR blockade in preclinical models. Whether HER2-pos is a prognostic and/or predictive biomarker of benefit from anti-EGFRs/bevacizumab (bev) in mCRC patients (pts) is still debated. Similarly, the role of activating *HER2* mutations (mut) is unclear. **Methods:** We collected individual patient data from 8 randomized clinical trials (RCTs) in the first-line treatment of mCRC: TRIBE2, TRIPLETE, VALENTINO, ATEZOTRIBE, PANDA, PANAMA, PARADIGM and CALGB/SWOG80405. Only pts with *RAS/BRAF* wt pMMR mCRC with available HER2 *status* by means of immunohistochemistry $\pm$ *in situ hybridization* and/or Next-generation sequencing on tumor or circulating DNA and treated with triplet or doublets + bev or an anti-EGFR were included. The prognostic and predictive impact of HER2-pos and *HER2* mut was assessed in terms of PFS, OS and ORR. **Results:** 1604 pts were eligible. 81 (5%) tumours were HER2-pos. HER2-pos was associated with shorter PFS (mPFS: 9.8 vs 12.2 months (mos), HR: 1.31, p = 0.02) and OS (mOS: 28.0 vs 34.9 mos, HR: 1.37, p = 0.01), and similar ORR (77 vs 72%, p = 0.47) compared to HER2-neg pts. P-values adjusted for clinically meaningful covariates (p_{adj}) were p_{adj}PFS = 0.075 and p_{adj}OS = 0.036. We found no interaction between HER2-pos and treatment effect according to the use of bev vs anti-EGFRs in terms of PFS (p_{int}= 0.76), OS (p_{int}= 0.76) and ORR (p_{int}= 0.64). Similar findings were reported restricting the analysis to pts treated with doublets (N = 1465), and to those with left-sided tumors (N = 1315). In the HER2-pos subgroup (N = 69) of pts with left-sided *RAS/BRAF* wild-type pMMR tumors no difference between chemotherapy/bev and chemotherapy/anti-EGFR was reported in terms of PFS (mPFS: 9.8 vs 9.3 mos, HR: 0.73, p = 0.30), OS (mOS: 29.8 vs 28.0 mos, HR: 1.29, p = 0.40), and ORR (59% vs 79%, p = 0.10). Activating *HER2* mut were found in 27 (2%) out of 1408 HER2-neg tumors with *HER2* mutational *status* available. Pts with *HER2* mut tumors had a shorter OS (median: 23.7 vs 34.4 mos, HR: 1.56, p = 0.04) than *HER2* wt. No interaction between *HER2* mutational status and treatment effect was evident, with no significantly different PFS (mPFS: 9.4 vs 5.7 mos, HR: 0.88, p = 0.76) and OS (mOS: 20.9 vs 23.7 mos, HR: 1.04, p = 0.93) in the *HER2* mut subgroup between bev and anti-EGFRs. **Conclusions:** This is the largest analysis of HER2 *status* in untreated mCRC pts enrolled in RCTs. Waiting for targeted approaches, HER2-pos is an independent negative prognostic factor and does not predict benefit between bev/anti-EGFRs also in left-sided tumors. *HER2* mut may exert a negative prognostic impact in HER2-neg *RAS/BRAF* wt pMMR mCRC. Research Sponsor: Gruppo Oncologico del Nord Ovest (GONO); Arbeitsgemeinschaft Internistische Onkologie (AIO); Hoffman - La Roche; Amgen; Genentech; National Cancer Institute (HHS - NIH); National Cancer Institute (HHS - NIH); National Cancer Institute (HHS - NIH).

3538 Poster Session

Assessing the predictive role of tumor sidedness in *RAS* and *BRAF* wild-type metastatic colorectal cancer (mCRC) treated with first-line doublets + anti-EGFRs/bevacizumab (bev) or triplet + bev: An individual patient data pooled analysis of 10 randomized clinical trials. First Author: Marco Maria Germani, Department of Translational Research and New Technologies in Medicine and Surgery, University of Pisa, Pisa, Italy

Background: Chemotherapy (chemo) + an anti-EGFR and chemo + bev are currently regarded as preferred upfront options for left- and right-sided pMMR *RAS/BRAF* wild-type (wt) mCRC patients (pts), respectively. This recommendation is mainly based on trial-level pooled analyses of *RAS* wt pts' cohorts, thus including also *BRAF* mutant cases. **Methods:** We collected individual patient data from 10 randomized clinical trials (RCT) in first-line mCRC: TRIBE, TRIBE2, TRIPLETE, VALENTINO, ATEZOTRIBE, PANAMA, FIRE-3, FIRE-4, PARADIGM and CALGB/SWOG80405. *RAS* and *BRAF* wt mCRC pts treated with doublets + anti-EGFR/bev or triplet + bev were included. **Results:** 2178 pts were eligible. Left- and right-sided tumors were 1780 (82%) and 398 (18%), respectively. As reported in the table, among 2051 pts treated with doublets/bev or doublets/anti-EGFR, no significant interaction effect between primary sidedness and treatment arm was reported in terms of ORR (p_{int}: 0.27) and PFS (p_{int}: 0.32), with a p-value for interaction for OS of 0.13. Anti-EGFR-based doublets were associated with higher ORR and longer OS among pts with left-sided tumors, while similar outcomes were reported in right-sided ones. Among 339 pts enrolled in trials where triplet was included as a treatment arm, a potential interaction effect between primary sidedness and treatment (triplet/bev or doublet/anti-EGFR) was evident in terms of PFS (p_{int}: 0.14) and OS (p_{int}: 0.08) but not ORR (p_{int}: 0.42). Triplet/bev was associated with longer PFS and OS among pts with right-sided tumors. **Conclusions:** This is the largest analysis assessing the differential effect of biologic agents and chemo intensification according to primary tumor origin in pts with untreated *RAS* and *BRAF* wt mCRC enrolled in RCTs. Doublets/anti-EGFR is superior to doublets/bev in left-sided tumors, with no significant differences in right-sided tumors, where triplet + bev appears as the most efficacious regimen for fit pts. Further analyses assessing the role of molecular hyperselection beyond *RAS* and *BRAF* are ongoing. Research Sponsor: Gruppo Oncologico del Nord Ovest (GONO); Merck KGaA; Arbeitsgemeinschaft Internistische Onkologie (AIO); Hoffman - La Roche; Amgen; Genentech; National Cancer Institute (HHS - NIH); National Cancer Institute (HHS - NIH); National Cancer Institute (HHS - NIH); National Cancer Center.

	Right		Left		P_{int}	Right		Left		P_{int}
	Doublets/ antiEGFR N=209	Doublets/ bev N=157	Doublets/ antiEGFR N=1120	Doublets/ bev N=565		Triplet/ bev N=95	Doublets/ antiEGFR N=189	Triplet/ bev N=32	Doublets/ antiEGFR N=23	
ORR (%)	65	62	74	66		66	83	72	78	
OR [95% CI]	1.13 [0.73-1.73]		1.48 [1.19-1.84]		0.27	0.42 [0.10-1.48]		0.72 [0.41-1.27]		0.42
p	0.58		< 0.001			0.16		0.25		
mPFS*	9.6	10.6	12.6	12.6		12.4	10.1	12.2	13.8	
HR [95% CI]	1.12 [0.90-1.40]		0.99 [0.89-1.10]		0.32	0.62 [0.35-1.09]		0.98 [0.75-1.27]		0.14
p	0.32		0.84			0.09		0.88		
mOS*	25.1	29.1	36.4	33.6		37.2	23.8	37.7	35.5	
HR [95% CI]	1.05 [0.83-1.32]		0.85 [0.76-0.96]		0.13	0.55 [0.30-1.01]		0.95 [0.70-1.30]		0.08
p	0.69		0.007			0.05		0.76		

*Months.

3539 Poster Session

Drug-eluting beads loaded with irinotecan-transarterial chemoembolization (DEBIRI-TACE) combined with hepatic artery infusion chemotherapy and regorafenib in colorectal liver metastases refractory to second-line and above standard systemic therapy: A single-center, phase II clinical trial (DREAM). First Author: Wenzhe Fan, Department of Interventional Oncology, The First Affiliated Hospital of Sun Yat-sen University, Guangzhou, Guangdong, China

Background: For patients with colorectal liver metastasis (CRLM) who have failed in first-line or second-line systemic treatment, the prognosis is extremely poor. Regorafenib is the standard third line treatment regimen. We aim to explore the safety and clinical efficacy of added drug eluting beads loaded with irinotecan (DEBIRI) plus hepatic arterial infusion chemotherapy (HAIC) to regorafenib in the combination treatment of second-line and above in patients with CRLM. **Methods:** For this single-center, single-arm, prospective, phase II trial, patients with unresectable progression of CRLM after previously receiving at least six cycles of standard systemic chemotherapy above the second line were enrolled. All of the patients received at least once DEBIRI-TACE and FOLFOX-HAIC (Oxaliplatin 85mg/m^2 2h + Calcium Levofolinate 200mg/m^2 2h + Fluorouracil 2400mg/m^2 46h) plus oral regorafenib 80/120/160 mg once daily during weeks 1-3 of each 4-week cycle until disease progression or unacceptable toxicity. The primary endpoint of this study was the best objective response rate (ORR) per RECIST 1.1, the secondary endpoints include progression-free survival (PFS), overall survival (OS), safety and tolerability assessments. **Results:** By the cutoff date of 17 November 2023, 21 patients were enrolled, with the median age of 61 (ranges, 38-71 years old), 14 (66.7%) of whom were male. 17(81.0%) patients had more than one tumor and 13(61.9%) patients had major tumor larger than 5cm. The most frequent primary cancer localization was colon (81.0%) and the primary had been resected in 14(66.7%) patients. Somatic mutation status was available for 15 patients: KRAS mutation was found in 7 patients. The ORR was 33.3% and the DCR was 100%. The median PFS was 7.8 months (95% CI: 5.8–NA), the median OS was 17.6 months (95% CI: 9.3–NA), the 1-year and 2-year OS rate were 54.6% (30.7%-73.4%) and 23.9% (4.6%-51.3%), respectively, and the 1-year PFS rate was 36.4% (15.7%-57.5%). The most common TRAEs were AST/ALT increase (81.8%), abdominal pain (63.6%), hyperbilirubinemia (63.6%), hand-foot skin reaction (59.1%), diarrhea (40.9%), etc. 9 patients presented with grade 3 or 4 TRAEs, which were the transient liver function injury and abdominal pain caused by TACE and HAIC. **Conclusions:** DEBIRI-TACE combined with HAIC and regorafenib is feasible, safe and shows promising efficacy in treating the patients with CRLM, even after second-line and above systemic chemotherapy. Clinical trial information: NCT06071052. Research Sponsor: None.

3540 **Poster Session**

Biomarkers of emergent resistance to sotorasib plus panitumumab in *KRAS* G12C-mutated metastatic colorectal cancer (mCRC) from the randomized, phase 3 CodeBreaK 300 study. First Author: Lisa Salvatore, Medical Oncology, Università Cattolica del Sacro Cuore and Medical Oncology, Comprehensive Cancer Center, Fondazione Policlinico Universitario Agostino Gemelli, IRCCS, Rome, Italy

Background: The use of sotorasib (soto; $KRAS^{G12C}$ inhibitor) alone in patients with *KRAS* G12C-mutated mCRC gives rise to several receptor tyrosine kinase (RTK) alterations, resulting in treatment resistance. In CodeBreaK 300 trial, the addition of panitumumab (pani; monoclonal anti-EGFR antibody) counters this resistance and significantly improves clinical outcomes compared with standard of care (SoC; trifluridine-tipiracil or regorafenib). Over time this combination (soto+pani) may lead to the emergence of new resistance patterns. This study reports the distribution, patterns, and prevalence of genetic alterations that arise after treatment with soto+pani. **Methods:** Patients from the phase 3 CodeBreaK 300 trial with chemorefractory *KRAS* G12C-mutated mCRC who had paired plasma samples at baseline and at progression, were included in the analysis. The samples were evaluated using the 753-gene Guardant Infinity ctDNA test. Gene alterations that were absent at baseline but present at progression were considered. **Results:** By December 2024, 99 patients (median age: 62 years, female: 48%) were evaluated (soto 960 mg-pani: 32 [60% of ITT population], soto 240 mg-pani: 33 [62% of ITT population], SoC: 34 [63% of ITT population]). Overall, 90% of patients had at least 1 emergent, likely pathogenic, genomic alteration at progression. Median time to progression in biomarker-evaluable patients was 3.8 months for soto 960 mg-pani arm, 3.6 months for soto 240 mg-pani arm, and 2.0 months for SoC arm. Overall, the distribution, patterns, and prevalence of pathogenic emergent alterations were similar across all treatment arms. The most common pathogenic emergent alterations included *TP53* (34%), *DNMT3A* (17%), *ERBB2* (12%), and *LRP1B* (11%), generally associated with the RTK, cell cycle control, DNA methylation, and DNA damage response pathways. The median copy number of emergent *KRAS* copy number variations (CNVs) was higher (p = 0.007) in the soto 960 mg-pani (4.18) and soto 240 mg-pani (4.24) arms compared with the SoC arm (2.05). Emergent *KRAS* CNVs were primarily present in the soto+pani arms (soto 960 mg-pani: 40.6% [n = 13], soto 240 mg-pani: 36.4% [n = 12], and SoC: 14.7% [n = 5]). The presence of emergent pathogenic variants in *ALK* (n = 7) and *KMT2D* (n = 4) was observed exclusively among patients treated with soto+pani. *DNMT3A* mutations, along with other diverse emergent alterations, were observed in all three evaluable patients with partial response in the soto 960 mg-pani arm. **Conclusions:** Dysregulation of the DNA methylation and RTK pathways and *KRAS* amplifications may contribute to the development of resistance to soto+pani combination. Further characterization of these acquired alterations, can help inform future therapeutic strategies. Clinical trial information: NCT05198934. Research Sponsor: Amgen Inc.

3541 **Poster Session**

Safety and efficacy of anti-CEA CAR-T cells to prolong relapse-free survival of colorectal cancer liver metastases patients after radical resection. First Author: Wei Zhang, Department of Colorectal Surgery, Changhai Hospital, Naval Medical University, Shanghai, China

Background: Approximately 75% of colorectal cancer liver metastasis patients relapse within two years after surgery due to circulating tumor cells and microscopic residual disease. Specific chimeric antigen receptor (CAR) T-cell therapy, effective for hematological tumors, may also treat recurrent colorectal cancer liver metastases. Carcinoembryonic antigen (CEA) is a glycoprotein which is highly expressed in colorectal tumor. Therefore, this study aimed to evaluate the safety and efficacy of this therapy in postoperative colorectal cancer liver metastasis patients. **Methods:** We conducted a single-arm, dose-escalating phase I clinical trial (NCT05240950). Key eligibility criteria were achieving no evidence of disease status after treatment and had CEA positivity of 30% or greater. Three dose levels of 1, 3, and 6 (10^6/kg) Anti-CEA CAR-T cells were administered in a dose-escalating manner. The primary endpoint is safety which measures are incidence and severity of adverse events within 28 days and relapse-free survival at 24 months. **Results:** From December 2021 to December 2024, 48 subjects were screened, and 12 received CAR-T cell infusion (2 in the 1 and 3×10^6/kg group, and 8 in the 6×10^6/kg group). Three subjects who had relapsed before the infusion still asked for the infusion, so we proceeded to infuse after fully informing about the benefits and risks of the infusion. 8 subjects experienced adverse events during treatment, including lymphopenia (5 subjects), arthralgia (1 subject), fever (1 subject), and rash (1 subject). No severe adverse events occurred. The median follow-up time for the 9 pre-infusion relapse-free subjects was 23 months, of which 5 relapsed after infusion. In the 6×10^6/kg dose group, 4 subjects remained relapse-free survival of 5, 7, 10 and 15 months after infusion, and their follow-up is ongoing. By infusing CAR-T cell, 57.14% of the subjects in the 6×10^6/kg dose group were free of recurrence within two years after radical resection. **Conclusions:** This is the first clinical trial of Anti-CEA CAR-T therapy for prolonging relapse-free survival of postoperative colorectal cancer liver metastases patients, showing no serious adverse events and significant reduced risk of recurrence with high doses. Clinical trial information: NCT05240950. Research Sponsor: National Natural Science Foundation of China; 82072750, 82203137, 82473479; Shanghai Shenkang Hospital Development Center; SHDC2022CRT007; Natural Science Fund of Shanghai; 20ZR1457200; Shanghai Sailing Program; 21YF1459300; Health Care Research Project 2024; 24BJZ10; Commission Health Industry Clinical Research Project; 20224Y0348.

Clinical information of 9 pre-infusion relapse-free subjects.

Subhects number	TNM Stage	Infusion dose (×10^6/Kg)[1]	Current NED status	Post-infusion relapse-free survival time (months)[2]	Post-infusion survival time (months)[2]	Overall survival time (months)[3]
S01002	T3N0M1a	1	No	3	27	33
S01037	T2N1bM1a	3	No	12	12	26
S01008	T3N0M1a	6	Yes	10	10	25
S01010	T3N1M1a	6	No	10	10	26
S01015	T3N0M1a	6	Yes	15	15	21
S01023	T3N0M1a	6	No	12	14	23
S01042	T3N2aM1a	6	No	3	10	16
S01033	T3N1bM1a	6	Yes	7	7	18
S01043	T3N1bM1a	6	Yes	5	5	14

[1]One subject in each of the 1, 3, and 6 dose groups relapsed before infusion.
[2]From the day of infusion.
[3]From the day of radical resection.

3542 **Poster Session**

Preliminary safety, pharmacokinetics, and clinical activity of RG6344 in patients with BRAF V600E-mutant metastatic colorectal cancer (mCRC). First Author: Elisa Fontana, Sarah Cannon Research Institute UK, London, United Kingdom

Background: RG6344 (RO7276389) is a novel paradox breaker and brain penetrant BRAF inhibitor (BRAFi) designed to overcome the MAPK paradoxical activity, a well-established liability of the first generation BRAF inhibitors. The BRAF V600E mutation, present in about 10% of mCRC patients, negatively impacts prognosis and response to standard therapies. **Methods:** Dose escalation of RG6344 is being conducted in participants with solid tumors harboring BRAF V600E mutation up to the protocol specified maximum daily dose, to define the maximum tolerated dose (MTD) and/or recommended Phase 2 dose and characterize safety, PK/PD, and clinical outcomes (ISRCTN13713551). **Results:** As of September 25, 2024, 51 patients with mCRC (27, 53% with prior BRAFi treatment; median number of treatments 3 [2-6]), including 4 patients with non-measurable brain lesions, have been treated with RG6344 in the monotherapy dose escalation part of the study. Patients received at least one dose of study drug as a single agent. MTD has not been reached up to the highest dose of 3600 mg/d. Of the 51 treated patients, Grade 3 treatment-related AEs (TRAEs) occurred in 8 patients (14.5 %), grade 4 TRAEs in 2 patients (3.6%; both laboratory findings) and no grade 5 TRAEs were reported. The most commonly reported TRAEs included diarrhoea (23.6%), nausea (21.8%) and fatigue (12.7%). 3 patients (5.5%) discontinued study treatment due to TRAEs. None of the typical BRAFi class toxicities, such as cutaneous squamous cell carcinomas (cSCCs), Palmar-Plantar Erythrodysesthesia (PPE) and keratoacanthoma, have been observed to date, highlighting the paradox breaking properties of this BRAF inhibitor. Linear and time-independent PK was demonstrated across the tested dose range, reaching Ctrough levels exceeding pERK inhibition > 80%. Strong and early (i.e. FDG PET at 15 days) metabolic response of 74% (6 CMR, 30 PMR out of 49 evaluable patients) was observed on FDG PET. Association between metabolic responses and exposure was observed. Observed ORR (RECIST v1.1) was 25% in BRAFi-naive mCRC patients and 14.8% in BRAFi-experienced patients, DCR was 100% for BRAFi-naive patients and 62.9% for BRAFi-experienced patients, mPFS was 7.3 months and 3.6 months, respectively, in the ongoing study. **Conclusions:** RG6344 is well tolerated allowing unprecedented exposure for pERK inhibition and shows promising preliminary single-agent activity. Clinical trial information: ISRCTN13713551. Research Sponsor: None.

3543 **Poster Session**

Impact of anti-EGFR and anti-VEGF antibodies on survival in $BRAF^{V600E}$ mutated metastatic colorectal cancer: A pooled analysis of eight clinical trials performed in the first-line treatment of mCRC (German AIO Study Group). First Author: Lena Weiss, Department of Medicine III, University Hospital Munich LMU, Munich, Germany

Background: $BRAF^{V600E}$ mutation in metastatic colorectal cancer (mCRC) is associated with poor prognosis. Registrational approval of anti-EGFR antibodies does not exclude their use in $BRAF^{V600E}$ mutated (mut) mCRC, while current guidelines explicitly advise against the use of anti-EGFR-directed therapy and recommend the use of chemotherapy plus anti-VEGF antibodies. The present analysis of single-patient data evaluates the therapeutic benefit from anti-EGFR- vs. anti-VEGF-directed therapy in $BRAF^{V600E}$ mut mCRC. **Methods:** We conducted a pooled analysis of eight first-line AIO-studies (FIRE-1, FIRE-3, FIRE-4, FIRE-4.5, CIOX, XELAVIRI, PANAMA, VOLFI) including 251 evaluable pts with $BRAF^{V600E}$ mut and RAS wild-type mCRC. Right-sided primary tumors (RSPT) included tumors from the caecum to the colon transversum, while left-sided tumors (LSPT) included the splenic flexure to the rectum. **Results:** Of 251 $BRAF^{V600E}$ mut pts, exact primary tumor location was available in 230 pts. In this cohort, 117 were male (50.9%) and 113 female (49.1%). LSPT was observed in 106 (46.1%) pts compared to 124 (53.9%) with RSPT. In the entire cohort, median OS (mOS) of LSPT vs. RSPT did not differ significantly (15.2 months vs. 13.4 months; HR 0.96; 95% CI, 0.70–1.29; P=0.77). Pts with LSPT showed a numerical survival benefit with anti-EGFR therapy compared to anti-VEGF therapy (17.8 months vs. 11.8 months; HR 0.71; 95% CI, 0.45–1.14; P=0.16). This effect was observed independent of sex. In contrast, pts with RSPT showed a trend towards inferior outcome with anti-EGFR vs. anti-VEGF therapy (11.6 months vs. 17.1 months; HR 1.31; 95% CI, 0.84–2.05; P=0.23). This effect was primarily driven by females, who experienced a significant survival disadvantage with anti-EGFR therapy (10.2 months vs. 17.1 months; HR 1.85; 95% CI, 1.05–3.25; P=0.031). For males, however, both anti-VEGF and anti-EGFR antibodies were associated with comparable outcome. **Conclusions:** The present analysis performed in the first-line treatment of $BRAF^{V600E}$ mut mCRC suggests a survival benefit from anti-EGFR antibodies in pts with LSPT, independent of gender. Male pts with RSPT appear to derive comparable benefit from anti-EGFR and anti-VEGF antibodies, while female pts exhibit a survival disadvantage from anti-EGFR antibodies. Clinical trial information: NCT00433927 (FIRE-3), NCT02934529 (FIRE-4), NCT04034459 (FIRE-4.5), NCT01249638 (ML22011), NCT00254137 (CIOX), NCT01991873 (PANAMA), NCT01328171 (VOLFI). [clinicaltrials.gov]. Research Sponsor: None.

3544 **Poster Session**

Circulating tumor DNA (ctDNA) dynamics in liver-limited metastatic colorectal cancer (mCRC) patients resected after first-line systemic treatment. First Author: Vittorio Studiale, Unit of Medical Oncology 2, Azienda Ospedaliera Universitaria Pisana and Department of Translational Research and New Technologies in Medicine and Surgery, University of Pisa, Pisa, Italy

Background: Liver-limited disease (LLD) occurs in 20-30% of metastatic colorectal cancer (mCRC) patients. Although 20-30% of patients who undergo resection can achieve a long-term overall survival benefit from liver surgery, most patients relapse during the first two years after hepatectomy. ctDNA is a promising tool in detecting the presence of minimal residual disease (MRD) after resection of colorectal liver metastases and a reliable prognostic tool for recurrence. ctDNA and its dynamics may also serve as a prognostic tool in patients candidate to liver resection following upfront chemotherapy. **Methods:** mCRC patients (N = 116) with initially unresectable LLD and R0/R1 resected after upfront chemotherapy were selected from 3 Italian academic centers. Blood samples were collected prospectively at baseline (T0), pre-surgery (TPrS) and post-surgery (TPoS). T0 samples were evaluable for 82 patients, TPrS for 116 and TPoS for 60. Biobanked plasma samples were analyzed with the Tempus xM MRD assay (xM), a tumor-naïve ctDNA MRD assay that integrates methylation and genomic variant classifiers to deliver a binary MRD call blinded to clinical outcomes. The methylation classifier detects fragments with CRC methylation signatures in differentially methylated regions trained by sequencing CRC and presumed-healthy samples on a 6 Mbp panel. The variant classifier detects highly prevalent CRC variants. **Results:** Methylation results were available for 60 TPoS patients with a clinical sensitivity of 56.4% and specificity of 100%. TPoS ctDNA status was associated with relapse-free survival (RFS) with the ctDNA- group experiencing longer median RFS (mRFS) than ctDNA+ (HR = 6.7, mRFS $>$ 24 mos vs. 5.5 mos, p $<$ 0.001). Patients who were persistently ctDNA- by methylation calls (n = 20) or converted to negative (n = 13) from TPrS to TPoS experienced longer RFS (mRFS 16.3 mos and $>$ 24 mos respectively). Those who remained persistently ctDNA+ (n = 9) or converted to ctDNA+ (n = 12) had a mRFS of 5.3 and 5.9 mos respectively. Patients with variant allele fraction (VAF) reduction of $\geq$50% from T0 to TPrS (N = 53) experienced longer RFS than those who had $<$ 50% reduction or increase in VAF (N = 18) (HR 2.21, mRFS 18.8 mos vs. 9.8 mos, p = 0.012). Lastly, patients that remained positive from T0 to TPrS (N = 23) experienced a numerically shorter RFS compared to those who converted to negative (N = 47) (median RFS 10.4 and 15.1 mos, HR 1.65, p = 0.10). **Conclusions:** xM demonstrates remarkable performance in predicting clinical recurrence and correlation to RFS at TPoS in LLD mCRC patients resected after upfront systemic therapy. Interestingly, patients with a VAF reduction $\geq$ 50% experience longer RFS following surgery, suggesting a potential role for this tool in multidisciplinary decision making in this setting. Research Sponsor: None.

3545 **Poster Session**

Tumour microbiome and immune dysregulation in early-onset colorectal cancer. First Author: Rachel Violet Purcell, Department of Surgery and Critical Care, Christchurch, New Zealand

Background: Early-onset colorectal cancer (EOCRC) in patients under 50 years is increasing incidence in many countries worldwide, including New Zealand. The reason for this trend is yet unclear, but is associated with such risk factors as obesity, alcohol intake, lifestyle and diet. This suggests a multi-factorial exposome-related aetiology, with changes to the gut microbiome likely to play a role. **Methods:** In this study, we investigated differences in the tumour-resident microbiome and molecular characteristics between patient cohorts of EOCRC and late-onset CRC (LOCRC). Transcriptomic analysis was carried out on pre-treatment tumours from a cohort of 19 EOCRC patients and compared to a control group of 196 LOCRC aged over 65 years. Bioinformatics analysis of RNA sequencing data was used to analyse tumour microbial abundance and taxonomy, differential gene expression and gene-set enrichment between the two groups, as well as assign consensus molecular subtypes (CMS) . **Results:** We found an increase in expression of genes involved in the cell cycle in the EOCRC cohort, and of specific genes (e.g. HOXA11-AS, STMN2) involved in cell proliferation and metastasis. Converesly, enriched gene sets in the late-onset category were predominantly related to immune function. When grouping CMS subtypes as immune-rich (CMS1/CMS4) versus immune-depleted (CMS2/CMS3), there was a significant difference between the two groups with 94% of EOCRC tumours being immune-depleted, compared to 67% of late-onset tumours (p = $<$ 0.05). Meanwhile, we found an increase in bacterial richness (observed alpha diversity) in the late-onset tumours compared to early-onset, while there were no differences in the Shannon alpha diversity measures (richness and evenness), and in beta diversity between the groups. We also found a depletion of the bacteria *Helicobacter canadensis* and *Campylobacteria ureolyticus* in the early-onset cohort, while there was an increase in *Lachnospiraceae* species. **Conclusions:** Our results add to the growing body of evidence that EOCRC is a distinct disease from LOCRC. EOCRC shows lower tumour-immune activation compared to LOCRC and very low rates of CMS1 and CMS4 subtypes, which is associated with a distinct tumour-resident microbiome. This may have implications for prognosis and targeted treatments. Research Sponsor: None.

3546 **Poster Session**

Prognostic and predictive impact of the baseline systemic proteome in patients with *RAS* wild-type metastatic colorectal cancer: Analysis from the randomized phase II PanaMa (AIO KRK0212) trial. First Author: Alexej Ballhausen, Department of Hematology, Oncology and Tumorimmunology, Charité-Universitätsmedizin Berlin, Freie Universität Berlin, Humboldt-Universität zu Berlin, and Berlin Institute of Health, Berlin, Germany

Background: Systemic proteomics offers a minimally invasive approach to identifying biomarkers in metastatic colorectal cancer (mCRC). This study analyzed the prognostic and predictive potential of the systemic proteome in *RAS* wild-type (wt) mCRC patients from the PanaMa trial, which investigated maintenance therapy with fluorouracil/folinic acid (FU/FA) $\pm$ panitumumab (Pmab) following induction with FU/FA plus oxaliplatin and Pmab. **Methods:** Baseline serum samples were analyzed using liquid chromatography-mass spectrometry to identify protein markers. Their impact on overall survival (OS) and progression-free survival (PFS) was evaluated using Kaplan-Meier estimates and Cox regression. Prognostic analyses utilized hierarchical clustering and random forest models to delineate protein groups associated with survival outcomes, enhanced by sparse partial least squares discriminant analysis for feature selection. Gene ontology analysis was used to identify biological functions of these markers. ROC analysis was performed to evaluate the accuracy of prognostic protein signatures. For predictive analysis, PFS outcomes of maintenance with FU/FA $\pm$ Pmab were assessed using Kaplan-Meier estimates and Cox regression. Hazard ratios (HR), differences in hazard ratios (delta HR), and statistical significance (p-values) were used to differentiate patient outcomes based on protein marker expression. **Results:** Of 378 patients treated in the trial, 231 had baseline serum samples. Proteomic clustering identified two survival clusters: the high-survivability cluster showed significantly longer induction PFS (HR 0.75, 95% CI 0.56–1.00, P = 0.05) and OS (HR 0.63, 95% CI 0.45–0.88, P = 0.01). Hierarchical clustering revealed 470 proteins, with specific proteins enriched in high-survivability (e.g., ALB, APOA2) and low-survivability (e.g., SERPINA3, CRP) clusters. Gene ontology analysis highlighted distinct pathways, such as enzyme inhibitor activity in low-survivability clusters and peptidase regulator activity in high-survivability clusters. For maintenance, prognostic arm-specific proteomic signatures linked to improved PFS with strong accuracy in the FU/FA + Pmab arm (AUC 0.99), and FU/FA arm (AUC 1.00). Predictive analysis revealed a total of eight proteins that predicted benefit of Pmab addition to maintenance. A positive combined proteomic biomarker including these proteins (ITIH4, FLNC, HP, CTPS1, SERPINA1, HRG, MAN1C1, C4A) predicted significant benefit of addition of Pmab to FU/FA maintenance (PFS: HR 0.68, 95% CI 0.49–0.95, P = 6.4e-09). **Conclusions:** Proteomic profiling identified prognostic clusters linked to distinct survival outcomes and predictive signatures for FU/FA $\pm$ Pmab maintenance, supporting its utility in guiding personalized treatment strategies for *RAS* wt mCRC. Research Sponsor: AIO-Studien gGmbH; Amgen Inc.

3547 **Poster Session**

Prognostic and predictive role of HLA supertypes in pMMR mCRC patients receiving FOLFOXIRI/bev $\pm$ atezolizumab in the AtezoTRIBE study. First Author: Daniele Rossini, Department of Experimental and Clinical Medicine, University of Florence. Oncology Unit, Careggi University Hospital, Florence, Italy

Background: The HLA system plays a crucial role in the development of the adaptive immune response, influencing antigen presentation and T-cell-mediated tumour recognition. Emerging evidence suggests that specific HLA allele groups named supertypes may influence the efficacy of immune-checkpoint inhibitors (ICIs). We investigated the impact of HLA supertypes in the pMMR cohort of mCRC patients (pts) treated with FOLFOXIRI/bev $\pm$ atezolizumab in the AtezoTRIBE study. **Methods:** Genomic DNA from blood samples was genotyped using Oncoarray, a custom array manufactured by Illumina including approximately 530K SNP markers. HLA class I and II alleles were characterized with minimac3 algorithm using the Four-digit Multi-ethnic HLA v2 (2022) reference panel. The presence of 22 HLA supertypes were assigned based on the imputed dosages across relevant alleles. The effects of HLA supertypes on survival were evaluated with Cox proportional hazard models. Given the exploratory nature of the analysis, no adjustments for multiple comparisons were applied. **Results:** Among 153 assessed pts (102 and 51 treated with FOLFOXIRI/bev/atezo and FOLFOXIRI/bev, respectively), B44 and DR9 supertypes were associated with worse prognosis in terms of both PFS (mPFS 11.4 months (mos) for B44 pos vs 13.9 mos for B44 neg; HR 1.74; 95% CI 1.19–2.52; p = 0.004, and mPFS 11.4 mos for DR9 pos vs 13.2 mos for DR9 neg; HR 2.37; 95% CI 1.01–5.60; p = 0.04, respectively) and OS (mOS 29.6 mos for B44 pos vs 36.6 mos for B44 neg; HR 1.59; 95% CI 1.03–2.45; p = 0.038, and mOS 26.6 for DR9 pos vs 33.9 mos for DR9 neg; HR 3.22; 95% CI 1.24–8.38; p = 0.017, respectively) in multivariable analysis. As summarized in the Table, PFS and OS benefit from the addition of atezolizumab to FOLFOXIRI/bev was reported among A3 neg but not A3 pos patients, and B8 pos patients derived higher benefit than B8 neg. **Conclusions:** Our exploratory findings suggest that HLA supertypes could influence prognosis and ICIs-based treatment efficacy in pMMR mCRC pts. In particular, B8 and A3 supertypes could identify patients more likely to benefit from the addition of ICIs to FOLFOXIRI/bev. These findings highlight the potential of HLA profiling to optimize the use of immunotherapy in pMMR mCRC pts. Research Sponsor: GONO Foundation.

	Median PFS				Median OS			
	FOLFOXIRI/bev/ atezo (months)	FOLFOXIRI/bev (months)	HR 95%CI	P for interaction	FOLFOXIRI/bev/ atezo (months)	FOLFOXIRI/bev (months)	HR 95%CI	P for interaction
A3				0.048				0.064
Pos	12.5	11.6	0.89 (0.53-1.51)		27.0	31.7	0.96 (0.53-1.73)	
Neg	15.0	10.1	0.43 (0.26-0.71)		NR	27.3	0.44 (0.24-0.81)	
B8				0.014				0.040
Pos	13.7	5.6	0.16 (0.05-0.60)		35.9	16.7	0.21 (0.06-0.76)	
Neg	13.3	11.6	0.63 (0.43-0.93)		36.1	31.4	0.70 (0.44-1.11)	

3548 Poster Session

Impact of Medicare Advantage (MA) on timely initiation of pembrolizumab among dMMR/MSI-h metastatic colorectal cancer patients. First Author: Baqir Jafry, Charleston Area Medical Center, Charleston, WV

Background: With MA plans covering over half of Medicare beneficiaries, concerns remain about their ability to manage complex cancer care due to pre-authorization and limited provider network. This study evaluates MA versus Traditional Medicare (TM) regarding timely initiation of Pembrolizumab for dMMR/MSI-H colorectal cancer (CRC), following its 2020 FDA approval. **Methods:** This study utilized nationwide Flatiron Health Electronic Health Record-derived de-identified database. We included patients diagnosed with dMMR/MSI-H CRC from 2020 onward, aged ≥65 years, who had at least one clinic visit within six months of diagnosis and were insured under MA or TM. The primary endpoint was initiation of Pembrolizumab within 30-, 45-, and 90-days post-diagnosis. Multivariable logistic regression with Inverse Probability Weighting, adjusted for SES (defined by Yost score), age, race, ECOG, practice type and diagnosis year, evaluated impact of insurance type on timely treatment initiation. **Results:** Out of 597 dMMR/MSI-H metastatic CRC patients identified since 2020, 219 had at least one clinical visit under MA (N = 86) or TM (N = 133) plans. Predominantly, patients in our cohort were non-Hispanic White (72%), with higher SES (59%), diagnosed with de novo dMMR/MSI-H (59%), and treated in community hospitals (86%). Of 95 patients who commenced pembrolizumab as initial therapy, 62 (65%) had TM and 33 (35%) had MA. The adjusted analysis revealed that MA patients were significantly less likely to start pembrolizumab within 90 days of diagnosis compared to TM patients (OR: 0.58; 95% CI: 0.34-0.97; P: 0.04). There were no statistical differences in starting treatment at 30 (OR: 0.79; 95% CI: 0.39-1.56; P: 0.5) or 45 days (OR: 0.87; 95% CI: 0.48-1.57; P: 0.7). Subgroup analysis indicated substantial delays in pembrolizumab initiation within 90 days among lowest SES (OR: 0.31; 95% CI: 0.13-0.71; P: 0.007; P-interaction: 0.087) and those treated in community hospitals (OR: 0.49; 95% CI: 0.27-0.87; P: 0.016; P-interaction: 0.095). **Conclusions:** Patients with TM were more likely to initiate pembrolizumab earlier than those with MA. This underscores necessity to scrutinize the influence of MA on cancer delivery, especially for patients with lower SES. Research Sponsor: None.

Baseline characteristics.

Variable	TM	MA	P
Age			0.4
>=65	66 (50%)	40 (47%)	
>=75	67 (50%)	45 (52%)	
>=85	0 (0%)	1 (1%)	
Race			1
NHW	97 (73%)	62 (72%)	
Non-NHW	36 (27%)	24 (28%)	
ECOG			0.7
0/1	95 (71%)	68 (79%)	
2	18 (14%)	8 (9%)	
3/4	8 (6%)	4 (5%)	
Unknown	12 (9%)	6 (7%)	
SES			0.04
0/1	38 (29%)	36 (42%)	
3/4/5	88 (66%)	42 (49%)	
Unknown	7 (5%)	8 (9%)	
Diagnosis Year			0.5
2020	36 (27%)	22 (26%)	
2021	41 (31%)	34 (40%)	
2022	39 (29%)	18 (21%)	
2023	17 (13%)	12 (14%)	
DeNovo			0.7
Yes	80 (60%)	49 (57%)	
No	53 (40%)	37 (43%)	
Practice			0.4
Academic	16 (12%)	15 (17%)	
Community	117 (88%)	71 (83%)	
Time to Pembrolizumab Initiation (days)		**OR (95CI)**	**P**
30	1	0.79 (0.39-1.56)	0.50
45	1	0.87 (0.48-1.57)	0.66
90	1	0.58 (0.34-0.97)	0.04

3549 Poster Session

Outcomes of young-onset colorectal cancer vs late-onset colorectal cancer patients on phase 1 matched and non-matched therapies. First Author: Daniel Aaron Fox, Baylor College of Medicine, Houston, TX

Background: Systemic therapy recommendations for young-onset colorectal cancer (YOCRC), CRC diagnosed at < 50 years old, are similar for late-onset CRC (LOCRC) despite possible differences in biologic behavior. This study aims to compare outcomes among YOCRC and LOCRC patients on Phase 1 matched and non-matched therapies. **Methods:** This was a single-institution retrospective analysis of patients with CRC who received treatment on a Phase 1 clinical trial. Only the first Phase 1 therapy for each patient was included in analysis. Matched therapy was defined as therapy targeting genomic alterations or their signaling pathways. Distributions of progression-free survival (PFS) were estimated by the Kaplan-Meier method. Log-rank test was performed to test the difference in survival between groups. A propensity score matched analysis was created using a multivariate logistic regression model. Covariates in the model included: gender, race, lung metastasis, liver metastasis and tumor sidedness. **Results:** 577 patients were included in analysis (Table 1). 252 patients had YOCRC (43.7%) and 325 had LOCRC (56.3%). 100 YOCRC patients (39.7%) and 90 LOCRC patients (27.7%) received matched therapies. Before propensity score matching YOCRC patients on matched therapy had higher odds of achieving a response compared to LOCRC patients on matched therapy (complete response/partial response) (10.5% vs 3.4%, odds ratio (OR): 3.294 (95% confidence interval (CI)): 0.876, 12.390), p=0.0777). After propensity score matching YOCRC patients on matched therapy had higher odds of achieving a response compared to LOCRC patients on matched therapy (13.3% vs 3.9%, OR was not estimable, p=0.0082). No significant differences in overall response rate were detected between YOCRC and LOCRC patients on non-matched therapy before or after propensity score matching (5.4% vs. 4.1%, OR: 1.362 (95% CI: 0.513, 3.615), p=0.5348; 5.5 vs. 4.3%, OR: 1.167 (CI: 0.392, 3.472), p=0.7815). No significant differences in PFS were detected between patient with YOCRC and those with LOCRC in any of the patient cohorts before or after propensity score matching (all patients: p=0.743, p=0.639; patients receiving matched therapy: p=0.497, p=0.909; patients receiving non-matched therapy: p=0.999, p=0.62). **Conclusions:** YOCRC patients were more likely than LOCRC patients to achieve a response on matched therapy though this did not translate to improved PFS. Nevertheless, matched therapies are associated with increased response rate for YOCRC patients. Research Sponsor: None.

Patient demographics.

Trait	n (%)
Age at diagnosis (median, range)	51 (18-83)
White/Caucasian	425 (74.7%)
Black/African American	67 (11.6%)
Asian	40 (6.9%)
Hispanic/Latino	79 (13.7%)
Microsatellite Instability-High Tumor	5 (0.9%)
***KRAS* mutation**	352 (61.0%)
***BRAF* V600E mutation**	38 (6.6%)
Prior Unique Lines of Therapy (median, range)	4 (0-11)

3550 Poster Session

Amivantamab treatment and intra-tumoral gene expression and immune cell changes in refractory metastatic colorectal cancer (mCRC): Whole transcriptome RNA-sequencing analysis from the OrigAMI-1 study. First Author: Cathy Eng, Vanderbilt-Ingram Cancer Center, Nashville, TN

Background: Amivantamab (ami) is an FDA- and EMA-approved EGFR-MET bispecific antibody with immune cell–directing activity for *EGFR*-mutated advanced non-small cell lung cancer. Ami monotherapy has shown promising activity in participants (pts) with refractory mCRC, independent of primary tumor sidedness (left- or right-sided). Here, we analyzed gene expression data from the OrigAMI-1 study to identify mechanisms of sensitivity and action in response to ami monotherapy. **Methods:** The phase 1b/2 OrigAMI-1 study (NCT05379595) enrolled pts with mCRC harboring wild-type *KRAS*, *NRAS*, *BRAF*, and *EGFR* ectodomain, without *ERBB2*/*HER2* amplification. Pts with left-sided mCRC without prior anti-EGFR therapy (Cohort A) and with prior anti-EGFR therapy (Cohort B), as well as pts with right-sided mCRC (Cohort C) received intravenous ami monotherapy (1050 mg; ≥80 kg: 1400 mg). Tumor biopsy samples were collected at screening and Cycle 3 Day 1 (C3D1; if feasible). Whole transcriptome RNA-sequencing data of paired baseline and C3D1 tumor samples were generated by Foundation Medicine. Gene expression data were analyzed using standard bioinformatic methods to identify gene signatures associated with ami treatment in baseline tumor samples (n = 76) and paired baseline and C3D1 tumor samples (n = 17). **Results:** High baseline mRNA expression of AREG and EREG ligands was associated with treatment response across all cohorts (n = 76). In Cohort A (n = 16), median progression-free survival was significantly longer for pts with high (n = 8) vs low (n = 8) AREG expression (9.1 mo vs 4.5 mo, respectively; $P < 0.01$). Differential expression analyses after ami treatment showed significant changes in > 800 genes ($P < 0.01$) across all cohorts (n = 17). The EGFR pathway was significantly downregulated after ami treatment ($P < 0.01$). Pathway enrichment analyses identified significant enrichment of cell cycle and natural killer (NK) cell–mediated cytotoxicity pathways. The cell cycle pathway score was significantly downregulated following ami treatment ($P < 0.01$), implying reduced cell proliferation. A significant upregulation of dendritic cell ($P < 0.005$) and T-cell–inflamed signature scores ($P < 0.05$) was observed with ami treatment, potentially implying increased immune cell infiltration of the tumor microenvironment. Ami also increased the cytolytic ($P < 0.05$) and NK cell–mediated cytotoxicity pathway scores ($P < 0.05$), implying an increase in cytotoxic immune cells. Additional biomarker analyses are ongoing and will be presented at the meeting. **Conclusions:** Amivantamab downregulates EGFR and cell cycle pathways and increases cytotoxic immune cell signatures consistent with immune cell infiltration into tumors. Elevated AREG and EREG ligand expression correlated with response in wild-type refractory mCRC. Clinical trial information: NCT05379595. Research Sponsor: Janssen Research & Development, LLC, a Johnson & Johnson company.

3551 Poster Session

Phase 1 dose escalation results of the WEE1 inhibitor, azenosertib (A), in combination with encorafenib (E) and cetuximab (C) in patients (pts) with previously treated *BRAF V600E* mutant metastatic colorectal cancer (mCRC). First Author: Jeanne Tie, Department of Medical Oncology, Peter MacCallum Cancer Centre, Melbourne, VIC, Australia

Background: Encorafenib + cetuximab was approved for treating pts with *BRAF V600E* mutant mCRC after prior systemic therapy based on the Phase 3 BEACON study (observed response rate 20%; Kopetz et al. 2019). Azenosertib is a highly selective WEE1 inhibitor that causes mitotic catastrophe and cell death. Combining BRAF targeting treatment (E+C) with orthogonal pathway inhibitors may allow for an additive or synergistic combination effect of A. This study aimed to evaluate safety and tolerability, determine the maximum tolerated dose (MTD), and assess anti-tumor activity in pts with *BRAF* V600E mutant mCRC receiving A+E+C. **Methods:** This phase 1 dose escalation, open-label, multicenter study (NCT05743036) evaluated safety, tolerability, and activity of A administered in combination with E+C in adult pts with *BRAF V600E*-mutant mCRC who received 1-3 prior regimens for metastatic disease. Azenosertib is a CYP3A4 substrate and is predicted to moderately inhibit CYP3A4 while weakly inhibiting CYP2C19. Encorafenib is primarily metabolized by CYP3A4 and CYP2C19, and acts as a CYP3A4 inducer. To allow for exposures to optimize treatment benefits and minimize toxicity, the recommended starting dose of E is 150 mg once a week. The primary endpoint was dose-limiting toxicities (DLTs) in cycle 1. Pts were treated across 5 dose-finding cohorts, receiving A (dose range: 100 mg-400 mg once a day [QD] oral [PO] on a continuous schedule) and E (dose range: 75 mg or 150 mg QD PO), and C (500 mg/m^2 intravenous twice a week) until disease progression or unacceptable toxicity. **Results:** As of Nov 25, 2024, 44 pts were enrolled and treated with a median age of 64 years. 52.3% of pts received ≥2 prior lines of therapy, 34 pts were BRAF inhibitor (BRAFi)-naïve. The most frequent treatment-related Grade ≥3 adverse events were asthenia (11.4%) and fatigue (6.8%). DLTs were observed at the dose levels of A300+E150 and A400+E75 and included dose-limiting fatigue, atrial fibrillation, recurring elevated bilirubin (all Grade 3), and Grade 4 neutropenia. The MTD was determined to be A300+E75 and C. Twelve of 34 (35.3%) BRAFi-naïve pts achieved confirmed response per RECIST v1.1 (2 complete response, 10 partial response [PR]) while none of the BRAFi-pretreated pts responded. Seven of 17 (41.2%) BRAFi-naïve pts treated at A300+75 or A300+150 achieved confirmed PR. The median duration of response and the median progression-free survival in the BRAFi-naïve pts were 5.6 and 5.4 months, respectively. **Conclusions:** The combination of A+E+C was well tolerated at the MTD and yielded response rates in BRAFi-naïve mCRC pts which exceeded the historical data from the E+C doublet. Clinical trial information: NCT05743036. Research Sponsor: Zentalis.

3552 **Poster Session**

Low-pass whole methylome sequencing–based liquid biopsy for metastatic colorectal cancer monitoring in the VALENTINO trial. First Author: Paolo Manca, Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy

Background: The amount of ctDNA is a proxy for metastatic colorectal cancer (mCRC) disease burden, with potentials for prognostic stratification and treatment monitoring. We investigated two methods based on low-pass whole genome and methylome sequencing (WGS and WMS) for ctDNA detection and quantification in the VALENTINO trial. **Methods:** All patients from the VALENTINO trial - a phase II trial comparing the addition of 5FU to Panitumamb-based maintenance after first line FOLFOX+Panitumamb induction in RAS wild-type mCRC - were eligible. Baseline (BL) and 8-week (8w) plasma samples were collected for low-pass WGS and WMS analysis. Two methods for ctDNA quantification based on DNA methylation (METER) and copy number alterations (ichorCNA) were assayed. Chi-squared, Wilcoxon and Cox regression tests were used. Performances of WMS and variant allele fraction (VAF) of a 14-gene panel were compared. **Results:** A BL liquid biopsy was available for 154 patients, with 142 also having an 8w assessment. METER and ichorCNA detected ctDNA in 112 (72.7%) and 94 (59.7%) BL samples, respectively; all discordant cases were METER+ but ichorCNA-. Detection rate increased in the presence of liver metastases (86.0% vs 42.6% for METER, 75.7% vs 23.4% for ichorCNA; both $p < 0.001$) and decreased with peritoneal metastases (55.6% vs 78.0% for METER, 38.9% vs 66.1% for ichorCNA; p = 0.011, p = 0.006). Tumor fraction (TF) of both BL METER and ichorCNA correlated with the diameter of measurable lesions (both $p < 0.001$) and CEA ($p < 0.001$ and p = 0.010). Both PFS and OS were shorter after baseline ctDNA detection with METER (mPFS: 10.6 vs 18.6 months, HR: 1.65, p = 0.010; mOS: 28.7 vs 62.2 months; HR: 2.24, 95%CI: 1.37-3.66; p = 0.001) or ichorCNA (mPFS: 10.6 vs 15.0 months, HR: 1.42, 95%CI: 1.00-2.00, p = 0.047; mOS: 27.8 vs 48.4 months, HR: 1.35, 95%CI: 1.29-2.95; p = 0.002). In the multivariate analysis, METER ctDNA detection was the strongest predictor of both PFS and OS (p = 0.005 and p = 0.001) while ichorCNA ctDNA detection was significantly associated with OS but not with PFS (p = 0.002 and p = 0.093). METER ctDNA TF decreased significantly at 8w in patients with CR, PR, or SD (paired Wilcoxon p = 0.015, $p < 0.001$, $p < 0.001$) but not PD (p = 0.560) as the best radiological response. Patients without METER ctDNA clearance at 8w had a higher risks of progression (HR: 2.70, 95%CI: 1.63-4.49; $p < 0.001$) and death (HR: 3.37, 95% CI: 2.00-5.69; $p < 0.001$). Among 123 patients with both METER and VAF available, concordance was 78.0% and in 10 and 17 patients, respectively, ctDNA was detected only with METER or only with VAF. The mPFS and mOS of discordant cases were longer than METER+ / VAF+ cases and shorter than METER− / VAF− cases. **Conclusions:** CtDNA quantification with low-pass WMS by METER retains a prognostic significance, can be used for disease monitoring during treatment and refines ctDNA detection based on a restricted gene panel assay. Clinical trial information: NCT02476045. Research Sponsor: None.

3553 **Poster Session**

Vilastobart (XTX101), a tumor-activated, Fc-enhanced anti–CTLA-4 monoclonal antibody, in combination with atezolizumab in patients with MSS CRC. First Author: Marwan Fakih, City of Hope Comprehensive Cancer Center, Duarte, CA

Background: Vilastobart (XTX101) is tumor-activated, high affinity, Fc-enhanced aCTLA-4 designed to focus activity toward the tumor and minimize systemic adverse events. Fc-enhancement augments FcγR co-engagement on antigen presenting cells and has been linked with efficacy of aCTLA-4 combinations in patients (pts) with microsatellite stable (MSS) colorectal cancer (CRC) and other tumors [Fakih ASCO GI 2025]. Vilastobart was generally well-tolerated and demonstrated evidence of anti-tumor activity in pts with immunologically "cold" advanced solid tumors, both as a monotherapy and in combination with atezolizumab [Davar SITC 2024]. **Methods:** Phase 2 of the NCT04896697 study evaluated the initial recommended Phase 2 dose of vilastobart 100 mg Q6W in combination with atezolizumab 1200 mg Q3W in pts with MSS CRC who had at least 1 prior chemotherapy regimen in the metastatic setting, excluding pts with prior immune checkpoint inhibitors. Pts with (LM) and without liver metastasis (NLM) were eligible. Tumor biopsies were obtained before and during treatment for translational analyses. **Results:** As of January 13, 2025, 40 pts were dosed in Phase 2. Median age was 55 (25-82) and 70% of pts had 3 or more prior lines of therapy. Of the 24 enrolled NLM pts, 11 were response-evaluable with an available on-treatment scan as of the data cut. In these 11 pts, two confirmed and one unconfirmed partial response (PR) were reported, all accompanied by significant decreases in ctDNA and serum tumor marker CEA and with each pt ongoing on therapy, for a preliminary ORR of 27%. One additional pt (with peritoneal metastasis) had a 24% reduction in target lesions (first scan) and was ongoing on therapy. Of the 16 enrolled LM pts, 7 were response evaluable, with one stable disease and another pt reporting a mixed response with significant serum tumor marker reductions, both ongoing on therapy. Of note, one LM pt in Phase 1C dose escalation treated with vilastobart (150 mg Q6W) combination had a confirmed PR with LM resolution. Six pts (15%) reported G3+ treatment-related adverse events (TRAEs), with two G4 laboratory TRAEs and no G5 TRAEs. Only three pts discontinued therapy for TRAEs. TRAEs occurring in ≥10% (all grade) or ≥5% (G3) of pts are summarized in the Table. **Conclusions:** The combination of vilastobart, a novel tumor-activated, Fc-enhanced a-CTLA-4, and atezolizumab demonstrated initial evidence of anti-tumor activity in late line, metastatic MSS CRC where immune checkpoint blockade has historically been relatively ineffective. Vilastobart was observed to have a differentiated safety profile distinct from systemically active a-CTLA-4, consistent with tumor-selective activation. Clinical trial information: NCT04896697. Research Sponsor: Xilio Therapeutics.

AE term	All Grade n (%)	Grade 3 n (%)
Fatigue	12 (30%)	0
Diarrhea	8 (20%)	0
Infusion related reactions	5 (13%)	0
Pyrexia	4 (10%)	0
ALT increased	4 (10%)	0
AST increased	4 (10%)	1 (3%)
Colitis	2 (5%)	2 (5%)

3554 **Poster Session**

mFOLFIRINOX efficacy as rescue regimen for patients with metastatic refractory colorectal cancer: The RE-PLAY trial. First Author: Paulo Marcelo Hoff, Instituto do Câncer do Estado de São Paulo, University of São Paulo and Instituto D'Or de Pesquisa e Ensino, São Paulo, Brazil

Background: Doublets with Fluoropyrimidines (F), oxaliplatin (Ox), and irinotecan (Ir) are standard chemotherapy agents used to treat metastatic colorectal cancer (mCCR). The role of triplet combination with modified FOLFIRINOX (mFOLFIRINOX) in refractory patients (pts) previously treated with doublets or monotherapy sequential regimens remains unclear. **Methods:** This single-arm, open-label phase II trial employed a Simon two-stage design. Eligible pts had mCCR with documented progression after treatment with doublets or sequential monotherapy regimens containing F, Ox, and Ir. Pts with RAS wild-type tumors were required to be refractory to anti-EGFR therapy. The mFOLFIRINOX regimen consisted of 5-FU (2400 mg/m², continuous infusion over 46 hours), Ox (85 mg/m², D1), Ir (150 mg/m², D1), and leucovorin (200 mg/m², D1), administered every 14 days. The primary endpoint was the disease control rate (DCR) as assessed by RECIST v1.1. According to the Simon design, the study would be considered positive if 4 or more pts achieve disease control among 25 pts in the second stage. Secondary endpoints included objective response rate (ORR), progression-free survival (PFS), overall survival (OS), and safety. **Results:** Between October 2021 and October 2024, 25 pts were enrolled. Three pts did not receive treatment due to consent withdrawal (n = 1) or clinical deterioration from disease progression before treatment initiation (n = 2). All pts had proficient mismatch repair (pMMR) tumors; 16 (64%) had KRAS/NRAS mutations, and most tumors were left-sided (n = 20, 80%). At Intention to Treat analyses, 16.6% (n = 4) achieved a partial response, 44% (n = 11) had stable disease, and 28% (n = 7) experienced disease progression as their best radiologic response. The DCR was 60% (n = 15), and the ORR was 16.6% (n = 4). With a median follow-up of 6.8 months, 17 pts experienced disease progression or death. The median PFS was 5.7 months, and the median OS was 9.3 months. No significant differences in DCR, ORR, PFS, or OS were observed based on RAS mutation status or tumor sidedness; among 22 pts who received at least one cycle of mFOLFIRINOX, 68.1% (n = 15) experienced grade 3 or higher adverse events, including one treatment-related death. **Conclusions:** mFOLFIRINOX demonstrated efficacy as a rescue regimen for refractory mCCR previously refractory to doublets or sequential monotherapy regimens containing Ox, Ir, fluoropyrimidines, and anti-EGFR therapy. Clinical trial information: NCT05354817. Research Sponsor: None.

LBA3555 **Poster Session**

Safety and efficacy of reduced-port laparoscopic surgery for patients with colon and upper rectal cancer. First Author: Jun Huang, Department of Colorectal Surgery, The Sixth Affiliated Hospital, Sun Yat-sen University, Guangzhou, China

The full, final text of this abstract will be available at meetings.asco.org on the day of presentation and in the online supplement to the June 10, 2025, issue of the *Journal of Clinical Oncology*.

3556 **Poster Session**

Analysis of mutational profiles and their correlation with organ-specific metastases in MSS and *BRAF*wt colorectal cancer (mCRC). First Author: Francesc Salva, Vall d'Hebron Institute of Oncology (VHIO), Vall d'Hebron University Hospital, Barcelona, Spain

Background: In *BRAF*wt/ MSS mCRC, the mechanisms driving distinct metastatic dissemination patterns remain unclear. Understanding them is crucial, as dissemination profiles influence therapeutic strategies, such as immunotherapy for patients (pts) without liver metastasis (mets) or locoregional approaches and liver transplantation for those with liver-limited disease. NGS advances provide genomic data, offering opportunities to identify predictive signatures that link molecular profiles to metastatic patterns. This study investigates mutational profiles to uncover correlations with organ-specific mets in pts treated at our institution. **Methods:** This study included pts with unresectable MSS/ *BRAF*wt mCRC treated at Vall d'Hebron Hospital (2010–2020). Pts were grouped into three clinical categories based on metastatic patterns: liver-limited disease (LLD), exclusively extrahepatic disease (EXTRAHEP), and hepatic and extrahepatic disease (BOTH). Molecular analyses were performed using NGS prescreening data available at our institution. Mutations were grouped in two approches: (1) by biological significance using cancer hallmark genes from published datasets (Zhang, *Front Genet* 2020; Sondka, *Nat Rev Cancer* 2018), and (2) by molecular pathways based on the Sanchez-Vega dataset (*Cell* 2018). Statistical analyses were conducted using R version 4.3.2. **Results:** A total of 1,026 pts were included (204 LLD, 297 EXTRAHEP, and 525 BOTH), with molecular analyses performed on 360 samples (35% overall; 31.8%, 39.7%, and 33.7%, in each group, respectively). The median number of genes with pathogenic mutations per sample differed significantly between groups: 2.28 in LLD, 2.44 in EXTRAHEP, and 2.65 in BOTH (p = 0.01). BOTH showed significantly greater increase than LLD in mutated genes associated with five of the ten analyzed hallmarks: activation of invasion and mets, resistance to cell death, evasion of growth suppressors, sustaining proliferative signaling, and replicative immortality. Compared to EXTRAHEP, BOTH also had more mutations in invasion and mets activation and proliferative signaling (adjusted p-value $<$ 0.05 for all the hallmarks mentioned). For pathway associations, WNT pathway activation was higher in BOTH than EXTRAHEP (p = 0.004), driven by more frequent APC mutations in BOTH (82% vs. 69%, adj. p = 0.049). **Conclusions:** This study provides evidence that pts with both hepatic and extrahepatic disease exhibit enrichment in five cancer hallmarks and the WNT pathway compared to other metastatic patterns. This suggests the tumor's potential to adapt to diverse microenvironments. Despite the statistical significance, the magnitude of the observed differences in mutated genes is not yet clinically useful. These findings highlight the need for collaborative efforts to develop mutational profiles that predict organotropism and guide therapy. Research Sponsor: None.

3557 **Poster Session**

Patterns of immunotherapy use in dMMR/MSI-H metastatic CRC. First Author: Hayley Lemisch, Temple University Lewis Katz School of Medicine, Philadelphia, PA

Background: Immune checkpoint inhibitors (ICI) are more effective in mismatch repair deficient/microsatellite instability high (dMMR/MSI-H) metastatic colorectal cancers (mCRC) compared to chemotherapy (chemo). However, real-world data and patterns of use are limited. We evaluated real-world ICI use in mCRC after FDA approval in 2017 and approval as first-line (1L) therapy in 2020, and the impact on survival. **Methods:** We used the nationwide Flatiron Health electronic health record (EHR) derived de-identified database to determine patterns of ICI usage in patients diagnosed with dMMR/MSI-H mCRC since 2013. Trends in ICI use were estimated with the Cochran-Armitage test, while real-world time to next treatment (rwTTNT), progression free survival (rwPFS), and overall survival (OS) between ICI vs chemo only groups were estimated with Kaplan Meier curves and log-rank test. Multivariate Cox Proportional-Hazards Models were fitted to adjust for potential cofounding variables (ie sex, performance status (ECOG) and treatment). Hazard ratios, p-values and 95% confidence intervals are presented. Proportional hazards assumptions were tested for violations. **Results:** Of 41,431 patients diagnosed with mCRC since 2013, 1,707 were dMMR/MSI-H and received therapy; thus were included in the analyses. Mean age was 66 years, 925 (54%) were female, and 884 (52%) had de novo mCRC. BRAF and RAS mutations were detected in 604 (35%) and 372 (22%) patients, respectively. Of 1,707 eligible patients, 573 (34%) received 1L ICI and 1,116 (66%) received 1L chemo. Of those who received 1L ICI, 480 (43%) received a single ICI and 56 (5%) received dual ICI. There was a linear increase in the proportion of ICI-based treatments used over time in both the 1L and second line (2L). With a median follow-up of 38.2 months (mo); median OS for patients who received 1L chemo was 25.9 mo vs 51.6 mo with 1L ICI (HR 0.62, p $<$ 0.0001, 95% CI 0.52-0.73). Presence of a BRAF mutation was associated with worse OS (median OS 44.4 mo, 95% CI 31.2-61.1) vs. no BRAF mutation (median OS not reached (NR), 95% CI 51.6-NR) in patients receiving 1L ICI (p = 0.0046). The presence of a RAS mutation was not significantly associated with OS. Median rwTTNT after 1L ICI was 31.8 mo (95% CI 23.7-50.2), compared to patients whose first ICI was in the 2L (21.9 mo [95% CI 12.9-36.8]) or third line (3L) (9.5 mo [95% CI 5.7-18.0]) (p = 0.0041). Median rwPFS for first receipt of ICI in the 1L was 18.1 mo (95% CI 13.2-30.1) compared to first receipt in 2L (8.3 mo [95% CI 6.5-14.5]) or 3L (4.8 mo [95% CI 4.0-13.7]) (p = 0.0032). **Conclusions:** There was a linear increase in the proportion of patients with dMMR/MSI-H mCRC treated with ICI, associated with FDA approvals in 2017 and 2020. Male gender and presence of a BRAF mutation in patients receiving 1L ICI and receipt of 1L chemo were inversely associated with OS. Receipt of ICI in earlier treatment lines was associated with increased rwPFS and rwTTNT. Patients with dMMR/MSI-H mCRC benefit from receiving early ICI. Research Sponsor: None.

3558 **Poster Session**

Colorectal cancer with gene fusions: Navigating the genomic landscape and treatment selection in a phase I unit. First Author: Camila Braganca Xavier, Department of Investigational Cancer Therapeutics, The University of Texas MD Anderson Cancer Center, Houston, TX

Background: Gene fusions are rare genomic events in colorectal cancer (CRC) and can co-occur with other potentially actionable alterations. Navigating early-phase trial selection in this scenario can be challenging. Objectives: To evaluate the genomic landscape, treatment selection, and clinical outcomes of patients (pts) with CRC harboring gene fusions enrolled in at least one clinical trial in the Department of Investigational Cancer Therapeutics, The University of Texas, MD Anderson Cancer Center. **Methods:** We used a computerized data extraction tool to review clinical and genomic data of pts with CRC harboring gene fusions between June 2011 and June 2024. The actionability of the genomic alterations was classified by the Precision Oncology Decision Support team. Median overall survival (mOS) was defined as the time from consent to the date of death or last follow up. Kaplan-Meier method was used to estimate survival and the Cox proportional hazards model to evaluate the impact of multiple variables. **Results:** 56 pts were included (28 female; 28 male) with a median age of 50.5 years (range 25-84). Colon was the most frequent tumor location (n=29, 51.8%) followed by rectal (n=15, 26.8%), small bowel (n=8, 14.3%), and appendiceal (n=3, 5.3%). Most cases had adenocarcinoma histology (n=54, 96.4%). The median time from diagnosis to completion of the molecular test identifying the gene fusion was 3 mo (range 0-36) for pts whose tumors were diagnosed in the metastatic setting. A total of 65 fusions were identified (range 1-3 per pt); 48 of them occurring in actionable or potentially actionable genes (78.8%) and 17 in non-actionable genes (26.2%). RAS alterations were present in 27 cases (48.2%) and BRAF alterations in 10 cases (17.9%). 8 patients had alterations in ERBB2 (14.3%) and 32 in genes related to DNA damage repair (DDR; 57.1%). In total, patients were enrolled in 91 trials (range 1-7 per pt). Target therapy (TT) was offered to 33 pts (58.9%) while the remaining were offered non-TT (n=23, 41.1%). Treatment selection was fusion-driven in 10 cases (17.9%; 4 NTRK, 3 FGFR, 1 RET, 1 ROS1, and 1 ALK). Notably, one pt with a ETV6-NTRK fusion was enrolled sequentially in 4 immunotherapy (IO) and TT trials, surviving on-trial for over 3.5 years. 3 patients received TT for KRAS (5.4%), 4 for BRAF (7.1%), 4 for ERBB2 (7.1%), and 8 for DDR alterations (14.3%). The mOS was 10.0 mo (95% CI, 5-NR) for pts receiving non-TT and 11 mo (95% CI, 3-21) for patients receiving TT (p 0.985). Age group (cutoff 50 years), gender, cancer stage at diagnosis, RAS, BRAF and DDR alterations, and treatment type (TT vs. non-TT or IO) were not related to survival in the multivariate level (p=0.9). **Conclusions:** A comprehensive genomic evaluation of pts with CRC harboring gene fusions can expand early-phase treatment possibilities. DDR alterations are more frequent in this group than in unselected CRC cohorts and can represent an additional target for TT. Research Sponsor: None.

3559 **Poster Session**

The efficacy of watch and wait strategy or surgery after neoadjuvant immunotherapy for locally advanced colorectal cancer with dMMR/MSI-H guided by ctDNA dynamic monitoring (WINDOW): A single-center, open-label, prospective, phase II study. First Author: Xuan Zhang, Yunnan Cancer Hospital, Kunming, Yunnan, China

Background: Circulating tumor DNA (ctDNA) has shown potential in predicting the efficacy of neoadjuvant treatment for colorectal cancer (CRC). However, evidence is limited for patients with deficient mismatch repair (dMMR) / microsatellite instability-high (MSI-H) CRC, who respond well to immunotherapy. This study explores an optimal ctDNA-guided neoadjuvant immunotherapy (nIT) strategy in locally advanced CRC (LACRC) patients with dMMR/MSI-H. **Methods:** We conducted a single-center, open-label, phase 2 trial named WINDOW involving dMMR/MSI-H LACRC patients. Patients received the anti-PD-1 antibody tislelizumab every three weeks. ctDNA was monitored at baseline, after 2, 4, 5, or even 6 to 8 cycles, and during post-watch-and-wait (W&W) or post-surgery periods using the Signatera platform. Starting from the 4th cycle, patients with two consecutive ctDNA-negative results were eligible for the W&W approach. Those who did not achieve ctDNA-negative or turned positive during follow-up continued immunotherapy. Surgery was performed for patients not meeting W&W criteria by the 8th cycle. The primary endpoint was the complete response (CR) rate, including ctDNA-negative clinical complete response (cCR) and pathological complete response (pCR). The trial is registered at ClinicalTrials.gov (NCT06477991). **Results:** From January 2023 to May 2024, 24 patients with stage II-III dMMR/MSI-H CRC were enrolled, including 18 with colon cancer and 6 with rectal cancer. At baseline, all patients had detectable ctDNA. After nIT, 87.5% (21/24) achieved two consecutive ctDNA-negative results. Among the remaining three, two underwent surgery due to sustained ctDNA-positivity (both TRG3), while one showed continuous ctDNA decrease despite obstruction and achieved pCR. One patient required emergency surgery for perforation (confirmed as pCR), while 20 were managed with the W&W strategy. Of these, 90% (18/20) achieved ctDNA negativity after two cycles, and 95% (19/20) after five cycles of nIT. With a median follow-up of 20.3 months (range: 8.7–25.0 months), none experienced recurrence, resulting in an overall CR rate of 91.7% (22/24). Notably, if ctDNA remained positive after the 5th cycle, the CR rate was only 25% (1/4), while it reached 100% (20/20) if ctDNA became negative. From the perspective of organ preservation, only 45.5% (10/22) of patients avoided surgery based on imaging alone; however, with ctDNA-guided management, 83.3% (20/24) avoided surgery. **Conclusions:** NIT demonstrates high efficacy in dMMR/MSI-H LACRC. The ctDNA-guided W&W strategy significantly improves organ preservation rates. Monitoring ctDNA negativity after the 5th cycle of nIT is a crucial marker of high CR rates, suggesting this cycle may represent the optimal monitoring window during nIT. Clinical trial information: NCT06477991. Research Sponsor: The Joint Special Funds for the Department of Science and Technology of Yunnan Province-Kunming Medical University; 202201AY070001-149.

3560 **Poster Session**

Laparoscopic versus open liver resection for colorectal liver metastasis: An individual participant data meta-analysis of randomized controlled trials. First Author: Åsmund Avdem Fretland, Oslo University Hospital, Oslo, Norway

Background: Laparoscopic surgery for colorectal liver metastases (CRLM) is associated with lower physical impact, shorter length of stay and less postoperative morbidity than open surgery. To analyze oncological and procedural outcomes, a European consortium including principal investigators of all 4 completed RCTs on laparoscopic (LLR) vs open (OLR) liver resection performed an individual participant data meta-analysis (IPDMA), including updated survival data. **Methods:** This was an IPDMA with a primary endpoint of postoperative morbidity. Secondary endpoints included overall survival (OS), disease-free survival (DFS) and resection margin status. A generalized linear mixed model was used to compare OLR and LLR , with trial as a fixed-effect. Logistic regression analysis was performed for dichotomous variables and negative binominal regression analysis for continuous variables. Survival analyses were performed using Cox-regression. **Results:** A total of 761 patients with CRLM were randomly allocated to LLR (n = 384) or OLR (n = 377). Preoperative chemotherapy was administered as recommended by the local multidisciplinary team (40% vs 46%). Whilst LLR was associated with significantly less postoperative morbidity overall (19% vs 27%, adjusted OR 0.62 [95%CI 0.44 to 0.88]), this was not observed in the subgroup of patients receiving neoadjuvant chemotherapy (25% vs 24%, adjusted OR 1.06 [95%CI 0.63 to 1.79]), p-value for interaction < 0.001). Hospital stay was shorter after LLR (median 4 vs 5 days, adjusted percentage difference: -27 [95%CI -37 to -15]) All cause 90-day mortality was not significantly different (1.9% vs 0.8%, adjusted OR: 3.2 [95%CI 0.65 to 16.00]). At 5-year follow-up OS and DFS were not significantly different (adjusted HR 0.97 [95%CI 0.79 to 1.20] and 1.05 [95%CI 0.86 to 1.27], respectively). In patients who received preoperative chemotherapy, a trend towards fewer R0 resections in LLR compared to OLR was noted (84% vs 90%, adjusted OR 2.00 [95%CI 0.99 to 4.03], p-value for interaction = 0.053). In patients who did not receive preoperative chemotherapy there was no difference in R0 resections (90% vs 86%, adjusted OR 0.76 [95%CI 0.41 to 1.40]). Liver specific recurrence was not different between LLR and OLR (37% vs 37%, adjusted OR 1.02 [95%CI 0.76 to 1.34), neither was time to adjuvant chemotherapy (45 days vs 49 days, adjusted OR 1.12 [95%CI 0.91 to 1.38]) nor median number of adjuvant courses (8 vs 8, adjusted percentage difference 0.07 [95%CI -0.11 to 0.24]). **Conclusions:** This IPDMA of 761 patients in 4 RCTs across Europe confirms that laparoscopic resection for CRLM is superior to open resection with regards to short term outcomes, with no differences observed on long term oncological outcomes. However, in patients who received preoperative chemotherapy, the benefit of the laparoscopic approach is questionable. Research Sponsor: None.

3561 **Poster Session**

Prognostic factors of survival and recurrence after liver transplantation for unresectable colorectal liver metastases: Results from the TransMet trial. First Author: Rene Adam, Paul Brousse Hospital, Villejuif, France

Background: Liver transplantation (LT) has recently proved to improve the survival of selected patients with unresectable colorectal liver metastases (uCRLM) compared to chemotherapy (C) alone. However, recurrence rates remain high, stressing the need for a better patient selection. This exploratory study aimed to identify prognostic factors associated with recurrence and death in patients undergoing LT as part of the TransMet trial. **Methods:** Data from 36 patients of the LT+C arm (per protocol population) were analyzed including age, gender, TNM and RAS status of the primary tumor, characteristics of metastases at diagnosis and at LT, chemotherapy regimen, tumor response (RECIST), and timeframe from primary resection to LT. Associations with recurrence and death were explored. Variables with > 5 observations per group and p-values ≤ 0.10 in univariable analysis were included in multivariable models. **Results:** Among the 36 transplanted patients, 27 experienced recurrence and 9 died after 50-month follow-up. Recurrence: At univariable analysis two factors were associated to a higher risk: serum CEA levels > 5 ng/ml at time of LT (11/11 vs 11/18, p 0.01) and oxaliplatin-based first line chemotherapy (14/16 vs 13/20, p 0.04). Two other factors showed a trend toward statistical significance: Female sex (14/15 vs 13/21, p 0.10) and > 20 metastases at diagnosis (11/17 vs 16/19, p 0.09). At multivariable analysis, CEA levels at LT > 5 ng/ml (HR: 2.91; 95% CI: 1.0–8.2; p 0.04) emerged as an independent predictor of recurrence. Female sex (HR: 2.2; 95% CI: 0.8–5.3; p 0.08) and oxaliplatin-based first line chemotherapy (HR: 2.0; 95% CI: 0.8–4.8; p 0.13) were also associated with around 2-fold higher risk of recurrence, although not reaching statistical significance. Death**:** At univariable analysis,two factorswere significantly associated with a higher risk: female sex (7/15 vs 2/21 for male, p 0.03) and > 24 cycles of chemotherapy before LT (8/19 vs 1/15, p 0.05). Two other factors showed a trend toward higher mortality: no response to 1st line chemotherapy (6/14 vs 3/22, p 0.06) and stable disease (vs partial response) before LT (8/22 vs 1/14, p 0.08). At multivariable analysis, female sex emerged as independent predictor of death (HR 5.1; 95% CI: 1.0-25.0; p = 0.04). More than 24 cycles of chemotherapy (HR 7.1; 95% CI: 0.9 – 51.0; p 0.07) and stable disease (vs partial response) at LT, showed an approximately 7-fold increase in the risk of mortality, although not reaching statistical significance. **Conclusions:** Within the limits of a reduced sample size, these results suggest that LT should be envisaged early in the history of potential candidates to LT to reduce the number of cycles of chemotherapy. Both morphological and biological tumor response, initially and at time of LT, are essential. The notable influence of female sex on post-LT outcome needs to be further explored. Clinical trial information: NCT02597348. Research Sponsor: None.

3562 **Poster Session**

Impact of inflammatory bowel disease on outcomes of colorectal cancer patients undergoing open resection. First Author: Abhinav Malik, Freelance Physician, New Delhi, India

Background: Colorectal cancer(CRC) is, at present, the fourth most common cause of cancer in the United States, with more than 140,000 new cases and 52,000 deaths yearly. Patients with inflammatory bowel disease(IBD) are at increased risk of CRC secondary to the pro-neoplastic effects of chronic mucosal inflammation. Open resection is one of the treatment modalities among CRC patients. Research evaluating the impact of IBD on the short-term outcomes of open resection is limited. **Methods:** The National Inpatient sample was utilized to identify open resection procedures among colorectal cancer patients through International Classification of Diseases, 10th edition (ICD-10) codes. Our study contained patients ages 18 and older. We created two groups of patients consisting of cases with and without a history of IBD. Descriptive statistics were conducted for patient demographics and pre-existing comorbidities. We reported the adjusted odds ratio(aOR) and their 95% confidence intervals for differences in surgical and post-surgical complications. **Results:** This study investigated 318115 open resections among colorectal cancer patients, which involved 3675(1.2%) with IBD. The cases of IBD contained a younger sample with a mean age of 60.95 years, while our non-IBD group had a mean age of 66.95 years($p < 0.01$). In addition, IBD patients expressed a lower mean Charlson Comorbidity Index(CCI) score of 4.21(vs. 4.34, $p < 0.01$). Our IBD group presented with higher aOR of severe sepsis with septic shock (1.224, 95% CI 1.030-1.455, p = 0.022), acute kidney injury(AKI)(1.172, 95% CI 1.059-1.297, $p < 0.01$), cardiopulmonary resuscitation (CPR)(2.148, 95% CI 1.437-3.212, $p < 0.01$), and wound infection(1.377, 95% CI 1.139-1.664, $p < 0.01$). On the other hand, IBD was linked with lower odds of bleeding(aOR 0.808, 95% CI 0.686-0.952, p = 0.011) but was more likely to undergo blood transfusion(aOR 1.153, 95% CI 1.036-1.284, $p < 0.01$). However, events of acute respiratory failure (aOR 1.024, 95% CI 0.877-1.195, p = 0.767), postoperative pneumothorax(aOR 1.286, 95% CI 0.684-2.417, p = 0.436), use of mechanical ventilation(aOR 1.181, 95% CI 0.996-1.400, p = 0.056), vasopressors (aOR 1.012, 95% CI 0.780-1.315, p = 0.926), and all-cause mortality (aOR 1.026, 95% CI 0.808-1.304, p = 0.831) did not differ. **Conclusions:** Among CRC patients undergoing open resection, patients with IBD were younger and had higher odds of septic shock, AKI, CPR, wound infection, and blood transfusion. Although we failed to find differences in short-term mortality, it is crucial to conduct long-term studies to evaluate responses and relapses following open resection and post-discharge complications. Research Sponsor: None.

3563 **Poster Session**

A multicenter randomized phase II trial assessing the efficacy and safety of mCapOX plus cetuximab and mFOLFOX6 plus cetuximab as first-line treatment for patients with RAS/BRAF wild-type metastatic colorectal cancer: Primary results of the CAPCET study. First Author: Yuwen Zhou, Colorectal Cancer Center, West China Hospital, Sichuan University, Chengdu, China

Background: This CAPCET randomized phase II trial was designed to assess the efficacy and safety of modified capecitabine and oxaliplatin (mCapOX) plus cetuximab (CET) and modified fluorouracil, leucovorin, and oxaliplatin (mFOLFOX6) plus cetuximab (CET) for the first-line treatment of left-side unresectable RAS/BRAF wild-type (wt) metastatic colorectal cancer (mCRC). **Methods:** CAPCET was an open-label, multicenter, randomized, non-comparative phase II trial. Patients with unresectable RAS/BRAF wt mCRC were randomly assigned (1:1) to receive up to 12 cycles biweekly mCapOX (capecitabine 1000mg/m^2 orally twice daily on Day 1-7 and oxaliplatin 85 mg/m^2 iv on Day 1) plus CET (500mg/m^2 iv on day 1) (arm A) or biweekly mFOLFOX6 (oxaliplatin 85 mg/m^2 iv on day 1, leucovorin 400 mg/m^2 iv on day 1, fluorouracil 400mg/m^2 iv bolus on day 1, then fluorouracil 2400 mg/m^2 continuous infusion over 46-48h) plus CET (500mg/m^2 iv on day 1)(arm B) followed by maintenance(either capecitabine plus CET or capecitabine alone at the discretion of the investigators) or treatment-free intervals until progression on treatment, toxicity, or death. The primary endpoint was progression-free survival (PFS) rate at 9 months from randomization. **Results:** Between September 2021 and April 2024, 168 patients (84 in arm A and 84 in arm B) were enrolled in 20 China centres. Baseline characteristics were well balanced between arms. After a median follow-up of 21.0 months (IQR,19.5-22.5), the 9 months-PFS rates were 70.9% (95% CI 61.1%-82.3%) in arm A and 66.8% (95% CI 56.7%-78.6%; HR = 1.11, P = 0.558) in arm B, and the primary endpoint was met. The median PFS (arm A/B) was 12.7 months (95% CI 10.8–15.2)/12.0 months (95% CI 9.7–14.1). The overall response rate (ORR) and disease control rate (DCR) in arm A were higher than those in arm B with 69.2% versus 60.3% and 96.2% versus 89.7%, respectively. The 2-year overall survival (OS) rate (arm A/B) was 66.8% (95% CI 54.2%–82.3%)/65.6% (95% CI 52.5%–82.0%), and the median OS not reached. Grade≥3 adverse events (AEs) occurred in 28.8% of safety population set (n = 156), with 7.7% in arm A and 21.2% in arm B. The most commonly Grade≥3 AEs was neutropenia, rash, leukopenia and there were no grade 5 AEs reported. **Conclusions:** The CAPCET study met its first endpoint of 9-month PFS rate in patients with RAS/BRAF wt mCRC. Biweekly mCapOX plus CET had higher ORR and DCR than mFOLFOX6 plus CET, with signally reduced toxicity. Longer follows-up and a multicenter, open-label, randomized, controlled Phase CAPCET- III study (NCT06616259) will be further validate this innovative regimen. Clinical trial information: NCT05022030. Research Sponsor: The Department of Science and Technology of Sichuan Province; The Postdoctor Research Fund of West China Hospital, Sichuan University; The Nation-Sponsored Postdoctor Researcher Program; The Science and Technology Innovation 2030-Major Project (Young Talent Cultivation Program); The 1.3.5 Project for Disciplines of Excellence, West China Hospital, Sichuan University.

3564 Poster Session

A medically tailored meal (MTM) delivery program to reduce nutritional decline and improve treatment tolerance in patients with colorectal cancer (CRC): A pilot study. First Author: Kara Stromberg, Fox Chase Cancer Center, Philadelphia, PA

Background: Colorectal cancer (CRC CA) is the 3rd most common CA among US adults. Over 50% of CRC patients (pts) present with advanced disease, necessitating adjuvant or palliative chemotherapy. Nearly 50% CRC pts will be diagnosed with malnutrition (MN) during their CA journey. MN is associated with reduced quality of life, poorer response to chemotherapy, and reduced survival. The provision of medically tailored meals (MTM) improves access to nutritious foods to support pts' caloric/nutrient needs and preferences. Remote delivery of MTMs could serve as an impactful intervention for pts at highest risk of MN and to improve treatment tolerance. **Methods:** Primary outcomes were feasibility (enrollment/adherence/retention) and acceptability of an MTM program in pts undergoing 5-FU based therapy for CRC; secondary included weight maintenance, MN measured by PG-SGA (Patient-Generated Subjective Global Assessment), HEI (Healthy Eating Index) score generated by VioScreen, a validated computerized food frequency tool, QOL measured by FACT-C/FACT-G, and treatment disruption. The MTM program included daily meals delivered weekly and nutritional counseling at 4 timepoints. **Results:** Among 100 eligible CRC pts approached, 48 consented and 52 declined, primarily due to lack of interest in MTMs (35/52, 67%). 40/48 (83%) initiated the MTM program and 32/40 (80%) completed it, including 13 (41%) Stage II/III and 19 (59%) Stage IV patients. 16/48 (33%) consented pts discontinued the study due to non-compliance (n = 4), post-consent refusal (n = 4), dissatisfaction w/ meals (n = 7) or death (n = 1). Pts had mean age of 56 yrs (range 32-78), with 51% female, 20% African American, and 15% Hispanic. 34% had < HS diploma, and 56% reported income of <$50,000. Enrollment (44%, goal > 50%, minimum 40%), counseling adherence (52.5%, goal > 66%, minimum 50%) and study retention rate (81%, goal > 70%) measured by end-of-study survey completion all surpassed a priori unfavorable result threshold (lower feasibility limit), but only retention met its target. Acceptability was high: 92% were satisfied with the MTM program and 91% would recommend it. Mean weight was maintained during study (181.2 lbs start, 181.6 lbs end) and mean PG-SGA score declined (7.5 to 5.4, indicating lower risk of MN at the end of the study). Mean HEI scores decreased slightly (63.3 start, 61.6 end, indicating a slight reduction in dietary quality) throughout the program; however, more than half of pts (56%, n = 14) demonstrated an increase in their HEI scores, suggesting improved quality of food consumed. **Conclusions:** Our MTM delivery program was highly acceptable and was associated with weight maintenance and improved PG-SGA scores in CRC pts receiving 5-FU based therapy. Further research of MTM delivery programs should consider retention challenges among pts facing advanced GI cancers. Research Sponsor: Manna Pilot Funding.

3566 Poster Session

Relapse patterns, risk factors, re-resectability and survival after curative treatment for metastatic colorectal cancer (mCRC): A RAXO substudy. First Author: Pia J. Osterlund, Tampere University Hospital and Tampere Univeristy, Tampere, Finland

Background: In mCRC, metastasectomy and/or local ablative treatment (LAT) cures some. However, over 70% of the patients relapse, with liver, lung and peritoneum being the most common recurrence sites. Data on recurrence patterns and prognostic factors are mainly limited to patients with liver metastases treated before 2008. An update including patients also with multisite metastases treated up-to-date is needed. **Methods:** In this study, 323 patients from the RAXO-study (2012–2018) were analyzed, 312 patients had undergone R0–1 metastasectomy and 11 patients had A0–1 LAT. Three patients with postoperative death were excluded. The remaining 320 patients were prospectively followed for at least five years, with radiological imaging and blood tests every 3–6 months in the first two years and every 6–12 months thereafter. Median time to recurrence (mTTR), and overall survival (mOS) were estimated with Kaplan-Meier from the date of curative surgery/LAT for metastases known at baseline and compared using log-rank. Hazard ratios (HR) were estimated using Cox regression. **Results:** mTTR was 17 months (CI 95% 13–23 months) with 221 patients (69% of all) relapsing during follow-up. Totally 135 recurrences (42% of the patients at risk) occurred during the first year. During the second, third, fourth and fifth year, recurrence occurred in 48 (26%), 27 (20%), 7 (7%) and 1 (1%) patients at risk, respectively. Of patients relapsing during the first year, 65 (60%) were re-resected with numbers for subsequent years being 18 (67%), 3 (43%), 0 (0%) and 1 (33%), respectively. mTTR, mOS, and re-resectability outcomes for the most common recurrence sites are presented in the table. Regional lymph node metastasis (HR 1.4), RAS mutation (1.4), R1 resection (2.3) and treatment with LAT (2.4) were prognostic for recurrence ($p < 0.05$). **Conclusions:** Two-thirds of curatively treated mCRC patients relapse within the first four years. Curative-intent re-resection provides good OS for most sites of recurrence and should be considered when possible. Clinical trial information: NCT01531621. Research Sponsor: Finska Läkaresällskapet; 2016, 2018, 2019, 2020, 2021, 2022, 2023, 2024, 2025; The Finnish Cancer Foundation; 2019-2020, 2021, 2022-2023, 2025; Relander´s foundation; 2020-2022; The Competitive State Research Financing of the Expert Responsibility Area of Tampere, Helsinki, Turku, Kuopio, Oulu, and Satakunta Hospitals; 2012, 2016, 2017, 2018, 2019, 2020, 2021, 2022, 2023, 2024, 2025; Tampere University Hospital Fund; Tukisäätiö 2019, 2020, 2023, 2024 and OOO-project 2020, 2022; Helsinki University Hospital research fund; 2019, 2020, 2021, 2022, 2023, 2024; Mary and Georg C. Ehrnrooth Foundation; 2023; Liv & Hälsa; 2023; Radiumhemmets fonder; 2022-2023, 2025-2027; Cancerfonden Sweden; 2023-2024; Amgen; Unrestricted grant 2012–2020, 2023, 2024; Eli Lilly and Company; 2012-2017; Merck KGaA; 2012–2020; Roche Oy; 2012–2020; Sanofi; 2012–2017; Servier; 2016–2024.

	Resected, n (%)	mTTR, months	mOS 1st resection, months	Re-resection, n (%)	mOS re-resected, months	Non-re-resected, n (%)	mOS non-re-resected, months	p
R0–1 resected patients	320	16	92					
Recurrence at any site	221 (100%)	10	61	116 (52%)	79	105 (48%)	44	< 0.01
– Lung	96 (43%)	10	64	45 (20%)	103	51 (23%)	52	< 0.01
– Liver	72 (33%)	8	54	44 (20%)	77	28 (13%)	39	< 0.01
– Distant lymph nodes	37 (17%)	9	56	5 (2%)	58	32 (14%)	48	0.31
– Peritoneum	23 (10%)	10	60	11 (5%)	92	12 (5%)	29	< 0.01
– Local recurrence	21 (10%)	10	58	9 (4%)	58	12 (5%)	56	0.31
– Intrahepatic only	56 (25%)	9	56	41 (19%)	77	15 (7%)	38	< 0.01
– Intrapulmonary only	61 (28%)	11	91	41 (19%)	103	20 (9%)	61	< 0.01

TTR, time to recurrence; m, median; OS, overall survival.

3567 Poster Session

Single-slide histology-based deep learning model for mismatch repair deficiency prediction in colorectal cancer. First Author: Masoud Tafavvoghi, Oslo University Hospital, Oslo, Norway

Background: Mismatch repair deficiency (dMMR) is a critical predictive biomarker for determining eligibility and response to immunotherapy in colorectal cancer (CRC). The current gold standards for detecting dMMR include next-generation sequencing (NGS) for microsatellite instability (MSI) detection and immunohistochemistry (IHC) for mismatch repair protein expression. However, discrepancies between these techniques have been observed, potentially impacting clinical decisions and patient outcomes. To address this, we developed a histology-based deep learning (DL) model to predict MMR status, with a specific focus on resolving cases of discordance. **Methods:** Paired hematoxylin and eosin (H&E) slides from 974 CRC tumors were retrospectively collected from the Dana-Farber Cancer Institute, all of which had NGS Oncopanel and IHC MMR reports available. Using NGS-determined MMR status as the training reference, we developed a multi-instance deep learning model to predict MMR status from single H&E slides. Feature extraction employed various pathology foundation models (FMs). The dataset was split into training and tuning sets. A hold-out test set (n = 52, 65% dMMR) was curated including patients treated with immune checkpoint inhibitors or those with NGS-dMMR/IHC-proficient discordance. **Results:** Among the overall cohort, NGS/IHC concordance identified 82 dMMR patients (9%), 881 proficient MMR (pMMR) patients (90%), and 11 cases (1%) with NGS-dMMR/IHC-proficient discordance. In the hold-out test set, the fine-tuned CTransPath FM demonstrated the highest performance, achieving an area under the curve (AUC) of 0.88 (95% CI 0.77–0.98), a positive predictive value of 0.93, and correctly classifying 8 of 11 discordant cases (73%) as dMMR. Comparative FMs, CONCH and UNI, exhibited slightly lower AUCs (0.86 and 0.85, respectively) and lower accuracy in classifying discordant cases (Table). **Conclusions:** Our histology-based DL model shows promise as a complementary tool for IHC in predicting dMMR status in CRC. The single-slide approach offers a rapid, robust and cost-effective method to prioritize IHC-proficient cases for further validation by NGS. Cohort expansion and validation in an external dataset are underway. Research Sponsor: Norwegian Cancer Society.

Test set (n=52, 65% dMMR).

Model	AUC (CI,95%)	Sensitivity	Specificity	PPV	NPV	Accuracy NGS+/IHC-
CTransPath	0.88 (0.77-0.98)	0.85	0.89	0.93	0.76	8/11
CONCH	0.86 (0.76-0.96)	0.88	0.76	0.67	0.93	5/11
UNI	0.85 (0.74-0.96)	0.78	0.82	0.70	0.87	6/11

3568 Poster Session

Time to treatment initiation (TTI) in patients with colorectal cancer and liver metastases. First Author: Kamran Steppe, The University of Oklahoma Health Sciences Center, Oklahoma City, OK

Background: In colorectal cancer (CRC), the liver represents a common site of metastatic disease, and patients with colorectal liver metastases (CRLM) may sometimes still achieve surgical resection of hepatic metastases. In oncology, delays initiating cancer treatment usually correspond with worse outcomes, yet factors associated with time to treatment initiation (TTI) in patients with CRLM remain unstudied. **Methods:** We utilized the National Cancer Database (NCDB) to identify adults (≥18 years old) with confirmed CRLM diagnosed between 2010-2021. We defined TTI as the number of days between cancer diagnosis and the first non-surgical treatment (radiation, immune, or chemotherapy). We excluded cases in which TTI equaled zero or exceeded 120 days. We compared median TTI across sociodemographic (i.e., age, race, income) and clinical (i.e., primary tumor site, tumor grade, comorbidities [Charlson-Deyo score]) factors reported in the NCDB using a non-parametric Kruskal-Wallis test. **Results:** We included 15,456 patients with CRLM diagnosed between 2010-2021 (55.1% of patients age < 60 years, 44.8% female, 76.3% White, 12.3% Black, 6.3% Hispanic, 3.6% Asian, 0.3% American Indian, 1.2% Other). The median (m) TTI for this cohort was 41 days, with TTI values trending down between subsequent years from 2010 (m = 45) to 2020 (m = 38) until 2021 (m = 41). We found significant differences ($p < 0.0001$) in median TTI across sociodemographic and clinical factors, as detailed in the following sentences. Advanced age (80+) had longer TTI (m = 53), compared with young patients (m = 33). For race/ethnicity, Black patients (m = 47) had the longest TTI, while Asian patients had the shortest (m = 39). Patients earning in the highest income quartile had the shortest TTI (m = 38) compared with those earning in the lowest quartile (m = 44). Patients living in ZIP codes with the highest quartile of high school diploma attainment had the lowest TTI (m = 38) compared with those in the lowest quartile (m = 43). TTI varied significantly by reported geographic location, with the Pacific region having the lowest (m = 37) and the East South Central having the highest TTI (m = 44). Patients with Charlson-Deyo comorbidity scores of 2 had the highest TTI (m = 48) and patients with scores of 0 the lowest (m = 41). Right sided primary tumor locations (m = 46) had longer TTI compared to left sided primary sites (m = 39). Tumor sizes greater than 6 cm (m = 45) received treatment later than tumor sizes less than 2 cm (m = 35). Lower grade tumors had longer TTI (m = 34) compared to high grade tumors (m = 28). **Conclusions:** In our study of patients with CRLM in the NCDB, the median TTI was just under 6 weeks. Our findings suggest that certain patient groups may be at risk of experiencing delays in care. These results could help to motivate and inform future efforts to enhance care delivery and access for patients with CRLM. Research Sponsor: None.

3569 **Poster Session**

Immune checkpoint inhibitor (ICI) reuse after failure of first-line ICI in patients with metastatic dMMR/MSI gastrointestinal cancers: The INFLATE study. First Author: Léa Mercier, Institut Bergonié, Bordeaux, France

Background: Immune checkpoint inhibitors (ICIs) are a standard treatment for gastrointestinal (GI) cancers with mismatch repair deficiency (dMMR) or microsatellite instability (MSI). However, around 50% of patients develop resistance to ICIs, during treatment or after discontinuation. In these patients, the efficacy of reuse an ICI in patients progressing during a previous ICI (rechallenge), or in patients who progressed after discontinuation (reintroduction), remains unknown. The INFLATE study evaluates the efficacy of ICI reuse in patients who progressed on or after discontinuing ICI. **Methods:** This is a multicenter international retrospective study from the IMMUNODIG cohort, including patients from 34 centers in France, the United States, Italy, Belgium and Spain. All patients received ICI for dMMR/MSI GI cancer. We analyzed patients who had progressed following initial ICI (ICI-1) and subsequently received a rechallenge or a reintroduction with ICI (ICI-2), either monotherapy (mono-ICI) or biotherapy (bi-ICI). **Results:** A total of 77 patients were included, receiving bi-ICI (N = 34) or mono-ICI (N = 43) during ICI-2. The majority (76%) had a metastatic colorectal cancer. The reason for discontinuing ICI-1 was disease progression in 53% of cases, end of treatment in 15%, toxicity in 5% and other reasons in 26%. Patients who discontinued ICI-1 due to progression received MONO-ICI-2 in 29% of cases and BI-ICI-2 in 71%, whereas those who stopped for other reasons received MONO-ICI-2 in 86% and BI-ICI-2 in 14% of cases. Efficacy results are shown in Table 1. The ORR and DCR were 26% and 79% with MONO-ICI-2, and 16% and 71% with BI-ICI-2. Among patients who discontinued ICI-1 due to progression, BI-ICI-2 (N = 29) achieved an ORR and DCR of 8% and 65%, with a median PFS of 5.5 months (95%CI 4.07-10.4). These outcomes were 17%, 67%, and 3.7 months (95%CI 2.37-NA), respectively, with MONO-ICI-2 (N = 12). For patients who discontinued ICI-1 for reasons other than progression, BI-ICI-2 (N = 5) achieved an ORR and DCR of 60% and 100%, with a median PFS not reached (95%CI 11.5-NR), while MONO-ICI-2 (N = 31) achieved 29%, 82%, and 14.2 months (95%CI 11.2–NR), respectively. **Conclusions:** This is the first multicenter real-world study evaluating ICI reuse in dMMR/MSI GI cancers. In patients who discontinued ICI for reasons other than progression, reintroduction of ICI therapy upon progression achieves tumor control in 85% of cases. In cases of progression on mono-ICI, Bi-ICI re-challenge achieve tumor control in two-thirds of cases and might be to consider in some patients. Research Sponsor: None.

	ORR %	DCR %	PFS median (95%CI)	OS median (95%CI)
Overall N=77	21	76	7.65 months (5.5–11.5)	27.6 months (22.2–55.7)
Discontinued ICI-1 due to Progression N=41	11	68	5.03 months (3.7–8.05)	26.7 months (21.1–NR)
Discontinued ICI-1 for Other Reasons N=36	33	85	14.22 months (11.24–NR)	27.6 months (22.2–NR)

3570 **Poster Session**

Comparison of *MET* genomic alterations (GA) identified in colorectal cancer (CRC) vs gastric cancer (GCA). First Author: Faiza Yasin, Yale School of Medicine, New Haven, CT

Background: MET signaling promotes tumor progression and therapeutic resistance across many solid tumors through diverse oncogenic signaling pathways. While MET-targeted therapies are approved in non-small cell lung cancer with novel agents in clinical trials for tumors with *MET* exon 14 splice site mutations, *MET* amplifications, and MET expression, their role in CRC and GCA is still emerging. We aim to understand the co-mutation landscape and genomic context of MET alterations across a large cohort of CRC and GCA cases to identify potential therapeutic targets. **Methods:** FFPE blocks of clinically advanced CRC (50,500 cases) and GCA (9,566 cases) were analyzed by hybrid capture-based comprehensive genomic profiling (CGP) that evaluated all classes of genomic alterations (GA). MSI-high status, tumor mutational burden (TMB), genomic ancestry, mutational signature, and homologous recombination deficiency signature (HRDsig) were assessed for patients with activating *MET* GA. PD-L1 expression was determined by IHC (Dako 22C3 with TPS scoring system). Results were compared using the Fisher exact test with the Benjamini-Hochberg adjustment. **Results:** MET GA (METmut) were more frequently identified in GCA than CRC (4.4% vs 1.0%; $p < .0001$). Median ages were similar in all groups with MET altered CRC and GCA. Median GA per tumor was higher in the METmut cases in both tumor types ($p > .0001$ for both). MSI-high status was less frequent in METmut GCA (1.7% vs 5.5%; p = .001) compared with METwt tumors. CRC cases featured higher frequencies of TMB > 10 mutations/Mb in both METmut and METwt groups ($p < .0001$ for all comparisons). Low level PD-L1 expression (1-49% TPS) was higher in CRC than GCA, but similar within tumor type across METmut and METwt tumors. METmut CRC had lower frequencies of GA in *KRAS* (34.7% vs 48.8%; $p < 0.0001$) which was also found in GCA (6.6% vs 16.9%; $p < .0001$). *CDK6* GA were more frequent in GCA than CRC and also were more frequent in METmut cases in both tumor types (19.6% vs 5.2% in GCA and 10.2% vs 0.6%; $p < 0.0001$). *ERBB2* GA were more frequent in both METmut and METwt GCA (13.5% vs 13.8%; NS) than CRC (9.6% vs 5.2%; p = 0.0004). *TP53* GA were more frequent in METmut vs METwt CRC (84.1% vs 75.9%; $p < 0.0001$) and GCA (81.8% vs 60.8%; $p < .0001$). BRAF V600E GA were identified in 5.9% METmut CRC and 8.4% METwt CRC (p = .051). BRAF V600E GA were uncommon in both METmut and METwt GCA (0.2% vs 0.4%; p = 1.0). **Conclusions:** This large-scale analysis reveals distinct genomic profiles of MET-altered tumors in CRC and GCA, characterized by lower prevalence of *KRAS* and MSI-high status, with enrichment for *CDK6*. These molecular differences suggest distinct biologic subsets that could inform patient selection and rational drug combination strategies for novel MET-targeted therapies. Research Sponsor: None.

3571 **Poster Session**

The role of gut microbiome composition in the IBD-CRC pathway: A retrospective study of 428 patients. First Author: Sabina Sayeed, Maimonides Medical Center, Brooklyn, NY

Background: The progression from inflammatory bowel disease (IBD) to colorectal cancer (CRC) is a significant clinical challenge, driven partly by inflammation and dysbiosis of the gut microbiome. This study aimed to investigate the relationship between gut microbiome composition, systemic inflammation, and CRC risk in patients with IBD. A secondary aim was to evaluate the potential protective effects of microbial diversity and specific bacterial taxa in mitigating CRC progression. **Methods:** This retrospective study analyzed data from 428 patients with a confirmed diagnosis of IBD, of whom 162 (37.9%) were diagnosed with CRC. Stool samples collected within one year of diagnosis were subjected to 16S rRNA gene sequencing to characterize microbial composition and diversity. Alpha and beta diversity indices were calculated to evaluate microbial richness and community dissimilarity, respectively. Specific microbial taxa, including Bacteroides fragilis, Escherichia coli, and Akkermansia muciniphila, were quantified due to their established roles in inflammation and carcinogenesis. Inflammatory biomarkers, including C-reactive protein (CRP), fecal calprotectin, IL-6, and IL-17 were measured from serum and stool samples. Clinical data, including demographics, disease duration, staging, and treatment history, were obtained from electronic medical records. Multivariate regression models were used to determine associations between microbial profiles, inflammatory markers, and CRC risk, adjusted for confounders such as age, sex, BMI, and immunosuppressive therapy. **Results:** Patients with CRC demonstrated reduced gut microbial diversity compared to IBD patients without CRC (Shannon Index: 2.3 ± 0.4 vs. 3.1 ± 0.5; $p < 0.001$). Dysbiosis in CRC patients was marked by an overrepresentation of pro-inflammatory bacteria (Escherichia coli and Bacteroides fragilis) and a depletion of protective taxa (Akkermansia muciniphila and Faecalibacterium prausnitzii). Pro-inflammatory biomarkers, including CRP (14.2 ± 3.6 mg/L vs. 6.7 ± 2.1 mg/L; $p < 0.001$) and fecal calprotectin (378.5 ± 85.2 μg/g vs. 215.3 ± 64.7 μg/g; $p < 0.001$), were elevated in patients with CRC. Regression analyses revealed that reduced microbial diversity (OR: 2.87, 95% CI: 1.92–4.28) and the presence of specific pathogenic taxa (Bacteroides fragilis: OR: 3.12, 95% CI: 2.03–4.79) were independently associated with increased CRC risk. Conversely, patients with higher relative abundances of Akkermansia muciniphila exhibited lower levels of inflammation and reduced CRC risk (OR: 0.52, 95% CI: 0.35–0.76), likely due to its role in maintaining mucosal integrity and modulating immune responses. **Conclusions:** This study underscores the critical role of gut microbiome composition in the IBD-CRC pathway, and highlights the need for microbiome-targeted interventions to prevent CRC progression in patients with IBD. Research Sponsor: None.

3572 **Poster Session**

Clinicogenomic landscape and outcomes of metastatic colorectal cancer patients with pathogenic *GNAS* variants. First Author: Faran Polani, Inova Schar Cancer Institute, Fairfax, VA

Background: Colorectal cancer (CRC) is a leading cause of cancer-related mortality, with 20-25% of cases presenting with metastatic disease (mCRC). Pathogenic variants in the *GNAS* gene, which encodes the stimulatory alpha subunit of the G protein complex, are found in 1.5% to 4.8% of CRC cases and are more prevalent in mucinous adenocarcinomas. Presence of these mutations have been associated with a lower likelihood of regression following first-line (1L) systemic therapy. However, the specific impact of *GNAS* mutations on treatment (tx) outcomes and overall survival in mCRC patients (pts) remains under investigation. **Methods:** We retrospectively analyzed de-identified data from 5,967 pts with stage IV mCRC treated with 1L oxaliplatin-based chemotherapy in the Tempus Database. Samples were sequenced with the Tempus xT (648-gene panel) or xF DNA assay (105 or 523 genes depending on version) and were divided into *GNAS* wild-type (GNASwt) and *GNAS* mutated (GNASmut) groups. Tumor mutational burden (TMB) and microsatellite instability (MSI) were calculated. Short variant pathogenic/likely pathogenic mutations and copy number alterations were analyzed for patients that underwent xT testing. Real-world (rw) objective response rate (rwORR) was defined as the proportion of pts with a documented complete or partial response within 90 days of tx start. Rw overall survival (rwOS) was defined as the time from 1L start to death from any cause. Hazard ratio (HR) was calculated using a Cox proportional hazards model and p-values were calculated using the Wald test. **Results:** The study included 5,854 *GNAS*wt and 113 *GNAS*mut mCRC pts (prevalence *GNAS*mut = 1.9%). *GNAS*mut pts exhibited higher prevalence of mucinous adenocarcinoma (26% vs. 2.8%) and peritoneal metastases (51% vs. 22%, $p < 0.001$), while liver metastases were more prevalent in the *GNAS*wt group compared to the *GNAS*mut group (77% vs 51%, $p < 0.001$). *KRAS*, *ARID1A*, *MSH2/3/6*, and *ATR* were more frequently altered in the *GNAS*mut group, while *TP53* and *APC* mutations were more frequent in the *GNAS*wt group. Immunophenotype markers such as high TMB and high MSI were also more often observed in the *GNAS*wt pts compared to *GNAS*mut pts ($p < 0.001$). rwORR was significantly lower in *GNAS*mut pts compared to *GNAS*wt (42% vs. 66%, p = 0.002). Pts with *GNAS*mut had reduced rwOS compared to pts with *GNAS*wt (HR = 1.31, p = 0.05). **Conclusions:** mCRC pts with pathogenic *GNAS* variants exhibit distinct clinicogenomic features and poorer outcomes with first-line oxaliplatin-based chemotherapy compared to *GNAS*wt pts. These findings highlight the need for alternative tx and further research on *GNAS* as a prognostic biomarker in mCRC. Research Sponsor: Tempus AI.

3573 **Poster Session**

Clinicopathologic features of complement activation signatures in colorectal cancer. First Author: Mir Lim, The University of Texas MD Anderson Cancer Center, Houston, TX

Background: Activation of the complement cascade pathway is associated with pro-oncogenic inflammation and immune-suppressing, myeloid-derived M2 macrophages for many solid tumors. Most colorectal cancers (CRC) are microsatellite stable that do not respond to immunotherapy. The role of complement activation (CA) in the "immune cold" CRC phenotype remains poorly detailed. We sought to identify molecular annotations of CRC subpopulations enriched for CA to guide future therapeutic strategies. **Methods:** CRC tumors from 207 patients with stages II-IV CRC at MDACC underwent bulk RNA sequencing. Transcriptomes were analyzed per GSEA "Hallmark Complement" gene set to assign a normalized enrichment score (NES) for CA to each patient and considered "complement high" ("CH"; N = 103) or "complement low" ("CL"; N = 104) if the complement NES score was above or below the median. Associations between CA and clinical and pathologic characteristics - e.g., demographics, mutation status, and Consensus Molecular Subtype (CMS) - were evaluated by chi-squared analysis. Single cell RNA (scRNA) sequencing was performed on a separate cohort of CRC primary tumors (N = 85) and liver metastases (N = 60) to compare CA among different cell types using a Wilcoxon's test. To assess for an association between CA and response to immunotherapy in a previously annotated clinical trial of patients with MSS, $BRAF^{V600E}$ metastatic CRC (NCT04017650), we evaluated pretreatment biopsies by bulk RNA sequencing and compared transcriptomic differences in CA between responders versus non-responders to encorafenib, cetuximab, and nivolumab (E+C+N). **Results:** CH CRC featured a higher prevalence for MSI-H CRC (21.3% vs 4.2%; p = .005), CMS1 (30.1% vs 6.7%; $p < .001$), and CMS4 (26.2% vs 7.7%; $p < .001$) relative to CL CRC. CMS2 was more common among CL CRC (54.8% vs 14.6%, $p < .001$). CH CRC was associated with $BRAF^{V600E}$ mutations (29.7% vs 9.2% for CL, p = .002) but not with *KRAS/NRAS* mutations or $RAS/BRAF^{wild\text{-}type}$ CRC (p = n.s. for both). On scRNA analysis, CA scores were highest in myeloid cells and lowest for B cells ($p < .0001$). Among patients with MSS, $BRAF^{V600E}$ CRC, CH signature was associated with non-response to E+C+N (fold-change 3.0 relative to responders, p = .046). **Conclusions:** Association of CH status with MSI-H CRC is a novel finding that warrants further study in understanding differential patterns of benefit to immune checkpoint blockade. CH CRC, associated uniquely with $BRAF^{V600E}$ CRC, was distributed bimodally across the immune-activated CMS1 and the immune-suppressing CMS4 CRC, similar to known transcriptomic heterogeneity of $BRAF^{V600E}$ CRC. Our data suggest high CA, linked to immune-suppressing myeloid cell subpopulations, as a negative predictive biomarker for response to immunotherapy in MSS $BRAF^{V600E}$ CRC and support broader study of complement-targeting agents to improve treatment for selected patients with CRC. Research Sponsor: None.

3574 **Poster Session**

Impact of SARS-CoV-2 mRNA-BNT162b2 vaccination on survival outcomes in metastatic colorectal cancer patients treated with bevacizumab-based therapy. First Author: Coskun Yazgan, Ankara University Faculty of Medicine Department of Medical Oncology, Ankara, Turkey

Background: Colorectal cancer (CRC) is a leading cause of cancer-related mortality worldwide. Bevacizumab, an anti-vascular endothelial growth factor (VEGF) antibody, is widely used in metastatic CRC (mCRC) treatment to inhibit tumor angiogenesis and modulate the immunosuppressive tumor microenvironment. Recent evidence suggests that mRNA-based COVID-19 vaccines, such as SARS-CoV-2 mRNA-BNT162b2, may enhance anti-tumor immune responses. This study aimed to evaluate the impact of SARS-CoV-2 mRNA-BNT162b2 vaccination on progression-free survival (PFS) and overall survival (OS) in mCRC patients treated with bevacizumab-based therapy. **Methods:** This retrospective, single-center study included 92 mCRC patients treated with bevacizumab between June 2021 and October 2024. Patients were divided into vaccinated (n=50) and unvaccinated (n=42) groups. Baseline demographic, clinical, and pathological characteristics were collected. PFS and OS were analyzed using Kaplan-Meier estimates and Cox proportional hazards regression models to identify independent predictors of survival. **Results:** The vaccinated group demonstrated significantly longer median PFS (8.0 months vs. 5.6 months, p=0.010) and OS (39.4 months vs. 17.8 months, p=0.014) compared to the unvaccinated group. Multivariate analysis identified SARS-CoV-2 mRNA-BNT162b2 vaccination as an independent predictor of improved PFS (HR 0.44, p=0.003) and OS (HR 0.39, p=0.018). Vaccinated patients also had a higher proportion of favorable ECOG PS and a lower prevalence of RAS mutations. **Conclusions:** SARS-CoV-2 mRNA-BNT162b2 vaccination was associated with improved PFS and OS in mCRC patients receiving bevacizumab-based therapy, potentially through enhanced anti-tumor immune responses. These findings highlight the potential of mRNA-based vaccines to modulate the tumor microenvironment and improve outcomes in mCRC. Further prospective studies are needed to confirm these results and explore underlying mechanisms. Research Sponsor: None.

3575 **Poster Session**

Effect of race/ethnicity on clinical outcomes for metastatic colorectal cancer (mCRC) patients in phase 1 trials: A dual institution experience. First Author: Hasan Musanna Zaidi, Rutgers Cancer Institute of New Jersey, New Brunswick, NJ

Background: Patients with mCRC who progress on standard of care therapies have limited therapeutic options and are associated with poor prognoses. Phase 1 trials are a valuable resource for these patients, offering novel treatment options. However, the appropriate time of consideration for phase 1 trials remains unclear. We sought to analyze the outcomes in a multi-racial cohort of patients with mCRC enrolled in prospective phase I clinical trials to describe clinical characteristics and gauge efficacy of such trials. **Methods:** We reviewed medical records of patients with mCRC enrolled in phase 1 trials at two institutions from 1999 to 2018 and 2021 to 2024. We collected patient demographics, key clinical characteristics, responses, and deaths. Time on study was calculated as time between first dose of study drug and decision to discontinue study. Overall survival (OS) was calculated as time between the first dose of study drug to date of death or last contact date (censored). Outcomes were analysed by Mantel–Cox test using Prism GraphPad v 10. **Results:** There were 283 enrollments on 66 phase I trials. Median age (range) was: 59 (29-83) years; non-Hispanic whites (NHW, 126; 44.5%), non-Hispanic blacks (NHB, 69; 24.4%), Hispanic (H, 69; 24.4%), Asian (A, 17; 6.0%), and unknown (UNK, 2; 0.7%). Median number of prior therapies was 3 (range 0-11). ECOG performance status was 0, 1, 2, and unknown, among 62 (21.9%), 181 (63.9%), 11 (3.9%), and 29 (10.2%) patients, respectively. Median number of sites of metastases was 3 (range 0-10). Sites of metastases included liver 77.0%, lung 60.1%, lymph nodes 39.9%, peritoneum 24.4%, bone 20.5%, and brain 1.8%. The primary site of cancer for patients on study was colon (84.1%), followed by rectum (11.7%), rectosigmoid (0.7%), and (simply documented as) CRC (3.5%). The median time on study was 1.8 months for all patients, with NHW 1.9 months, NHB 1.8, H 1.7, A 1.6, and UNK 7.4; p = 0.72. The OS was 8.6 months among all patients, and 7.9, 7.8, 8.8, 9.4, and 9.5 months for NHW, NHB, H, A, and UNK, respectively (p = 0.82). Response evaluable patients were n = 236; including complete response (CR, n = 2, 0.8%), partial response (PR, n = 8, 3.4%), stable disease (SD, n = 80, 33.9%), and clinical benefit rate (CBR = CR+PR+SD, n = 90) 38.1%. **Conclusions:** Patients with mCRC enrolled onto phase 1 trials showed CBR of 38.1% and OS of 8.6 months, which is comparable to standard third-line therapies that were available during the time period of this study, thus showing promise for their use in clinical practice. No racial/ethnic variation was observed. There was a non-significant trend towards a lower OS with increase in number of prior lines of therapy. A multivariate model will be presented. Research Sponsor: None.

3576 **Poster Session**

Understanding and addressing unmet needs in colorectal cancer: Findings from the Colorectal Cancer Alliance's Patient and Survivor survey. First Author: Kimberley Lynn Newcomer, Colorectal Cancer Alliance, Washington, DC

Background: Colorectal cancer (CRC) is the third most commonly diagnosed cancer and the second leading cause of cancer-related deaths worldwide. Despite advances in survival rates, CRC patients and survivors often face unmet needs, including emotional support, coping strategies, and access to treatment-related information. Beyond physical challenges, patients report emotional distress, disruptions to quality of life (QoL), and difficulty navigating the healthcare system. Even after remission, survivors frequently struggle with lingering psychosocial and physical impacts. **Methods:** The Colorectal Cancer Alliance conducted an IRB-approved cross-sectional survey to assess the needs of CRC patients, survivors, and caregivers. The survey included over 150 questions about demographics, diagnosis experiences, QoL, access to care, and treatment outcomes. Participants (n = 283) were recruited through the Alliance's social media, email campaigns, and online communities to ensure diverse representation. **Results:** The study revealed critical insights into the challenges faced by CRC patients and survivors. The median age group of participants was 46–55. Most respondents (74%) reported difficulty finding someone who could understand and relate to their experience. Furthermore, 41% noted a reduction in support from others after their treatment ended. Many participants faced ongoing challenges, with 54% reporting fatigue and 51% experiencing stress. CRC had a profound impact on several aspects of life: 64% said it negatively affected their career or work life, 58% cited negative effects on their relationship with a spouse or partner, 80% reported a decline in their sex life, and 65% struggled to participate in social activities. Additionally, 51% noted challenges with dating, and 43% indicated that their cancer journey affected their desire to have children. While most patients felt informed before treatment, 46% expressed unmet needs for information on complementary or alternative therapies. These findings highlight the broad and far-reaching effects of CRC on patients and survivors, revealing significant gaps in emotional, psychosocial, and informational support. **Conclusions:** CRC patients and survivors face substantial unmet needs that significantly affect their quality of life and well-being. The Colorectal Cancer Alliance plans to use these insights to develop care programs and targeted support initiatives designed to address these gaps. By tailoring resources to the unique needs of patients and survivors, these efforts aim to improve outcomes and offer hope for a better future for those affected by CRC. Research Sponsor: None.

3577 **Poster Session**

Drivers of homologous recombination deficiency (HRD) in metastatic colorectal cancer (mCRC). First Author: Paula Romero Lozano, VHIO, Barcelona, Spain

Background: HRD is linked to sensitivity to platinum-based chemotherapy and poly (ADP-ribose) polymerase inhibitors across various tumor types. However, the presence of HRD, driver events (such as pathogenic mutations in HR genes or other genomic alterations), and its clinical relevance in mCRC remain underexplored. **Methods:** We performed the VHIO-300 test, an ISO15189 accredited custom NGS panel profiling over 450 genes (including HR-related genes: *ATM, BRCA1, BRCA2, BRIP1, CHEK2 or PALB2*) on 356 Stage IV mCRC patients (corresponding to 247 primary colorectal and 109 to metastatic samples) enrolled in the Vall d'Hebron Institute of Oncology's Molecular Prescreening Program from June 2021 to December 2024. All samples had a tumor cellularity $>$ 40% as per pathologist evaluation. An HR score (sHR) based on genome-wide copy number alterations (CNA) and loss of heterozygosity (LOH) patterns is generated. After cross-validation with Myriad MyChoice, sHR $\geq$ 56 was established based on a cohort of ovarian tumors and used to identify HRD in mCRC tumor samples. **Results:** HRD prevalence was 3.4% in our mCRC cohort (12/356), but, much higher in metastatic lesions, (6.4%, 7/109) than in primary samples (2.03%, 5/247) (p = 0.05). In fact, the median sHR between primary (21) vs. metastases (30) in CRC was significantly different ($p < 0.01$). Regarding HR gene status, HR-mutated samples were not significantly within the HRD group (p = 0.27) and only 6.5% (2/31) were HRD. Noteworthy, *BRCA2* exhibits a frameshift deletion in a homopolymer stretch, that is a frequent hotspot in microsatellite instable (MSI) tumors, but this event was not found to be associated with HRD. In fact, all HRD tumors (n = 12) were microsatellite stable (MSS). Other frequent alterations in mCRC were studied and *BRAF* mutations were found to be present in 42% of HRD tumors ($p < 0.01$). Inversely, HRD was rare in *KRAS*-mutated samples (0.7%; 1/140) and, in fact, highly correlated with non-HRD status (p = 0.02), especially the G12 mutation ($p < 0.01$). Interestingly, CNA profiles also revealed a strong association between the *BCL2L1* loci gain and HRD ($p < 0.01$). Clinically, HRD was not significantly associated with prognostic value nor clinical benefit to oxaliplatin-based combinations. However, the limited sample size and heterogeneous treatment lines restricted robust statistical analysis. **Conclusions:** This study identified a small, yet significant subset of mCRC that displays HRD. sHR and HRD rates were higher in metastatic lesions vs primary tumors, indicating HR scarring could be accumulating over time in some mCRC patients. No clear association between pathogenic HR gene mutations and HRD were found, suggesting the involvement of alternative molecular mechanisms in this process. Frequent co-occurring events, such as *BRAF* mutations or *BCL2L1* gains could be drivers in CRC HRD, and shape, eventually, new therapeutic options for these patients in the metastatic setting. Research Sponsor: None.

3578 **Poster Session**

Real-world efficacy of trifluridine/tipiracil and bevacizumab combination according to baseline prognostic factors: The BeTAS study. First Author: Nieves Martinez Lago, Hospital Clínico Universitario e Instituto de Investigación Sanitaria de Santiago de Compostela, Santiago De Compostela, Spain

Background: The Sunlight Trial demonstrated that trifluridine-tipiracil (FTD/TPI) and bevacizumab (BEV) significantly improved Overall Survival (OS) and Progression-Free Survival (PFS) in patients with pretreated metastatic colorectal cancer (mCRC) after two treatment lines. However, the real-world efficacy and influence of baseline prognostic factors are not fully understood. **Methods:** This retrospective, observational, multicenter study across 18 Spanish hospitals included mCRC patients treated with FTD/TPI+BEV in a real-world setting. Prognostic factors were analyzed, including Tabernero's subgroups, which categorize patients according to time to diagnosis from first metastasis ($<$ 18 vs. $>$ 18 months), number of metastatic sites ($<$ 3 vs. $>$ 3), and liver metastasis (yes vs. no). Patients were grouped into Best (BPC), Good (GPC), and Poor (PPC) prognostic categories. **Results:** 398 patients were treated from July 2019 to December 2024. Median age was 67 years (range 26-92), 65.8% male, and 88.4% had ECOG PS 0-1. 56.3% had RAS mutations. Liver metastases were present in 75.3%, 27.7% had $>$ 3 metastatic sites, and 28.2% had $<$ 18 months from diagnosis of first metastasis, resulting in 47.2% of patients categorized as PPC. 67.8% received FTD/TPI+BEV as third-line treatment. ORR was 6.8%, and DCR was 49.9%. With a median follow-up of 14 months, median PFS was 4.9 months (95% CI, 4.1-5.1) and OS was 10.8 months (95% CI, 9.2-12.4). Neutropenia was the most common toxicity, with 33.1% of patients experiencing grade 3-4 neutropenia. OS by ECOG PS 0 vs. 1 vs. 2 was 12.5 vs. 11.1 vs. 5.7 months ($p < 0.0001$). PFS by ECOG PS 0 vs. 1 vs. 2 was 5.6 vs. 4.9 vs. 3.5 months (p = 0.102). OS by BPC vs. GPC vs. PPC was 18.3 vs. 12.8 vs. 7.5 months ($p < 0.0001$), and PFS was 7.3 vs. 5.8 vs. 3.7 months ($p < 0.0001$). OS in patients with grade 3-4 neutropenia vs. no neutropenia was 17.7 vs. 8.1 months ($p < 0.0001$), and PFS was 8.7 vs. 3.9 months ($p < 0.0001$). **Conclusions:** Our series confirms the effectiveness of FTD/TPI + BEV in real-world clinical practice, with a median OS of 10.8 months and a median PFS of 4.9 months. The ECOG performance status, Tabernero subgroups, and the occurrence of grade 3-4 neutropenia help identify patients who may obtain the maximum benefit from FTD/TPI + BEV treatment. Interestingly, all subgroups analyzed showed a greater benefit compared to the outcomes previously reported for FTD/TPI monotherapy, highlighting the potential of this combination in clinical practice. Research Sponsor: None.

3579 **Poster Session**

Safety and efficacy of ADG126 (an anti-CTLA-4 masking antibody) in combination with pembrolizumab: Updated results of phase 1b/2 study in advanced MSS CRC. First Author: Daneng Li, City of Hope National Comprehensive Cancer Center, Duarte, CA

Background: ADG126 is an anti-CTLA-4 IgG1 masked antibody that is preferentially activated in the tumor upon cleavage of masking peptides in the tumor microenvironment. Cleaved ADG126 binds to a unique epitope on CTLA-4, blocks CTLA-4 function, primes T cells and depletes Tregs. ADG126 in combination with pembrolizumab (Pembro) has been evaluated in a Phase 1b/2 clinical trial (NCT05405595) and we have reported outcome in 3L MSS CRC patients (Pts) free of liver metastasis (NLM).[1-4] We update results from additional dose expansion (EXP) in Pts of advanced MSS CRC. **Methods:** This is a Phase 1b/2, open-label, multicenter dose escalation and expansion study. Primary endpoints were safety and tolerability, and early signal of efficacy. Secondary endpoints were PK, ADA, ORR, DCR, DOR, PFS and OS. **Results:** As of Jan.15, 2025, a total of 54 MSS CRC Pts were treated with ADG126/Pembro (200 mg Q3W) in EXP phase across 3 dose levels of ADG126 (Table 1). 18% Pts had $\geq$ 3 prior therapies and none had prior IO therapy. There was no Grade 4/5 TRAE, and MTD was not reached. Grade 3 TRAEs were dose-dependent: 38% (5/13), 20% (6/30) and 0% (0/11) for 20 mg/kg LD[1], 10 mg/kg Q3W and 10 mg/kg Q6W cohorts, respectively. The discontinuation rate remains low for the EXP cohorts (6%). The ORR, CBR, mPFS and 12-mon OS of MSS CRC Pts without liver and peritoneal metastasis (NLPM) are listed in Table 1. ORR increased as a function of ADG126 dose. Although 10 mg/kg Q6W/Pembro did not yield PR, all 6 EE Pts remain on study (1 on treatment) at 18-mon of follow-up. Correlation between dose level/regimen, ORR, CBR and mPFS between 10 mg/kg Q6W and Q3W cohorts has been observed. mOS is not reached for 10 mg/kg Q3W NLPM after 15.5-mon follow up. Longer term efficacy data from 20 mg/kg LD cohort will be reported. **Conclusions:** Dose-dependent ORR has been observed for ADG126/Pembro IO doublet across multiple dose levels/regimens of ADG126 (10 mg/kg Q6W to 20 mg/kg LD) that is associated with well-tolerated to acceptable safety profile, which is enabled by a relatively large therapeutic window. The overall performance of ADG126/Pembro IO doublet warrants further clinical development including combination with SOCs targeting earlier lines/broader populations, such as MSS CRC with liver metastasis. Clinical trial information: NCT05405595. Research Sponsor: Adagene Inc.

Key efficacy results from MSS CRC patients.

		ADG126 Dose/Pembrolizumab (200 mg, Q3W)			
		10 mg/kg Q6W	10 mg/kg Q3W	20 mg/kg LD[1]	Total #
Safety Evaluable		11	30	13	54
Efficacy Evaluable (NLPM)		10 (6)	29 (22)	12 (12)	51 (40)
MSS CRC NLPM≥≥>=	Objective Response Rate (ORR)	0	PR = 23% (5/22)[2] (CI: 8-45)	PR = 33% (4/12)[3] (CI: 10-65)	NA
	6-mon CBR%	33%	55% (CI: 32-76%)	NM	NA
	mPFS (mon)	5.9	6.7 (CI: 4.6-9.0)	NM	NA
	12-mon OS	100%	75.1 (CI: 50-89%)	NM	NA

[1]20 mg/kg LD: ADG126 20 mg/kg x1 cycle followed by 10 mg/kg Q3W. [2]Including 1 unconfirmed PR. [3]All confirmed. CI: 95% confidence interval (report for n >=12 Pts cohort). NM: data not mature. NA: not applicable.

3580 **Poster Session**

Real-world treatment patterns and outcomes with trifluridine/tipiracil monotherapy or in combination with bevacizumab in metastatic colorectal cancer. First Author: Donald A. Richards, Texas Oncology, Tyler, TX

Background: Trifluridine/tipiracil (FTD-TPI; Lonsurf) is an oral antineoplastic agent approved for 3rd-line use in combination with or without bevacizumab (BEV) in metastatic colorectal cancer (mCRC). In the Phase III SUNLIGHT trial, the addition of BEV to FTD-TPI was associated with a significant improvement in overall survival (OS) and progression-free survival (PFS) compared to FTD-TPI monotherapy. However, data on the use of FTD-TPI in combination with BEV in the real-world community setting are currently limited. **Methods:** This was a retrospective observational study involving electronic medical records and (where available) chart reviews from mCRC patients treated by the Texas Oncology community practice from Jan 2020 to Oct 2024. Patients had to have received FTD-TPI with or without BEV after progressing on a prior line of therapy with oxaliplatin and irinotecan. Variables included patient characteristics, clinical characteristics, treatment patterns and clinical outcomes. OS and time to next treatment or death (TTNTD) were analyzed using the Kaplan-Meier method. **Results:** In total, 265 patients were included (166 FTD-TPI + BEV; 99 FTD-TPI monotherapy), with the majority receiving FTD-TPI as 3rd-line (83%; n = 220) or 4th-line (14%; n = 38) therapy. The population was 59% male, 66% white, and 35% were $\geq$65 years of age. The most common previous 1st- and 2nd-line treatment for 3rd-line FTD-TPI patients was chemotherapy + an antiangiogenic (1st-line, 67%; 2nd-line, 74%), which was similar regardless of current BEV use. Median duration of therapy was 2.8 months (range 0.3 to 12.5) with FTD-TPI + BEV and 2.8 months (range 0.1 to 10.4) with monotherapy. Median OS was 11.6 months with FTD-TPI + BEV and 6.2 months with monotherapy (hazard ratio [HR] = 2.1; 95% confidence interval [CI]: 1.5-3.0; $p < 0.001$). At 6 months, OS probability was 0.69 (95% CI: 0.61-0.77) with FTD-TPI + BEV and 0.50 (95% CI: 0.40-0.63) with monotherapy; 12-month OS probability was 0.49 (0.39-0.61) and 0.15 (0.07-0.28), respectively. Median TTNTD was 9.4 months for FTD-TPI + BEV and 5.8 months for FTD-TPI alone (HR = 1.7, 95% CI: 1.2-2.4; $p < 0.001$). The safety/tolerability profile was generally similar irrespective of BEV use, with the most common adverse events being fatigue/asthenia (73%), abdominal discomfort/pain (55%), and nausea (54%). The most notable difference was neutropenia (37% FTD-TPI + BEV, 27% monotherapy). **Conclusions:** In this large real-world community practice setting in the US, FTD-TPI use in mCRC was mostly in the 3rd-line setting and approximately two-thirds of use was in combination with BEV. Patient characteristics were similar to the SUNLIGHT trial, with high rates of previous antiangiogenic use. A statistically significant and clinically relevant OS benefit was seen with the addition of BEV versus monotherapy consistent with the results of the SUNLIGHT trial. Research Sponsor: Taiho Oncology Inc.

3581 **Poster Session**

A phase 1 dose-escalation study of GCC19CART: A novel CAR T-cell therapy for metastatic colorectal cancer in the United States. First Author: Benjamin L. Schlechter, Dana-Farber Cancer Institute, Boston, MA

Background: GCC19CART, the first clinical candidate of the CoupledCAR solid tumor platform, pairs a solid tumor chimeric antigen receptor (CAR) T-cell with CD19-targeting CAR T-cells. The CD19 target enhances proliferation and persistence of the CoupledCAR, overcoming the limitations seen in other solid tumor CAR T-cells. Guanylate cyclase-C (GCC) is an appealing CAR target due to apical-basal polarity of expression in normal colon, which may hamper on-target effects on the mucosa. GCC is present on nearly all colorectal cancers (CRC). GCC19CART showed promise in a prior trial in China, demonstrating expansion, response, and persistence, consistent with the proposed mechanism. The US phase 1 study was initiated for refractory CRC to assess the safety and efficacy of GCC19CART in this population. **Methods:** Eligible patients underwent leukapheresis, lymphodepleting chemotherapy (fludarabine 30mg/m^2 and cyclophosphamide 300mg/m^2 on day-3), and a single dose of GCC19CART. Safety was the primary endpoint. Efficacy was assessed by RECIST v1.1 based on local review. **Results:** As of January 23, 2025, 9 patients were treated: 4 at dose-level (DL) 1 (1x10^6 cells/kg) and 5 at DL2 (2x10^6 cells/kg). Cytokine release syndrome occurred in all subjects (grade [G] 1: 6/9 [66.7%] and G2: 3/9 [33.3%]), and diarrhea was reported in 8/9 (G1: 3/9 [33.3%], G2: 3/9 [33.3%], G3: 2/9 [22.2%]). Immune effector cell associated neurotoxicity syndrome occurred in 2/9 subjects (G2: 1/9 [11.1%], G3: 1/9 [11.1%]). A DL2 patient experienced a dose limiting toxicity (G3 diarrhea, G4 enterocolitis, and G5 sepsis) and died 48 days post-infusion. The overall response rate (ORR) in DL1 was 25% (1/4 partial response [PR]) and 80% in DL2 (4/5 with 3 PR and 1 pathological complete response). The PR in DL1 was achieved by month 2, while 3/4 responders in DL2 achieved a PR by month 1, demonstrating dose-dependent tumor-killing activity. Two DL2 patients maintained responses at data cut-off. One patient achieved a complete metabolic response by PET at month 2 and maintained a PR by CT at month 6 with continuous tumor shrinkage (month 1: 38.33%, month 2: 40.77%, month 4: 82.58%, month 6: 75.61%). Another patient maintained a PR at month 6 with progression at month 8. The median progression-free survival (PFS) was 5.0 months in DL1 and 7.8 months in DL2. The median duration of response was 2.2 months in DL1 and 6.9 months in DL2. Compared to the prior trial in China (≥G3 diarrhea: 22.2% vs. 53.3%; ORR: 66.7% vs. 40%, PFS: 7.8 vs 6.0 months in DL2, 5.0 vs 1.9 in DL1. Chen, *JAMA Oncol*., September 2024), the US study suggests a potential trend towards improved safety and efficacy. **Conclusions:** GCC19CART demonstrated significant clinical activity and durability in refractory CRC. Optimization of diarrhea/colitis management is ongoing. Updated data will be presented. Clinical trial information: NCT05319314. Research Sponsor: None.

3582 **Poster Session**

Impact of obesity and lifestyle-associated risk factors on outcomes of early-onset colorectal cancer in patients younger than 50 years old: A propensity-matched analysis. First Author: Syeda Ashna Fatima Kamal, Saint Louis University, Saint Louis, MO

Background: Early-onset colorectal cancer (CRC) incidence is rising in individuals under 50 years old. This study aims to understand the factors influencing outcomes in this population. We evaluated the impact of obesity and other lifestyle-associated risk factors, such as smoking, alcohol use, and diabetes mellitus, on outcomes in patients with early-onset CRC. **Methods:** A comprehensive retrospective cohort study using the TriNetX database identified adults aged 18–49.9 diagnosed with CRC. Using propensity score matching (PSM), we compared patients with obesity (body mass index [BMI] ≥30 kg/m²) and other lifestyle-associated risk factors (smoking, alcohol use, and diabetes mellitus) to those without any risk factor, while accounting for demographics, comorbidities, and treatment. The primary outcome is the 10-year mortality in obese patients as compared to non-obese patients. Secondary outcomes included the 10-year mortality in patients with other lifestyle-associated risk factors. **Results:** A total of 10,220 matched pairs of obese and non-obese patients were included. Before matching, obese CRC patients were older, more likely to be male, Hispanic, or non-Hispanic Black, and had higher rates of colonoscopy, surgery, and comorbidities ($p < 0.001$). After PSM, obese CRC patients had significantly lower odds of 10-year mortality compared to non-obese patients (7.9% vs. 14%; adjusted odds ratio [aOR] = 0.53; 95% confidence interval [CI]: 0.47–0.60). Diabetes, smoking, and alcohol use showed no significant association with 10-year mortality in patients with early-onset CRC (e.g., diabetes: aOR = 0.96; 95% CI: 0.73–1.26). **Conclusions:** Our study suggests that obesity may confer a protective effect on 10-year mortality in patients with early-onset CRC, whereas other lifestyle-associated risk factors showed limited-to-no significant impact. These findings underscore the need for targeted strategies to improve access to CRC screening and treatment, particularly in younger patients with obesity, and they also open up new avenues for research into the potential mechanisms underlying these associations. Prospective studies are warranted to validate these results and explore these potential implications, further enriching our understanding of this complex disease and potentially leading to novel approaches for its management. Research Sponsor: None.

	Incidence % (N)		Propensity score matching analysis
Lifestyle risk factors	CRC< 50 + risk factor	CRC<50 - risk factor	Adjusted odds ratio (aOR)* [95%CI]
Obesity (BMI ≥ 30)	7.9% (406)	14.0% (714)	0.53 [0.47 - 0.60]

Propensity matching analysis assessing the odds of 10-year mortality when comparing patients with early-onset colorectal cancer (< 50 years) with lifestyle-associated risk factors (e.g., obesity (N=5110) compared to equal numbers of patients without lifestyle-associated risk factors.

3583 **Poster Session**

Colorectal cancer mortality dynamics: Uncovering critical disparities in U.S. population health (2018–2023). First Author: Pranav Chalasani, Wayne State University, Rochester Hills, MI

Background: Colorectal cancer(CRC) remains the third leading cause of cancer-related deaths in the United States, with a disproportionate burden on underserved populations. Despite established screening protocols and preventive measures, fewer than 35% of cases are detected early, significantly impacting survival rates. This study examines mortality patterns across demographic and geographic divides, revealing urgent public health priorities. **Methods:** This retrospective analysis was performed in adults aged 25 and older using the CDC WONDER database (2018-2023) using ICD-10 codes. We stratified mortality data by age, gender, race, geographic region and urbanization level to identify critical disparities and emerging trends. Crude mortality rates (CMRs) and Age-adjusted mortality rates (AAMRs) per 100,000 were calculated by age, gender, region and race, with 95% confidence intervals (CI) for precision. Temporal trends and annual percentage changes (APCs) were analyzed using Joinpoint regression. **Results:** From 2018 to 2023, among 313,744 deaths, mortality increased from 51,891 to 53,497, while the AAMR for CRC consistently declined from 12.92 to 12.44. The highest CMR was in the 85+ group (156.11 per 100,000, 95% CI: 153.05–159.17), followed by 75-84 (74.18, 95% CI: 72.87–75.49), 65-74 (40.27, 95% CI: 39.58–40.96), and 55-64 (23.83, 95% CI: 23.37–24.30). The 45-54 group had a CMR of 11.74 (95% CI: 11.40–12.07), the 35-44 group 3.56 (95% CI: 3.38–3.74), the 25-34 group 0.77 (95% CI: 0.69–0.86), and the 15-24 group had the lowest at 0.09 (95% CI: 0.06–0.12). Males had a higher CMR of 17.23 per 100,000 (AAMR: 15.19, APC: -0.68, p = 0.21) than females, who had 14.42 per 100,000 (AAMR: 10.69, APC: -0.30, p = 0.56). The Midwest had the highest AAMR at 13.33 per 100,000 [APC: -0.78 (95% CI: -2.54 to 1.01, p = 0.31)], followed by the South at 13.54 [APC: 0.05 (95% CI: -0.80 to 0.92, p = 0.91)], the West at 11.90 [APC: 0.09 (95% CI: -0.79 to 0.95, p = 0.82)], and the Northeast at 11.54, with a significant decline in trends [APC: -1.90 (95% CI: -3.24 to -0.58, $p < 0.01$)]. Large central metro areas accounted for 25.3% of deaths (83,341), followed by large fringe metro areas (22.4%), medium metros (19.9%), micropolitan areas (10.0%), small metros (9.4%), and noncore areas (8.2%). Racial disparities showed White individuals with the highest CMR at 17.01 per 100,000 (AAMR: 12.69, APC: -0.78), while Black or African American individuals had a slightly lower CMR at 15.70 per 100,000 but the highest AAMR at 16.18 (APC: -1.63, $p < 0.01$), followed by American Indian or Alaska Native, Asian, Native Hawaiian, and other groups. **Conclusions:** These findings reveal critical gaps in CRC prevention and care, disproportionately affecting young adults, males, and minorities. Public health initiatives must expand screening, improve access to care, and address regional inequities to reduce mortality and promote health equity. Research Sponsor: None.

3584 **Poster Session**

Analytic and clinical validation of a negative prediction algorithm for actionable mutations utilizing genomic and epigenomic profiling in cfDNA. First Author: Andrew Gross, Guardant Health, Palo Alto, CA

Background: One challenge in cell-free DNA (cfDNA) profiling for genomic tumor profiling is the inability to confidently confirm the absence of actionable genomic mutations. This limitation arises from the challenge of determining whether key driver mutations are truly absent or if tumor levels are below the detection threshold of the assay. Accurate negative variant prediction could enable clinicians to expedite clinical decisions based on cfDNA results without relying on tissue biopsy sequencing when no actionable alterations are found. Here, we report analytic and clinical validation of a novel algorithm to enable negative prediction from liquid biopsy to address this critical clinical need. **Methods:** Using the Guardant Infinity platform, which simultaneously profiles genomic and epigenomic signals in a single sample, we integrated highly sensitive and precise tumor fraction estimates and developed a negative prediction algorithm to allow for confident reporting of samples that do not detect an actionable genomic finding. The algorithm estimates the post-test probability of a cfDNA sample harboring genomic biomarkers with FDA approved therapies relevant to treatment selection, based on population priors, epigenomic tumor fraction (TF), and the analysis of mutant and non-mutant coverage across variants of interest which was assessed for advanced colorectal (CRC) and lung cancer (NSCLC) patients. **Results:** In 3973 CRC and 7654 NSCLC analyzed patients, 41% of CRC and 22.6% of NSCLC were found to have an actionable mutation. Among the remaining samples, 66% of CRC and 56.3% of NSCLC had sufficient tumor fraction to assess the sample as variant negative with > 95% confidence. Reasons why the remaining samples could not be confidently assessed included low tumor shedding (including 15% with nondetectable tumor), low genomic coverage over loci of interest, and mutant allele support below the confident call threshold. An additional cohort of 237 CRC and 316 NSCLC patients with paired tissue and cfDNA results was used to clinically validate the negative prediction algorithm. All samples with sufficient tumor fraction for > 95% confidence and predicted to be negative by the algorithm for genomic biomarkers with FDA-approved therapies were confirmed to be negative in tissue results. **Conclusions:** A plasma-based epigenomics-based approach for confident negative prediction is feasible in CRC and NSCLC, as demonstrated by validation results. Confident negative prediction has the potential to enhance the utility of liquid biopsy and accelerate clinical decision-making in advanced solid tumors with biomarker-guided treatment pathways and should be validated in additional clinical datasets. Research Sponsor: None.

3585 **Poster Session**

Cell-free DNA 5-hydroxymethylcytosine profiling for the assessment of colorectal cancer biology and treatment response in blood. First Author: Ceyda Coruh, ClearNote Health, San Diego, CA

Background: Colorectal cancer is the third most common cancer worldwide, accounting for about 10% of all cancer cases, and is expected to claim more than 50,000 lives in 2025. Approximately 33% of CRC patients will develop metastases throughout their cancer continuum, and their 5-year survival rate is about 15%. The majority of patients with metastatic colorectal cancer (mCRC) cannot be cured. However, a subset of mCRC patients with localized recurrence or isolated metastases in the liver and/or lungs may achieve a cure through surgical intervention. Yet, current methods for identifying patients who are candidates for more favorable responseremain inadequate. Therefore, there is a critical need for predictive biomarkers to accurately identify patients who are likely to experience better outcomes following surgery. 5-hydroxymethylcytosine (5hmC) is an epigenetic modification that is associated with active genes and regulatory regions that are cell type- and disease-specific. Here, we developed a model using cell-free DNA (cfDNA) 5hmC profiles to detect CRC and identified pathways distinguishing mCRC patient outcomes following treatment. **Methods:** Plasma was collected from 294 CRC patients and 588 non-cancer individuals to obtain cfDNA. cfDNA was enriched for 5hmC-containing DNA fragments. Input and 5hmC-enriched cfDNA were subsequently used to generate sequencing libraries to obtain WGS and 5hmC profiles, respectively. Machine learning operating on 5hmC and WGS data was used to develop a CRC detection model which was subsequently tested on an independent set of mCRC (n = 69) and non-cancer samples (n = 70). Differential 5hmC analysis was performed using edgeR and Gene Set Enrichment Analysis (GSEA). **Results:** The performance of the CRC prediction model was evaluated through 10-fold cross-validation producing an auROC curve of 0.86. An independent validation set of mCRC and non-cancer patients displayed an auROC of 0.94. Comparative GSEA using gene body 5hmC levels revealed biological pathways associated with CRC biology such as Myc signaling. cfDNA 5hmC profiling of plasma obtained from mCRC patients before surgery revealed quantitative differences in patients who show recurrence of disease within 2 years post-surgery from the patients who remain recurrence-free for at least 2 years after surgery. These differences between relapsed and non-relapsed groups included 5hmC changes over genes involved in pathways known in mCRC, such as the Wnt/β-catenin signaling ($p < 0.05$). Lastly, quantitative changes in 5hmC profiles measured in pre-surgery plasma samples enabled prediction of disease recurrence in patients within 2 years post-surgery. **Conclusions:** 5hmC analysis of cell free DNA) offers a novel, non-invasive approach for identification of colorectal cancer biology and assessment of treatment response in blood samples. Research Sponsor: ClearNote Health.

3586 **Poster Session**

Sintilimab plus bevacizumab, oxaliplatin, and capecitabine as perioperative therapy in microsatellite-stable, resectable colorectal cancer liver metastases: An open-label, single-arm, phase II trial. First Author: Yu-hong Li, Sun Yat-sen University Cancer Center, Guangzhou, China

Background: Immunotherapy has revolutionized cancer treatment, yet its efficacy in proficient mismatch repair and/or microsatellite stable (pMMR/MSS) colorectal cancer liver metastases (CRLM) remains uncertain. Optimizing neoadjuvant regimens for such patients is crucial. **Methods:** A prospective, open-label, single-arm phase II clinical trial was conducted from June 2021 to January 2023. Patients with resectable pMMR/MSS CRLM were enrolled and received 4 cycles sintilimab combined with bevacizumab, oxaliplatin, and capecitabine preoperatively followed by 4 cycles oxaliplatin, and capecitabine postoperatively. The primary endpoints were safety and feasibility of neoadjuvant therapy and surgery. Secondary endpoints encompassed pathological response rates, objective response rate, progression-free survival (PFS), and overall survival (OS). Biomarker analyses were performed to identify potential predictors related to efficacy and prognosis. The study protocol was registered in ClinicalTrials.gov (NCT04940546). **Results:** Between June 2021 to January 2023, 36 patients were enrolled, and included in the safety analysis. The most common treatment-related adverse events (TRAEs) were fatigue (55.6%), peripheral neuritis (52.8%). Of the 36 patients, 30 received local treatment for liver metastases. 26 of them underwent CRLM surgery resection, and 7 of the 26 experienced surgery - related complications graded from 1-2 such as cholecystitis and pulmonary infection, one patient died from respiratory failure due to a pulmonary infection (immune pneumonia not excluded) a month after liver metastases resection. 34 were analyzed for efficacy. The objective response rate (ORR) was 67.6%, with a disease control rate (DCR) of 88.2%. 26 patients underwent surgery; the pathological complete response rate (pCR) was 11.5%, and the major pathological response rate (MPR) was 38.5%. After a median follow-up of 32.9 months, the median PFS was 14.2 months ((95% CI: 11.6 - 29.0 months), and the median OS had not yet been reached. Biomarker analysis revealed that *RAS* wild-type (mPFS: 29.0 months (15.0 - NA) vs 11.5 months (9.8 - 15.7), log-rank $P = 0.0087$), *SMAD4* wild-type population (mPFS: 20.2 months (12.3 - NA) vs 6.9 months (5.2 - NA), log-rank $P < 0.0001$) may benifit from immunotherapy combination treatment. The single cell RNA sequencing analysis revealed that higher intrafiltion of FIB_PLAG2A in the TME of CR/PR were associated with favorable prognosis, while higher intrafiltion of MPH_TREM2, FIB_POSTN in the TME of non CR/PR were linked to poor prognosis. **Conclusions:** The neoadjuvant regimen demonstrated acceptable safety and efficacy. *RAS*, *SMAD4* wild-type patients may be a potential beneficiary population. Clinical trial information: NCT04940546. Research Sponsor: Bethune Public Welfare Foundation.

3587 **Poster Session**

Safety and efficacy evaluation of neoadjuvant chemoradiotherapy plus thymalfasin and tislelizumab for treating MSS/pMMR locally advanced rectal cancer. First Author: Zhengyang Yang, Department of General Surgery, Beijing Friendship Hospital, Capital Medical University & National Clinical Research Center for Digestive Diseases, Beijing, China

Background: Neoadjuvant chemoradiotherapy is currently the standard strategy for microsatellite stable (MSS) / mismatch repair-proficient (pMMR) locally advanced rectal cancer (LARC) patients. This study aimed to explore the safety and efficacy of combining specific (thymalfasin) and non-specific (tislelizumab) tumor immunotherapy with chemoradiotherapy in MSS/pMMR LARC. **Methods:** This trial is an open, prospective, multi-center, single-arm phase II clinical study assessing the efficacy and safety of neoadjuvant chemoradiotherapy combined with thymosin andtislelizumab in MSS/pMMR LARC. Stage II/III MSS/pMMR LARC patients ($cT_{3\text{-}4a}N_0M_0$ and $cT_{1\text{-}4a}N_{1\text{-}2}M_0$) with the tumor distal location $\leq$ 10 cm from anal verge at two centers in China were consecutively enrolled. Patients received chemoradiotherapy (50 Gy/25 f, 2 Gy/f, 5 days/week, 5 weeks; plus capecitabine 850-1000 mg/m^2, bid, po, 5 days/week, day1-5), thymalfasin (4.8 mg, biw, ih, day 1 and day 4 from week 1-11) and three 21-day cycles tislelizumab (200 mg, iv.gtt, week 2, 5 and 8) as neoadjuvant therapy. Adjuvant therapies after neoadjuvant were nonuniformly specified and decided according to clinical experiences. The primary endpoint is the complete response (CR) rate, defined as the achievement of clinical complete response (cCR) after neoadjuvant therapy or pathological complete response (pCR) after total mesorectal excision (TME). **Results:** From Feb 2024 to Aug 2024, a total number of patients (n = 25) were enrolled and 3 patients were excluded because of T4b and dMMR. Finally, 2 patients were discontinued and 20 completed neoadjuvant therapy. The median age was 67.5 (from 36 to 74) years while the median tumor distal location was6.0 (from 3.5 to 8.5) cm. The CR, PD, and SD rate was 40.0% (8/20), 45.0% (9/20), and 15.0% (3/20) correspondingly, with the ORR rate of 85.0% (17/20). Grade 3 treatment-related adverse events (trAEs) including leukopenia and neutropenia were observed in 1 (5%) patient, while grade 1-2 trAEs were observed in 15(75.0%) patients. As for Dec 31, 2024, the EFS rate was 100% (20/20) with median follow-up time of 18.57 weeks (from 6.86 to 31.86). **Conclusions:** Neoadjuvant chemoradiotherapy plus thymalfasin and tislelizumab show promising anti-tumour activity in MSS/pMMR LARC patients, with manageable toxicities. This study suggests that such combination could be a promising therapeutic strategy for patients with MSS/pMMR LARC. Clinical trial information: NCT06056804. Research Sponsor: Beijing Li Huanying Medical Foundation.

3588 **Poster Session**

Neoadjuvant ONO-4578, an EP4 antagonist, in combination with nivolumab after chemoradiation therapy in locally advanced resectable rectal cancer. First Author: Yusuke Takahashi, Department of Gastroenterological Surgery, NHO Osaka National Hospital, Osaka, Japan

Background: Neoadjuvant nivolumab (NIV) after preoperative chemoradiation therapy (CRT) demonstrated promising pathologic complete response (pCR) in patients (pts) with locally advanced resectable rectal cancer (LARC) (Bando, *Clin Cancer Res* 2022). On the other hand, the prostaglandin E_2-EP4 signaling is known to induce immunosuppression in tumors. ONO-4578 (4578), an antagonist of EP4, in combination with NIV has shown a manageable safety profile and signs of anti-tumor activity in pts with solid tumors. In this ONO-4578-03 study, we evaluated safety, preliminary efficacy, and biomarkers of 4578 plus NIV after preoperative CRT in pts with LARC. **Methods:** Pts with LARC who received preoperative CRT (50.4 Gy with capecitabine 1,650 mg/m^2) were eligible. Pts were divided into two groups for neoadjuvant therapy: 4578 monotherapy lead-in (lead-in) and the combination group. Pts in the lead-in group received 4578 (40 mg, oral, daily) alone for 6 weeks, and then 4578 plus NIV (240 mg, intravenous, every 2 weeks) for 4 weeks, while pts in the combination group received 4578 plus NIV for 10 weeks. Subsequently, pts in both groups received radical resection. The primary endpoint was safety. Secondary endpoint was efficacy, including pCR rate using the AJCC tumor regression grading. Ongoing exploratory endpoints include tissue and blood biomarkers. **Results:** We enrolled 31 pts: 10 and 21 to the lead-in and combination groups, respectively. The median age was 62.0 (range, 39–76) years, 20 pts (64.5%) had a disease stage of III, and all pts were classified as microsatellite stable. The pCR (AJCC grade 0) rates in the lead-in group, the combination group, and overall population were 50.0% (5/10 pts), 23.8% (5/21 pts), and 32.3% (10/31 pts), respectively; the major pathological response (MPR; AJCC grade 0+1) rates were 70.0% (7/10 pts), 71.4% (15/21 pts), and 71.0% (22/31 pts), respectively. Among all pts, any-grade treatment-emergent adverse events (TEAEs) occurred in 23 pts (74.2%). including 3 pts (9.7%) with grade 3 TEAEs (appendicitis, ileus, drug-induced liver injury, hypertension) and 1 pt with serious TEAEs (ileus, drug-induced liver injury). None of the TEAEs led to treatment discontinuation or death. Any-grade treatment-related adverse events (TRAEs) occurred in 11 pts (35.5%), including 1 pt with a serious TRAE (grade 3 drug-induced liver injury). Radical resection was not performed within the protocol-defined window in 1 pt in the lead-in group and in 2 pts in the combination group due to progressive disease, a TRAE (grade 1 hyperthyroidism), or clinical CR, respectively. As of the final analysis, 5 pts experienced recurrence and 1 pts died in the overall population, after the median follow-up of 23.29 (range, 15.9–32.9) months. **Conclusions:** Neoadjuvant 4578 plus NIV after CRT showed a manageable safety profile and promising pCR rates and MPR rates in pts with LARC. Clinical trial information: jRCT2051200096. Research Sponsor: Ono Pharmaceutical Co., Ltd.

3589 **Poster Session**

Single-incision laparoscopic surgery vs conventional laparoscopic surgery for colorectal cancer: Short-term outcomes of a multi-center, randomized, controlled trial. First Author: Yaqi Zhang, Ruijin Hospital, Affiliated by Shanghai Jiaotong University School of Medicine, Shanghai, China

Background: Single-incision laparoscopic surgery (SILS) is increasingly being embraced in the medical community due to its potential to offer less-invasiveness and quick recovery. This multi-center randomized controlled trial compared the short-term and long-term outcomes of single-incision laparoscopic surgery (SILS) with conventional laparoscopic surgery (CLS) for colorectal cancer, which might be the first of its kind that involved both colon and rectal cancer. Study recruitment has completed, and the follow-up is ongoing. Here we report the short-term outcomes of this trial. **Methods:** The trial was conducted across 11 hospitals in 6 provinces of China. Participants included patients with histologically confirmed colorectal carcinoma that situated above the peritoneal reflection, clinically staged as I-III. Patients were randomly assigned in a 1:1 ratio to SILS or CLS group. Comprehensive perioperative data were meticulously gathered, and follow-up assessments were scheduled postoperatively. The primary endpoint was 3-year disease-free survival (DFS), secondary endpoints included overall survival (OS), oncological efficacy, and postoperative outcomes. **Results:** Between May 2021 and April 2023, a total of 712 patients were randomly assigned to either the Single-incision Laparoscopic Surgery (SILS) group (n = 354) or the Conventional Laparoscopic Surgery (CLS) group (n = 358). The distribution of surgical procedures included 162 (22.8%) right hemicolectomies, 326 (45.8%) left hemicolectomies, and 224 (31.4%) proctectomies. The pathological TNM stages I, II, and III of the mITT population were 10.7%, 36.9%, and 52.4%, respectively. In the SILS group, 92.9% (n = 329) of the cases were completed entirely with a single incision. An additional trocar was used to assist the surgical procedure in 5.6% (n = 20) of the cases, and 0.8% (n = 3) were converted to conventional laparoscopic surgery. Two patients in the SILS group required conversion to open surgery, compared to 10 patients in the CLS group. The incidence of postoperative complications and oncological efficacy were statistically equivalent between the two groups. Moreover, patients in the SILS group reported significantly less postoperative pain (p = 0.02). There were no significant differences in short-term overall survival (OS) and disease-free survival (DFS) between the two arms. **Conclusions:** Single-incision laparoscopic surgery (SILS) for colorectal cancer has demonstrated with feasibility, safety, and efficacy. The less painful postoperative experience was aligned with the principles of Enhanced Recovery After Surgery (ERAS). This surgical approach extended the concept of minimally invasiveness and represents a logical progression towards Natural Orifice Transluminal Endoscopic Surgery (NOTES) or single-incision robotic surgery. Clinical trial information: NCT04527861. Research Sponsor: SHANGHAI HOSPITAL DEVELOPMENT CENTER.

3590 **Poster Session**

The association of ctDNA with recurrence in patients with stage II-IV colorectal cancer: The β-CORRECT study. First Author: Tadayoshi Hashimoto, Department of Gastroenterology and Gastrointestinal Oncology, National Cancer Center Hospital East, Kashiwa, Japan

Background: CRC is a leading cause of cancer-related mortality globally. Detection of molecular residual disease (MRD) is an early indicator of recurrence and may allow for timely intervention. Here, we evaluated an analytically validated tumor-informed ctDNA MRD assay (Oncodetect) in a cohort of patients with CRC. **Methods:** This retrospective study utilized data and specimens from 468 patients with Stage II, III or resectable Stage IV CRC consecutively enrolled from June 1, 2020 through November 30, 2022 in the GALAXY study with available residual samples. Tumor tissue underwent whole-exome sequencing to identify up to 200 tumor-specific variants for designing a personalized MRD test. The test was used to assess ctDNA status in plasma at three timepoints: post-surgical (PS), post-definitive therapy (PDT) and in the surveillance period, which included the PDT and subsequent timepoints. The primary endpoint was the association of ctDNA status during surveillance with disease-free survival (DFS). An analysis of the association between RNA-seq expression and DFS was also planned. **Results:** Analysis included a total of 1648 ctDNA results from 417 patients with ≥1ctDNA result from ≥1 timepoint. Among these patients, 296 (71.0%) had colon and 121 (29.0%) had rectal cancer, 141 (33.8%) had Stage II, 249 (59.7%) Stage III and 27 (6.5%) Stage IV disease, and 255 (61.2%) received adjuvant chemotherapy. Median follow-up was 1.9 years. The median ctDNA level among detections, measured in mean tumor molecules per ml (MTM/ml) was 1.187 (range 0.006-3180.5). During surveillance, ctDNA detection was strongly prognostic for DFS (HR 36.6; CI 21.9 – 61.2; ctDNA status as a time-dependent variable). Similarly, ctDNA detection was strongly associated with DFS at the PS and PDT timepoints (Table). Multivariable analysis showed ctDNA status remained strongly associated with DFS while other clinicopathological factors did not. The median lead time between ctDNA detection and clinical recurrence was 97 days (95% CI: 51-114). RNA-seq analysis is ongoing. **Conclusions:** In a cohort of 468 patients who underwent curative-intent surgery for stage II-IV CRC, a tumor-informed quantitative ctDNA assay using up to 200 variants was strongly prognostic for DFS at all timepoints. The prognostic ability of RNA-seq expression analysis for ctDNA status and outcome in this cohort is currently being determined. Research Sponsor: Exact Sciences; Japan Agency for Medical Research and Development.

Association of ctDNA status with DFS.

	Statistic	Result
Surveillance (n= 398)	HR (95% CI)	36.6 (21.9 – 61.2), p<0.0001
	Sensitivity (95% CI)	64.8% (53.2 - 74.9%)
	Specificity (95% CI)	98.8% (96.8 - 99.5%)
PS (n = 241)	HR (95% CI)	7.5 (4.3 – 13.1), p<0.0001
	Sensitivity (95% CI)	44.2% (31.6% - 57.7%)
	Specificity (95% CI)	95.6% (91.6% - 97.8%)
PDT (n = 367)	HR (95% CI)	24.0 (13.8 – 41.7), p<0.0001
	Sensitivity (95% CI)	45.5% (34.0% - 57.4%)
	Specificity (95% CI)	99.0% (97.1% - 99.7%)

3591 **Poster Session**

Biologic correlates of circulating tumor DNA (ctDNA) shedding in the INTERCEPT colorectal cancer (CRC) study. First Author: Emerik Osterlund, Department of Gastrointestinal Medical Oncology, Division of Cancer Medicine, The University of Texas MD Anderson Cancer Center, Houston, TX

Background: ctDNA is a promising tool for early cancer detection and monitoring of minimal residual disease (MRD). The relationship between vesicle trafficking of ctDNA-laden exosomes and shedding of detectable ctDNA in patients is poorly understood and was therefore explored in a large prospective patient cohort. **Methods:** The INTERCEPT program prospectively enrolled patients undergoing curative intent surgery for stage I-IV CRC at MD Anderson Cancer Center. Tumor informed MRD assays (Signatera) were drawn postoperatively and every three months according to reimbursement guidelines. RNA analyses were done from FFPE. Gene set enrichment analyses (GSEA) and Z-Scores comparing ctDNA+ and ctDNA− were analyzed using log2 normalized RNA expression values. **Results:** The cohort included 579 patients with RNA and post-operative ctDNA analyses; median age 56 years, 56% male and 47% stage IV. Of these, 122 (20%) were ctDNA+ in their first draw (32% of stage IV vs. 11% of stage I-III). In GSEA analyses of Hallmark gene sets between ctDNA+ and ctDNA−, an upregulation was seen for 15/50 gene sets among ctDNA+, with p-value < 0.05 and false discovery rate < 0.25. Two of the top signatures (UV response up and Unfolded protein response) were significant also in analyses stratified by stage. Analysis of the leading-edge genes in these gene set identified several members of the vacuolar ATPase (V-ATPase) family of genes which were highly enriched in ctDNA+. The full V-ATPase gene set substantially differed between ctDNA+ and ctDNA− (mean Z-score 0.48 vs. -0.13, $p < 0.001$), including when stratified by stage (I-III: 0.46 vs. -0.28, p = 0.002; IV: 0.49 vs. 0.10, p = 0.051). Sixty percent of patients (n = 346) had relapse event data with sufficient follow up. V-ATPases had higher mean Z-scores in those with relapses than those without (0.33 vs. −0.91, p = 0.012), also seen in the ctDNA− group (0.30 vs. -0.20, p = 0.021). **Conclusions:** V-ATPase genes are differentially expressed in patients with ctDNA+ regardless of tumor stage, a result also mirrored in relapse events. V-ATPases may play a significant role in ctDNA release through regulating intracellular multivesicular bodies to exosome release, thereby providing a potential mechanistic link between tumor biology and ctDNA shedding. This finding may explain the clinical limitations of ctDNA in selected patients and provide personalization of ctDNA testing performance in the future. Research Sponsor: None.

3592 **Poster Session**

Phase II study of short-course radiotherapy (SCRT) followed by consolidation chemotherapy with FOLFOXIRI as total neoadjuvant therapy (TNT) for locally advanced rectal cancer (LARC) patients (pts): The ShorTrip study. First Author: Martina Carullo, Unit of Medical Oncology 2, Azienda Ospedaliera Universitaria Pisana and Department of Translational Research and New Technologies in Medicine and Surgery, University of Pisa, Pisa, Italy

Background: TNT is a recognised option for the treatment of LARC. The efficacy of both FOLFIRINOX followed by long-course CTRT and SCRT followed by FOLFOX or CAPOX was demonstrated in two phase III trials. No data are available regarding the feasibility and activity of SCRT followed by the triplet as TNT in LARC. **Methods:** ShorTrip is an Italian, prospective, multicentre, single-arm phase II trial (NCT05253846). Pts ≤70 years with medium-high (5-10 cm from the anal verge) LARC with at least one of the following features: cT4, cN2, involved mesorectal fascia (MRF+) or cT3N+, received SCRT followed by 8 cycles of FOLFOXIRI and surgery. The primary endpoint was the pCR rate. According to the Fleming single stage design, hypothesizing p0 = 0.25 and p1 = 0.40, setting 90% power with an α error of 0.10 (one-sided), the experimental regimen would have been considered promising if at least 21 pCRs were observed out of 63 enrolled pts. After the first 11 pts starting consolidation treatment, a higher than expected occurrence of severe neutropenia after the 1st cycle of FOLFOXIRI (N = 7, 64%) was observed and the protocol was amended to administer one cycle of FOLFOX after SCRT followed by 7 cycles of FOLFOXIRI. **Results:** From January 2022 to February 2024, 64 pts were enrolled in 9 centres with the following characteristics: median age 62 years (IQR 55-66), male 66%, ECOG PS = 0 89%, medium/high rectum 76%/24%, cT2/cT3/cT4 5%/76%/19%, cN0/cN1/cN2 2%/35%/63%, MRF+ 42%, lateral nodes 35%, EMVI+ 41%. The 52 tumors tested for MMR were pMMR. One patient withdrew consent after the 1st cycle of chemotherapy and was not evaluated for pathological response. 21 (33%) and 43 (67%) pts achieved pCR and major pathological response (MPR), respectively. Almost all pCRs (N = 20, 95%) and MPRs (N = 42, 98%) were observed in pts receiving at least 5 cycles of FOLFOXIRI (N = 56). Among 63 resected pts, 62 (98%) and 1 (2%) achieved R0 and R1 resections, respectively. All pts completed SCRT and the only grade 3/4 acute toxicity was diarrhoea in 7 (11%) pts. 49 (77%) pts received 8 cycles of consolidation treatment as planned. Irinotecan was never administered in 5 (8%) pts. Main grade 3/4 toxicity during consolidation are listed in the Table. Early post-surgical complications were reported in 8 (13%) pts. **Conclusions:** SCRT followed by one cycle of FOLFOX and 7 cycles of FOLFOXIRI showed a promising activity and a feasible safety profile and is therefore worth of further studies especially in the NOM scenario. Clinical trial information: NCT05253846. Research Sponsor: GONO Foundation.

Main G3/4 Adverse Events during consolidation CT	Overall population N=64 n (%)	Pre-amendment N=11 n (%)	Post-amendment N=53 n (%)
Any event	40 (62)	9 (82)	31 (58)
Neutropenia	33 (52)	8 (72)	25 (47)
Febrile Neutropenia	3 (5)	1 (9)	2 (4)
Anaemia	5 (8)	1 (9)	4 (8)
Diarrhoea	6 (9)	2 (18)	4 (8)
Stomatitis	5 (8)	1 (9)	4 (8)
Neurotoxicity	1 (2)	1 (9)	-
Asthenia	4 (6)	2 (18)	2 (4)

3593 **Poster Session**

Digital spatial profiling: Mapping tumor responses to radiotherapy in rectal cancer. First Author: Rachel Violet Purcell, Department of Surgery and Critical Care, Christchurch, New Zealand

Background: Variation in response to radiotherapy for the treatment of rectal cancer is likely due to heterogeneity in the tumour microenvironment. However, to date, no reliable predictive biomarkers of response are in clinical use and the mechanisms underlying response are unknown. Tertiary lymphoid structures (TLS), which are ectopic lymphoid aggregates found in the tumour microenvironment, have been linked to response to immunotherapy, but little is known about their role in radiotherapy. Here, we aimed to explore the potential of lymphocytes and tertiary lymphoid structures as predictive biomarkers of response to radiotherapy and profile the tumour immune microenvironment in the context of response to radiotherapy. **Methods:** For this study, we accessed pre-treatment biopsies from 20 rectal cancer patients with known pathological response to long-course chemoradiotherapy (LCCRT). We selected regions of interest based on immunohistological identification of tumour and lymphocytic infiltrate in formalin-fixed paraffin-embedded tissue. We performed targeted proteomic profiling of 87 immuno-oncology proteins using the Nanostring GeoMx Digital Spatial Profiler to quantify protein expression with spatial resolution within regions of interest, including TLSs, in the tumour microenvironment. **Results:** Unsupervised clustering based on normalised protein expression showed a clear separation between the complete responders to LCCRT and all other tumours, and this separation is driven by differences in T cells within TLSs (CD3+). Differentially expressed proteins within CD3+ aggregates include depletion of the natural killer cell marker, CD56 and increased expression of the apoptosis marker, cleaved caspase 9. The distribution of TLS-tumour distance was also significantly different between response groups. **Conclusions:** The study highlights the role of TLSs in modulating the immunogenic landscape of the tumour microenvironment in rectal cancer, likely influencing the response to radiotherapy. Spatially resolved proteomic analyses identifies potential biomarkers for radiotherapy response and underscores the importance of profiling tumour-immune microenvironment complexity when stratifying patients for therapy. Research Sponsor: Health Research Council of New Zealand; Maurice Wilkins Centre for Biomolecular Discovery.

3594 **Poster Session**

Clinical and immunopathological evaluation and its comparison with consensus molecular subtypes of colorectal cancer. First Author: Eduardo Feliciangeli, Hospital General Universitario Santa Lucia, Cartagena, Spain

Background: This study aims to elucidate the prognostic impact of the immunoscore within the context of consensus molecular subtypes (CMS), tumor budding (TB), and macrophage infiltration in colorectal cancer (CRC), addressing a gap in current research. **Methods:** A retrospective observational study analyzing 255 colorectal cancer cases. Demographic, histopathological, and clinical variables were examined. Molecular classification, immunoscore, and macrophage infiltration were determined via immunohistochemistry. The study adhered to ethical guidelines and received approval from our ethics committee. CMS assessment used automated staining for specific markers, with molecular subtype determined using an online classifier (Ten Hoorn et al.). Immunoscore calculation involved evaluating CD3+ and CD8+ immune cells, classifying patients into low or intermediate-high groups (Jiang et al.). Macrophage assessment focused on CD163+ cells, categorizing them as spindle-cell and round-cell. Statistical analysis employed SPSS, using descriptive statistics, chi-square tests, Kaplan-Meier survival curves, and multivariate analyses. **Results:** In this study of 255 colorectal cancer patients, predominantly with localized disease, 34.9% had stage III disease. Conventional and serrated adenocarcinomas were the main histological subtypes. CMS classification revealed mostly CMS2-3 (69.4%), with relapse occurring across all subtypes. Low immunoscore was common in conventional and serrated histology and CMS2/3, while MSI-H correlated with intermediate-high immunoscore. Tumor budding (TB) was prevalent in relapsed patients, especially in CMS2/3 and CMS4, and associated with serrated histology. Metastatic patterns varied by CMS subtype, with TB $>$ 20 foci linked to hepatic metastases. CD163 macrophage infiltration was associated with CMS1 and CMS2/3, and a high immune score. Over 9.6 years of follow-up, tumor budding was associated with overall and relapse-free survival, while CMS was linked to overall survival. Immunoscore showed no association with survival outcomes. **Conclusions:** This cohort shows heterogeneous disease progression and prognosis, with CMS2/3 exhibiting high tumor budding and relapse rates, especially in serrated histology. Molecular subtypes have distinct metastatic patterns: CMS1 to the peritoneum, CMS2/3 to the liver, and CMS4 to both. Relapsed CMS2/3 cases had low immunoscore, while CD163+ macrophage infiltration correlated with higher immune scores in CMS1 and CMS2/3, highlighting the complex interactions between molecular subtypes, immune responses, and tumor behavior. Research Sponsor: SEOM (Spanish Society of Medical Oncology); Instituto de Salud Carlos III; ICI20/00044; European Commission H2020; GA: 848098.

3595 **Poster Session**

Neoadjuvant chemotherapy and surgery for rectal cancer: Omission of radiation in clinical practice. First Author: Matthew B. Hill, Memorial Sloan Kettering Cancer Center, New York, NY

Background: PROSPECT proved efficacy of induction chemotherapy and surgery, without radiation, for select stage II and III rectal cancer patients with improvements in bowel function and less diverting ileostomy. This approach also avoids radiation-associated alteration in fertility which is particularly important in the rising early onset population. In this study we review our broader current use of induction chemotherapy without radiation in locally advanced rectal cancer patients. **Methods:** Review of a prospectively maintained IRB approved, institutional database for patients treated with induction chemotherapy and surgery between 2015-2024. Clinicopathologic features are summarized, and disease-free survival (DFS) measured with the Kaplan-Meier method. **Results:** A total of 171 patients, median age 50 years (IQR 43-61), were identified with tumors located $\leq$5cm (n = 4, 2.3%), 6-10cm (n = 75, 44%), and 11-15cm (n = 92, 54%) from the anal verge. Pre-treatment MRI staging was available for 169/171 patients. 2 (1.2%) and 167 (99%) were MRI stage II and III including 23 with T4 lesions, 15 with extra-TME lymph nodes, and 28 with EMVI. Neoadjuvant chemotherapy regimens included CAPEOX (n = 71, 42%), FOLFOX (n = 98, 57%), and FOLFIRINOX (n = 2, 1.2%). 166 (97%) underwent low anterior resection with (n = 94, 57%) or without (n = 72, 43%) diverting ileostomy, 4 (2.3%) underwent abdominoperineal resection (APR), and 1 (0.6%) underwent a Hartmann procedure. Pathologic responses included: 28 (16%) AJCC TRG 0 (no viable cancer cells); 32 (19%) TRG 1 (small cluster/single cancer cells); 77 (45%) TRG 2 (residual cancer with predominant fibrosis); and 34 (20%) TRG 3 (extensive residual cancer). Tumor deposits were present in 24 (14%) and positive/close margin was noted in 2 (1.2%). With a median follow-up of 24 months, 4 (2.3%) patients developed local recurrence (salvaged with chemotherapy, radiation, and surgery) and 18 (11%) developed distant metastases. 1-year DFS was 92% (CI: 88-97) and 2-year DFS was 87% (CI: 81-93). **Conclusions:** Since PROSPECT, induction chemotherapy and surgery is being offered to higher risk rectal cancer patients, including those with T4 lesions and EMVI, with favorable results. Continued individualized care based on response to chemotherapy and omission of radiation can limit treatment related toxicity while maintaining excellent oncologic outcome. Research Sponsor: P30 CA008748.

3596 **Poster Session**

Performance of a targeted enzymatic methylation-based early detection test by different colorectal cancer subgroups. First Author: Xiaojian Wu, The Sixth Affiliated Hospital, Sun Yat-sen University, Guangzhou, China

Background: Colorectal cancer (CRC) is the second most frequently diagnosed cancer in China and early detection could prevent over 90% of CRC-related deaths. Blood-based tests that analyze molecular features of CRC cell-free DNA (cfDNA), such as methylation and fragmentation patterns, hold great promise for early detection. However, the impact of molecular characteristics related to tumor location or mismatch repair (MMR) status on test performance has not been thoroughly investigated. In this study, we developed a blood-based CRC early detection test and analysed its performance across different CRC subgroups. **Methods:** A targeted enzymatic methyl sequencing panel was developed to identify tumor-specific hyper- and hypo-methylation markers and fragmentation profiles. A case-control cohort of 536 participants (268 CRC patients, 268 controls) was enrolled and startified into training and validation sets base on case/control status and cancer stage with 5-fold cross-validation. A gradient-boosted tree model was built by combining probabilities from methylomic and fragmentomic features. The optimal cutoff value for the early detection was determined by Youden's index, High specificity and High sensitivity methods, respectively. **Results:** The overall performance of Youden's index, High specificity and High sensitivity methods was as follows: specificity of 93.7%, 99.3%, 90.3%, and sensitivity of 96.6%, 86.2%, 97.0%, respectively. The area under the curve (AUC) value is 0.989 (95% CI: 0.981-0.996) , which is higher than those in current reports. When employing the High specificity method, the sensitivities were comparable between left and right-sided colon cancer (86.3% vs 85.7%, p = 1.0), and also similar between the dMMR (deficient mismatch repair) and pMMR (proficient mismatch repair) (87.5% vs 85.8%, p = 1.0), indicating that this model is applicable to various CRC subtypes. Additionally the TNM staging, pathological differentiation status, and the expression of Ki67, which are closely related to aggressiveness, were correlated with the sensitivity (Table). **Conclusions:** We have established CRC early detection model based on ctDNA methylation and fragmentation profiles, which shows excellent overall performance. Notably, this newly developed blood-based model shows no significant differences in sensitivity between distinct tumor locations or varying MMR statuses, suggesting its broader applicability across different types of CRC. Research Sponsor: Shanghai Xiaohe Medical Laboratory Co., Ltd.

Subgroup	Positive/Total no.	Sensitivity	p_value
Left-sided	195/226	86.3%	1
Right-sided	36/42	85.7%	
dMMR	7/8	87.5%	1
pMMR	200/233	85.8%	
Stage I	34/50	68%	< 0.001
Stage II	92/108	85.2%	
Stage III	72/76	94.7%	
Stage IV	33/34	100%	
Well differentiated	3/3	100%	0.029
Moderately differentiated	160/192	83.3%	
Poorly differentiated	41/42	97.6%	
Ki67_high	138/159	86.8%	0.147
Ki67_low	32/42	76.2%	

3597 Poster Session

ctDNA dynamics and targeted therapies associated with genetic mutations in patients with colorectal cancer. First Author: Midhun Malla, University of Alabama at Birmingham, Birmingham, AL

Background: Colorectal cancer (CRC) is a heterogeneous disease with various genetic mutations that guide targeted therapy decisions, as outlined by NCCN guidelines. Here we evaluated the proportion of CRC patients receiving targeted therapies using Natera's proprietary Real-World Database. **Methods:** Whole-exome sequencing (WES) data of tumor samples from CRC patients undergoing tumor-informed ctDNA testing CRC were analyzed. WES was performed on tumor tissue as part of the assay design workflow for Signatera™ molecular residual disease testing, ordered between June 2019 and July 2024. From the overall cohort of 47,476 CRC cases, we selected those with *BRAF* V600 (prevalence 13.7%) or *KRAS* G12C (prevalence 3.3%) actionable mutations, resulting in 8,473 patients included in the analysis. We utilized commercially available claims data to identify targeted therapy usage among clinical cases in our database. We examined the use of 3 different FDA-approved targeted therapies in patients with CRC. **Results:** Among 8,473 CRC patients with clinically actionable mutations in BRAF or KRAS, the majority had a *BRAF* V600 mutation (78.6%; N = 6,662) followed by *KRAS* G12C (21.4%; N = 1,811). Staging information was available for 93.9% (7,953/8,473) cases, with 15.6% stage IV at first ctDNA testing and 1.5% (123/7953) upstaged to stage IV at subsequent testing. An additional 6.7% (487/7,233) cases were categorized as recurrent/metastatic based on treatment information from claims records. Overall rates of treatment with corresponding targeted therapies were 4.0% (264/6,662) and 3.3% (60/1,811) for *BRAF* and *KRAS*, respectively. Within the subgroup of confirmed recurrent/metastatic cases (N = 1,727), targeted therapy rates were 18.9% (233/1241) for *BRAF* and 10.7% (52/486) for *KRAS*. No therapy overlap and no discordant cases (i.e., BRAF therapy was not given to KRAS mutated cases, and vice versa) were observed. Targeted therapy was typically started after the start of ctDNA testing (*KRAS*: in 96.7%, 58/60 cases, median 422 days after, *BRAF*: in 75.8%, 200/264 cases, median 200 days after). ctDNA clearance rate on therapy (i.e. conversion from ctDNA+ to ctDNA-) was observed to be 37.6% (56/149) which matches objective response rates previously reported for radiological assessment. **Conclusions:** In this analysis, we demonstrate the utility of the commercial claims database to provide insights into different treatment modalities considered for patients with actionable mutations. Understanding patterns of ctDNA dynamics during targeted therapy can potentially act as a surrogate of treatment efficacy and may guide future clinical trials. Research Sponsor: None.

3598 Poster Session

Oncologic outcomes of organ preservation in patients with rectal adenocarcinoma treated with total neoadjuvant therapy: A single-center study. First Author: Mariem Galuia, AdventHealth Cancer Institute, Orlando, FL

Background: Total neoadjuvant therapy (TNT) reduces the risk of local recurrence and distant metastases in patients (pts) with locally advanced rectal cancer (RC). Selected pts who achieve a complete clinical response (cCR) after TNT who can undergo a strict surveillance protocol may be considered for non operative management (NOM) to preserve rectal function. **Methods:** We conducted an observational, retrospective, single-center study to evaluate watch-and-wait strategy in those achieved organ preservation & survival in pts with locally advanced or resectable metastatic pMMR RC treated with TNT. Pts received either induction chemotherapy followed by chemoradiation (INCT-CRT) or chemoradiation followed by consolidation chemotherapy (CRT-CNCT). INCT and CNCT consisted of 6-8 cycles of FOLFOX or 5 cycles of CAPEOX. CRT consisted of a total dose of 5,040-5,750 CGy to the tumor and lymph nodes along with capecitabine. Pts were assessed for treatment response with digital rectal exam, MRI, flexsig 8 weeks after TNT. Pts who achieved cCR or a near-cCR were offered NOM with WW. Close surveillance with the above-mentioned modalities was repeated every 3 months, CT chest/abdomen or PET scan was performed every 6 months. Data on local recurrence, distant metastases and survival was collected. **Results:** From Dec 2017 to Jan 2024, a total of 109 pts with RC went on WW after TNT in our center. Most pts were males (66%). Median age was 59 (30-88). The proportions of stages I to IV were 2.7%, 19.2%, %, 76.1%, and 3.6% respectively. After a median follow-up of 20.2 months, median time of sustained cCR was 67 weeks, tumor regrowth occurred in 7/109 (6.4%) pts. 3/109 pts developed distant metastases (8.5%). Median time from cCR to local regrowth/metastasis was 42 weeks. Recurrence was detected within the first 2 years in all 7 patients. 3/7 patients are in remission after salvage surgery, 2/7 pts were scheduled for surgery, 1/7 pts died of disease progression and another pt was a poor surgical candidate. 93% (102/109) of our pts are with no evidence of disease. **Conclusions:** Organ preservation for locally advanced rectal cancer is feasible and successful in a large community-based hospital system for selected pts who achieve cCR to TNT. WW is a reasonable and attractive strategy for both patients and oncologists that minimizes post-operative morbidity . Ongoing trials like JANUS aim at increasing cCR rate. Research Sponsor: None.

Demographic and clinical characteristics of the pt cohort.

Variables	All pts (n=109)
Age, median (years)	59.0 (30-88)
Gender	
Male	73 (66%)
Female	36 (34%)
Ethnicity	
Caucasian	78 (71.5%)
Hispanic	23 (21.1%)
Other	8 (7.3%)
Clinical stage at diagnosis	
I	3 (2.7%)
II	21 (19.2%)
III	83 (76.1%)
IV	2 (1.8%)
TNT Strategy	
NCT-CRT	45 (41.2%)
CRT-CNCT	64 (58.8%)
CT regimen	
FOLFOX	91 (84.4%)
CAPEOX	14 (12.8%)
Other	3 (2.7%)
Months of follow-up, median	20.2
Tumor Grade	
1	7 (6.4%)
2	53 (48.6%)
3	2 (1.8%)
Unknown	47 (43.11%)

3599 Poster Session

Neoadjuvant mFOLFOXIRI chemotherapy with or without cadonilimab versus mFOLFOX6 alone in locally advanced colorectal cancer: A randomized phase II study (OPTICAL2). First Author: Jianwei Zhang, Department of Medical Oncology, the Sixth Affiliated Hospital of Sun Yat-sen University, Guangzhou, China

Background: The current standard treatment for locally advanced rectal cancer is chemoradiotherapy (CRT) followed by total mesorectal excision (TME) . For locally advanced colon cancer, neoadjuvant FOLFOX is also an option. In the era of immunotherapy, several studies have explored the efficacy of CRT combined with immunotherapy treatment. However, no studies have yet investigated the efficacy and safety of chemotherapy combined with immunotherapy in locally advanced colorectal cancer. We aim to explore the efficacy of mFOLFOXIRI with or without cadonilimab (AK104) compared to mFOLFOX6 neoadjuvant chemotherapy in locally advanced colorectal cancer (LACRC). **Methods:** OPTICAL-2 was a randomized, phase II trial in patients with II/III rectal ancer and locally advanced colon cancer (T3 $\geq$5 mm or T4). Patients were randomly assigned (1:1:1) to 3 groups: preoperative mFOLFOXIRI plus AK104 for 6 cycles or mFOLFOXIRI for 6 cycles, or mFOLFOX6 alone for 6 cycles, followed by TME and adjuvant chemotherapy. The primary endpoint was pCR rate in mITT population, and the secondary endpoint was major pathological response (MPR) rate, 3-year disease-free survival, overall survival and safety. **Results:** From July 2023 to August 2024, 123 patients with LACRC were enrolled, with 41 patients in each group, including 22 colon cancer and 101 rectal cancer. As the data cutoff, 121 patients had underwent surgery (41 in mFOLFOXIRI plus AK104, 39 in mFOLFOXIRI group and 41 in mFOLFOX6 group). Preoperative radiotherapy was added after induction treatment in 5 (12.2%), 4 (9.7%) and 3 (7.3%) patients among the 3 groups. In the mITT analysis, the pCR rate was 26.8% vs. 15.4% vs. 9.8% among the 3 groups, respectively. The downstaging (ypStage 0 to 1) was 65.9%, 46.2% and 41.5%, respectively. The MPR rate was 68.3%, 48.7% and 43.9%, respectively. While in the PP analysis (completed 6 cycles of preoperative treatment), the pCR rates were 30.6%, 17.1%, and 10.8%, respectively. The downstaging was 63.8%, 45.7% and 37.8%, respectively. Safety assessments was generally well-tolerated. **Conclusions:** mFOLFOXIRI with AK104 demonstrated a higher pCR rate, downstaging rate and MPR rtae compared with FOLFOX chemotherapy in patients with LACRC. This study suggests that the combination of Intensified chemotherapy and dual immunotherapy may be a promising approach for improving treatment outcomes. Clinical trial information: NCT05571644. Research Sponsor: None.

Pathologic outcome and surgical parameters.

Characteristics	mFOLFOXIRI+AK104 (A)	mFOLFOXIRI (B)	mFOLFOX6 (C)	P1 (A vs. C)
mITT analysis	n=41	n=39	n=41	
pCR	11 (26.83%)	6 (15.38%)	4(9.76%)	0.046
ypStage 0-I	27 (65.9%)	18 (46.2%)	17 (41.5%)	0.026
MPR	28 (68.3%)	19 (48.7%)	18 (43.9%)	0.026
PP analysis	n=36	n=35	n=37	
pCR	11 (30.6%)	6 (17.1%)	4 (10.8%)	0.036
ypStage 0-I	23 (63.8%)	16 (45.7%)	14 (37.8%)	0.026

Footnote: pCR, pathological complete response; MPR, major pathological response.

3600 Poster Session

Impact of perioperative complications on ctDNA-based MRD detection and prognosis: Insights from the GALAXY study. First Author: Eiji Oki, Department of Surgery and Science, Graduate School of Medical Sciences, Kyushu University Hospital, Fukuoka, Japan

Background: The GALAXY study (UMIN000039205) demonstrated the utility of circulating tumor DNA (ctDNA)testing to detect molecular residual disease (MRD) and monitor postoperative recurrence. This analysis evaluates the influence of perioperative complications and the timing of blood sampling on MRD detection rates and predicting clinical outcomes. **Methods:** From the 6,032 patients enrolled in GALAXY, 2,400 were available for this analysis after excluding those enrolled in randomized trials or with insufficient follow-up. A clinically validated, tumor-informed ctDNA assay (Signatera, Natera, Inc.) was utilized to prospectively detect and quantify ctDNA. MRD was assessed within a defined postoperative "MRD window" of 2-10 weeks post-surgery. Perioperative complications were classified as Grade 2 or higher according to the Clavien-Dindo classification. **Results:** Perioperative complications occurred in 302 cases (12.6%), with anastomotic leakage (2.4%), ileus (2.0%), and intra-abdominal abscesses (1.3%) being the most common. Complications were more frequent in males and patients with rectal cancer. Cell-free DNA (cfDNA) concentrations measured at 2–4 weeks post-surgery were significantly higher in cases with complications compared to those without complications (9.2 vs. 6.9 ng/mL; $p < 0.001$). Three-year recurrence-free survival (RFS) was significantly worse in MRD-negative cases with complications (80.7%) compared to those without complications (87.0%; HR 1.63; 95% CI 1.143–2.323; p = 0.007). In MRD-positive cases, 3-year RFS was 15.6% in patients with complications versus 19.9% in those without (HR 1.16; 95% CI 0.831–1.608; p = 0.389). Among patients with complications, ctDNA testing conducted at 2–4 weeks post-surgery versus 4–10 weeks showed marked differences in 3-year RFS based on landmark analysis at 10 weeks. For MRD-negative cases, 3-year RFS was 75.32% versus 90.71% (HR 2.875; 95% CI 1.252–6.605; p = 0.013). In MRD-positive cases, 3-year RFS was 27.7% versus 6.25% (HR 0.46; 95% CI 0.230-0.929; p = 0.030). This trend was similar even when colon and rectal cancer were analyzed separately. In contrast, no timing-related differences were observed in cases without complications. **Conclusions:** Perioperative complications may elevate cfDNA levels, potentially confounding MRD assessment. Our findings suggest delaying ctDNA testing to at least 4 weeks postoperatively in patients experiencing Clavien-Dindo Grade $\geq$2 complications. These results provide essential guidance for optimizing clinical trial designs involving MRD evaluation through ctDNA analysis. Clinical trial information: UMIN000039205. Research Sponsor: AMED.

3601 **Poster Session**

Long-term survival and treatment efficacy in dMMR/MSI-H rectal cancer: A real-world cohort from seven large medical college–affiliated hospitals. First Author: Siyuan Mi, Sun Yat-sen University Cancer Center, Guangzhou, China

Background: Neoadjuvant immunotherapy provides considerable advantages for patients with dMMR/MSI-H rectal cancer. However, treatment strategies in real-world settings vary depending on tumor characteristics, economic conditions, and the choices made by physicians and patients. **Methods:** We screened more than 10,000 rectal cancer cases from seven large medical college-affiliated hospitals. We used the Kaplan-Meier curve to compare survival and progression, applied Cox regression to analyze impact factors, and examined tumor regression grades with chi-square analysis. **Results:** From March 2010 to April 2024, 502 patients were enrolled and diagnosed with dMMR/MSI-H rectal adenocarcinoma through immunohistochemistry or PCR. 100 patients underwent neoadjuvant immunotherapy, demonstrating a 96.34% 5-year overall survival (95% CI: 86.08-99.08%), and 90.74% 5-year disease-free survival (95% CI: 74.67-96.82%). This indicated a 16.50% enhancement in overall survival ($p = 0.042$) and a 16.87% increase in disease-free survival ($p = 0.002$) compared to conventional chemoradiotherapy (5-year OS: 79.84%, 95% CI: 71.69-85.87%; 5-year DFS: 73.87%, 95% CI: 65.15-80.73%). Neoadjuvant immunotherapy demonstrated significant superiority in tumor regression ($p < 0.0001$), however, the combination with chemotherapy did not enhance the effect ($p = 0.622$), and varying chemotherapeutic agents did not improve tumor regression in conventional chemoradiotherapy either. Additionally, elevated serum CEA levels were associated with an increased risk of both death and disease progression. Patients with advanced age, lower clinical stages, and fewer risk factors were more likely to undergo direct surgical resection. **Conclusions:** Neoadjuvant immunotherapy is advantageous for dMMR/MSI-H rectal cancer patients, as it leads to better tumor regression and enhanced disease control. Research Sponsor: None.

3602 **Poster Session**

Phase 1b study to assess the safety of neoadjuvant trifluridine/tipiracil with concurrent radiation in resectable stage II/III rectal cancer: Initial results of the FIERCE study. First Author: Emerson Yu-sheng Chen, Oregon Health & Science University, Portland, OR

Background: Total neoadjuvant therapy (TNT) with chemo-radiation (CRT) followed by doublet chemotherapy for rectal cancer can yield clinical complete response (CR) to allow successful surgery or organ-sparing. Trifluridine exhibited cytotoxic effect of ionizing radiation superior to fluorouracil in colonogenic survival assay (dose modification factor: 2.7). The FIERCE trial (NCT04104139) sought to determine the maximum tolerated dose (MTD) of trifluridine/tipiracil (FTD-TPI) with concurrent CRT during TNT with future goals of improving CR. **Methods:** MRI-staged participants (pts) with stage II (T3-4N0M0) or stage III (TxN+M0) resectable rectal adenocarcinoma, underwent CRT with FTD-TPI for 6 weeks followed by either FOLFOX or CAPOX for 4 months. Cohorts of 3 pts were examined at three dose levels (DLs) until a total of 18 pts were reached per Bayesian Optimal Interval design. FTD-TPI was taken orally BID for five days/week on weeks 1, 3, and 5 at the assigned dose (DL1 = 25mg/m2; DL2 = 30 mg/m2; DL3 = 35 mg/m2) with concurrent pelvic radiation of 25-28 fractions. Dose limiting toxicity (DLT) was defined by sustained hematologic, gastrointestinal, and serious adverse events related to FTD-TPI. Primary endpoint was the proportion of DLT from CRT at MTD. **Results:** Among 22 screened patients (3 ineligible and 1 removed for non-compliance in week 1), 18 pts were evaluable. Median age was 52 years (range 37-73), female sex was 4 (22%), and 16 (89%) were ECOG 0. All pts had proficient mismatch repair. All 18 pts were staged as cT3, with 8 (44%) N0 (stage II), 7 (39%) N1, and 3 (17%) N2. All 18 pts completed CRT in their assigned DL (6 DL1, 3 DL2, 9 DL3) followed by chemotherapy (16 FOLFOX; 2 CAPOX) with the 18th pt scheduled to finish treatment in February 2025. One pt was switched to irinotecan due to intolerable oxaliplatin-related neuropathy. During CRT, grade 3 neutropenia without fevers (4/18, 22%) led to 1/6 DLT in DL1 and 1/9 DLT in DL3, which were mitigated by dose interruptions (2/18 missed last week of FTD-TPI). No grade 4 adverse events were observed during CRT. At data cutoff, 10 (56%) pts entered into watch-and-wait surveillance, 6 (33%) pts had surgery, and 2 (11%) pts await final assessment. **Conclusions:** FTD-TPI at DL3, the MTD of 35 mg/m2 on days 1-5, 15-19, and 29-33, is the recommended phase 2 dose for CRT in TNT for locally-advanced rectal cancer. Short-course filgrastim, or day 29-33 adjustment to DL2, may be needed in last 2 weeks of CRT to prevent dose interruptions. A dose expansion study is being explored as the next step. Clinical trial information: NCT04104139. Research Sponsor: Taiho Oncology; OHSU Knight Cancer Institute.

3603 **Poster Session**

Enhancing colorectal cancer precision medicine through multi-omics and clinical data integration with artificial intelligence. First Author: Enrique Velazquez Villarreal, City of Hope National Medical Center, Duarte, CA

Background: The integration of multi-omics and clinical data in precision medicine research for colorectal cancer (CRC) is a complex task that requires advanced computational tools. Artificial Intelligence agent for High-Optimization and Precision mEdicine (AI-HOPE) has emerged as a transformative platform, streamlining data integration, analysis, and discovery efforts. AI-HOPE is designed to integrate and analyze multi-omics alongside clinical data, facilitating novel insights into CRC pathogenesis, therapeutic responses, and precision medicine applications. **Methods:** AI-HOPE leverages Large Language Models (LLMs) to interpret natural language inputs and convert them into executable pipelines for multi-omics and clinical data analysis. Data from The Cancer Genome Atlas (TCGA) and other publicly available CRC datasets were utilized to demonstrate its capabilities. AI-HOPE supports analyses such as identifying mutation and gene expression patterns, pathway enrichment, survival analysis, and therapeutic outcome predictions. Three case studies were conducted: (1) identifying WNT and TGFβ pathway alterations in early-onset CRC (EO CRC) versus late-onset CRC, (2) evaluating the association between specific multi-omics signatures and progression-free survival in patients treated with FOLFOX chemotherapy, and (3) performing a precision medicine query to identify actionable gene mutations and tailored medications for CRC treatment. **Results:** Overall AI-HOPE answered queries with an accuracy of 0.98 and an F1 score of 0.89 (precision = 0.80). AI-HOPE identified significant alterations in the WNT and TGFβ pathways among EO CRC patients compared to late-onset cases, aligning with findings from published literature. In the second study, the platform revealed that patients with specific transcriptomic signatures (e.g., upregulation of MYC targets) had significantly worse progression-free survival when treated with FOLFOX chemotherapy, further supporting its utility in identifying clinically relevant biomarkers. AI-HOPE was used to query CRC datasets for actionable gene mutations, such as KRAS, BRAF, and MSI-H (microsatellite instability-high), and cross-referenced these findings with drug databases to identify tailored therapies. The analysis highlighted FDA-approved targeted treatments, such as EGFR inhibitors (cetuximab and panitumumab) for KRAS wild-type patients and immune checkpoint inhibitors (pembrolizumab and nivolumab) for MSI-H tumors. AI-HOPE also identified emerging therapeutic options from ongoing clinical trials, showcasing its potential for guiding precision medicine strategies in CRC. **Conclusions:** This study demonstrates the transformative potential of AI-HOPE in advancing CRC precision medicine research by seamlessly integrating multi-omics and clinical data. Research Sponsor: National Cancer Institute; National Cancer Institute; National Cancer Institute.

3604 **Poster Session**

Complementary value of a digital pathology biomarker to post-surgery circulating tumor DNA in risk stratification of stage III colon cancer patients receiving adjuvant chemotherapy. First Author: Ingrid Franken, Department of Medical Oncology, University Medical Center Utrecht, Utrecht University, Utrecht, Netherlands

Background: The current standard of care for patients with stage III colon cancer (CC) is resection followed by adjuvant chemotherapy (ACT). About half of patients are cured by surgery and hence overtreated with ACT, whereas ~30% experience recurrence despite ACT. Several studies show that patients with no detectable circulating tumor DNA (ctDNA) after surgery are at a lower risk of recurrence (RR), although false negative ctDNA results remain a concern. Other studies show prognostic value of digital pathology biomarkers on resected CC tissue, like the Combined Analysis of Pathologists and Artificial Intelligence (CAPAI; Kleppe Lancet Oncol 2022). This study aimed to explore the potential added value of CAPAI to post-surgery ctDNA in risk stratification of patients with stage III CC receiving ACT. **Methods:** Patients were selected from the Prospective Dutch ColoRectal Cancer (PLCRC) cohort substudy PROVENC3 (Rubio-Alarcon AACR 2024), based on stage III CC treated with radical resection and adjuvant capecitabine or CAPOX. Post-surgery ctDNA status was determined using Labcorp Plasma Detect. From the resected tumor, a representative H&E slide was digitalized to generate a DoMore-v1-CE-CRC score, which was combined with the pT and pN stage and number of assessed lymph nodes for classification as CAPAI high-, intermediate- or low-risk. Three-year RR and Cox proportional hazard ratios (HR) were reported for ctDNA-based and CAPAI-based risk groups. Time to recurrence was compared between risk groups using the log-rank test. **Results:** Post-surgery ctDNA status and CAPAI risk classification were available for 163 patients. The 20 patients (12%) with detectable ctDNA had a higher recurrence risk (3-year RR 60% [32-77], HR 4.9 [2.5-9.6], $p < 0.001$) than patients with no detectable ctDNA (N = 143, 3-year RR 18% [11-25]). Within the subgroup with no detectable post-surgery ctDNA, 50 patients (35%) were classified as CAPAI high-risk. These CAPAI high-risk patients had a higher recurrence risk (3-year RR 35% [20-48], HR 4.2 [2.0-9.1], $p < 0.001$) than patients classified as CAPAI low/intermediate-risk, who were combined based on their observed similar RR (N = 93, 3-year RR 9% [3-15%]). **Conclusions:** In patients with stage III colon cancer treated with adjuvant CAP(OX), CAPAI risk classification has potential to further stratify RR in the subgroup with no detectable post-surgery ctDNA. These preliminary results suggest that CAPAI high-risk may help identify patients with false negative post-surgery ctDNA results. Over half of all patients had both no detectable ctDNA and were CAPAI low/intermediate-risk. Given their low RR in our preliminary results, future studies on larger patient cohorts should focus on the ability to combine biomarkers to select very low-risk patients and evaluate whether these patients can potentially be spared ACT. Research Sponsor: None.

3605 Poster Session

A novel active chromatin cell-free DNA (cfDNAac) assay for early detection of colorectal cancer. First Author: Yue Wendy Zhang, Aqtual, Hayward, CA

Background: Colorectal cancer (CRC) is the third most common cancer and the second leading cause of cancer-related deaths globally (Xi et al. 2021). In the U.S., it is estimated that 152,810 new cases and 53,010 deaths will occur in 2024, with an increasing incidence among younger adults (ACS, 2024). CRC is a multifactorial disease influenced by both genetic and environmental factors and typically progresses from normal epithelial tissue to adenocarcinoma through a well-established sequence of molecular events. Despite advancements in treatment, early detection remains a key driver of improved survival outcomes. While current screening methods— such as fecal immunochemical testing, fecal DNA testing, and colonoscopy— have reduced CRC mortality and morbidity, low compliance continues to be a significant challenge. In this study, we developed a proof-of-concept machine learning (ML) classifier leveraging active chromatin cell-free DNA ($cfDNA_{ac}$) signals in peripheral blood to differentiate CRC patients from healthy individuals. **Methods:** Plasma samples from treatment-naive colorectal cancer (CRC) patients (stages I–IV, n = 54), advanced adenoma patients (n = 14), and healthy volunteers (n = 40) were processed using Aqtual's proprietary active chromatin capture workflow to enrich regulatory-active chromatin cfDNA. Samples were split into a training set, which included 31 early-stage CRC samples (stage I: n = 13, stage II: n = 13, stage III: n = 5) and 19 healthy samples, and a hold-out set, comprised 37 disease samples (stage I/II: n = 6, stage III: n = 6, stage IV: n = 11, advanced adenoma: n = 14) and 21 healthy samples. A machine learning classifier was trained using 5-fold cross-validation with 5 repeats on the training set, and the performance was assessed on the hold-out set to ensure robustness and generalizability. **Results:** A machine learning classifier trained on genome-wide $cfDNA_{ac}$ signals demonstrated robust performance, achieving a mean AUC of 0.94 (95% CI: 0.92 - 0.96). It exhibited 93% sensitivity (95% CI: 84% -100%) for colorectal cancer detection (Stage I/II: 94%, Stage III: 95%, Stage IV: 91%) and 81% sensitivity (95% CI: 67% - 95%) for advanced adenoma, with a specificity of 90% in the hold-out set. Analysis of the top contributing $cfDNA_{ac}$ signals identified 852 promoter and 2,594 exon features derived from 2,678 unique genes. Gene-set enrichment analysis revealed significant associations with key cancer hallmarks, including KRAS signaling and epithelial-mesenchymal transition (EMT). **Conclusions:** This study highlights the potential of Aqtual's active chromatin capture assay to identify molecular features in plasma that differentiate CRC and advanced adenoma from healthy individuals. The ML classifier based on these signatures shows promise for future development as a non-invasive tool for early colorectal cancer and advanced adenoma detection and monitoring. Research Sponsor: None.

3606 Poster Session

Analysis of early onset colorectal cancer: Implications for research and clinical practice. First Author: Heather Halperin, University of Calgary, Calgary, AB, Canada

Background: Young onset colorectal cancer(YOCRC), diagnosed $<$ 50 years old, presents distinct challenges, including life transitions, and psychosocial needs. In Alberta, Canada an Adolescent and Young Adult(AYA) program was introduced at our tertiary cancer centres to address these unique needs through tailored resources and services. This study aimed to explore the YOCRC patients' adjuvant care experiences and describe resource utilization prior to and after the AYA program was established. **Methods:** A retrospective review of YOCRC patients diagnosed with StageIII disease from 2012-2022 and referred to Cancer Care Alberta for adjuvant therapy was performed. This study evaluated the adjuvant care experiences of YOCRC patients, focusing on demographics, tumor characteristics, toxicity, and psychosocial visits. Incidence rates over time was assessed using Joinpoint regression. The Edmonton Symptom Assessment System(ESAS) scores collected during treatment visits were used to characterize symptomatic concerns. Analysis included descriptive statistics and multivariate regression analysis. **Results:** Among 576 patients, the mean age at diagnosis was 42.9 years. There was a positive trend in incidence of diagnoses per year($p < 0.0001$), with an increase in diagnosis of 3.96%(CI 1.30-7.13) per year in patients aged 40-49. Patients with stages IIIB disease were older at time of diagnosis compared to stage IIIC($p = 0.025$). Higher stages had poorer outcomes with stage IIIA, IIIB and IIIC($p < 0.001$), however median survival was not reached for any stages due to a low death rate. Patients reported psychological related symptoms(well-being, sleep problems and tiredness) more commonly than physical symptoms. Psychosocial visits increased after AYA program initiation with annual rates rising from 7.8 visits/year(pre-AYA program implementation) to 24 visits/year(post-AYA implementation). Further, patients who attended psychosocial visits were more likely to be younger($p < 0.001$) and had higher overall mortality($p < 0.001$). Of patients with an ESAS of $\geq$4, patients who were 40-49 were more likely to attend psychosocial service appointments than those aged 20-39, odds ratio of 3.23(95% CI: 1.28-8.78). There was no difference comparing patients attending psychosocial visits or higher ESAS score with sex or stage. **Conclusions:** Stage III YOCRC patients are increasing in Alberta. An AYA program can improve resource utilization, psychosocial support, and enhance visit frequency for this population with unique needs. Greater prominence of psychological symptoms on ESAS highlight areas that could benefit from focused resources for this population. Research Sponsor: None.

Demographics of stage III YOCRC patients.

Demographics		n=576
Sex		
	Male	320
	Female	256
Site		
	Colon	291
	Rectum	245
	Rectosigmoid	40
Stage (AJCC 7)		
	IIIA	52
	IIIB	348
	IIIC	171
	IIINOS	3
Incidence		
	Year	
	2012	46
	2013	40
	2014	41
	2015	55
	2016	43
	2017	50
	2018	50
	2019	61
	2020	52
	2021	64
	2022	74

3607 Poster Session

Changes in demographics and patterns of colon cancer in the United States: A comprehensive SEER analysis 2010–2021. First Author: Guy Loic Nguefang Tchoukeu, Texas Tech University Health Science Center, Odessa, TX

Background: Over the past two decades, colon cancer has remained a leading cause of cancer-related morbidity and mortality in the United States. Changes in population dynamics, environment, and lifestyle have contributed to shifts in age, gender, tumor site, and stage at diagnosis. However, the extent of these changes over time remains underexplored. Understanding these temporal changes is crucial for improving screening strategies, identifying at-risk populations, and optimizing resource allocation. **Methods:** We conducted a cohort study of initial colon cancer diagnoses using the National Cancer Institute, Surveillance Epidemiology and End Results Program (SEER) over the period 2010 through 2021. The SEER data is comprised of 22 different registries across the United States (US), which captures approximately 47.9% of the US population. The exposure was the year of diagnosis, and the outcomes were the distributions of age, sex, site, and stage at initial diagnosis. Temporal trends in proportions were measured using Spearman correlation (ρ). The differences between distributions in 2010 vs. 2021 were measured using Fisher's test with the standardized mean difference (SMD) as effect size. 95% confidence intervals (95% CI) for proportions were determined using the normal approximation. **Results:** A total of 670,923 records were included in the study. The distribution of ages at initial diagnosis changed significantly over the study period (SMD = 0.1713, p-value $<$ 0.0001). In 2010, the mode of age group distribution was $\geq$ 85 years, 12.1% (11.8%–12.4%). The proportion aged $\geq$ 85 trended down over the period (ρ = -0.9930, p value $<$ 0.0001) from 12.1% (11.8%–12.4%) to 9.6% (9.3%–9.8%). In 2021 the mode of age group distribution at diagnosis was 65 to 69 years, 13.2% (12.9% - 13.5%). The proportion of males trended up over the period (ρ = +0.9021, p value $<$ 0.0001), increasing from 51.8% (51.4% - 52.2%) to 53.2% (52.8% - 53.6%). The difference in cancer stage was significant (SMD = 0.1818, p value $<$ 0.0001), with localized colon cancer decreasing (ρ = -0.9371, p value $<$ 0.0001) from 38.9% (38.5% - 39.3%) to 33.8% (33.4% - 34.1%) and distant colon cancer increasing (ρ = +0.9301, p value $<$ 0.0001) from 20.1% (19.8% - 20.5%) to 22.9% (22.5% - 23.2%). The difference in location was significant (SMD = 0.1185, p value $<$ 0.0001), with rectum as location trending up (ρ = +0.9330, p value $<$ 0.0001) from 21.7% (21.3% to 22.0%) to 24.6% (24.3% to 25.0%). **Conclusions:** The current findings suggest a significant shift in colon cancer presentation in the United States over the past decade. There is a significant increase in incidence among younger males, a trend towards more distant-stage cancers indicating delay in detection, and a growing prevalence of rectal cancers as the primary site. Changes in screening strategies and reinforcement of community awareness are necessary to improve the mortality rate. Research Sponsor: None.

3608 Poster Session

Time-weighted ctDNA dynamics for precision monitoring of relapse risk in colon cancer. First Author: Alessandro Leal, Perlmutter Cancer Center, NYU Langone Health, New York, NY

Background: Effective monitoring for relapse is a critical component of post-surgical care in colorectal cancer (CRC), particularly for patients who remain at risk of recurrence despite curative-intent treatment. Circulating tumor DNA (ctDNA) is a powerful biomarker for detecting minimal residual disease (MRD) and predicting relapse with high sensitivity and specificity. However, its predictive value varies over time, with negative results closer to surgery being less reliable than results obtained later. Here we introduce a novel time-weighted approach to ctDNA monitoring using a tumor-informed assay (Signatera), assigning greater predictive power to negative results collected further from surgery. **Methods:** A Bayesian logistic regression model using 1,246 Signatera serial measurements was developed to predict recurrence risk across 167 patients with early-stage colon cancer, with time-weighted ctDNA dynamics as the primary predictive feature. Negative ctDNA values were assigned greater predictive power based on their temporal distance from surgery. Secondary covariates included clinical stage and adjuvant treatment status. Time-weighted ctDNA was calculated as the product of the ctDNA level at each timepoint and an inverse time factor ($1/(t+1)$), where t represents the weeks since surgery. The weighted values were aggregated for each patient to compute cumulative and average time-weighted ctDNA levels, which served as inputs to the model. Survival analysis was performed to evaluate recurrence-free survival (RFS), stratified by MRD status. **Results:** Tumor-informed ctDNA levels were measured longitudinally, with a median of 7 timepoints per patient (range, 2-16) collected over a median follow-up of 2.5 years. Stage distribution was 50% stage III (n = 83), 44% stage II (n = 74), and 6% stage I (n = 10). Mismatch repair deficiency was observed in 22 patients (13.2%). Adjuvant chemotherapy was administered in 102 patients (61.1%), and 16 patients (9.6%) experienced recurrence. Survival analysis revealed a significantly worse recurrence-free survival for MRD-positive patients compared to MRD-negative patients (HR = 4.2, 95%CI:2.8–6.4, Log-rank $p <$ 0.0001). The Bayesian logistic regression model demonstrated robust predictive performance, with a posterior probability of recurrence $<$ 5% for patients with three consecutive negative ctDNA results obtained $>$ 6 months after surgery. Conversely, the model assigned a $>$ 90% probability of recurrence for patients with persistent ctDNA positivity beyond the initial 3-month post-operative window. **Conclusions:** Time-weighted ctDNA dynamics demonstrated promising predictive capability for CRC recurrence. Our findings suggest that incorporating the temporal context of ctDNA measurements and leveraging the increasing reliability of negative results over time could refine risk stratification and improve personalized care strategies for CRC patients. Research Sponsor: None.

3609 **Poster Session**

Exploring transcriptomic regulation of the tissue-associated microbiome in oncogenic progression of colorectal cancer. First Author: Amanda Stafford, BioCorteX Inc., New York, NY

Background: The association between the tissue microbiome and colorectal cancer (CRC) etiology continues to be explored, and it has been proposed that certain bacteria drive oncogenesis. However, this field is hindered by a lack of mechanistic links. Considering the relationship between bacterial abundance and human gene expression allows us to traverse this functional gap. To date, work in this field has been largely restricted to considering the relationship between bacteria and Consensus Molecular Subtypes (CMS) of CRC. Here, we hypothesise that CRC-associated bacteria correlate with distinct expression profiles that drive CRC progression. **Methods:** Analysis was performed using BioCorteX's knowledge graph and proprietary engines, v20250128_100953. 16S rRNA sequencing and whole RNA data were collated from tissue samples across 3 independent cohorts from CRC patients (n = 59) and healthy volunteers (n = 23). In CRC patients, paired tumour and normal adjacent samples were analysed yielding 108 samples in total. The Pearson correlation between differentially abundant (DA) OTUs and differentially expressed (DE) genes was calculated, and false discovery rates (FDR) were applied. **Results:** 14,460 DE genes (FDR $<$ 0.05) were identified between tumour and normal adjacent tissues, 5,097 of which had an absolute log-fold change greater than 1. Seven OTUs were increased in CRC compared to normal adjacent (FDR $<$ 0.05) and were present in at least 20% of samples; Fusobacterium nucleatum, Akkermansia muciniphila, and five Streptococcus species. Of the 61,164 OTU-gene pairs analysed, 108 were significant (FRD $<$ 0.05) with a Pearson correlation greater than 0.5. The abundance of all five Streptococcus species was correlated with the expression of nine genes including: SPSB4 (r= 0.51, p = 1.86x10-8), which has previously been associated with CRC metastasis, and REN (r= 0.71, p = 1.21x10-17), which is associated with increased Wnt signaling. Moreover, the expression of LY6G6D, a recently discovered CRC-specific antigen, was positively associated with F. nucleatum abundance (r= 0.53, p = 4.94x10-9). **Conclusions:** This study identifies novel interactions between the CRC-associated microbiome and expression profiles. The consistent relationships between five Streptococcus species and specific genes is highly indicative of a functional co-evolution between host transcriptomics and microbiome, and implies relationships have less to do with the specific bacteria and are more related to function. This analysis adds a mechanistic explanation for some of the associations previously identified between the microbiome and CRC. Further analysis is required to identify if the host transcriptome creates a niche for these species or whether the presence of these species is altering the microbiome. This study demonstrates the value of integrated multi-omic analysis in understanding CRC pathogenesis. Research Sponsor: BioCorteX Inc.

3610 **Poster Session**

Postoperative cfDNA levels and ctDNA detection rates in patients with stage II colon cancer screened for CIRCULATE (AIO-KRK-0217, ABCSG). First Author: Sebastian Stasik, Technical University Dresden, Dresden, Germany

Background: Postoperative circulating tumor DNA (ctDNA) has emerged as a prognostic biomarker for disease recurrence in patients (pts) with resected colorectal cancer (CRC) and may potentially guide adjuvant treatment decisions. The timing of ctDNA screening is critical, as postop. plasma cell-free DNA (cfDNA) levels may vary due to factors such as tissue disruption from the surgical resection. The CIRCULATE trial (NCT04089631) investigates ctDNA guided adjuvant therapy in stage II CRC pts in $>$ 140 centres in Germany and Austria. **Methods:** To investigate the impact of blood sampling time points on cfDNA concentrations and the ctDNA positivity rates, we analyzed the postop. plasma samples of 1439 pts with stage II CRC screened for CIRCULATE between 2020 and 2024. Blood samples were collected within 5-60 days post tumor resection in stabilizing tubes (Streck or PaxGene). Samples were analyzed for postop. cfDNA concentration and tumor-informed ctDNA in plasma samples by an error-reduced Next-Generation Sequencing (NGS) approach [Stasik S Front Genet. 2022]. **Results:** Plasma cfDNA concentrations (measured by qPCR for beta-globin gene) ranged from 0.02 to 20.32 ng/μL (mean: 0.689 ng/μL; median: 0.360 ng/μL). The highest cfDNA levels were observed within 2 weeks after surgery (mean: 1.079 ng/μL; median: 0.540 ng/μL), with a significant decrease in samples collected $>$ 3 weeks postop. (mean: 0.631 ng/μL; median: 0.355 ng/μL; $p<$ 0.0001), suggesting an impact of surgical trauma and subsequent cfDNA release from normal tissue. In ctDNA-neg. pts, cfDNA concentrations stabilized between 0.405 and 0.449 ng/μL during weeks 4-8. In contrast, ctDNA-pos. pts had significantly elevated cfDNA levels at 2 months post-surgery (mean: 0.972 ng/μL; p= 0.419), indicating ongoing tumor-specific DNA shedding associated with recurrent disease. Variant allele frequencies (VAFs) in ctDNA-pos samples were negatively correlated with cfDNA concentrations, particularly in early postop. samples (Spearman r = -0.508), suggesting a dilution effect of ctDNA post-surgery. This correlation diminished at later time points, supporting the potential advantage of later sampling to improve ctDNA sensitivity. Despite temporal variations in cfDNA concentrations, ctDNA positivity was consistent across all sampling intervals (i.e. week 1: 4.1%; week 6-8: 5.64%), demonstrating the assay's robust sensitivity. **Conclusions:** We observed a significant variation in cfDNA levels depending on the timing of postop. sampling. Different kinetics, such as cfDNA release from normal tissue and tumor shedding, may influence cfDNA levels and the sensitivity to ctDNA detection. Nonetheless, our assay demonstrates consistent and reliable sensitivity for ctDNA detection across all postop. sampling time points. Clinical trial information: NCT04089631. Research Sponsor: German Federal Ministry for Education and Research (Bundesministerium für Bildung und Forschung) / DLR; 01KG1817.

3612 **Poster Session**

Multicentric evaluation of an artificial intelligence model to stratify stage II colon cancer patients from whole slide images. First Author: Abdelhakim Khellaf, Centre Hospitalier de l'Université de Montréal (CHUM), Montreal, QC, Canada

Background: Stage II colon cancer (IIA T3N0; IIB T4aN0; IIC T4bN0) represents nearly 25% of all colon cancers and includes a wide range of outcomes (5-year overall survival rate (OS) of 58.4% to 87.5%). We aim to test if a deep-learning-based analysis of whole slide histology images (WSI) can predict survival and highlight the most relevant morphologic characteristics underlying prognosis. **Methods:** We identified adult stage II colon cancer cases from the multimodal Cancer Genome Atlas (TCGA) and retrospective consecutive cases diagnosed between 2014-2019 (inclusive) from two independent centers (CHUM, Canada and IHP, France; IRB approved). We tested on these two independent datasets, an artificial intelligence (AI) algorithm trained on TCGA, using a cross-validation and cross-testing (80:20) framework. The model relies on a weakly-supervised attention-based pipeline that extracts survival driven histologic features from H&E WSI and assigns a risk score for each patient. The concordance index (c-index) was used as the primary outcome metric. Further testing of the survival score was performed with a multivariate Cox regression model. The stratification of the cohorts based on the risk scores was evaluated using Kaplan-Meier curves and log-rank test. 95% confidence intervals (CI) are provided. An adjusted two-tailed P value $<$0.05 was considered significant. The specific morphologic characteristics involved in the AI outcomes are under analysis. **Results:** The Discovery TCGA cohort consisted of n=463 colon cancer patients; 5-year OS: 68.7% (CI: 60.0%-75.9%). The external validation cohorts included (1) from CHUM, n=124 patients, 5-year OS: 67.0% (CI: 58.0%-75.0%), and (2) from IHP, n=123 patients, 5-year OS: 55.6% (CI 45.0%-67.0%). Cross-validation and testing yielded a c-index of 0.72 and 0.68 respectively, 0.67 for CHUM and 0.65 for IHP cohorts. After external validation, patients with a 'low-risk' score showed significantly higher 5-year OS than patients with a 'high-risk' score: CHUM: 75.0% (CI: 64.0%-84.0%) vs 53.0% (CI 38.0%-67.0%), P$<$0.05; and IHP 65.0% (CI: 44.0%-80.0%) vs 34% (CI: 21.0%-46.0%), P$<$0.01. Cox regression showed a significant effect of WSI-based survival score on 5-year OS: TCGA cohort HR=8.3 (CI: 3.1-12.8), P$<$0.001; CHUM: 7.6 (CI 2.7-21.8), p$<$0.005; IHP: 5.5 (CI 2.1-16.8), P$<$0.005. **Conclusions:** AI-based risk scoring for stage II colon cancer consistently correlated with 5-year OS across multiple independent cohorts, achieving good performances. These findings highlight the potential of modern computational pathology methods requiring minimal supervision to improve risk stratification of stage II colon cancer and patient care. Research Sponsor: IHP Group (France).

3613 **Poster Session**

Development and validation of machine learning risk prediction models for detection of early-onset colorectal cancer: Data from 30 health systems in the United States. First Author: Wilson Lau, Truveta Inc, Bellevue, WA

Background: Incidence of early-onset colorectal cancer (EoCRC) in patients without any family history has been increasing in recent years. Our study leveraged advanced Large Language Models (LLM), like GPT-4, to predict EoCRC in a population comprised of multiple health systems across the United States. There is potential to improve patient care by suggesting early screening for patients who are predicted to be at risk by the model. **Methods:** We identified a population of 5532 patients aged between 18 and 44 in the Truveta data, which is a collection of 120+ million patient journeys across 30 U.S. health systems. 1376 (24.87%) were diagnosed of CRC based on their ICD and SNOMED-CT codes. Data was split into training (80%) and testing (20%) sets. For the prediction task, we applied GPT-4o and compared with XGBoost, one of the strongest non-generative machine learning models. We used patient demographics (age, gender, race, ethnicity), conditions, and lab results within the last 2 to 7 months prior to CRC diagnosis for model training. The last month before CRC diagnosis was excluded to avoid highly predictive signals. For XGBoost, the demographics were represented as one-hot feature vectors, indicating their presence or absence. Conditions were encoded by their diagnosis frequency within the time frame, while the actual values of the lab results were used as model features. For the LLM model, all patient information was input as plain text. Both conditions and lab results were represented by the names of ICD and LOINC codes in order to capture the clinical context. A Chain-of-Thought prompting strategy, incorporating detailed instructions and CRC-specific knowledge, was employed to guide the LLM. **Results:** Our test set consisted of 1105 patients in which 279 (25.25%) were diagnosed with CRC. Both XGBoost and GPT-4o achieved comparable results. Despite the uneven distribution of CRC diagnoses in the test samples, the fine-tuned GPT-4o achieved the highest precision (87.43%) and recall (57.35%). This indicates that the model can accurately predict EoCRC in the near future for over half of the patients. **Conclusions:** This study highlights the potential of using LLM to predict EoCRC in younger population. While the GPT-4o base model contains general medical knowledge, supervised fine-tuning with explicit guideline enhances its predictive capabilities. The high precision of the model performance minimizes the burden of unnecessary screening by identifying patients with relatively high risk. As AI technologies continues to advance, with sufficient governance policy in place, predictive models can be valuable tools for clinicians to suggest early screening and mitigate EoCRC for patients. Research Sponsor: Truveta.

Model	Precision	Recall	F1 score	Accuracy
XGBoost	83.77%	57.35%	68.09%	86.43%
GPT-4o (base)	68.61%	54.84%	60.69%	82.26%
GPT-4o (fine-tuned)	87.43%	57.35%	69.26%	87.15%

3615 Poster Session

Use and benefit of adjuvant chemotherapy in early- vs average-onset colorectal cancer. First Author: Carolina Bernabe, Montefiore Einstein Comprehensive Cancer Center, Bronx, NY

Background: Despite improved mortality rates in colorectal cancer (CRC), the incidence of early onset-colorectal cancer (EO-CRC) has been rising in the United States. We aimed to explore trends in adjuvant chemotherapy (ACT) administration and evaluate its impact on overall survival (OS) and cancer-specific survival (CSS) in patients with EO-CRC (< 50 years old) and average-onset colorectal cancer (AO-CRC) [> 50 years old]. **Methods:** Adult patients (age >18) with Stage II-low risk (T1-T3 disease and more than 12 lymph nodes examined), stage II-high risk (T4 disease or less than 12 total lymph nodes examined) or stage III CRC diagnosed between 2010-2020 were identified in the Surveillance, Epidemiology, and End Results Program (SEER) Database. Cox proportional hazard models were used to assess the effect of ACT on OS and CSS in patients with EO-CRC and AO-CRC. **Results:** The final dataset included 8,998 patients with EO-CRC and 64,987 patients with AO-CRC (Stage II-low =27,446, Stage II-high =9,060, and Stage III = 37,479). Patients with AO-CRC were less likely to receive ACT compared to patients with EO-CRC across all stages: stage II-low (odds ratio [OR]: 0.27), stage II-high (OR 0.28), and stage III (OR: 0.32). From 2010 to 2020, the use of ACT decreased for EO-CRC (68% to 64%) but increased for AO-CRC (36% to 45%). In patients with AO-CRC, ACT improved OS and CSS in stage II-high (OS Hazard ratio(HR):0.48, 95%CI 0.42-0.54; CSS HR:0.48, 95%CI 0.42-0.54) and stage III (OS HR:0.38, 95%CI 0.37-0.40; CSS HR:0.38, 95%CI 0.37-0.40), but had no benefit in CSS for stage II-low disease (CSS HR: 1.01, 95%CI 0.84-1.22). In patients with EO-CRC, ACT improved OS (HR 0.70, 95% CI 0.56-0.88) and CSS (HR: 0.70, 95% CI 0.56-0.88) in stage III disease. No statistically significant survival benefit was observed for patients with stage II-low (CSS HR:1.11, 95%CI 0.66-1.86) or stage II-high (CSS HR:0.83, 95%CI 0.53-1.31).The 5-year survival probabilities by stage are shown in the table. **Conclusions:** Despite being used more frequently, the benefit of ACT in EO-CRC seems to be of less magnitude than in AO-CRC. These differences might be partially explained by the better survival outcomes of EO-CRC even without ACT. Though recommended by most clinical guidelines, ACT does not improve survival outcomes in patients with stage II high-risk EO-CRC. These findings highlight the need to improve risk stratification in early stage EO-CRC to better identify patients who may benefit from ACT. Research Sponsor: None.

5-Year survival probabilities by stage (II-Low, II-High, III).

Variable	OS II-Low	OS II-High	OS III	CSS II-Low	CSS II-High	CSS III
AO; Chemo	84.77%	72.51%	69.66%	88.86%	76.96%	75.08%
AO; No Chemo	74.11%	53.47%	41.54%	89.63%	70.93%	56.55%
EO; Chemo	93.53%	84.34%	78.72%	94.54%	86.34%	80.18%
EO; No Chemo	93.68%	80.19%	71.77%	95.32%	84.28%	75.84%

3616 Poster Session

Detection of early-stage colorectal cancer using multiplexed extracellular vesicle proteomic biomarkers. First Author: Todd A. Hembrough, Nexosome Oncology, Durham, NC

Background: Colorectal cancer (CRC) is very common worldwide, and detection of early-stage cancer is critical for improved survival rates. Advanced adenoma (AA) and early-stage CRC present challenges due to their small size and very low plasma expression of tumor-specific biomarkers. Genomics-based diagnostics struggle to detect these lesions, making it imperative to develop more sensitive approaches. Extracellular vesicles (EVs) are emerging as a promising solution for early-stage CRC detection. EVs are produced by tumor, tumor microenvironment and host cells, thus, unbiased analysis of all plasma EVs offers an expanded set of cancer specific biomarkers, and may aid in detection of small early-stage tumors. **Methods:** EVs were purified from patient plasma using size exclusion chromatography and a proprietary buffer system that enhances EV and corona recovery. TrueDiscovery Data-independent acquisition mass spectrometry (MS) analysis was conducted on EVs purified from 24 advanced adenoma (AA)/stage 0 dysplasia, 25 Stage 1 CRC and 75 normal patient plasma samples. An in-house Machine Learning (ML) pipeline was developed to identify differentially expressed proteins and to define protein multiplexes with extremely high Sens/Spec (> 0.99). **Results:** Around 2,500 QC'd proteins were ID'd per sample and ML identified 336 (AA/Stage 0) and 493 (Stage 1) differentially expressed proteins (DEP: absolute Log2FC>0.5; q-value <0.001; AUC>0.5). The DEPs from AA/Stage 0 and Stage 1 were trained and tested using ML and SMV to identified dozens of MS based multiplexes for each stage with near perfect diagnostic accuracy (~98-100%). These biomarkers were enriched with metabolic, immune and inflammatory proteins in line with our unbiased approach. MS protein multiplexes were then translated to ELISAs to build simple, high throughput assays. ELISA analysis of multiple biomarkers was performed in the training cohort, ML/SMV was used to define multiplex ELISA-based classifiers for Stage 1 CRC (Sen=0.95/Spec=0.96). This Stage 1 CRC training assay was locked and tested on a blinded cohort of Stage 1 CRC (30 control, 30 cancer). In this blinded cohort, we targeted maximal specificity yielding Sen=0.80, Spec=0.97 and AUC=0.95. These data represent significantly higher Sen/Spec than current genomic based liquid biopsy assays. Training and validation of AA and Stage 0 ELISAs is underway and will be presented. **Conclusions:** Blinded validation of EV proteomic biomarkers yielded extremely high Sen/Spec early-stage CRC. The unbiased EV analysis underscores the need to assess cancer specific biomarkers from TME and host response and highlights the value and opportunity of expanding liquid biopsy analysis beyond tumor specific genomics. Taken together this platform provides an exceptional opportunity to increase early-stage cancer detection which should result in better patient outcomes. Research Sponsor: None.

3617 Poster Session

An early colorectal cancer screening programme based on bisulfite-free sequencing of methylated circulating tumor DNA. First Author: Rushan Fei, The First Affiliated Hospital, Zhejiang University School of Medicine, Hangzhou, China

Background: Colorectal cancer (CRC) screening tests based on colonoscopy and fecal DNA testing are limited due to their invasive nature and low compliance rates. Herein, we develop a non-invasive early screening test for CRC based on ColoSeer assay, which combines methylated DNA immunoprecipitation and bisulfite-free sequencing to analyze methylation patterns of circulating tumor DNA (ctDNA). **Methods:** Tumor and ctDNA methylation patterns in 1,336 subjects (430 healthy controls, 202 colorectal precursor lesions (CPLs), 704 CRCs) undergoing colonoscopy were evaluated using the ColoSeer assay. **Results:** In the discovery phase, we identified a set of 46 differential methylation markers to screen for CPLs or CRCs from healthy controls. The overall detection sensitivity of ColoSeer was 85.6% for CPL and 97.5% for TMN stage (0-II) CRC, with 92.8% specificity. **Conclusions:** The ColoSeer assay demonstrated a high degree of accuracy for predicting subjects with CPL or early-stage malignant tumors and has potential as a first-tier health screen for early detection of CRC. Research Sponsor: None.

3618 Poster Session

The impact of dietary patterns on inflammation and colon cancer risk: A retrospective study of 796 patients. First Author: Alina Zatsepina, Maimonides Medical Center, Brooklyn, NY

Background: Colon cancer significantly contributes to global cancer rates, with rising incidence linked to dietary and lifestyle changes. Diets high in ultra-processed foods promote systemic inflammation, while anti-inflammatory diets may reduce inflammation and cancer risk. This study investigates the relationship between dietary patterns, inflammatory biomarkers, and colon cancer risk. **Methods:** This retrospective study analyzed data from 796 patients with histologically confirmed colon cancer (2015–2023). Dietary habits were assessed using validated food frequency questionnaires (FFQs), categorizing participants by adherence to ultra-processed or anti-inflammatory diets using the Dietary Inflammatory Index (DII). Systemic inflammation was evaluated via biomarkers: C-reactive protein (CRP), interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF-α), and white blood cell (WBC) count. Clinical data, including age, sex, BMI, smoking, physical activity, co-morbidities like metabolic syndrome and obesity, were extracted from medical records. Multivariate logistic regression was used to assess associations between dietary patterns, inflammation, and colon cancer risk. Subgroup analyses stratified by metabolic conditions and cancer stage identified potential interactions. The study adhered to STROBE guidelines. **Results:** Patients consuming diets high in ultra-processed foods (top DII quartile) had elevated inflammatory biomarkers (CRP: 14.8 $\pm$ 3.2 mg/L; IL-6: 8.6 $\pm$ 2.4 pg/mL; TNF-α: 7.2 $\pm$ 1.9 pg/mL) compared to those on anti-inflammatory diets (CRP: 4.3 $\pm$ 1.1 mg/L; IL-6: 2.9 $\pm$ 0.8 pg/mL; TNF-α: 2.3 $\pm$ 0.7 pg/mL; $p < 0.001$). Dietary patterns strongly correlated with colon cancer risk. Ultra-processed food consumers had an adjusted odds ratio (aOR) of 2.47 (95% CI: 2.01–3.03) for colon cancer, while anti-inflammatory diets had a protective effect (aOR: 0.62, 95% CI: 0.51–0.76). Subgroup analysis showed anti-inflammatory diets' protective effects were more pronounced in patients with metabolic syndrome or obesity, reducing cancer risk by 45% ($p < 0.001$). Early-stage colon cancer patients (Stage I–II) adhering to anti-inflammatory diets exhibited lower inflammation, suggesting potential benefits for disease progression and prognosis. Further analysis highlighted omega-3 fatty acids and polyphenols in anti-inflammatory diets as key in reducing inflammation by downregulating NF-κB signaling and pro-inflammatory cytokine production. **Conclusions:** Diets high in ultra-processed foods elevate inflammation and colon cancer risk, while anti-inflammatory diets provide protective benefits, especially in individuals with metabolic conditions. These findings emphasize the need for dietary interventions promoting anti-inflammatory patterns in cancer prevention and management. Further research should validate these results and explore underlying mechanisms. Research Sponsor: None.

3619 Poster Session

Risk of pre-cancerous advanced adenomas of the colon in long distance runners. First Author: Timothy Lewis Cannon, Inova Schar Cancer Institute, Fairfax, VA

Background: Exercise induced gastrointestinal injury is believed to be associated with reduced blood flow to the intestines during long distance running. To our knowledge, there has not been evidence linking this type of exercise- induced bowel ischemia to carcinogenesis. After observing multiple "ultramarathoners" present to our cancer center with advanced colorectal cancer, we initiated a prospective IRB-approved study to evaluate the risk of advanced adenomas (AA) in long distance runners between the ages of 35-50. **Methods:** NCT 05419531 was a prospective study of subjects aged 35-50 years who had completed at least two registered ultramarathons (50 km or longer) or five registered marathons (26.2 miles). Subjects were excluded if they were known or suspected to have inflammatory bowel disease, familial adenomatous polyposis (FAP), or Lynch Syndrome. Prior to colonoscopy, each subject completed a questionnaire regarding dietary habits, bowel habits, and long-distance running history, with results to be reported in the future. All polyps discovered during colonoscopy were reviewed by a panel of gastroenterologists, pathologists, and oncologists to determine if they met the criteria for advanced adenomas, defined as lesions >10 mm, >25% tubulovillous features, or high-grade dysplasia. **Results:** Between October 2022 and December 2024, 102 subjects were screened, and 100 underwent colonoscopy as part of the study. The median age was 42.5 years; 55 of the participants were female and 45 were male. The historical benchmark used for expected AAs in average-risk individuals aged 40-49 years was 1.2%. Among the 100 subjects in this study, 15% (95% exact confidence interval: 7.9%- 22.4%) had confirmed AAs. 39 out of 100 subjects had at least one adenoma. Three additional subjects had three or more adenomas but did not meet our predefined criteria for AA and were not included among the 15 patients with AA. **Conclusions:** NCT 05419531 achieved its predefined endpoint for advanced adenomas, suggesting that "intensive" long distance running is a risk factor for advanced adenomas of the colon. Consideration of refined screening strategies for this population is warranted. Future pathological and epidemiological evaluations should explore causation and ancillary risk factors in this unique population. Clinical trial information: NCT05419531. Research Sponsor: Inova Schar Cancer Institute.

Subjects with advanced adenoma.

Participant ID	3	9	15	16	37	53	55	67	69	71	77	87	91	98	100
Gender	F	M	M	F	F	M	F	F	F	F	F	M	M	F	M
Age	44	45	48	41	45	49	40	40	45	39	42	50	42	44	41
Endurance Eligibility (U – Ultramarathons; M – Marathons)	4 - 6 U	4 - 6 U	> 15 U	4 - 6 U	> 15 U	7 - 15 U	6 M	5 M	7 - 15 U	1 U / 7-8 M	> 15 U	> 15 U	10 M	> 15 U	5 M
# of Polyps	3 on primary; 2 on secondary	5	2	3	1	1	3	2	7	1	2	4	2	6	3
Size of largest polyp (Colonoscopy/Pathology) (mm)	25 / 15	12 / 15	10 / 13	10 / 10	3 / 3	20 / 9	5-6 / 5	12/ 11	12 / 12	5 / 5	5 / 5	15-20 / 12	6 / 7	10 / 7	10 / 19
>25% Tubulovillous Features (Y/N)	N	N	N	N	Y	N	Y	N	N	Y	Y	N	N	Y	N
High-grade Dysplasia (Y/N)	N	N	N	N	N	N	N	N	N	N	N	N	Y	N	N

3620 Poster Session

Reassessing colorectal cancer recurrence in solid organ transplant recipients: Implications for revised management guidelines. First Author: David Bradley Meyer, Sidney Kimmel Comprehensive Center, Johns Hopkins University School of Medicine, Baltimore, MD

Background: Patients with solid organ transplants (SOT) are at an increased risk of developing secondary malignancies, including colorectal cancer (CRC). However, the influence of SOT and associated immunosuppression on recurrence risk following definitive treatment is poorly understood. This study characterizes the recurrence risk of CRC in a cohort of patients that developed CRC after SOT. **Methods:** Patients treated within the Johns Hopkins and University of Wisconsin medical systems meeting study criteria were identified using SlicerDicer Epic reports. Manual chart review was performed to determine treatment course, patient/disease characteristics, and whether or not their disease recurred. **Results:** Fifty-two patients with CRC following SOT were identified, including those who had liver (n = 12), kidney (n = 26), combined liver and kidney (n = 5), combined pancreas and kidney (n=4), lung (n = 4), and heart (n = 1) transplants. Among these patients, 30 were male and 22 were female. Ten patients had recurrent CRC after curative intent treatment. Recurrence rates were as follows: 1 of 10 (10.00%) patients with stage I CRC, 5 of 12 (41.67%) patients with stage II CRC, and 4 of 18 (22.22%) patients with stage III CRC. The overall CRC recurrence rate in the cohort was 32.26%. **Conclusions:** In summary, a multi-institution retrospective cohort study of patients with CRC diagnosis following SOT demonstrated higher than traditionally expected recurrence rates in patients with stage I and II disease when compared to patients diagnosed with CRC without history of SOT. Further multi-institutional studies are warranted to validate this finding. If confirmed, this would suggest transplant status may alter adjuvant treatment decisions and warrant future prospective studies in this patient population. Research Sponsor: None.

Study cohort variables stratified by CRC staging.

Stage at Diagnosis	Avg. Age at Time of Diagnosis	Sex	Race	Transplant Type	Avg. Time from Transplant to CRC Diagnosis (months)	Recurrence Rate	Avg. Time to CRC Recurrence (months)	Avg. Overall Survival (months)
Stage 0	72.00	1 Female	1 Caucasian	1 Liver	34.73	0.00%	N/A	4.70
Stage I	57.50	6 Male, 4 Female	3 African American, 6 Caucasian, 1 Pacific Islander	5 Kidney, 2 Liver, 2 Pancreas/Kidney, 1 Lung	159.73	10.00%	51.78	54.42
Stage II	56.33	7 Male, 5 Female	3 African American, 9 Caucasian	7 Kidney, 1 Liver, 2 Liver/Kidney, 2 Pancreas/Kidney	172.35	41.67%	29.87	61.34
Stage III	62.39	12 Male, 6 Female	3 African American, 14 Caucasian, 1 Asian	9 Kidney, 4 Liver, 3 Liver/Kidney, 1 Lung, 1 Heart	148.76	22.22%	18.03	52.15
Stage IV	52.18	5 Male, 6 Female	2 African American, 9 Caucasian	5 Kidney, 4 Liver, 2 Lung	148.83	N/A	N/A	18.70
All Stages	58.08	30 Male, 22 Female	11 African American, 39 Caucasian, 1 Asian, 1 Pacific Islander	26 Kidney, 12 Liver, 5 Liver/Kidney, 4 Pancreas/Kidney, 4 Lung, 1 Heart	154.14	32.26%	27.33	46.72

3621 Poster Session

Impact of COVID-19 on the stage at diagnosis and mortality of colorectal cancer. First Author: Soyun Lim, Seoul National University College of Medicine, Seoul, South Korea

Background: When the COVID-19 pandemic started in 2020 in the US, the Centers for Medicare and Medicaid Services (CMS) recommended delaying all non-urgent procedures, including screening colonoscopies to prevent virus spread. An analysis of the CMS claims data showed a decrease in all screening modalities for colorectal cancer (CRC) including colonoscopy, fecal occult blood test, and blood-based gene analysis in 2020 compared to 2013-2019. We investigated the impact of COVID-19 on stage at diagnosis and mortality of CRC across racial groups. **Methods:** We utilized the Surveillance, Epidemiology, and End Results (SEER) database to obtain the age-adjusted incidence of localized, regional, and distant CRC at the time of diagnosis from 2013 to 2021. The year-over-year (YOY) change in the proportion of advanced (regional + distant) CRC was calculated. YOY changes in age-adjusted CRC mortality rates from 2014 to 2021 were also calculated. **Results:** From 2014 to 2019, the average YOY change in the proportion of advanced CRC across all races was 1.0% whereas in 2020, the rate was 3.9%. The increase in proportion of advanced CRC in 2020 was greatest in non-Hispanic Asian/Pacific Islanders (NHAPI), followed by Hispanics, non-Hispanic Whites (NHW), non-Hispanic American Indian/Alaskan Natives (NHAIAN), and non-Hispanic Blacks (NHB; 7.9%, 4.7%, 3.6%, 3.3%, and 3.3%, respectively). From 2014 to 2019, the average YOY change in CRC mortality across all races was -0.7% while in 2020, it increased by 5.4%. In 2020, the YOY change in mortality was greatest in NHAIAN, followed by Hispanics, NHB, NHW, and NHAPI (25.3%, 16.5%, 15.1%, 3.2%, and 1.2%, respectively). **Conclusions:** The proportion of advanced CRC increased in 2020 likely due to decreased screening most significantly in NHAPI. Also, mortality increased in 2020 possibly due to delay in access to care during COVID-19. Further studies are needed to evaluate the long-term effect of COVID-19 on the screening and mortality of CRC. Research Sponsor: None.

Proportion of advanced colorectal cancer and mortality rates of colorectal cancer from 2013 to 2021 by race.

Proportion of advanced colorectal cancer (%)	2013	2014	2015	2016	2017	2018	2019	2020	2021
Total	59.9	59.7	59.8	63.1	63.8	62.6	63.3	65.8	64.6
Non-Hispanic White	59.9	59.6	59.6	62.2	63.3	62.3	62.9	65.1	64.4
Non-Hispanic Black	60.7	60.8	61.2	64.6	65.1	64.1	65.2	67.3	64.8
Non-Hispanic American Indian/Alaska native	60.9	62.6	59.0	64.2	64.5	65.0	66.3	68.5	65.3
Non-Hispanic Asian/Pacific	59.0	59.2	59.1	64.8	66.4	61.6	63.2	68.1	64.1
Hispanic	61.6	61.2	61.0	65.3	64.8	64.2	65.0	68.1	66.7
Mortality (per 100,000)									
Total	24.9	24.6	24.7	24.3	24.6	24.5	24.0	25.3	25.0
Non-Hispanic White	25.5	25.5	25.6	25.1	25.6	25.6	25.1	25.9	26.2
Non-Hispanic Black	33.3	31.5	32.7	31.7	31.8	31.0	30.4	35.0	32.0
Non-Hispanic American Indian/Alaska native	31.3	23.0	23.1	29.6	28.7	31.7	24.9	31.2	31.7
Non-Hispanic Asian/Pacific	16.9	17.1	17.1	16.9	17.3	16.3	16.6	16.8	17.0
Hispanic	19.9	19.1	19.1	20.3	18.9	20.0	18.8	21.9	20.9

3622 Poster Session

Leveraging EHRs and a phenome-wide association study to identify pre-diagnostic clinical markers in early-onset colorectal cancer. First Author: Sachleen Kaur Tuteja, Center for Health Information Partnerships, Institute for Public Health and Medicine, Northwestern University Feinberg School of Medicine, Chicago, IL

Background: The incidence of colorectal cancer (CRC) has undergone a significant demographic shift, with diagnosis in individuals under 55 years escalating from 11% in 1995 to 20% in 2019 (Siegal et al., 2019). Traditional risk factors, such as obesity, diabetes, and colon microbiome changes, fail to fully explain this emerging clinical phenomenon, necessitating new approaches to identify pre-diagnostic markers in younger patients. Our study leverages electronic health records (EHR) and employs a Phenome-Wide Association Study (PheWAS) to characterize age-specific manifestations prior to diagnosis. **Methods:** A PheWAS was conducted with a cohort of 2,799 CRC patients from Northwestern Medicine (NM, 2012 – 2022). ICD-9/10 codes were categorized into 527 phenotypes using the PheCode framework. Logistic regression models were employed to examine associations between age groups ($<$ 55 vs. $\geq$55 years) and each phenotype during the 6 months preceding diagnosis. A control cohort of 294,590 non-cancer NM patients adjusted for age-related and baseline disease patterns. **Results:** Our approach revealed significant associations with age in 9 of 527 analyzed phenotypes, identifying well-documented CRC features and less recognized clinical markers. Younger patient cohorts exhibited elevated probabilities of critical clinical indicators, including lower gastrointestinal hemorrhage (22% [95% CI: 19-25%] vs. 11% [95% CI: 10-13%]; $p = 1.0 \times 10^{-11}$), hepatic dysfunction (6% [95% CI: 4-8%] vs. 4% [95% CI: 3-4%]; $p = 2.7 \times 10^{-6}$), and diverticular disease (4% [95% CI: 3-6%] vs. 3% [95% CI: 2-3%]; $p = 2.4 \times 10^{-11}$) compared to older patients. Furthermore, an analysis of 1,866 NM pathology reports revealed single-institution trends consistent with global CRC literature. Notably, younger patients showed higher prevalence of hereditary CRC (28% vs. 24%; χ^2 $p = 6.3 \times 10^{-8}$), greater left-sided tumor localization (51% vs. 45%; χ^2 $p = 0$), and increased proximal tumors (58% vs. 53%; χ^2 $p = 0$), corroborating studies that show a rise in proximal tumor incidence in patients under 50 and a decline in those aged 50–79. **Conclusions:** Our PheWAS study uncovered clinicopathological distinctions, revealing statistically significant variations in pre-diagnostic clinical markers that suggest a more aggressive and complex disease progression mechanism in early-onset CRC. The increased probabilities of clinical indicators—such as gastrointestinal hemorrhage, hepatic dysfunction, and diverticular disease—underscore the need for tailored diagnostic and screening strategies for younger populations. These results also highlight the value of utilizing phenotype-based methodologies to identify nuanced clinical features that may enable earlier detection and improve outcomes for younger CRC patients. Towards this goal, ongoing research aims to further delineate CRC clinical profiles between age groups. Research Sponsor: Northwestern University Office of Undergraduate Research.

3623 **Poster Session**

Colorectal cancer screening and detection following USPSTF recommendations for ages 45-49: Insights from a large EHR cohort. First Author: Patricia Jane Rodriguez, Truveta Inc, Bellevue, WA

Background: Rising colorectal cancer (CRC) incidence in relatively younger adults prompted the US Preventative Services Task Force (USPSTF) to recommend screening in average-risk adults aged 45-49 in May 2021. While screening has increased for ages 45-49, differences in polyp and CRC detection by age group are unclear. **Methods:** Using a subset of Truveta Data, we identified patients aged 40-64, with no prior history of CRC, who underwent CRC screening procedures (colonoscopy or sigmoidoscopy) between 2018 and 2024, and for whom an associated report was available. Truveta Data contains de-identified electronic health record (EHR) data from a collective of US health care systems. Screening outcomes were extracted from pathology reports using natural language processing, including findings of polyps (tubular adenoma/adenomatous polyp, hyperplastic polyp, tubulovillous adenoma, sessile serrated adenoma, traditional sessile adenoma, juvenile polyp, and inflammatory polyp), adenocarcinoma, and benign/normal colonic mucosa. For patients with multiple screenings, the first was used. Family history of CRC and related syndromes (e.g., Lynch, Peutz-Jeghers) were similarly extracted from notes. Patient characteristics and screening outcomes were described by 5-year age band, before and after May 2021 USPSTF recommendations. **Results:** Of85,062 patients aged 40-64 who underwent CRC screening, 46,168 had first screening records in May 2021 or earlier ('pre period') and 38,894 after ('post period'). In the pre period, 4,270 (9%) patients were aged 45-49, compared to 7,403 (19%) in the post period. Sex balance improved for the 45-49 age group (56% were female pre vs. 50% post; $p < 0.05$), compared to younger and older age groups (40-44: 57% vs. 57%, 50-54: 48% vs. 48%, 55-59: 51% vs.49%, 60-64: 50% vs. 49%; $<$ 0.05 for 55-59 only). Adenomatous polyp findings increased for all age groups, but to the greatest degree for the 45-49 group (45-49: 45.7% pre vs. 53.4% post; $p < 0.01$) compared to other groups (40-44: 33.1% vs. 35.9%, 50-54: 58.3% vs. 59.9%, 55-59: 60.4% vs. 62.5%, 60-64: 63.2% vs. 64.5%; all $p < 0.05$). In contrast, adenocarcinoma findings occurred less frequently for ages 45-49 (2.1% pre vs. 1.0% post, $p < 0.01$), while remaining stable in both younger and older groups (40-44: 1.6% vs. 1.4%, 50-54: 1.2% vs. 1.1%, 55-59: 1.4% vs. 1.6%, 60-64: 1.3% vs. 1.3%; all $p > 0.05$). **Conclusions:** Following 2021 USPSTF CRC screening recommendations for average-risk adults aged 45-49, sex balance in screening increased, findings of adenomatous polyps increased, and findings of adenocarcinoma declined in this group. These results may reflect expected decreases in adenocarcinoma detection with expansion of screening to average-risk adults, or suggest that recommendations contributed to earlier detection of pre-cancerous polyps, before progression to adenocarcinoma. Additional studies are needed to explore complex causal relationships. Research Sponsor: None.

3624 **Poster Session**

Sex differences in chemotherapy completion and adverse events among patients with colon cancer (CALGB/SWOG 80702) (Alliance). First Author: En Cheng, Department of Epidemiology and Population Health, Albert Einstein College of Medicine, Bronx, NY

Background: Increasing chemotherapy completion and reducing chemotherapy adverse events (AE) are critical to improve survival after colon cancer diagnosis. Sex, as a biological variable, may impact chemotherapy treatment differently, and thus further investigation is needed to examine sex differences in chemotherapy completion and adverse events among patients with colon cancer. **Methods:** Among an NCI-sponsored trial conducted among patients with stage III colon cancer (CALGB/SWOG 80702), all patients received standard adjuvant chemotherapy FOLFOX (fluorouracil, leucovorin, and oxaliplatin). To signal chemotherapy completion, we utilized relative dose intensity (RDI) calculated as the ratio of the delivered dose intensity to planned dose intensity; and reduced RDI (RDI $<$85%) was considered as a clinically significant deviation from standard FOLFOX. From clinicians' records of NCI's Common Terminology Criteria for Adverse Events (CTCAE), we primarily focused on clinically significant AE such as neutrophils decrease, nausea, platelets decrease, hypertension, peripheral neuropathy, diarrhea, fatigue, gastritis, creatinine increase, gastric ulcer, myocardial ischemia, and cerebral ischemia; and severe AE was defined as the occurrence of any above AE with CTCAE grade $\geq$3. Using multivariable logistic regression that adjusted for body surface area (BSA) and other clinicopathological confounders, we estimated adjusted odds ratios (OR) for the associations of sex with reduced RDI and severe AE. **Results:** Of 2201 patients, mean (standard deviation [SD]) age was 60.9 (10.9) years, 1019 (46.3%) were female, 1750 (79.5%) were White, 172 (7.8%) were Hispanic, 964 (43.8%) experienced reduced RDI, and 1156 (52.5%) had severe adverse events. Compared to males, females were at significantly higher risks of experiencing reduced RDI (OR [95% CI]: 1.57 [1.27-1.93], $P < 0.001$) and severe AE (OR [95% CI]: 1.73 [1.41-2.12], $P < 0.001$). **Conclusions:** Our findings suggested females are more likely than men to experience reduced RDI and severe AE during colon cancer chemotherapy. Clinical Impact: In the era of precision medicine, sex (as a biological variable) should be considered in optimizing colon cancer chemotherapy to improve completion and reduce toxicities. Clinical trial information: NCT01150045. Research Sponsor: National Cancer Institute; U10CA180821; National Cancer Institute; U10CA180882; National Cancer Institute; U24CA196171; National Cancer Institute; U10CA180863; Canadian Cancer Society; CCS707213; National Cancer Institute; UG1CA233234; National Cancer Institute; U10CA180820; National Cancer Institute; U10CA180868; National Cancer Institute; U10CA180888; Pfizer; https://acknowledgments.alliancefound.org; Health and Environmental Sciences Institute.

3625 **Poster Session**

Comprehensive analysis of outcomes of patients with colorectal cancer in a racially diverse cohort. First Author: Manasawee Tanariyakul, University of Hawaii Internal Medicine Residency Program, Honolulu, HI

Background: Disparate outcomes have been reported among patients with colorectal cancer (CRC) as those with Medicare or Medicaid insurance and those of Native Hawaiian ancestry experience inferior survival. However, many CRC studies addressing Native Hawaiians and other Pacific Islanders and insurance status have not adjusted for a comprehensive range of confounding variables. In this study, we perform a comprehensive analysis of CRC outcomes adjusted for clinicopathological and socioeconomic factors. **Methods:** Data were abstracted for patients diagnosed with colorectal cancer between 2000 and 2022 in Hawaii. Overall survival of Asians, Whites, and Native Hawaiian or Other Pacific Islanders (NHOPI) was assessed using Cox proportional hazards regression models adjusting for clinical, pathological, and sociodemographic factors. **Results:** A total of 3275 patients were included in the final analysis. NHOPI were more likely to be younger ($p<0.001$), had a higher proportion of stable microsatellite status tumors($p=0.049$) and were more likely to have Medicaid insurance or be uninsured($p<0.001$) compared to Whites and Asians. NHOPI patients more often had high grade cancers compared to White and Asian groups. Medicaid or no insurance was associated with significantly higher mortality compared to private insurance in both univariate(HR: 1.373, 95% CI: 1.202–1.568, $p < 0.001$) and multivariate analysis(HR: 1.505, 95% CI: 1.309–1.729, $p < 0.001$). However, while Medicare showed higher mortality in univariate analysis(HR: 1.409, 95% CI: 1.245–1.594, $p < 0.001$), this association normalized after adjustment(HR: 1.088, 95% CI: 0.958–1.237, $p = 0.195$) (Table). NHOPI had significantly higher mortality compared to Whites after adjustment for variables(HR: 1.293, 95% CI: 1.107–1.510, $p = 0.001$). Interestingly, rectal tumors demonstrated higher mortality compared to right-sided tumors(HR: 1.318, 95% CI: 1.156–1.503, $p < 0.001$), while left-sided tumors showed no significant difference (Table). **Conclusions:** This study of a racially diverse population that NHOPI patients with CRC had significantly worse mortality compared to Whites after adjusting for clinicopathological and socioeconomic variables. We did not identify a significant association between Medicare insurance and increased mortality. Having Medicaid or being uninsured was significantly associated with worse survival outcomes, emphasizing the critical impact of healthcare access on survival. Research Sponsor: None.

Univariate and multivariate analysis.

	Univariate analysis Hazard ratio (95% CI), p-value	Multivariate analysis Hazard ratio (95% CI), p-value
Private insurance		
Medicaid and Uninsured	1.373 (1.202 - 1.568), <0.001	1.505 (1.309 - 1.729), <0.001
Medicare	1.409 (1.245 - 1.594), <0.001	1.088 (0.958 - 1.237), 0.195
White		
Asian	0.947 (0.844 - 1.063), 0.354	0.908 (0.808 - 1.02), 0.103
NHOPI	1.143 (0.982 - 1.33), 0.084	1.293 (1.107-1.51), 0.001
Age at diagnosis	1.032 (1.028 - 1.036), <0.001	1.044 (1.039 - 1.048), <0.001
Grade 1&2		
Grade 3&4	1.786 (1.586 - 2.012), <0.001	1.485 (1.313 - 1.681), <0.001
Stage 1		
Stage 2	1.466 (1.249 - 1.722), <0.001	1.401 (1.192 - 1.647), <0.001
Stage 3	1.644 (1.41 - 1.918), <0.001	1.64 (1.403 - 1.916), <0.001
Stage 4	6.943 (5.898 - 8.173), <0.001	7.681 (6.495 - 9.082), <0.001
Unknown Stage	3.063 (2.525 - 3.714), <0.001	2.99 (2.455 - 3.641), <0.001
Female	0.853 (0.775 - 0.939), 0.001	0.844 (0.765 - 0.931), <0.001
MSI Stable		
MSI Unstable	1.146 (0.808 - 1.626), 0.444	1.015 (0.71 - 1.449), 0.936
Unknown MSI	1.197 (1.055 - 1.357), 0.005	1.142 (1.003 - 1.3), 0.044
Right sided		
Left sided	0.899 (0.802 - 1.007), 0.066	1.081 (0.961 - 1.216), 0.197
Rectal	1.016 (0.9 - 1.147), 0.797	1.318 (1.156 - 1.503), <0.001
Time to treatment <31 days		
Time to treatment >31 days	0.674 (0.593 - 0.766), <0.001	1.064 (0.957 - 1.183), 0.09

3626 **Poster Session**

Dietary risk factors associated with colorectal polyp risk and potential for progression to malignancy. First Author: Melissa Rachel Goldin, Vanderbilt University School of Medicine, Nashville, TN

Background: Colorectal polyp development and progression to cancer are associated with diet and microbial dysbiosis. Red and processed meat intakes have been associated with colorectal polyps, but evidence on probiotic and prebiotic usage is inconclusive. This study examines the association of dietary factors with colorectal adenomas (ADs) and sessile serrated polyps (SSPs) of low and high potential of progression to cancer. **Methods:** In the Colorectal Molecular Atlas Project, 1082 participants underwent a colonoscopy, and completed a questionnaire. Individuals were classified as polyp-free controls, and polyp cases with high potential for progression to cancer ($\geq$ 1 cm, villous component, high-grade dysplasia, or multiple AD and/or SSPs) or low potential (all other AD or SSP cases). Frequency of dietary intake derived from questionnaire responses was divided into quartiles (total meat, total red meat, total processed meat, chicken, and fish) or no intake/tertiles (total probiotic food: yogurt, kefir, sauerkraut, kimchi, fermented cabbage, kombucha, other fermented beverages). Multinomial logistic regression models were used to derive odds ratios and 95%CI after adjusting for confounders. **Results:** Highest intake of total meat was associated with increased risk of high progression potential polyps (OR 1.63, 95%CI 1.03-2.60) and sessile serrated lesions (OR 1.60, 95%CI 1.03-2.50) in comparison to lowest intake. Highest intake of red meat was associated with increased risk of high progression potential polyps (OR 1.80, 95%CI 1.16-2.80) and SSPs (OR 1.68, 95%CI 1.10-2.56) in comparison to lowest intake. The second quartile of fish intake was significantly associated with a reduced risk of polyps with low progression potential (OR 0.63, 95%CI 0.44-0.99) and ADs (OR 0.63, 95%CI 0.42-0.96) compared to lowest intake; however, the third and fourth quartiles were not significantly associated with risk. Chicken, processed meat, probiotic food, probiotic supplement, and prebiotic supplement intake were not associated with risk. **Conclusions:** Dietary risk factors may vary by type of polyp, thus, dietary recommendations should reflect these differences. Increased total and red meat intake may increase risk of polyps with high progression potential and sessile serrated lesions, and fish intake may reduce risk for polyps with low progression potential and adenomas. Probiotics and prebiotics may not be an effective risk reduction strategy. Research Sponsor: None.

3627 **Poster Session**

Characterizing clinical outcomes and DNA co-alterations of ERBB2-amplified colorectal cancer. First Author: Mohamed Nuh, Baylor College of Medicine, Houston, TX

Background: A subset of colorectal cancer (CRC) features amplification (amp) of the ERBB2 gene. The prognostic role and treatment in these patients are poorly understood. This study aims to characterize the clinical outcomes and molecular profiles of ERBB2-amp CRC. **Methods:** This is a retrospective analysis of clinical outcomes data and next-generation sequencing at MD Anderson from 2006-2025 in patients with ERBB2-amp CRC including all classes of genomic alterations (GA) in other genes. Progression-free survival (PFS) and overall survival (OS) were assessed by Kaplan-Meier, log-rank, and cox regression. Chi square goodness of fit was assessed for the proportion of left versus right sided CRC. **Results:** 100 pts with ERBB2-amp CRC were identified. Patients (Table) who received ERBB2-directed therapy (n = 36) did not have significantly longer OS compared to those who received other systemic therapy (n = 57) (53.8 vs. 45.5 m, p = 0.35). Patients who underwent surgery (n = 64) (56.8 vs. 23.2 m, p = 0.01) or non-surgical localized therapy (n = 45) had longer OS (64.4 vs 45.5 m, p = 0.01). ERBB2-amp was more associated with left sided CRC (n = 80) than right-sided CRC (n = 19) (X^2= 39.34, df = 1, $p < 0.0001$) but there was no significant OS difference (53.8 vs. 45.5 m, p = 0.76). Median PFS (mPFS) for all 1st (n = 93), 2nd (n = 80), and 3rd line (n = 61) systemic therapy was 8.0, 5.1, and 4.9 m, respectively. mPFS for all ERBB-2 directed therapy (n = 59) was 3.5 m. The most common concurrent co-GA were TP53 (90%) and APC (64%) and most common co-amp were CDK12 (31%) and EGFR (23%). Concurrent APC mutation was associated with improved OS (53.8 vs. 26.2 m, p = 0.003). No other co-GA or co-amp, including KRAS, showed significant survival outcome associations. TP53 co-GA was present in 90% of both left and right-sided ERBB-2 CRC and KRAS co-GA in 15% and 32%, respectively. **Conclusions:** There was no difference in OS in ERBB2 amp CRC in patients who received ERBB2 directed therapy, however patients had improved OS with surgery or localized therapy options and should be offered to eligible patients if possible. Co-GA with APC mutation correlated with improvement in survival outcomes. Research Sponsor: None.

Baseline data, initial staging, treatments, and mutational profile for ERBB2 co-amp CRC.

Age at Diagnosis (median)	55 years
Gender — no.	M (56), F (44)
Stage at Initial Diagnosis — no.	I (6), II (6), III (18), IV (69)
Location of Primary Tumor — no.	R-sided (19), L-sided (80), Cecum (7), Ascending (8), Transverse (5), Descending (7), Sigmoid/Rectum (73)
Surgery — no.	Primary tumor (55), Liver metastectomy (24), Lung metastectomy (8)
Localized Therapy — no.	RT (36), Ablation (6), Y90 (4), Cryotherapy (1)
ERBB2 Directed Therapy (excluded if n=1) — no.	Trastuzumab (TRA) + Pertuzumab (20), ERBB2-directed trial drug (14), Trastuzumab deruxtecan (8), TRA (7), TRA + Tucatinib (4)
Mutational Profile	Co-GA: TP53 (90%), APC (64%), SMAD4 (18%), KRAS (18%) Co-amp: CDK12 (31%), EGFR (23%), MYC (19%), BRAF (13%)

3628 **Poster Session**

Effects of marital status on survival in patients with colorectal cancer. First Author: Lisa Liu, George Washington University, Washington, DC

Background: Demographic factors such as marital status have been shown to have differential effects on cancer outcomes. It has been shown that married patients have higher 5-year survival rates compared with unmarried patients with colorectal cancer (CRC). However, most of these studies looked at patients diagnosed prior to 2015. This study compares the survival trends between 2000–2010 and 2011–2021 and analyzes marital status associations with stage at diagnosis. **Methods:** Patients with CRC diagnosed between 2000 and 2021 were identified in the SEER database and stratified by marital status (single, separated/divorced/widowed (SDW), and married). 5-year survival rates with 95% confidence intervals were calculated for each marital status group across three periods: 2000–2010, 2011–2021, and 2000–2021. Kaplan-Meier survival analysis was used to compare survival outcomes across these variables. Disease severity was classified into three stages: localized, regional, and distant. The distribution of patients across disease stages is reported as the proportion of individuals within each marital status group at each cancer stage. **Results:** Overall survival was statistically different amongst patients with different marital statuses ($p < 0.01$). Our results show that the highest 5-year overall survival rate is seen in married individuals at 62.1% (61.9% - 62.2%), followed by single individuals at 53.0% (52.6% - 53.3%), and SDW individuals at 44.6% (44.3% - 44.8%). Overall survival improved over time across all marital groups when comparing the 2000–2010 and 2011–2021 periods. For married individuals, 5-year overall survival rate increased from 61.2% (61.0%–61.4%) to 63.1% (62.9%–63.4%). Similarly, survival improved for single individuals (51.1% [50.6%–51.6%] to 54.5% [54.0%–54.9%]) and for SDW individuals (43.8% [43.5%–44.1%] to 45.7% [45.3%–46.1%]). Our results show that married individuals were most commonly diagnosed with localized cancer compared with single and SDW individuals (41.8% vs 36.5% vs 39.0%, $p < 0.01$), SDW individuals with regional cancer compared with single and married individuals (38.3% vs 37.06% vs 37.5%, $p < 0.01$) and single individuals with distant disease compared with married and SDW individuals (26.4% vs 20.69% vs 22.69%, $p < 0.01$). **Conclusions:** Marital status significantly impacts CRC survival, with married individuals having higher survival rates than single or SDW patients. This suggests that social support may contribute to improved outcomes, although it is important to note that the higher survival rates may be associated with earlier diagnosis in married individuals. These findings highlight the potential need for additional support services for single and SDW individuals, underscoring the importance of considering marital status when addressing demographic disparities in cancer care. Research Sponsor: None.

3629 **Poster Session**

Clinicopathological features of colorectal cancer in adolescents and young adults (AYA) at a tertiary referral centre in Nigeria. First Author: Sharif Adeniyi Folorunso, Obafemi Awolowo University Teaching Hospital Complex, Ile Ife, Nigeria

Background: Colorectal cancer (CRC) is traditionally considered a disease of older adults; however, its incidence among AYA has been rising globally. In sub-Saharan Africa, including Nigeria, there is limited data on the clinicopathological characteristics of CRC in this age group. Understanding the patterns of CRC in AYA in Nigeria is crucial for developing targeted screening, early detection, and treatment strategies in this population. This study aims to investigate the clinicopathological features of CRC in AYA at a tertiary referral centre in Nigeria. **Methods:** A retrospective review of the ARGO-OAUTHC database was conducted to identify adolescents and young adults (age less than 40) diagnosed with colorectal cancer between 2013 and 2024. We compared AYA patients with middle-aged adults (ages 40-65) to assess differences in clinical presentation and histopathological features. Only patients with complete histopathology were included in the analysis while patients older than 65 years were excluded. Descriptive statistics were used to summarize the data, and statistical tests were performed to assess significant differences between the two groups. **Results:** 866 patients diagnosed with CRC were identified. Of these, 150 (18%) were AYA, with a median age of 33 years, and 448 (54%) were middle-aged adults (ages 40-65). The presenting symptoms were similar between the AYA and middle-aged groups, however, AYA patients were less likely to be diagnosed by colonoscopy (14.9% vs 29.4%, p = 0.002). Additionally, more AYA patients presented with symptoms that did not limit their daily activities , leading to a delay in seeking medical attention (9.3% vs 2.8%, p = 0.016). AYA patients were less likely to present with early-stage disease (Stages I and II) compared to middle-aged patients, (13.1% vs 20.9%, p = 0.045). Histopathological features were similar between the two groups overall, though mucin production was more prevalent in AYA patients (64.1% vs 45.2%, p = 0.044). Lung metastasis was less common in AYA patients (8.3% vs 23.5%, p = 0.011), the pattern of metastasis to other organs was however similar between the two groups. **Conclusions:** AYA patients in Nigeria tend to present at more advanced stages, partly due to the non-restrictive nature of their symptoms. They were less likely to be diagnosed via colonoscopy and were more likely to exhibit mucin production in their tumors. These findings underscore the need for increased awareness and early screening efforts for colorectal cancer in AYA populations to facilitate earlier diagnosis. Research Sponsor: African Research Group for Oncology.

3630 **Poster Session**

Adherence to repeat screening for colorectal cancer using the multi-target stool DNA test: Real-world analysis of patients from federally qualified health centers. First Author: Mallik Greene, Exact Sciences Corporation, Madison, WI

Background: Initial and repeat colorectal cancer (CRC) screening rates are suboptimal and fall short of national goals in adults from historically disadvantaged backgrounds. This real-world study examined adherence to repeat mt-sDNA screening among patients from federally qualified health centers (FQHCs) across the US and among different payer types. **Methods:** Laboratory data from Exact Sciences Laboratories LLC were utilized for the period between January 1, 2023, and December 31, 2023, for those who had previously completed a mt-sDNA test. Study outcomes included adherence rate to mt-sDNA repeat screening and time to test return. The mt-sDNA screening adherence rate was defined as the percentage of patients who completed and returned the test kit and received a valid test result within 180 days of the initial shipment date. Time to test return was defined as the number of days from the date the test kit was shipped to the patient to the date ESL received the test kit with a specimen. **Results:** The study sample consisted of 19,536 eligible patients, including 9,592 (49.1%) aged 45-64 years, 8,689 (44.5%) aged 65-75 years and 1,225 (6.4%) aged 76-85 years. Overall, the mt-sDNA repeat screening adherence rate was 79.7% and the mean time to return the kit was 21.1 ± 20.8 days. A total of 2,375 (15.3%) individuals tested positive for CRC. Screening adherence for patients with Medicare was 84.7%, Medicare Advantage was 80%, commercial insurance was 78.2%, managed care organization was 74.6% and Medicaid was 65.9% ($p < 0.001$). Compared with patients covered by commercial insurance, those covered by Medicaid had 42% lower odds of adhering to mt-sDNA screening (OR: 0.582, 95% CI]: 0.461-0.733, $p < 0.001$). Patients with 2 or more prior successful tests had a numerically shorter mean time to test return compared to those with only 1 prior successful test, both overall and within each payer type. **Conclusions:** Findings from this real-world study suggest that patients receiving care from FQHCs had relatively high repeat mt-sDNA screening rates. While repeat screening adherence was generally high across patient demographic categories, there were significant differences by type of insurance coverage and number of prior successful mt-sDNA screenings. Research Sponsor: None.

3631 **Poster Session**

Quality-adjusted time without symptoms of disease or toxicity (Q-TWiST) analysis of pembrolizumab (pembro) versus chemotherapy (chemo) in microsatellite instability–high (MSI-H)/mismatch repair–deficient (dMMR) metastatic colorectal cancer (mCRC) in the KEYNOTE-177 trial. First Author: Elena Elez, Vall d'Hebron University Hospital and Institute of Oncology (VHIO), Barcelona, Spain

Background: In KEYNOTE-177 (NCT02563002),first-line pembro provided significantly longer progression-free survival and a trend toward improvement in overall survival (OS) compared with chemo in participants (pts) with MSI-H/dMMR mCRC after > 5 years of median follow-up. The objective of this analysis was to assess Q-TWiST for pts treated in KEYNOTE-177. **Methods:** Q-TWiST combines efficacy, safety, and quality of life in a single measure. The analysis categorized survival time into 3 health states: time with grade ≥3adverse events before disease progression or death (toxicity [TOX]), time without symptoms or toxicity before disease progression (TWiST), and time from disease progression to death (relapse [REL]). In all randomly assigned pts, the restricted mean survival time (RMST) in each state was first weighted by a quality-of-life utility value, measured as treatment-specific EQ-5D-3L scores for each health state using the US value set, and then summed to calculate the Q-TWiST value. Relative gains (defined as the Q-TWiST differences between pembro and chemo divided by the RMST of chemo) of ≥15% were defined as "clearly clinically important." Treatment difference 95% CIs were generated using the nonparametric bootstrapping method. The data cutoff date was July 17, 2023. **Results:** At a maximum follow-up of 84 months, pts in the pembro arm had a 13.8-mo (95% CI, 4.8-21.7) longer RMST in TWiST (24.3 vs 10.5 mo), a 4.8-mo (95% CI, −0.5 to 10.2) longer RMST in TOX (10.7 vs 5.9 mo), and an 11.1-mo (95% CI, −21.2 to −0.8) shorter RMST in REL (18.1 vs 29.3 mo) compared with chemo. As a proportion of overall pre-progression time, pts in the pembro arm spent less time in TOX than the chemo arm (31% vs 36%). For the analysis of restricted mean Q-TWiST based on treatment-specific utility weights, the difference between pembro and chemo favored pembro by 9.1 mo (95% CI, 2.3-15.5), a 20.0% (95% CI, 4.8-36.8) relative Q-TWiST gain. When TOX definition included grade ≥2 adverse events, the relative Q-TWiST gain was 19.7% (95% CI, 4.7-36.5). When OS was adjusted for crossover to anti–PD-(L)1 therapy as second-line treatment, relative Q-TWiST gain was 39.7% (95% CI, 20.1-63.7). **Conclusions:** Pembro provided clearly clinically important improvement in quality-adjusted survival time based on Q-TWiST analyses compared with chemo as first-line treatment in pts with MSI-H/dMMR mCRC. The magnitude of results related to established thresholds for clinically important Q-TWiST gain suggests that results from this analysis provide additional evidence for the use of pembro in this population. Clinical trial information: NCT02563002. Research Sponsor: Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA.

3632 **Poster Session**

Association between fine particulate matter exposure and colorectal cancer mortality by age at diagnosis: Insights from county-level analysis in the United States. First Author: Sara F. Haddad, Cleveland Clinic Foundation, Cleveland, OH

Background: Colorectal cancer (CRC) remains a leading cause of cancer mortality in the U.S., with environmental factors like air pollution potentially contributing to mortality. This study examines the association between fine particulate matter (PM2.5) exposure and CRC mortality rates, stratified by average-onset (aoCRC [≥50 years at diagnosis]) and early-onset (eoCRC [< 50 years at diagnosis]) cases. **Methods:** Age-adjusted county CRC mortality data (1999–2020, n = 2981 counties) were obtained from CDC Underlying Cause of Death (ICD-10: C18-C19 [excluding C18.1], C20), while 1999-2019 PM2.5 estimates (ug/m3), derived from Atmospheric Composition Analysis Group data, were mapped to U.S. county boundaries using R v.4.3.2. Covariates were derived from Census American Community Survey (ACS) 5-year estimates, CDC data, and County Health Rankings (CHR) data and included county-level area deprivation index (ACS), non-Hispanic Black % (ACS), Hispanic % (ACS), obesity prevalence (CDC), smoking prevalence (CHR), binge alcohol consumption (CHR), and uninsured % (ACS). Negative binomial count models were fit to explore associations between PM2.5 and CRC mortality rates, adjusted for covariates. Deviance R^2 was computed to examine model fits. **Results:** We found that for every 1% increase in PM2.5 exposure, aoCRC mortality increased by 0.98% ($p < 0.001$) and eoCRC mortality increased by 0.24% ($p = 0.435$), after adjustment for covariates. Deviance R^2 values indicated that PM2.5 and covariates explained 32.0% and 37.0% of the deviance in aoCRC and eoCRC mortality, respectively. **Conclusions:** PM2.5 exposure was a significant predictor of CRC mortality, but only for aoCRC cases. Air pollution and other covariates accounted for roughly one-third of the county-level deviance, suggesting the influence of additional factors. Systemic and individual-level interventions to reduce air pollution exposure may mitigate CRC mortality disparities in older populations. Further studies are needed to explore other potential contributors to CRC mortality. Research Sponsor: None.

TPS3633 **Poster Session**

A phase II study of pembrolizumab, carboplatin, paclitaxel, and radiation for the treatment of early-stage anal cancer: Big Ten Cancer Research Consortium GI22-588. First Author: Anita Turk, Indiana University Melvin and Bren Simon Comprehensive Cancer Center, Indianapolis, IN

Background: Anal squamous cell carcinoma (SCC) is an evolving public health challenge, with increasing incidence and mortality rates, particularly in older women with long-standing HPV infections. Standard-of-care treatment for early-stage anal SCC—5-fluorouracil (5FU) and mitomycin-C (MMC) with radiation—achieves high cure rates but poses significant toxicity risks, with grade 3-5 adverse events occurring in up to 70% of patients. Recent clinical trials, such as DECREASE and ACT4, have explored radiation de-escalation strategies, but limited progress has been made in expanding systemic treatment options for locally advanced disease. Building on pilot data demonstrating favorable clinical complete responses (cCR) with carboplatin and paclitaxel combined with radiation in patients ineligible for SOC regimens, this phase II trial evaluates the addition of pembrolizumab to this combination to enhance efficacy while reducing toxicity. **Methods:** This is a single-arm, phase II trial evaluating concurrent chemo-radiation with weekly carboplatin (AUC 2), paclitaxel (50 mg/m²), and pembrolizumab (200 mg every three weeks during chemoradiation and 400 mg every six weeks during maintenance) for early-stage anal SCC in patients ineligible for 5FU and MMC. The chemoradiation phase consists of up to six weeks of therapy with 50.4 Gy delivered over 28 fractions. Maintenance pembrolizumab is administered for up to eight cycles. The primary endpoint is the cCR rate at six months post-chemoradiation. Secondary endpoints include safety, tolerability, tumor downstaging, and disease-free survival. Exploratory objectives include the evaluation of genomic alterations and biomarkers such as versican and keratin 17 as predictors of therapeutic response. Major eligibility criteria include histologically confirmed stage I-IIIA anal SCC, measurable disease per RECIST v1.1, and treatment-naïve status. Key exclusions include active autoimmune disease requiring immunosuppression within two years and prior checkpoint inhibitor therapy. The target enrollment is 23 patients, with an accrual period of 12 months and an anticipated study duration of two years. The study is currently enrolling participants through the Big Ten Cancer Research Consortium. Clinical trial information: NCT06493019. Research Sponsor: Merck.

TPS3634 **Poster Session**

Alliance A022101/NRG-GI009: A pragmatic randomized phase III trial evaluating total ablative therapy for patients with limited metastatic colorectal cancer—Evaluating radiation, ablation, and surgery (ERASur). First Author: Eric David Miller, Ohio State University, Columbus, OH

Background: For patients with oligometastatic colorectal cancer (CRC), aggressive local therapy of isolated metastases, particularly in the liver, has been associated with long-term progression-free and overall survival (OS) primarily based on retrospective evidence. However, in patients with limited metastatic CRC that is deemed inoperable or those with additional disease outside of the liver or lungs, the role of local ablative therapies, including microwave ablation (MWA) and stereotactic body radiation therapy (SBRT), to render patients disease free is less clear. Despite the long history of treating oligometastatic CRC with local therapy, which is largely provider biased, questions remain regarding the benefit of extending the paradigm of metastatic directed therapy to patients with more extensive disease. This trial seeks to use a pragmatic multimodality approach that mirrors the current clinical dilemma. This study is designed to evaluate the safety and efficacy of adding total ablative therapy (TAT) of all sites of disease to standard of care systemic treatment in those with limited metastatic CRC. **Methods:** A022101/NRG-GI009 is a National Clinical Trials Network randomized phase III study planned to enroll 364 patients with newly diagnosed metastatic CRC (BRAF wild-type, microsatellite stable) without peritoneal metastasis or liver-only disease on baseline imaging. Patients receive first-line systemic therapy for 12-39 weeks. Patients with ≤4 sites of metastatic disease following initial systemic therapy that are amenable to any combination of surgical resection, MWA, and/or SBRT are then randomized 1:1, stratified by number of metastatic organ sites (1-2 vs. 3-4), timing of metastatic disease diagnosis (de novo vs. secondary), and presence of metastatic disease outside the liver/lungs in at least 1 site. Patients in Arm 1 will receive TAT consisting of treatment of all metastatic sites with SBRT, MWA, and/or surgical resection followed by standard of care systemic therapy. Patients in Arm 2 will continue with standard of care systemic therapy alone. The primary endpoint is OS. Secondary endpoints include event-free survival, treatment-related toxicities, and local recurrence with exploratory biomarker analyses. The study needs 346 evaluable patients combined in the 2 arms to demonstrate an improvement in OS with a hazard ratio of 0.7 to provide 80% power with a one-sided alpha of 5%. The trial utilizes a group sequential design with two interim analyses (25% and 50% of events) for futility. The trial activated in January 2023 and recruitment is ongoing. Support: U10CA180821, U10CA180882; https://acknowledgments.alliancefound.org. U10CA180820 (ECOG-ACRIN); U10CA180868 (NRG); U10CA180888 (SWOG); Clinical trial information: NCT05673148. Research Sponsor: U.S. National Institutes of Health.

TPS3635 **Poster Session**

Telisotuzumab adizutecan (ABBV-400; Temab-A) monotherapy vs trifluridine/tipiracil plus bevacizumab in patients with refractory metastatic colorectal cancer with increased c-Met protein expression: An open-label, randomized, phase 3 trial. First Author: John H. Strickler, Duke University School of Medicine, Durham, NC

Background: c-Met protein expression is increased in several solid tumors, including colorectal cancer (CRC). Temab-A is a c-Met–directed antibody-drug conjugate consisting of the antibody telisotuzumab conjugated to a potent topoisomerase 1 inhibitor payload. Preliminary data from the ongoing first-in-human study of Temab-A (NCT05029882) indicate a tolerable safety profile and promising antitumor activity in patients with third-line or later metastatic (m)CRC (Sharma et al. *JCO* 2023;41:3015). Herein, we describe a phase 3 study comparing Temab-A monotherapy with the standard of care (trifluridine/tipiracil plus bevacizumab) in patients with refractory mCRC with c-Met expression of 3+ in ≥10% of tumor cells by immunohistochemistry (IHC). **Methods:** This is an open-label, randomized, controlled, global phase 3 study(NCT06614192). Patient eligibility includes age ≥18 years, confirmed c-Met expression of 3+ in ≥10% of tumor cells, metastatic adenocarcinoma of the colon/rectum, measurable disease per RECIST v1.1, ECOG performance status 0–1, prior treatment with a fluoropyrimidine (eg, 5-FU or capecitabine), oxaliplatin, irinotecan, and an anti-VEGF antibody (unless locally not approved) or an anti-EGFR antibody if indicated, and appropriate targeted therapy or immunotherapy if targetable mutations present (eg, *BRAF* V600E or *HER2*) or MSI-H/dMMR. Prior treatment with regorafenib and/or fruquintinib is permitted, but no prior treatment with trifluridine/tipiracil Study-specific c-Met protein expression IHC cutoff is defined as 3+ intensity in ≥10% of tumor cells. The study consists of 2 stages. In stage 1, at least 60 patients will be randomized 1:1 to receive 2 different doses of intravenous (IV) Temab-A. In stage 2, 400 patients will be randomly assigned 1:1 to receive either the optimized dose of IV Temab-A or oral trifluridine/tipiracil plus IV bevacizumab. In stage 1, primary objectives are to determine the recommended phase 3 dose and to evaluate the efficacy, as measured by objective response (OR), and safety of Temab-A; secondary objectives are to assess progression-free survival (PFS), overall survival (OS), duration of response (DOR), disease control rate (DCR), and pharmacokinetics. In stage 2, the primary objectives are to demonstrate the superiority of Temab-A over trifluridine/tipiracil plus bevacizumab in terms of OR and OS; secondary objectives are to evaluate PFS, DOR, DCR, and safety of Temab-A treatment, and its impact on patient-reported outcomes. Response will be assessed by blinded independent central review per RECIST v1.1. Safety evaluations include adverse event monitoring, vital sign measurements, ECG variables, and clinical laboratory testing. Enrollment began in December 2024. Clinical trial information: NCT06614192. Research Sponsor: AbbVie Inc.; n/a.

TPS3636 **Poster Session**

OrigAMI-2: A randomized, phase 3 study of amivantamab vs cetuximab, both in combination with FOLFOX or FOLFIRI, as first-line treatment in left-sided *RAS/BRAF* wild-type metastatic colorectal cancer. First Author: Dirk Arnold, Asklepios Tumorzentrum Hamburg, AK Altona, Hamburg, Germany

Background: Approximately 50% of patients diagnosed with metastatic colorectal cancer (mCRC) are wild-type for *KRAS*, *NRAS*, and *BRAF* (*RAS/BRAF* WT). Standard initial therapy for left-sided *RAS/BRAF* WT mCRC is doublet chemotherapy (FOLFOX or FOLFIRI) combined with anti-EGFR therapy. However, resistance is nearly inevitable. *MET* alterations are known resistance mechanisms to EGFR inhibition, with *MET* amplification occurring in 5%-23% of EGFR-resistant mCRC. Amivantamab is an EGFR-MET bispecific antibody with immune cell-directing activity that is approved by the FDA for 4 indications in *EGFR*-mutated advanced non-small cell lung cancer. In the phase 1b/2 OrigAMI-1 study (NCT05379595), the combination of amivantamab plus FOLFOX or FOLFIRI demonstrated rapid and durable antitumor activity, regardless of tumor sidedness, in participants with *RAS/BRAF* WT mCRC (Pietrantonio ESMO 2024). The objective of this phase 3 randomized study is to assess the efficacy of amivantamab, as compared with cetuximab, both in combination with FOLFOX or FOLFIRI, as first-line therapy for participants with left-sided *RAS/BRAF* WT unresectable or metastatic CRC. **Methods:** The multicenter, global OrigAMI-2 study (NCT06662786) is planned to open in 216 sites in 21 countries. Eligible participants will be WT for *KRAS*, *NRAS*, and *BRAF* by local testing, have left-sided unresectable or metastatic colorectal cancer, and be treatment-naïve for advanced disease. Left-sided disease will be defined as a primary tumor arising from the splenic flexure, descending colon, sigmoid colon, rectosigmoid, or rectum. Key exclusion criteria include known dMMR/MSI-H status, HER2-positive or amplified tumor, and prior exposure to EGFR or MET targeting agents. Approximately 1000 participants will be randomly assigned 1:1 to receive subcutaneous amivantamab (co-formulated with recombinant human hyaluronidase [rHuPH20]) or intravenous cetuximab, both combined with FOLFOX or FOLFIRI (investigator's choice). Randomization will be stratified by chemotherapy choice (FOLFOX or FOLFIRI), limited disease (yes or no), and prior adjuvant therapy (yes or no). The primary endpoint will be progression-free survival by blinded independent central review. Secondary endpoints include overall survival, objective response rate, duration of response, and patient-reported outcomes. Safety assessments will include monitoring adverse events and laboratory abnormalities. Clinical trial information: NCT06662786. Research Sponsor: Janssen Research & Development, LLC, a Johnson & Johnson Company.

TPS3637 **Poster Session**

An observational/translational study to conduct real-world evidence and develop biomarkers of fruquintinib for patients with metastatic colorectal cancer (mCRC): FruBLOOM trial (JACCRO CC-19). First Author: Yu Sunakawa, Department of Clinical Oncology, St. Marianna University School of Medicine, Kawasaki, Kanagawa, Japan

Background: The FRESCO-1/2 trials demonstrated a survival benefit of fruquintinib (FRU) in mCRC after 3rd-line therapy. FRU can be considered as one of the standard treatments for mCRC. The FRESCO-2 trial was conducted in patients (pts) treated with FTD/TPI and/or regorafenib (Rego) and did not include pts who were not using either agent. Although FTD/TPI + bevacizumab (Bev) is currently one of 3rd-line standard treatments for mCRC, there are few data regarding the efficacy and safety of FRU in pts after FTD/TPI + Bev. Therefore, this study will accumulate real-world-data of FRU in clinical practice and evaluate the efficacy and safety of FRU after FTD/TPI + Bev. Also, we will evaluate clinical outcomes of FRU as 3rd- or later-line treatment after both FTD/TPI + Bev and Rego. The predictive biomarkers of FRU in the later-line setting hold significant clinical promise, for choosing personalized treatment plans (e.g., FRU vs. FTD/TPI + Bev / Rego) and enhancing the prognosis of mCRC pts. Therefore, this translational study approaches developing biomarkers for predicting FRU efficacy by analyzing pre-treatment blood samples. Furthermore, we will explore treatment resistance mechanisms using post-treatment blood samples. **Methods:** This is a multicenter observational/translational study to prospectively evaluate the efficacy and safety of FRU as a 3rd- or later-line treatment, mainly after FTD/TPI + Bev in mCRC pts in clinical practice. We will enroll 200 pts receiving FRU after FTD/TPI + Bev to the cohort A, and 100 pts receiving FRU as 3rd-line or after both FTD/TPI + Bev and Rego to the cohort B. Eligibility criteria are (1) pts with CRC confirmed as adenocarcinoma, (2) pts planning to receive FRU monotherapy as 3rd- or later-line treatment, (3) prior treatments with fluoropyrimidine-, oxaliplatin- and irinotecan-based chemotherapy, an anti-VEGF biological therapy, an anti-EGFR therapy (if *RAS*/*BRAF* wild-type), BRAF therapy (if *BRAF* mutant), and immune checkpoint inhibitor (if MSI-high), (4) pts with ECOG Performance Status of 0-2, (5) pts must be at least 18 years of age at the time of consent, and (5) pts have measurable or evaluable lesions in RECIST v1.1. The primary endpoint is overall survival in pts of the cohort A. The secondary endpoints are clinical outcomes including response rate, progression-free survival, duration of response, and safety in pts of the cohort A and B. In the biomarker study, blood samples will be prospectively collected before and after treatment, for translational research including genomic alteration analysis in circulating tumor-DNA by DNA exome sequencing, gene expression measurement in cfRNA by tumor-educated blood platelets (TEP)-Seq RNA analysis, and plasma proteins analysis by multiplex immunoassay panels. Enrollment opens in February 2025 (UMIN000056813). Clinical trial information: UMIN000056813. Research Sponsor: Takeda.

TPS3638 **Poster Session**

OrigAMI-3: A randomized, phase 3 study of amivantamab plus FOLFIRI vs cetuximab or bevacizumab plus FOLFIRI in participants with recurrent, unresectable, or metastatic *RAS/BRAF* wild-type colorectal cancer. First Author: Joel R. Hecht, UCLA Jonsson Comprehensive Cancer Center, Santa Monica, CA

Background: Among patients with metastatic colorectal cancer (mCRC), approximately 50% are wild-type for *KRAS*, *NRAS*, and *BRAF* (*RAS/BRAF* WT) without actionable genomic alterations. Standard first-line therapy for *RAS/BRAF* WT mCRC is 5-FU-based doublet chemotherapy (FOLFOX or FOLFIRI) plus anti-EGFR or anti-VEGF therapy. The choice of second-line treatment is dependent on first-line treatment (eg, oxaliplatin-based chemotherapy in the first-line necessitates irinotecan-based in the second-line, and vice versa). Known resistance mechanisms to anti-EGFR therapy are *MET* alterations, with *MET* amplification occurring in 5%-23% of EGFR-resistant mCRC and increasing in prevalence over subsequent lines of therapy. Amivantamab is an EGFR-MET bispecific antibody with immune cell-directing activity and is FDA-approved for 4 indications in *EGFR*-mutated advanced non-small cell lung cancer. In the phase 1b/2 OrigAMI-1 study (NCT05379595), amivantamab plus FOLFIRI demonstrated promising antitumor activity, independent of line of therapy, in participants (pts) with *RAS/BRAF* WT mCRC without prior anti-EGFR exposure (Pietrantonio ESMO 2024). The objective of this phase 3 randomized study is to assess the efficacy of amivantamab plus FOLFIRI vs cetuximab or bevacizumab plus FOLFIRI, as second-line therapy for pts with recurrent *RAS/BRAF* WT mCRC. **Methods:** The global OrigAMI-3 study (NCT06750094) is planned to open in 230 sites in 25 countries. Eligible pts will be WT for *KRAS*, *NRAS*, and *BRAF*, have recurrent unresectable or mCRC, and must have had disease progression on one prior line of systemic therapy for metastatic disease (prior regimen must be fluoropyrimidine-based and oxaliplatin-based therapy). Pts with treated, stable, and asymptomatic brain metastases are allowed. Key exclusion criteria include known dMMR/MSI-H status without prior immunotherapy, HER2-positive or amplified tumor, and prior exposure to irinotecan or agents targeting EGFR or MET. Approximately 700 pts will be randomly assigned 1:1 to receive subcutaneous amivantamab (co-formulated with recombinant human hyaluronidase [rHuPH20]) plus FOLFIRI vs intravenous cetuximab or bevacizumab (investigator's choice, per local guidelines) plus FOLFIRI. Randomization will be stratified by choice of cetuximab or bevacizumab, primary tumor location (left vs right-sided), duration of first-line therapy (< 6 months or ≥6 months), and prior anti-VEGF therapy (yes or no). The dual primary endpoints will be progression-free survival by blinded independent central review and overall survival. Secondary endpoints include objective response rate, duration of response, and patient-reported outcomes. Safety assessments will include monitoring adverse events and laboratory abnormalities. Clinical trial information: NCT06750094. Research Sponsor: Janssen Research & Development, LLC, a Johnson & Johnson company.

TPS3639 **Poster Session**

Stereotactic body radiotherapy combined with PD-1 antibody in unresectable colorectal liver metastases: A prospective, multicenter, single-arm, phase II study (SPARKLE-L). First Author: Fang He, Department of Radiation Oncology, the Sixth Affiliated Hospital, Sun Yat-sen University, Guangzhou, China

Background: Colorectal cancer liver metastasis (CRLM) significantly decreases colorectal cancer (CRC) patient prognosis, affecting 30-50% of CRC patients at diagnosis or thereafter. Notably, up to 70%-90% CRLM are diagnosed as unresectable. Standard treatments include systemic chemotargeted-therapies (CT). However, only 10-30% CRLM can be converse to resectable state by CT, with an objective response rate (ORR) of just 15%-20% and a median overall survival (OS) of approximately 20-30 months. Improving prognosis of CRLM patients remains challenging. Stereotactic body radiation therapy (SBRT) combined with immunotherapy might offer promising alternatives. SBRT provides high-dose tumor control while protecting surrounding tissues better than conventional radiotherapy. It also facilitates the release of tumor-associated antigens, reshaping the immune microenvironment and inducing stronger immune responses. The combination of SBRT and PD-1 antibodies might synergistically enhance the anti-tumor efficacy. Despite SBRT's demonstrated efficacy in unresectable CRLM with few adverse reactions, no prospective studies have explored its combination with PD-1 antibodies. **Methods:** This is a multicenter, open-label, single-arm, phase II trial conducted in China. Patients will receive SBRT at 8-12 Gy per fraction over 5 fractions, combined with 5-FU-based CT and PD-1 antibody therapy before and after SBRT. Eight weeks ($\pm$2 weeks) post SBRT, imaging assessments or multi-point liver biopsies will be performed. Multidisciplinary teams (MDT) will determine subsequent plans: cCR/pCR patients will undergo maintenance CT or enter a watch-and-wait phase; non-cCR/pCR patients will continue maintenance CT or exit the study. This is the first study exploring whether SBRT combined with PD-1 monoclonal antibody can improve ORR, OS, quality of life (QOL) and potentially achieve no evidence of disease (NED) status for unresectable CRLM. Key inclusion criteria: pMMR/MSS CRC, MDT-assessed unresectability due to main portal vein invasion, multiple hepatic vein invasion or lack of R0 resection/ablation feasibility. Main exclusion criteria encompass active hepatitis, cirrhosis, Child-Pugh B/C, checkpoint inhibitor therapies history and ECOG performance status $\geq$2. Twenty-four patients are planned for enrollment, with two already enrolled as of January 25, 2025. The study is registered with ClinicalTrials.gov (NCT06794086) and is ongoing. Clinical trial information: NCT06794086. Research Sponsor: None.

TPS3640 **Poster Session**

Neoadjuvant cetuximab plus tislelizumab combined with chemotherapy in pMMR RAS/BRAF wild-type (wt) locally advanced rectal cancer (LARC): A prospective, multicenter, phase II study. First Author: Gang Liu, Tianjin Medical University General Hospital, Tianjin, Tianjin, China

Background: For patients (pts) with locally advanced rectal cancer (LARC), chemoradiotherapy followed by total mesorectal excisionis is recommended as standard therapy according to the NCCN guidelines. However, there is no stratification strategy for neoadjuvant therapy based on molecular alterations, and radiotherapy is insufficient with pathologic complete response (pCR) rates at 11%-15%. There is an urgent need for new therapeutical options to improve the pCR rate in these pts. Adding anti-EGFR therapy to neoadjuvant chemotherapy may improve progression-free survival for RAS/BRAF WT LARC pts. Furthermore, previous studies demonstrated that combining anti-EGFR with immune checkpoint inhibitors could further improve pCR rate. Cetuximab, an anti-EGFR monoclonal antibody, has gained FDA approval for RAS WT metastatic colorectal cancer. Tislelizumab, an anti-PD-1 monoclonal antibody, is effective in blocking PD-1/PD-L1 interaction in preclinical experiments. This study introduces an innovative approach, combining Cetuximab, Tislelizumab and chemotherapy, as a total neoadjuvant therapy for pMMR RAS/BRAF wt LARC pts. **Methods:** This prospective, multicenter, phase II study investigated the efficacy and safety of neoadjuvant treatment with FOLFOX chemotherapy plus Cetuximab and Tislelizumab for MSS-RAS/BRAF WT LARC. Eligible participants were 18 years or older, with an ECOG PS of 0–2, primary, and a biopsy-proven tumors meeting all the following criteria: clinical tumour stage cT3-4 N0M0 or cT1-4N+M0, tumor distance from the anus$\leqq$10 cm, no distant metastasis. Pts initially received a cycle chemotherapy of FOLFOX pending genetic results. Eligible pts with MSS-RAS/BRAF WT LARC then underwent 5 preoperative neoadjuvant cycles of mFolfOx6 (oxaliplatin 85 mg/m², D1; leucovorin 200 mg/m²,D1; 5-FU bolus 400 mg/m2 D1 then 2.4 g/m²,D2-3) + Cetuximab (500mg/m2, D1, q2w) + Tislelizumab (200mg, D1, q2w). Subsequently, pts underwent TME about 4 weeks after the last cycle. Imaging evaluation will be conducted 6 weeks after the initiation of treatment, pts with regressed tumors will receive a standard chemoradiotherapy. The primary endpoint was pCR rate. Secondary endpoints included the Neoadjuvant Rectal Score, Objective Response Rate, R0 resection rate, Major Pathological Response rate, Anal Sparing rate, 3-year Disease-Free Survival, 3-year Local Recurrence Rate, 3-year Overall Survival. Based on a review of the literature, the estimated pCR rate for standard preoperative neoadjuvant chemoradiotherapy is approximately 15%. The expected pCR rate for the MSS-RASwt/BRAFwt group is around 30%, with a one-sided significance level (α) of 0.05 and a power (1-β) of 0.8, using the Simon two-stage method, the sample size is calculated to be 25 cases. The study started in middle 2022 and is recruiting. Clinical trial information: ChiCTR2200062002. Research Sponsor: None.

TPS3641 **Poster Session**

Node-sparing modified short-course radiotherapy combined with CAPOX and tislelizumab versus conventional short-course preoperative chemoradiotherapy for proficient mismatch repair or microsatellite stable locally advanced rectal cancer (mRCAT-III): A multicenter, randomized, open-label, phase 3 trial. First Author: Zhangfa Song, Sir Run Run Shaw Hospital, Zhejiang University School of Medicine, Hangzhou, Zhejiang, China

Background: Total neoadjuvant chemoradiotherapy is the standard of care for locally advanced rectal cancer (LARC) to control local recurrence and achieve organ preservation. However, for proficient mismatch repair (pMMR) or microsatellite stable (MSS) LARC, which accounts for nearly 90% of rectal cancers, conventional chemoradiotherapy has limited efficacy and is associated with significant side effects. Recent studies have shown that combining radiotherapy with immunochemotherapy can improve pathological complete response (pCR) rates, but the inclusion of tumor-draining lymph nodes (TDLNs) in the conventional irradiation field may impair T-cell immunity and reduce response to immunotherapy. Our previous phase II trial demonstrated that node-sparing modified short-course radiotherapy combined with chemotherapy and PD-1 blockade could achieve a high pCR rate of 78.8% in pMMR LARC[1]. Building on these findings, we initiated this phase III trial to compare this novel treatment regime with conventional short-course chemoradiotherapy in improving pCR rates. **Methods:** This is a phase III, open-label, multicenter, randomized trial conducted across 17 hospitals in China. A total of 170 eligible MSS/pMMR middle or low rectal cancer patients (cT3-4N0/+M0) will be recruited and randomly assigned (5:5:1) to three groups: control group (conventional short-course chemoradiotherapy), experimental group (node-sparing modified short-course chemoradiotherapy plus PD-1 blockade), and exploratory group (conventional short-course chemoradiotherapy plus PD-1 blockade). The innovative node-sparing modified short-course radiotherapy targets only the primary tumor bed, excluding TDLNs. Following randomization, patients will receive short-course radiotherapy (conventional or node-sparing) followed by four cycles of CAPOX $\pm$ tislelizumab: tislelizumab 200 mg IV on day 1, oxaliplatin 130 mg/m² IV on day 1, and capecitabine 1000 mg/m² orally on days 1-14, and Total mesorectal excision (TME) will be performed at weeks 14-15. The primary endpoint is pCR rate, while secondary endpoints include organ preservation rate, disease-free survival, overall survival, adverse effects, and quality of life. As of January 2025, 46 of the planned 170 patients have been enrolled. The Data Monitoring Committee (DMC) reviewed the trial in December 2024 and recommended continuing as planned. Reference: Annals of Oncology (2024) 24 (suppl_1): 1-20. 10.1016/iotech/iotech100744 Clinical trial information: NCT06507371. Research Sponsor: Sir Run Run Shaw Hospital Clinical Research Cultivation Program.

TPS3642 **Poster Session**

A phase II study of encorafenib and cetuximab (EC) beyond progression in combination with FOLFIRI in *BRAF* V600E-mutated metastatic colorectal cancer (mCRC). First Author: Maria Alessandra Calegari, Medical Oncology, Comprehensive Cancer Center, Fondazione Policlinico Universitario Agostino Gemelli, IRCCS, Rome, Italy

Background: *BRAF* V600E mutation occurs in approximately 10% of metastatic colorectal cancers (mCRC) and confers poor prognosis. While the combination of encorafenib and cetuximab (EC) has demonstrated improved outcomes in previously treated *BRAF* V600E-mutated mCRC patients (pts), the duration of response remains suboptimal with median progression-free survival (mPFS) of 4.3 months (m). Approximately half of pts (45%) receive subsequent treatment after EC progression, predominantly with chemotherapy (ChT). Data from the safety lead-in (SLI) of the BREAKWATER trial, assessing EC in combination with ChT doublet in the first-line setting, demonstrated manageable safety profile and promising early efficacy signals for EC in combination with FOLFIRI, despite pharmacokinetic interaction. **Methods:** ECLYPse (NCT06640166; EU CT Number 2023-508615-24-00) is a multicenter, single-arm, phase II study evaluating EC continuation beyond progression in combination with FOLFIRI in pts with *BRAF* V600E-mutated mCRC who progressed on second-line EC. Key eligibility criteria include: histologically confirmed colorectal adenocarcinoma, *BRAF* V600E mutation, documented disease progression on EC in second-line setting, benefit to previous treatment with EC (best response: complete response, partial response or stable disease lasting for at least 3 months), measurable disease according to RECIST 1.1 criteria, ECOG PS $\leq$1, and availability of archival tumor tissue. Patients receive encorafenib 300 mg daily, cetuximab 500mg/m2 iv every 2 weeks, and standard FOLFIRI regimen. The primary endpoint is 6-month PFS rate. Secondary endpoints include PFS, overall survival, duration of response, objective response rate, disease control rate, and safety. Translational analyses include comprehensive genomic profiling on archival tissue and serial ctDNA analysis. Tumor assessment with contrast-enhanced CT scan of thorax, abdomen and pelvis is performed every 8 weeks. Using a single-stage design with one-sided α = 0.05 and 80% power, 25 patients will be enrolled to detect an improvement in 6-month PFS rate from 10% (null hypothesis) to 30% (alternative hypothesis). If at least 7 pts will be alive and not progressing at 6 months, the treatment will be considered sufficiently active to warrant further investigation. The study is currently enrolling at multiple sites in Italy. Clinical trial information: NCT06640166. Research Sponsor: Pierre Fabre.

TPS3643 **Poster Session**

Combining low-dose regorafenib with pembrolizumab as a front-line therapy for patients with MSI-H colorectal cancer: REGPEM-CRC-01. First Author: Ibrahim Halil Sahin, University of Pittsburgh Medical Center (UPMC), Pittsburgh, PA

Background: Currently, pembrolizumab is one of the front-line therapies for patients with MSI-H CRC. However, approximately 40% of patients who received pembrolizumab experienced disease progression early in the course of disease (KEYNOTE 177). Therefore, there is still an unmet need to enhance the efficacy of checkpoint inhibitors in MSI-H CRC. MSI-H CRC has a higher level of expression of VEGF in blood compared to patients compared to its MSS counterpart (Hansen et al. Colorectal Dis. 2011). Consistently, exploratory analysis of CALBG-80405 and PARADIGM trial showed that patients with MSI-H CRC were more likely to benefit from anti-VEGF therapy than anti-EGFR therapy regardless of the side of the tumor. NSABP C-08 also suggested that anti-VEGF therapy may have biological activity even in as adjuvant therapy for patients with MSI-H colon cancer. Regorafenib is a potent VEGF and multikinase inhibitor involved in pathologic processes such as oncogenesis, tumor angiogenesis, metastasis and tumor immunity, with preclinical evidence showing its immune modulatory effect in the tumor microenvironment. In this trial, we hypothesize that adding low-dose regorafenib to pembrolizumab may induce synergistic activity beyond their independent clinical efficacy and create deep and durable responses for patients with MSI-H CRC. **Methods:** In the lead arm of this prospective randomized study, 22 patients will be enrolled through Hoosier Cancer Research Network (HCRN-GI23-643). In this first line clinical trial, patients will receive regorafenib 60 mg daily in combination with pembrolizumab 200mg IV in cycle 1, followed by regorafenib 90mg in subsequent cycles to optimize the treatment tolerance and compliance. The primary outcome that will be measured is ORR, defined as the percentage of partial or complete response to the treatment within 12 months. ORR will be measured using RECIST 1.1. criteria. A formal one-sided hypothesis test will be conducted for futility, assuming that we will reject the null hypothesis of a target ORR only if we have strong evidence. In this study, we assume a null hypothesis that ORR is 0.60, which would reflect significant clinical improvement over the current standard of ORR = 0.43 from KEYNOTE 177. The alternative hypothesis is that ORR is less than 0.60. For the lead-in phase of the study, the emphasis is on controlling Type I error to be small, to be 0.05 or lower. An exact binomial test will be conducted, based on the number of ORRs in the 22 patients. The study is currently accruing through Hoosier Cancer Research Network was activated in July 2024. Clinical trial information: NCT06006923. Research Sponsor: None.

TPS3644 **Poster Session**

Colon adjuvant chemotherapy based on evaluation of residual disease (CIRCULATE-NORTH AMERICA): NRG-GI008. First Author: Arvind Dasari, The University of Texas MD Anderson Cancer Center, Houston, TX

Background: Currently, there are no biomarkers validated prospectively in randomized studies for resected colon cancer (CC) to determine need for adjuvant chemotherapy (AC). However, circulating tumor DNA (ctDNA) represents a highly specific and sensitive approach (especially with serial monitoring) for identifying minimal/molecular residual disease (MRD) post-surgery in CC patients (pts), and may outperform traditional clinical and pathological features in prognosticating risk for recurrence. CC pts who do not have detectable ctDNA (ctDNA-) are at a much lower risk of recurrence and may be spared the toxicities associated with AC. Furthermore, for CC pts with detectable ctDNA (ctDNA+) who are at a very high risk of recurrence, the optimal AC regimen has not been established. We hypothesize that for pts whose CC has been resected, ctDNA status may be used to risk-stratify for making decisions about AC. **Methods:** In this prospective phase II/III trial, up to 1,912 pts with resected stage IIB, IIC, and III CC will be enrolled. Based on the post-operative ctDNA status using personalized and tumor-informed assay (Signatera™, bespoke assay), those who are ctDNA- (Cohort A) will be randomized to immediate AC with fluoropyrimidine (FP)+oxaliplatin (Ox) for 3-6 mos per established guidelines *v* serial ctDNA monitoring. Patients who are ctDNA+ post-operatively, or with serial monitoring (Cohort B), will be randomized to FP+Ox *v* more intensive AC with addition of irinotecan (I) for 6 mos. One cycle of chemotherapy is allowed while awaiting ctDNA testing results for cohort assignment. The primary endpoints for Cohort A are time to ctDNA+ status (phase II) and disease-free survival (DFS) (phase III) in the immediate *v* delayed AC arms. The primary endpoint for Cohort B is DFS in the FP+Ox *v* FP+Ox+I arms for both phase II and phase III portions of the trial. Secondary endpoints include prevalence of detectable ctDNA post-operatively, time-to-event outcomes (overall survival and time to recurrence) by ctDNA status, and the assessment of compliance to adjuvant therapy. Biospecimens including archival tumor tissue, as well as post-operative plus serial matched/normal blood samples, will be collected for exploratory correlative research. Active enrollment across the NCTN started in June 2022 with CCTG sites joining in August 2023. Current accrual (as of 1-27-2025): 647/1,912. NCT: 05174169. Support: U10 CA180868, -180822; -180888; UG1 CA189867; Natera, Inc. Clinical trial information: NCT05174169. Research Sponsor: National Cancer Institute; U10CA180868; National Cancer Institute; U10 CA180822; National Cancer Institute; UG1CA189867; Natera, Inc.

TPS3645 **Poster Session**

Platform study of circulating tumor DNA–directed adjuvant chemotherapy in colon cancer (CLAUDIA Colon Cancer, KCSG CO22-12). First Author: Yongjun Cha, Center for Colorectal Cancer, Research Institute and Hospital, National Cancer Center, Goyang, Korea, Republic of (South)

Background: Tumor-informed circulating tumor DNA (ctDNA) analysis allows for the sensitive detection of minimal residual disease (MRD) and has the potential to enhance patient stratification for adjuvant chemotherapy (AC). In patients with stage II-III colon cancer, we demonstrated that postoperative MRD is associated with poor disease-free survival (DFS) despite oxaliplatin-based AC. We hypothesize that intensifying AC in colon cancer patients with postoperative MRD may improve survival outcomes. **Methods:** This multi-center platform trial (NCT05534087) consists of a prospective observational study (Part 1) and an interventional randomized trial (Part 2). In Part 1, approximately 1,200 patients with colon cancer will be screened for MRD at 3–6 weeks postoperatively using atumor-informed hybrid-capture-based ctDNA MRD assay (CancerDETECT) which tracks ~100 patient-specific somatic variants identified through tumor whole-exome sequencing. Key eligibility criteria include: age $\geq$19 years, $\leq$6 weeks post-curative resection, pathological diagnosis of colon cancer, stage III or stage II with high-risk features requiring AC with FOLFOX/CAPOX, and no macroscopic residual disease. All patients in Part 1 will complete 3 months of standard adjuvant FOLFOX/CAPOX while awaiting MRD results. After 3 months of AC, MRD-negative patients are managed at the investigator's discretion. Patients with MRD positivity will be screened for Part 2 clinical trial following the completion of initial 3 months of standard AC titled "*Randomized Controlled Phase III Trial of Treatment Intensification in Stage II–III Colon Cancer Patients with Positive MRD after Curative Resection*." Part 2 investigates the superiority of an experimental arm (modified FOLFIRINOX for 3 months) compared to a control arm (FOLFOX/CAPOX for 3 months). The primary endpoint is the 3-year DFS rate, while secondary endpoints include the 5-year overall survival rate, treatment-related adverse events, treatment adherence, and patient-reported outcomes. A total of 236 patients will be enrolled, assuming a hazard ratio of 0.64, 80% power, a two-sided alpha of 0.05, and a 10% dropout rate. As of November 2024, 630 patients have been screened in Part 1, and 99 patients have been enrolled in Part 2. Both studies are ongoing, and an interim analysis is planned after $\geq$ 48 events. Clinical trial information: NCT05534087. Research Sponsor: National R&D Program for Cancer Control through the National Cancer Center (NCC) funded by the Ministry of Health & Welfare, Republic of Korea (HA22C0062).

TPS3646 **Poster Session**

mFOLFOX6 + bevacizumab + PD-1 monoclonal antibody vs. mFOLFOX6 in locally advanced pMMR/MSS CRC: A multicenter, randomized controlled phase III study (BASKETIII). First Author: Jun Huang, Department of Colorectal Surgery, The Sixth Affiliated Hospital, Sun Yat-sen University, Guangzhou, China

Background: Immunotherapy has shown promising therapeutic effects in mismatch repair-deficient or microsatellite instability-high (dMMR/MSI-H) colorectal cancer (CRC). However, for patients with mismatch repair-proficient or microsatellite stable (pMMR/MSS) CRC, the efficacy of single-agent PD-1 monoclonal antibody remains limited. Previous studies reported that combining anti-angiogenic drugs with PD-1 monoclonal antibody might improve the efficacy of immunotherapy. Our BASKETII study (NCT04895137) demonstrated that the neoadjuvant therapy regimen of mFOLFOX6 combined with Bevacizumab and sintilimab significantly enhanced the immunotherapy sensitivity of pMMR/MSS locally advanced CRC (LACRC), resulting in improved pathological complete response (pCR) rates and higher R0 resection rates. **Methods:** BASKETIII is a multicenter, randomized controlled, phase III study with a parallel design conducted in China. This trial aims to evaluate whether the neoadjuvant therapy regimen of mFOLFOX6 combined with Bevacizumab and sintilimab can further improve survival outcomes, and maintain the higher pCR rate and acceptable safety profile compared to mFOLFOX6 in pMMR/MSS LACRC patients. Eligible participants will be randomly assigned in a 1:1 ratio to either the experimental group or the control group. Participants in the experimental group will receive the neoadjuvant therapy regimen of mFOLFOX6 + Bevacizumab + sintilimab. The first five doses will follow the mFOLFOX6 combined with Bevacizumab and sintilimab regimen, and the sixth dose will receive only mFOLFOX6 and sintilimab but without Bevacizumab, in order to avoid delay of surgery. Participants in the control group will receive the neoadjuvant therapy regimen of mFOLFOX6 alone. Participants in both groups will undergo radical surgical treatment after neoadjuvant therapies. Participants who achieve pCR based on postoperative pathology will be regularly followed up. Participants who do not achieve pCR will receive adjuvant therapy with a maxim of six doses and will be regular followed up after the final dose of adjuvant therapy. The primary outcome of this study is to evaluate the 3-year disease-free survival (DFS). The key inclusion criteria include histologically confirmed adenocarcinoma of the colon or upper rectum; tumor biopsy immunohistochemical identified pMMR or MSS identified through next-generation sequencing or polymerase chain reaction; Clinical staging of cT4NxM0. The main exclusion criteria include evidence of distant metastasis beyond the pelvic region; history of pelvic or abdominal radiotherapy; multiple CRC or multiple primary tumors; history of immunotherapy and other malignancies within the past 5 years. A total of 122 patients are planned to be enrolled in this study. This study is registered with ClinicalTrials.gov (NCT06791512) and is recruiting. Clinical trial information: NCT06791512. Research Sponsor: National Natural Science Foundation of China.

TPS3647 **Poster Session**

A precision medicine trial leveraging tissue and blood-based tumor genomics to optimize treatment in resected stage III and high-risk stage II colon cancer (CC) patients (pts): The SAGITTARIUS trial. First Author: Clara O. Montagut, Hospital del Mar Research Institute, Barcelona, Spain

Background: Circulating tumor DNA (ctDNA) testing has emerged as a transformative tool for detecting molecular residual disease (MRD). Multiple prospective trials have demonstrated the potential of ctDNA in guiding treatment decisions for stage II-III CC pts. Numerous ongoing randomized clinical trials (RCTs) are adjusting adjuvant chemotherapy (ACT) intensity based on MRD status. However, data from ctDNA-guided trials, including PEGASUS (NCT04259944), reveal that intensified ACT is curative in only a small proportion of MRD cases. To address this limitation, the SAGITTARIUS RCT was designed to evaluate whether combining ctDNA detection with targeted agents selected on the basis of tissue-based comprehensive genomic profiling (CGP) can optimize treatment in high risk (i.e. MRD+) pts while sparing low risk (i.e. MRD−) from unnecessary toxicity. **Methods:** SAGITTARIUS is a Phase III RCT evaluating ctDNA and tissue-guided personalized post-surgical management in resected stage III and high-risk stage II CC pts. Tumor-informed, personalized ctDNA test (Signatera, Natera, Inc.) and CGP (TruSight™ Oncology Comprehensive EU, Illumina, Inc.) are used to determine MRD status and tumor genomic landscape, respectively, including genetic mutation (mut) and amplification (ampl), tumor mutational burden (TMB) and microsatellite instability (MSI) status. Pts are stratified based on post-surgery (3-5 weeks) ctDNA status into two embedded RCTs:Trial-1)ctDNA-positive (ctDNA+) ptsare further stratified based on MSI and RAS/RAF status and randomized 1:1 to standard 6-month ACT (CAPOX/FOLFOX) or personalized treatment (PT) guided by CGP biomarkers with reassessment of ctDNA status to guiding subsequent therapies (chemotherapy regimens in ctDNA+ or maintenance and follow-up in seroconverted; Trial-2) ctDNA-negative (ctDNA−) ptsare randomized 1:1 to a physician-choice strategy or observation with ctDNA reassessed at 2 and 4 months and, in cases of positivity, cross over to Trial-1. PT include 3-month CAPOX followed by FOLFIRI or TEMIRI based on MGMT status (RAS/RAFmut), Ipilimumab + nivolumab (MSI and TMB-high POLEmut), pertuzumab + trastuzumab (HER2ampl), FOLFOX + panitumumab (RAS/RAF/HER2 wild-type). The primary endpoint (EP) is 2-year recurrence-free survival (RFS) in ctDNA+ pts. Secondary EPs include 2-year RFS in ctDNA− pts, 3- and 5-year overall survival, and ctDNA conversion rate. Quality of life and health costs data are collected for cost effectiveness analysis. Biospecimens, including archival tumor tissue, serial blood samples, and buccal swabs, are collected for exploratory analyses. To detect a hazard ratio of 0.6325 for ctDNA-guided PT vs standard ACT, 200 ctDNA+ pts will be randomized in Trial-1. Recruitment began in October 2024 across 26 institutions in Italy, Spain, and Germany. Clinical trial information: NCT06490536. Research Sponsor: European Union; 101104657.

TPS3648 **Poster Session**

Phase II study of epacadostat (INCB024360) added to preoperative chemoradiation in patients with locally advanced rectal cancer. First Author: Moh'd M. Khushman, Washington University School of Medicine, St. Louis, MO

Background: Indoleamine 2,3-dioxygenase 1 (IDO1) metabolizes tryptophan along the kynurenine pathway and is recognized as a potent suppressor of tumor reactive immunity. Epacadostat is an orally active, potent and selective inhibitor of IDO1. In preclinical studies, IDO1 was found to promote resistance to radiation in rectal cancer, irrespective of microsatellite instability (MSI) status. IDO1 inhibition with epacadostat improved tumor radiosensitivity by relieving immune suppression and augmenting radiation-induced apoptosis while protecting the normal intestine from radiation damage. In a phase 1 trial, 17 patients were enrolled from 4/2019 to 8/2023. Epacadostat in combination with short-course radiation therapy (SCRT) and CAPOX was well-tolerated and the recommended phase 2 dose (RP2D) of epacadostat was determined to be 400 mg BID. An NCI supported Phase 2 trial is ongoing to further evaluate the promising disease responses reported in the dose escalation phase. **Methods:** This phase 2 multicenter, open-label trial includes treatment and biomarker cohorts. In the treatment cohort, epacadostat at 400 mg BID will be administered concurrently with SCRT followed by epacadostat monotherapy until 1 day prior to neoadjuvant chemotherapy, followed by standard-of-care (SOC) neoadjuvant chemotherapy and, ultimately, surgical resection or non-operative management (NOM). Biomarker cohort enrollment will commence at completion of treatment cohort accrual. Enrolled patients will be treated with SOC SCRT followed by SOC neoadjuvant chemotherapy and surgical resection or NOM. Eligible patients must be a treatment-naïve, newly diagnosed, pathologically confirmed, locally advanced rectal cancer (defined by 8th edition AJCC stage 2 or 3, or stage 1 not eligible for sphincter-sparing surgery) with plans to proceed with neoadjuvant SCRT and chemotherapy. The primary endpoint is the neoadjuvant rectal (NAR) score. Secondary endpoints are pathologic complete response (pCR) rate, complete clinical response (cCR) rate and progression-free survival (PFS). Exploratory endpoints are pharmacodynamics, PDX and organoid generation, identification of molecular predictors of response and resistance, correlation of radiographic and pathologic response and effect of treatment on patient quality of life. We aim to enroll 27 patients in the treatment cohort and 10 in the biomarker cohort. Clinical trial information: Clinical Trial Registration: NCT03516708. Research Sponsor: NIH (grant number 1R01CA278197-01A1); Incyte (drug only).

TPS3649 **Poster Session**

AZUR-4, a phase 2, open label, randomized study of neoadjuvant dostarlimab plus capecitabine plus oxaliplatin (CAPEOX) versus CAPEOX alone in previously untreated T4N0 or stage III mismatch repair proficient/microsatellite stable resectable colon cancer. First Author: Gertjan Rasschaert, Department of Gastroenterology/Digestive Oncology, University Hospital Leuven, Leuven, Belgium

Background: Colon cancer is the third most common cancer globally, with a standard of care in the nonmetastatic setting that includes surgery followed by adjuvant chemotherapy. Results of recent clinical trials suggest that neoadjuvant therapy may be beneficial in locally advanced colon cancer. Neoadjuvant immunotherapy has shown impressive responses in mismatch repair deficient (dMMR)/microsatellite instability-high (MSI-H) disease with pathological complete responses of up to 67% and 3-year disease-free survival of 100% reported in the NICHE 2 trial. However, most colon cancer (85%–90%) is mismatch repair proficient (MMRp)/microsatellite stable (MSS), which has been shown to have poor response to conventional immunotherapy. Dostarlimab, a programmed cell death protein-1 (PD-1) inhibitor, has a high affinity for binding to PD-1, blocking the interaction between PD-1 and its ligands (PD-L1 and PD-L2). Dostarlimab monotherapy has been approved in the US for the treatment of adults with dMMR advanced/recurrent solid tumors. The AZUR-4 trial (NCT06567782) evaluates dostarlimab + CAPEOX versus CAPEOX alone as neoadjuvant treatment to identify early signals of efficacy in resectable MMRp/MSS colon cancer. The study will assess the relationship between conventional and advanced blood- and tumor-based immune response to better understand the contribution of dostarlimab to pathological response. **Methods:** AZUR-4 is a multicenter, randomized, open-label phase 2 study in MMRp/MSS resectable colon cancer. Approximately 120 patients will be enrolled and randomized 3:1 to the dostarlimab + CAPEOX and CAPEOX arms, respectively, in which they will receive 4 cycles of Q3W neoadjuvant therapy. Key eligibility criteria include age ≥18 years, confirmed resectable MMRp/MSS colon adenocarcinoma with no prior treatment, clinically staged as T4N0 or stage III, Eastern Cooperative Oncology Group performance status of 0 or 1, and required tissue biopsies providing fresh tumor tissue either at prescreening or screening. Primary endpoints are major pathologic response rate (mPR) assessed at ≤10% residual viable tumor (RVT) and treatment-emergent adverse events (AEs), serious AEs, immune-mediated AEs, and AEs leading to death or discontinuation of study drug. Secondary endpoints include primary tumor resection not being excluded by either disease progression or treatment-related toxicities, and pathological response categories that include complete pathological response (cPR) and partial pathologic response (pPR). Exploratory endpoints include overall survival, event-free survival, effects on circulating tumor DNA dynamics, and pathological response rate in biomarker subsets. Clinical trial information: NCT06567782. Research Sponsor: GSK.

TPS3650 **Poster Session**

Trials in progress: Alliance A022104/NRG-GI010—A randomized phase II/III trial testing the efficacy of triplet versus doublet chemotherapy regarding clinical complete response and disease-free survival in patients with locally advanced rectal cancer (LARC; the Janus Rectal Cancer trial). First Author: Caleah Simone Kitchens, Memorial Sloan Kettering Cancer Center, New York, NY

Background: A total neoadjuvant therapy (TNT) approach improves compliance with chemotherapy and increases rates of tumor response compared to neoadjuvant chemoradiation (CRT) alone in those with locally advanced rectal cancer. Recent data indicate that optimal sequencing of TNT involves consolidation (rather than induction) chemotherapy to improve complete response rates. The use of FOLFIRINOX has shown to improve response and outcomes compared to CRT and surgery alone. Data have also shown that patients with clinical complete response (cCR) after TNT may be managed with a watch and wait approach (WW) instead of preemptive total mesorectal resection (TME). However, the optimal consolidation chemotherapy regimen to improve cCR rates has not been established, and a randomized clinical trial has not robustly evaluated cCR as a primary endpoint. We designed this NCI-sponsored study of chemotherapy intensification to address this and to increase cCR rates, provide opportunity for organ preservation, and survival outcomes. **Methods:** In this multigroup randomized, seamless phase II/III trial (1:1), up to 760 patients with LARC, T4N0, any T with node positive disease (any T, N+) or T3N0 requiring abdominoperineal resection or coloanal anastomosis and distal margin within 12 cm of anal verge will be enrolled. Stratification factors include tumor stage (T4 vs T1-3), nodal stage (N+ vs N0) and distance from anal verge (0–4; 4–8; 8–12 cm). Patients will be randomized to receive neoadjuvant long-course chemoradiation (LCRT) followed by consolidation doublet (mFOLFOX6 or CAPOX (control arm)) or triplet chemotherapy (FOLFIRINOX (experimental arm)) for 3–4 months. LCRT in both arms involve 4500 cGy in 25 fractions over 5 weeks +900 cGy boost in 5 fractions with a fluoropyrimidine. Patients will undergo assessment 8–12 (±4) weeks post-TNT completion. The primary endpoint for the phase II portion will compare cCR between treatment arms. A total number of 312 patients (156 per arm) will provide statistical power of 90.5% to detect a 17% increase in cCR rate, at a one-sided alpha = 0.048. The primary endpoint for the phase III portion will compare disease-free survival (DFS) between arms. A total of 285 DFS events will provide 85% power to detect an effect size of hazard ratio 0.70 at a one-sided alpha of 0.025, requiring enrollment of 760 patients (380 per arm). Secondary objectives include overall survival, organ preservation time, time to distant metastasis, and adverse event rates. This study has accrued 587 patients as of January 2025, and is investigating exploratory correlatives (e.g., ctDNA). Support: U10CA180821, U10CA180882, U24CA196171. https://acknowledgments.alliancefound.org. Clinicaltrials.gov ID: NCT05610163 Clinical trial information: NCT05610163. Research Sponsor: National Cancer Institute; U10CA180821; National Cancer Institute; U10CA180882; U.S. National Institutes of Health; U24CA196171; ECOG-ACRIN MEDICAL RESEARCH FOUNDATION; U10CA180820; National Cancer Institute; U10CA18086; National Cancer Institute; U10CA180888.

4000 **Oral Abstract Session**

Adjuvant nivolumab in resected esophageal or gastroesophageal junction cancer (EC/GEJC) following neoadjuvant chemoradiotherapy (CRT): First results of overall survival (OS) from CheckMate 577. First Author: Ronan Joseph Kelly, Charles A. Sammons Cancer Center at Baylor University Medical Center, Dallas, TX

Background: At 24.4-month (mo) median follow-up, adjuvant nivolumab demonstrated a statistically significant and clinically meaningful improvement in disease-free survival (DFS) vs placebo with a well-tolerated safety profile in patients (pts) with resected EC/GEJC with residual pathologic disease following neoadjuvant CRT and surgery in the primary analysis from the global, phase 3 CheckMate 577 study (NCT02743494). We report the final analysis of the hierarchically tested secondary endpoint of OS along with longer follow-up of DFS. **Methods:** Adults with resected (R0) stage II/III EC/GEJC who received neoadjuvant CRT and had residual pathologic disease were randomized 2:1 to nivolumab 240 mg or placebo Q2W for 16 weeks, followed by nivolumab 480 mg or placebo Q4W. Maximum treatment duration was 1 year. The primary endpoint was DFS. OS was a secondary endpoint, and exploratory endpoints included safety, distant metastasis-free survival (DMFS), and progression-free survival on subsequent systemic therapy (PFS2). **Results:** 794 pts were randomized (nivolumab, n = 532; placebo, n = 262). With a median follow-up of 78.3 (range, 60.1–96.6) mo, adjuvant nivolumab continued to show DFS benefit vs placebo (HR 0.76 [95% CI 0.63–0.91]; Table). Median OS was numerically longer with nivolumab vs placebo (51.7 vs 35.3 mo), although the difference was not statistically significant (HR 0.85 [95.87% CI 0.70–1.04]; *P* = 0.1064; Table). OS rates at 3 and 5 years with nivolumab vs placebo were 57% vs 50% and 46% vs 41%, respectively. OS subgroup analyses will be presented. Clinically meaningful improvement in DMFS with nivolumab vs placebo was maintained (Table). PFS2 favored nivolumab vs placebo (HR 0.81 [95% CI 0.67–0.98]). In the nivolumab group, 46% of pts received subsequent therapy vs 60% in the placebo group; 5% vs 15% received subsequent immunotherapy. No new safety signals were identified. **Conclusions:** Adjuvant nivolumab demonstrated sustained long-term DFS benefit and numerical improvement in OS vs placebo in pts with resected EC/GEJC and residual pathologic disease following neoadjuvant CRT. The safety profile of adjuvant nivolumab remained well-tolerated with longer follow-up. These results further support the use of adjuvant nivolumab in this pt population. Clinical trial information: NCT02743494. Research Sponsor: Bristol Myers Squibb.

Efficacy	Nivolumab (n = 532)	Placebo (n = 262)
Median DFS (95% CI), mo	21.8 (16.6–29.7)	10.8 (8.3–14.3)
HR (95% CI)	0.76 (0.63–0.91)	
Median OS (95% CI), mo	51.7 (41.0–61.6)	35.3 (30.7–48.8)
HR (95.87% CI; *P* value)	0.85 (0.70–1.04; *P* = 0.1064)	
Median DMFS (95% CI), mo	27.3 (21.4–36.0)	14.6 (10.9–20.3)
HR (95% CI)	0.75 (0.62–0.90)	
Safety, n (%)	**n = 532**	**n = 260**
Any-grade/grade 3–4 TRAEs	379 (71)/75 (14)	124 (48)/17 (7)
Any-grade/grade 3–4 TRAEs leading to discontinuation	48 (9)/26 (5)	8 (3)/7 (3)

TRAE, treatment-related adverse event.

4001 **Oral Abstract Session**

Lenvatinib plus pembrolizumab and chemotherapy versus chemotherapy in advanced, metastatic gastroesophageal adenocarcinoma: The phase 3, randomized LEAP-015 study. First Author: Kohei Shitara, National Cancer Center Hospital East, Chiba, Japan

Background: LEAP-015 (NCT04662710), is a randomized, open-label, phase 3 study of pembrolizumab plus lenvatinib and chemotherapy as first-line treatment for advanced/metastatic gastroesophageal adenocarcinoma. We report results from the interim and final analyses of LEAP-015. **Methods:** Eligible participants (pts) had untreated HER-2 negative locally advanced unresectable or metastatic gastroesophageal adenocarcinoma, measurable disease and ECOG PS 0-1. All pts were randomly assigned 1:1 to induction with pembrolizumab 400 mg IV Q6W (x2) plus oral lenvatinib 8 mg QD and investigators choice chemotherapy (CAPOX Q3W x4 or mFOLFOX6 Q2W x6) then consolidation with pembrolizumab 400 mg Q6W for ≤16 doses plus lenvatinib 20 mg QD (only if 8 mg tolerated for at least 3 weeks), or chemotherapy alone (CAPOX or FOLFOX). Randomization was stratified by region, ECOG PS, and chemotherapy choice. Dual primary endpoints were PFS (RECIST v1.1, BICR) and OS in pts with PD-L1 combined positive score (CPS) ≥1 and in all pts; secondary endpoints included ORR and DOR (RECIST v1.1, BICR) in pts with PD-L1 CPS ≥1 and in all pts, and safety and tolerability in all pts. The data cut-off date was Oct 29, 2024. **Results:** A total of 880 pts (78% PD-L1 CPS ≥1; 75% gastric primary) were randomized (443 pembrolizumab plus lenvatinib and chemotherapy; 437 chemotherapy alone).Median follow-up was 32.2 mo (range 19.0 – 41.7) in pts with PD-L1 CPS ≥1 and 31.8 mo (range, 19.0 – 41.7) in all pts. At interim analysis, PFS difference was statistically significant with pembrolizumab plus lenvatinib and chemotherapy vs chemotherapy in pts with PD-L1 CPS ≥1 (median 7.3 vs 6.9 mo; HR 0.75; 95% CI, 0.62-0.9; P = 0.0012), with 24-mo PFS of 20% vs 7%, and in all pts (median 7.2 vs 7.0 mo; HR 0.78; 95% CI, 0.66-0.92; P = 0.0019), with 24-mo PFS of 21% vs 8%. ORR was 59.5% vs 45.4% in pts with PD-L1 CPS ≥1 and 58.0% vs 43.9% in all pts; P < 0.0001 for both. At final analysis, OS in pts with PD-L1 CPS ≥1 was not statistically significant (median 12.6 vs 12.9 mo; HR 0.84; 95% CI, 0.71-1.00; P = 0.0244 (P-value boundary for significance of 0.0204), with 24-mo OS of 31% vs 23%. OS in all pts was not tested per multiplicity strategy (median 13.1 vs 13.0; HR 0.87; 95% CI 0.75-1.01). Drug-related adverse event (AE) rates were 98% vs 92% in pts receiving pembrolizumab plus lenvatinib and chemotherapy vs chemotherapy. Grade ≥3 drug-related AE rates were 65% vs 49% (grade 5 AEs 5% vs < 1%). **Conclusions:** Pembrolizumab plus lenvatinib and chemotherapy vs chemotherapy provided statistically significant improvement in PFS and ORR in pts with advanced unresectable or metastatic gastroesophageal carcinoma at interim analysis. However, there was no significant improvement in OS in pts with PD-L1 CPS ≥1 at final analysis. Safety profiles were consistent with known regimens, with higher AE rates seen in pts receiving the experimental treatment. Clinical trial information: NCT04662710. Research Sponsor: Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA; N/A.

LBA4002 **Oral Abstract Session**

Trastuzumab deruxtecan (T-DXd) vs ramucirumab (RAM) + paclitaxel (PTX) in second-line treatment of patients (pts) with human epidermal growth factor receptor 2-positive (HER2+) unresectable/metastatic gastric cancer (GC) or gastroesophageal junction adenocarcinoma (GEJA): Primary analysis of the randomized, phase 3 DESTINY-Gastric04 study. First Author: Kohei Shitara, National Cancer Center Hospital East, Kashiwa, Japan

The full, final text of this abstract will be available at meetings.asco.org on the day of presentation and in the online supplement to the June 10, 2025, issue of the *Journal of Clinical Oncology*.

4003 **Oral Abstract Session**

Claudin18.2-specific CAR T cells (Satri-cel) versus treatment of physician's choice (TPC) for previously treated advanced gastric or gastroesophageal junction cancer (G/GEJC): Primary results from a randomized, open-label, phase II trial (CT041-ST-01). First Author: Changsong Qi, Peking University Cancer Hospital, Beijing, Beijing, China

Background: Claudin18.2 (CLDN18.2) has emerged as a promising therapeutic target in G/GEJC. Recently reported results showed CT041/satricabtagene autoleucel (satri-cel), an autologous CLDN18.2-specific CAR T-therapy, had encouraging efficacy in previously treated patients (pts) with advanced G/GEJC. Now we report the primary results from the phase II pivotal trial (CT041-ST-01, NCT04581473). **Methods:** In this open-label, multicenter, randomized controlled trial (RCT) conducted in China, CLDN18.2 positive, advanced G/GEJC pts with failure to at least 2 prior lines of treatment, were randomized (2:1) to satri-cel arm or TPC arm. For satri-cel arm, satri-cel dose of 250×10^6 cells were infused up to 3 times. For TPC arm, one of the standard of care (SOC) drugs (apatinib, paclitaxel, docetaxel, irinotecan or nivolumab) was given per physician's decision. Those who experienced disease progression or drug intolerance in TPC arm could receive subsequent satri-cel, if eligible. The primary endpoint was PFS assessed by the Independent Review Committee (IRC). Key secondary endpoint was OS. Data cutoff date was Oct 18, 2024. **Results:** From Mar 29, 2022 to Aug 16, 2024, a total of 156 pts were randomized to satri-cel arm (n = 104) or TPC arm (n = 52). Twenty pts in TPC arm received subsequent satri-cel. Median number of prior systemic therapies was 2 in both arms, and 26.9% vs 19.2% had received ≥3 lines; 69.2% vs 59.6% had peritoneal metastasis; 71.2% vs 65.4% were Lauren diffuse/mixed type. The median follow-up time of PFS and OS was 8.90 and 12.29 months (m). In ITT population, satri-cel arm showed significant improvement in mPFS by IRC (3.25m vs 1.77m; HR 0.366, 95% CI: 0.241, 0.557; p < 0.0001) and an obvious trend for longer mOS (7.92m vs 5.49m; HR 0.693, 95% CI: 0.457, 1.051; one-sided p = 0.0416) than TPC arm. Moreover, in 136 pts receiving study drug (mITT, satri-cel 88 pts vs TPC 48 pts), mPFS by IRC was 4.37m vs 1.84m, HR 0.304 (95% CI: 0.195, 0.474) and mOS was 8.61m vs 5.49m, HR 0.601 (95% CI: 0.385, 0.939). Notably, mOS of TPC pts with satri-cel was 9.20m. Among all pts receiving satri-cel (n = 108) vs TPC pts without satri-cel (n = 28), mOS was 9.17m vs 3.98m, HR 0.288 (95% CI: 0.169, 0.492). A summary of study drug-related adverse events (TRAEs) is shown in the Table. **Conclusions:** This is the first confirmatory RCT of CAR T-therapy in solid tumors. Satri-cel demonstrated significant PFS improvement and an obvious OS benefit with a manageable safety profile. These results support satri-cel as a potential new SOC for advanced G/GEJC. Clinical trial information: NCT04581473. Research Sponsor: None.

Safety, n (%)	Satri-cel (n=88)	TPC (n=48)
TRAEs	88 (100)	44 (91.7)
Serious TRAEs	31 (35.2)	12 (25.0)
TRAE leading to death	1 (1.1)[a]	1 (2.1)[b]
CRS	84 (95.5)	0
Grade 1-2	80 (90.9)	0
Grade 3	4 (4.5)	0
ICANS	0	0

[a]disseminated intravascular coagulation;
[b]coagulopathy.

LBA4004 **Oral Abstract Session**

Results of a randomized phase III trial of pre-operative chemotherapy with mFOLFIRINOX or PAXG regimen for stage I-III pancreatic ductal adenocarcinoma. First Author: Michele Reni, Department of Medical Oncology, Pancreas Translational and Clinical Research Center, IRCCS San Raffaele Scientific Institute, Vita-Salute San Raffaele University, Milan, Italy

The full, final text of this abstract will be available at meetings.asco.org on the day of presentation and in the online supplement to the June 10, 2025, issue of the *Journal of Clinical Oncology*.

LBA4005 **Oral Abstract Session**

PANOVA-3: Phase 3 study of tumor treating fields (TTFields) with gemcitabine and nab-paclitaxel for locally advanced pancreatic ductal adenocarcinoma (LA-PAC). First Author: Vincent J. Picozzi, Virginia Mason Medical Center, Seattle, WA

The full, final text of this abstract will be available at meetings.asco.org on the day of presentation and in the online supplement to the June 10, 2025, issue of the *Journal of Clinical Oncology*.

4006 **Oral Abstract Session**

Preliminary results from the randomized phase 2 study (1801 part 3B) of elraglusib in combination with gemcitabine/nab-paclitaxel (GnP) versus GnP alone in patients (pts) with previously untreated metastatic pancreatic ductal adenocarcinoma (mPDAC). First Author: Devalingam Mahalingam, Robert H. Lurie Comprehensive Cancer Center, Northwestern University, Chicago, IL

Background: Elraglusib (9-ING-41) is a first-in-class inhibitor of GSK-3ß, which may mediate drug resistance, EMT, and damaged DNA and tumor immune response in advanced cancer. In pancreatic cancer models in mice, elraglusib combined with chemotherapy enhanced anti-tumor effects and survival. In a single-arm clinical study, elraglusib/GnP showed antitumor activity and prolonged survival in pts with mPDAC. **Methods:** Pts with previously untreated mPDAC were randomized 2:1 to GnP plus elraglusib 9.3 mg/kg IV once weekly or GnP in an open-label phase 2 study. The primary endpoint was 1-yr OS in the primary analysis set. Upon study completion, mOS will be the primary endpoint once survival distributions are compared after the 12-month follow-up using log-rank analysis. Secondary endpoints included DCR, ORR, mPFS, and TEAEs/TRAEs. The planned sample size was 207 evaluable pts (130 for elraglusib/GnP and 77 for GnP), assuming 1-yr OS of 55% with elraglusib/GnP and 35% with GnP to achieve 80% power with a chi-square test at a 2-sided 5% α. For OS, nonparametric log-rank test was used with statistical significance at p-value $<$ 0.048. Cytokine/chemokine correlative biomarker assays were performed. The study completed enrollment in February 2024. **Results:** As of November 15, 2024 (preliminary data cut-off date), the primary analysis set included 155 pts in the elraglusib/GnP arm and 78 pts in the GnP arm, with 52.8% males and 57.5% ECOG PS 1. Median (range) CA 19-9 levels were 1568 U/mL (1 to 381,904 U/mL) in the elraglusib/GnP arm and 1590 U/mL (2 to 501,000 IU/mL) in the GnP arm. The 1-yr OS rate was 43.6% with elraglusib/GnP vs 22.5% with GnP (z-test p = 0.002); the mOS was 9.3 mo with elraglusib/GnP vs 7.2 mo with GnP (HR, 0.63; log rank p = 0.016; see Table). 38.1% of pts on elraglusib/GnP and 19.2% on GnP are censored, with the majority at $>$ 10 months OS. Several biomarkers appear to be predictive for OS including IFNβ and PD-L1. The most common TRAE with elraglusib/GnP was grade 1-2 transient visual impairment in $>$ 60% of patients (vs 9% with GnP). Grade $\geq$3 TEAEs occurred in 89.7% of pts on elraglusib/GnP and 80.8% on GnP. Most common grade $\geq$3 TEAEs with elraglusib/GnP (vs GnP) were neutropenia 51.6% (vs 29.5%), anemia 24.5% (vs 29.5%), and fatigue 16.1% (vs 5.1%). **Conclusions:** The preliminary results showed a statistically significant benefit for 1-yr OS and mOS and favorable trends for ORR and DCR with elraglusib/GnP over GnP, with manageable safety profile. The mOS for GnP is lower relative to MPACT and NAPOLI-3 but comparable to recent real-world meta-analyses, explained by advanced disease burden and higher mortality rate in the first 4 months in our study. Topline analysis (April 2025) and correlative biomarker analysis predictive for OS will be presented. Clinical trial information: NCT03678883. Research Sponsor: Actuate Therapeutics, Inc.

Preliminary efficacy results.

	Elraglusib/GnP n=155	GnP n=78
1-year OS, %	43.6	22.5
z-test p=0.002		
mOS, mo	9.3	7.2
HR=0.63; log-rank p=0.016		
Events, n (%)	96 (61.9)	63 (80.8)
mPFS, mo	5.6	4.9
HR=0.91; p=NS		
Events, n (%)	128 (82.6)	70 (89.7)
DCR, %	42.6	33.3
ORR, n (%)	43 (27.7)	16 (20.5)

4007 **Oral Abstract Session**

A phase III randomized clinical trial evaluating perioperative therapy (neoadjuvant chemotherapy versus chemoradiotherapy) in locally advanced gallbladder cancers (POLCAGB). First Author: Reena Engineer, Tata Memorial Centre (HBNI), Mumbai, India

Background: Locally advanced Gallbladder cancers (LAGBC)initially deemed not suitable for R0 resection receive either neoadjuvant chemotherapy (NACT)or neoadjuvant chemoradiation (NACRT)downstaging for resection and to improve outcomes. **Methods:** This is a randomized phase 3 trial (NCT02867865) that included fit patients with LAGBC adenocarcinoma,. T3/T4 with liver infiltration ($>$ 2cm, $<$ 5cm); N1 nodal status; obstructive jaundice (type I/II biliary obstruction) ;duodenal or colonic abutment with no mucosal infiltration , $<$ 180°vascular involvement. The patients were randomized (1:1) to NACT arm (Gemcitabine + platinum for four cycles) versus NACRT arm (55 -57Gy with concurrent gemcitabine followed by two cycles of chemotherapy) and were then evaluated for surgery. A sample size of 314 patients was required to detect a 5.5 months difference (11 mo.to 16.5 mo in the test arm) with median overall survival (OS) as the primary endpoint (hazard ratio, 0.7; 2-sided α = 0.05; β = 0.2). Secondary endpoints were event free survival (EFS),R0 resection rates and post-operative complication rates. Due to slow accrual Institutional Ethics committee requested the investigators for interim analysis and approval was obtained for the same. **Results:** From Oct 2016 to Sept 2024, 124 patients (64 NACT, 60 NACTRT)were enrolled at 2 centers. At the time of analysis 93 OS events were observed in 124 patients. Median follow-up was 62 (range 6.9-94) months. More number of patients underwent R0 resection in NACRT than NACT arm 51.6 vs 29.7% (p = 0.01) In the intention to treat analysis, the NACTRT arm showed improved OS compared to the NACT arm [21.8 mo.vs.10.1 mo. p = 0.006]. EFS was 10.6 mo. vs 4.9 months, p = 0.006]. Similar results were noted in the per protocol analysis(n = 110). Clavien Dindo postoperative morbidity of grade 3 and above was 4/22 (18.18%) in NACT arm vs 9/32(28.12%) in NACRT arm (p = 0.30). The interim analysis demonstrated a significant improvement in efficacy in the NACRT arm. Based on the current data, the conditional power was calculated to be 99.96%. **Conclusions:** This trial demonstrates that the addition of concurrent chemoradiation to chemotherapy improves overall survival and resection rates in patients with locally advanced gallbladder cancers. These results provide important evidence to guide treatment decisions in this traditionally difficult to treat set of gallbladder cancers. Clinical trial information: NCT02867865. Research Sponsor: Intramural funding - Tata Memorial Centre.

Treatment outcomes.

Outcome measures	NACTRT N=60	NACT N=64	HR	p
Patients surgically explored	39(65%)	29(45.3%)		0.03
Patients undergoing R0 resection	31 (51.6%)	19 (29.7%)		0.01
Median OS (months) (95% CI)	21.8 (14.6-29.14)	10.1 (8.5-11.7)	HR- 0.56	0.006
5 Year survival (95% CI)	27 (17.7-43)%	18 (10-31) %	95%CI- 0.37-0.84	
EFS (months) (95% CI)	10.6 (6.07-15.5-15)	4.89 (3.06-6.73)	HR-0.58	0.006
5 Yr EFS (%)	21 (12-35.7)%	12.7 (6-24.6)%	95%CI- 0.39-0.85	

4008 Oral Abstract Session

Neoadjuvant chemotherapy with gemcitabine plus cisplatin followed by radical liver resection versus immediate radical liver resection alone followed adjuvant therapy in biliary tract cancer: Final results from the phase III AIO/CALGP/ACO-GAIN-Trial. First Author: Thorsten Oliver Goetze, Institute of Clinical Cancer Research (IKF), Krankenhaus Nordwest, UCT-University Cancer Center, Frankfurt, Germany

Background: Radical surgical resection represents the only potentially curative treatment option for Biliary Tract Cancer (BTC) and (incidental) Gallbladder Carcinoma ((I) GBC). Nevertheless, 5-year OS is only 20–40% after curatively intended resection and data regarding pure adjuvant chemotherapy in BTCs are currently conflicting. Encouraging results of neoadjuvant/perioperative concepts in other malignancies provide a rationale to use this treatment in the early phase management of GBC and intrahepatic as well extrahepatic cholangiocarcinoma (ICC/ECC). **Methods:** GAIN is a multicenter, randomized, controlled, open-label phase III trial, including patients (pts) with localized or locally advanced resectable non metastatic biliary tract cancer (intra-/extrahepatic cholangiocarcinoma ICC/ECC; GBC in front of radical liver resection). Pts were randomized to either neoadjuvant (perioperative) systemic chemotherapy (Gemcitabine + Cisplatin 3 cycles pre- and post-surgery) followed by radical surgery (Arm A) or to direct surgery followed by adjuvant treatment (Arm B) according to investigators choice. Primary endpoint was OS; secondary endpoints were PFS/EFS, R0-resection rate, toxicity, perioperative morbidity, mortality and QoL. Recruitment was stopped after enrollment of 68 pts due to a slow enrollment rate. **Results:** Between Dec 2019 and Feb 2024, 68 pts were randomized and the ITT comprised 32 pts in Arm A and 30 pts in Arm B. Baseline characteristics were similar between arms (overall, male 55%; median age 66.0; cT3/T4 29.0%; cN+ 30.6%; 37.1% ICC, 30.6% ECC and 32.3% GBC). 90.6% of pts in Arm A completed all 3 pre-operative cycles. 43.8% in Arm A completed adjuvant treatment and 23.3% in Arm B received adjuvant treatment. Median follow-up was 11.8 months. Neoadjuvant treatment improved OS (mOS, Arm A 27.8 vs. 14.6 months Arm B; HR 0.46 [0.22 - 0.96]; p = 0.04) and R0 resection rate (62.5% vs 33.3%). This effect was also seen in event-free survival. Postoperative morbidity rates were similar in both arms (33.3% (A) vs. 32% (B)) and the 30- and 90-days mortality rates were lower for Arm A (30-days: 4.2% vs. 24%; 90-days: 4.2% vs. 28%). No new safety/toxicity signals were observed. In Arm A, 12 pts (38.7%) had at least one treatment related adverse event (TRAE) with grade 3 and 1 pt (3.2%) with grade 4. No fatal TRAEs were observed. **Conclusions:** Neoadjuvant / perioperative gem/cis clearly improved OS and R0 resection rate in pts with biliary tract cancer compared to direct surgery and was able to nearly double mOS while not increasing the morbidity rate and even decreasing mortality rates. Clinical trial information: NCT03673072. Research Sponsor: None.

4009 Clinical Science Symposium

Maintenance with OSE2101 plus FOLFIRI vs FOLFIRI alone after FOLFIRINOX (FFX) induction in patients (Pts) with advanced pancreatic ductal adenocarcinoma (aPDAC): Primary endpoint results of a randomized TEDOPAM GERCOR D17-01 PRODIGE 63 trial. First Author: Anthony Turpin, Lille University Hospital, University of Lille, Lille, France

Background: OSE2101 is an off the shelf vaccine made of 10 synthetic HLA-A2-restricted peptides targeting 5 tumor associated antigens. This multicenter, randomized, non-comparative, phase II study assessed FOLFIRI ± OSE2101 maintenance in aPDAC Pts without progression after 8 cycles of FFX. **Methods:** Eligible aPDAC Pts were randomized to FOLFIRI (Arm A) or FOLFIRI + OSE2101 (Arm B: subcutaneous injection on D1, D15, Q4W/6 doses then Q8W to M12 then Q12W up to M24). Stratification factors: tumor stage (locally advanced vs metastatic), best response to FFX (partial or complete response [CR, PR] vs stable disease [SD]), and center. Primary endpoint: overall survival (OS) rate at M12 in evaluable Pts (M12-OS; Fleming 2-stage design, H0: 25%; H1: 50%, 1-sided alpha: 2.5%, power: 90%); secondary endpoints: progression-free survival (PFS; RECIST v1.1), best response, duration of disease control (DDC), and safety. **Results:** 107 Pts (ITT) were randomized (53/Arm A, 54/Arm B) between 04/2021 and 05/2023. Median age 64 years (range:37-81), 53% men, 69% had metastases, 36%/64% had PR/SD to prior FFX. No evidence of imbalance in Pt characteristics was observed between arms. Median number of OSE2101 injections was 7.5 (1-14). Median treatment duration of FOLFIRI was 5.4 months in both arms. At data cut-off (Dec 9, 2024), median follow-up was 21.4 months with 101 evaluable Pts for M12-OS (49/Arm A, 52/Arm B; 4 consent withdrawals, 1 Pt's decision, 1 treatment interruption >4 weeks). Number of death events (n/%) was 19/35.8% in Arm A and 18/33.3% in Arm B. M12-OS (95%CI) was 61% (46.2%-74.8%) in Arm A and 65% (50.9%-78.0%) in Arm B. Median (95%CI) OS and PFS (ITT) were 17.3 months (10.6–23.2) and 8.2 months (5.3–11.6) in Arm A, and 15.5 months (12.4–19.3) and 7.8 months (5.4–10.6) in Arm B. Other secondary endpoints are described in Table. Among 33 Pts with SD to prior FFX in Arm B, 6 (18%) had CR/PR (1/5) when adding OSE2101 to FOLFIRI vs 5 (no CR) among 35 Pts in Arm A. In the safety population, 7 SAEs/6 Pts (12%) in Arm A and 22 SAEs/14 Pts (26%) in Arm B were reported. No unexpected SAEs were observed with OSE2101 except 1 inappropriate administration, and no evidence of increased toxicity of FOLFIRI with OSE2101. **Conclusions:** TEDOPAM met its primary objective with minimal toxicity and positive outcomes of adding OSE2101 cancer vaccine to maintenance FOLFIRI, albeit mitigated by unexpectedly favorable OS in the control arm. Two complete responses were observed when adding OSE2101. Further follow-up is ongoing and translational analysis planned. Clinical trial information: NCT03806309. Research Sponsor: OSE Immunotherapeutics.

ITT	Arm A N=53	Arm B N=54
Best response, n (%)		
CR	0 (0.0)	2 (3.7)
PR	12 (22.6)	10 (18.5)
SD	28 (52.8)	34 (63.0)
Progressive disease (PD)	8 (15.1)	8 (14.8)
Missing	5 (9.5)	0 (0.0)
DC rate, n (%)	40 (75.5)	46 (85.2)
DDC (95% CI)	8.8 (6.2-12.9)	9.8 (6.8-14.8)

4010 Clinical Science Symposium

Efficacy and safety of cafelkibart (LM-108), an anti-CCR8 monoclonal antibody, in combination with anti-PD-1 therapy in patients with pancreatic cancer: Results from phase 1/2 studies. First Author: Jifang Gong, Key Laboratory of Carcinogenesis and Translational Research (Ministry of Education/Beijing), Department of Early Drug Development Center, Peking University Cancer Hospital and Institute, Beijing, China

Background: Targeting tumor-infiltrating Tregs presents a promising strategy to overcome resistance to immunotherapy in cancer treatment. LM-108 is a novel Fc-optimized anti-CCR8 monoclonal antibody designed to selectively deplete tumor-infiltrating Tregs while sparing peripheral Tregs. This pooled analysis of two phase 1/2 trials assesses the efficacy and safety of LM-108 in combination with anti-PD-1 therapy in patients with pancreatic cancer. **Methods:** Eligible patients (pts) with pancreatic cancer who had progressed on or after at least one prior line of systemic therapy were included. Treatment regimens included LM-108 at doses of 3 mg/kg Q3W, 3 mg/kg Q2W, 10 mg/kg Q3W, or 10 mg/kg Q2W, in combination with pembrolizumab (400 mg Q6W) or toripalimab (240 mg Q3W). The primary endpoint was ORR. Secondary endpoints were DCR, PFS, OS, DoR, safety, and biomarkers analysis. Data cutoff: December 2, 2024. **Results:** A total of 80 pts (median age: 63 years; 58.8% male) from China and Australia were treated. Of these, 48 pts had progressed on or after 1 prior line of therapy, and 32 pts had ≥2 lines. Eighteen pts (22.5%) had prior anti-PD-1 therapy, and 52 pts (65.0%) had liver metastases at baseline. TRAEs were reported in 76 pts (95.0%). Common TRAEs (≥25%) included increased AST, increased ALT, anemia, rash, pyrexia, decreased platelet count and increased conjugated bilirubin. Grade ≥3 TRAEs occurred in 42 pts (52.5%), the most common events (≥5%) were lipase elevation (7.5%), increased ALT (6.3%), increased AST (5.0%), immune-mediated enterocolitis (5.0%), hypokalemia (5.0%), and rash (5.0%). Median follow-up was 10.48 months (95% CI 7.20-12.65). Among 74 efficacy-evaluable pts, ORR was 20.3% (95% CI 11.8-31.2%) and DCR was 62.2% (95% CI 50.1-73.2%). Median DoR was 5.49 months (95% CI 3.02-8.87), PFS was 3.12 months (95% CI 1.61-4.86), and OS was 10.02 months (95% CI 6.41-13.11). Among 45 pts who had progressed on or after one prior line of therapy, ORR was 24.4% (95% CI 12.9-39.5%) and DCR was 71.1% (95% CI 55.7-83.6%), with a median DoR of 6.93 months (95% CI 3.02-NA), PFS of 4.86 months (95% CI 2.79-6.90), and OS not reached. The 12-month OS rate was 51.6% (95% CI 31.4-68.5%). Among these, 9 pts with high CCR8 expression (7 with baseline liver metastases) showed ORR of 33.3% (95% CI 7.5-70.1%) and DCR of 77.8% (95% CI 40.0-97.2%). Median PFS was 6.90 months (95% CI 1.22-NA), and OS was 9.15 months (95% CI 3.61-NA). **Conclusions:** LM-108 in combination with anti-PD-1 therapy demonstrated encouraging antitumor activity and a manageable safety profile in patients with pancreatic cancer who had progressed on or after prior systemic therapies. These findings support further investigation of LM-108 in combination with anti-PD-1 therapy as a potential treatment option for pancreatic cancer. Clinical trial information: NCT05199753; NCT05518045. Research Sponsor: LaNova Medicines Limited.

4011 Clinical Science Symposium

NeoPancONE: GATA6 expression as a predictor of benefit to peri-operative modified FOLFIRINOX in resectable pancreatic adenocarcinoma (r-PDAC): A multicentre phase II study. First Author: Ronan Andrew McLaughlin, Division of Medical Oncology and Hematology, Princess Margaret Cancer Centre – University Health Network, University of Toronto, Toronto, ON, Canada

Background: Modified FOLFIRINOX (mFFX) is increasingly used in the perioperative setting in r-PDAC and patients (pts) would benefit from a biomarker approach. GATA6 expression enriches for the classical RNA subtype, associated with improved OS in advanced PDAC. Low expression identifies the basal subtype which may predict mFFX resistance. NeoPancONE is a single arm Phase II multicentre study evaluating clinical outcomes and investigating GATA6 as a biomarker of response to perioperative mFFX in r-PDAC. **Methods:** Pts were enrolled following central radiology review (CRR) and underwent an EUS FNB for GATA6 in-situ hybridization (ISH). Six cycles of mFFX were planned pre and postoperatively. The primary endpoint was 1 yr event-free survival (EFS) according to GATA6 ISH (high vs low). Secondary endpoints include OS, RECIST response, SAEs, R0 resection rates and RNA subtyping by PurIST. Statistical assumptions used a ratio of 3:1 GATA6 high:low, with a 1 yr EFS of 65% for high and 34% for low (HR 2.5, 80% power, 2 sided alpha 0.05). KM method and log-rank test were used. **Results:** Between Sep-2020– Sep 2023, 146 pts were screened and 84 enrolled (58%) at 8 Canadian centres. CRR deemed 39 (27%) ineligible. Clinical data are summarized (Table). GATA6 ISH was analysed in 74 (88%); 62 (84%) were high, 16% low. At a median follow up of 24.5 mos, the med EFS and OS in the ITT were 16.1 mos (95 CI; 13-21) and 34.2 mos (95 CI; 28-NE). Med OS in the 73 pts who underwent surgery was 35.6 mos (95 CI 33-NE). The 1 yr EFS was 71% in GATA6 high vs 58% in GATA6 low p= 0.53. 1 yr OS was 87% in high vs 75% for low p= 0.29. The proportion progressing within 6 mos of enrollment in the GATA6 low group was significantly higher (42% vs 12% p=0.02). PuriST subtyping was reported in 49 (67%) resections; 14% basal, 86% classical. The 1 yr EFS was 79% in classical vs 43% in the basal subtype p=0.1. The 1 yr OS was 95% in classical vs 57% in basal p=0.034. **Conclusions:** This is one of the first trials in r-PDAC to identify potential biomarkers to predict perioperative mFFX response. GATA6 by ISH can be assessed on baseline tissue. GATA6 high is a prognostic biomarker, although NS, trends towards improved EFS and an encouraging OS. Disease progression within 6 months of enrollment occurs in nearly 50% of patients with low GATA6 expression. Neoadjuvant mFFX should not be the standard of care in these patients. Basal/Classical subtyping had stronger prognostic value than GATA6 and should be considered at baseline EUS FNB for future perioperative strategies in r-PDAC studies. Clinical trial information: NCT04472910. Research Sponsor: Princess Margaret Cancer Foundation UHN; Pancreatic Cancer Canada.

Characteristic n=84	
Age med. (range) yrs	64 (44, 83)
Baseline EUS FNB tissue n (%)	83 (98)
Pre-op completed 6 cycles n (%)	62 (74)
Pre-op RECIST CR/PR/SD/PD/NE %	1/18/64/11/6
Surgery Completed Y/N n (%) / R0 / R1 n (%)	73 (87) / 11(13) / 62 (85) / 11 (15)
Adjuvant Chemotherapy Y / N n (%)	63 (86) / 10 (14)
mFFX associated SAE ≥G3 n (%)	13 (15)
Pre-op mFFX related deaths	3 (4)

LBA4012 **Rapid Oral Abstract Session**

Disitamab vedotin (DV) plus toripalimab (Tor) and chemotherapy (C)/trastuzumab (Tra) as first-line (1L) treatment of patients (pts) with HER2-expressing locally advanced or metastatic (la/m) gastric cancer. First Author: Lin Shen, Beijing Cancer Hospital, Beijing, China

The full, final text of this abstract will be available at meetings.asco.org on the day of presentation and in the online supplement to the June 10, 2025, issue of the *Journal of Clinical Oncology*.

4013 **Rapid Oral Abstract Session**

Long-term outcomes and overall survival (OS) for zanidatamab + chemotherapy in HER2-positive (HER2+) advanced or metastatic gastroesophageal adenocarcinoma (mGEA): 4-year follow-up of a phase 2 trial. First Author: Elena Elimova, Princess Margaret Cancer Centre, Toronto, ON, Canada

Background: Zanidatamab (zani), a dual HER2-targeted bispecific antibody, plus chemotherapy (chemo) has previously demonstrated antitumor activity and a manageable safety profile in the first-line (1L) treatment of patients (pts) with HER2+ mGEA. Here, we report a 4-year follow-up and the first report of both median OS and translational data from this phase 2 trial. **Methods:** The phase 2 trial (NCT03929666) evaluated zani + chemo (mFOLFOX6, CAPOX, or FP) in the 1L treatment of mGEA. In Part 1, pts had HER2-expressing (IHC 3+ or 2+) mGEA. Pts in Part 2 had HER2+ (IHC 3+ or IHC 2+/FISH+) mGEA by central assessment. After 25 pts were treated, antidiarrheal prophylaxis was added for cycle 1. The primary endpoint was confirmed objective response rate (cORR). Secondary endpoints included duration of response (DoR), progression-free survival (PFS), OS, and safety outcomes. Plasma ctDNA samples were collected for NGS testing (Guardant360). **Results:** In total, 46 pts were enrolled (zani + mFOLFOX6 [n = 24], CAPOX [n = 20], or FP [n = 2]). The majority (41 [89%]) of pts had HER2+ mGEA by central confirmation (ccHER2+); 35 (76%) pts had gastric/GEJ cancer. As of July 28, 2024, the median (range) follow-up was 48 (29-59) mo; 8 pts (17%) were on zani treatment and 19 (41%) in survival follow-up. Efficacy results are shown in the Table. The median OS was 36.5 mo; longest survival time was 57.9 mo (censored without death at data cutoff). The concordance between HER2 gene amplification by centrally assessed ISH vs plasma ctDNA was 90% (18/20). Of 14 pts with matched plasma samples at baseline and on-treatment (Cycle 2, day 15), 8 had a $>$ 90% decrease in total ctDNA levels and 2 had a decrease in HER2 copy number. Common ($>$ 5% of pts) grade 3 or 4 treatment-related AEs (TRAEs) were diarrhea (n = 18 [39%]), hypokalemia (n = 10 [22%]), vomiting (n = 4 [9%]), and nausea (n = 3 [7%]). Grade 3 or 4 diarrhea incidence was reduced from 52% to 24% after prophylaxis implementation. No deaths occurred due to TRAEs. **Conclusions:** After a median 4-year follow-up, zani + chemo demonstrated clinically meaningful efficacy in the 1L treatment of HER2+ mGEA, with durable responses and a median OS $>$ 3 years, and a manageable safety profile. Zani + chemo markedly reduced total plasma ctDNA levels early in treatment of mGEA. Clinical trial information: NCT03929666. Research Sponsor: Jazz Pharmaceuticals.

	All pts (N = 46)	ccHER2+ GEA pts (n = 41)
cORR[a], n (% [95% CI])	32 (76.2 [60.5, 87.9])	31 (83.8 [68.0, 93.8])
Median DoR[b] (95% CI), mo	18.7 (10.4, 44.1)	20.4 (8.3, 44.1)
24-mo DoR, % (95% CI)	40 (22, 58)	41 (22, 59)
Median PFS (95% CI), mo	12.5 (8.2, 21.8)	15.2 (9.5, 33.4)
Median OS (95% CI), mo	36.5 (23.6, NE)	36.5 (23.6, NE)
24-mo OS, % (95% CI)	65 (49, 77)	67 (49, 79)
36-mo OS, % (95% CI)	53 (37, 67)	53 (36, 67)
TRAEs, n (%)		
Any	46 (100)	41 (100)
Grade 3 or 4	30 (65)	26 (63)

[a]Response evaluable (n = 42 and 37).
[b]Complete or partial response. NE, non-estimable.

4014 **Rapid Oral Abstract Session**

Recurrence patterns in the prospective, randomized, controlled, multicenter phase III ESOPEC trial comparing perioperative chemotherapy with preoperative chemoradiotherapy in patients with esophageal adenocarcinoma. First Author: Jens Hoeppner, University of Bielefeld, University Medical Center OWL, Campus Hospital Lippe, Bielefeld, Germany

Background: The ESOPEC trial (NCT02509286) showed that perioperative chemotherapy improved overall and progression free survival in pts with esophageal adenocarcinoma (EAC) compared with preoperative chemoradiotherapy. Understanding of the pattern of recurrence is important for the development of more effective future treatment strategies. **Methods:** Pts with cT1 cN+ cM0 or cT2-4a cNany cM0 EAC undergoing preoperative chemotherapy with FLOT (5-FU/leucovorin/oxaliplatin/docetaxel) or preoperative chemoradiotherapy with CROSS (41.4Gy/carboplatin/paclitaxel) plus tumor resection from the ESOPEC trial were eligible. Recurrence-free survival (RFS), distant metastasis-free survival (DMFS), and patterns of local, regional and distant recurrence were analyzed. Treatment groups were compared with respect to sites of recurrence by calculating 3-year cumulative incidences considering competing events, and by Cox regression models for event-specific hazards stratified by trial center and including treatment assignment (FLOT vs CROSS), cN stage (cN0 vs cN+), and age as covariates. Event-specific hazard ratios (HR) with two-sided 95% confidence intervals (CI) and p-values are presented. **Results:** Of the 438 pts enrolled in ESOPEC, 192 of 221 (86.9%) in the FLOT group and 179 of 217 (82.5%) in the CROSS group underwent tumor resection and represent the population for this analysis. R0 resection was achieved in 354 pts (182 (94.8%) FLOT; 172 (96.1%) CROSS). 142 (74.0%) pts in FLOT received postoperative chemotherapy. After a median follow-up of 56 months 178 pts had disease recurrence (81 FLOT; 97 CROSS), and 28 pts died without recurrence (12 FLOT; 16 CROSS). The 3-year RFS rate was 54.5% in FLOT vs 39.0% in CROSS (HR for recurrence or death 0.67; 95% CI, 0.51 - 0.89, p = 0.005). The 3-year DMFS rate was 57.6% in FLOT vs 41.0% in CROSS (HR for distant recurrence or death 0.64; 95% CI, 0.48 – 0.85, p = 0.002). **Conclusions:** Perioperative chemotherapy with FLOT improves RFS and DMFS compared to preoperative chemoradiotherapy with CROSS in EAC. The prognosis of pts is determined by distant recurrence, which is less common after FLOT than CROSS. Clinical trial information: NCT02509286. Research Sponsor: German Research Foundation (DFG); 264590883.

Treatment group comparisons regarding site of recurrence.

	FLOT N=192	CROSS N=179	FLOT vs CROSS		
Site of recurrence	N (%)*	N (%)*	HR (for recurrence)	95% CI	P-value
Locoregional	39 (20.2)	32 (17.4)	1.00	0.62 – 1.61	0.99
Local	19 (9.5)	15 (8.1)	1.03	0.51 – 2.06	0.94
Regional	29 (15.1)	27 (14.5)	0.89	0.52 – 1.52	0.68
Distant	64 (31.5)	89 (47.2)	0.59	0.43 – 0.82	0.002
Distant lymphatic	21 (9.3)	31 (15.6)	0.60	0.34 – 1.05	0.074
Hematogenous	33 (17.2)	48 (26.1)	0.59	0.37 – 0.92	0.021
Pleural/Peritoneal	24 (12.0)	31 (16.4)	0.63	0.36 – 1.09	0.10

*% calculated as 3-year cumulative incidence.

4015 **Rapid Oral Abstract Session**

Decoding the response and resistant features to the Claudin18.2-specific CAR-T cell CT041 in gastric cancer: A multi-omics exploratory biomarker analysis of the phase 1 clinical trial. First Author: Haoxin Peng, Department of Gastrointestinal Oncology, Peking University Cancer Hospital & Institute, Beijing, China

Background: CT041, a Claudin18.2-specific CAR-T cell therapy against gastric cancer (GC), has demonstrated encouraging efficacy and a manageable safety performance. However, the characteristics of response and resistance to CT041 therapy remain unclear. **Methods:** An exploratory biomarker analysis of the phase 1 CT041-CG4006 clinical trial (NCT03874897) was conducted. Baseline samples were collected from primary tumors (PT), and dynamic samples were collected from peripheral blood and malignant ascites at day 0, 3, and 7 of 35 patients. These samples underwent single-cell RNA sequencing (n = 41), spatial transcriptomics (ST, n = 8 for Visium V2 and n = 5 for Xenium 5K), and multiplex immunofluorescence detection (n = 28). **Results:** In the responders, significantly higher GZMK+CD8+ T-lymphocyte infiltrates, which were in a progenitor-like exhausted (Tpex) state, were identified within PT. More GZMK+ Tpex infiltration also correlated with better prognosis (high vs. low: progression-free survival 9.98 vs. 5.45 months, P = 0.020; overall survival 18.03 vs. 8.03 months, P = 0.038), manifesting superior potential as a predictor of CT041 response (AUC 0.87, 95%CI 0.72-1.00). Moreover, strong and positive associations between GZMK+ Tpex and IRF8+ B-lymphocytes were discovered. ST detection further uncovered that they tended to co-localize within tertiary lymphoid structures and intimately interacted via the MHC-I and CCL5-CXCR4 pathways. In cases resistant to CT041, significantly higher infiltrates of IQGAP3+ cancer cells, a subset characterized by augmented proliferative activity, were discovered. While IQGAP3+ cancer cells hindered the infiltration of GZMK+ Tpex, they exhibited a co-infiltrated pattern with IL6+ fibroblasts, wherein enhanced epithelial-to-mesenchymal transition pathway activity was noted. Through dynamically parsing the blood and ascites samples, an initial activated and subsequent exhausted state of GZMK+ cytotoxic T-lymphocyte was observed after the infusion of CT041. Additionally, significant up-regulation of NR4A1, a crucial regulator of Tpex, and CCR9, a key homing molecule to the gastrointestinal mucosa, of peripheral T-lymphocytes was detected in responsive cases. **Conclusions:** This exploratory analysis first unveiled the biological underpinnings and clinical implications of GZMK+ Tpex in determining response and resistance to the Claudin18.2-specific CAR-T therapy. Research Sponsor: Integrated Project of Major Research Plans of the National Natural Science Foundation of China; Joint Fund for Regional Innovation and Development of the National Natural Science Foundation of China.

4016 Rapid Oral Abstract Session

Cosiporfin sodium (DVDMS)-mediated photodynamic therapy (PDT) versus treatment of physician's choice (TPC) in patients (pts) with advanced esophageal cancer (aEC): A phase III, randomized, open-label, multicenter trial. First Author: Jun Zhou, Peking University Cancer Hospital & Institute, Beijing, China

Background: Challenges persist in the treatment of aEC, particularly for pts with esophageal stenosis and dysphagia, conditions that deteriorate the nutrition status and hinder anti-tumor therapies, leading to dismal prognosis. Building on the promising anti-tumor activity and improvement in dysphagia in a phase II single-arm trial, the phase III DYNA-Esophagus03 trial assessed DVDMS, a novel photosensitizer, -mediated PDT in aEC, comparing to TPC. **Methods:** Pts with local recurrence or metastasis EC and Stoller dysphagia grade ≥2, stratified by previous treatment lines (1st vs 2nd-line), were randomized 2:1 to DVDMS-mediated PDT (PDT delivered 24 hours after 0.2 mg/kg DVDMS injection at a light dose of 102 J/cm² and wavelength of 630±5 nm) or TPC. The primary endpoint was esophageal stenosis overall response rate (es-ORR) assessed by endoscopy at 28 days. A sample size of 186 pts achieved a 90% power to detect an es-ORR increase from 10% to 35% at a 1-side 2.5% level, considering a 30% drop-off rate. **Results:** As of November 11, 2024, 186 pts were randomly assigned (124 DVDMS-PDT group/62 TPC group). The baseline characteristics were: mean age 67.6 ± 8.7 years, 32.3% distant metastasis, 52.2% grade 3 dysphagia, and 1.1% grade 4. The es-ORR was 51.6% with DVDMS-PDT vs 8.1% with TPC at day 28 ($P < 0.0001$). At a median follow-up of 8.9 months (mos), the median progression-free survival was 2.8 vs 2.2 mos (HR = 0.61, 95%CI 0.40-0.93; P = 0.0244), respectively. Time to progression was 5.9 vs 3.9 mos (HR = 0.45, 95% CI: 0.25-0.82, P = 0.0056). Median overall survival (OS) was 7.0 vs 6.4 mos (HR = 0.88, 95%CI 0.59-1.32; P = 0.5169), respectively. Considering the high cross-over rate (45.2%), the rank preserving structural failure time-adjusted median OS was 7.0 vs 4.7 mos (HR = 0.64, 95%CI 0.42-0.97; P = 0.0223). The improvement of dysphagia and quality of life are detailed in the Table. Phototoxicity was negative in 64.9% pts in DVDMS-PDT group on day 7, increasing to 91.4% by day 28. Grade ≥3 treatment-emergent adverse events occurred in 38.2% of the DVDMS-PDT group and 49.2% of the TPC group. Six deaths were due to treatment-related adverse events (4.9%) were reported in the DVDMS-PDT group and 5 (8.5%) in the TPC group. **Conclusions:** DVDMS-PDT significantly improved esophageal stenosis and dysphagia compared to the treatment of physician's choice in pts with aEC, with prolonged PFS and TTP, potential better OS and a manageable safety profile. Clinical trial information: CTR20221271. Research Sponsor: None.

	DVDMS-PDT (n=124)	TPC (n=62)
Reduction at least 1 grade in Stooler's score in 6 mons, %	47.8%	8.6% (P<0.0001)
Change in EORTC QLQ-C30 total score	-26.7 ± 2.5	-39.8 ± 4.3
Change in dysphagia score	16.0 ± 2.6	24.6 ± 4.3
Change in eating score	16.9 ± 2.4	30.6 ± 4.1

Values are least-squares mean ± standard error unless otherwise noted.
Symptom scores were assessed using EORTC QLQ-OES18.

4017 Rapid Oral Abstract Session

Claudin18.2 (CLDN18.2) expression and efficacy in pancreatic ductal adenocarcinoma (PDAC): Results from a phase I dose expansion cohort evaluating IBI343. First Author: Xianjun Yu, Department of Pancreatic Surgery, Fudan University Shanghai Cancer Center, Shanghai, China

Background: CLDN18.2 is highly expressed in nearly 60% of PDAC cases. Yet to date, there are no approved targeted therapies and prognoses for these patients (pts) remain poor. IBI343, consisting of an anti-CLDN18.2 Fc silenced monoclonal antibody and the topoisomerase I inhibitor, exatecan, is the first CLDN18.2 antibody-drug conjugate to have shown encouraging efficacy in PDAC. Here, we report results from a phase 1 study (NCT05458219) in pts with PDAC treated with IBI343 by CLDN18.2 expression status (≥60% vs < 60%). **Methods:** Eligible pts with advanced PDAC and moderate to high expression of CLDN18.2 (defined as immunohistochemistry [IHC] membrane staining intensity ≥2 in ≥40% of tumor cells by IHC VENTANA CLDN18 [43-14A] Assay) who failed or were intolerant to standard treatment were enrolled. IBI343 was administered every 3 weeks at multiple dose levels (1, 3, 4.5, 6, 8, and 10 mg/kg). Endpoints included safety, objective response rate (ORR), disease control rate (DCR), duration of response (DoR), progression-free survival (PFS) per RECIST v1.1, and overall survival (OS). **Results:** As of December 27, 2024, 83 pts from China and Australia were enrolled. 44 and 12 pts with CLDN18.2 expression ≥1 in ≥60% (+) and < 60% (-) of tumor cells, respectively, received IBI343 at 6mg/kg in the dose expansion phase (median age, 60 and 64 years; male, 54.5% and 66.7%; received prior treatments ≥2L, 61.4% and 83.3%). Among all treated pts (n = 83), treatment-emergent adverse events (TEAEs) occurred in 82 (98.8%) pts and ≥Grade 3 (G3) TEAEs in 42 (50.6%) pts. TEAEs led to treatment discontinuation in 6 (7.2%) pts. No TEAE led to death. Most common TEAEs were anemia (66.3%, 15.7% ≥G3), neutrophil count decreased (48.2%, 9.6% ≥G3), and WBC count decreased (47.0%, 9.6% ≥G3). The safety profile of IBI343 in PDAC was comparable to previous reports. Among CLDN18.2+ pts (n = 44), confirmed ORR was 22.7% (95% CI, 11.5–37.8); DCR was 81.8% (95% CI: 67.3–91.8), median PFS was 5.4 (95% CI, 4.1–7.4) months (mos), median OS was 8.5 (95% CI, 6.6–12.1) mos, and in 10 pts with confirmed partial response median DOR was 6.7 (95% CI, 3.2–7.7) mos. Among CLDN18.2+ pts who received 1 and 2 lines of prior treatment, median OS was 12.1 (95% CI, 6.6–not calculable [NC]) mos and 9.1 (95% CI, 5.1–NC) mos, respectively. Among CLDN18.2- pts (n = 12), no pt had an objective response, DCR was 41.7% (95% CI: 15.2–72.3), median PFS was 1.4 (1.3–3.2) mos, which was shorter than what was seen in CLDN18.2+ pts (Ad hoc analysis: nominal P < .0001; HR = 0.198 [95% CI: 0.089-0.439]) and median OS was 6.2 (95% CI,1.4–9.0) mos. **Conclusions:** IBI343 was well tolerated and continues to show encouraging efficacy in pts with PDAC. Efficacy benefit was most pronounced in those with CLDN18.2 expression ≥60%, suggesting that CLDN18.2 can be a predictive biomarker for response to IBI343 in PDAC. The trial is enrolling in Australia, China, and US. Clinical trial information: NCT05458219. Research Sponsor: None.

4018 Rapid Oral Abstract Session

Clinical activity of EBC-129, a first-in class, anti N256-glycosylated CEACAM5 and CEACAM6 antibody-drug conjugate (ADC), in patients with pancreatic ductal adenocarcinoma (PDAC) in a phase 1 study. First Author: Robert William Lentz, Division of Medical Oncology, Department of Medicine, University of Colorado Anschutz School of Medicine, Aurora, CO

Background: Pancreatic ductal adenocarcinoma (PDAC) is an aggressive malignancy with limited treatment options. EBC-129 is a first in class MMAE-linked ADC against N256-glycosylated CEACAM5/6 antigen. Pre-screening data shows 73% of PDAC express surface antigen (IHC positive cut-off ≥20% at 2+ or 3+) or 82% (≥1% at 3+). Previously reported dose escalation data identified 1.8 and 2.2 mg/kg every 3 weeks as the RP2Ds. Here we report pooled safety and efficacy data of the PDAC patients enrolled in the dose escalation (DEs) and expansion (DEx) cohorts of the phase 1 study. **Methods:** This study consisted of DEs and DEx cohorts. Previously treated histologically confirmed, locally advanced or metastatic PDAC patients with antigen expression levels of ≥20% at 2+ or 3+ intensity or ≥1% at 3+ intensity (IHC on archival samples) were enrolled. Objectives were to evaluate safety, efficacy, and PK of EBC-129, administered every 3 weeks. **Results:** A total of 21 PDAC patients were enrolled (6 in DEs and 15 in DEx). Patients received 1.8 (n = 8), 2.0 (n = 2) or 2.2 (n = 11) mg/kg EBC-129 every 3 weeks. 52% were male; mean age 63 years; median 3 (range 1-7) lines of previous treatments with 81% prior taxane treated. At data cut-off (Jan 16th, 2025), 5 patients are continuing treatment, 12 patients had radiological progression, 3 had clinical progression, and 1 patient withdrew treatment. The overall response rate, disease control rate (first assessment), and median PFS, at 1.8 mg/kg, 2.2 mg/kg and overall group, respectively, were 25.0%, 18.2% and 19.0% (unconfirmed), 87.5%, 63.6% and 71.4%, and 18, 12 and 12 weeks. 43% of patients had any tumour shrinkage overall. Infusion related reactions (IRR) were seen in 57% of patients; most were grade 1/2, more frequent at 2.2 mg/kg, and resolved or reduced with premedication. Grade ≥3 treatment related adverse events included neutropenia (50.0% and 81.8%) and anaemia (12.5% and 18.2%) at 1.8 and 2.2mg/kg, respectively; amylase/lipase increase, vomiting, and aspartate aminotransferase increase occurred in 1 patient each. Grade ≤2 peripheral neuropathy was seen in 2 patients. No drug related discontinuations occurred in this cohort. In this cohort, selected for target antigen expression, no apparent correlation was seen between IHC score and treatment response. Based on a cut-off of > 25% CEA decrease (either local or central), biomarker response was seen 42.9% at 1.8 mg/kg and 36.4% at 2.2 mg/kg. **Conclusions:** EBC-129 shows promising clinical activity in heavily treated PDAC patients with a manageable tolerability profile, consistent with MMAE-based ADCs. Further evaluation of EBC-129 in PDAC, both as monotherapy and in combination with chemotherapy, is planned. Clinical trial information: NCT05701527. Research Sponsor: Experimental Drug Development Centre (EDDC).

4019 Rapid Oral Abstract Session

10-year follow up of a phase 2 clinical trial of pembrolizumab (pembro) in microsatellite instability-high (MSI-H)/mismatch repair deficient (dMMR) advanced solid tumors. First Author: Katherine M. Bever, Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins University, Baltimore, MD

Background: Inhibitors of Programmed Cell Death Protein-1 (PD-1) have demonstrated remarkable activity in dMMR/MSI-H cancers, leading to the first tissue agnostic FDA approval for an oncologic indication. We report herein results of long-term follow up of KEYNOTE-016, the first study to demonstrate pan-tumor activity of the PD-1 inhibitor pembro in dMMR/MSI-H solid tumors. **Methods:** KEYNOTE-016 was a multicenter open-label phase 2 study evaluating pembro in patients with advanced colorectal cancer (CRC) (Cohort A) or non-CRC solid tumors (Cohort C) that were dMMR and had progressed after ≥1 prior line of therapy (or ≥2 prior lines for CRC). Eligible patients were age ≥ 18, and had measurable disease per RECIST 1.1. Patients with active CNS metastases, who were on immunosuppressive therapy, had autoimmune disease, or were previously treated with immune checkpoint inhibitors were excluded. Patients received pembro IV every 2 weeks until progression, intolerance, withdrawal of consent or up to a maximum of 2 years. **Results:** Between 9/2013 - 9/2017, 88 patients (Cohort A: 41; Cohort C: 47) enrolled at 7 sites and received ≥1 dose of pembro. Tumor types enrolled on Cohort C included endometrial (N = 15), pancreatic (N = 9), small intestinal (N = 5), gastroesophageal (N = 5), biliary (N = 4), ampullary (N = 4), and other (N = 5). Median follow up time was 49.7 mos for all patients and 99.8 mos for alive patients. Objective response rate (ORR) was 58% with 23 partial (PR) and 28 complete responses (CR). 16 patients experienced a best response of stable disease (SD) for a disease control rate of 76%. Median PFS and OS were 34.9 mos (95% CI: 14.8-NR) and 80.8 mos (95% CI: 33.2-NR) respectively. The 3-, 5-, and 10-year OS rates were 55.1%, 53.7% and 47.4% respectively. Outcomes were similar between Cohorts A and C (see Table). **Conclusions:** In summary, long term follow up of KEYNOTE-016 confirms high rates of durable remission from pembro in patients with dMMR/MSI-H solid tumors, with several patients remaining alive and in remission at 10+ years follow up. Responses were seen across tumor types. Clinical trial information: NCT01876511. Research Sponsor: Swim Across America; Merck.

Results by cohort.

	Cohort A CRC N=41	Cohort C non-CRC N=47
ORR, %	56.1	59.6
PR, N (%)	11 (27)	12 (25)
CR, N (%)	12* (29)	16 (34)
SD, N (%)	10 (24)	6 (13)
PD, N (%)	5 (12)	9 (19)
NE, N (%)	3 (7)	4 (9)
PFS, median months (95% CI)	38.8 (8.1-NR)	20.5 (14.3-NR)
OS, median months (95% CI)	80.8 (33.2-NR)	86.4 (21.8-NR)
Follow up time, median months	51.2	35.9
3-year OS rate (%)	60.5	50.3
5-year OS rate (%)	57.5	50.3
10-year OS rate (%)	47.3	47.2

*Includes 3 patients with unconfirmed CR.

4020 **Rapid Oral Abstract Session**

Health-related quality of life (HRQOL) in the phase 3 trial of cabozantinib vs placebo for advanced neuroendocrine tumors (NET) after progression on prior therapy (CABINET, Alliance A021602). First Author: Amylou C. Dueck, Alliance Statistics and Data Management Center, Mayo Clinic, Scottsdale, AZ

Background: In previously treated patients (pts) with advanced extra-pancreatic NET (epNET) or pancreatic NET (pNET), cabozantinib (cabo) demonstrated improved progression-free survival compared to placebo (pbo) in the CABINET trial (NCT03375320). Here we present HRQOL data from CABINET. **Methods:** Pts with previously treated unresectable, locally advanced or metastatic epNET or pNET were randomized (2:1) in separate cohorts to receive cabo 60 mg daily vs pbo. HRQOL was an exploratory endpoint measured using the EORTC QLQ-C30, QLQ-GI.NET21, Patient Global Impression of Change (PGIC), and PRO-CTCAE questionnaires. Optional participation was by paper surveys at baseline and every 12 weeks (wks) until disease progression or new anticancer therapy. Mean changes from baseline were compared between treatment arms at wk12 using general linear mixed models. Minimally important within-arm improvements and between-arm differences were defined as 8 points on the C30 Global Health Status (GHS)/QOL Scale. PGIC was dichotomized as improved vs unchanged/worsened and compared using Chi-squared tests. Rates of pt-reported adverse events (AEs) by PRO-CTCAE were baseline-adjusted and compared using Fisher's exact tests. **Results:** 172 pts (113 cabo, 59 pbo) with epNET and 81 pts (53 cabo, 28 pbo) with pNET consented for survey participation. Pts completed 524 (82%) of 640 expected surveys across baseline, wk12, and wk24. For epNET, C30 GHS/QOL was significantly improved at wk12 in pts receiving cabo (mean change 9.5, standard error (SE) 2.2, $p < 0.001$) but not pbo (mean change 0.2, SE 3.1, p = 0.95) resulting in significantly different mean changes from baseline between arms (p = 0.02). For pNET, C30 QHS/QOL was significantly improved at wk12 in pts receiving cabo (mean change 8.0, SE 3.0, p = 0.008) but not pbo (mean change 6.8, SE 4.4, p = 0.12); mean changes from baseline did not statistically differ between arms (p = 0.82). No significant differences in mean changes from baseline at wk12 in C30 Physical, Role, Emotional, Cognitive and Social Function were observed between arms in the epNET or pNET cohorts. In both cohorts at wk12, pts on cabo reported improved overall status as measured by PGIC more often than those on pbo (epNET: 38% vs 19%, p = 0.04; pNET: 57% vs 18%, p = 0.006). Rates of pt-reported AEs were statistically significantly higher in cabo for diarrhea (68% vs 53%), hand-foot syndrome (57% vs 26%), mouth or throat sores (47% vs 27%), and dysgeusia (67% vs 37%) [all $p < 0.05$]. GI.NET21 data will be presented. **Conclusions:** Although cabo is associated with pt-reported AEs consistent with its known safety profile, global HRQOL was maintained. A higher proportion of patients receiving cabo reported improved overall status. Results support cabo as a treatment option for pts with previously treated advanced NET that preserves patient HRQOL. Clinical trial information: NCT03375320. Research Sponsor: UG1CA189823; U10CA180821; U10CA180882; Exelixis; https://acknowledgments.alliancefound.org.

4021 **Poster Session**

Claudin-18.2 expression in gastro-oesophageal adenocarcinoma in a Western population: Overlap with other biomarkers and prognostic value. First Author: Filip Van Herpe, Gastrointestinal Oncology Department, University Hospitals Leuven, Leuven, Belgium

Background: Claudin 18.2 (CLDN18.2) is a novel biomarker for response to anti-CLDN18.2 therapy in gastroesophageal adenocarcinoma (GEA). Based on prevalence data, originating mostly from an Asian population, 40% of GEA are CLDN18.2 positive. We currently lack information on the cross-prevalence of CLDN18.2, HER2-status, microsatellite instability (MSI) and PDL1 expression in a Western population of localized and metastatic GEA. **Methods:** We present a single-center, retrospective study including localized and metastatic GEA patients diagnosed between 2019-2023. Histopathology with MMR status, HER2 status (IHC/SISH) and PDL1 CPS was obtained. CLDN18.2-positivity defined as ≥75% of tumor cells showing moderate-to-strong membranous staining was determined by IHC using the VENTANA CLDN18 [43-14A] RxDx Assay and underwent blind review by independent expert pathologists. Baseline characteristics and clinical follow-up data were gathered until august 2024. Kaplan-Meier curves were constructed for overall survival (OS), progression/relapse free survival (PFS/RFS) and survival after recurrence (SAR). Unrestricted grants/support was provided from Astellas, AMGEN and Roche diagnostics. **Results:** Of 405 patients with GEA, 261 presented with localized and 144 with metastatic disease. The majority were male (71%) with a median age of 65 years. 59% of tumors were junction tumors and 41% were gastric cancers. dMMR was detected in 6%. HER2 positivity (cfr. TOGA criteria) was seen in 16% of cases. PDL1 CPS ≥1 prevalence was 58%. CLDN18.2 positivity was seen in 42% of patients. Double CLDN18.2-HER2 and CLDN18.2-dMMR positivity was rare (5% and 3%), but strikingly in absolute numbers, about one third of HER2 positive tumors and half of dMMR tumors were CLDN18.2 positive. Double CLDN18.2-PDL1 ≥1//≥5//≥10 positivity was seen in 23%,15% and 9%. In patients with localized disease CLDN18.2 positivity did not affect RFS (HR: 0.99; 95%CI(0.68-1.43); p = 0.95) and OS (HR: 0,78; 95%CI(0.52-1.16) p = 0,22) with a median follow-up (FU) of 42 months. In the remaining 113 patients with primary metastatic disease no difference in terms of PFS (HR: 1.17; 95%CI(0,79-1.73); p = 0,43) or OS (HR: 1.43; 95%CI(0,94-2.16); p = 0,1) was seen according to CLDN18.2 status with a median FU of 39 months. Median SAR in the localized group was statistically longer in the PDL1 CPS≥1 subgroup(HR: 0.51; 95% CI(0,34-0,79); p = 0,002). SAR was not different in CLDN18.2+ and CLDN18.2- patients (HR: 1,07; 95%CI(0,69-1.65) p = 0,77). **Conclusions:** We confirmed a 42% positivity rate of CLDN18.2 in a combination of localized and metastatic GEA in a Western population. dMMR was present in 6% of cases, PDL1 CPS ≥1 and HER2+ was seen in 58% and 16% of patients. CLDN18.2 positivity was strikingly present in half dMMR and one third of HER2+ cases. CLDN18.2 positivity did not affect survival in localized and metastatic disease. Research Sponsor: Astellas; Amgen.

4022 **Poster Session**

Preliminary results of a phase 1 study of LB1908, an autologous Claudin 18.2–targeted chimeric antigen receptor T-cell product, in patients with advanced gastroesophageal adenocarcinoma. First Author: David Bing Zhen, Fred Hutchinson Cancer Center, Seattle, WA

Background: Claudin 18.2 (CLDN18.2) is a potential therapeutic target expressed on most gastric, gastroesophageal, and esophageal adenocarcinomas (GC/GEJC/EC), with normal tissue expression limited to gastric epithelium. We present preliminary results of the dose-escalation trial of LB1908, a CLDN18.2-targeted autologous CAR-T cell product, in adults with advanced GC/GEJC/EC. **Methods:** This trial is an ongoing, open-label, multicenter, first-in-human phase 1 study of LB1908 in patients with advanced GC/GEJC/EC relapsed/refractory to ≥1 prior line of therapy (LOT), and with ≥1+ CLDN18.2 expression in ≥50% of tumor cells by central testing (43-14A antibody). A modified 3+3 design is used for dose escalation with planned dose levels of 0.5, 1.5, and 3×10^6 CAR+ T cells/kg. The primary objective is evaluation of safety and dose-limiting toxicities (DLTs) with secondary objectives of antitumor activity and pharmacokinetics. **Results:** As of the data cutoff of January 4, 2025, 6 patients were dosed with LB1908 at dose level 1 (0.5×10^6 cells/kg). Four patients had EC and 2 had GC, all with metastatic disease. Patients had a median of 2 prior LOTs; all had received fluoropyrimidine/platinum agents. Bridging therapy was administered to all patients between apheresis and LB1908 infusion, and patients received standard lymphodepletion (LD) with cyclophosphamide/fludarabine. All patients experienced treatment-emergent adverse events (TEAEs); the most common grade ≥3 TEAEs were hematologic and attributable to the LD regimen. Of grade ≥3 TEAEs related to LB1908, only gastritis/gastric mucosal injury occurred in more than 1 patient (n = 3), including 1 DLT. After implementation of toxicity management guidelines using prophylactic enteral beclomethasone and early systemic steroids, no patients experienced prolonged grade ≥3 upper GI AEs. CRS occurred in all patients, with no grade ≥3 events. No ICANS was observed. CAR-T cell expansion was seen in all patients, with a median C_{max} of 1594 copies/μg genomic DNA (range, 264-6922) and T_{max} of 14 days (range, 11-15). All 6 patients were evaluable for response, with 5 (83%) experiencing target lesion shrinkage (maximal 1%, 9%, 25%, 31%, and 41% reduction from baseline). Responses deepened over time in the 2 patients with multiple postinfusion scans (-25% and -41%, respectively), including 1 patient achieving a RECIST partial response 7 months after treatment. **Conclusions:** LB1908 demonstrates peripheral expansion and encouraging antitumor activity at the lowest dose tested, with a manageable safety profile. Implementation of a toxicity mitigation strategy ameliorated on-target gastric mucosal injury without compromising expansion kinetics or antitumor activity. Longer follow-up and data from patients treated with higher cell doses will be presented at the meeting. Clinical trial information: NCT05539430. Research Sponsor: Legend Biotech USA Inc.

4024 **Poster Session**

Genomic landscape and biomarker analyses utilizing circulating-tumor DNA in advanced esophageal squamous cell carcinoma: Sub-analysis of SCRUM-MONSTAR GOZILA. First Author: Yuqing Duan, National Cancer Center Hospital East, Kashiwa, Japan

Background: Advanced esophageal squamous cell carcinoma (ESCC) is a cancer type with a poor prognosis, with limited survival benefits from current multimodal approaches. The incomplete understanding of molecular mechanisms in advanced ESCC has hindered the development of effective targeted therapies, emphasizing the critical need for identifying predictive biomarkers and novel therapeutic targets. **Methods:** SCRUM-MONSTAR GOZILA is a nationwide plasma-based genomic profiling study utilizing Guardant360 in Japan, which aimed to analyze circulating tumor DNA (ctDNA) genomic alterations in patients with advanced solid tumors, including ESCC. We evaluated the genomic landscape with advanced ESCC patients and investigated associations between genomic alterations and overall survival (OS) using the log-rank test. The correlation between progression-free survival (PFS) and blood tumor mutation burden (bTMB) in immune checkpoint inhibitor (ICI) monotherapy was also assessed using multiple cut-off values (2, 4, 6, 8, and 10 mutation/Mb). **Results:** The present study included 313 patients with available genomic and clinical data. The gene alteration spectrum comprised mutations (single nucleotide variants, 71.6%; and insertions/deletions, 10.7%), copy number alterations (CNAs, 17.3%), and fusions (0.48%). TP53 was the most frequently altered gene (88.5%), followed by PIK3CA (36.4%), NFE2L2 (24.3%), CCND1 (22.4%), EGFR (20.1%), ATM (16.3%), FGFR1 (10.2%), BRCA2 (10.2%), MET (9.6%) and ARID1A (9.6%). Regarding the survival outcomes, PIK3CA CNA was significantly associated with worse OS compared to those with PIK3CA wild type [hazard ratio (HR), 1.84; 95% confidence interval (CI), 1.24–2.74; p-value, 0.0002], and PIK3CA mutation showed a trend toward shorter OS (HR, 1.43; 95%CI, 0.94–2.17; p-value, 0.06). Patients with both PIK3CA mutation and CNA exhibited significantly worse OS compared to those with PIK3CA wild type (HR, 1.94; 95%CI, 0.85–4.45; p-value, 0.03). Both FGFR1 CNA and mutation were associated with poorer OS (HR, 1.98; 95%CI, 1.03–3.79; p-value, 0.005; and HR, 2.84; 95%CI, 0.89–9.07; p-value, 0.002, respectively). CNA in CCND1 and EGFR, and mutation in NFE2L2 and RB1 also significantly correlated with worse OS (any p-value≤0.01). Among 142 patients treated with ICI monotherapy, no statistically significant differences in PFS were observed at any cut-off value of bTMB (any p-value > 0.1). **Conclusions:** This comprehensive analysis of ctDNA profiles revealed distinct genomic alterations with prognostic significance in advanced ESCC. Multiple alterations demonstrated significant associations with poor OS, meanwhile bTMB was not validated as an effective predictive biomarker for ICI efficacy. These findings provide insights into potential therapeutic targets and prognostic biomarkers in advanced ESCC. Clinical trial information: 2021-GB-009. Research Sponsor: None.

4025 **Poster Session**

HER2 expression dynamics and prognostic significance in the treatment of gastric cancer. First Author: Min Lai, Department of General Surgery, Nanfang Hospital, Southern Medical University, Guangzhou, Guangdong, China

Background: The human epidermal growth factor receptor 2 (HER2) expression undergoes changes during the treatment of gastric cancer. This study aims to evaluate post-treatment HER2 expression changes and the impact on survival. **Methods:** From a prospectively maintained database, we extracted clinical and pathological data, treatment information, and survival outcomes of gastric cancer patients (pts) with paired pre- and post-treatment HER2 immunohistochemistry (IHC) results (2018-2024). Cohen's Kappa was used to assess HER2 expression concordance. Logistic regression was performed to identify factors associated with HER2 change, while the Kaplan-Meier method and Cox regression were used for survival analysis. **Results:** 274 gastric cancer pts with paired HER2 IHC results were enrolled, including IHC 0 (67.5%, 185/274), 1+ (14.6%, 40/274), 2+ (13.5%, 37/274), 3+ (4.4%, 12/274) before treatment and IHC 0 (63.8%, 175/274), 1+ (21.9%, 60/274), 2+ (11.7%, 32/274), and 3+ (2.6%, 7/274) after treatment. The overall HER2 change rate was 42.7% (21.5% HER2 expression increased, 21.2% decreased), indicating low concordance (Kappa = 0.179, $p < 0.001$). Among 7.6% (17/225) of pts with HER2 changes from 0/1+ to 2+/3+, 23.5% (4/17) received anti-HER2 therapy (trastuzumab or anti-HER2 ADCs), achieving a 75.0% response rate. 38.5% (5/13) of initially confirmed HER2-positive pts (IHC 3+/2+ and FISH+) exhibited loss of HER2 positivity after treatment. 3 of 8 initially HER2-negative pts who converted to HER2-positive received trastuzumab for metastatic diseases, achieving a 66.7% response rate. Based on efficacy evaluation on the second HER2 testing, 197 pts were classified into the PR/SD group and 77 into the PD group, with comparable HER2 changes rate (41.6% vs. 45.5%, p = 0.565). Anti-HER2 therapy (n = 28) was associated with a higher HER2 changes rate (67.9% vs. 39.8%, p = 0.005), mainly driven by HER2 reduction (60.7% vs. 16.7%, $p < 0.001$). Multivariate logistic regression showed that combined immunotherapy (OR [odds ratio] 1.85, p = 0.028) or targeted immunotherapy (OR 4.71, $p < 0.001$) was associated with a higher HER2 change rate than chemotherapy alone. The median follow-up time was 31.2 months. HER2 expression changes were associated with worse PFS (HR [hazard ratio] 1.52, p = 0.040) and OS (HR 1.51, p = 0.043), with decreased HER2 expression showing the poorest PFS (Log-rank p = 0.030) and OS (Log-rank p = 0.025). Subgroup analysis showed in PR/SD group, HER2 expression changes was associated with significantly worse PFS (HR 2.48, p = 0.003) and OS (HR 2.56, p = 0.002), while no survival differences were observed in PD group. **Conclusions:** HER2 expression frequently changes during the treatment of gastric cancer, particularly after immunotherapy and targeted therapy, and is associated with worse survival outcomes. Dynamic HER2 testing contributes to guiding precision therapy for gastric cancer. Research Sponsor: None.

4027 **Poster Session**

Tislelizumab (TIS; BGB-A317) plus chemotherapy (CT)/chemoradiotherapy (CRT) as positron emission tomography (PET)–guided neoadjuvant (n) treatment (tx) for resectable esophageal squamous cell carcinoma (R-ESCC): RATIONALE-213 final analysis. First Author: Longqi Chen, Department of Thoracic Surgery, West China Hospital, Sichuan University, Chengdu, China

Background: Studies have shown overall survival improvements with nCRT + surgery vs surgery alone in locally advanced ESCC. However, preoperative CRT may have additional safety concerns, leading to some patients (pts) receiving nCT rather than nCRT. PET-computed tomography maximum standardized uptake value (SUV_{max}) change after induction CT (IC) has been shown to have reliable predictive value of pathological complete response (pCR) for R-ESCC in pts with nCRT and may optimize neoadjuvant tx selection. TIS (anti-PD-1) has improved survival in pts with ESCC. We report the final analysis of RATIONALE-213, a phase 2, open-label, multicenter study in China evaluating PET-guided nTIS + CT/CRT in R-ESCC (NCT04974047). **Methods:** Eligible adult pts had histologically confirmed R-ESCC (cT1-2N + M0 or cT3N any M0), ECOG performance status 0/1, adequate organ function, no fistula risk, and had received no prior tx. Pts had a baseline (BL) PET scan, 1 cycle of IC (cisplatin-paclitaxel [Cis-Pac]), and a PET scan 15-21 days later. Pts were grouped into 2 cohorts by response to IC based on the percentage decrease in 2nd PET SUV_{max} in the primary tumor: responders (R, ≥35%) or nonresponders (NR, < 35%). Both cohorts received 3 cycles of TIS 200 mg IV Q3W, the first 2 with CT (2 cycles Cis-Pac) for R, or with CRT (2 cycles investigator [Inv]-chosen CT [Cis-Pac, or 5-FU + Cis] + RT [40 Gy/20 fractions]) for NR, then surgery. Primary endpoint was pCR per local pathologist. Secondary endpoints were 1-year disease-free survival (DFS), 1-year event-free survival (EFS), objective response rate (ORR) before surgery, R0 resection rate by Inv, and safety. **Results:** Of 70 pts enrolled, 15 (21.4%), 48 (68.6%), and 7 (10.0%) had stage II, III, and IVA disease at BL, respectively. As of 25 Oct 2024 (median follow-up 25.5 mo), 30 pts were R and 40 NR. Of R, 20 (66.7%) had surgery. Of NR, 32 (80.0%) had surgery. Efficacy endpoints are shown in the table. Median DFS and EFS were not reached for R and NR. Grade ≥3 treatment-related adverse events (TRAEs) in R (15 [50.0%]) and NR (33 [82.5%]) were consistent with known CT or CRT toxicity; serious TRAEs occurred in 5 R (16.7%) and 7 NR (17.5%). No TRAEs led to surgery cancellation or death. **Conclusions:** APET-guided approach may help optimize neoadjuvant tx of R-ESCC. nTIS + CT/CRT showed promising efficacy and a tolerable safety profile in both responders and nonresponders. Clinical trial information: NCT04974047. Research Sponsor: BeOne Medicines Ltd.

	R	NR
pCR,[a] n (%)	6 (30.0)	11 (34.4)
(95% CI)	(11.9, 54.3)	(18.6, 53.2)
1-year DFS,[b] %	79.0	74.2
(95% CI)	(47.9, 92.7)	(53.3, 86.8)
1-year EFS,[c] %	87.1	67.8
(95% CI)	(64.3, 95.8)	(48.3, 81.2)
R0 resection,[a] n (%)	19 (95.0)	29 (90.6)
ORR,[d] n (%)	15 (71.4)	14 (42.4)

[a]Efficacy analysis set (EAS) R=20; NR=32.
[b]EAS with R0 resection R=19; NR=29.
[c]Safety analysis set (SAS) R=30; NR=40.
[d]SAS with measurable disease at BL R=21; NR=33.

4028 **Poster Session**

Efficacy and safety of surufatinib (Sur) plus paclitaxel (Pac) as second line (2L) treatment for advanced gastric cancer (aGC): Final results from a phase 2 trial. First Author: Xiuying Xiao, Department of Oncology, Renji Hospital, School of Medicine, Shanghai Jiao Tong University, Shanghai, China

Background: Standard chemotherapy (ChT) provides unsatisfactory efficacy for patients with aGC in the 2L setting. Recent studies have suggested improved efficacy with an antiangiogenic agent plus Pac. Although ramucirumab plus Pac have been approved as a 2L treatment, access to this combination regimen is limited in China. Sur is a potent VEGFRs, FGFR1 and CSF-1R inhibitor. This trial is aimed to assess the efficacy and safety of Sur plus ChT as a 2L treatment for aGC. Our previous report (ASCO-GI 24) revealed promising anti-tumor activity of this regimen. Now we are presenting the final analyses including long-term survival results. **Methods:** This single-arm, phase 2 clinical trial enrolled patients with HER2-negative aGC who had failed standard first-line treatment. Eligible patients received Sur (250mg, po, qd) plus Pac (150mg/m^2, iv, d1) at 21-day cycles for 6 cycles, followed by maintenance with single-agent Sur until disease progression or intolerable toxicity. Tumor responses were assessed every 6 weeks by investigators per RECIST v1.1. The primary endpoint was ORR, and secondary endpoints were DCR, PFS, OS, and safety. **Results:** As of Dec 20, 2024, of the 35 patients enrolled, median age was 65 (range: 33-75), 26 (74.3%) were male, 31 (88.6%) had an ECOG PS of 1, 12 (34.3%) had positive PD-L1 (defined as CPS ≥1), and 26 (74.3%) had received 1L immunotherapy (IO). Seven (20.0%) patients had primary GEJC, and all patients had stage IV disease, with lymph nodes (23, 65.7%), liver (16, 45.7%) and peritoneum (14, 40.0%) being the most common metastatic sites. Tumor response assessments were available in 32 patients, the ORR was 25.0% and DCR was 87.5%. Primary GEJC (42.9% vs 20.0%, *P*= 0.327) and baseline liver metastases (40.0% vs 11.8%, *P*= 0.106) seemed correlated to a better ORR, while baseline peritoneal metastases (8.3% vs 35.0%, *P*= 0.204) the reverse. With a median follow-up of 12.6 (95% CI: 10.4-14.9) months (mo), the mPFS was 5.7 (95% CI: 4.7-6.93) mo and the mOS was 10.8 (95% CI: 7.0-17.2) mo. Within the subgroup patients who had IO exposure in the 1L setting (n = 26), the ORR was 25.0%, the DCR was 91.7%, the mPFS was 5.9 (95% CI: 4.7-10.5) mo, and the mOS reached 14.4 (95% CI: 8.5-NR) mo. Treatment-related adverse events of grade ≥3 included neutropenia (40.0%), leukopenia (34.3%), hypertension (11.4%), and proteinuria (5.7%). There were no treatment-related serious adverse events or on-treatment deaths. **Conclusions:** These encouraging long-term efficacy results and the manageable safety profile suggested a preferable position of Sur plus Pac as the 2L treatment for aGC, notably, following the current standard 1L IO-containing regimens. Clinical trial information: ChiCTR2200063336. Research Sponsor: HUTCHMED.

4029 **Poster Session**

A multicenter randomized phase II study of trastuzumab biosimilar (CT-P6) and chemotherapy (SOX or CapeOX) in HER2-positive advanced/recurrent gastric cancer (KSCC: TROX study). First Author: Teppei Yamada, Department of Gastroenterological Surgery, Fukuoka University Faculty of Medicine, Fukuoka, Japan

Background: The efficacy and safety of the trastuzumab biosimilar (CT-P6) combined with S-1/oxaliplatin (SOX) or capecitabine/oxaliplatin (CapeOX) were investigated in patients with HER2-positive advanced or recurrent gastric cancer who had not previously received chemotherapy. CT-P6 is a biosimilar of trastuzumab, which has demonstrated comparable safety and efficacy to trastuzumab in breast cancer. However, no clinical trials have evaluated CT-P6 in gastric cancer to date. **Methods:** This randomized, open-label, multicenter phase II study enrolled patients with HER2-positive unresectable or recurrent gastric cancer. Participants were randomized to receive SOX plus trastuzumab biosimilar therapy (S-1 orally, 40–60 mg twice daily for 14 days every 3 weeks, oxaliplatin intravenously at 130 mg/m² on day 1 every 3 weeks, and CT-P6 at 8 mg/kg on day 1 and 6 mg/kg every 3 weeks thereafter) or CapeOX plus trastuzumab biosimilar therapy (replacing S-1 with capecitabine [1,000 mg/m²] as described above) until disease progression. The primary endpoint was overall response rate (ORR) in both arms, with a null hypothesis response rate set at 43%, the lower bound of the 90% confidence interval reported in previous trastuzumab trials. Secondary endpoints included progression-free survival (PFS), overall survival (OS), and safety. **Results:** Between May 2019 and November 2022, 67 patients were enrolled in the study. Patient characteristics were as follows: male/female ratio of 49/18, median age 68 years (range: 34–80), and performance status (PS) of 0/1 in 53/14 patients. The ORR was 76.1% (90% CI: 67.6–84.7%), with the lower limit of the confidence interval exceeding the threshold response rate of 43%, confirming the efficacy of trastuzumab biosimilar therapy. The one-year survival rate was 65.2% (95% CI: 49.8–78.6%), meeting the primary endpoint. The median OS was 18.7 months (90% CI: 15.1–23.1), and the median PFS was 9.0 months (90% CI: 6.5–10.7). Although the study was not designed to compare SOX and CapeOX, the response rate was slightly higher in the CapeOX group (81.3% [90% CI: 69.9–92.6%]) compared to the SOX group (71.4% [90% CI: 58.9–84.0%]). Similarly, OS was slightly better in the CapeOX group (22.3 months [90% CI: 15.1–42.1]) than in the SOX group (16.7 months [90% CI: 12.7–19.6]). The most frequent grade 3 or 4 adverse events were neutropenia (15.2%), appetite loss (12.1%), and diarrhea (7.6%). **Conclusions:** Trastuzumab biosimilar (CT-P6) combined with SOX or CapeOX demonstrated robust antitumor efficacy and manageable toxicity in patients with advanced or recurrent gastric cancer. Clinical trial information: jRCTs071190007. Research Sponsor: None.

4030 **Poster Session**

Neoadjuvant serplulimab in combination with chemotherapy for locally advanced gastric or gastro-esophageal junction cancer. First Author: Hongjie Zhan, Tianjin Medical University Cancer Institute and Hospital, Tianjin, China

Background: Perioperative therapy combined with surgery is the standard treatment for locally advanced gastric or gastro-esophageal junction (G/GEJ) cancer; however, long-term survival remains suboptimal. Immunotherapy has demonstrated antitumor activity and an acceptable safety profile in advanced G/GEJ cancer. This study aimed to evaluate the efficacy and safety of neoadjuvant Serplulimab, a PD-1 inhibitor, in combination with chemotherapy in previously untreated, locally advanced G/GEJ cancer. **Methods:** Eligible patients with resectable G/GEJ adenocarcinoma staged as cT3-4aN+M0 were enrolled. The treatment regimen included Serplulimab (300 mg on day 1, every 3 weeks [Q3W]) plus SOX chemotherapy (oxaliplatin 130 mg/m^{2}on day 1; and S-1 60 mg twice daily on days 1-14, Q3W) for three cycles. Following the preoperative treatment, patients underwent surgery 6-8 weeks after the therapy. The primary endpoint was pathological complete response (pCR) rate. Secondary endpoints included major pathological response (MPR) rate, R0 resection rate, disease-free survival (DFS), overall survival (OS), and toxicity. **Results:** From October 13, 2023, to December 31, 2024, 25 patients were enrolled, all of whom completed neoadjuvant therapy and underwent radical surgical. The R0 resection rate was 100%. Five patients achieved pCR (pCR rate: 20%), and an additional five patients achieved MPR (MPR rate: 40%). Median DFS and OS were not reached. Safety analysis included all patients who received at least one cycle of neoadjuvant therapy. The most common treatment-related adverse events (TRAEs) of any grade included nausea, anorexia, thrombocytopenia, fatigue, and thyroid dysfunction. No grade ≥3 TRAEs were observed. **Conclusions:** Neoadjuvant Serplulimab combined with SOX chemotherapy demonstrated promising efficacy and a favorable safety profile in patients with locally advanced, resectable G/GEJ adenocarcinoma. These findings support the potential role of immune-based neoadjuvant therapy in this setting. Research Sponsor: None.

4031 **Poster Session**

Safety, efficacy, and biomarker analysis from a phase II trial of intensive chemotherapy combined with serplulimab and trastuzumab in patients with advanced HER2-positive gastric cancer. First Author: Tianshu Liu, Zhongshan Hospital, Fudan University, Shanghai, Shanghai, China

Background: Keynote-811 has proven the efficacy of combined PD-1 and HER2 blockade with chemotherapy in HER2-positive gastric cancer. Our study aims to enhance the survival of patients by replacing standard chemotherapy with intensive chemotherapy and conducting biomarker analysis. **Methods:** This prospective, single-arm, open-label study was carried out across five centers in China, recruiting patients (pts) with unresectable locally advanced or metastatic HER2-positive gastric cancer. Pts receive Serplulimab (4.5 mg/kg, D1, Q3W), Trastuzumab (initial 8 mg/kg, D1, then 6 mg/kg, D1, Q3W), and the DOS regimen: oxaliplatin (100 mg/m^2, IV), docetaxel (40 mg/m^2, IV), and S-1 (40-60mg, BID, D1-14, Q3W). Chemotherapy is up to 8 cycles. Serplulimab and Trastuzumab can be administered until tumor progression. Gastroscopic biopsy was taken before the treatment and dynamic blood samples were collected at C1D1 (T0), C2D1 (T1) and C7D1 (T2) for biomarker analysis. Genomic DNA from tumor tissue and circulating tumor DNA (ctDNA) underwent targeted DNA sequencing containing 571 genes. **Results:** From July 2022 to September 2024, 40 pts were recruited. The median follow-up was 7.9 months. There were 10 females and 30 males, with a median age of 59 (31-74). 37 pts were eligible for efficacy assessment. The objective response rate (ORR) was 92% (95% CI: 0.87, 0.96), with a complete response rate of 3% (95% CI: 0, 0.05), and a partial response rate of 89% (95% CI: 0.84, 0.94). Median progression free survival has not been reached. 38 pts (95%) experienced adverse events (AEs) of any grade. Grade 3 or above AEs occurred in 14 pts (35%), 2 pts with grade 4 AEs (1 with thrombocytopenia and 1 with myelosuppression). No grade 5 events were observed. The most common AEs were anemia (35%), neutropenia (23%), nausea and vomiting (20%) and leukopenia (20%). 15 (38%) pts had dose interruptions due to AEs, with no treatment discontinuation. HER2 CNV gain was detected in 82.1% (23/28) of tissue samples and 74.3% (26/35) of ctDNA samples. In matched ctDNA and tissue samples (N = 26), 88.5% (23/26) showed concordant HER2 CNV gain results. Elevated tissue HER2 CNV were associated with more pronounced tumor shrinkage (R = -0.35, P = 0.073). Plasma HER2 gain detection rate decreased from 79.1% (19/24) at T0 to 16.7% (4/24) at T1 ($P < 0.001$). Similar results were observed from T0 to T2 ($P < 0.001$). **Conclusions:** This regimen demonstrated remarkable efficacy with a high ORR and manageable toxicity. Tumor HER2 CNV and ctDNA dynamic monitoring correlated with treatment efficacy. The subsequent results of biomarker analysis will be presented at the upcoming conference. Clinical trial information: NCT05311189. Research Sponsor: None.

Pts characteristics.

	N=40
Age, ≥65 years	38%
Male	75%
PD-L1 status	
CPS ≥1	65%
CPS <1	13%
Unknown	22%
HER2 status	
IHC 2+ ISH positive	25%
IHC 3+	75%
Primary gastrectomy or esophagectomy	
Yes	15%
No	85%
Metastatic sites	
0–2	60%
≥3	40%

4032 **Poster Session**

First-line osemitamab (TST001) plus nivolumab and CAPOX for advanced G/GEJ cancer (TranStar102): Updated results of cohort G from a phase I/IIa study. First Author: Jifang Gong, Early Drug Development Center, Key Laboratory of Carcinogenesis and Translational Research (Ministry of Education), Peking University Cancer Hospital and Institute, Beijing, China

Background: Claudin 18.2 (CLDN18.2) is a clinically validated therapeutic target and has been broadly explored with different modalities in gastric/gastroesophageal (G/GEJ) cancer treatment. Osemitamab is a humanized monoclonal antibody with improved affinity to CLDN18.2, reduced fucosylation and enhanced ADCC activity and has been observed to upregulate PD-L1 expression on CLDN18.2-positive tumor cells. *In vivo* anti-tumor activity of combination of osemitamab plus an anti-PD-1/PD-L1 antibody and chemotherapies was significantly stronger than any of the doublet combinations, regardless of the PD-L1 CPS levels, making the triple combination of osemitamab, nivolumab and CAPOX an attractive combination to explore. **Methods:** Cohort G from TranStar102 (NCT04495296, a phase I/II study) was designed to evaluate the safety and preliminary efficacy of osemitamab at two dose levels (3mg/kg or 6mg/kg Q3W) plus nivolumab and CAPOX as the first-line treatment in patients with G/GEJ cancer. 40 patients were planned to be enrolled in each dose level. Key eligible criteria included HER2 negative or unknown, unresectable locally advanced or metastatic G/GEJ cancer, regardless of CLDN18.2 or PD-L1 expression and treatment naïve for advanced disease. The endpoints include safety, efficacy, PK and predictive value of the different levels of CLDN18.2 expression, etc. **Results:** As of Jan 13, 2025, 82 patients were dosed with osemitamab plus nivolumab and CAPOX (40 at 3mg/kg, 42 at 6mg/kg) with median follow-up of 21.3 months. All patients experienced treatment-related adverse events (TRAEs). The safety profile was similar with the previously presented data (2024 ESMO poster), and the most commonly observed TRAEs were on-target and off-tumor toxicities, such as nausea, vomiting and hypoalbuminemia, and were manageable. 44 out of 82 patients had confirmed partial response and the objective response rate (ORR) was 55.7%. There was a clear trend between anti-tumor efficacy and CLDN18.2 expression, with a confirmed ORR of 68% and median progression-free survival of 16.6 months (95% CI: 5.8, 21.7) for the patients with CPS known and CLDN18.2 high/medium expression (defined as CLDN18.2 membranous staining ≥2+ in ≥40% of tumor cells by immunohistochemistry in the central laboratory) (n=26). By the cut-off date, there were 33 patients in survival follow-up including 12 patients still with ongoing treatment. The median overall survival was 20.4 months (95% CI:15.0, NE) for all the 82 patients. Updated clinical data and details by biomarkers levels will be reported at the time of conference. **Conclusions:** The updated data indicate that the combination of TST001 plus nivolumab and CAPOX for the first-line treatment of patients with G/GEJ cancer is safe and well tolerated with encouraging durable PFS and survivals, especially for the patients with high/medium CLDN18.2 expression. Clinical trial information: NCT04495296. Research Sponsor: Suzhou Transcenta Therapeutics Co, Ltd.

4033 **Poster Session**

Real-world analyses to evaluate the role of TIGIT as a target in first-line (1L) gastric, gastroesophageal junction, and esophageal adenocarcinomas (GC/GEJC/EAC). First Author: Linda Su-Feher, Gilead Sciences, Inc, Foster City, CA

Background: Anti-programmed death protein 1 (PD-1) immune checkpoint inhibitors (ICIs) are approved for GC/GEJC/EAC.T-cell immunoreceptor with Ig and ITIM domains (TIGIT) is a potential anti-tumor ICI target.Understanding how PD-L1 (*CD274*), effector T-cell (Teff), and *TIGIT* RNA expression levels correlate with real-world outcomes of 1L treatment can inform the potential for TIGIT as a target. **Methods:** Deidentified real-world data for patients (pts) with metastatic GC/GEJC/EAC were included from the Tempus AI, Inc. clinicogenomic database. Data were analyzed for pts with available longitudinal clinical data and biopsies (whole transcriptome RNA-sequencing [seq], 648 gene panel DNA-seq, and PD-L1 immunohistochemistry). Gene expression comparisons, including between *TIGIT* and a Teff gene set (geometric mean of *CD8A*, *GZMA*, *GZMB*, *IFNG*, *EOMES*, and *PRF1*), used the Wilcoxon test, Kruskal-Wallis test, and Spearman correlation. Real-world time to next treatment or death (rwTTNTD; maximum follow-up 24 months) was assessed for 1L ICI + chemotherapy (chemo) or chemo using the Kaplan-Meier method and compared by expression level (high [≥ median] vs low [< median]) of *TIGIT*, Teff gene set, and *TIGIT* normalized by Teff gene set. **Results:** Among 545 pts (1L ICI + chemo, n = 50; 1L chemo, n = 124) *TIGIT* expression was most highly correlated with Teff ($R = 0.80$, $P < 0.001$) and *FOXP3* expression ($R = 0.78$, $P < 0.001$), followed by *CD274* expression ($R = 0.57$, $P < 0.001$). Positive correlations with PD-L1 combined positive score were observed for *TIGIT* and Teff expression ($P < 0.001$ for both) but not *TIGIT* normalized to Teff levels ($P > 0.05$). Biopsies from liver metastases, which tend to show a poor response to ICIs, had lower immune signatures vs stomach tumor biopsies ($P < 0.001$). High vs low expression of *TIGIT* and Teff were associated with numerically longer rwTTNTD for ICI + chemo, with HRs (95% CI) of 0.82 (0.43–1.54) for *TIGIT* (n = 29 vs 21) and 0.78 (0.42–1.48) for Teff (n = 28 vs 22). Corresponding HRs (95% CI) for chemo were 1.04 (0.70–1.54) for *TIGIT* (n = 53 vs 71) and 1.26 (0.85–1.87) for Teff (n = 64 vs 60). When *TIGIT* expression was normalized to Teff levels, HRs (95% CI) for rwTTNTD for high vs low expression were 0.92 (0.49–1.71) for ICI + chemo (n = 23 vs 27) and 0.81 (0.54–1.20) for chemo (n = 57 vs 67). **Conclusions:** *TIGIT* expression was highly correlated with *FOXP3* and Teff gene set expression in GC/GEJC/EAC tumors. The improved rwTTNTD seen in pts with high *TIGIT* expression may be driven by these patients also having high Teff expression. When *TIGIT* is normalized to Teff, pts with high *TIGIT* expression lose this added benefit. Combining anti-TIGIT and anti–PD-1 treatments may lead to enhanced T cell activation, which could bring benefit to pts with 1L GC/GEJC/EAC. Larger studies will help confirm these findings. Research Sponsor: Gilead Sciences, Inc.

4034 **Poster Session**

Distinct microenvironment phenotypes across tumor, vascular, and immune compartments from ramucirumab plus pembrolizumab in refractory gastric cancer: A phase II trial. First Author: Sung Hee Lim, Division of Hematology-Oncology, Department of Medicine, Sungkyunkwan University School of Medicine, Samsung Medical Center, Seoul, South Korea

Background: Combining immune checkpoint inhibitor (ICI) with vascular endothelial growth factor (VEGF)/VEGF receptor inhibition has yielded promising results in multiple tumor types. This phase II trial investigated the efficacy and molecular mechanisms of ramucirumab plus pembrolizumab in refractory gastric cancer patients. **Methods:** We conducted a prospective phase II single-arm trial of ramucirumab plus pembrolizumab as salvage treatment in patients with metastatic GC who failed to respond to standard fluoropyrimidine plus platinum with or without programmed cell death protein 1 (PD-1) inhibitors. Eligible patients had programmed death-ligand 1 (PD-L1) combined positive score more than five. The primary objective was to objective response rate (ORR) and secondary end points included disease control rate, duration of response, progression-free survival and overall survival, and toxicity. Comprehensive molecular profiling, including Digital Spatial Profiling, and mass cytometry was performed on tumor samples and peripheral blood. **Results:** Twenty-six patients were enrolled in this study between June 2021 and May 2023. No patient attained complete response (CR), while 6 patients achieved confirmed partial response (PR), resulting in a response rate (RR) of 23.1% (95% CI, 4.06–34.4). The median PFS for all patients was 2.7 months (95% CI, 1.84 - 3.56 months), and median OS was 10.9 months (95% CI, 2.31 – 18.29). Grade $\geq$ 3 treatment-related adverse events occurred in 38.5 % of patients. Digital Spatial Profiling revealed distinct tumor microenvironment (TME) phenotypes between responders and non-responders. Responders had high CTL infiltration and vascular normalization in their tumor specimen after treatment which led to favorable treatment outcome. In support of this, spatial profiling revealed the shortest median distance between immune cells and vessels, suggesting enhanced transendothelial migration of immune cells. Nonresponders had significantly upregulated TGF-β pathway and low tumor vascularity. On-treatment analysis demonstrated a shift towards increased immune cell infiltration and decreased tumor cellularity. Mass cytometry of peripheral blood revealed lower proportions of myeloid-derived suppressor cells in responders. **Conclusions:** Ramucirumab+pembrolizumab showed modest clinical efficacy, with manageable toxicity and durable responses. Although limited to a small subset of patients, a few patients who had previously responded to ICI benefited from ramucirumab+pembrolizumab. Clinical trial information: NCT0005753. Research Sponsor: None.

4035 **Poster Session**

GABRP as a biomarker for predicting anti-PD1 therapeutic efficacy in advanced gastric cancer (WJOG10417GTR study). First Author: Naoki Takahashi, Department of Gastroenterology, Saitama Cancer Center, Saitama, Japan

Background: GABRP, Gamma-aminobutyric acid type A receptor subunit π, is a key molecule that influences tumor properties and patient prognosis in various cancers, including gastric cancer (GC): GABRP is significantly upregulated in tumor tissues, and promotes tumor progression and metastasis via chemokine signaling and macrophage recruitment, leading to poor prognosis. Thus, GABRP seems to be a promising potential target for cancer treatment. However, it remains unclear whether the GABRP-targeting strategy can contribute to GC treatment, especially anti-PD1/PDL1 therapy, which has recently attracted great attention. **Methods:** We collected biopsy tumor tissues from 96 patients with advanced GC before and one month after nivolumab monotherapy in the WJOG10417GTR study according to the protocol (No. 2017-473) approved by the IRB, and analyzed for GABRP expression by RNA-sequencing (RNAseq) and immunohistochemical staining (IHC; only at pre-treatment). Progression-free survival (PFS) and overall survival (OS) were compared between high and low groups divided by the cutoff value determined by change point of the larger log hazard ratios (HRs) based on the method for modeling continuous-scale covariates. This study was supported by Ono Pharmaceutical and Bristol Myers Squibb. **Results:** RNAseq data revealed that high levels of GABRP gene expression in tumors at baseline were significantly associated with shorter PFS (median PFS [mPFS] 1.643 months [95% CI = 1.281 - 3.253] vs 3.170 months [1.971 - 10.251], HR = 2.798, P = 0.005) and shorter OS (median mOS [mOS] 5.092 months [3.450 - NA] vs 15.409 months [13.733 - NA], HR = 5.145, P $<$ 0.001), and the high post-treatment levels were significantly associated with shorter PFS (mPFS 1.873 months [1.511 - 3.253] vs 4.123 months [2.073 - NA], HR = 3.333, P = 0.009) and shorter OS (mOS 7.162 months [5.092 - 15.310] vs NA [13.733 - NA], HR = 4.524, P = 0.015), as compared to low levels. This was confirmed by IHC data that showed similar results, albeit only baseline data: patients with high baseline levels of GABRP protein expression in tumors had significantly shorter PFS (mPFS 1.528 months [0.986 - 1.971] vs 3.121 months [1.873 - 4.238], HR = 1.727, P = 0.016). **Conclusions:** These results suggest that GABRP expressed in tumors is a significant poor prognostic factor for nivolumab monotherapy in advanced GC. GABRP may be a promising biomarker for predicting anti-PD1/PDL1 therapeutic efficacy in advanced GC, and targeting it may contribute to improving the clinical outcomes in GC as a new therapeutic strategy. Research Sponsor: Ono Pharmaceutical and Bristol Myers Squibb.

4036 **Poster Session**

KEYNOTE-859: 4.5-year median follow-up of pembrolizumab plus chemotherapy for previously untreated advanced HER2-negative gastric or gastroesophageal junction (G/GEJ) adenocarcinoma. First Author: Sun Young Rha, Yonsei Cancer Center, Yonsei University College of Medicine, Yonsei University Health System, Seoul, South Korea

Background: In the phase 3KEYNOTE-859 study (NCT03675737), first-linepembrolizumab (pembro) + chemotherapy (chemo) continued to provide longer OS (HR, 0.79; 95% CI, 0.71-0.88) and PFS (HR, 0.76; 95% CI, 0.68-0.85), and a higher ORR (51.0% vs 42.0%) vs placebo + chemo in participants (pts) with HER2-negative G/GEJ adenocarcinoma, after a median follow-up of 41.6 mo (August 22, 2023). We present results after an additional 13 mo of follow-up. **Methods:** Eligible pts with untreated locally advanced or metastatic HER2-negative G/GEJ adenocarcinoma with PD-L1 status, measurable disease, and ECOG PS 0 or 1 were randomly assigned 1:1 to receive pembro 200 mg or placebo IV Q3W for $\leq$35 cycles + investigator's choice of chemo (5-FU + cisplatin [FP] vs capecitabine + oxaliplatin [CAPOX]). The primary end point was OS. Secondary end points included PFS, ORR, and DOR, all per RECIST v1.1 by BICR, and safety. The data cutoff was September 27, 2024. **Results:** Median follow-up was 54.8 mo (Q1-Q3, 46.8-62.1). In all randomly assigned pts in the intention-to-treat population (N = 1579), median OS was 12.9 mo (95% CI, 11.9-14.0) for pembro + chemo vs 11.5 mo (95% CI, 10.6-12.1) for placebo + chemo (HR, 0.78; 95% CI, 0.70-0.86). In pts with PD-L1 CPS $\geq$1, median OS was 13.0 mo (95% CI, 11.6-14.2) vs 11.4 mo (95% CI, 10.5-12.0; HR, 0.74 [95% CI, 0.66-0.84]). In pts with PD-L1 CPS $\geq$10, median OS was 15.8 mo (95% CI, 14.0-19.3) vs 11.8 mo (95% CI, 10.3-12.7; HR, 0.64 [95% CI, 0.53-0.77]). PFS, ORR, and DOR were also consistent between the intention-to-treat population and pts with PD-L1 CPS $\geq$1 and PD-L1 CPS $\geq$10 (Table). Treatment-related AEs were reported in 751 pts (95.7%; grade 3-5, 466 [59.4%]) for pembro + chemo and 736 (93.5%; grade 3-5, 404 [51.3%]) for placebo + chemo. **Conclusions:** Pembro + chemo continued to show improved OS, PFS, and ORR vs placebo + chemo after a median study follow-up of 54.8 mo, regardless of PD-L1 status. The findings further support pembro + chemo as a first-line treatment option for locally advanced or metastatic HER2-negative G/GEJ adenocarcinoma. Research Sponsor: None. Clinical trial information: NCT03675737. Research Sponsor: None.

	All pts N = 1579		PD-L1 CPS ≥1 n = 1235		PD-L1 CPS ≥10 n = 553	
	Pembro + chemo n = 790	Pbo + chemo n = 789	Pembro + chemo n = 618	Pbo + chemo n = 617	Pembro + chemo n = 280	Pbo + chemo n = 273
OS, median (95% CI), mo	12.9 (11.9-14.0)	11.5 (10.6-12.1)	13.0 (11.6-14.2)	11.4 (10.5-12.0)	15.8 (14.0-19.3)	11.8 (10.3-12.7)
HR (95% CI)	0.78 (0.70-0.86)		0.74 (0.66-0.84)		0.64 (0.53-0.77)	
PFS, median (95% CI), mo	6.9 (6.3-7.2)	5.6 (5.5-5.7)	6.9 (6.0-7.2)	5.6 (5.4-5.7)	7.8 (6.8-8.5)	5.6 (5.4-6.7)
HR (95% CI)	0.76 (0.68-0.85)		0.72 (0.64-0.82)		0.62 (0.51-0.76)	
ORR, % (95% CI)	51.1 (47.6-54.7)	42.0 (38.5-45.5)	51.9 (47.9-55.9)	42.6 (38.7-46.6)	60.4 (54.4-66.1)	43.2 (37.3-49.3)
DOR, median (range), mo	8.0 (1.2+ to 66.3+)	5.7 (1.3+ to 58.1+)	8.3 (1.2+ to 66.3+)	5.6 (1.3+ to 58.1+)	10.0 (1.2+ to 66.3+)	5.7 (1.4+ to 55.0+)

4037 **Poster Session**

Co-expressing pattern of multiple biomakers and dynamic change of Claudin18.2 expression after systemic chemotherapy in advanced gastric cancer. First Author: Sun Young Rha, Yonsei Cancer Center, Yonsei University College of Medicine, Seoul, South Korea

Background: Gastric cancer (GC) is a heterogeneous disease classified by Lauren classification and TCGA's four molecular subtypes. Targeting Claudin (CLDN)18.2 has emerged as a promising therapy. However, a comprehensive understanding of CLDN18.2 in advanced GC, its clinicopathologic correlations, and prognostic significance remains limited. We analyzed the co-expression of multiple biomarkers and dynamic changes in CLDN18.2 following systemic chemotherapy. **Methods:** This retrospective study included 402 patients with stage IV GC at Yonsei Cancer Center (2015–2023) treated with palliative doublet chemotherapy. Paired pre- and post-treatment tissues were available for 124 patients. CLDN18.2 expression was assessed using the VENTANA CLDN18 (43-14A) RxDx Assay, with positivity defined as $\geq$75% of tumor cells. HER2, EBV, dMMR, and PD-L1(22C3) were also evaluated by immunohistochemistry. Overall survival (OS) was estimated using the Kaplan-Meier method, and a log-rank test was performed to compare survival according to CLDN18.2 positivity. **Results:** The CLDN18.2 positivity rate was 30.6%, consistent with previous reports. It was slightly higher in HER2-negative (31.5%) than HER2-positive (27.3%) (p = 0.44). CLDN18.2 positivity was significantly higher in EBV-positive than negative (63.6% vs 29.4%, p $<$ 0.05) and in pMMR versus dMMR (31.7% vs 9.5%, p $<$ 0.05). Regarding PD-L1 status, the positivity rate was higher in the PD-L1 negative compared to the positive by CPS 1(36.1% vs 25.8%, p $<$ 0.05). We observed that CLDN18.2 expression seems to be decreasing with higher PD-L1 expression (28.5 % in patients with CPS $\geq$5, 24% in CPS $\geq$10). The OS (median months, 95% CI) based on CLDN 18.2 expression was similar [22.5 (18.6-25.2) vs 23.2 (17.9-27.4) in CLDN18.2 positive group], regardless of HER2 status. Among 124 patients with paired samples, pre-treatment CLDN18.2 positivity was 22.8%, increasing to 36.5% post-treatment. The increase was more pronounced in HER2 negative (39.0%) compared to positive (29.5%). Notably, 79.9% of patients showed consistent CLDN18.2 expression between pre- and post-treatment samples, while 20.1% demonstrated changes in expression. These changes were not associated with other markers such as HER2, EBV, dMMR, or PD-L1. **Conclusions:** Higher CLDN18.2 positivity rates in specific subgroups, such as pMMR and PD-L1 negative, suggest the potential role of anti-CLDN therapy in these subgroups. This study also highlights the dynamic changes of CLDN18.2 expression in advanced gastric cancer, with an increase observed after first-line systemic treatment in a subset of patients. Further studies should focus on prospective analyses and stratify changes in CLDN18.2 expression by treatment regimen to better understand its role as a therapeutic target and its implications for treatment resistance and disease progression. Research Sponsor: None.

4038 **Poster Session**

Camrelizumab plus albumin-bound paclitaxel and S-1 as first-line treatment of HER-2 negative unresectable locally advanced or advanced gastric and gastroesophageal junction adenocarcinoma: A phase II clinical trial. First Author: Xinfang Hou, The Affiliated Cancer Hospital of Zhengzhou University & Henan Cancer Hospital, Zhengzhou, Henan, China

Background: Gastric cancer is a common malignant tumor of the digestive tract. For nearly 90% of HER2 negative advanced gastric and gastroesophageal junction adenocarcinoma (G/GEJ) patients (pts), the current first-line treatment options and efficacy are limited, and new therapeutic drugs are urgently needed to improve the efficacy of advanced G/GEJ. **Methods:** This is a prospective, single center, single arm, open label phase II clinical trial involving HER-2 negative G/GEJ diagnosed by histopathology. Pts received 4-6 cycles of treatment with camrelizumab combined with albumin bound paclitaxel and S-1, followed by camrelizumab maintenance therapy until progression or 2 years. By following up with pts and evaluating clinical efficacy based on imaging examinations, the effectiveness and safety of the protocol can be assessed. **Results:** From December 2020 to December 2024, a total of 47 pts obtained informed consent based on exclusion criteria. As of the deadline (January 6, 2025), the average follow-up period was 17.4 months, with a median follow-up time of 16.7 months (range: 1.6-42.2 months). One patient had completed 2 years of treatment and ended maintenance therapy with camrelizumab, 5 pts (12.5%) were still receiving treatment, 34 pts (85.0%) stopped treatment, and 28 pts (70%) developed disease progression (PD). The best therapeutic effect was achieved in 2 cases with CR, 25 cases with PR, 11 cases with SD, and 2 cases with PD. The experiment reached the primary endpoint with an ORR of 67.5%. The secondary endpoint DCR was 95.0%, the median PFS was 7.8 months [95% confidence interval (CI): 6.2-9.4 months], and the median OS was 23.8 months [95% confidence interval (CI): 15.2-32.4 months]. For all study subjects, there was no correlation between OS, PFS, and baseline characteristics of the study (age, gender, ECOG, microsatellite status, mismatch repair protein status, EBER status, PDL1 level, number of metastatic sites, presence of liver metastasis, presence of lung metastasis, presence of abdominal metastasis, presence of bone metastasis). Among all enrolled pts, 36 experienced adverse events (76.6%) and 18 experienced grade 3-4 TRAE (38.3%), mainly bone marrow suppression and immune related rash. **Conclusions:** As the first-line treatment for HER-2 negative advanced gastric and gastroesophageal junction adenocarcinoma, the combination of Carilizumab with albumin bound paclitaxel and S-1 has shown encouraging efficacy. Clinical trial information: ChiCTR2300069672. Research Sponsor: None.

4039 **Poster Session**

Efficacy and safety of LM-302 (anti-claudin 18.2 ADC) in combination with anti-PD-1 therapy for advanced gastric, gastroesophageal junction cancer and esophageal adenocarcinoma: Early-phase study results. First Author: Haiping Jiang, The First Affiliated Hospital, Zhejiang University School of Medicine, Hangzhou, China

Background: Claudin 18.2 (CLDN18.2), a tight junction protein highly expressed in gastric and gastroesophageal junction (GEJ) cancers, has emerged as a promising therapeutic target. LM-302 (tecotabart vedotin), a novel and potent MMAE-based ADC targeting CLDN18.2, has shown promising efficacy and safety as monotherapy in heavily pretreated advanced gastric cancer. This pooled analysis evaluates the efficacy and safety of LM-302 in combination with the anti-PD-1 antibody toripalimab as a first-line treatment option for patients with gastric, GEJ, or esophageal adenocarcinoma (EAC). **Methods:** Eligible patients with histologically confirmed, previously untreated, unresectable, HER2-negative gastric, GEJ, or EAC were included. Patients received LM-302 (1.6 mg/kg Q3W, 2.0 mg/kg Q3W or 1.8 mg/kg Q2W) and toripalimab (240 mg Q3W or 3 mg/kg Q2W). Endpoints included safety, objective response rate (ORR), disease control rate (DCR), progression-free survival (PFS), OS, and biomarker analysis. Data cutoff: January 7, 2025. **Results:** A total of 43 gastric, GEJ, or EAC patients (median age: 62.3 years; 65.1% male) from Australia and China were treated. No dose-limiting toxicities (DLT) were observed across all these dose levels. Treatment-related adverse events (TRAEs) related to LM-302 were reported in 39 patients (90.7%), with common events ($\geq$20%) including anemia, decreased white blood cell count, decreased neutrophil count, increased aspartate transaminase (AST), vomiting, loss of appetite, and nausea. Grade $\geq$3 TRAEs related to LM-302 occurred in 16 patients (37.2%), the most common events ($\geq$5%) were decreased neutrophil count (14.0%), increased alanine transaminase (11.6%), increased AST (9.3%), and anemia (7.0%). Among 41 efficacy-evaluable patients (median follow-up: 6.01 months), ORR was 65.9% (95% CI: 49.4-79.9%), and DCR was 85.4% (95% CI: 70.8- 94.4%). In 32 GC patients with CLDN18.2 expression in $\geq$25% of tumor cells (IHC 2+/3+), ORR was 71.9% (95% CI: 53.3-86.3%) and DCR was 96.9% (95% CI: 83.8-99.9%). Among these patients, ORR was 63.3% (95% CI: 35.1-87.2%) for patients with PD-L1 CPS $<$ 1 and 77.8% (95% CI: 52.4-93.6%) for patients with PD-L1 CPS $\geq$1. Median PFS and OS were not reached; one patient with PD-L1 CPS $<$ 1 achieved PR and remained on treatment for 14.70 months. **Conclusions:** LM-302 combined with toripalimab demonstrated encouraging anti-tumor activity and manageable safety as first-line treatment for patients with CLDN18.2-positive gastric, GEJ, and EAC, including those with low-to-moderate CLDN18.2 expression. These findings support further large-scale clinical trials to confirm efficacy, safety and clinical utility. Clinical trial information: NCT05188664; NCT05934331. Research Sponsor: LaNova Medicines Limited.

4040 **Poster Session**

Efficacy and safety results of a multi-center phase II study of utidelone injection in combination with PD-1 inhibitor and chemotherapy for the first-line treatment of advanced gastric and esophagus cancers. First Author: Meili Sun, Department of Oncology, Shandong University First Medical University Affiliated Central Hospital, Jinan, Shandong, China

Background: Utidelone is a novel microtubule inhibitor that offers several advantages including improved efficacy and safety, broader anti-cancer spectrum, blood-brain barrier penetrance, and response against multidrug-resistant tumors. Utidelone injection (UTD1) has been approved for advanced breast cancer in China. Previous studies have shown that utidelone monotherapy is effective for advanced gastric and gastroesophageal junction adenocarcinoma (GC) and esophageal squamous cell carcinoma (ESCC). This phase II study further explored the efficacy and safety of utidelone in combination with PD-1 inhibitor and chemotherapy for the 1st line treatment of advanced GC and ESCC. **Methods:** Eligible patients were recruited into the two cohorts of metastatic and/or unresectable HER2 negative GC or ESCC, receiving utidelone (30mg/m^2/day iv on days 1–5 every 21-day) plus sintilimab (200 mg iv Q3W) and oxaliplatin (130 mg/m^2/day Q3W for up to 6 cycles), or utidelone (30mg/m^2/day iv on days 1–5 every 21-day) plus tislelizumab (200 mg iv Q3W) and capecitabine (2000mg/m^2/day po on days 1–14 every 21-day), respectively, until disease progression or unacceptable toxicity. The primary endpoint is ORR and second endpoints are CBR, PFS and safety. **Results:** The enrolment has been completed for both cohorts from April 2023 to October 2024. There were 27 eligible patients enrolled in the GC cohort with median age of 60 years (range 34-70), 6 females and 21 males. 23 patients were evaluable for efficacy with an outcome of 11 confirmed PRs and 12 SDs including 4 unconfirmed PR, and 5 patients were still receiving treatment (1-23 cycles). The confirmed ORR was 47.8% and CBR was 100%. The mPFS was $>$ 5.3 months. The most common $\geq$Grade 3 TEAEs included diarrhea (25.93%), neutropenia (14.81%), vomiting (14.81%), peripheral sensory neuropathy (11.11%), anemia (11.11%) and leukopenia (11.11%). Other AEs were all Grade 1 or 2, with no treatment-related deaths. There were 20 eligible patients enrolled in the ESCC cohort with median age of 61.5 years (range 47-70), 5 females and 15 males. 18 patients were evaluable for efficacy with an outcome of 6 confirmed PRs and 12 SDs, and 6 patients were still receiving treatments (1-12 cycles). The confirmed ORR was 33.3% and CBR was 100%. TEAEs $\geq$Grade 3 occurred in 8 patients including hypokalemia, lymphopenia/leukopenia, peripheral sensory neuropathy, hiccup, rash, pain, hypotension and anemia with one occurrence for each (5.5%). Other AEs were all Grade 1 or 2, with no treatment-related deaths. **Conclusions:** Utidelone plus PD-1 inhibitor and chemotherapy demonstrated promising efficacy and acceptable safety as first-line treatment for advanced GC and ESCC. There are 11 patients still on the study receiving continuous treatment. The final data will be provided at the time of presentation. Clinical trial information: NCT04911907. Research Sponsor: Beijing Biostar Pharmaceuticals Co., Ltd.

4042 **Poster Session**

Fruquintinib in combination with camrelizumab and paclitaxel liposome and nedaplatin as first-line treatment for advanced esophageal squamous cell carcinoma (ESCC): A single-arm, phase II study. First Author: Yanhong Gu, The First Affiliated Hospital of Nanjing Medical University, Nanjing, China

Background: Previous studies have indicated a synergistic effect of fruquintinib in combination with chemotherapy or immunotherapy. Therefore, we conducted a phase II study to evaluate the efficacy and safety of fruquintinib plus camrelizumab, paclitaxel liposome, and nedaplatin as a first-line treatment for advanced esophageal squamous cell carcinoma (ESCC). **Methods:** This study consisted of a dose-finding and a dose-expansion phase. A total of 33 to 36 eligible patients with untreated advanced ESCC were planned for enrollment. In the dose-finding phase, based on a standard 3+3 design, patients were treated with fruquintinib (3 mg, 4 mg, 5 mg, days 1-14, every 3 weeks, respectively, the initial fruquintinib dose was 4mg), in combination with a fixed dose of camrelizumab 200 mg, paclitaxel liposome 135 mg/m^2, and nedaplatin 70 mg/m^2 on day 1, every 3 weeks. In the dose-expansion phase, patients received camrelizumab, paclitaxel liposome, nedaplatin and recommended phase 2 dose (RP2D) of fruquintinib. A maximum of six cycles was administered, followed by maintenance therapy with fruquintinib in combination with camrelizumab. The primary endpoint was objective response rate (ORR). Secondary endpoints included disease control rate (DCR), progression-free survival (PFS), and safety. **Results:** As of December 28, 2024, 22 patients (20 males) were enrolled with a median age of 65 years (range 50-76). Among the 21 patients with metastases, 19.0% (4/21) had a single metastatic site and 81.0% (17/21) had multiple metastatic sites. In the dose-finding phase, no DLTs occurred in 3 patients at 4 mg and 6 patients at 5 mg, establishing fruquintinib's RP2D as 5 mg. Of the 19 patients evaluable for efficacy, 13 achieved a partial response, and 6 had stable disease. The confirmed ORR was 68.4% (95% CI: 47.5%-89.3%) for all evaluable patients and 68.8% (95%CI: 41.3%-89.0%) for patients receiving 5 mg dose of fruquintinib. The confirmed DCR was 100.0% (95%CI: 82.4%-100.0%). At a median follow-up of 5.1 (95% CI: 4.2-7.2) months, the median PFS was 8.7 (95%CI: 5.2-not available [NA]) months, the 6-month PFS rate reached 81.7%. The most common treatment-related adverse events (TRAEs) were anemia 72.7% (16/22), neutropenia 40.9% (9/22), leukopenia, hypertension 31.8% (7/22). Grade$\geq$3 TRAEs were identified in seven patients, including neutropenia 13.6% (3/22), leukopenia 13.6% (3/22), oral mucositis 9.1% (2/22), nausea 4.5% (1/22), vomiting 4.5% (1/22), headache 4.5% (1/22), and anemia 4.5% (1/22). No treatment-related serious adverse events (TRSAEs) or deaths occurred. **Conclusions:** The combination of fruquintinib, camrelizumab, paclitaxel liposome, and nedaplatin demonstrated significant efficacy and manageable toxicity profile as a first-line treatment for advanced ESCC, suggesting a potential new treatment strategy. Clinical trial information: NCT06010212. Research Sponsor: None.

4043 Poster Session

Immune checkpoint inhibition in EBV-associated gastric cancer: A multicenter international retrospective analysis. First Author: Darren Cowzer, Memorial Sloan Kettering Cancer Center, New York, NY

Background: Epstein-Barr virus associated gastric cancer (EBVaGC) is found in ~9% of GC and is associated with a unique immunophenotype. Prior studies suggest 15-100% objective response rates (ORR) to immune checkpoint inhibition (ICI), but survival outcomes are limited by small cohort size. This study sought to clarify outcomes of ICI in EBVaGC across 9 global tertiary cancer centers, evaluate if next-generation sequencing (NGS) can replace EBER ISH as the gold standard for detection, and identify molecular features of ICI-responsive EBVaGC. **Methods:** Retrospective data were collected on patients (pts) with metastatic EBVaGC and stratified into patients receiving ICI alone or with chemotherapy, and by 1L vs. 2L+. Progression-free survival (PFS) and overall survival (OS) were analysed using the Kaplan-Meier method and were calculated from the start of treatment to the date of progression or death for PFS, and last follow up or death for OS. Cox regression model stratified by regions was used to examine factors associated with PFS. EBV viral reads were detected by NGS using independent cohorts by MSK-IMPACT and Caris Life Sciences and concordance with EBER ISH was evaluated in each cohort. Additional phenotypic classification was performed using clinicogenomic data from the Caris Precision Oncology Alliance. **Results:** A total of 91 pts who received ICI in the metastatic setting were included. Median age was 62 years (range 30-86) and 91% were male with pts from US (n = 15), Europe (n = 5), and Asia (n = 71). ECOG PS at the time of ICI was $\leq$1 in 97%. PD-L1 CPS score was $\geq$5 in 69%. Pts who received first-line chemotherapy + ICI (n = 42) achieved a 49% investigator-assessed ORR (CR/PR), median PFS (mPFS) 8.3 months (mo), and median OS (mOS) 38 mo compared with mOS 18 mo in pts receiving first-line chemotherapy alone (n = 35). Pts who received ICI-alone achieved a similar 49% ORR with 1L and later line mPFS 6 mo and 3.2 mo, respectively, which increase to 10.0 mo and 6.6 mo, when limiting to PD-L1 CPS $>$5. Univariate analysis for PFS among all pts demonstrated improved outcomes in those where PD-L1 CPS score was $\geq$5 (HR = 0.57, 95%CI:0.34,0.97). EBV detection by MSK-IMPACT and Caris achieved over 98% positive agreement and 99.9% negative agreement. Additional EBVaGC transcriptomic immune phenotyping data will be presented. **Conclusions:** This global EBVaGC experience demonstrated that EBVaGC can reliably be identified from NGS, negating the need for costly EBER ISH. Furthermore, pts with EBVaGC achieve a high ORR on ICI with or without concurrent chemotherapy. While 1L PFS was similar to non-EBVaGC, prolonged mOS was achieved, potentially reflecting frequent conversion surgeries and regional differences. Even among EBVaGC, immune heterogeneity exists, and PD-L1 CPS $>$5 identified pts who derived ICI benefit. Further research is needed to examine the patterns of disease progression in EBVaGC treated with ICI. Research Sponsor: None.

4044 Poster Session

Second-line ASKB589 plus chemotherapy for advanced gastric or gastroesophageal cancers: Results from cohort 5 of a phase I/II study. First Author: Miao Zhang, Department of Gastrointestinal Oncology, Beijing Cancer Hospital, Beijing, China

Background: ASKB589 is a humanized monoclonal antibody with enhanced affinity for CLDN18.2 and increased ADCC activity. It has shown favorable safety profiles and promising antitumor effects in phase I/II clinical study (NCT04632108) involving first-line patient(pt)s with advanced gastric or gastroesophageal (G/GEJ) cancers. Here, we present the findings from cohort 5 that ASKB589 in combination with chemotherapy as second-line treatment for patients with advanced G/GEJ cancers. **Methods:** Cohort 5 from NCT04632108 is designed to evaluate the safety and preliminary efficacy of ASKB589 (at 2 doses: 6mg/kg or 10mg/kg Q3W) plus chemotherapy as second line treatment in pts with G/GEJ cancers. Eligible pts who had confirmed progressive disease during treatment with first line standard of therapy were enrolled. CLDN18.2 statuses were analyzed retrospectively using IHC DS-3 LDT assay. Primary endpoint was safety. Secondary endpoints included objective response rate (ORR), disease control rate (DCR), duration of response (DoR), progression free survival (PFS) assessed by investigator per RECIST v1.1 and overall Survival (OS). **Results:** As of December 20, 2024, 47 pts were enrolled in the 2L cohort and received 6mg/kg ASKB589 plus chemotherapy. Among them, 44 pts were treated with 6mg/kg ASKB589 plus paclitaxel, while 2 pts received 6mg/kg ASKB589 plus docetaxel, and 1 pt received 6mg/kg ASKB589 plus irinotecan. 17 (27%) pts had received immunotherapy previously.The confirmed ORR was 34.2% in 38 measurable and evaluable CLDN18.2 moderate to high GC/GEJ pts (CLDN18.2 moderate to high was defined as $\geq$40% of tumor cells with $\geq$2+ intensity by immunohistochemistry). 14 pts (36.8%) had stable disease, and the DCR was 71.1%. For the ASKB589 plus paclitaxel subgroup (n = 35, with evaluable response), the confirmed ORR was 31.1%, DCR was 71.4%. In the intention-to-treat analysis, the median PFS with 6mg/kg ASKB589 plus chemotherapy was 5.26 months (95%CI: 2.66, 7.06), and the median OS was 11.14 months (95%CI: 8.80, 18.20). In the ASKB589 plus paclitaxel subgroup, the median PFS was 4.63 months (95%CI: 2.04, 7.06) and median OS of 13.73 months (95%CI: 8.80, 18.20) respectively. Treatment related adverse events (TRAEs) occurred in all pts including 26 (55.3%) pts with grade $\geq$3 TRAEs. The most common grade $\geq$3 TRAEs ($\geq$5%) were neutrophil count decreased (42.6%), white blood cell count decreased (17%), lymphocyte count decreased (8.5%), and hypoalbuminemia (8.5%). **Conclusions:** The results of cohort 5 from NCT04632108 have shown that ASKB589 plus chemotherapy, as 2L treatment in pts with advanced GC/GEJ cancers have promising antitumor activity and response durability, especially in the ASKB589 plus paclitaxel subgroups. Both treatment regimens are well tolerated. Further development of ASKB589 combination therapy for CLDN18.2-positive GC/GEJ pts 2nd line treatment is planned. Clinical trial information: NCT04632108. Research Sponsor: None.

4045 Poster Session

Efficacy of venadaparib plus irinotecan in homologous recombination deficiency (HRD) gene mutations as 3+ line treatment in patients with metastatic gastric cancer (mGC). First Author: Won Sik Lee, Idience Co., Ltd., Seoul, South Korea

Background: Tumors with homologous recombination deficiency (HRD) have been suggested to be associated with a favorable response to poly (adenosine diphosphate [ADP]–ribose) polymerase (PARP) inhibitors. The aim of this analysis was to evaluate the association between the presence of HRD gene mutations and the efficacy of venadaparib, a novel PARP inhibitor, plus irinotecan in patients with metastatic gastric cancer (mGC) who had progressed after at least at least 2 lines of therapy. **Methods:** This was an exploratory analysis from a multi-national, phase 1b/IIa trial of venadaparib plus irinotecan in patients with mGC (NCT04725994). Tumor response was evaluated according to RECIST v. 1.1. Genomic analysis was conducted using ctDNA (GuardantOMNI Gene Panel version 1.0, Redwood City, CA) on Day 1 pre-dose. Results of the exploratory genomic analysis, which includes pathogenic or deleterious mutations of following genes: *BRCA1/2, ATM, ATR, CHEK2, BARD1* were analyzed for association with efficacy outcomes. **Results:** As of Dec 2024, 43 patients enrolled and objective response (ORR), median progression-free survival (mPFS) and median overall survival (mOS) were 20.9%, 4.2 (2.9-9.6) and 8.1 (6.8-11.5) months. 14 (32.6%) out of the 43 patients had at least one HRD mutation (6 with *ATM*, 3 with *BRCA1*, 2 with *BRCA2*, 1 with *BARD1*, 1 with *CHEK2* and 1 with *ATR* mutations, respectively). For the 14 patients with HRD mutation and 29 patients with no HRD mutation, the ORR, mPFS (95% CI) and mOS (95% CI) were 35.7% vs. 13.8%, 5.6 (1.3-9.1) vs. 4.0 (2.7-5.4) months and 10.1 (6.8-12.0) vs. 8.0 (5.9-11.5) months respectively. For 11 patients with *ATM* or *BRCA1/2* mutation, mPFS (95% CI) and mOS (95% CI) were 8.4 (1.2-24.0) and 10.1 (6.8-34.4) months. At the maximum tolerable dose (MTD) level of venadaparib 20 mg/d on days 1 to 7 and irinotecan 100 mg/m^2 at day 1 of a 2-week cycle, six of 15 patients had HRD mutation, and mPFS (95% CI) and mOS (95% CI) were 4.1 (2.9-5.4) and 7.9 (5.9-11.5) months; these data are still maturing. **Conclusions:** Venadaparib in combination with irinotecan demonstrated promising efficacy in patients with mGC, particularly those with HRD gene mutations. Further development of this combination may warrant a biomarker-based approach. Clinical trial information: NCT04725994. Research Sponsor: Idience Co., Ltd.

Efficacy results in patients with homologous recombination deficiency mutation.

Patient #	Mutations in HRD-related Genes	Number of Prior Palliative Treatment	Best Overall Response (%)	Treatment Duration (months)	Overall Survival (months)
82001-2103	*BRCA2*	3	SD	25.1	33.9
82004-2101	*ATM*	2	PR	38.3	37.3
82002-2103	*ATR*	3	PD	1.4	8.0
82004-2103	*ATM*	3	PD	1.3	6.7
82004-2102	*BARD1*	2	CR	5.6	11.6
82005-2101	*ATM*	2	SD	3.1	11.8
82005-2103	*ATM*	2	PR	4.9	8.3
82003-2203	*BRCA2*	2	SD	9.4	11.5
82005-2202	*BRCA1*	2	SD	6.2	7.0
82003-2201	*CHEK2*	3	PR	3.1	3.1
82002-2203	*ATM*	2	SD	1.0	1.0
82004-2201	*ATM*	2	SD	0.5	0.5
82003-2205	*BRCA1*	2	SD	2.8	2.8
82001-2201	*BRCA1*	2	SD	5.3	7.8

4046 Poster Session

Updated results of fruquintinib combined with PD-1 inhibitors and chemotherapy in the first-line treatment of HER2-negative advanced gastric or gastroesophageal junction adenocarcinoma (FDZL-FIX): A single-arm, open-label phase 2 study. First Author: Chenchen Wang, Department of Medical Oncology, Fudan University Shanghai Cancer Center, Shanghai, China

Background: For unresectable locally advanced or metastatic HER2-negative gastric cancer (GC), the combination of chemotherapy with immunotherapy, specifically PD-1 inhibitors, has emerged as a new standard of care in first-line treatment of advanced GC, but the patients' outcomes remain poor. Fruquintinib (Fru) is a highly selective inhibitor of VEGFR1/2/3. We sought to explore the efficacy and safety of fruquintinib combined with PD-1 inhibitors and chemotherapy in the first-line treatment of HER2-negative advanced gastric or gastroesophageal junction adenocarcinoma. Here, we report the updated results. **Methods:** Eligible pts with HER2 negative locally advanced unresectable or metastatic gastric or gastrooesophageal junction adenocarcinoma, without any systemic anticancer treatment for advanced disease were included in the study. pts received 6 cycles of combined first line treatment with Fru (4mg p.o. qd, d1-14, q3w,) combined with PD-1 inhibitor (investigator's choice of sintilimab 200mg or nivolumab 360mg intravenously q3w) and chemotherapy (investigator's choice of XELOX or SOX) regimen. The following maintenance treatment was Fru combined with PD-1 inhibitor and S-1/capecitabine until disease progression or intolerable toxicity. The primary endpoint was progression-free survival (PFS). Secondary endpoints included objective response rate (ORR), overall survival (OS), disease control rate (DCR) and safety. **Results:** As of Jan 24, 2025, a total of 33 pts (22 male, 11 female) median age 62 (range: 35-77) were enrolled and received at least one dose of treatment. 30 patients had at least one tumor assessment post treatment, with an ORR of 80.0% (24/30; 95%CI 61.4-92.3) and DCR of 100%(30/30; 95%CI 88.4-100.0). In the intention to treatment (ITT) population, the median PFS was 9.43 months (95% CI 5.29-13.24) and the 9-month PFS rates was 57% (95%CI 40.0-83.0). The most common AEs of all grades were neutrophil count decreased (33.3%), palmar-plantar erythrodysesthesia syndrome (33.3%), and fatigue (30.3%). **Conclusions:** The combination of fruquintinib and chemotherapy with PD-1 blockade in the first-line treatment for unresectable locally advanced or metastatic HER2-negative GC had shown promising efficacy and acceptable safety profile. The results warrant further investigations in a large cohort. Clinical trial information: NCT06158919. Research Sponsor: None.

4047 **Poster Session**

Artificial intelligence-based prediction of claudin 18.2 expression and immune phenotype to guide treatment decisions in patients with gastric cancer. First Author: Hyung-Don Kim, Asan Medical Center, Seoul, South Korea

Background: With the increasing availability of immune checkpoint inhibitor (ICI)- and targeted agent-based treatments for gastric cancer, evaluating predictive biomarkers to guide first-line treatment has become increasingly complex. Claudin 18.2 (CLDN18.2) is a clinically relevant target for zolbetuximab-based chemotherapy, typically assessed by immunohistochemistry. However, limitations such as inadequate tumor specimens, high costs, and long turnaround times pose a practical challenge. **Methods:** An artificial intelligence (AI) model was developed to predict CLDN18.2 expression based on hematoxylin and eosin (H&E) slides from 459 patients with gastric cancer (derivation cohort). CLDN18.2 positivity was defined as moderate-to-strong expression in ≥75% of tumor cells. The AI model utilized a Vision Transformer-based architecture with a multiple-instance learning framework and was trained using five-fold cross-validation. Model performance was validated in two independent cohorts: an internal cohort of 381 patients treated with first-line ICI plus chemotherapy (ICI-Chemo) or chemotherapy alone (Chemo-only) and an external cohort of 100 patients from diverse ethnic backgrounds. Immune phenotypes (IPs) were assessed using an AI-powered whole slide image analyzer to further stratify patient outcomes. **Results:** The prevalence of CLDN18.2 positivity was 43.4% (derivation), 37.3% (internal validation), and 26.0% (external validation). The model achieved an AUROC of 0.753 in the derivation cohort, with sensitivity and specificity of 0.638 and 0.723, respectively. In the internal and external validation cohorts, AUROCs were 0.752 and 0.746, with similar sensitivity and specificity levels. Among the internal validation cohort, patients were stratified into subgroups based on predicted CLDN18.2 positivity and IP status. Among these, the subgroup predicted to be CLDN18.2-negative and inflamed IP demonstrated the most significant benefit from ICI-Chemo compared to the Chemo-only group. **Conclusions:** The AI model reliably predicted CLDN18.2 expression from H&E slides and exhibited reliable performance. The differential survival outcomes observed in subgroups stratified by AI-predicted CLDN18.2 expression and IP suggest its potential utility in guiding first-line treatment decisions for gastric cancer patients. Research Sponsor: Lunit.

Hazard ratio (HR) for progression-free survival (PFS) and overall survival (OS).

Groups	HR for PFS (95% CI)	HR for OS (95% CI)
CLND18.2-negative and inflamed IP	0.37 (0.17–0.78, p=0.009)	0.41 (0.19–0.88, p=0.021)
CLDN18.2-negative and non-inflamed IP	0.75 (0.54–1.05, p=0.095)	0.81 (0.59–1.13, p=0.224)
CLDN18.2-positive and inflamed IP	0.67 (0.40–1.12, p=0.128)	0.62 (0.37–1.04, p=0.073)
CLDN18.2-positive and non-inflamed IP	1.60 (0.74–3.46, p=0.229)	1.23 (0.59–2.58, p=0.579)

reference: Chemo-only.

4048 **Poster Session**

Predictive value of homologous recombination-related gene mutations in survival outcomes of first-line nivolumab plus chemotherapy for gastric cancer. First Author: Yuna Lee, Department of Oncology, Asan Medical Center, University of Ulsan College of Medicine, Seoul, South Korea

Background: Homologous recombination repair (HRR) gene mutations are associated with genomic instability; however, their clinical value in the context of immune checkpoint inhibitor (ICI)-based treatments in gastric cancer remains unclear. We investigated the efficacy of nivolumab plus chemotherapy according to the HRR mutation status in advanced gastric cancer patients. **Methods:** This single-center study included gastric cancer patients with available panel sequencing results who were treated with first-line nivolumab plus chemotherapy (n = 115) or chemotherapy alone (n = 172) between July 2021 and March 2024. Mutation status of 17 HRR genes (*BARD1, BLM, BRCA1, BRCA2, BRIP1, MRE11A, NBN, PALB2, PARP1, POLD1, RAD50, RAD51, RAD51C, RAD51D, RAD52, RAD54L,* and *XRCC2*) was assessed using targeted next-generation sequencing. Treatment outcomes were compared according to the presence of HRR mutations. **Results:** Among patients treated with nivolumab plus chemotherapy, 36.5% harbored HRR mutations. Compared to the no HRR mutation group, the HRR mutation group exhibited a higher objective response rate (92% vs. 63.2%, P = 0.010), longer progression-free survival (PFS) (median 12.8 vs. 6.5 months; hazard ratio [HR] 0.57, 95% confidence interval [CI] 0.36–0.91, P = 0.019) and overall survival (OS) (median not reached vs. 14.2 months; HR 0.40, 95% CI 0.23–0.71, P = 0.002). Among patients with HRR mutation, those treated with nivolumab plus chemotherapy showed favorable survival outcomes compared to those treated with chemotherapy alone (PFS: HR 0.44, 95% CI 0.27–0.71, P < 0.001; OS: HR 0.45, 95% CI 0.25–0.80, P = 0.007), but this was not the case for patients without HRR mutation (PFS: HR 0.79, 95% CI 0.56–1.10, P = 0.156; OS: HR 0.90, 95% CI 0.63–1.28, P = 0.554). **Conclusions:** The presence of HRR mutations was associated with favorable survival outcomes in patients treated with nivolumab plus chemotherapy. Our findings suggest that HRR mutations may serve as a potential predictive biomarker for first-line ICI-based chemotherapy in gastric cancer. Research Sponsor: None.

4049 **Poster Session**

Clinical outcomes of first-line immune checkpoint inhibitors with chemotherapy in advanced EBV-associated gastric cancer. First Author: Dongwoo Cho, Division of Medical Oncology, Department of Internal Medicine, Seoul St. Mary's Hospital, College of Medicine, The Catholic University of Korea, Seoul, South Korea

Background: EBV-associated gastric cancer (EBVaGC) is a distinct subgroup of GC with high PD-L1/PD-L2 expression and immune cell infiltration. While several rationales support the potential efficacy of immune checkpoint inhibitors (ICIs) in EBVaGC, clinical evidence from large-scale trials is limited, and their effectiveness remains inconclusive. This retrospective study evaluated the clinical outcomes of palliative first-line chemotherapy with or without the addition of ICIs in patients with EBVaGC. **Methods:** We identified 217 patients diagnosed with EBVaGC via in situ hybridization and evaluated their baseline characteristics, including HER2 expression, MSI status, and PD-L1 expression. Among these, 83 patients with metastatic disease received palliative first-line treatment. Of the 77 HER2-negative patients, 23 were treated with ICIs (nivolumab or pembrolizumab) combined with cytotoxic chemotherapy (ICI+chemo), while 54 received chemotherapy alone. Survival outcomes and response rates were compared between ICI+chemo and chemotherapy-alone groups. **Results:** Among 217 EBVaGC patients, 8.5% were HER2-positive, 2.6% were MSI-High, and PD-L1 CPS ≥10 and ≥5 was observed in 59.1% and 84.1%, respectively. In HER2-negative EBVaGC patients, ICI+chemo showed significantly prolonged progression free survival (PFS) compared to chemotherapy alone (median: 9.28 vs. 6.07 months; HR = 0.48; p = 0.031). There was no significant difference in overall survival (OS) (median: 20.72 vs. 18.89 months; HR = 0.78; p = 0.508). The objective response rate (ORR) and disease control rate (DCR) were significantly higher in the ICI+chemo group than in the chemotherapy-alone group (ORR, 78.3% vs. 51.9%; OR = 3.29; p = 0.042; DCR, 100% vs. 79.6%; p = 0.028). In the ICI+chemo group, PD-L1 expression (cutoff: CPS 5 or 10) was not significantly associated with survival outcomes or response rates. For CPS ≥5, the median PFS was 7.84 months compared to 8.99 months in the CPS < 5 group (p = 0.944), the median OS was 20.75 vs. 16.51 months (p = 0.131), and the ORR was 76.5% vs. 75.0%. For CPS ≥10, the median PFS was 13.9 months compared to 8.69 months in CPS < 10 group (p = 0.580), the median OS was 24.95 months vs. 20.33 months (p = 0.061), and the ORR was 81.8% vs. 70.0%. **Conclusions:** To our knowledge, this study represents one of the largest cohorts including patients with EBVaGC who received first-line ICI+chemo. The addition of ICIs to chemotherapy showed clinical benefit, including survival and response rates, compared to chemotherapy alone in EBVaGC. Interestingly, the clinical benefit of ICI+chemo was observed in PD-L1 low group as well as PD-L1 high group. Our results highlight the clinical potential of ICI addition to chemotherapy in EBVaGC, and PD-L1 expression alone is insufficient as a predictive biomarker, warranting further exploration of alternative predictors for immunotherapy efficacy in this subgroup. Research Sponsor: None.

4050 **Poster Session**

Phase II trial of transarterial chemoembolization followed by sintilimab (anti-PD-1), oxaliplatin, and S-1 combined with either trastuzumab (HER-2 positive) or apatinib (HER-2 negative) as first-line therapy for gastric cancer with liver metastases. First Author: Wei Song, Department of Minimally Invasive Treatment of Cancer, Shandong Provincial Hospital Affiliated to Shandong First Medical University, Jinan, China

Background: Liver metastases contribute to immunotherapeutic resistance and unfavorable outcomes. Transarterial chemoembolization (TACE) may alter the immune microenvironment and enhance immunotherapy efficacy. In this trial, we assessed the efficacy and safety of TACE followed by sintilimab (anti-PD-1), oxaliplatin and S-1 combined with either trastuzumab (HER-2 positive) or apatinib (HER-2 negative) in the treatment of gastric cancer with liver metastases (GCLM). Additionally, we explored gene mutations and the immune microenvironment between gastric cancer and its paired liver metastases. **Methods:** This single-center, single-arm, phase II trial enrolled 31 treatment-naive patients with GCLM. Patients received TACE for liver metastases, followed by sintilimab (200mg), oxaliplatin (130mg/m^2) and S-1 (40-60 mg bid for 14 days) every 3weeks combined with either trastuzumab (HER-2 positive, 8 mg/kg then 6 mg/kg, q3w) or apatinib (HER-2 negative, 250mg qd) until disease progression or intolerable toxicities. Tissue samples from gastric cancer and liver metastases were collected before treatment for DNA and RNA detection. The primary endpoints were PFS and ORR. The secondary endpoints were DCR, OS, and safety. **Results:** A total of 31 patients were enrolled, median 63 (41-76) years old, 27 male, 26 multiple liver metastases and all adenocarcinoma. Of them, 10 (32.3%) were HER2 IHC 3+, 7 (22.6%) HER2 IHC 2+/FISH+. Patients with PD-L1 CPS≥5, < 1 accounted for 19.4%, 51.6% respectively. With the median follow-up time of 396 days, the patients received a median of 6 treatment cycles. As of January 25, 2025, 27 patients were included in the efficacy and safety analyses. The ORR was 74.1%, with 5 CR, 15 PR, 3 SD, and 4 PD. DCR was 85.2%. The median PFS was 12 months, and the median OS was not reached. One- and two-year PFS rates were 51.6 and 27.1 %, respectively. One- and two-year OS rates were 89.1 and 74.0 %, respectively. Grade 3/4 treatment-related adverse events occurred in 18.5% of the patients, notably neutropenia, neurotoxicity and thyroid and liver dysfunctions. Forty-four unique mutated genes were identified in gastric cancer, which were involved in PI3K-Akt and drug resistance pathways. In its paired liver metastases, 59 specific mutated genes associated with *MMR* and cell cycle were identified. Liver metastases had more macrophages and CD8+ T cells, whereas NK and CD4+ memory resting cells were fewer than those in paired gastric cancer. **Conclusions:** TACE followed by sintilimab, oxaliplatin and S-1 combined with either trastuzumab or apatinib demonstrated promising efficacy and manageable safety as first-line therapy for GCLM. Gastric cancer and its paired liver metastases exhibited distinct gene mutations and immune microenvironment. Clinical trial information: ChiCTR2200057726. Research Sponsor: None.

4051 **Poster Session**

Improving evidence-based treatment selection and patient-centered care in upper GI cancers: A Project ECHO initiative. First Author: Elena Elimova, Princess Margaret Cancer Centre, Toronto, ON, Canada

Background: Accurate assessment of biomarkers (including HER2 and PD-L1) is integral to treatment selection in upper gastrointestinal (GI) cancers. However, challenges in integrating biomarker testing and targeted therapies are commonly reported in community settings. The Project Extension for Community Healthcare Outcomes (Project ECHO) model addresses this gap by connecting experts in tertiary care settings with rural healthcare teams. Through case-based teaching, the model builds the knowledge and skills needed to provide evidence-based, equitable care regardless of geographic location. **Methods:** In October 2024, 57 healthcare professionals (HCPs) from 2 US and 4 Canadian community oncology clinics participated in Project ECHO sessions. Led by an expert oncologist, each session featured interactive discussions of real-world anonymized case presentations to address key practice gaps in integrating biomarker-based therapies and coordinating multidisciplinary care for patients (pts) with upper GI cancers. Following each session, HCPs developed and implemented site-specific action plans to address gaps in care. Pre-activity and post-activity surveys measured the impact on knowledge, confidence, and competence and 90-day follow-up surveys will be collected to assess ongoing performance. **Results:** The top HCP-reported barriers to individualized care for pts with upper GI cancer included *keeping up with the latest efficacy and safety data* (44%), *selecting and sequencing treatments based on individual and disease factors* (40%), and *limited availability/cost of biomarker* testing (39%). Additionally, relatively few HCPs reported providing supportive care services for the majority of their patients, such as *palliative care referrals* (40%), *distress screening* (26%), *psychosocial support* (35%), and *end of life counseling* (19%). Following the Project ECHO sessions, HCPs demonstrated improved knowledge, competence, and confidence in biomarker testing and managing adverse events. Additionally, HCPs planned to *increase patient education about disease and treatment-related side effects* (65%), *improve team education on biomarker testing and treatment selection* (61%), *establish standardized biomarker testing protocols (35%),* and *increase supportive care referrals (22%).* Team action plans included implementing routine testing protocols, establishing a network of specialists to coordinate care, and increasing education on the use of immunotherapy. **Conclusions:** Project ECHO-based education improved HCP capacity to integrate biomarker-directed therapies and coordinate multidisciplinary care for patients with upper GI cancers. Full findings will detail long-term impacts on practice and inform future community-based ECHO initiatives. Research Sponsor: Bristol Myers Squibb.

4052 **Poster Session**

Comparison of postoperative adjuvant therapy and surgery alone in pathological N1-2 esophageal squamous cell carcinoma: A prospective multicenter randomized controlled trial. First Author: Yizhou Huang, Fujian Medical University Union Hospital, Fuzhou, Fujian, China

Background: Due to the lack of prospective randomized controlled clinical studies, current guidelines do not recommend postoperative adjuvant therapy, but rather observational follow-up regardless of any stage. The aim of this study was to evaluate the effect of postoperative adjuvant chemoradiotherapy and adjuvant chemotherapy on pathologic lymph node-positive (pN1-2) esophageal squamous cell carcinoma (ESCC). **Methods:** Patients with pathologically confirmed pN1-2 ESCC were randomly assigned to three groups: surgery alone (SA), postoperative chemotherapy (POCT), or postoperative chemoradiotherapy (POCRT). The POCT regimen included 2 to 4 cycles of docetaxel and cisplatin (75 mg/m²), while the POCRT regimen comprised 28 fractions of 5040Gy radiotherapy combined with docetaxel and cisplatin. Overall survival (OS) was the primary endpoint. Recruitment was terminated early due to the significant benefit observed in the adjuvant therapy group and difficulties in enrollment. **Results:** A total of 145 patients were enrolled (SA: n = 50, POCT: n = 48, POCRT: n = 47), with a median follow-up of 55 months. The overall survival rates at 3 and 5 years were 76.1% and 56.2% in the POCRT group, compared with 56.6% and 43.4% in the POCT group and 49.1% and 25.0% in the SA group, respectively. The POCRT group showed significantly improved OS and DFS compared to the SA group (OS, P = 0.003; DFS, P = 0.003). The incidence of grade 3 or higher adverse events was 39.6% in the POCT group and 44.7% in the POCRT group (P = 0.615). **Conclusions:** For patients with pN1-2 ESCC, postoperative therapy, especially postoperative chemoradiotherapy, significantly improved the prognosis of patients compared with surgery alone. Clinical trial information: NCT04009265. Research Sponsor: Fujian Minimally Invasive Medical Center (Thoracic Surgery), China; Key Laboratory of Cardio-Thoracic Surgery(Fujian Medical University), Fujian Province University; Fujian Institute of Cardio-thoracic Surgery, China.

4053 **Poster Session**

Combined PD-L1 expression and PD-1+ CD8 T cells to predict immunotherapy outcomes in esophageal squamous cell carcinoma. First Author: Qian Zhao, Department of Radiation Oncology, Shandong Cancer Hospital and Institute, Shandong First Medical University and Shandong Academy of Medical Sciences, Jinan, China

Background: Esophageal squamous cell carcinoma (ESCC), the predominant subtype of esophageal cancer in Asia, remains a challenging disease with poor prognosis due to frequent late-stage diagnoses. Immune checkpoint inhibitors (ICIs), particularly those targeting the PD-1/PD-L1 axis, have revolutionized cancer treatment but benefit only a subset of patients. The identification of robust predictive biomarkers is critical to enhance patient selection and optimize immunotherapy outcomes. In this study, we leveraged multiplex immunofluorescence to comprehensively evaluate the roles of PD-L1 and PD-1 expression, immune cell subsets, and clinical factors in predicting immunotherapy efficacy in ESCC. **Methods:** We analyzed baseline tumor samples from 147 ESCC patients treated with first-line ICIs using multiplex immunofluorescence to assess the expression of PD-1, PD-L1, CD4, CD8, CD20, and CD68. Patients were stratified by biomarker expression levels, with cut-off values determined through ROC curve analysis to calculate AUC. Survival outcomes were analyzed, and multivariate Cox regression identified independent predictors of progression-free survival (PFS) and overall survival (OS). **Results:** PD-L1 expression (HR 0.266, 95%CI 0.087-0.816, p = 0.021) and PD-1+CD8+ T cells (HR 2.694, 95%CI 1.162-6.246, p = 0.021) emerged as independent predictors of PFS. High PD-L1 expression was associated with superior outcomes (mPFS: 7.6 vs. 5.5 months), while elevated PD-1+CD8+ T cell infiltration correlated with poorer outcomes (mPFS: 6.0 vs. 7.2 months). Patients with a combination of high PD-L1 expression and low PD-1+CD8+ T cells demonstrated the best prognosis, with a median PFS of 8.5 months, whereas those with low PD-L1 expression and high PD-1+CD8+ T cells had the worst prognosis, with a mPFS of 3.5 months. Clinical stage (HR 1.570, 95%CI 1.059-2.327, p = 0.025), BMI (HR 0.935, 95%CI 0.883-0.990, p = 0.015), and CD8+ T cell density (HR 0.896, 95%CI 0.824-0.975, p = 0.011) were identified as independent predictors of OS. **Conclusions:** Our findings uncover the dual importance of PD-L1 expression and PD-1+CD8+ T cell infiltration as critical biomarkers for predicting PFS in ESCC patients undergoing ICIs. Moreover, clinical factors such as BMI, tumor stage, and intratumoral CD8+ T cell density significantly impact OS. Research Sponsor: None.

4054 **Poster Session**

Temporal and spatial expression of CLDN18.2 in gastric cancer and gastroesophageal junction cancer. First Author: Qiaoqi Li, West China Hospital, Chengdu, Sichuan, China

Background: Recent studies have demonstrated the promising efficacy of CLDN18.2-targeted therapy in patients with gastric cancer (GC) or gastroesophageal junction cancer (GEJC) who are positive for CLDN18.2. This study aims to investigate the temporal and spatial consistency of CLDN18.2 expression in GC and to provide a comprehensive overview of its expression patterns. **Methods:** The expression of CLDN18.2 in primary GC tumors (biopsy/surgical) and corresponding peritoneal metastases (PM) was evaluated by quantifying cell membrane staining intensity with a validated semi-quantitative assay. CLDN18.2 positivity was defined when tumor cells with staining intensity (2+) and (3+) summed up to $\geq$ 75% of all. The Kappa test evaluated CLDN18.2 expression consistency across sample types, and the McNemar test compared its positive rates in paired samples. **Results:** Between February 2023 and April 2024, 536 patients were enrolled at the Gastric Cancer Center of West China Hospital, Sichuan University. The cohort comprised 399 in-situ biopsy samples, 240 radical gastrectomy samples, and 27 peritoneal biopsy samples. Among them, 109 patients had biopsy and surgical specimens, and 26 underwent preoperative neoadjuvant therapy. Among 399 biopsy specimens, 131 (32.8%) had positive CLDN18.2. In 240 surgical specimens, 167 (27.9%) were positive. In 27 peritoneal nodule specimens, 10 (37.0%) were positive. No significant differences were found (χ^2 = 2.128, *P* = 0.345). Among 109 patients with paired biopsy and postoperative pathology, CLDN18.2 expression concordance was 80.7% (88/109, Kappa = 0.562). In 27 peritoneal metastasis patients, it was 77.8% (21/27, Kappa = 0.503). For 26 chemo-resected patients, the pre- and post-chemo positive concordance was 80.8% (21/26, Kappa = 0.524). All showed moderate consistency. CLDN18.2 expression significantly correlated with several factors, including gender (*P* = 0.002), histological subtype (*P* = 0.003), tumor location (*P* = 0.007), histological classification (*P* = 0.035), and EBV status (*P* = 0.006). Higher rates were in females, signet-ring cell carcinoma, non-GEJ tumors, poorly differentiated tumors, and EBV-positive patients. **Conclusions:** CLDN18.2 is widely present in both primary gastric cancer and peritoneal metastatic lesions. Expression consistency exists moderately between biopsy and surgical specimens, and primary and metastatic tissues. Consistency stays strong pre- and post-neoadjuvant therapy. Its expression links to clinical and molecular traits. This study comprehensively analyzed it, providing a better basis for CLDN18.2-targeted patient selection. Research Sponsor: None.

4055 Poster Session

Safety and efficacy of endoscopic treatment with mucosal resection, radiofrequency ablation, and cryotherapy in the curative treatment of early esophageal squamous cell cancer and dysplasia. First Author: Sidra Naz, The University of Texas MD Anderson Cancer Center, Houston, TX

Background: Endoscopic esophageal treatment (EET), by radiofrequency ablation (RFA), cryoablation (Cryo), and endoscopic mucosal resection (EMR) has not been extensively studied in early esophageal squamous cell carcinoma (SCC). Aim: To assess the safety and success of EET in curative treatment of early esophageal SCC: (T1a, T1b, T2) and squamous cell dysplasia (SCD) **Methods:** We retrospectively reviewed records of patients with SCC (T1a, T1b, T2) and SCD treated with EET from January 2010 to August 2024. All patients had at least one follow-up endoscopic biopsy after treatment. **Results:** 62 patients met the eligibility criteria. Table. 46 patients (74%) had T1a (n=36.5%) or T1b (n=10.1%) SCC. T2 patients (21%) received ETT for local recurrence after chemoradiation. The most frequent ETT was EMR + RFA, n= 26 (41.9%) and RFA, n=20 (32%). In the first biopsy after treatment, 46 of the 62 patients (74.1%) had no residual cancer. This number increased after further ETT. 2 years after treatment only 4 patients had persistent cancer. BMI is significantly associated with survival status. No patient had disease progression that required surgery. Strictures formed in 15 patients (24%) post- ETT. **Conclusions:** ETT provides curative treatment of early SSC in up to 94% of patients. Research Sponsor: None.

Association between cancer persistence at first post-biopsy with various demographic and clinical variables.

Patient Characteristics		Total N=62	P-value
Sex (%)			
	Male	28 (45.16%)	0.49
	Female	34 (54.84%)	
Race (%)			
	White / Caucasian	52 (83.87%)	0.716
	Hispanic	2 (3.23%)	
	Black	2 (3.23%)	
	Asian	4 (6.45%)	
BMI, median (range)	N = 62	24.02 (15, 44.5)	0.045
Smoking Status (%)			
	No	25 (40.32%)	0.182
	Yes	37 (59.68%)	
Alcohol Drinking (%)			
	No	22 (35.48%)	>0.99
	Yes	40 (64.52%)	
Squamous Dysplasia (%)			
	none	59 (95.16%)	>0.99
	Low	1 (1.61%)	
	High	2 (3.23%)	
Squamous tumor staging (%)			
	none	3 (4.84%)	0.174
	T1a	36 (58.06%)	
	T1b	10 (16.13%)	
	≥T2	13 (20.97%)	
Squamous Tumor Differentiation (%)			
	Well	5 (8.2%)	0.707
	Moderate	47 (77.05%)	
	Poor	9 (14.75%)	
Lymphovascular Invasion (%)			
	No	57 (91.94%)	>0.99
	Yes	5 (8.06%)	

1b) Patient survival status - Immediate Post-Treatment Pathology Finding

Patient Characteristics	Total N=62
First biopsy post-treatment finding (%)	
No dysplasia or cancer	37 (59.68%)
Persistent cancer (Failure of t/t)	16 (25.81%)
Persistent Dysplasia	9 (14.52%)

1c) Patient survival status ≥2 years post-treatment, excluding patients with no data or recurrent cancer/dysplasia

Patient Characteristics	Total N=21
Biopsy finding (%)	
No dysplasia or cancer	15 (71.43%)
Persistent cancer (Failure of t/t)	4 (19.05%)
Persistent Dysplasia	2 (9.52%)

4057 Poster Session

Safety and efficacy of camrelizumab combined with radiotherapy as neoadjuvant therapy for locally advanced esophageal squamous cell carcinoma: A prospective single-arm phase II clinical trial. First Author: Yizhou Huang, Fujian Medical University Union Hospital, Fuzhou, Fujian, China

Background: Neoadjuvant chemoradiotherapy followed by esophagectomy is the standard of care for locally advanced esophageal squamous cell carcinoma (ESCC). However, approximately 30% of patients still develop distant metastases and have a high incidence of treatment-related adverse events. Immunotherapy, as a new modality for anti-cancer treatment, has shown promising clinical benefits for patients with ESCC. The synergistic effects of immunotherapy and radiotherapy make their combination promising as neoadjuvant treatment for locally advanced ESCC. **Methods:** All participants who meet the inclusion criteria will be enrolled after signing the informed consent form. Patients with thoracic segment esophageal cancer with clinical stage T2-3 N0 M0 or T2-3 N+ M0 will be included. They will be treated with radical surgery within 4–8 weeks after the completion of two cycles of neoadjuvant radiotherapy in combination with camrelizumab according to the study schedule. The primary endpoint is the major pathological remission rate of all per-protocol patients. The secondary endpoints are the R0 resection rate, pathological complete remission rate, and adverse events. The interim analysis will be conducted after half of the planned number of patients have been enrolled. The trials will be terminated when more than two treatment-related deaths occur or fewer than five patients have major pathological remission. **Results:** A total of 25 patients were enrolled, 3 patients did not undergo surgery, of which 1 had imaging CR after neoadjuvant therapy and refused surgical treatment; 1 progressed during neoadjuvant therapy, and the other had immune pneumonitis and renal insufficiency during neoadjuvant therapy. The final results of the study noted that of the 22 patients who underwent surgery. Twelve of 22 (54.5%) patients had a pathologic response, all consisting of an MPR with ≤10% RVT, including 8 of 22 (36.4%) pathologic complete responses. **Conclusions:** The NRIT regimen is safe and feasible for patients with ESCC. Clinical trial information: NCT05176002. Research Sponsor: Key Laboratory of Cardio-Thoracic Surgery (Fujian Medical University), Fujian Province University; Fujian Minimally Invasive Medical Center (Thoracic Surgery), China; Fujian Institute of Cardiothoracic Surgery, China.

4058 Poster Session

A real-world, propensity-matched analysis of second-line (2L) FOLFIRI-Ram versus Ram-Pac in advanced upper gastrointestinal cancers. First Author: Jonathan Hyak, UT Southwestern Medical Center, Dallas, TX

Background: Given historically poor outcomes for advanced upper gastrointestinal (UGI) cancers, there is an urgent need for effective 2L treatments. Since the phase III RAINBOW trial, combination ramucirumab and paclitaxel (Ram-Pac) has filled this role; however, this regimen is plagued by dose-limiting toxicities, specifically neuropathy. The phase II RAMIRIS trial demonstrated the efficacy and tolerability of FOLFIRI-Ram as an alternative 2L, even if it did not improve survival over Ram-Pac. Real-world data to support its use, however, are lacking. **Methods:** The nationwide Flatiron Health electronic health record-derived de-identified database, which includes treatment data from around 280 cancer clinics across the United States, was queried for patients treated for unresectable or metastatic UGI cancers with 2L Ram-Pac or FOLFIRI-Ram from January 2011-June 2024. Demographics and lab values at time of treatment were extracted. Study cohorts were derived using a greedy match based on a logit model to predict propensity scores from key clinical and laboratory characteristics; patients were matched 1:6 (FOLFIRI-Ram:Ram-Pac) given expected imbalances in sample size. The endpoints of interest were overall survival (OS) and real-world time to treatment discontinuation (rwTTD), determined via Kaplan-Meier method, log-rank test, and Cox proportional hazards model. A hybrid approach was used to construct a multivariate Cox model. **Results:** Of 15,908 UGI cancer patients identified, 631 received 2L Ram-Pac and 40 received 2L FOLFIRI-Ram. After matching, 40 FOLFIRI-Ram and 240 Ram-Pac patients were included. Median OS from initiation of 2L therapy was 9.7 months with FOLFIRI-Ram (95% CI 6.9-12.3) and 7.7 months with Ram-Pac (95% CI 6.2-8.8), with a hazard ratio (HR) for death of 0.74 with FOLFIRI-Ram versus Ram-Pac (95% CI 0.50-1.11, p = 0.14). Similar results were seen in the multivariate model (HR 0.72, 95% CI 0.49-1.08, p = 0.114) after adjustment for albumin, neutrophil:lymphocyte ratio, and alkaline phosphatase. The median rwTTD with FOLFIRI-Ram was 5.2 months (95% CI 4.1-6.2), compared to 3.7 months with Ram-Pac (95% CI 3.2-4.3). The HR for treatment discontinuation was 0.70 with FOLFIRI-Ram versus Ram-Pac (95% CI 0.48-1.00, p = 0.048). The reduced hazard for treatment discontinuation with FOLFIRI-Ram persisted in the multivariate model (HR 0.67, 95% CI 0.46-0.97, p = 0.033) after adjustment for ECOG status, history of prior surgery, PDL1, albumin, and neutrophil:lymphocyte ratio. **Conclusions:** In a real-world propensity-score matched analysis, no survival difference was noted with the combination of FOLFIRI-Ram compared to Ram-Pac, however FOLFIRI-Ram was associated with a significantly longer rwTTD. Altogether, these data suggest FOLFIRI-Ram is a viable and tolerable alternative for 2L treatment of UGI cancers. Research Sponsor: None.

4059 Poster Session

Disitamab vedotin (RC48), tislelizumab, and S-1 as first-line therapy for HER2-overexpressing advanced gastric or gastroesophageal junction adenocarcinoma (GC/GEJC): Updated results from the RCTS trial. First Author: Lian Liu, Qilu Hospital of Shandong University, Jinan, China

Background: Anti-PD1 antibody has significantly improved survival in patients with HER2-overexpressing and PD-L1 combined positive score (CPS) ≥1 GC/GEJC when added to trastuzumab and chemotherapy. Recent trials revealed that HER2-targeted antibody-drug conjugates, including RC48 and Trastuzumab Deruxtecan, combined with anti-PD1 antibody, have also shown promising efficacy in this population. This study reports updated survival results of RC48 combined with tislelizumab and the oral fluoropyrimidine S-1 as first-line therapy for patients with HER2-overexpressing GC/GEJC. **Methods:** This single-arm, multicenter clinical trial enrolled patients with unresectable or metastatic HER2-overexpressing (IHC 3+ or 2+, regardless of FISH status) first-line GC/GEJC. Patients received RC48 (2.5 mg/kg), tislelizumab (200 mg), and S-1 (40-60 mg BID for 14 days) every 3 weeks until disease progression (PD) or intolerable toxicity. The primary endpoint was objective response rate (ORR). Secondary endpoints were progression-free survival (PFS), overall survival (OS) and safety. **Results:** 57 patients from 9 centers were enrolled, 71.9% HER2 IHC 3+, 17.5% IHC 2+/FISH+, and 10.5% IHC 2+/FISH-. 14.9% and 36.2% had CPS≥5 and ≥1, respectively. Median follow-up was 11.8 months. In the intent-to-treat population, the confirmed ORR (cORR) was 89.4% (51/57, 95% CI: 78.5-96.0%), the median PFS (mPFS) was 12.7 months (95% CI: 10.9-NA), and the 18-month OS rate (18m-OSr) was 72.7% (95% CI: 60.0-88.5%). In the per-protocol set (excluding patients with no PD at the first assessment but refused a second evaluation), the cORR was 92.7% (51/55, 95% CI: 82.4-98.0%), the mPFS was 13.2 months (95% CI: 10.9-NA), and the 18m-OSr was 76.3% (95% CI: 63.0-91.7%). In the HER2-positive and -negative subgroups, the ORRs were 92.1% (95% CI: 81.1-97.8%) and 66.7% (95% CI: 22.3-95.7%), the mPFS was 12.6 months (95% CI: 11.0-NA) and 7.7 months (95% CI: 7.1-NA), and the 18m-OSr was 74.7% (95% CI: 61.3-91.1%) and 62.5% (95% CI: 32.0-100%), respectively. In the CPS ≥1 and CPS < 1 subgroups, ORRs were 92.3% (95% CI: 74.9-99.1%) and 87.1% (95% CI: 70.2-96.4%), the mPFS was 16.8 months (95% CI: 11.3-NA) and 11.4 months (95% CI: 8.5-NA), and the 18m-OSr was 80.4% (95% CI: 62.1-100%) and 67.4% (95% CI: 50.7-89.5%), respectively. The grade 3-4 treatment-related adverse events (AEs) was 63.2%. The most common AEs were neutropenia, fatigue, and leukopenia. An exploratory study with longitudinal sequencing of circulating tumor DNA is ongoing. **Conclusions:** The combination of RC48, tislelizumab and S-1 as a first-line therapy shows encouraging response rates and survival benefits in HER2-overexpressing GC/GEJC, especially in HER2-positive or CPS ≥1 patients, supporting further evaluation in randomized controlled trials. Clinical trial information: NCT05586061. Research Sponsor: None.

4060 **Poster Session**

Health-related quality of life (HRQoL) with paclitaxel plus ramucirumab (PTX-RAM) switch maintenance versus continuation of first-line fluoropyrimidine and oxaliplatin (FOX) chemotherapy (ChT) in patients (pts) with advanced HER2-negative gastric or gastroesophageal junction (G/GEJ) cancer: A secondary endpoint of the ARMANI phase 3 randomized trial. First Author: Eleonora Cristarella, Fondazione IRCCS Istituto Nazionale dei Tumori di Milano, Milan, Italy

Background: PTX-RAM switch maintenance significantly improved PFS (HR 0.61, 95%CI 0.48–0.79; p = 0.0002) and OS (HR 0.75, 95%CI 0.58–0.96; p = 0.025) versus continuation of FOX first-line ChT in the ARMANI trial, with a higher incidence of grade ≥3 treatment-related adverse events and an increased number of hospital visits. Here we present HRQoL results. **Methods:** ARMANI was an Italian multicenter, open-label, randomized, phase 3 trial enrolling pts with HER2-negative G/GEJ cancer who had disease control after a 3-month FOX induction ChT, and randomized to switch maintenance with PTX-RAM or the continuation of FOX. European Organisation for Research and Treatment of Cancer (EORTC) QLQC30, QLQOG25 and EuroQol EQ5D were assessed at randomization and every 8 weeks until progression. HRQoL changes over time were described by: (i) mean changes from baseline at each time point, (ii) distribution of improved/stable/worse at 8 weeks and (iii) time to QoL deterioration (TTD), defined as the time from randomization to a worsening ≥ 10 points of global QoL in EORTC QLQC30. Mean changes were compared by a linear regression model, with baseline values as covariates. Proportion of improved/stable/worse was compared by Chi square test. Kaplan-Meier and Cox proportional hazards model were used for TTD estimation. **Results:** Of the 280 pts randomized, 198 (71%; 109/144 with PTX-RAM and 89/136 with FOX) and 133 (48%; 81/144 and 52/136) completed baseline and 8-weeks assessment of EORTC and EQ5D, respectively. Mean baseline scores of global HRQoL were 66.90 (standard deviation [SD] 20.71) with PTX-RAM and 70.97 (SD 19.39) with FOX. Global QoL at 8-weeks assessment was better with PTX-RAM versus FOX both in terms of mean changes from baseline (+2.17 vs -8.51, delta 10.68, p = 0.015) and in terms of proportion of improved/stable/worse (improved 24.7% vs 4.2%, stable 56.2% vs 64.6%, worse 19.2% vs 31.3%, p = 0.009). TTD was significantly longer for PTX-RAM versus FOX (median TTD 7.6 vs 3.8 months, HR 0.52, 95%CI 0.33-0.82; p = 0.005). Mean changes from baseline after 8 weeks for functional scales and symptoms of QLQC30 and QLQOG25 showed significant improvement for PTX-RAM vs FOX for role functioning (p = 0.006), nausea/vomiting (p = 0.002), pain (p = 0.016), appetite loss (p = 0.03) and dysphagia (p = 0.028); hair loss was worse with PTX-RAM (p = 0.024). VAS score from EQ5D was not significantly different between the two treatments for all the assessments. **Conclusions:** In pts with HER2-negative advanced G/GEJ cancer, PTX-RAM switch maintenance, beyond a significant benefit in PFS and OS, showed significant benefit in terms of HRQoL, reducing symptoms and delaying global QoL deterioration. Clinical trial information: NCT02934464. Research Sponsor: None.

4061 **Poster Session**

Feasibility of circulating tumor DNA-based minimal residual disease (ctDNA-MRD)-guided adjuvant chemotherapy in patients with stage II-III gastric cancer (GC): An adaptive trial (MRD-GATE). First Author: Lian Liu, Department of Medical Oncology, Qilu Hospital of Shandong University, Jinan, China

Background: Although adjuvant chemotherapy (ACT) is the standard treatment for stage II-III GC, this strategy lacks precision treatment options, and many patients cannot tolerate the adverse events (AEs) of ACT. ctDNA-MRD detection has been shown to predict recurrence risk. The aim of this study (NCT06157216) was to evaluate the feasibility of MRD-guided treatment in these patients. **Methods:** Patients with stage II-III GC who underwent R0 resection and D2 gastrectomy were enrolled. Tumor-informed ctDNA-MRD testing was performed at baseline (28 days after surgery) and subsequently at 3, 6, 9, 12, 18, 24, 30, and 36 months after surgery. ACT was tailored according to MRD status: baseline MRD-negative (MRD (-)) patients received de-escalated therapy (observation for stage II and S-1 monotherapy for stage III) and switched to combined ACT (SOX, S-1 plus oxaliplatin, or XELOX, capecitabine plus oxaliplatin) if MRD became positive, while baseline MRD-positive (MRD (+)) patients underwent combined ACT. The primary endpoint was 3-year disease-free survival rate (yDFSr). Secondary endpoints included the treatment de-escalation rate, DFS by MRD status, cumulative recurrence risk (CRR), 3-year overall survival rate (yOSr) and safety. **Results:** 65 patients were enrolled, with a median age of 60 years (range: 34-83), and 83.1% (54/65) were male, 31 patients had stage II and 34 patients had stage III GC. At baseline, 21.5% patients (14/65) were MRD(+) and received combination ACT. Among the 51 baseline MRD(-) patients, 45 received de-escalated therapy at onset (9 received combination ACT after MRD conversion) and 6 received combination ACT. The median follow-up time was 13.3 (range: 9.3-15.7) months. In the intention-to-treat population, the overall 1-yDFSr was 86.2% (90% CI: 79.4-93.5%), the 1-yOSr was 96.9% (90% CI: 93.5-100%) and the CRR was 13.8% (95% CI: 6.5-24.7%). The treatment de-escalation rate was 69.2% (45/65, 95% CI: 56.6-80.1%). Grade 3-4 AEs occurred in 24.6% (95% CI: 14.8%-36.9%) of patients. Baseline MRD (+) patients had a shorter DFS compared to MRD (-) ones (1-yDFSr: 57.1% vs. 94.1%, HR = 9.66, 95% CI: 2.40-38.81, log-rank P < 0.0001). Patients with sustained MRD (-) had the best DFS (1-yDFSr: 100%), while those with sustained MRD (+) had the shortest DFS. Patients with MRD conversion from positive to negative or from negative to positive had intermediate DFS (1-yDFSrs: 72.7% and 70.0%, respectively). In 9 patients with recurrence, ctDNA-MRD positivity identified recurrence a median of 3.4 months earlier than radiology. **Conclusions:** MRD-guided ACT for stage II-III GC significantly reduced the ACT rate, and increased the de-escalated CT rate, resulting in good disease-free survival and fewer side effects. The results of this MRD-guided precision of ACT deserve to be confirmed by large randomized clinical trials. Clinical trial information: NCT05585580. Research Sponsor: None.

4062 **Poster Session**

Development and validation of the gastric risk immuno-progression score (GRIPS) in advanced gastric and gastroesophageal junction adenocarcinoma treated with first-line chemotherapy plus nivolumab: Results from the ORACLE study. First Author: Dario Spanu, Medical Oncology Unit, University Hospital and University of Cagliari, Cagliari, Italy

Background: The addition of nivolumab to chemotherapy is approved for advanced gastric and gastroesophageal junction (GEJ) adenocarcinoma with PD-L1 CPS ≥5. Identifying predictive tools for disease progression in this setting remains a clinical need. This study introduces the Gastric Risk Immuno-Progression Score (GRIPS), a novel score derived from variables associated with progression-free survival (PFS) in a real-world cohort. **Methods:** We conducted a multicenter retrospective study on 90 patients with gastric/GEJ adenocarcinoma treated with first-line chemotherapy plus nivolumab between 2022 and 2024. The GRIPScore was constructed using five dichotomous variables associated with unfavorable PFS in univariate analysis: Neutrophil-to-Lymphocyte Ratio (NLR > 2.68), ECOG Performance Status (≥2), Smoking status (never smoker), CA19.9 at diagnosis (UNL) and primary tumor resection (no resection). Each variable was scored as 1 (prognostically negative) or 0 (prognostically positive), and a total score (0–5) was calculated. Patients were categorized into low-risk (GRIPS 0–2) and high-risk (GRIPS 3–5) groups. PFS and OS were analyzed using Kaplan-Meier methods. Hazard Ratios (HRs) were calculated, and the discriminatory ability of the GRIPS was evaluated using Harrell's C-index. **Results:** The median PFS for the entire cohort was 11.55 months (95% CI: 7.60–13.26). Stratifying patients by GRIPS revealed a marked difference in outcomes between the low-risk and high-risk groups. Low-risk patients (GRIPS 0–2) had a median PFS of 13.16 months (95% CI: 9.01–18.91), while high-risk patients (GRIPS 3–5) had 4.11 months (95% CI: 2.37–11.77). This difference was significant (log-rank test, p = 0.0023; HR: 3.55, 95% CI: 1.58–8.02). Similarly, low-risk patients had a median OS of 21.25 months (95% CI: 13.77–21.25) compared to 11.90 months (95% CI: 4.03–16.10) for high-risk patients (log-rank test, p = 0.0313; HR: 2.73, 95% CI: 1.09–6.81). Harrell's C-index for PFS was 0.648 (95% CI: 0.552–0.743), indicating moderate discriminatory ability. **Conclusions:** The GRIPS effectively stratifies patients with advanced gastric and gastroesophageal junction adenocarcinoma treated with a combination of chemotherapy + nivolumab into distinct risk groups for PFS and OS. High-risk patients experience significantly shorter survival, highlighting the potential clinical utility of GRIPS for personalized treatment strategies. Further prospective validation is warranted to refine its application in clinical practice. Research Sponsor: None.

GRIPScore	N° of patients (%)	mOS (m)	mPFS (m)
Low-risk (0-2)	51 (45.9)	21.25 (95% CI: 13.77–21.25)	13.16 (95% CI: 9.01–18.91)
High-risk (3-5)	21 (18.9)	11.90 (95% CI: 4.03–16.10)	4.11 (95% CI: 2.37–11.77)
Not evaluable	18 (16.2)		

4063 **Poster Session**

Multicenter phase I/II study of abemaciclib and ramucirumab in metastatic gastroesophageal adenocarcinoma (GEA): CDK4/6 and cyclin D1 alterations as a predictor of response and survival. First Author: Ronan Joseph Kelly, Baylor University Medical Center, Dallas, TX

Background: CDK4/6 and Cyclin D1 are highly expressed in GEA cancers, suggesting that CDK4/6 inhibition may be a promising strategy. *In vitro and in vivo* studies have shown that abemaciclib (A) demonstrates potent antitumor efficacy in GEA by directly inhibiting this pathway. Currently, ramucirumab (RAM) ± paclitaxel is an approved 2nd line treatment for metastatic GEA cancers. **Methods:** This multicenter, open-label, phase I/II study investigated the safety and efficacy of A combined with RAM in pretreated advanced GEA (2nd or 3rd line). The primary objective was to describe the safety profile of A (150mg po bid) and RAM (8mg/kg iv every 2 weeks) using CTCAE version 4.03. Secondary objectives included assessing the objective response rate (ORR), disease control rate (DCR), median progression-free survival (mPFS), and median overall survival (mOS). Correlative studies to evaluate alterations in CDK4/6 and Cyclin D1 as determined by next generation sequencing as predictive biomarkers of efficacy were performed. **Results:** From July 2021 to December 2024, 20/30 patients were enrolled. The study was terminated prematurely due to slow accrual. The median age was 61.5 years (Range: 30.0, 80.0) and most patients were male (18/20). Seven patients (35%) were HER-2 positive, 11/18 patients (61.1%) were PDL1 CPS > 1 and 15 patients (75%) had cancer localized in the E. Baseline ECOG performance status was 0 in 8 patients (40%) and 55% of patients had received prior immunotherapy with 1st line chemotherapy. A combined with RAM was generally well-tolerated without unexpected toxicities. The most common treatment-related adverse events (AEs) were anemia (10%), hypertension (10%), and dysphagia (10%). Treatment-related AEs ≥ grade 3 occurred in 50% of the patients. Median PFS and mOS were 2.7 months (95% CI: 1.5 - 14.5) and not reached (NR) (95% CI: 3.4 - NR), respectively. ORR was 10% (2/20) and DCR was 40% (8/20). In evaluable patients, 64.7% (11/17) patients with baseline tissue CDK4/6 pathway alterations trended towards longer mPFS (3.4 vs. 1.3 months; HR:1.1) and mOS (NR vs. 5.2 months; HR: 1.4) compared to patients without alterations (p > 0.05). Notably, one study patient with a CDK6 amplification had a partial response of 64% and has been on treatment for > 24 months. **Conclusions:** A plus RAM demonstrated promising antitumor activity in previously treated E/GEJ adenocarcinomas in the 2nd and 3rd line metastatic setting with manageable toxicities. Alterations in the CDK4/6 and Cyclin D1 pathways appear to enrich for efficacy and may be predictive but need future validation. In-depth molecular studies investigating changes in the expression of selected serum/tissue genomic markers of response for the cytostatic regimen will be presented at the meeting. Clinical trial information: NCT04921904. Research Sponsor: None.

4066 **Poster Session**

Sequential chemo-immunotherapy as a novel bridging strategy for non-complete responders after neoadjuvant chemoradiotherapy in esophageal cancer: First prospective phase 2 trial challenging the immediate-surgery paradigm. First Author: Lin Peng, Department of Thoracic Surgery, Sichuan Cancer Hospital & Institute, Sichuan Cancer Center, School of Medicine, University of Electronic Science and Technology of China, Chengdu, Sichuan, China

Background: Locally advanced esophageal squamous cell carcinoma (LA-ESCC) patients with non-clinical complete response (non-CCR) after neoadjuvant chemoradiotherapy (NCRT) face >50% recurrence risk with direct surgery (DS), yet no standardized bridging strategy exists. This first study evaluates the efficacy and safety of sequential chemo-immunotherapy (SCI) as a bridge to surgery in this population. **Methods:** In this phase 2 cohort study (NCT05189730), 169 LA-ESCC pts who underwent NCRT were prospectively enrolled from June 2021 to January 2025. The NCRT regimen included paclitaxel and carboplatin every 3 weeks for two cycles. Concurrent radiotherapy (40–41.4 Gy) was administered. Post-NCRT, patients were assessed for non-CCR and stratified into two groups: the SCI group received two additional cycles of chemotherapy and tislelizumab (200 mg intravenously every 3 weeks) before surgery, while the DS group proceeded to surgery. The primary endpoint was pCR rate, secondary endpoints included major pathological response (MPR) rates and safety. **Results:** Eighty-seven non-CCR pts were included (SCI: n = 54; DS: n = 33). The median age was 63 years, with 78.0% male patients. Most patients were stage IIIB(83.9%). Surgery rates were 85.2% in the SCI group (46/54) and 81.8% in the DS group (27/33). In the ITT population, SCI significantly improved pCR rates (40.7% [22/54] vs. 18.1% [6/33]; OR: 3.06, p = 0.024, , one-sided Fisher's Exact Test) and showed a trend toward higher MPR rates (51.8% [28/54] vs. 33.3% [11/33]; OR: 2.14, p = 0.071). In the PP population, pCR rates remained higher in SCI (47.8% [22/46] vs. 22.2% [6/27]; OR: 3.16, p = 0.026) and showed higher MPR rates (60.9% [28/46] vs. 40.7% [11/27]; OR: 2.02, p = 0.078) . At 12 months, PFS rates were 95.6% in the SCI group versus 77.3% in the DS group (p = 0.094) in the ITT population, and 97.4% versus 77.8% (p = 0.064) in the PP population. SCI-related adverse events included lymphopenia (97.7%), leukopenia (84.6%), and fatigue (50.0%). In the no-surgical pts in SCI group, three cases experienced immune pneumonitis and thyroid dysfunction, respectively. Treatment-related adverse events in the SCI group included lymphopenia (97.7%), leukopenia (84.6%), and fatigue (50.0%).The main postoperative complications in the SCI group and DS group were anastomotic leakage and recurrent laryngeal nerve injury (3/46 vs. 2/27, P = 0.629). No significant treatment-related adverse events occurred in the SCI group. **Conclusions:** This pioneering study demonstrates that SCI as a bridging strategy significantly improves pCR rates by >2-fold (OR>3) and shows promising PFS trends with manageable toxicity in non-CCR LA-ESCC, challenging the immediate surgery paradigm. These results warrant validation in randomized phase 3 trials to redefine standard-of-care. Clinical trial information: NCT05189730. Research Sponsor: None.

4067 **Poster Session**

Tumor-informed liquid biopsy in predicting recurrence in patients with operable gastroesophageal adenocarcinoma: The LIQUID study. First Author: Michele Prisciandaro, Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy

Background: Gastroesophageal cancers (GEC) shows high recurrence rates after curative surgery with or without perioperative/adjuvant chemotherapy. Pathological stage is currently the only prognostic tool, but its accuracy should be improved. Liquid biopsy, analyzing circulating tumor DNA (ctDNA), offers a non-invasive method to detect molecular residual disease (MRD) and monitor disease status. The LIQUID study aimed to evaluate the prognostic utility of liquid biopsy in GC patients, for whom observational studies are still scarce. **Methods:** This single-institutional study enrolled patients with resectable GC treated or not with perioperative/adjuvant chemotherapy. Liquid biopsies were collected before neoadjuvant chemotherapy (optional), pre- and post-surgery (minimum 2 weeks interval) and every six months during follow-up, until disease progression or the last follow-up for alive and progression-free patients. MRD analysis was performed using a clinical trial assay based on the tumor-informed ctDNA assay FoundationOne®Tracker, which identified somatic mutations by tissue comprehensive genomic profiling and tracked them in patients' plasma samples. **Results:** Between December 2019 and February 2024, 119 patients were enrolled. Of these, 40 were excluded due to screen failure (mostly peritoneal disease at surgery), and 27 due to technical failure (n = 18) or loss to follow-up (n = 9), leaving 52 patients (median 4 timepoints per patient) for analysis. Median age was 70 years (range: 23–86), with 55.8% male, and 86.5% of tumors located in the stomach. Pathological staging revealed pT0 (3.8%), pT1 (21.2%), pT2 (21.2%), pT3 (34.6%), and pT4 (19.2%) tumors, with nodal involvement in 69.6%. Additionally, 51.9% and 46.2% of patients received neoadjuvant or adjuvant treatment respectively, and 32.7% experienced peritoneal relapse. ctDNA presence was not significantly associated with known clinico-pathological baseline risk factors, except for postoperative N-stage (*p = 0.04*). With a median follow-up of 49.0 months (IQR 30.6 -54.0), post-surgery MRD+ patients had a significantly worse relapse-free survival (RFS) than those with ctDNA- (13.2 months vs not reached; HR 2.81 95% CI 1.23-6.45; *p = 0.011*). Similar results were observed in longitudinal ctDNA monitoring, (RFS 16.3 months for ctDNA+ vs not reached for ctDNA-; HR 2.70, 95% CI 1.22–5.97, *p = 0.011*). Notably, absence of ctDNA after completing the treatment plan (post-surgery or adjuvant therapy) or clearance/seroreversion after treatment were associated with significantly longer RFS (*p = 0.001* and *p = 0.036*, respectively). **Conclusions:** Post-surgical landmark and longitudinal ctDNA detection demonstrates robust evidence of MRD and identifies GC patients at high risk of relapse. These findings support ctDNA as a valuable tool for postoperative surveillance and early intervention strategies in GEC. Research Sponsor: None.

4068 **Poster Session**

Recurrence-free survival as a surrogate endpoint for overall survival in resectable esophageal cancer: An individual patient data analysis of phase III RCTs. First Author: Jun Okui, Department of Surgery, Keio University School of Medicine, Tokyo, Japan

Background: Overall survival (OS) is regarded as the gold standard efficacy endpoint but requires long follow-up. This study aimed to determine the validity of recurrence-free survival (RFS) as a surrogate endpoint for OS in resectable esophageal cancer. **Methods:** A systematic review of phase III randomized controlled trials (RCTs) comparing perioperative treatments for resectable advanced esophageal and gastroesophageal junction cancer was conducted. Individual patient data (IPD) were requested from all included trials. Surrogacy between RFS and OS was assessed at the individual level using the Kendall rank correlation coefficient (τ) and at the trial level using the coefficient of determination (R^2) from a meta-regression model. A τ of 0.8 and an R^2 of 0.65 were considered thresholds indicative of a good surrogate endpoint. **Results:** Twenty-two eligible trials were identified by the systematic review, and IPD were available from 10 RCTs (JCOG1109, JCOG9907, JCOG9204, FFCD9901, FFCD9102, SAKK75/08, CROSS, KOK, NeoRes2 and CMISG1701), including 2,145 patients who underwent R0 resection (cStage IV, cT1N0 and cT4b excluded). Of these, 1563 patients had squamous cell carcinoma, and 575 patients had adenocarcinoma. The 5-year OS and RFS rates were 53.2% and 46.2%, respectively, with a median OS of 6.2 years and a median RFS of 3.6 years. For individual-level surrogacy, Kendall's τ was 0.823 (95% CI: 0.807–0.839). Subgroup analysis based on treatment modality revealed τ values of 0.830 (95% CI: 0.800–0.861) for patients receiving neoadjuvant chemotherapy (NAC; n = 586), 0.827 (95% CI: 0.803–0.850) for those receiving neoadjuvant chemoradiotherapy (NACRT; n = 982), 0.770 (95% CI: 0.713–0.828) for the surgery-alone group (n = 320), and 0.861 (95% CI: 0.824–0.898) for the adjuvant chemotherapy group (n = 257). Trial-level surrogacy analysis across all 22 trials demonstrated an R^2 of 0.735 (95% CI: 0.512–0.939). The surrogate threshold effect was 0.929, indicating the minimum RFS treatment effect required to predict a nonzero effect on OS. **Conclusions:** This study demonstrated strong individual-level and trial-level surrogacy between RFS and OS in surgically resectable esophageal cancer across all perioperative treatment modalities. These findings hold promise for expediting the development of novel perioperative treatment by shortening the follow-up of clinical trials on esophageal cancer. Research Sponsor: None.

4069 **Poster Session**

Neoadjuvant toripalimab plus CapeOX in patients with locally advanced EBV-positive gastric or esophagogastric junction adenocarcinoma (GC/EGJC): Results from the phase II NICE trial. First Author: Liying Zhao, Department of General Surgery & Guangdong Provincial Key Laboratory of Precision Medicine for Gastrointestinal Tumor, Nanfang Hospital, Southern Medical University, Guangzhou, Guangdong, China

Background: Surgery remains the cornerstone of curative therapy for locally advanced GC/EGJC. EBV-positive tumor is a distinct molecular subtype that would be potentially sensitive to immunotherapy, but no consistent reports. Given that chemotherapy may enhance antitumor immunity, perioperative immunochemotherapy may be a promising modality for EBV-positive patients. **Methods:** The NICE trial is a multicenter, multi-cohort phase II study (NCT04744649) evaluating the safety and efficacy of toripalimab plus CapeOX as perioperative treatment in patients with locally advanced GC/EGJC. The Cohort B was first of its kind to assess the efficacy of the immunochemotherapy on the EBV-positive GC/EGJC , in which patients received toripalimab (240 mg) combined with standard-dose CapeOX every 3 weeks for 4 cycles preoperatively and 4 cycles postoperatively. Eligibility criteria included clinical tumor stages of cT3-4aNxM0 or cT2N+M0 disease as determined by both imaging scan and staging laparoscopy with negative peritoneal cytology. The primary endpoint was major pathologic response (MPR, defined as < 10% viable tumor cells). The tumor immune microenvironment (TIME) of tissue samples obtained before and after treatment was analyzed using multiple immunofluorescence assays to assess changes in immune cell infiltration and other biomarkers related to treatment response. **Results:** From May 2021 to September 2023, 17 patients with EBV-positive GC/EGJC (GC, n = 15; EGJC, n = 2) were enrolled, with cT2N0 (n = 1), cT3N1-3 (n = 5), and cT4aN1-3 (n = 11). All patients completed 4 preoperative cycles of treatment, and none experienced progression before surgery. Only one patient withdrew the inform content after preoperative therapy, the 16 patients underwent radical resection, achieving a 100% R0 resection rate (16/16). The MPR rate was 37.5% (6/16), and pathological complete response rate (pCR) was 25.0% (4/16). Of the 16 participants, 15 received postoperative adjuvant therapy, while 1 declined further treatment. The TIME analysis results showed that tumor-infiltrating CD8+ T cells in post-treatment tumor tissues significantly clonally expanded compared with pre-treatment paired tissues. Treatment-related grade 3/4 adverse events were observed in 6 patients (35.3%, 6/17). Until Dec 31 2024, none of the patients experienced disease recurrence. **Conclusions:** Neoadjuvant toripalimab combined with CapeOX is a safe and effective treatment option for patients with EBV-positive, locally advanced GC/EGJC, with moderate MPR and pCR, indicating further investigating for this distinct type of cancer. Clinical trial information: NCT04744649. Research Sponsor: None.

4070 Poster Session

Early detection and neoadjuvant efficacy prediction for esophageal cancer using cfDNA methylation-based liquid-biopsy assay. First Author: Zhigang Li, Shanghai Chest Hospital, Shanghai Jiaotong University, Shanghai, China

Background: Esophageal cancer (EC) is a major malignancy of the upper gastrointestinal tract globally. Early detection and timely therapeutic intervention are pivotal in improving patient outcomes. However, current diagnostic methods often fail to detect EC at an early stage and lack the ability to predict treatment response. There is an urgent need for non-invasive, sensitive, and specific biomarkers to enhance early detection and guide personalized treatment strategies. This study aims to develop a tool to detect EC and predict the neoadjuvant efficacy. **Methods:** This is a prospective multicenter diagnostic study. From July 2023 to October 2024, a total of 236 esophageal cancer cases (stage I: 19.9%, stage II: 24.6%, stage III: 39.4%, stage IV: 16.1%), 31 chronic esophagitis cases, and 441 healthy controls were enrolled from multiple centers. Methylation features and fragmentomic characteristics derived from methylation sequencing data were integrated to develop a gradient-boosted tree model. A nested cross-validation framework was employed to ensure robustness and reliability. Additionally, predictive models for therapeutic responses to neoadjuvant treatment were constructed. **Results:** The detection model achieved an area under the curve (AUC) of 0.954 (95% CI: 0.936-0.971. At a specificity of 97.9% (95% CI: 96.1%-99.0%), the overall sensitivity reached 84.7% (95% CI: 79.5%-89.1%) , with stage-specific sensitivities of 69.5% for early-stage (I/II) and 97% for advanced-stage (III/IV) disease. The detection model maintained robust performance across various clinicopathological parameters, including differentiation grade, neural invasion, vascular invasion, tumor count, and tumor location, with no significant differences in subgroup performance. Among the cohort, 44 patients underwent neoadjuvant therapy, with 90.9% (40/44) receiving immunochemotherapy. The major pathological response (MPR) rate was 52.3% (23/44) and the pathological complete response (pCR) rate was 15.9% (7/44). No clinical features were found to correlate with MPR or pCR rates. Differential methylation profiles between MPR/pCR and non-MPR/pCR patients were analyzed to construct predictive models for neoadjuvant therapy outcomes. Using logistic regression and leave-one-out cross-validation, the MPR prediction model achieved an accuracy of 86.3%, while the pCR prediction model demonstrated an accuracy of 90.9%. **Conclusions:** Our cfDNA-methylation based assay demonstrated high performance in early EC detection and promising value in predicting neoadjuvant therapy responses. This non-invasive approach has the potential to revolutionize EC management by enabling earlier diagnosis and personalized treatment strategies. Research Sponsor: None.

4071 Poster Session

Effectiveness of a multidomain mHealth-based intervention in enhancing recovery and quality of life for esophageal cancer patients undergoing esophagectomy. First Author: Xiaodong Su, Department of Thoracic Oncology, Sun Yat-Sen University Cancer Center, Guangzhou, China

Background: Esophagectomy, a primary treatment for esophageal cancer (EC), often compromises patients' quality of life (QOL), leading to malnutrition, reduced physical function, and psychological distress. Multidomain mHealth-based interventions, which leverage technology to deliver comprehensive nutritional, physical, and psychological support, offer a promising approach to address these challenges during prehabilitation and Enhanced Recovery After Surgery (ERAS) phases. Despite their potential, high-quality evidence demonstrating their effectiveness remains limited. This study evaluates the effectiveness of a multidomain mHealth intervention on QOL and recovery outcomes in EC patients undergoing esophagectomy. **Methods:** Between April 27, 2021 and June 30, 2023, this single-center, randomized controlled trial was conducted, enrolling 76 patients with pathologically confirmed EC scheduled for esophagectomy. Participants were randomized to either a multidomain mHealth-based intervention group (n = 38) or a usual care group (n = 38). The intervention delivered tailored nutritional, physical, and psychological support via a self-developed WeChat-based management platform, spanning from 2 weeks pre-admission to 11 weeks post-discharge. The primary outcome was the change in QOL, assessed using the EORTC QLQ-C30 and QLQ-OES-18. Secondary outcomes included changes in nutritional status (e.g., weight), physical fitness (e.g., 6-minute walk distance), and psychological health (e.g., PHQ-9, GAD-7, SCSQ-20). Outcomes were assessed at baseline, hospital admission, and 3 and 11 weeks post-discharge. **Results:** At 11 weeks post-discharge, the intervention group showed a significant improvement in QOL, with a 15.56-point increase in Global Health Status (EORTC QLQ-C30) compared to a 5.91-point decline in the usual care group (difference: 21.47 points; 95% CI: 9.86–33.08; $p < 0.001$). Functional and symptom scores, including social functioning, appetite, and eating, improved markedly in the intervention group. The intervention group also demonstrated superior outcomes in weight change (+2.19 kg; 95% CI: 0.09–4.30; p = 0.041) and 6-minute walk distance (+80.65 meters; 95% CI: 41.64–119.66; $p < 0.001$). Psychological well-being improved significantly, with reductions in PHQ-9 (-4.70; 95% CI: -6.59 to -2.80; $p < 0.001$) and GAD-7 (-4.63; 95% CI: -6.52 to -2.74; $p < 0.001$), and an increase in positive coping scores (+11.83; 95% CI: 7.20–16.45; $p < 0.001$). **Conclusions:** This multidomain mHealth intervention significantly enhanced QOL, nutritional and physical outcomes, and psychological health in EC patients undergoing esophagectomy. These findings underscore the potential of mHealth platforms to optimize prehabilitation and recovery, offering a scalable and impactful approach to improving outcomes in oncology care. Clinical trial information: ChiCTR2100045650. Research Sponsor: None.

4073 Poster Session

Exome analysis of over 5000 esophagogastric cancers. First Author: Reetu Mukherji, Ruesch Center for the Cure of Gastrointestinal Cancers, Lombardi Comprehensive Cancer Center, Georgetown University Medical Center, Washington, DC

Background: Esophagogastric cancers (EGCs) encompass a heterogenous group of cancers. The genomic drivers that overlap or differentiate among each cancer type are not well studied, despite the availability of therapies that target specific genetic alterations in driver genes. **Methods:** Genomic data from Natera's Real-World Database (N = 5,872) was analyzed to investigate genomic patterns in EGC patients (09/2019-11/2024) receiving standard-of-care treatment. This exploratory analysis was conducted on tumor tissue data available from whole-exome sequencing, generated as part of SignateraTM testing.Microsatellite instability (MSI) status was determined using the MSIsensor and 96-trinucleotide contexts and was correlated with COSMIC SBS signatures (v3.3). Prevalence analysis included only non-synonymous mutations, with ranking adjusted for gene length. **Results:** Patients included 4050 men and 1822 women, with median age 65.3 years, and stage distribution as follows: I: 7.9%, II:14.7%, III: 32.9%, IV: 32.2%, and 12.3% unknown. Gastric cancer (GC) was most common (48.1%), followed by esophageal (EC, 45.9%) and gastroesophageal junction (GEJ, 7.2%). MSI-high cases (7.7% prevalence overall, 2.2% in squamous EC, 5.2% in EC adenocarcinoma, 6.1% in GEJ, 10.9% in GC) had a distinct mutational landscape with frequent missense deletions. The most common signatures were clock-like (SBS1, SBS5), MMR-deficiency-related (SBS6, SBS15), and Thiopurine-chemotherapy-related (SBS87). *PIK3CA* mutations were found in 7.9% of cases, with the most common being E545 (2.6%), H1047 (1.1%), and E542 (1.0%). Notably, *PIK3CA* exon 9/20 mutations displayed a trend of higher prevalence in ctDNA-positive cases. **Conclusions:** These data provide insights into the mutational landscape of EGC and enhance our understanding of differences between histological subtypes. Future studies will continue to explore the associations between genomic subtypes, treatment patterns, and clinical outcomes. Research Sponsor: None.

Top mutated genes and variants in esophagogastric cancers.

Group	N	Genes	Variants
EGC, all	5872	*TP53* (49.8%) *ARID1A*(16.1%)	*ACVR2A* K437X (5.5%) *RPL22*K15X (5.3%) *RNF43*G659X (4.0%)
EGC, MSS	5411	*TP53* (47.9%) *ARID1A*(11.9%)	*G2E3* T361fs (3.1%) *TP53*R175H (2.7%) *LRRIQ3*Q245fs (2.3%)
EGC, MSI-high	422	*ARID1A* (71.7%) *KMT2D*(68.7%) *RPL22*(60.3%)	*ACVR2A* K437X (58.6%) *RPL22*K15X (56.6%) *RNF43*G659X (44.1%)
GEJ, MSS	448	*TP53* (50.5%) *CSMD1*(13.4%) *PCLO*(12.0%)	*TMBIM4* Y174fs (3.2%) *TP53*R273C (3.2%) *TP53*R175H (3.2%)
GC, MSS	2487	*TP53* (33.5%) *CDH1*(14.4%) *ARID1A*(13.8%)	*G2E3* T361fs (3.1%) *PIK3CA*E545K (2.3%) *LRRIQ3*Q245fs (2.2%)
EC Adenocarcinoma, MSS	1599	*TP53* (33.5%) *CDKN2A*(13.5%) *ARID1A*(12.6%)	*TP53* R175H (4.0%) *TP53*R248Q (3.4%) *G2E3*T361fs (3.1%)
EC Squamous carcinoma, MSS	348	*TP53* (61.8%) *NOTCH1* (17.2%)	*PIK3CA* E545K (3.9%) *TMBIM4*Y174fs (3.4%) *TP53*Y220C (2.9%)

4074 Poster Session

The lost evidence: A phase III, multicenter randomized controlled trial of neoadjuvant chemotherapy paclitaxel plus cisplatin versus surgery alone for stage IIA–IIIB esophageal squamous cell carcinoma. First Author: Yin Li, Department of Thoracic Surgery, National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China

Background: The efficacy of neoadjuvant chemotherapy (NAC) vs primary surgery alone for treatment of locally advanced esophageal squamous cell carcinoma (ESCC) remain controversial between Western and Eastern countries. The daily NAC practice in China was without the high level evidence. The Esophageal Cancer Committee of the China Anti-Cancer Association tried to connect the the lost chain of evidence. To compare safety and long-term survival of NAC followed by surgery with that of surgery alone. **Methods:** A prospective, multicenter, open-label, randomized phase III clinical trial that compared safety and efficacy of NAC vs primary surgery for ESCC. From July 18, 2015, to March 29, 2018, we enrolled 605 clinical stage IB-III thoracic ESCC (excluding stage T4b, N3, 7th UICC-TNM staging, 2009). They were randomized to NAC plus surgery (group NAC; n=304) or primary surgery alone (group S; n=301). In group NAC, paclitaxel 175 mg/m2 intravenously (IV) and cisplatin 75 mg/m2 every 3 weeks for two cycles. All patients underwent McKeown, Ivor Lewis or minimally invasive esophagectomy and extended 2-field lymph node dissection. The primary outcome was 5-year overall survival (OS). Secondary outcomes included disease free survival (DFS), R0 resection rate, pathologic complete response rate and toxicities. The intention-to-treat principle was followed for analysis. The SPSS, version 23.0 (IBM Corp). The statistically significant was assumed as a 2-sided $P<0.05$. The Kaplan-Meier method was used to calculate OS and DFS with the log-rank test. The last follow-up data was April 12, 2024. The 5-year OS of primary surgery was 30%. A 5-year survival with a 12% increase for the NAC group was assumed. The sample size was calculated with a two-sided alpha level of 5%, a power of 80%, an expectation of 2 years accruement and a 5-year followup period. The total sample size was set at 528 patients with 10% of patients lost to follow-up. **Results:** Among 605 patients (432 men [71.4%]; mean [SD] age, 61.7 [7.9] years; most frequent clinical stages IIIA 170 [30.2%]), Leukopenia (28%) and neutropenia (49.8%) were the most common grade 3 or 4 adverse events during NAC. Complications was similar between the 2 groups based on Clavien-Dindo classification. The 90-day perioperative mortality rate was 1.6% for the NAC group (4 of 244) and 2.2% for the Surgery alone group (6 of 268) (P = 0.754). The pathologic complete response rate was 6.58% (20 of 304) in NAC group. NAC group had a higher R0 resection rate (98.8% v 98.5%; $P > 0.999$), a better 5 years OS rate (61.1% vs 51.6%; hazard ratio, 0.79; 95% CI, 0.63 to 1.0; P = 0.0469), and a prolonged DFS (58.5% vs 46.2% months; hazard ratio, 0.71; 95% CI, 0.56 to 0.91; P=0.0067). 0.71 (0.56,0.91). The max follow up period of NAC group was 110 months, S group 105 months. The median follow up period of NAC group was 79.4, whereas 55.2 in surgery group. **Conclusions:** This trial showed that NAC plus surgery improves survival over surgery alone among patients with locally advanced ESCC, with acceptable and manageable adverse events. Clinical trial information: NCT02395705. Research Sponsor: None.

4076 **Poster Session**

An interim analysis of phase III study on neoadjuvant chemotherapy versus perioperative toripalimab plus neoadjuvant chemotherapy for locally advanced esophageal squamous cell carcinoma: Henan Cancer Hospital Thoracic Oncology Group 1909 (HCHTOG1909). First Author: Yan Zheng, The Affiliated Cancer Hospital of ZhengZhou University/Henan Cancer Hospital, Zhengzhou, Henan, China

Background: In the era of immunotherapy, whether neoadjuvant immunochemotherapy (NAIC) would be standard treatment of locally advanced esophageal squamous cell carcinoma (ESCC) is without conclusion. The HCHTOG1909 was aimed to compare the safety and long-term efficacy of NAIC followed by minimally invasive esophagectomy (MIE) with those of neoadjuvant chemotherapy followed by MIE. This second interim analysis was aim to compare the short term results of two groups. **Methods:** A prospective, single-center, open-label, randomized phase III clinical trial. Between May 15, 2020 and April 23, 2024, 401 resectable ESCC with clinical stage T1N1-3M0 to T2-3N0-3M0 were enrolled(8th UICC-TNM), 196 in the toripalimab group and 205 in the chemotherapy group. The patients receive either neoadjuvant paclitaxel (175 mg/m2) and cisplatin (75 mg/m2) plus toripalimab (240mg) (toripalimab group) or paclitaxel and cisplatin alone (chemotherapy group) every 3 weeks for 2 cycles. After MIE, the toripalimab group received toripalimab (240 mg every 3 weeks for up to 6 months). The event-free survival (EFS) was the primary endpoint. The pathological complete response (pCR) was the key secondary endpoints. Other endpoints included postoperative complications, mortality, adverse events, overall survival and disease free survival. We planned 3 interim analyses. This was a planned second interim analysis. The sample size was calculated based on the primary endpoint EFS. The hazard ratio assumed to be 0.68 between two groups. A type I error allocated (two-sided) 0.05, 90% power and drop-out rate of 10% in 5 years. The χ^2 test and the Fisher exact test was employed for categorical parameters, the t test or analysis of variance was adopted for continuous variables. **Results:** Among 401 patients (305 men [76.1%]; mean [SD] age, 70.7 [3.5] years; most frequent clinical stages III 213 [53.1%]). The toripalimab group had a higher pCR rate (26.1% vs. 6.2%; $P < 0.001$). The 90-day perioperative mortality rate was 2.42%(4) for the toripalimab group and 2.5%(4) for the chemotherapy alone group ($P = 0.9790$). The most frequent irAE was hypothyroidism. There was no significant difference observed for postoperative complication rate ($P = 0.453$). The grade 3 or 4 treatment-related adverse events did not differ between the two groups (13.8% versus 10.8%). **Conclusions:** The interim results of HCHTOG1909 showed the addition of perioperative toripalimab to NAC is safe in resectable ESCC, and the pCR rate is significantly improved. Clinical trial information: NCT04280822. Research Sponsor: None.

4077 **Poster Session**

Circulating tumor DNA (ctDNA) analysis for improved treatment response assessment and prediction of clinical outcomes in patients with esophageal cancer. First Author: Zexi Allan, Division of Cancer Research, Peter MacCallum Cancer Centre, Melbourne, Australia

Background: Despite curative-intent treatment, patients with esophageal cancer experience a high risk of recurrence, and optimal patient management is limited by poor risk stratification and treatment response assessment strategies. ctDNA has demonstrated value as a prognostic biomarker in esophageal cancer; however, improved analytical and clinical performance of ctDNA analysis is necessary to reliably support patient management decisions in clinical practice. **Methods:** Between September 2017 and June 2023, plasma samples were collected from patients with esophageal cancer before, during, and after standard of care treatment in the routine care setting. In this retrospective analysis, ctDNA testing was performed on a subset of patients using a next-generation tumor-informed assay interrogating up to 50 personalized variants (Haystack MRD, Quest Diagnostics). **Results:** ctDNA was assessed in 149 samples from 51 patients with stage I-III esophageal adenocarcinoma (n= 40) or squamous cell carcinoma (n= 11). Fifteen patients with clinical follow-up (FU) available at the time of analysis had at least one sample collected after curative-intent treatment [neoadjuvant chemoradiotherapy (nCRT) and surgery (n=10) or definitive CRT (n=5)]. ctDNA was detected (ctDNA+) following curative-intent treatment in 5/15 (33%) patients, all 5 (100%) of whom experienced disease recurrence or were deceased at FU (median time from ctDNA+ result to FU: 14.4 months, range: 0.1-24.5). Of the 10 (67%) patients with no ctDNA detected (ctDNA-) following curative-intent treatment, 7 (70%) were disease-free at FU (median time from ctDNA- result to FU: 46.7 months, range: 6.3-65.5). In the neoadjuvant setting, paired pre- and post-nCRT samples were evaluated in 18 patients, demonstrating ctDNA detection in 18/18 (100%) patients prior to nCRT versus 8/18 (44%) following nCRT. ctDNA positivity following nCRT was strongly associated with poor pathological response (p=0.0026), and ctDNA dynamics observed longitudinally during nCRT served as a robust indicator of response. Of note, one patient experienced metastatic progression during nCRT, discovered at surgery, and ctDNA levels in this patient increased 550-fold while on nCRT. **Conclusions:** Evaluation of ctDNA using a next-generation tumor-informed platform supports improved response assessment to nCRT as well as accurate risk stratification following curative-intent treatment in patients with esophageal cancer. ctDNA positivity following curative-intent treatment predicted disease recurrence with a lead time of up to 22 months. Additional analyses are ongoing to further validate these findings. Research Sponsor: None.

4078 **Poster Session**

Clinical implication of MDM2 amplification in advanced biliary tract cancer (BTC): A propensity score-matched, retrospective cohort study of 813 patients. First Author: Hyunseok Yoon, Department of Oncology, Asan Medical Center, University of Ulsan College of Medicine, Seoul, South Korea

Background: Restoring p53 tumor suppressor activity by blocking the interaction between p53 and MDM2, its endogenous negative regulator, has emerged as a potential therapeutic target for several tumors including BTC. However, the frequence and clinical implication of MDM2 amplification (amp) has not been investigated for BTC. **Methods:** Patients with unresectable or metastatic BTC who had available tissue-based targeted next generation sequencing (NGS) data and were treated with first-line gemcitabine plus cisplatin (GemCis)-containing chemotherapy at Asan Medical Center, Seoul, Korea between January 1, 2016, and December 31, 2023, were included. MDM2-amp was defined 5 or greater copies per tumor cell. Baseline characteristics and clinical outcomes to GemCis-containing therapy were compared according to the presence of MDM2-amp/TP53 wild-type (WT). Propensity score matching (PSM) with a 1:4 ratio was performed to balance the baseline characteristics between the patients with and without MDM2-amp/TP53-WT. **Results:** Among 813 patients, 41 (5.0%) had MDM2-amp/TP53-WT and there was no significant association with primary tumor sites: 4.7% in intrahepatic cholangiocarcinoma, 3.7% in extrahepatic cholangiocarcinoma, and 8.0% in gallbladder cancer (p=0.111). Patients with MDM2-amp/TP53-WT significantly had less frequent viral hepatitis B infection (2.4% vs. 18.4%, p=0.009) and lung metastasis (2.4% vs. 13.2%, p=0.043); otherwise, no significant association with baseline characteristics was noted. After PSM (40 for MDM2-amp/TP53-WT vs. 155 for non-MDM2-amp/TP53-WT), patients with MDM2-amp/TP53-WT showed significantly longer progression-free survival compared to those in the matched group (median, 9.6 vs. 6.9 months; p=0.034) and non-significant tendency toward longer overall survival (median, 20.3 vs. 16.4 months; p=0.103). **Conclusions:** In patients with unresectable or metastatic BTC, MDM2-amp/TP53-WT occurred in 5% and it was associated with better survival outcomes of first-line GemCis-containing chemotherapy. Our findings suggest that MDM2-amp/TP53-WT serves as a biomarker for a distinct subgroup of BTC, warranting active investigation into MDM2 inhibitors. Research Sponsor: Boehringer Ingelheim.

4079 **Poster Session**

Real-world outcomes of first-line therapies for unresectable hepatocellular carcinoma in the United States. First Author: Masafumi Ikeda, National Cancer Center Hospital East, Kashiwa, Japan

Background: Unresectable hepatocellular carcinoma (uHCC) remains a significant clinical challenge despite advances in systemic therapies. Real-world evidence complements clinical trials by evaluating treatment effectiveness in diverse patient populations. This study assessed real-world progression-free survival (rwPFS) and overall survival (rwOS) for current standard-of-care first-line (1L) systemic therapies for uHCC. **Methods:** This retrospective study used the Flatiron Health database and included untreated uHCC patients diagnosed on or after January 1, 2018, who initiated 1L systemic therapies (atezolizumab + bevacizumab [atezo + bev], lenvatinib, sorafenib, or durvalumab + tremelimumab [durva + treme]) on or after May 29, 2020. Baseline characteristics, including ECOG status, ALBI grade, and demographic factors, were reported across cohorts. Kaplan-Meier method was used to estimate rwPFS and rwOS for each cohort. **Results:** A total of 1,539 patients were included: atezo + bev (n = 1,070), durva + treme (n = 238), lenvatinib (n = 139), and sorafenib (n = 92). Baseline characteristics were similar across cohorts. Most patients had ECOG (Eastern Cooperative Oncology Group) status 0–1 (57%–70%), with 15%–21% having ECOG 2+. ALBI (Albumin-Bilirubin) grade 2 was observed in 41%–60% of patients, while ALBI grade 3+ was present in 8.1%–17%. The median rwPFS for atezo + bev, lenvatinib, and durva + treme were similar at 4.7 months (95% CI: 4.1–5.4), 4.6 months (95% CI: 3.8–5.5), and 4.2 months (95% CI: 3.2–5.7), respectively. Sorafenib had a significantly shorter rwPFS at 3.0 months (95% CI: 2.5–4.4). The median rwOS for atezo + bev, lenvatinib, and sorafenib were similar at 10.7 months (95% CI: 9.5–11.8), 10.4 months (95% CI: 7.8–13.4), and 10.5 months (95% CI: 5.6–14.9). Durva + treme had a significantly shorter rwOS at 7.6 months (95% CI: 5.7–18.6). At 12 months, the survival probabilities for rwOS were 45% (95% CI: 42%, 48%) for Atezo + Bev, 41% (95% CI: 33%, 50%) for Durva+Treme, 45% (95% CI: 36%, 55%) for lenvatinib, and 43% (95% CI: 33%, 56%) for sorafenib. At 24 months, survival probabilities for rwOS were 27% (95% CI: 24%, 31%) for Atezo + Bev, 26% (95% CI: 19%, 36%) for lenvatinib, 21% (95% CI: 12%, 35%) for sorafenib, and data were undetermined for Durva + Treme. **Conclusions:** Findings from this real-world analysis show that atezo + bev demonstrated comparable outcomes versus lenvatinib, and potential benefits in rwPFS versus sorafenib and rwOS versus durva + treme. The median rwOS was approximately 10 months across treatments and highlights the need for novel therapies to improve long-term survival in uHCC. These results underscore the importance of evaluating treatment effectiveness in real-world populations, which may differ from clinical trial cohorts. Further analyses are warranted to explore these findings and optimize treatment strategies for uHCC. Research Sponsor: Bristol Myers Squibb.

4080 Poster Session

First-line rilvegostomig (rilve) plus chemotherapy (CTx) in advanced biliary tract cancer (BTC): Primary analysis of GEMINI-Hepatobiliary substudy 2 Cohort A. First Author: Jian Zhou, Zhongshan Hospital, Fudan University, Shanghai, China

Background: Immune checkpoint inhibitors plus CTx have improved outcomes in first-line advanced BTC (median progression-free survival [PFS] 6.5–7.2 months), but survival remains limited. Rilve, an anti-PD-1/TIGIT bispecific antibody, may provide benefit by targeting two immune checkpoints. GEMINI-Hepatobiliary (NCT05775159) is a phase 2 study evaluating rilve or volrustomig alone or in combination regimens in patients (pts) with advanced hepatocellular carcinoma (substudy 1) or BTC (substudy 2). We report data from Cohort A (rilve plus CTx) in substudy 2. **Methods:** Pts aged ≥18 years with previously untreated unresectable/metastatic BTC and an ECOG performance status 0–1 received rilve every 3 weeks (Q3W) for up to 2 years plus gemcitabine 1000 mg/m^2 and cisplatin 25 mg/m^2 on days 1 and 8 Q3W for up to 8 cycles. Coprimary endpoints were investigator-assessed 6-month PFS per RECIST v1.1 and safety and tolerability; secondary endpoints included median PFS, objective response rate (ORR), duration of response (DoR; all investigator-assessed per RECIST v1.1), and pharmacokinetics (PK). Tumoral PD-L1 expression, peripheral PD-1 and TIGIT receptor occupancy (RO), and T cell profiles were also evaluated. **Results:** Thirty pts were treated; median age was 60 years, 70.0% were Asian, and 83.3% had metastatic disease. As of Nov 4 2024, the median follow-up in all pts was 6.9 months (interquartile range 5.6–9.5) and rilve treatment was ongoing in 36.7% of pts. Efficacy and safety data are shown in the Table. The 6-month PFS rate was 73.0%; median PFS was 8.3 months. Median PFS was numerically longer in pts with PD-L1 tumor area positivity ≥1% (9.4 months, n = 18) vs the overall study population. The safety profile was manageable and consistent with prior studies. Rilve exposure was consistent with historical monotherapy data, indicating an absence of PK drug interactions and cross-indication differences. Rilve achieved ≥90% PD-1 and TIGIT RO on peripheral T cells and induced peripheral T cell proliferation. **Conclusions:** Rilve plus CTx demonstrated promising efficacy with a manageable safety profile and sustained target engagement. Longer follow-up for data maturity is warranted. Phase 3 studies with rilve in BTC (ARTEMIDE-Biliary 01; DESTINY-BTC01) are ongoing. Clinical trial information: NCT05775159. Research Sponsor: AstraZeneca.

	N=30*
PFS	
Events in all dosed pts, n (%)	19 (63.3)
6-month rate, % (95% CI)	73.0 (53.2–85.5)
Median, months (95% CI)	8.3 (6.7–9.6)
ORR, % (95% CI)	31.0 (15.3–50.8)
Best overall response, n (%)	
Partial response	9 (31.0)
Stable disease	18 (62.1)
Progressive disease	2 (6.9)
Median DoR, months (95% CI)	6.9 (2.8–not calculated)
Any / rilve-related AEs, n (%)	30 (100) / 21 (70.0)
Grade ≥3	26 (86.7) / 4 (13.3)
Serious AEs	12 (40.0) / 2 (6.7)
Leading to rilve discontinuation	1 (3.3) / 0
Leading to death	2 (6.7) / 0

*N=29 for response outcomes.
AE, adverse event; CI, confidence interval.

4081 Poster Session

Combined treatment of durvalumab, bevacizumab and tremelimumab in subjects with hepatocellular carcinoma (HCC) or biliary tract carcinoma (BTC). First Author: Joy Awosika, Thoracic and Gastrointestinal Malignancies Branch, Center for Cancer Research, National Cancer Institute, National Institutes of Health, Bethesda, MD

Background: Anti-VEGF in combination with anti-PD1/PD-L1 represents a synergistic therapeutic strategy that has demonstrated efficacy, prolonging survival in cancers like HCC, RCC, and NSCLC. This combination induces modifications in the tumor microenvironment, leading to a reduction in immunosuppressive cells, improved dendritic cell maturation, antigen presentation, downregulation of immune checkpoint molecules, and enhanced T-cell activity. Combining CTLA-4 inhibitors with anti PD-1/PD-L1 enhances T-cell mediated anti-tumor responses by leveraging distinct yet complementary mechanisms. Targeting VEGF, PD-L1, and CTLA-4 pathways simultaneously in HCC and BTC provides a novel approach that hasn't been tested in clinical trials. Our group previously reported *in vivo* activity in murine BTC models and preliminary clinical results supporting this triplet combination in BTC. The aim of this study is to determine if VEGF inhibition with anti-CTLA-4 and anti-PD-LI therapy augments antitumor immunity and clinical responses in HCC and BTC patients. **Methods:** This was a Phase II trial conducted to evaluate efficacy of durvalumab, bevacizumab and tremelimumab in advanced HCC BCLC stage C or BTC. Participants received bevacizumab at 7.5mg/kg and durvalumab 1150mg every 3 weeks by IV infusion on Day 1 of Cycle 1 (durvalumab) and Day 1 of Cycle 2 (bevacizumab). Tremelimumab at a dose of 300mg was administered by IV infusion only once on Day 1 of Cycle 1. The combination of durvalumab and bevacizumab continued in 3-week cycles until disease progression or unacceptable toxicity. Primary endpoint was 6-month progression-free survival (PFS) and secondary endpoints were safety, overall survival (OS) and best overall response (BOR). Correlative studies assessing immune response were performed. **Results:** Between March 2021 and August 2024, 27 patients were enrolled (HCC: 6pts, BTC: 21pts). The median age was 66y (39-80) and 62% were male. 37% of the patients enrolled received prior ICI. As of November 4th, 2024, with a median follow-up of 8mos, mPFS was 3.5mos and mOS 9.5mos in all 27 efficacy-evaluable pts. The estimated 6 months PFS rate was 37%. The BOR was partial response in 4 pts (18%) followed by stable disease in 9pts (40%). The most common grade 3-4 TRAEs were lymphopenia (6pts, 22%), anemia (9pts, 33%), diarrhea/colitis (7pts, 25.9%), elevated lipase (4pts, 14.8%). Treatment discontinuation related to AEs occurred in 7pts (26%). One treatment-related death occurred secondary to an upper gastrointestinal bleed. **Conclusions:** The combination of durvalumab, bevacizumab and tremelimumab did not meet its primary endpoint but demonstrated a clinically meaningful overall survival benefit. No new safety signals were seen. Clinical trial information: NCT03937830. Research Sponsor: None.

4083 Poster Session

Outcomes by baseline tumor burden using the 6-and-12 score in EMERALD-1: A phase 3 study of durvalumab (D) ± bevacizumab (B) with transarterial chemoembolization (TACE) in embolization-eligible unresectable hepatocellular carcinoma (uHCC). First Author: Joseph Patrick Erinjeri, Interventional Radiology Service, Memorial Sloan Kettering Cancer Center, New York, NY

Background: In EMERALD-1 (NCT03778957), D + B + TACE significantly improved progression-free survival (PFS) vs TACE in participants (pts) with embolization-eligible uHCC. Tumor burden is a prognostic factor in HCC. Prior analyses showed improvements in PFS with D + B + TACE vs TACE in pts who met or exceeded the up-to-7 criterion (a measure based on tumor number and size), and in those with max tumor diameters of < 10 cm or ≥10 cm. The 6-and-12 score measures tumor burden based on tumor number and size. We assessed outcomes in EMERALD-1 by baseline tumor burden using the 6-and-12 score. **Methods:** Pts were randomized 1:1:1 to D + B + TACE, D + TACE, or TACE. Pts received D (1500 mg) or PBO for D (Q4W) + TACE. After completing the last TACE, pts received D (1120 mg) + B (15 mg/kg), D (1120 mg) + PBO for B, or PBOs for D and B (Q3W). In pts who received D + B + TACE and TACE, PFS, time to progression (TTP), and objective response rates (ORR), per BICR RECIST v1.1 in the intent-to-treat (ITT) population, and safety and number of TACE cycles in the safety analysis set (SAS; pts received ≥1 dose of study treatment [tx], regardless of randomization) are reported by baseline tumor burden using 6-and-12 scores: ≤6, > 6–12, or > 12. **Results:** Overall, 40.0%, 43.9%, and 16.2% of pts belonged to the ≤6, > 6–12, and > 12 groups, respectively. The number of pts who received ≥2 TACE cycles increased across the groups (≤6: 63.8%; > 6–12: 81.7%; > 12: 89.8%). PFS and TTP improved with D + B + TACE vs TACE, regardless of baseline tumor burden, with the best relative improvement in hazard ratios (HRs) in the > 12 group (Table). ORRs were higher for D + B + TACE vs TACE in all groups. Max Grade 3–4 tx-related adverse event (TRAE) frequencies were numerically higher with D + B + TACE vs TACE across tumor burden groups; differences were reduced when adjusted for exposure. No tx-related deaths occurred with D + B + TACE. **Conclusions:** PFS, TTP, and ORR benefits were seen with D + B + TACE vs TACE with manageable safety, regardless of tumor burden, further supporting a favorable risk-benefit profile with D + B + TACE in embolization-eligible uHCC. Clinical trial information: NCT03778957. Research Sponsor: AstraZeneca.

	≤6		>6–12		>12	
ITT	**D + B + TACE n=81**	**TACE n=82**	**D + B + TACE n=84**	**TACE n=95**	**D + B + TACE n=38**	**TACE n=28**
Median PFS (95% CI), months	19.4 (13.7–24.9)	11.1 (7.0–13.6)	13.9 (7.2–19.6)	9.7 (6.9–16.3)	11.1 (4.4–16.6)	4.8 (2.9–6.9)
PFS HR vs TACE (95% CI)	0.69 (0.47–1.01)		0.85 (0.59–1.22)		0.61 (0.33–1.13)	
Median TTP (95% CI), months	22.1 (15.1–30.5)	11.1 (7.0–13.9)	22.0 (13.9–27.7)	15.4 (7.2–16.7)	16.6 (6.9–25.1)	5.1 (3.0–7.1)
TTP HR vs TACE (95% CI)	0.60 (0.40–0.90)		0.66 (0.43–1.01)		0.42 (0.20–0.87)	
ORR, n (%)*	47 (58.8)	27 (33.8)	31 (36.9)	32 (33.7)	10 (26.3)	1 (3.6)
SAS	**n=71**	**n=81**	**n=61**	**n=92**	**n=22**	**n=27**
Max Grade 3–4 TRAE, n (%)	17 (23.9)	9 (11.1)	17 (27.9)	3 (3.3)	7 (31.8)	0
event rate per 100 pt-years	15.9	7.9	19.9	3.1	22.2	

*In pts with evaluable disease at baseline.

4084 Poster Session

Phase I study of Ori-C101, an armored GPC3-directed CAR-T, in patients with advanced hepatocellular carcinoma (HCC). First Author: Jia Fan, Department of Liver Surgery and Transplantation, Liver Cancer Institute, Zhongshan Hospital, Fudan University; Key Laboratory of Carcinogenesis and Cancer Invasion (Fudan University), Ministry of Education, Shanghai, China

Background: Previously, we reported the results of Ori-C101 from investigator initiated trial in China (ChiCTR1900028121). The data demonstrated that Ori-C101 owned a favorable safety profile and promising efficacy. Among 10 GPC3$^+$ HCC patients (pts) treated with Ori-C101, 9 pts (90%) achieved disease control and 6 pts (60%) met partial response per RECIST 1.1. Two pts with PR attained progression-free survival of one and two years respectively, with an overall survival close to 3 years. These results implied that Ori-C101 potentially held significant clinical benefits. Subsequently, extensive optimizations and improvements in the manufacturing process were implemented to enhance its clinical efficacy and persistency. Hence, a multicenter registration study was launched in China (the BEACON study), and herein, we will present the preliminary results. **Methods:** This is an open-label, multi-center, dose-escalation (3+3 design) study. GPC3$^+$ advanced HCC pts who failed at least 2 lines of systemic treatments received a single hepatic arterial infusion with a total dose of 0.9 to 6×10^8 CAR-T cells. Primary endpoints are rate of dose-limiting toxicities (DLTs) and safety with the aim to determine a recommended phase II dose (RP2D). Secondary endpoints are cellular kinetics, overall response rate by investigator assessment, duration of response, overall survival and overall safety. **Results:** As of Dec 17th, 2024, a total of 10 eligible pts received Ori-C101 infusion at 3 dose levels (DLs). All pts had BCLC stage B or C, with 20% (2/10) had extrahepatic metastasis. The median number of prior lines of therapy was 4.5 (range 2-9), 100% pts received immune checkpoint inhibitors and tyrosine kinase inhibitors. All pts were evaluable for safety. All adverse events were reported regardless of study drug relationship. Of 10 pts evaluable for safety, the most common ≥ grade (G) 3 AEs were lymphocyte count decreased (100%), neutrophil count decreased (60.0%), blood fibrinogen decreased (40.0%), transaminases increased (40.0%), platelet count decreased (20.0%), blood bilirubin increased (20.0%). CRS was observed in 10 (100%) pts with 3 (30.0%) ≥ G3 CRS. No ICANS was observed. One pt developed DLT event due to CRS and secondary disseminated intravascular coagulation. 9 pts were evaluable for efficacy per RECIST 1.1. While 6 pts (66%) achieved disease control at DL2 or higher, all pts at the DL3 achieved objective response. Particularly, one pt who achieved CR showed encouraging durability and no signs of relapse at 9 months follow up evaluation, and follow up is ongoing. **Conclusions:** These preliminary data showed Ori-C101 has manageable safety profile and exciting efficacy with encouraging sign of good durability. Currently, more pts have been enrolled at dose expansion to confirm the DLs of RP2D. More information will be presented at coming ASCO conference. Clinical trial information: NCT05652920. Research Sponsor: None.

4085 **Poster Session**

Modifiable risk-factors, genetic characteristics, and survival in early-onset cholangiocarcinoma. First Author: Jordan Nunnelee, Mayo Clinic, Rochester, MN

Background: Cholangiocarcinoma (CC) is a rare disease with an increasing incidence among younger adults, which is poorly understood. Genomic profiling of tumors is both prognostic and predictive of benefit for targeted therapies. We investigated if there are clinical and molecular differences between younger vs older patients with CC. **Methods:** We collected TEMPUS genetic data via retrospective chart review from tumors in young vs old patients seen at our institution, defined as $\leq$50 vs $>$ 50 years of age at time of diagnosis. We included patients diagnosed with CC between January 2008 and July 2024 with available clinical follow up and TEMPUS genetic sequencing data. We collected mutation data on the following actionable genes: FGFR2, IDH1/2, BRCA1, BRCA2, BRAF, ATM, ERBB2/3, and KRAS. Patient characteristics and gene expression variables were compared using Chi-square, Fisher's exact and Wilcoxon rank-sum tests. Kaplan-Meier, log rank tests and a multivariable Cox model were used for survival analysis. This study was IRB exempt. **Results:** We included 410 patients, 84 in the young group with median age at diagnosis of 40.8 years, and 326 in the old group with median age 68.5 years. 91.5% of patients were white. There was no difference in BMI between groups, however the older group had higher rates of hypertension (15.5% vs 57.7%), hyperlipidemia (6.0% vs 49.7%), cardiovascular disease (1.2% vs 20.6%), and type 2 diabetes (6.0% vs 21.5%), (all $p < 0.01$). Primary sclerosing cholangitis was more common in the young group (26.2% vs 4.3%, $p < 0.01$). ECOG status of 0 at first treatment was seen in 65.3% of young vs 52.5% of old patients ($p = 0.02$). FGFR2 alterations were more common in the young group (17.9% vs 8.0%, $p < 0.01$), while ATM mutations were more common in old vs young (5.5% vs 0%, $p = 0.03$). There was no age difference seen for the other genetic alterations. Mean tumor mutational burden was higher in the old group (4.1 vs 3.8 mut/mb, $p = 0.01$). MSI-high was found in 2% of cases with no difference between groups. There was no significant difference in overall survival between age groups. There was a numeric difference in overall survival in stage IV patients, though not statistically significant (17.8 months vs. 16.3 months, $p = 0.08$). In a multivariable Cox analysis, female sex, earlier stage at diagnosis and clinical trial enrollment were associated with favorable prognostics. **Conclusions:** Our data highlight relatively low rates of comorbidities associated with metabolic dysfunction in younger adults with CC, suggesting alternative factors are likely to explain the increasing incidence of early-onset disease. FGRFR2 is a more common pathogenic alteration among the young and could inform targeted therapies. Younger patients with CC may not have improved survival outcomes compared to their older counterparts. This underscores the aggressive nature of CC and the need for more effective therapies to improve outcomes. Research Sponsor: None.

4086 **Poster Session**

Real world efficacy and safety of ivosidenib in US veterans with IDH1 mutated cholangiocarcinoma. First Author: Katherine Ismei Zhou, Durham VA Health Care System and Duke University, Durham, NC

Background: IDH1 mutations occur in 13% of patients with intrahepatic cholangiocarcinoma. Ivosidenib is FDA approved for the treatment of advanced, previously treated, IDH1-mutated cholangiocarcinoma. In the ClarIDHy trial, ivosidenib led to an objective response rate of 2%, stable disease rate of 51%, median progression-free survival (PFS) of 2.7 months, and median overall survival (OS) of 10.3 months. Treatment-emergent adverse events resulted in study drug discontinuation in 7% of patients. Data on the real-world efficacy and safety of ivosidenib in cholangiocarcinoma remains limited. **Methods:** Patients with IDH1-mutated cholangiocarcinoma who were prescribed ivosidenib before December 1, 2024, were retrospectively identified from the national Veterans Affairs (VA) Corporate Data Warehouse. Demographic, clinical, and molecular data were abstracted from the National Precision Oncology database and electronic medical records. Response was assessed based on provider notes and radiology reports. Survival was assessed by the Kaplan-Meier method, and covariates evaluated by the Cox proportional hazards model. **Results:** Of 1094 veterans with cholangiocarcinoma who underwent molecular testing, 82 (7.5%) had an IDH1 mutation. 33 (40%) patients received ivosidenib at 27 VA medical centers. The median age was 74 years (range 46–82). 2 patients (6%) had a partial response (PR), 10 (30%) had stable disease (SD), 19 (58%) had progressive disease, and 2 were not assessed. 20 patients (60%) had received one and 5 patients (15%) received two prior lines of therapy. Of the 8 patients (24%) who received first-line ivosidenib, 2 (25%) had a PR and 3 (38%) had SD. Most patients (94%) started ivosidenib at the labeled dose (500 mg daily). Two patients who started ivosidenib at reduced dose (250 mg daily) had PR and SD as their best response. The median PFS from start of ivosidenib was 4.0 months, and the median OS was 10.5 months. In a multivariable analysis, PFS and OS were not significantly associated with age, line of therapy, IDH1 variant allele frequency, or IDH1 mutation (17 IDH1 R132C vs. 8 other). Patients with IDH1-mutated, advanced cholangiocarcinoma treated with ivosidenib had a median OS of 25.3 months from diagnosis, compared to 8.7 months for patients who did not receive ivosidenib. Toxicities leading to dose reduction, interruption, or discontinuation of ivosidenib occurred in 3 patients (9%). **Conclusions:** In this real-world cohort, patients with IDH1-mutated advanced cholangiocarcinoma treated with ivosidenib had similar response rate, PFS, and OS compared to ClarIDHy. Toxicities leading to dose reduction, interruption, or discontinuation were rare. The only two partial responses were observed in the first-line setting, including one with a reduced starting dose. This suggests that frontline ivosidenib may be a reasonable alternative for patients with advanced cholangiocarcinoma. Research Sponsor: None.

4087 **Poster Session**

HAIC plus TAE combined with tislelizumab and surufatinib in unresectable intrahepatic cholangiocarcinoma: The REACH-01 trial. First Author: Kangshuai Li, Qilu Hospital of Shandong University, Jinan, Shandong, China

Background: REACH-01 (NCT06239532) is a single-arm, open label, prospective trial, aiming to evaluate the safety and preliminary effectiveness of hepatic artery infusion chemotherapy (HAIC) plus transcatheter arterial embolization (TAE) combined with tislelizumab and surufatinib as first-line therapy for unresectable intrahepatic cholangiocarcinoma (iCCA). **Methods:** Twenty-eight patients with pathologically confirmed iCCA received TAE with undrugged microspheres and hepatic arterial infusion of oxaliplatin (85 mg/m^2) and raltitrexed (3 mg/m^2) at an interval of at least 3 weeks along with intravenous tislelizumab (200 mg) Q3W and oral surufatinib (150 - 250 mg) once daily. The primary endpoint was the objective response rate (ORR). Secondary outcomes included progression-free survival (PFS), conversion to surgical resection rate, overall survival (OS), 1-year OS rate, disease control rate (DCR), and incidence of adverse events. **Results:** As of December 18, 2024, the median follow-up time was 9.33 months, 15 patients achieved partial response and the ORR was 57.69 % per RECIST v1.1 criteria. The conversion to surgical resection rate was 15.38 %. The DCR was 80.77 %. Secondary endpoints of progression-free survival, overall survival and 1-year OS rate were not mature at the time of the analysis. Further, treatment related adverse effects (TRAEs) of any grade occurred in 28 patients. Manageable grade 3 adverse events (AEs) occurred in 32.14% of patients, commonly elevated alanine aminotransferase (7.14%), anorexia (7.14%), and hypokalemia (7.14%). **Conclusions:** HAIC plus TAE combined with tislelizumab and surufatinib are safe and promising first-line treatment selection for unresectable iCCA. Clinical trial information: NCT06239532. Research Sponsor: Key Research and Development Program of Shandong Province; 2021CXGC011105; BeiGene Co. Ltd.

4088 **Poster Session**

Efficacy and safety of regorafenib combination with PD-1 inhibitors vs. regorafenib monotherapy in second-line treatment for patients with unresectable hepatocellular carcinoma after failure of different first-line treatments: A multicenter retrospective real-world study. First Author: Weihong Ma, Comprehensive Liver Cancer Center, The 5th Medical Center of PLA General Hospital, Beijing, China

Background: Regorafenib is the first oral targeted drug as a second-line agent in patients with unresectable hepatocellular carcinoma (HCC) who progressed on sorafenib treatment.There is a lack of data to validate the second-line therapy after progression of targeted-immune combination therapy. Our aim was to investigate the efficacy and safety of regorafenib alone or in combination with a programmed death-1 (PD-1) inhibitor in second-line treatment for patients who have failed tyrosine kinase inhibitor (TKI) in combination with PD-1 or TKI monotherapy, respectively. **Methods:** A total of 288 patients were enrolled in this multicenter, retrospective study. These patients received regorafenib with or without PD-1 inhibitor (Sintilimab/Camrelizumab/Pembrolizumab) as second-line therapy after failure of TKI (sorafenib/lenvatinib) or such TKIs combined with PD-1 inhibitor (Sintilimab/Camrelizumab/Pembrolizumab). The primary study endpoint was the evaluation of overall survival (OS), while secondary study endpoints were progression-free survival (PFS), objective response rate (ORR), disease control rate (DCR), and treatment safety. **Results:** In the first line treatment, 126 patients received TKI and 162 patients received TKI plus PD-1. In the TKI cohort, the Reg-PD-1 group exhibited markedly higher ORR (29.69% vs 4.84%; $p<0.001$) and DCR (89.06% vs 67.74%; $p=0.004$), as well as longer median PFS (10.5 vs 4.7 months; $p<0.001$) and median OS (18.9 vs 14.0 months; $p=0.03$) compared to the Reg monotherapy group.There was no significant difference in PFS, OS, ORR, and DCR between the two groups in the TKI plus PD-1 cohort.The incidence of AEs was higher in the Reg-PD-1 group compared to the Reg group (81.25 % vs 58.06%; $p=0.005$) in the TKI cohort. And Reg-PD-1 group was comparable to Reg group (76.70% vs 66.10%; $p=0.144$) in the TKI Plus PD-1 cohort. **Conclusions:** Regorafenib plus PD-1 may enhance efficacy in uHCC patients who failed first-line TKI therapy. However, in patients who have progressed after first-line TKI plus PD-1 therapy, using regorafenib alone or in combination with PD-1 in second-line therapy does not show a significant difference in efficacy.These findings have significant implications for the selection of second-line treatment strategies for HCC patients, indicating that the combination of regorafenib and PD-1 might not provide additional benefits in certain patient subgroups. Research Sponsor: None.

Outcomes in the two cohorts.

	TKI			TKI plus PD-1		
Outcomes	**Reg (n=62)**	**Reg-PD-1 (n=64)**	**P value**	**Reg (n=59)**	**Reg-PD-1 (n=103)**	**P value**
CR	2	3	-	3	2	-
PR	1	16	-	6	21	-
SD	39	38	-	35	62	-
PD	20	7	-	15	18	-
ORR	4.84%	29.69%	< 0.001	15.25%	22.33%	0.276
DCR	67.74%	89.06%	0.004	74.58%	82.52%	0.227
PFS(m)	4.7	10.5	< 0.001	6.3	9.2	0.062
OS(m)	14.0	18.9	0.03	13.2	16.2	0.13

4089 **Poster Session**

Characterization of CLDN18 expression in a Western biliary tract cancer population. First Author: Alexander Bray, University of Michigan, Ann Arbor, MI

Background: Patients with advanced biliary tract cancer (BTC) have poor survival despite recent advances in chemoimmunotherapy. Claudin 18 (CLDN18) directed therapy has shown benefit in combination with FOLFOX or CAPOX in gastric cancer and may also have therapeutic utility in advanced BTC. However, there are limited data on CLDN18 RNA and protein expression in BTC, especially in Western populations. **Methods:** Exome-capture based RNA sequencing was performed on BTC tissue samples through the MI-ONCOSEQ study at the University of Michigan. Fragments per Kilobase of transcript per Million mapped reads (FPKM) was used to normalize raw read counts. Immunohistochemical staining was completed on a BTC tissue microarray (n = 28), and Western blotting was done on human BTC cell lines (SNU-1079, RBE, and SSP-25) using CLDN18 recombinant rabbit monoclonal antibody (34H14L15, Invitrogen). Statistical significance was defined as $p < 0.05$. **Results:** We identified transcriptomic data from 148 consecutive BTC cases with median age 61 (range 17-81) years and 75 (50.7%) were female. Of these patients, 45 (30.4%) expressed CLDN18 mRNA with FPKM > 1. A lower proportion of intrahepatic cholangiocarcinoma (CCA) patients (n = 23/110; 20.9%) expressed CLDN18 mRNA relative to extrahepatic CCA (n = 13/25; 54.2%) and gallbladder cancer (n = 8/11; 72.7%) ($p < 0.006$). CLDN18 mRNA expression was not associated with stage at diagnosis, but was higher in metastatic versus primary sites (35.6 vs 16.1%, $p < 0.05$). Overall survival was not associated with CLDN18 gene expression in univariate analysis (hazard ratio 1.02, $p > 0.9$). CLDN18 protein expression was observed in 8/28 (28.6%) patients using a cutoff defined in prior gastric cancer clinical trials (2+ to 3+ staining intensity in $\geq$ 75% of tumor cells). In human BTC cell lines, SSP-25 expressed CLDN18, but the SNU-1079 and RBE lines did not. **Conclusions:** CLDN18 is expressed in a modest subset of Western patients with advanced BTC and CLDN18-directed therapy may be effective in this disease, particularly in ECC and gallbladder cancer given their higher frequency of expression. CLDN18 positive human BTC cell lines represent a promising preclinical model system for further investigation of this therapeutic strategy. Research Sponsor: National Cancer Institute; 5T32CA009357-42; Rogel Cancer Center.

4090 **Poster Session**

TACE-HAIC combined with donafenib and immune checkpoint inhibitors for BCLC stage C HCC patients (THEME study): A retrospective IPTW adjusted cohort study. First Author: Linan Yin, Harbin Medical University Cancer Hospital, Harbin, China

Background: Transarterial chemoembolization (TACE) combined with hepatic arterial infusion chemotherapy (HAIC) has demonstrated superior objective response rate (ORR) and progression-free survival (PFS) compared to TACE alone, particularly in patients with unresectable hepatocellular carcinoma (uHCC) with portal vein tumor thrombosis (PVTT), as shown in previous studies. Additionally, Donafenib exhibited significant survival benefits and better safety profiles compared to Sorafenib in a Phase III clinical trial. We aimed to retrospectively compare the efficacy and safety of TACE-HAIC combined with Donafenib and immune checkpoint inhibitors (Quadruple Therapy Group) versus the standardized targeted therapy (TKIs or bevacizumab) plus immune checkpoint inhibitors (Targeted-Immunotherapy Group) in patients with BCLC stage C hepatocellular carcinoma (HCC). **Methods:** We conducted a retrospective analysis of patients with BCLC stage C hepatocellular carcinoma (HCC) who received quadruple therapy or targeted-immunotherapy at the Harbin Medical University Cancer Hospital between September 2019 and October 2024. To minimize baseline imbalances between the groups, we applied stabilized inverse probability of treatment weighting (sIPTW) methods. **Results:** A total of 195 patients were included in the study, of whom 125 were assigned to the Quadruple Therapy Group and 70 to the Targeted-Immunotherapy Group. Within the Targeted-Immunotherapy Group, 44 patients received TKIs combined with immune checkpoint inhibitors, while 26 patients received bevacizumab combined with immune checkpoint inhibitors. After applying sIPTW to balance the baseline characteristics between the two groups, patients in the Quadruple Therapy Group demonstrated a significantly higher median overall survival (OS) compared with the Targeted-Immunotherapy Group(29.4 months [95% CI: 23.9–NA] vs 18.0 months [14.7–31.8]; P = 0.045). Additionally, the median progression-free survival (PFS) assessed by the modified Response Evaluation Criteria in Solid Tumors (mRECIST) was longer in the Quadruple Therapy Group(16.4 months [95% CI: 12.7–NA] vs 10.0 months [3.3–31.8]; P = 0.013). The objective response rate (ORR) evaluated according to mRECIST was also higher in the Quadruple Therapy Group(68.4% vs 28.2%, $P < 0.001$).The incidence of any adverse events in the Quadruple Therapy Group was 95.2%, compared with 97.1% in the Targeted-Immunotherapy Group.Among these the incidence of grade $\geq$3 adverse events was 40.8% in the Quadruple Therapy Group and 38.6% in the Targeted-Immunotherapy Group. **Conclusions:** Compared with Targeted-Immunotherapy Group, patients with BCLC stage C HCC treated with TACE-HAIC combined with Donafenib and immune checkpoint inhibitors therapy demonstrated superior efficacy and acceptable safety. Research Sponsor: None.

4091 **Poster Session**

Multimodal evaluation of metabolic dysfunction–associated steatotic liver disease (MASLD)–related biliary tract cancer (BTC) and immunotherapy outcomes. First Author: Nakul Manish Shah, The University of Texas MD Anderson Cancer Center, Houston, TX

Background: Rising incidence of BTC, particularly intrahepatic cholangiocarcinoma (iCCA), may be linked to increasing incidence of obesity, MASLD and type 2 diabetes mellitus (T2DM). Immunotherapy with immune checkpoint inhibitors (ICIs) has modestly extended survival in biliary tract cancer. However, the prevalence of MASLD in BTC, its immune microenvironment (TME) and outcome of MASLD-BTC with ICIs are unknown. **Methods:** Retrospective analysis of BTC patients (pts) treated with ICI between 5/2021-5/2024 with durvalumab, cisplatin, and gemcitabine. We used American Association for Liver Diseases (AASLD) criteria for MASLD: 1) metabolic dysfunction and 2) steatosis on imaging or biopsy. We calculated liver proton-density fat fraction (PDFF) in pre-treatment non-contrast CT scans (PDFF estimate 5% labelled as steatosis). We examined the statistical association between BMI and both tumor genotype and gene expression patterns using data from institutional genomic platforms (MAPP2 and RTI). **Results:** 179 BTC pts (65% of whom were iCCA) treated with durvalumab, cisplatin, and gemcitabine, 103 (57.5%) met AASLD MASLD criteria. In evaluable pts, the median overall survival (OS) was 18.4 months, and median follow-up time was 16.7 months. Non-MASLD pts had a median OS of 23.0 months (95% CI: 16.2, NA) versus 16.7 months (95% CI: 12.4, 21.2) with MASLD (p = .056). T2DM was associated with a worse OS (10.6 versus 21.2 months, p = .004). Multivariable cox model for OS demonstrated a hazard ratio (HR) of 1.45 (95% CI: 0.87, 2.4; p = .1564) for MASLD and 1.61 (95% CI: .99, 2.65; p = .0575) for T2DM. The median progression-free survival (PFS) was 8.5 months. MASLD BTC had a median PFS of 8.2 months (95% CI: 5.7, 10.1) versus 9.2 months (95% CI: 6.9, 16.2) without MASLD (p = .459). BTC pts with T2DM had median PFS of 5.8 months vs 13.0 months without T2DM (p = .001). Multivariable cox model for PFS had HR of 1.7 (95% CI: 1.1, 2.6; p = .014) for T2DM. Within our institutional database (n = 919), we observed depletion of *KRAS* (p = .008) and *STK11* (p = .02) mutations in BTC pts with high BMI. RNA-seq (n = 77) suggests that elevated BMI was associated with low expression of pan-immune and epithelial-to-mesenchymal transition and increased expression of oxidative phosphorylation signatures. **Conclusions:** BTC is commonly associated with MASLD and may correlate with reduced OS and PFS with ICI, particularly in T2DM pts. Our findings suggest a distinct immunogenomic signature in MASLD-BTC and highlight the importance of further investigating the TME in this population. Research Sponsor: None.

4092 **Poster Session**

Phase 1 expansion study of FF-10832 (liposomal gemcitabine) antitumor activity in patients with advanced biliary carcinomas. First Author: Gerald Steven Falchook, Sarah Cannon Research Institute at HealthONE, Denver, CO

Background: FF-10832 has demonstrated improved pre-clinical anti-tumor activity compared to gemcitabine (GEM). Associated factors may include its prolonged circulating half-life, tumor accumulation, and immune activation.The first in human dose finding trial of FF-10832 demonstrated a tolerable safety profile and anti-tumor activity in heavily pre-treated patients (pts) with solid tumors who progressed on prior gemcitabine. A biliary tract cancer (BTC) pt maintained a PR $>$60 weeks after progression on prior GEM based therapy. We subsequently enrolled an expansion cohort evaluating FF-10832 monotherapy in BTC and describe the results (NCT03440450). **Methods:** Pts $\geq$18 years with advanced BTC who had progressed on up to 3 lines of therapy were treated with FF-10832 40 mg/m^2 IV Day 1 Q 21 days until disease progression or unacceptable toxicity. Response was assessed by RECIST 1.1. Modulation of immune cells (flow cytometry/multiomics) and population PK were assessed. **Results:** 18 pts [12M/6F; median age 68 (34-79), ECOG PS 0 (3) PS 1 (15)] were treated; median # prior therapies, 2 (1-3); all had prior GEM and 16 had progressed on prior GEM. Pts received a median of 4 (1 - 22+) cycles with a median time on study of 10.4 (3.3 -77+) weeks. FF-10832 was well-tolerated. The most common drug-related AEs were nausea, pyrexia, and decreased appetite (39% each). No Gr 4 toxicity was observed; Gr 3 AEs in $>$1 pt included anemia (2) and muscular weakness (2). All AEs were successfully managed using standard therapies. Two pts withdrew and 1 pt died of cholangitic sepsis before 1st evaluation. Best overall response in 15 remaining pts was 2 PR, 8 SD, 4 PD and 1 NE. The median PFS and OS were 3.4 and 9.1 months, respectively. Both PRs had received prior GEM/platinum-based therapy: 1) a gallbladder adenocarcinoma pt achieved a 48% decrease in target lesions with FF-10832 by cycle 2, which was maintained through cycle 10; dose was reduced to 30 mg/m^2 at cycle 5 for Gr 3 muscle weakness, 2) a hilar cholangiocarcinoma pt achieved a PR by cycle 2,with complete resolution of target lesions before withdrawing. Four additional pts maintained SD $\geq$ 6 cycles, with 2 continuing on therapy after 9 and 26 cycles. PK was similar to that previously reported (terminal $t_{1/2,}$ 30 hours), with similar log decreases observed in Ki67+ regulatory T cells and increases observed in CD8+ cells, indicative of anti-tumor immune activation. **Conclusions:** FF-10832 is well-tolerated and has anti-tumor activity in pts with advanced BTC who progressed on prior GEM. Although preliminary, these results of a single agent therapy compare favorably to those reported for 2nd line combination therapies. This warrants further investigation of FF-10832 efficacy and safety in BTC patients. Clinical trial information: NCT03440450. Research Sponsor: FUJIFILM Pharmaceuticals USA Inc.

4093 Poster Session

SHR-8068 plus adebrelimab and bevacizumab for advanced hepatocellular carcinoma (aHCC): A phase 1b/2 study. First Author: Lianxin Liu, The First Affiliated Hospital of the University of Science and Technology of China/Anhui Provincial Hospital, Hefei, China

Background: Combination of an anti-PD-1/L1 antibody with an anti-angiogenic agent is currently the preferred 1L treatment for aHCC. Addition of a CTLA-4 inhibitor may further improve anti-tumor activity, with complementary immunostimulatory effects from CTLA-4 and PD-1/L1 blockade. We conducted a multicenter, open-label, phase 1b/2 trial (NCT05444088) to assess SHR-8068, a novel anti-CTLA-4 monoclonal antibody (mAb), combined with adebrelimab (A, anti-PD-L1 mAb) and bevacizumab (B) in patients (pts) with aHCC. **Methods:** Pts with or without prior treatment were enrolled (phase 1b: failed or refused standard therapy; phase 2: ≤1L systemic therapy, no immunotherapy [IO]). SHR-8068 was evaluated in 2 dosing regimens with AB: 1 mg/kg Q6W (Combo 1) or 4 mg/kg priming dose (Combo 2). An additional cohort evaluated AB alone (Combo 3). A was dosed at 20 mg/kg Q3W and B at 15 mg/kg Q3W for all regimens. **Results:** As of Oct 31, 2024, a total of 27, 53 and 21 pts received Combo 1, 2, and 3, respectively, across 2 study phases (overall: IO naïve, 97.0%; prior anti-angiogenic therapy, 32.7%); median follow-up was 16.7, 11.1 and 11.3 mo, respectively. In pts treated with Combo 2, the objective response rate (ORR) was 47.2% (25/53; 95% CI 33.3%–61.4%), with a median duration of response (DoR) of 12.7 mo (95% CI 5.8–NR). The median progression-free survival (PFS) was 8.7 mo (95% CI 5.5–11.6); median overall survival (OS) was not reached, with a 12-mo OS rate of 76.0% (95% CI 59.3%–86.6%). Numerically improved ORR and survival outcomes were seen with Combo 2 *vs* Combo 1 and 3 (Table 1). Overall, grade ≥3 treatment-related adverse events (TRAEs) occurred in 55.6%, 41.5% and 42.9% of pts with Combo 1, 2 and 3. The most common grade ≥3 TRAEs (incidence ≥10% for any Combo) were decreased platelet count (22.2%, 5.7%, and 4.8% for Combo 1, 2, and 3) and hypertension (18.5%, 7.5%, and 9.5%, respectively). TRAE led to discontinuation of any study agent in 11.1%, 1.9% and 9.5% of pts, respectively. There was 1 treatment-related death (Combo 3). **Conclusions:** SHR-8068 combined with adebrelimab and bevacizumab showed promising efficacy and manageable safety in aHCC. A more favorable benefit-risk profile was observed for SHR-8068 given as a priming dose. A phase 3 trial (NCT06618664) is currently underway to further assess the combination as 1L treatment for aHCC. Clinical trial information: NCT05444088. Research Sponsor: Jiangsu Hengrui Pharmaceuticals, Co., Ltd.

Efficacy outcomes.

	Combo 1 (n=27)	Combo 2 (n=53)	Combo 3 (n=21)
ORR, % (95% CI)	29.6 (13.8–50.2)	47.2 (33.3–61.4)	19.0 (5.5–41.9)
Median DoR*, mo (95% CI)	NR (9.4–NR)	12.7 (5.8–NR)	NR (7.0–NR)
9-mo DoR rate*, % (95% CI)	100.0 (NR–NR)	69.8 (41.7–86.3)	66.7 (5.4–94.5)
DCR, % (95% CI)	77.8 (57.7–91.4)	77.4 (63.8–87.7)	81.0 (58.1–94.6)
Median PFS*, mo (95% CI)	6.9 (2.7–NR)	8.7 (5.5–11.6)	6.7 (2.8–9.5)
12-mo OS rate*, % (95% CI)	70.4 (49.4–83.9)	76.0 (59.3–86.6)	70.8 (46.2–85.7)

Tumor response was assessed by investigator per RECIST v1.1.
*Kaplan-Meier method. NR, not reached.

4094 Poster Session

Hepatic arterial infusion chemotherapy combined with donafenib and tislelizumab versus transcatheter chemoembolization alone for hepatocellular carcinoma: A propensity score matching study. First Author: Zhongguo Zhou, Department of Liver Surgery, Sun Yat-Sen University Cancer Center, Guangzhou, Guangdong, China

Background: Although tyrosine kinase inhibitors combined with PD-1/L1 inhibitors have been established as first-line treatment for advanced hepatocellular carcinoma (HCC), the survival benefit remains unsatisfactory. Hepatic arterial infusion chemotherapy (HAIC) has emerged as an effective therapy to improve the prognosis of HCC patients. This study aimed to investigate the efficacy and safety of HAIC combined with donafenib and tislelizumab in HCC. **Methods:** 421 patients diagnosed as HCC and treated in Sun Yat-sen University Cancer Center from January 2017 to December 2024 were enrolled in this retrospective study, included 151 patients received FOLFOX-HAIC combined with donafenib and tislelizumab (DT-HAIC) and 270 received transcatheter chemoembolization (TACE) alone. To avoid the selection bias and balance covariates, we conducted propensity score matching (PSM). The primary outcomes are progression-free survival (PFS) and overall survival (OS); the secondary outcomes include objective response rate (ORR), disease control rate (DCR) and safety. Tumor response was evaluated per RECIST v1.1. **Results:** PSM resulted in 151 matched pairs with comparable baseline characteristics between the DT-HAIC and TACE cohorts. Compared with the TACE cohort, Patients receiving DT-HAIC exhibited significantly better median PFS (10.3 vs 4.9 months, $P < 0.01$) and median OS (not reached vs 10.9 months, $P < 0.01$). The ORR and DCR were significantly higher in the DT-HAIC cohort than in the TACE cohort (ORR: 33.8% vs 11.3%, $P < 0.01$; DCR: 77.9% vs 65.3%, P = 0.03). There was no treatment-related death. Serious adverse events were similar between the two groups, except for alanine aminotransferase (ALT), aspartate aminotransferase (AST), platelet count, abdominal pain and allergic reaction. In the TACE cohort, the occurrence of Grade 3-4 elevations in ALT (11.3% vs 21.9%, P = 0.02) and AST (21.2% vs 36.4%, $P < 0.01$), as well as abdominal pain (2.6% vs 16.6%, $P < 0.01$), was more prevalent. In contrast, the DT-HAIC cohort exhibited a higher incidence of Grade 3-4 thrombocytopenia (11.3% vs 1.3%, $P < 0.01$) and allergic reactions (4.6% vs 0, P = 0.02). **Conclusions:** DT-HAIC significantly improved PFS, OS, ORR, and DCR compared with TACE alone, with manageable adverse events, suggesting that the combination of HAIC with donafenib and tislelizumab may be a promising treatment option for HCC patients. Research Sponsor: None.

	DT-HAIC (n=151)	TACE (n=151)	P Value
mPFS	10.3m	4.9m	P<0.01
mOS	Not reached	10.9m	P<0.01
ORR	33.8%	11.3%	P<0.01
DCR	77.9%	65.3%	P=0.03

4095 Poster Session

LEAP-002 long-term follow-up: Lenvatinib plus pembrolizumab versus lenvatinib plus placebo for advanced hepatocellular carcinoma. First Author: Richard S. Finn, David Geffen School of Medicine at UCLA, Los Angeles, CA

Background: LEAP-002 was a randomized, double-blind, phase 3 study (NCT03713593) that was conducted to evaluate the efficacy and safety of first-line lenvatinib plus pembrolizumab versus lenvatinib plus placebo in participants with advanced hepatocellular carcinoma (HCC). The study did not meet its primary end points of OS at final analysis and PFS at interim analysis. After a median study follow-up of 43.6 months, OS, PFS, and ORR remained consistent with the primary efficacy analysis (OS: HR, 0.84 [95% CI, 0.71-0.98]; PFS: HR, 0.81 [95% CI, 0.69-0.95]; ORR, 26.3% vs 17.5%); no new safety signals were observed. Here, we present results based on an additional 15 months of follow-up. **Methods:** Eligible participants with advanced HCC were randomly assigned 1:1 to receive lenvatinib (8 mg/day if bodyweight [BW] < 60 kg; 12 mg/day if BW ≥60 kg) plus pembrolizumab (200 mg IV Q3W) or lenvatinib plus placebo. Dual primary end points were OS and PFS (per RECIST v1.1 by BICR). Secondary end points included ORR and DOR, both per RECIST v1.1 by BICR, and safety. The database cutoff was September 24, 2024. **Results:** 794 participants were randomly assigned to receive lenvatinib plus pembrolizumab (n = 395) or lenvatinib plus placebo (n = 399). Median study follow-up was 59.2 mo (range, 52.9-68.3). The HR for OS was 0.80 (95% CI, 0.69-0.94; median, 21.1 months with lenvatinib plus pembrolizumab vs 19.0 months with lenvatinib plus placebo). 60-month OS rates were 19.7% with lenvatinib plus pembrolizumab versus 10.7% with lenvatinib plus placebo. Grade 3-5 treatment-related adverse event (AE) rates were 62.8% with lenvatinib plus pembrolizumab and 58.0% with lenvatinib plus placebo. No additional deaths due to treatment-related AEs were reported since the final analysis (database cutoff, June 21, 2022). Overall, 47.3% of participants treated with lenvatinib plus pembrolizumab versus 56.1% of participants treated with lenvatinib plus placebo received subsequent systemic therapy (TKI/VEGF, 38.5% vs 42.6%; immunotherapy, 17.2% vs 26.8%; chemotherapy, 5.3% vs 4.0%); 21.5% versus 25.6% received subsequent liver-directed therapy (locoregional therapy, 20.0% vs 23.8%; surgery, 2.8% vs 2.8%). **Conclusions:** The LEAP-002 study did not meet its primary end points; however, with a long-term follow-up of 5 years, almost twice as many participants randomly assigned to receive lenvatinib plus pembrolizumab versus lenvatinib plus placebo were alive at database cutoff; no new safety signals were observed. Clinical trial information: NCT03713593. Research Sponsor: Eisai, Inc., Nutley, NJ, USA, and Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA.

4097 Poster Session

Membrane-specific HER2 expression by artificial intelligence-based quantitative scoring for prediction of efficacy of trastuzumab deruxtecan in biliary tract cancer (HERB trial): Exploratory analysis of a multicenter, single arm, phase II trial. First Author: Mitsuho Imai, Translational Research Supporting Office, National Cancer Center Hospital East, Kashiwa, Japan

Background: Trastuzumab deruxtecan (T-DXd) showed promising results in patients with HER2-positive biliary tract cancer (BTC). With T-DXd's expanding indication into HER2-low cancers, quantitative Artificial Intelligence (AI)-based scoring of HER2 expression at the cellular level becomes increasingly important. This study investigated whether the intensity and subcellular pattern of HER2 staining would correlate with response to T-DXd. **Methods:** HER2 immunohistochemistry (IHC) whole slide images from the phase II HERB trial were analyzed. These participants had unresectable or recurrent BTC refractory or intolerant to gemcitabine-containing regimen and received T-DXd based on confirmed HER2-positive or low status. Lunit SCOPE universal IHC, a deep learning based IHC analyzer, was used to provide cell level classes (AI-H0, H1+, H2+, H3+) and continuous scoring of HER2 staining intensities of subcellular compartments (membrane, cytoplasm and nucleus) for each tumor cell. Membrane specificity was calculated for each cell as the ratio of membrane intensity to the sum of all three subcellular compartments. **Results:** The 29 patients analyzed showed continuous improvement in response rates with an increasing proportion of AI-H3+ cells. The ORR was 37.5%, 42.9% and 50.0% for patients with more than 10%, 25%, and 50% of tumor cells classified as AI-H3+, respectively. The HER2 intense cohort (n=4), defined by tumors with over 50% of tumor cells classified as AI-H3+, had a significantly better PFS (HR 0.15, $p<0.05$) and OS (HR 0.10, $p<0.05$) compared to the rest of the treatment group. The high membrane specificity group defined by ≥80% of tumor cells with membrane specificity ≥0.4 (N=6) had a confirmed ORR of 50%. These patients also demonstrated significantly longer PFS (HR 0.30, $p<0.05$) and OS (HR 0.27, $p<0.05$). The six cases identified by membrane specificity included all four cases of the HER2 intense cohort and two more cases, showing improved sensitivity in identifying likely responders. **Conclusions:** AI based quantification of HER2 intensity and membrane specificity was predictive of therapeutic response to T-DXd in HER2 expressing BTC. Membrane specificity analysis was more sensitive in identifying exceptional responders compared to intensity alone. Research Sponsor: None.

Confirmed response and survival based on AI defined biomarkers.

	By AI-H3+ proportion		By AI-MB specific cell proportion	
	< 50%	≥ 50%	< 80%	≥ 80%
Sample size	25	4	23	6
ORR, %	28.0	50.0	26.1	50.0
mPFS	4.21 (2.83-4.40)	11.04 (5.68-12.91)	4.21 (2.83-4.40)	11.04 (1.45-12.91)
HR (95% CI, p-value)	REF	0.15 (0.03-0.67, <0.05)	REF	0.30 (0.10-0.92, <0.05)
mOS	7.00 (4.37-8.94)	NR (5.68-NR)	7.00 (4.27-8.94)	NR (9.63-NR)
HR (95% CI, p-value)	REF	0.10 (0.01-0.79, <0.05)	REF	0.27 (0.08-0.93, <0.05)

4098 **Poster Session**

A prospective, observational phase II clinical study evaluating hepatic artery infusion chemotherapy in combination with HLX10 and HLX04 as first-line treatment for patients with advanced hepatocellular carcinoma. First Author: Huikai Li, Department of Hepatobiliary and Pancreatic Oncology, Tianjin Cancer Hospital Airport, Tianjin, China

Background: Advanced hepatocellular carcinoma (HCC) presents limited treatment options. Immunotherapy has emerged as an effective treatment, demonstrating encouraging outcomes and acceptable adverse reactions in advanced HCC. This study aims to assess the efficacy and safety of HLX10 (recombinant anti-PD-1 humanized monoclonal antibody) and HLX04 (recombinant anti-VEGF humanized monoclonal antibody), in combination with hepatic artery infusion chemotherapy (HAIC), as first-line treatment for advanced HCC. **Methods:** This prospective, observational, single-center Phase II trial enrolled untreated HCC patients with BCLC stage C. All patients received HLX10 (4.5 mg/kg, intravenous infusion, every 3 weeks) and HLX04 (15.0 mg/kg, intravenous infusion, every 3 weeks) on Day 1 of each treatment cycle, followed by HAIC with the FOLFOX regimen. HAIC was administered for a maximum of 8 cycles, while HLX10 and HLX04 were continued for up to 2 years, until death, disease progression, or intolerable toxicity occurred. The primary endpoint was the objective response rate (ORR), assessed by the investigator according to RECIST v1.1 criteria. Secondary endpoints included the disease control rate (DCR), progression-free survival (PFS), and safety. **Results:** Between August 2023 and September 2024, a total of 35 eligible patients were enrolled in the study. As of the data cut-off, 28 (80.0%) patients had received at least 3 cycles of treatment. Of the 35 patients, 32 underwent at least one assessment of treatment response, with the best outcomes as follows: 17 (53.1%) achieved partial remission (PR), and 12 (40.0%) had stable disease (SD). The ORR and DCR were 53.1% and 90.6%, respectively. Notably, among patients who had received at least 3 cycles of treatment, 17 patients achieved PR, resulting in an ORR of 63.0%. Moreover, 5 patients underwent successful hepatectomy after at least 3 cycles of treatment, and postoperative pathological evaluation revealed extensive tumor necrosis in the excised tissues. The median follow-up duration was 8.4 months, during which 6 (18.8%) patients experienced disease progression, yielding a one-year PFS rate of 70.5% (95% CI: 47.0%–85.0%). In terms of safety, 17 patients (48.6%) experienced at least one grade 3 or 4 adverse event (AE), with the most frequent being decreased lymphocyte count (20%). **Conclusions:** The combination of HLX10, HLX04, and HAIC as first-line treatment for advanced HCC has demonstrated promising efficacy, particularly in patients completing three or more cycles. The safety profile of this combination therapy was acceptable, with manageable AEs. Further investigation in larger trials is warranted. Clinical trial information: NCT06370065. Research Sponsor: None.

4099 **Poster Session**

Cobolimab and dostarlimab in the first-line treatment of unresectable hepatoma: A multi-center, single arm, phase 2 trial. First Author: Jared David Acoba, University of Hawaii Cancer Center, Honolulu, HI

Background: TIM-3 is highly expressed in cancer and mediates T cell exhaustion/dysfunction that can be an important mechanism of immune escape. Cobolimab, an anti-TIM-3 monoclonal antibody, in combination with dostarlimab (a PD-1 inhibitor), has been shown to enhance T-cell activity in preclinical assessments. This study aimed to investigate the efficacy and safety of cobolimab and dostarlimab in the treatment of unresectable hepatocellular carcinoma (HCC). **Methods:** This is a multi-center, single-arm, phase II study. Eligible patients with unresectable hepatoma (Barcelona Clinic Liver Cancer Stage B or C) and Child Pugh A or B7 (limit 6) liver function received cobolimab 300mg and dostalimab 500mg every 3 weeks for up to 2 years. The primary endpoint was the objective response rate (ORR) per Response Evaluation Criteria in Solid Tumors version1.1. Secondary endpoints were disease control rate (DCR) and duration of response (DoR), progression-free survival (PFS), overall survival (OS), and safety. **Results:** 40 patients were treated (mean age 67 years [range: 24–85]). The analysis presented here is for all 34 Child Pugh A patients. As of November 6, 2024, the median follow-up was 12.9 months. The ORR and DCR were 37.1% and 85.2% respectively (3.7% CR, 33.3% PR, 48.1% SD). The median PFS was 11.0 mo (95% CI: 4.6-17.4), and the median OS was 27.3 mo (95% CI: 21.1-33.5). The median DoR was 14.8 mo (95% CI: 9.4-20.2). Overall incidences of adverse events (AEs) of any grade was 97.1% and immune-related AEs (irAEs) of any grade was 64.7%. The most common irAEs of any grade were dermatologic (47.1%) and endocrine (14.7%). There were two patients (5.8%) who experienced mild elevations of AST and ALT. Grade $\geq$3 irAEs were observed in two patients (5.8%), which included decreased neutrophil count, hypophysitis, and hypothyroidism. There were no treatment-related discontinuations or deaths. **Conclusions:** Cobolimab plus dostarlimab yielded promising response rates and survival outcomes with acceptable safety as first-line treatment in patients with CP A, unresectable HCC. This represents a potential therapy regimen for this population. Clinical trial information: NCT03680508. Research Sponsor: GSK.

4100 **Poster Session**

Sorafenib plus hepatic arterial infusion chemotherapy versus sorafenib plus transarterial chemoembolization in advanced hepatocellular carcinoma: An update on SHATA-001 study. First Author: Zefeng Du, Department of Hepatobiliary Oncology, Sun Yat-Sen University Cancer Center, State Key Laboratory of Oncology in South China, Collaborative Innovation Center for Cancer Medicine, Guangzhou, China

Background: Although sorafenib plus transcatheter arterial chemoembolization (SoraTACE) has been widely applied for advanced hepatocellular carcinoma (HCC) in most Asian countries, sorafenib plus hepatic arteria infusion chemotherapy (SoraHAIC) may be a better alternative. Herein, we compared the efficacy and safety between the two groups in advanced HCC. Additionally, we validated a predictive model from our previous phase III trial (NCT02973685, cohort1). **Methods:** This phase III trial (NCT02856126) recruited participants with advanced HCC. Eligible participants were randomly assigned (2:1) to receive Sorafenib (400mg orally twice daily) plus HAIC per 3 weeks or TACE until disease progression or unacceptable toxicity. The Primary endpoint was overall survival (OS). Whole-exome sequencing (WES), RNA sequencing, and DNA methylation analysis of tumor biopsy samples were performed for predictive biomarker exploration (cohort 1) and validation (SHATA-001). **Results:** From August 2016 to October 2020, a total of 207 participants were allocated to receive SoraHAIC (n = 141) or SoraTACE (n = 66). The trial met the prespecified endpoints. SoraHAIC significantly prolonged OS compared to SoraTACE (median OS, 15.7 versus 11.2 months; $p < 0.001$). In the SoraTACE group, 56.7% of participants experienced grade 3 or 4 treatment-related adverse events, which were significantly higher than the SoraHAIC group (39.3%; $p < 0.023$). Severe adverse events were also more frequent in SoraTACE (15.7% vs 26.7%, p = 0.07). WES analysis found no ideal indicator in the mutational landscape for treatment outcome. We identified 1226 and 506 differentially methylated probes (DMPs) among the non-responsive specimens in the HAIC and TACE groups. Then we performed RNA-seq analysis. By comparing the transcriptome between the responsive and non-responsive groups, 685 and 600 differentially expressed genes (DEGs) were generated in the two treatment groups, respectively. In the HAIC group, pathways including leukocyte-mediated immunity and immune response-activating signaling pathway were enriched in the responders, while metabolic-related pathways including steroid metabolic process and alcohol biosynthetic process were enriched in the non-responders in the TACE group. Integrative analysis of DEGs and DMPs indicated phosphofructokinase (PFKM) could potentially stratify patients to HAIC or TACE as higher expression of PFKM was associated with favorable outcomes accepting TACE. Such performance could also be validated in this study as participants with elevated PFKM tended to benefit from SoraTACE. **Conclusions:** This trial demonstrated SoraHAIC significantly improved OS over SoraTACE in participants with advanced HCC. Participants with high PFKM expression benefited more from TACE. Clinical trial information: NCT02856126. Research Sponsor: None.

4101 **Poster Session**

Survival outcomes for zanidatamab-hrii compared to chemotherapy in previously treated HER2-positive (IHC3+) biliary tract cancer (BTC): HERIZON-BTC-01 vs a real-world (RW) external control arm (ECA). First Author: Richard D. Kim, Moffitt Cancer Center, Tampa, FL

Background: Zanidatamab-hrii, a bispecific HER2-directed antibody, received accelerated approval for adults with previously treated, unresectable or metastatic HER2-positive (IHC 3+) BTC based on results from the single-arm phase 2 HERIZON-BTC-01 trial. The results here compare survival outcomes with zanidatamab-hrii from HERIZON-BTC-01 vs a comparable RW cohort of patients who received second-line (2L) chemotherapy. **Methods:** HERIZON-BTC-01 (NCT04466891) evaluated zanidatamab-hrii (20 mg/kg IV every 2 weeks) in patients with HER2-amplified, unresectable locally advanced or metastatic BTC (gallbladder cancer [GBC], intra-/extra-hepatic cholangiocarcinoma [ICC/ECC]) who had received prior gemcitabine-containing therapy. HERIZON-BTC-01 patients with HER2 IHC3+ (n = 62) were included in this analysis. The US-based ECA was constructed using deidentified data from the Flatiron Health Electronic Health Record. Key inclusion criteria for the ECA included a diagnosis of GBC or ICC/ECC with initiation of 2L chemotherapy between 2011-2023, HER2 IHC3+ prior to 2L initiation, and 1L treatment with a gemcitabine-containing regimen. Patients with ECOG $>$ 1 or CNS metastases were excluded. Standardized mortality ratio (SMR) weighting was used to account for potential imbalance of key prognostic factors. Overall survival (OS) and progression-free survival (PFS) were evaluated using SMR-weighted Kaplan-Meier and Cox proportional hazards regression. **Results:** Among 290 RW patients initiating 2L treatment with HER2 testing, 12 met all eligibility criteria and were included in the ECA. The most common reason for exclusion was lack of HER2-positivity (n = 209). Median follow-up times were 16.1 (interquartile range [IQR]: 9.4, 19.9) and 4.7 (IQR: 2.6, 8.1) months for the zanidatamab-hrii and ECA arms, respectively. After weighting, baseline characteristics were similar across arms with standardized mean differences $\leq$0.2. The most common 2L chemotherapy regimen in the ECA was FOLFOX (n =6), followed by gemcitabine-based regimens (n = 3) and FOLFORI (n = 2). Compared with chemotherapy, zanidatamab-hrii resulted in longer median OS (18.07 vs 3.29 months; hazard ratio [HR]:0.29) and PFS (7.26 vs 2.30; HR: 0.47) (Table). The 6- and 12-month survival for zanidatamab-hrii patients were 90% and 65% (vs. 29% and 13% for the ECA), respectively. **Conclusions:** Among patients with previously-treated HER2-positive (IHC3+) BTC, zanidatamab-hrii resulted in longer survival, including a $>$ 14 month increase in median OS, vs ECA patients treated with chemotherapy. Research Sponsor: Jazz Pharmaceuticals.

	Zanidatamab-hrii (N=62)	ECA (N=12)
OS		
Median, mos	18.07	3.29
Survival % (95% CI)		
6 mos	90% (83%, 98%)	29% (11%, 75%)
12 mos	65% (54%, 78%)	13% (3%, 55%)
PFS		
Median, mos	7.26	2.30
Survival % (95% CI)		
6 mos	55% (44%, 69%)	14% (4%, 47%)
12 mos	32% (22%, 46%)	14% (4%, 47%)

4102 Poster Session

Concordance analysis between tumor tissue HER2 status by immunohistochemistry (IHC) and in situ hybridization (ISH) and a translational analysis of plasma ctDNA in patients (pts) with biliary tract cancer (BTC): An exploratory analysis from the phase 2 HERIZON-BTC-01 trial. First Author: James J. Harding, Memorial Sloan Kettering Cancer Center, New York, NY

Background: HER2 is a target for precision oncology. HER2 protein overexpression and/or gene amplification is observed in a subset of pts with BTC. Zanidatamab (zani), a dual HER2-targeted bispecific antibody, received accelerated approval as a treatment for adults with previously treated, unresectable, or metastatic HER2-positive (IHC 3+) BTC based on the phase 2b HERIZON-BTC-01 trial. In this exploratory analysis, we evaluated concordance between tissue-based HER2 IHC and ISH in screened pts, and *HER2* gene amplification between tissue-based HER2 ISH and plasma ctDNA by NGS in zani-treated pts. **Methods:** In HERIZON-BTC-01 (NCT04466891) pts were screened for *HER2* gene-amplified tumors by ISH (VENTANA HER2 Dual ISH DNA Probe Cocktail assay) at a central laboratory. Pts with *HER2* gene amplification were prospectively assigned to cohorts based on centrally determined HER2 IHC score (Ventana PATHWAY [4B5] IHC assay); cohort 1: IHC 2+ or 3+; cohort 2: IHC 0 or 1+. HER2 status was assessed in a fresh biopsy or an archived sample per ASCO/CAP guidelines, with gastric cancer algorithm. Enrolled pts received zani 20 mg/kg IV Q2W in 28-day cycles. Plasma ctDNA samples were collected prior to the first cycle of zani (baseline) and on-treatment at cycle 2 day 28 for testing with NGS Guardant360 (Guardant Health). Guardant360 Molecular Response (MR) scores were calculated based on changes in plasma ctDNA levels from baseline. **Results:** Overall, 756 screened pts had central results for both HER2 IHC and ISH. Nearly all pts (94%) with HER2 IHC 3+ BTC had *HER2*-amplified tumors per ISH (Table). Among all 87 pts treated with zani across both cohorts, 48 samples from 25 pts were available for testing with NGS. The concordance between *HER2* gene amplification by ISH and ctDNA NGS was 59%. Co-mutations at baseline in plasma ctDNA occurring in $>$ 10% of pts included KRAS (n = 1 [3%]), *HER2* S310F (n = 3 [9%]), and PIK3CA (n = 6 [18%]). Overall, 18/25 (72%) pts had a decrease in ctDNA levels from baseline at cycle 2 day 28; decreases $>$ 90% were observed in pts with a best response of partial or stable disease. MR scores correlated with tumor response (ANOVA, P = 0.0189). **Conclusions:** In this analysis, there was a high concordance (94%) observed between tumor tissue HER2 IHC 3+ status and *HER2* gene amplification among pts screened in HERIZON-BTC-01. Exploratory translational analysis shows that treatment with zani after 2 cycles was associated with a decrease in plasma ctDNA levels in the majority of pts. Clinical trial information: NCT04466891. Research Sponsor: Jazz Pharmaceuticals.

HER2 IHC and ISH status among screened patients.

	ISH Status			Amplification
IHC Status	Amplified	Non-Amplified	Total	n/N (%)
0	12	330	342	12/342 (3.5)
1+	8	94	102	8/102 (7.8)
2+	34	167	201	34/201 (16.9)
3+	104	7	111	104/111 (93.7)
Total	158	598	756	158/756 (20.9)

4103 Poster Session

The efficacy of atezolizumab plus bevacizumab for advanced hepatocellular carcinoma in relation to tumor-infiltrating lymphocytes: Histological assessment of CD8+ T cell spatial features as predictive biomarkers. First Author: Hiroaki Kanzaki, Department of Gastroenterology, Graduate School of Medicine, Chiba University, Chiba, Japan

Background: The combination of atezolizumab and bevacizumab (Atez/Bev) has improved prognosis in advanced hepatocellular carcinoma (HCC), though its therapeutic mechanisms remain unclear. While the tumor microenvironment (TME) holds promise for biomarker discovery, current studies rely on archived diagnostic samples. We aimed to elucidate molecular determinants of treatment efficacy and identify predictive biomarkers through comprehensive TME analysis of pre-treatment samples. **Methods:** We analyzed biopsy samples from 94 advanced HCC patients immediately before initiating Atez/Bev treatment using immunohistochemistry (IHC), RNA-sequencing, flow cytometry, and multiplexed imaging. Our analysis focused on spatial characteristics of CD8+ T cells and effector regulatory T (eTreg) cells, with longitudinal assessment of immune responses during treatment. **Results:** High programmed death-1 (PD-1) positivity in CD8+ T cells was significantly associated with favorable progression-free survival (PFS) (HR 0.24, 95% CI 0.11-0.52), while CD8+ T cell density showed no significant correlation (HR 1.12, 95% CI 0.64-1.95). Through multiplexed imaging analysis using PD-1 positivity as a key indicator, we identified two critical determinants of response: CD8+ T cells localizing within tumor parenchyma rather than fibrous stroma, and maintaining diffuse distribution throughout the tumor parenchyma. These features, assessable with routine hematoxylin and eosin and CD8 IHC staining, stratified patients into four prognostic groups (p = 0.019), with median PFS ranging from 14.3 months (both favorable features) to 3.5 months (neither feature). The PD-1 positivity in eTreg cells was not associated with prognosis (HR 0.75, 95% CI 0.34-1.62). Notably, bevacizumab counteracted the potential negative effects of programmed death-ligand 1 blockade by suppressing eTreg cell activation, as demonstrated through analysis of patients who discontinued bevacizumab and in vitro experiments showing reduced expression of eTreg activation markers. **Conclusions:** We demonstrate that routine histological assessment of CD8+ T cell localization and distribution patterns can predict Atez/Bev efficacy in advanced HCC. The identified synergistic mechanism of bevacizumab-mediated eTreg suppression provides a framework for future combination immunotherapy development. Research Sponsor: CHUGAI PHARMACEUTICAL CO., LTD.

4104 Poster Session

Radiomic analysis on pretreatment MRI to predict response to atezolizumab plus bevacizumab in advanced hepatocellular carcinoma: A multicenter study. First Author: Hui-Chuan Sun, Department of Hepatobiliary Surgery and Liver Transplantation Liver Cancer Institute and Zhongshan Hospital, Fudan University, Shanghai, China

Background: The combination of atezolizumab and bevacizumab is the standard treatment for advanced hepatocellular carcinoma approved in China and many other countries. However, the objective response rate of this combination treatment was around 30%. Consequently, identifying individuals with the potential to respond favorably prior to initiating therapy remains a pressing challenge. **Methods:** This multi-center retrospective study included advanced hepatocellular carcinoma patients who received atezolizumab plus bevacizumab as first-line therapy between December 2020 and February 2024. The training cohort consisted of eligible patients who have complete baseline, treatment and tumor evaluation records and MRI imaging data from Zhongshan Hospital, while eligible patients from other centers constituted the external validation cohort. A deep learning model based on nnU-Net was developed to automatically segment intrahepatic lesions. All segmentations were reviewed and revised by two radiologists. The radiomic features were extracted using PyRadiomics, then a radiomic feature-based model for predicting response to atezolizumab plus bevacizumab therapy was constructed using the Extreme Gradient Boosting Decision Tree (XGBoost) algorithm. Additionally, three radiologists evaluated 53 visually-assessed MRI features on MRI scans. Finally, the predictive performance of radiomic feature model, as well as the relationship between radiomic and MRI features, was assessed. **Results:** A total of 240 eligible patients were recruited from 14 centers in China, of which 161 and 79 were classified as training and validation cohorts, respectively. During a median follow-up period of 13.7 months (IQR: 8.3–20.6) in the training cohort and 10.5 months (IQR: 7.4–17.2) in the validation cohort, 19.0% (30/161) and 23.0% (18/79) of patients, respectively, achieved an objective response by RECIST v1.1 (p = 0.559). The radiomic feature model demonstrated a promising predictive performance, achieving an AUC of 0.913 (95% CI: 0.874–0.953) in the training cohort and 0.825 (95% CI: 0.700–0.949) in the validation cohort. Fat surpassing liver mass was the only MRI feature associated with an objective response (p = 0.020). When the MRI feature was combined with radiomic features, the predictive model further improved, yielding an AUC of 0.951 (95% CI: 0.924–0.979) in the training cohort and 0.835 (95% CI: 0.725–0.945) in the validation cohort. A significant correlation was observed between radiomic features and MRI features of intrahepatic lesions with a univariate analysis $p < 0.2$. **Conclusions:** Radiomic features derived from pretreatment MRI scans can effectively predict personalized objective responses to combination therapy with atezolizumab and bevacizumab in patients with unresectable or advanced HCC. Research Sponsor: National Natural Science Foundation of China; 82372037.

4105 Poster Session

Efficacy and safety of atezolizumab and bevacizumab with or without transarterial chemoembolization as first-line therapy for advanced hepatocellular carcinoma: An international multicenter real-world study. First Author: Ningning Zhang, Department of Lymphoma, Tianjin Medical University Cancer Institute and Hospital, National Clinical Research Center for Cancer, Key Laboratory of Cancer Prevention and Therapy, the Sino-US Center for Lymphoma and Leukemia Research, Tianjin, Tianjin, China

Background: Transarterial chemoembolization (TACE) combined with immunotherapy and targeted therapy provides a promising therapy for advanced hepatocellular carcinoma (HCC).This study aimed to compare the efficacy and safety of atezolizumab and bevacizumab combined with (TACE-Ate-Bev) or without TACE (Ate-Bev) as first-line treatment for advanced HCC. **Methods:** This international multicenter, retrospective study included 311 advanced HCC cases administered TACE-Ate-Bev (n = 152) or Ate-Bev (n = 159). Inverse probability of treatment weighting (IPTW) was employed to minimize bias. Overall survival (OS), progression-free survival (PFS), and adverse events (AEs) were observed. **Results:** The TACE-Ate-Bev group demonstrated significantly improved OS (26.8 [95% CI 23.1-NA] vs. 14.9 months [95% CI 11.4-19.9]; hazard ratio [HR] = 2.66 [95% CI 1.87-3.77], $p < 0.0001$) and PFS (16.0 months [95% CI 12.8-17.8] vs. 6.5 months [95% CI 5.4-7.6]; HR = 2.50 [95% CI 1.90–3.28], $p < 0.0001$) compared to the Ate-Bev group, especially across BCLC stage B (mOS: NA [95% CI 23.5-NA] vs. 15.6 months [95% CI 11.4-NA], $p < 0.0001$; mPFS: 16.9 months [95% CI 16.2-NA] vs. 6.7 months [95% CI 5.7-10.9], $p < 0.0001$) and BCLC stage C (mOS: 25.2 months [95% CI 19.7-NA] vs. 14.3 months [95% CI 10.1-20.5], p = 0.00018; mPFS: 12.8 months [95% CI 11.3-17.0] vs. 6.5 months [95% CI 5.0-7.7], $p < 0.0001$) disease. The superior efficacy of TACE-Ate-Bev indicated same trends after IPTW adjustment. Grade 3 or 4 AEs were observed in 36 patients (24.3%) in the TACE-Ate-Bev group and 34 (21.4%) in the Ate-Bev group. There was no statistically significant difference in the proportion of gastrointestinal bleeding between the TACE-Ate-Bev and Ate-Bev groups (9.9% vs. 10.1%, p = 0.954). Notably, patients with portal hypertension, portal vein tumor thrombus vp3-4, extrahepatic metastasis or Child-Pugh grade B exhibited improved OS and PFS in the TACE-Ate-Bev group versus the Ate-Bev group. **Conclusions:** TACE-Ate-Bev significantly improves OS and PFS with acceptable toxicity compared to Ate-Bev as first-line therapy for advanced HCC. Research Sponsor: None.

4106 Poster Session

Factors associated with immunotherapy response for hepatocellular carcinoma. First Author: Matthew Shing Hin Chung, The University of Hong Kong, Hong Kong, Hong Kong

Background: Immunotherapy has shown remarkable progress in treating hepatocellular carcinoma (HCC) in recent years. We aim to investigate the clinical factors associated with treatment response to HCC immunotherapy in Asian population. **Methods:** We identifiedHCC patients receiving immunotherapy (nivolumab, pembrolizumab, atezolizumab, durvalumab, tremelimumab, ipilimumab; including monotherapies or combinations) from January 2008 to June 2024 from a population-based cohort in Hong Kong. Primary outcomes were all-cause mortality and hospitalization stratified by etiology of HCC [Viral-HCC, defined as hepatitis B virus (HBV)-related or/and hepatitis C virus (HCV)-related HCC vs non-viral-HCC], other clinical factors including age, sex, type 2 diabetes (T2D), cirrhosis, antiviral therapy for HBV, and history of receiving other oncological treatment (curative: surgical resection, liver transplant, radiofrequency ablation, microwave ablation; non-curative: transcatheter arterial chemoembolization and radiotherapy). Hazard ratios (HR) were estimated by Cox regression models. **Results:** This study included 1363 patients on immunotherapy (mean age 63.1 years, 84.2% male; 87.2% viral-HCC; 23.0% had prior curative therapy; 34.5% had prior non-curative therapy). Over 240-days of median follow-up, viral-HCC had similar risk of all-cause mortality (54.5% vs 58.9%, p = 0.169) and hospitalization (34.8% vs 30.9%, p = 0.360) compared to non-viral-HCC. Patients with prior curative therapy compared to those without had lower risk of all-cause mortality (HR 0.81 [95% CI: 0.69-0.95], p = 0.011). Among HBV-related HCC, those with antiviral treatment ≥2 years prior to immunotherapy were associated with lower risk of liver-specific mortality (HR 0.83 [95% CI 0.70-0.99], p = 0.036) and HCC-specific mortality (HR 0.80 [95% CI 0.67-0.96], p = 0.014). Patients with cirrhosis had higher risk of all-cause mortality (HR 1.42 [95% CI 1.18-1.71], p < 0.001). No associations with treatment response were observed in subgroups stratified by age < 60/ ≥60, sex, and T2D. **Conclusions:** Among patients with HCC receiving immunotherapy, treatment outcomes were similar in viral-etiologies and non-viral etiologies. Antiviral treatment improves treatment response in HBV-related HCC, while cirrhosis is detrimental to mortality outcomes. HCC immunotherapy following curative treatment, in contrast to non-curative therapies, has improved treatment response. Research Sponsor: None.

	All-cause mortality			Hospitalization		
	HR	95% CI	P value	HR	95% CI	P value
Viral-HCC	0.86	(0.70, 1.06)	0.169	1.14	(0.86, 1.51)	0.360
Age (<60/ ≥60)	0.91	(0.79, 1.06)	0.238	0.90	(0.76, 1.08)	0.276
Sex	0.98	(0.81, 1.18)	0.812	0.99	(0.78, 1.26)	0.939
T2D	1.00	(0.86, 1.15)	0.957	0.84	(0.70, 1.02)	0.082
Cirrhosis	1.42	(1.18, 1.71)	<0.001	1.23	(0.99, 1.52)	0.062
Curative therapy	0.81	(0.69, 0.95)	0.011	1.09	(0.88, 1.33)	0.434
Non-curative therapy	1.11	(0.96, 1.29)	0.147	1.60	(1.34, 1.92)	<0.001

4107 Poster Session

Evolutionary divergence of the HLA-B genotype as a predictor of immune checkpoint inhibitor (ICI) therapy efficacy in hepatobiliary cancers. First Author: Nan Zhang, Department of Liver Surgery, State Key Laboratory of Complex Severe and Rare Diseases, Peking Union Medical College Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China

Background: The role of human leukocyte antigen class I (HLA-I) molecules in shaping the immune response to immune checkpoint inhibitors (ICIs) has been recognized in several solid malignancies. However, the prognostic significance of HLA-I characteristics in hepatobiliary cancers remains poorly understood. **Methods:** Patients with advanced hepatocellular carcinoma (aHCC) and biliary tract cancer (aBTC) receiving ICI-based therapy were prospectively enrolled (NCT03892577). Retrospective analyses were performed to evaluate the association between HLA-I evolutionary divergence (HED), HLA-I genotype, and HLA-I heterozygosity with clinical outcomes. HLA-I genotyping was conducted using germline DNA from peripheral blood, and HED was quantified based on the Grantham distance metric, which measures evolutionary divergence between HLA-I alleles. Patients were stratified into high and low HED groups using the 25th percentile as the cutoff. **Results:** A total of 118 patients (41 with aHCC and 77 with aBTC) were included in the analysis. High HED at the HLA-B genotype was significantly associated with improved overall survival (OS) in patients treated with ICIs ($p < 0.05$). Specifically, in aHCC patients, the median OS was 17.43 (95% confidence interval, 17.43-NE) months in the HLA-B HED^{high} group compared to 7.83 months (95% confidence interval, 4.13-NE) in the HLA-B HED^{low} group ($p < 0.05$). Similarly, in aBTC patients, the median OS was 12.7 (95% confidence interval, 9.07-20.90) months versus 9.8 (95% confidence interval, 6.40-13.5) months, respectively ($p < 0.05$). In contrast, HED at the HLA-B genotype did not exhibit a significant association with progression-free survival. **Conclusions:** This study demonstrates that the evolutionary divergence of the HLA-B genotype may serve as a prognostic biomarker for ICI therapy in hepatobiliary cancers. High HED at HLA-B is associated with improved OS, underscoring the potential role of HLA-I genetic diversity in modulating therapeutic response to ICIs. These findings provide a foundation for further investigations into HLA-mediated mechanisms underlying ICI efficacy in hepatobiliary cancers. More patients will be enrolled to validate the conclusions. Clinical trial information: NCT03892577. Research Sponsor: Beijing Natural Science Foundation; National High Level Hospital Clinical Research Funding; National Ten-thousand Talent Program.

4108 Poster Session

Hepatic arterial infusion chemotherapy plus lenvatinib and PD-1 inhibitors as first-line treatment for hepatocellular carcinoma with high tumor burden and portal vein tumor thrombus. First Author: Jiaxi Liu, The First Hospital of China Medical University, Department of Interventional Radiology, Shenyang, China

Background: Advanced-stage hepatocellular carcinoma (HCC) is usually associated with poor survival outcomes. Rapid tumor control usually benefits long-term outcomes, which could be hardly achieved by solely systematic targeted and immunotherapy in current guidelines. This study aimed to evaluate the efficacy of hepatic arterial infusion chemotherapy (HAIC) combined with lenvatinib and PD-1 inhibitors (HLP) as first-line treatment for HCC patients with high tumor burden and portal vein tumor thrombus (PVTT). **Methods:** This retrospective multicenter study screened advanced HCC patients who received HLP combination therapy as first-line treatment at ten centers from Jan 2021 to Dec 2023. The inclusion criteria included high tumor burden (up to seven criteria out), PVTT, no extrahepatic metastasis, and liver function of Child-Pugh B7 or better. PD-1 inhibitors permitted 3 different products, including Tislelizumab. Tumor response was assessed using both RECIST 1.1 and mRECIST criteria. Survival outcomes were analyzed using Kaplan-Meier methods. The primary endpoint was overall survival (OS), while secondary endpoints comprised progression-free survival (PFS), objective response rate (ORR), disease control rate (DCR), as well as depth of response (DpR) within 3 months. Baseline time point was defined as start of any designed treatment except DpR related survival as 3 months after initial treatment. **Results:** A total of 94 patients were included. The median age was 53 years (range: 31-78) and 87.2% (82/94) were male. In all the patients, 58.5% (55/94) had a largest tumor diameter ≥10 cm, and 80.4% (74/92) had PVTT classified as Vp3 or Vp4. The median follow-up time was 13.3 (8.9-25.2) months, the 12-month OS rate was 75.6% (95% CI: 67.0-85.3), and the 24-month OS rate was 57.6% (95% CI: 46.9-70.7). Median PFS was 9.7 months (95% CI: 8.1-16.0), with 12- and 24-month PFS rates of 46.3% (95% CI: 37.1-57.8) and 32.1% (95% CI: 23.3-44.3), respectively. Based on RECIST 1.1 or mRECIST, the ORR was 42.6% (95% CI: 32.4-53.2) or 70.2% (95% CI: 59.9-70.2), and the DCR was 96.8% (91.0-99.3) or 100% (96.2-100), respectively. Regarding DpR within 3 months, 46.8% (44/94) of the patients had > 25% tumor diameter reduction per RECIST 1.1, while 73.4% (69/94) showed > 25% reduction per mRECIST. In subgroup analyses, DpR was significantly correlated with PFS and OS (see table), while largest tumor diameter, tumor number, and Vp classification had no correlation with survival outcomes. **Conclusions:** Combination of HLP as a first-line treatment for advanced HCC with high tumor burden and PVTT is promising, with high ORR and survival outcomes. DpR might be a predictor for survival. Clinical trial information: NCT06631326. Research Sponsor: None.

Outcomes		DpR≤25%		DpR>25%
PFS	Events/N	37/50		24/44
	Median (m)	6.8 (5.4-10.9)		16.0 (11.0-NR)
	P		0.004	
OS	Events/N	24/50		12/44
	Median (m)	19.2 (12.6-NR)		35.0 (24.5-NR)
	P		0.034	

4109 Poster Session

Molecular characteristics, treatment patterns, and survival outcomes in biliary tract cancers: A retrospective analysis from a high-prevalence region. First Author: Ashish Joshi, MOC Cancer Care & Research Centre, Mumbai, India

Background: Biliary tract cancers (BTC) present significant challenges in management due to their aggressive nature and often late-stage presentation. We present demographic trends, molecular characteristics, treatment patterns, and survival outcomes. **Methods:** This retrospective study included patients diagnosed with BTC between March 2018 and September 2024. Survival analysis was done using the Kaplan-Meier analysis. **Results:** Total of 743 patients were diagnosed with BTC, median age of the cohort was 61 years (IQR 52-69); with F: M ratio being 1.15:1. Distribution according to the stage at presentation was: stage I (n=15, 2%), stage II (n=49,6.6%), Stage III (n=160, 21.5%) and stage IV (n=509, 68.5%). History of gallstones was reported in 183 patients (24.6%). Out of the total cohort, 436 patients (58.7%) had gallbladder cancers (GBCs) while 307 patients (41.3%) had cholangiocarcinoma (CCA), where n=202 (65.8%) were intrahepatic, n=22 (7.2%) were perihilar and n=33 (10.7%) were distal bile duct. Predominant histologic patterns among GBCs were: adenocarcinomas n=331 (75.9%), small cell carcinomas n=13(3%) adenosquamous n=11(2.5%), and others n=81(18.5%). Molecular testing was done in 132 patients (17.8%), out of which 11/132 (8.3%) had HER2 alteration, wherein overexpression was seen in n=3,while amplification was seen in n=8; TP53 mutation was seen in 21/132 (16%), while others alterations were MSI-high (n=2), TMB-high (≥10 mut/Mb) (n=3), PDL1 positive (n=24), FGFR(n=3), IDH (n=2), BRCA2 (n=2). Treatment and survival outcomes were available for 492 patients, surgery was done in 177 patients (35.9%), systemic therapy (adjuvant/palliative) was done in 431 (87.6%) patients while targeted or immunotherapy was used in 99 patients (20.1%). Median Overall survival (mOS) of the cohort was 16.1 months (13.6-18.6) with a median follow-up duration of 28.2 months (23.2 – 33.2). mOS for GBC was 10.8(8.2-13.3) months and CCA was11.6(9.3-14.0) months. mOS for Metastatic BTC was 9.6 months while for Non-metastatic it was 20.4 months($p<0.001$). The median mOS for patients with HER2 mutations, TP53 mutations, and PD-L1 positivity were 23.8 months, 16.6 months, and 10.0 months, respectively (p = 0.165). **Conclusions:** In high-prevalence countries like India, biliary tract cancer (BTC) management is challenged by advanced stage presentation, limited molecular testing and resource constraints. Efforts to enhance molecular testing and treatment access are critical for practicing precision oncology and improving treatment outcomes. Research Sponsor: None.

4110 **Poster Session**

Comparison of outcomes between open and minimally invasive hepatic resections for hepatocellular carcinoma: A retrospective analysis. First Author: Harjeevan Kalra, Independent Researcher, Brampton, ON, Canada

Background: Recent data from the United States indicate that the incidence of hepatocellular carcinoma (HCC) has tripled over the past 40 years, with risk factors like obesity-related fatty liver disease and chronic hepatitis C on the rise. Despite advances in treatment, the five-year survival rate remains low at 14%. Minimally Invasive Surgery (MIS) has garnered popularity in hepato-pancreato-biliary (HPB) procedures, comprising 1 in 13 cases. MIS offers advantages such as shorter hospital stays and reduced morbidity, with better outcomes. However, the safety and efficacy of MIS, specifically for HCC resection, remain underexplored. To address this gap, we conducted this study to evaluate and compare the outcomes of MIS vs. open surgical approaches for HCC resection. **Methods:** The 2016–2022 National Inpatient Sample (NIS) was utilized for this study. Patients with a primary procedural code for hepatic resection, categorized as either open or minimally invasive approaches, were identified. This cohort was further narrowed to include only patients diagnosed with hepatocellular carcinoma (HCC). Differences in common postoperative complications between open and minimally invasive approaches were analyzed. **Results:** We studied 3,595 hepatic resections for HCC, with 87.5% performed as open procedures and 12.5% as minimally invasive surgeries. Both approaches were predominantly conducted in males (70.9% vs. 75.6%, p = 0.041), with open resection patients being younger (mean age 63.94 vs. 66.67, $p < 0.01$). Open resections were associated with higher complication rates, including critical care needs (aOR 6.428, 95% CI 2.606–15.858, $p < 0.001$), sepsis (aOR 3.728, 95% CI 1.508–9.215, p = 0.004), acute kidney injury(AKI) (aOR 2.406, 95% CI 1.714–3.337, $p < 0.001$), bleeding (aOR 2.314, 95% CI 1.838–2.914, $p < 0.001$), and blood transfusion requirements (aOR 4.514, 95% CI 2.661–7.658, $p < 0.001$). Open procedures also resulted in higher mean hospital charges ($180,561 vs. $131,566, $p < 0.01$) and more extended hospital stays (8.5 vs. 5.3 days, $p < 0.01$). Despite these differences, mortality rates between open and minimally invasive approaches were similar (aOR 1.486, 95% CI 0.85–2.595, p = 0.164). **Conclusions:** Our study found that open hepatic resection for HCC is associated with a higher rate of complications, including bleeding, AKI , increased critical care needs, and blood transfusion requirements, compared to minimally invasive surgery. However, mortality rates between the two approaches remain comparable. With the rising incidence of HCC, transitioning toward MIS may provide notable benefits in reducing postoperative morbidity. Since most hepatic resections are still performed using open techniques, further research is necessary to enhance surgical outcomes and explore alternative strategies. Research Sponsor: None.

4111 **Poster Session**

Association of gut microbiota with therapy efficacy and prognosis in biliary tract cancer. First Author: Fen Saj, The University of Texas MD Anderson Cancer Center, Houston, TX

Background: Biliary tract cancers (BTC) are rising in incidence and have poor prognosis. Microbial exposure via gut–liver axis may contribute to their development and progression. We profiled the gut microbiome of patients with BTC and assessed its correlation with chemoimmunotherapy outcome. **Methods:** For this prospective study, we collected baseline stool samples from newly diagnosed patients with BTC treated at a single center. Microbiome profiles were generated using 16S rRNA gene sequencing. Microbial alpha (intrasample variability) and beta (interindividual variability) diversity indices were calculated and correlated with treatment outcome. Taxonomical differential abundance was quantified using MaAsLin2. Statistical analyses included descriptive statistics for demographics, Kaplan-Meier for survival & Spearman's correlation for microbiome-clinical outcome. **Results:** From May 2021 to October 2024, 72 patients were enrolled. Median age was 66 years (range: 29–86) with 43% females. Primary sites included intrahepatic cholangiocarcinoma (CCA) (61%), distal extrahepatic CCA (18%), hilar CCA (11%), gallbladder Ca (3%), and mixed (7%). Stages were I (14%), II (33%), III (46%), IV (7%). 52% underwent surgery (14% upfront/others post neoadjuvant), 74% progressed to stage 4 disease and 67% received immune check point inhibitors. Therapy responses included complete (CR 3%), partial (PR 19%), stable (SD 32%), and progressive (PD 28%). At a median follow-up of 20 mos, mPFS was 14.6 (8.3-NR) mos for entire cohort [8 (5–11) mos for stage 4 patients] and mOS was not reached. Microbiome analysis of stool samples provided by immunotherapy-treated patients (n = 26) suggested that disease control (DCR: CR/PR/SD) correlated with higher alpha diversity (p = 0.063), while progression showed a trend toward lower diversity across all indices. Beta diversity (calculated by Bray-Curtis distances) showed no significant differences by response or progression. Differential abundance analysis using MaAsLin2 identified significant microbial associations (LogFC > 1.5, adjusted $p < 0.25$) with treatment outcomes. DCR associated bacterial genera included *Ruminococcus*, *Subdoligranulum*, *Romboutsia & Collinsella*, while PD correlated with higher abundances of *Streptococcus*, *Eggerthella*, *Paraprevotella & Enterococcus*. Genera such as *Ruminococcus*, *Romboutsia*, *Coprococcus & Christensenellaceae R-7 group* were linked to non-progression, whereas *Parasutterella*, *Streptococcus*, *Prevotella-9 & Monoglobus* were elevated in progressive disease. **Conclusions:** Our preliminary results suggest that gut microbiome should be studied as a multidimensional biomarker for predicting therapy response/prognosis in BTC. Higher microbial alpha diversity may link with better immunotherapy responses, and specific microbial taxa may correlate with treatment outcomes. Research Sponsor: None.

4112 **Poster Session**

CTC landscape during HCC immunotherapy. First Author: Marcos Santiago Figueroa, University of Chicago, Chicago, IL

Background: The treatment of hepatocellular carcinoma (HCC), the third leading cause of global cancer death, has significantly improved with the advent of immune checkpoint inhibitor regimens. Circulating tumor cells (CTCs) contain the precursors of metastasis and can be serially sampled while patients receive therapy. Quantification of CTC dynamics during HCC treatment with immune checkpoint inhibitor therapy may yield early insight into the systemic anticancer response profile. **Methods:** We used a commercially available microfluidic CTC purification methodology followed by quantification of CTCs expressing HCC cell surface markers (EPCAM, ASGR1, GPC3) and PD-L1 from patients receiving immune therapies, prior to cycle 1 and cycle 3 of therapy. We also captured and correlated clinical data, including conventional markers of liver function (Child-Pugh score) and radiographic tumor response for correlation with early changes in CTC number. **Results:** In this pilot study,we collected a total of 29 specimens from 14 participants, 10 of whom provided serial samples. The quantities of CTCs detected was (median:10, range: 1-516); (median:1, range: 0-139) were PD-L1 high,(-median: 8, range: 1-312) were PD-L1 medium, and (median: 3, range: 0-190) were PD-L1 low. There was no clear statistical difference in serial CTC enumeration data while on treatment, although the numbers of CTCs and CTC subsets numerically declined in many participants. **Conclusions:** There was no statistically significant relationship between CTC quantity and subsequent radiographic response. Future studies will involve enrollment of expanded numbers of participants, comparisons with circulating tumor DNA dynamics, and transcriptional profiling of CTCs to further explore these phenomena. Research Sponsor: UCCCC.

4113 **Poster Session**

Deep learning-based contouring of Couinaud segments on CT: Utility for volumetric analysis of future liver remnant. First Author: Tejas Mathai, National Institutes of Health, Bethesda, MD

Background: Hepatocellular carcinoma (HCC) is the most common primary liver tumor, and the liver is a frequent site of metastasis of other cancers. High tumor burden, proximity to hepatic vessels, and other comorbidities render only 30% of patients as candidates for curative treatment: transplantation, resection, or ablation. Surgical resection requires a 20 - 40% future liver remanent (FLR) to avoid post-operative complications. Delineation of the Couinaud segments is essential for volumetric analysis of FLR and targeted localization of tumors during pre-surgical treatment planning. Currently, manual annotation of the Couinaud segments in one CT volume can take two or more hours, which makes it cumbersome, and can benefit from automation. The purpose of this work is to develop an automated Couinaud segmentation tool for fast and accurate FLR estimation. **Methods:** Three CT datasets were used: 1) 161 patients from the public Medical Segmentation Decathlon (MSD) Hepatic Vessels dataset, 2) 43 patients with cirrhosis and metabolic diseases having ascites and splenomegaly imaged at the National Institutes of Health (NIH), and 3) 197 patients in the public TCIA Colorectal Liver Metastasis (CRLM) dataset. FLR annotation in the CRLM dataset was done by an expert radiologist. The Couinaud segments in the MSD and NIH datasets were manually annotated by two physicians using ITK-SNAP. The MSD and NIH datasets were used for training, while the CRLM dataset was reserved for testing. A 3D nnU-Net model was trained with default hyperparameters to outline the Couinaud segments. On the test dataset, the predicted Couinaud segments were overlaid on the FLR annotation, and metrics, such as Dice Similarity Coefficient (DSC), Hausdorff Distance (HD) error (in mm), and volume error (in cc) were calculated. The performance was compared to a previously described 3D U-Net model developed to quantify liver segmental volume ratio (LSVR) in patients with cirrhosis. **Results:** The 3D nnU-Net obtained a DSC of 0.99 ± 0.01 (IQR: 0.991, 0.998), HD error of 0.87 ± 1.83 mm (IQR: 0, 1.02), and volume error of 13.7 ± 28.1 cc (IQR: 3.4, 15.3). In contrast, the LSVR U-Net model attained a DSC of 0.97 ± 0.01 (IQR: 0.972, 0.984), HD error of 9.56 ± 3.61 mm (IQR: 7.14, 11.93), and volume error of 47.9 ± 51.8 cc (IQR: 24.5, 55.4). The 3D nnU-Net model achieved significantly different results for DSC ($p < 0.001$, large effect size 0.86), HD error ($p < 0.001$, large effect size 0.87), and volume error ($p < 0.001$, large effect size 0.91). **Conclusions:** The model showed acceptable generalizability to the external TCIA CRLM dataset. Future work may be directed towards accurate volumetric analysis on patients undergoing portal vein embolization to increase the FLR, and automatic tumor localization on specific Couinaud segments. Research Sponsor: None.

4114 **Poster Session**

AI-driven prediction of post-transplant survival and stratification of HCC recurrence risk. First Author: Junho Song, Pennsylvania State University College of Medicine, Hershey, PA

Background: Traditional selection criteria (e.g., Milan, UCSF) and scoring systems (MELD/PELD) for liver transplant eligibility in hepatocellular carcinoma (HCC) often fail to capture the complex interplay of tumor biology, patient factors, and bridging therapies. Although Milan and UCSF yield similar 1-, 3-, and 5-year survival rates, the debate over expanded criteria highlights the need for refined, individualized risk-stratification tools. **Methods:** We retrospectively analyzed 21,182 HCC patients from the UNOS database to develop deep learning and Cox regression models for overall survival (OS). Models incorporated demographic (e.g., age, race), clinical (e.g., diabetes, MELD differences), and tumor-specific variables (e.g., tumor count, size tiers). Performance was compared to standard MELD-based calculations using 5-fold cross-validation, with primary endpoints of 1-, 3-, and 5-year survival. For recurrence risk, we used 15,801 records to train gradient boosting (XGBoost) and Cox models. Key variables included tumor characteristics (size levels, vascular invasion), recipient factors (insurance type, functional status, initial MELD/PELD), and alpha-fetoprotein (when available). Model performance was evaluated via area under the curve (AUC) and concordance index (c-index); external validation was performed for the recurrence model. **Results:** Cox Regression (time-to-event): Final multivariable models achieved c-indices of 0.611 for OS and 0.601 for progression-free survival (PFS). Stepwise Logistic Regression (mortality): Mean AUCs were 0.664 (1-year), 0.705 (3-year), and 0.758 (5-year). Random Forest Classifier: Slightly higher AUCs than logistic regression (0.663 at 1-year, 0.714 at 3-year, 0.762 at 5-year). Gradient Boosting (recurrence): 1-year recurrence predictions achieved AUC $>$ 0.80, with microvascular invasion emerging as a key risk factor ($p<0.001$). Across approaches, incorporating multiple clinical and tumor-specific factors outperformed MELD-based models, consistently showing improved predictive accuracy. **Conclusions:** Machine learning–based models, including deep learning, random forests, and gradient boosting, offer enhanced risk prediction for post-transplant survival and HCC recurrence beyond traditional scoring criteria. These advanced tools enable more nuanced transplant selection, surveillance, and early intervention strategies, potentially improving long-term outcomes for HCC patients undergoing liver transplantation. Research Sponsor: None.

4115 **Poster Session**

A phase II study of pevonedistat in combination with carboplatin and paclitaxel in advanced intrahepatic cholangiocarcinoma: ECOG-ACRIN EA2187. First Author: Anita Turk, Indiana University Melvin and Bren Simon Comprehensive Cancer Center, Indianapolis, IN

Background: Cholangiocarcinoma is a rare and aggressive malignancy with limited therapeutic options, particularly in advanced stages. Resistance to first-line chemotherapy underscores the urgent need for novel therapeutic strategies. Pevonedistat, a first-in-class NEDD8-activating enzyme inhibitor, demonstrated promising activity in this disease in a phase I trial. This study evaluates pevonedistat alone and in combination with carboplatin and paclitaxel in patients with advanced intrahepatic cholangiocarcinoma (ICC). **Methods:** This was a randomized, non-comparative Phase II trial investigating two treatment arms: pevonedistat monotherapy (Arm A) and pevonedistat combined with carboplatin and paclitaxel (Arm B). Both arms utilized a two-stage minimax design, targeting an objective response rate (ORR) of 30% (null hypothesis: 10%). Eligible patients had unresectable or metastatic ICC with progression after gemcitabine-based therapy. The primary endpoint was ORR per RECIST v1.1. Secondary endpoints included clinical benefit rate (CBR), progression-free survival (PFS), overall survival (OS), and safety. Toxicities were graded using CTCAE v5.0. **Results:** A total of 40 patients were enrolled, with 34 eligible and treated (17 per arm). Median follow-up was 29.3 months. No objective responses were observed in either arm. Stable disease was the best response in 35.3% (n = 12) of patients (11.8% Arm A, 58.8% Arm B). One patient on Arm B achieved stable disease lasting $\geq$24 weeks, corresponding to a CBR of 5.9% (95% CI: 0.1%-28.7%). Median PFS was 1.54 months (Arm A) and 2.92 months (Arm B). Median OS was 4.80 months (Arm A) and 6.54 months (Arm B). Grade 3 or higher toxicities occurred in 44.1% of patients, with higher incidence in Arm B (70.6% vs. 17.6% in Arm A). Most common toxicities included fatigue, cytopenias, febrile neutropenia, nausea/vomiting, among others. Two treatment-related fatalities were reported on Arm B: sepsis and colonic perforation. **Conclusions:** Pevonedistat, alone or in combination with carboplatin and paclitaxel, did not demonstrate sufficient efficacy to warrant further evaluation in advanced ICC. These findings highlight the challenges in treating this aggressive malignancy. Despite the rarity of ICC, the rapid accrual of this study during a global pandemic indicates the potential for continued exploration of novel therapeutic approaches in this disease. Clinical trial information: NCT04175912. Research Sponsor: NCI/NCTN.

4116 **Poster Session**

Whole-genome sequencing of biliary tract cancer: Uncovering the genomic origins of evolutionary trajectories. First Author: Felix Beaudry, Ontario Institute for Cancer Research, Toronto, ON, Canada

Background: Biliary tract cancers (BTC) are rare, highly aggressive malignancies with limited treatment options, leading to consistently poor outcomes. An improved understanding of BTC tumor evolution could inform enhanced screening strategies, identify useful prognostic markers, and discover novel therapeutic targets. **Methods:** We performed whole genome and transcriptome sequencing (WGTS) at high depth ($>$ 80X) on a prospective cohort of BTC tumors. After detecting mutations and mutational signatures, we developed two novel methods for driver identification and evolutionary reconstruction. First, we created new oncogene and tumor suppressor-specific models that integrate copy number profiles, structural variant breakends, and expression changes to distinguish structural drivers from neutral chromosomal rearrangements. Second, we applied population genetics techniques to fit demographic models to tumor allele frequencies across 20 paired primary and metastatic samples. **Results:** We analyzed 130 tumor samples from 110 patients, representing the largest BTC whole-genome cohort to date. We identified hypermutated tumors (50-150 mutations/mb) with distinct etiologies, including mismatch repair deficiency, platinum exposure, tobacco use, and aristolochic acid-related damage, the latter of which was associated with response to immunotherapy. Ourintegrated-driver approach identified an association between selection on *RAD23A* and an increased structural variant load, resulting in a tandem-duplicator-like mutational phenotype. This also revealed an underappreciated impact of *SMAD4* in BTC, which is inactivated through multiple mutation types in 12%. Notably, *BAP1* mutations occurred in 24% of cases, including 4% that were inactivated through deletion of the *BAP1* promoter that lowered transcript expression, a previously undescribed mechanism. By pairing clinical data to the genomics, we observed a co-occurrence of *BAP1* mutations and *FGFR2* fusions in small-duct, mass-forming intrahepatic cholangiocarcinomas. These mutations were mutually exclusive with *TP53* mutations, which were enriched in patients with primary sclerosing cholangitis. Finally, our novel method for subclonal population reconstruction on paired samples illuminated recent tumor evolutionary dynamics and identified an *ARID1B* fusion with a potential role in metastasis. **Conclusions:** This study uncovered novel genomic mechanisms underlying the evolutionary origins of BTC beyond those previously identified with exome and panel sequencing, highlighting the value of WGTS. These results highlight the complex genomic heterogeneity of BTC, with potential implications for precision therapy. Research Sponsor: Ontario Institute for Cancer Research; Princess Margaret Cancer Foundation; Marathon of Hope.

4117 **Poster Session**

Real-world validation of the risk estimation of tumor recurrence after transplant (RETREAT) score: Insights from UNOS data on hepatocellular carcinoma recurrence after liver transplant. First Author: Donghoon Shin, Department of Internal Medicine, MetroWest Medical Center/Tufts University School of Medicine, Framingham, MA

Background: For over two decades, established criteria have guided the selection of liver transplantation (LT) candidates in hepatocellular carcinoma (HCC), yet recurrence remains a significant clinical challenge with limited treatment options. The Risk Estimation of Tumor Recurrence After Transplant (RETREAT) score was developed to address this gap. Further validation is needed to confirm its utility in real-world settings. **Methods:** We conducted a validation study using the United Network for Organ Sharing (UNOS) database to evaluate the predictive performance of the RETREAT score in adult liver transplant recipients with HCC from 2009 to 2024. The analysis included 4,975 patients. Kaplan–Meier survival analysis was performed, and recurrence rates were compared across RETREAT score groups using the log-rank test. The predictive accuracy of the RETREAT score for HCC recurrence was assessed by calculating the concordance index (C-index), area under the ROC curve (AUC) evaluating the model's ability to discriminate between recurrence and non-recurrence events. **Results:** Among the 4,975 liver transplant recipients with hepatocellular carcinoma (HCC), the distribution of the RETREAT score was as follows: 13 patients (0.26%) had a score of 0, 1,713 patients (34.43%) had a score of 1, 1,981 patients (39.81%) had a score of 2, 524 patients (10.53%) had a score of 3, 526 patients (10.57%) had a score of 4, and 218 patients (4.38%) had a score $\geq$5. Kaplan–Meier survival analysis demonstrated a significant association between the RETREAT score and HCC recurrence ($p < 2e\text{-}16$). The hazard ratio for recurrence with each unit increase in the RETREAT score was 1.685 (95% CI: 1.574 to 1.803). The model's predictive accuracy, as assessed by the C-index, was 0.697 (95% CI: 0.668–0.725), and the AUC was 0.684 (95% CI: 0.655–0.713). **Conclusions:** The RETREAT score demonstrates a C-index of 0.697 in predicting HCC recurrence after liver transplantation. This model offers valuable risk stratification but could benefit from further refinement to improve its predictive accuracy. Research Sponsor: None.

4118 **Poster Session**

Conversion therapy for initially unresectable intrahepatic cholangiocarcinoma: A multicenter real-world study. First Author: Xinhao Xiong, Department of Liver Surgery, Sun Yat-Sen University Cancer Center, Guangzhou, China

Background: Currently, studies on conversion therapy for intrahepatic cholangiocarcinoma (ICC) are relatively limited. Effectiveness and optimization strategies of conversion therapy in real world remain unclear. This study aims to analyze the efficacy of locoregional combined with systematic therapy in patients with unresectable ICC, optimizing conversion therapy strategies by retrospectively. **Methods:** In this multicenter retrospective study, patients with unresectable ICC who received hepatic arterial infusion chemotherapy combined with ICIs and target therapy were reviewed. Overall survival (OS), progression-free survival (PFS) , objective response rate (ORR) , disease control rate(DCR)(assessed by mRECIST criteria) and safety were analyzed. **Results:** Between June 2018 to May 2024,a total of 341 patients from six centers were included in this study. The median follow-up time was 21.7 months.Among them, 313 patients with complete imaging evaluations are eligible for efficacy analysis. Of which, 20 patients achieved complete response (CR), 93 patients partial response (PR), 161 patients stable disease (SD), illustrating an ORR of 36.1% and a DCR of 87.5%. Among them, 65 patients successfully underwent conversion surgery, with a median duration of conversion therapy of 4.1 months. Radical resection was achieved in 39 patients within the surgical cohort, and 3 patients demonstrated pathological CR. Systemic therapy regimens with the highest conversion success rates included apatinib plus toripalimab (42.9%), lenvatinib plus tislelizumab (32.4%), and apatinib plus tislelizumab (30.8%). Patients with tumor diameters less than 10 cm and those with unilobar tumor were more likely to achieve successful conversion. After propensity score matching (PSM) to balance baseline characteristics (ratio = 1, caliper = 0.01), the surgical group exhibited better survival outcomes compared to the non-surgical group (not reached vs. 27.2 months, hazard ratio: 0.36, 95% CI: 0.61–0.81, p= 0.001). The median PFS was 13.0 months in the surgical group versus 8.0 months in the non-surgical group (hazard ratio, 0.57; 95% CI, 0.30 to 1.09; p= 0.088).Within the surgical cohort, the 2-year survival rates for patients with palliative surgery and radical resection were 51.3% and 26.9%, respectively (p= 0.051). All patients experienced treatment-related adverse events (TRAEs), but no treatment-related deaths occurred. The incidence of Grade 3-4 TRAEs was 28.6%. **Conclusions:** Locoregional combined with systemic therapy is an effective strategy for conversion treatment. Conversion surgery offers substantial survival benefits, while palliative surgery may also serve as a viable therapeutic option. Research Sponsor: None.

4119 **Poster Session**

Clinico-molecular characteristics and enhanced efficacy of immune checkpoint inhibitors in *TP53*-mutated advanced biliary tract cancer. First Author: Taro Shibuki, Department of Hepatobiliary and Pancreatic Oncology, National Cancer Center Hospital East, Kashiwa, Japan

Background: *TP53* mutations are frequent genetic alterations in cancers and also prevalent in biliary tract cancer (BTC). In non-small cell lung cancer, *TP53* mutations have been reported to enhance immune checkpoint inhibitor (ICI) efficacy and improve outcomes. However, their impact on BTC remains unclear. This study investigated the clinico-molecular characteristics, prognosis, and ICI efficacy in *TP53*-mutated BTC. **Methods:** Patient data were collected from the SCRUM-Japan GOZILA and MONSTAR-SCREEN-1/2 databases (Japan) and the Duke university and Mayo clinic databases (U.S.), which included patients receiving first-line ICI therapy. Comparisons between *TP53* wild-type (WT) and mutation groups were performed in the Japanese cohort. Subsequently, analyses were expanded to include U.S. patients, focusing on comparisons between non-ICI and ICI groups. Tumor Immune Dysfunction and Exclusion (TIDE) scores were calculated using MONSTAR-SCREEN-2 whole transcriptome sequencing (WTS) data to evaluate ICI responsiveness, and gene set enrichment analysis (GSEA) explored pathways associated with *TP53* mutations. **Results:** In the Japanese cohort (n=594), *TP53* mutations were identified in 311 patients (52.4%). *KRAS*, *ERBB2*, *CDKN2A*, and *SMAD4* alterations were more frequent in the *TP53* mutation group, while *IDH1, BAP1*, and *FGFR2* fusions were more common in the WT group. Multivariable analysis showed *TP53* mutations were independent prognostic factors for poor outcomes (progression-free survival [PFS]: HR 1.37, 95% CI: 1.11–1.69, P=0.003; overall survival [OS]: HR 1.36, 95% CI: 1.06–1.75, P=0.017). Incorporating the U.S. cohort (n=625; non-ICI: 548; ICI: 77), no significant differences in overall response rate (ORR) or disease control rate (DCR) were observed in the non-ICI group between the groups. However, in the ICI group, *TP53* mutations tended to show higher ORR (21.1% vs. 38.5%, P=0.16) and DCR (47.4% vs. 66.7%, P=0.14). In the non-ICI group, *TP53* mutations were associated with worse PFS (HR 1.46, median PFS: 7.4 vs. 5.3 months, P$<$0.001), whereas, in the ICI group, no significant difference was observed; however, a trend toward better PFS was seen in the *TP53* mutation group (median PFS: 5.0 vs. 6.4 months, P=0.163). TIDE scores were significantly lower in the *TP53* mutation group, indicating higher ICI responsiveness. GSEA revealed enrichment of oxidative phosphorylation and hypoxia pathways. **Conclusions:** *TP53* mutations are independent prognostic factors for poor outcomes in BTC. However, patients with *TP53* mutations may derive greater benefits from ICIs, underscoring the importance of tailored therapeutic strategies in *TP53*-mutated BTC. Research Sponsor: None.

4120 **Poster Session**

Genomic and outcome analysis of recurrent versus de novo metastatic pancreatic ductal adenocarcinoma (PDAC) receiving systemic therapy: Results from the Australian MoST and CaSP screening programs. First Author: Frank Po-Yen Lin, NHMRC Clinical Trials Centre, The University of Sydney, Sydney, NSW, Australia

Background: The genomic and prognostic characteristics of recurrent (R, from curative surgery) v *de novo* (D) presentation in metastatic PDAC patients (pt) requiring systemic therapy (rx) remain underexplored. We examined the difference in genomic alterations (alts), overall survival (OS), and outcome to matched rx according to disease presentation (DP). **Methods:** The PDAC cohorts from the Australian Molecular Screening and Therapeutics (MoST) and Cancer Screening Programs (CaSP) completed sequencing from 2016 to July 2024 were analysed; archival tissue was sequenced using genomic profiling platforms (mainly TSO500 and FoundationOne CDx). Frequencies of genomic alts were compared between R and D groups; significance was assessed using Chi-square tests with the Benjamini-Hochberg method ($q < 0.05$). OS was calculated from the start of initial rx using Kaplan-Meier method, with hazard ratios (HR) from Cox regression used for comparison. OS outcomes were stratified by matched versus unmatched rx in pts harbouring genomic alts within clinically actionable Tier 1-3 categories per TOPOGRAPH knowledge base criteria. **Results:** 949 pts with PDAC with valid genomic results across both programs were included. The *KRAS* alts were numerically more frequent in D (n = 434/491, 88%, p = 0.02) than R (n = 380/458, 82%) groups. Both *CDKN2A* and *SMAD4* alts were enriched in the D group (*CDKN2A*, D: 248, 51% v R: 157, 34%; *SMAD4*, D: 139, 29% v R: 85, 19%, $p < 0.001$ both). Among the 821 pts who started systemic rx, those with R PDAC (n = 411) showed longer median OS compared to those with D PDAC (n = 410, 18.9 v 13.0 months, mo; HR 0.59, 95% CI 0.49-0.69, $p < 0.001$). Genomic *CDKN2A* alts were associated with worse OS (median 13.4 v 16.5 mo, HR 1.34, 95% CI 1.14-1.58); most favourable prognosis was seen in 267 pts with *CDKN2A* wildtype in the R group (median 22.1 mo, 95% CI 17.4-25.9). After adjusting for both *CDKN2A* and *SMAD4* alts, R group remained associated with a lower risk of death than D group (HR 0.61, 95% CI: 0.51-0.72, $p < 0.001$). Pts who received active matched rx (n = 23) showed longer OS than those who received unmatched rx (n = 314) in both D (30.1 v unmatched 14.0 mo) and R groups (34.6 v 24.1 mo). The prevalence of specific *KRAS* mutations showed no significant differences between D and R groups, including G12D (D: 192, 39% v R: 167, 36%, p = 0.44), G12V (D: 126, 26% v R: 113, 25%, p = 0.78), G12R (D: 59, 12% v R: 50, 11%, p = 0.67), G12C (D: 6, 1% v R: 10, 2%, p = 0.37), and Q61 mutations (D: 37, 8% v R: 26, 6%, p = 0.31). There were no differences in alts in *TP53*, *ARID1A, BRCA1/2,* or other DNA repair pathway genes. **Conclusions:** Genomic and prognostic differences were seen in metastatic PDAC according to presentation, with *CDKN2A* alts enriched in *de novo* cases and associated with poor OS, emphasising the need to consider stratification of DP in trials and observational studies. Research Sponsor: None.

4121 **Poster Session**

First results of an open-label, single arm phase II trial investigating the efficacy and safety of trifluridine/tipiracil combined with irinotecan as a second line therapy in patients with cholangiocarcinoma. First Author: Linde Kehmann, Charité University Medicine Berlin, Berlin, Germany

Background: Cholangiocarcinoma (CCA) is a rare and aggressive malignancy with poor prognosis. Although firstline therapy with gemcitabine, cisplatin and durvalumab has been established based on the TOPAZ-1 trial, treatment options for subsequnt therapies remain limited. The TRITICC study investigated the combination of trifluridine/tipiracil (FTD/TPI) and irinotecan in patients with disease progression after firstline treatment. **Methods:** TRITICC was a phase IIA, interventional, prospective, open-label, non-randomized, exploratory, multicenter, single-arm trial. Adult patients with histologically confirmed, locally advanced or metastatic biliary tract cancer received FTD/TPI (25 mg/m² BSA, BID, orally, days 1–5 of each 14-day cycle) combined with irinotecan (180 mg/m² on day 1 of each cycle). Progression free survival (PFS) was the primary endpoint. Secondary endpoints included the PFS rate at 4 months, median overall survival (OS), objective response rate (ORR), and quality of life. The trial was registered with ClinicalTrials.gov (NCT04059562) and EudraCT (2018-002936-26). **Results:** 28 patients were enrolled across six sites in Germany. The median PFS was 3.1 months (95% CI: 2.0–7.5), with PFS rates of 35% (95% CI: 21%–58%) at 4 months, 30% (95% CI: 17%–54%) at 6 months, and 13% (95% CI: 4.7%–37%) at 12 months. PFS and PFS rates were higher in patients with intrahepatic CCA (iCCA). The OS rates were 74% (95% CI: 59%–93%) at 6 months and 38% (95% CI: 22%–68%) at 12 months. Similar to the PFS rates the OS rates were higher in iCCA. Among 27 evaluable patients, partial responses were observed in 3 patients (11.1%, 2 iCCA, 1 eCCA), stable disease in 11 patients (40.7%, 7 iCCA, 4 eCCA). Thirteen patients (48.1%, 7 iCCA, 6 eCCA) experienced disease progression. Outcomes due to tumor location will have to be examined in higher patient numbers. The most frequently reported adverse events included neutropenia, thrombocytopenia, gastrointestinal symptoms and fatigue. The mean Global Health Status score (EORTC QLQ-C30) declined moderately from 56.2 at screening to 46.4 at the end of treatment. No severe, unmanageable or unexpected toxicities were reported. **Conclusions:** The combination of FTD/TPI and irinotecan demonstrated promising efficacy and manageable safety in CCA patients progressing after first-line gemcitabine-based therapy, aligning with recent findings in comparable populations (e.g., Tella et al.). Further investigations are warranted to validate these results. The NIFTY trial suggested that pegylated irinotecan may enhance efficacy compared to conventional irinotecan, a hypothesis that will be explored in the planned follow-up TRITICC-2 study. The study was funded by Servier Deutschland GmbH and Servier Affaires Médicale. Clinical trial information: NCT04059562. Research Sponsor: None.

4122 **Poster Session**

Sequential or up-front triple combination with durvalumab, tremelimumab, and bevacizumab for patients with unresectable hepatocellular carcinoma (AIO-MONTBLANC): Safety interim analysis. First Author: Najib Ben Khaled, Department of Medicine II, University Hospital, LMU Munich, Munich, Germany

Background: The combination of immune checkpoint inhibitors (ICI) durvalumab (durva) and tremelimumab (treme) has been approved for first-line (1L) therapy for advanced hepatocellular carcinoma (aHCC) and represents an alternative to combined atezolizumab and bevacizumab (bev). The MONTBLANC trial evaluates the efficacy and safety of combined durva, treme and bev in patients (pts) with aHCC (NCT05844046). **Methods:** This investigator-initiated, international, randomized phase 2 trial is the first to investigate the combination of durva, treme and bev. 70 pts with aHCC not amenable to curative treatment or locoregional therapy and preserved (Child-Pugh A) liver function are randomized in a 1:1 ratio to an early escalation arm (A) or triple treatment arm (B). Pts in arm A initially receive durva+treme with the addition of bev upon detection of disease progression or failure to achieving objective radiological response. Pts in arm B receive upfront durva, treme and bev. Durva, treme and bev are given in standard doses. The primary endpoint is overall response rate. Secondary endpoints include overall survival, progression-free survival and safety. We present the data of the second planned safety interim analysis. **Results:** 25 pts (arm A: 14, arm B: 11) were included in this analysis (04/2023 – 08/2024). Patients in arm A had a lower proportion of ECOG 0 (A: 78.6% vs B: 90.9%), higher proportion of Child Pugh A6 (A: 21.4% vs B: 9.1%), BCLC C (A: 78.6% vs B: 63.6%), macrovascular invasion (A: 42.9% vs B: 36.4%) and AFP $\geq$400 ng/mL (A: 42.9% vs B: 18.2%). Most adverse events (AE) were grade (G) 1 or 2. In arm A, there were 17 G3 AE, 1 G4 AE and 4 G5 AE. In arm B, 4 G3 AE and 1 G5 AE occurred. 18 serious AE (SAE) occurred in arm A and 2 SAE in arm B. There was one treatment-related death in arm A (ICI hepatitis) and none in arm B. In the first 6 months on treatment, there were no significant changes in ALBI score, Child Pugh score or ECOG performance status in both arms. **Conclusions:** This planned safety interim analysis did not reveal signals of unmanageable toxicity or deteriorating liver function through the addition of bev to durva/treme in the 1L treatment of pts with aHCC. Clinical trial information: NCT05844046. Research Sponsor: Astra Zeneca.

4123 **Poster Session**

Comparative efficacy of cabozantinib or lenvatinib following atezolizumab plus bevacizumzb in patients with advanced hepatocellular cancer. First Author: Sepideh Mehravar, Cedars-Sinai Medical Center, West Hollywood, CA

Background: Atezolizumab plus bevacizumab is the most commonly utilized first-line therapy for advanced HCC. However, the optimal choice for second-line treatment remains uncertain, particularly between different tyrosine kinase inhibitors including lenvatinib and cabozantinib. This study aims to compare survival outcomes of patients with metastatic HCC who received either lenvatinib or cabozantinib as second-line therapy following frontline treatment with atezolizumab plus bevacizumab. **Methods:** This retrospective cohort study utilized the TriNetX database, a large-scale platform providing access to deidentified electronic medical records from over 130 million patients across 94 healthcare organizations in the United States. The study included patients diagnosed with metastatic HCC (ICD-10 codes: C22, C22.8) who were aged 18 years or older, diagnosed between January 2019 and October 2024, and had received first-line chemotherapy with atezolizumab and bevacizumab. The cohort was divided into two groups: one receiving lenvatinib and the other cabozantinib as second-line therapy. The primary outcome was overall survival (OS), compared between the two treatment groups using 1:1 propensity score matching (PSM) to balance baseline demographics and comorbidities. Kaplan-Meier survival analysis, log-rank tests, and hazard ratios (HR) were employed to assess differences in OS. **Results:** Between January 2019 and October 2024, a total of 552 patients met the study criteria, including 397 patients who received Lenvatinib and 155 patients who received cabozantinib as second-line therapy. Median age was similar in two groups (65.2 vs 65.9 yrs). There were no differences between the two groups with respect to gender, albumin or bilirubin levels. Lenvatinib group had lower proportions of white patients (44.1% vs 55.3%). After PSM (matched on age, race, gender, albumin and bilirubin), the final analysis included 151 patients in each treatment group. Kaplan-Meier survival curves demonstrated no statistically significant difference in OS between the two groups (median OS: 16.6 vs 10.9 months; HR: 0.809; 95%CI: 0.576-1.136; p=0.597). **Conclusions:** This retrospective cohort study found no significant difference in OS in pts with metastatic HCC treated with lenvatinib or cabozantinib as second-line therapy following atezolizumab plus bevacizumab. These findings suggest that both agents may offer comparable survival benefits, highlighting the need for further prospective studies to refine second-line treatment strategies for advanced HCC. Research Sponsor: None.

4124 **Poster Session**

Molecular profile of hepatocellular carcinoma (HCC) in older (OA) versus younger adults (YA) receiving tyrosine kinase inhibitors: Does age matter? First Author: Jay Parekh, UT Health San Antonio, San Antonio, TX

Background: While age is not an independent risk factor for poor outcomes it can have significant influence on outcomes in HCC. The median age of diagnosis is 65 years, and HCC is associated with significant geriatric comorbidities. Further, multi-kinase inhibitors (MKIs) are associated with up to 60% of grade 3-4 toxicities. We aim to analyze survival association with age in HCC and identify molecular markers, associated with survival in older patients with HCC receiving tyrosine kinase inhibitors (TKIs). **Methods:** 1473 HCC specimens with DNA/RNA sequencing were profiled at Caris Life Sciences. The study cohort was stratified based on median age into two groups: OA: age $>$ 65 and YA: age $<$ = 65. Real-world overall survival (OS) information was obtained from insurance claims data, and Kaplan–Meier estimates of OS were calculated from specimen collection to last clinical contact; and MKI time on treatment (TOT) from the initiation to termination of treatment. Hazard ratios (HR) and p-values were calculated using the Cox proportional hazards model and the log-rank test, respectively. **Results:** Median OS (mOS) among patients with OA was 14.8 months(m) vs 17.1m among YA (HR: 1.18, $p < 0.01$). The difference in mOS was even more pronounced among White OA (HR:1.43, $p < 0.0001$) and Asian/Pacific Islanders (HR:1.62, p = 0.084). Interestingly, although not statistically significant, OA was associated with longer mOS in Black/African Americans (HR:0.73, p = 0.082). OA was not associated with MKI-TOT such as sorafenib or cabozantinib. However, OA was associated with a shorter TOT (HR 1.6, $p < 0.01$) on lenvatinib (len). No molecular alterations were statistically significantly different between the two age groups on len. CTNNB1, TP53, CDKN2A mutations and PDL1+ were among the most differentially altered and were more common in OA. DNAJB1-PRKACA fusions were prevalent only in YA (13%, potentially representative of Fibrolamellar HCC), while SLC45A2-AMACR fusions were more prevalent among OA (6.6 vs 1.1%). Multivariate analysis revealed that OA was independently associated with shorter len-TOT (HR 1.6, p 0.01), while CTNNB1 mutations and DNAJB1-PRKACA fusions were independently associated with longer len-TOT (HR 0.4-0.5, both $p < 0.05$). **Conclusions:** OA was associated with differing survival trends between whites and Asian/PI compared to Black/AA. Further, OA was associated with shorter len-TOT, potentially due to anti-angiogenic toxicity. Our limitations include an inability to investigate race-based differences on len-TOT due to small sample sizes (Black/AA: n = 18, Asian/PI: n = 15) and the lack of toxicity and geriatric assessment data. Future studies including race, geriatric assessments and toxicity profiles should be considered to understand survival and tolerability differences. Research Sponsor: None.

4125 **Poster Session**

Development and validation of a prognostic risk score for hepatocellular carcinoma recurrence post–liver transplant: Insights from the UNOS database. First Author: Donghoon Shin, Department of Internal Medicine, MetroWest Medical Center/Tufts University School of Medicine, Framingham, MA

Background: For over two decades, the criteria for liver transplantation (LT) in hepatocellular carcinoma (HCC) have been well-established, yet recurrence remains a major clinical challenge. This recurrence contributes to inferior post-LT survival in HCC patients compared to those without HCC. Prognostic index could serve as a valuable tool to identify patients who may benefit from adjuvant therapies and guide standardized post-LT HCC surveillance, which currently varies across transplant centers. **Methods:** We developed and validated a predictive model using the United Network for Organ Sharing (UNOS) database, analyzing adult liver transplant recipients with hepatocellular carcinoma (HCC) from 2009 to 2024, including 4,970 patients. Univariable analysis identified variables associated with 1-year, 3-year, and 5-year post-transplant HCC recurrence, applying a strict p-value threshold (< 0.01). Significant variables were selected for multivariable logistic regression to build the model. Internal validation was performed for each time point using Receiver Operating Characteristic (ROC) curve analysis and confusion matrix evaluation, with the best-performing model selected based on these metrics. **Results:** The most significant model was derived using 3-year recurrence as the outcome. The final model included the pre-transplant Model for End-Stage Liver Disease (MELD) score (p = 0.02), worst tumor histology grade ($p < 0.001$), and total tumor diameter (p = 0.03). The final logistic regression equation is as follows: $\log(1\text{-}p/p) = -3.9630 - 0.0621 \times$ Initial MELD score + $0.7657 \times$ Worst tumor histology grade + $0.1084 \times$ Total tumor diameter. Internal validation results showed an AUC of 0.761 (95% CI: 0.718 - 0.804), accuracy of 0.769 (95% CI: 0.757 - 0.7807), sensitivity of 77.2%, and specificity of 65.0% for 1-year recurrence. For 3-year recurrence, the model demonstrated an AUC of 0.733 (95% CI: 0.702 - 0.763), accuracy of 0.6696 (95% CI: 0.6563 - 0.6827), sensitivity of 66.7%, and specificity of 70.9%. For 5-year recurrence, the AUC was 0.714 (95% CI: 0.685 - 0.743), with accuracy of 0.655 (95% CI: 0.641 - 0.668), sensitivity of 65.2%, and specificity of 68.6%. **Conclusions:** We have developed and validated a predictive model for HCC recurrence following LT using UNOS data. This model shows promising performance, particularly for predicting 1-year recurrence, and may potentially serve as a useful tool for guiding post-transplant management and surveillance strategies. Research Sponsor: None.

4126 **Poster Session**

Transarterial chemoembolization plus donafenib and immune checkpoint inhibitors for intermediate hepatocellular carcinoma (CHANCE2410): A propensity score matching analysis. First Author: Bin-Yan Zhong, Department of Interventional Radiology, Zhejiang Key Laboratory of Imaging and Interventional Medicine, Zhejiang Cancer Hospital, Hangzhou Institute of Medicine (HIM), Chinese Academy of Sciences, Hangzhou, China

Background: Hepatocellular carcinoma (HCC) has high incidence and mortality, with over 80% of patients diagnosed at intermediate or advanced stages, limiting surgical options and worsening prognosis. Transarterial chemoembolization (TACE) is the standard treatment for intermediate HCC, inducing tumor ischemia and hypoxia, which alters the immune microenvironment and promotes immune activation. Combining TACE with immune checkpoint inhibitors (ICIs) and tyrosine kinase inhibitors (TKIs) has shown promise in enhancing treatment efficacy. Trials like EMERALD-1 and LEAP-012, along with real-world studies, suggest that TACE plus ICIs and TKIs improves progression-free survival (PFS) in intermediate HCC patients compared to TACE monotherapy. Donafenib, an oral TKI, has shown superior overall survival compared to sorafenib, being recommended as first-line treatment for advanced HCC in China. However, large real-world studies on the combination of TACE plus donafenib and ICIs in intermediate HCC are scarce. This study aims to compare the efficacy and safety between the combination therapy and the TACE monotherapy for intermediate HCC in a real-world setting. **Methods:** This nationwide, multicenter, retrospective cohort study included patients with intermediate HCC receiving either combination therapy or TACE monotherapy between January 2021 and May 2024 in China. The primary outcome was PFS. The secondary outcomes included overall survival (OS) rate, objective response rate (ORR) and safety. Tumor response was evaluated according to the mRECIST criteria. 1:1 propensity score matching (PSM) analysis was employed to minimize bias. Cox proportional-hazards regression model was used to analyze factors affecting PFS and OS. **Results:** A total of 364 patients were enrolled, with 192 receiving combination therapy and 172 receiving TACE monotherapy. After PSM, 127 patients from each group were included for analysis. The median PFS were significantly longer in the combination therapy group than it in the TACE monotherapy group (19.6 months [95% CI, 14.9-24.4] *vs.* 15.3 months [95% CI, 12.8-17.8], HR 0.647 [95% CI, 0.464–0.903], $p = 0.010$). The OS rate was higher in the combination therapy group (94.8% *vs.* 83.5%, 1-year OS rate; 76.4% *vs.* 64.8%, 2-year OS rate; HR 0.542 [95% CI, 0.327–0.989], $p = 0.016$). The ORR was also higher in the combination therapy group (78.9% *vs.* 62.5%, $p = 0.002$). Grade 3 or 4 adverse events from any cause were observed at a rate of 12.5% and 5.5% in the combination and monotherapy groups, respectively. Multivariate analysis identified combination therapy as an independent prognostic factor for both longer PFS and OS. **Conclusions:** Compared to TACE monotherapy, TACE plus donafenib and ICIs offers superior OS and PFS, which may be a viable first-line treatment option for intermediate HCC. Research Sponsor: None.

4127 **Poster Session**

Hepatitis B virus reactivation in hepatocellular carcinoma patients undergoing immune checkpoint inhibitor and concurrent antiviral prophylaxis agents: A prospective observational study. First Author: Zhicheng Lai, Department of Hepatobiliary Oncology, Sun Yat-Sen University Cancer Center, State Key Laboratory of Oncology in South China, Collaborative Innovation Center for Cancer Medicine, Guangzhou, China

Background: Immune checkpoint inhibitors (ICIs) have been recommended for the treatment of advanced hepatocellular carcinoma (HCC). However, due to the potential hazard of hepatitis B virus (HBV) reactivation, all ICI-related phase 3 studies had strict restrictions on HBV-DNA load (e.g., $<$ 500IU/ml). Meanwhile, delayed immunotherapy may lead to poor prognosis for patients with high HBV-DNA load. This study aims to compare the HBV reactivation between HCC patients with low or high HBV-DNA load undergoing ICIs and concurrent antiviral prophylaxis agents. **Methods:** This prospective, observational study (NCT04680598) recruited HCC participants who were consecutive hepatitis B surface antigen (HBsAg)-positive and received concurrent antiviral prophylaxis agents and initial ICIs. Participants were divided into low group (HBV-DNA$\leq$500 IU/ml) and high group (HBV-DNA $>$ 500 IU/ml) according to the baseline HBV-DNA level. HCC patients without ICIs from NCT02973685 were also included for analysis. The primary endpoint was the incidence of HBV reactivation. The secondary endpoints included HBV reactivation-associated hepatitis, ICIs disruption, overall survival (OS) and progression-free survival (PFS). **Results:** Between December 25, 2020 and February 23, 2024, a total of 1015 participants were enrolled: 356 in the low group and 659 in the high group. The median age was 51 years (range, 18-84) with majority being males (89.2%) and hepatitis Be antigen (HBeAg) positive (18.1%). Most participants did not receive previous anticancer treatment (84.5%). Participants in the high group were present with significantly higher HBeAg rate (7.0% vs 24.1%, $p< 0.001$), higher ALBI grade 2-3 rate (33.7% vs 49.9%, $p< 0.001$), larger tumor size (9.3 vs 10.9 cm, $p< 0.001$), more advanced BCLC stage C (72.5% vs 83.3%, $p< 0.001$). A significantly higher proportion of participants in the low group had previously received antiviral prophylaxis agents (16.3% vs 3.6%, $p< 0.001$). The HBV reactivation rate was 4.5% in the low group and 6.1% in the high group (relative risk, 1.24; 95% confidence internal [CI], 0.81-1.89, $p= 0.30$). The frequencies of HBV reactivation-associated hepatitis were 1.7% and 2.3%, respectively ($p= 0.53$). There were 92 participants (25.8%) in the low group and 201 participants (30.5%) in the high group had interrupted the ICIs treatment ($p= 0.12$). Compared with high group, the low group had shown significantly longer OS (29.8 vs 18.5 months, $p= 0.0057$) and PFS (9.1 vs 8.3 months, $p= 0.043$). However, participants in the high group had worse liver function and higher tumor burden compared with those in the low group, and the HBV-DNA group was not the independent risk factor for OS or PFS in the multivariable analysis. After included patients from NCT02973685 (n = 278), the HBV reactivation rate was 5.5% and 4.3% in patients treated with or without ICIs (p = 0.43). **Conclusions:** High HBV-DNA did not significantly increase the incidence of HBV reactivation in HCC patients treated with ICIs and concurrent antiviral prophylaxis. Clinical trial information: NCT04680598. Research Sponsor: None.

4128 **Poster Session**

Comparative analysis of ctDNA-MRD and MVI in predicting postoperative recurrence of hepatocellular carcinoma. First Author: Jianan Feng, Second Department of Hepatobiliary Surgery, Zhujiang Hospital of Southern Medical University, Guangzhou, China

Background: Microvascular invasion (MVI) is currently recognized as a pathological feature strongly associated with HCC recurrence. However, its predictive performance in clinical practice remains suboptimal. The detection of minimal residual disease (MRD), which has demonstrated significant prognostic value across multiple cancer types, represents a promising alternative. Therefore, the first goal of this study is to detail the genomic alterations that potentially drive MVI or MRD, the second goal aims to compare their predictive power for postoperative recurrence in early-stage HCC patients. **Methods:** This study profiles the genomic landscape of tumor samples from 126 BCLC 0/A/B stage HCC patients using WES. Patients' longitudinal MRD status was determined through ctDNA detection in peripheral blood at preoperative, 1-, 4-, and 7-month postoperative time points using a tumor-agnostic fixed panel. Postoperative recurrence, confirmed by radiographic imaging, served as the endpoint events for comparing the sensitivity and specificity of two prediction models, with one model based on MVI classification and the other on longitudinal MRD positivity. More patients are currently being recruited and analyzed. **Results:** Among 126 enrolled HCC patients, 71 (56.3%) were classified as MVI-positive (M1/M2), while 55 (43.7%) were MVI-negative (M0). Of the 121 patients with at least one MRD test, longitudinal MRD positivity was observed in 27 patients (22.3%), with 94 patients (77.7%) remaining negative. Both MVI positivity and longitudinal MRD positivity were associated with postoperative recurrence, with longitudinal MRD group showing stronger statistical significance ($p < 0.001$ vs. $p = 0.032$). However, no distinct high-frequency mutation patterns were observed within either the MVI or longitudinal MRD groups. The most frequently altered genes in both groups included TP53, CTNNB1, JAK1, ARID1A, CDKN2A, and AXIN1. Of note, we also developed two prediction models based on MVI classification and longitudinal MRD positivity. The longitudinal MRD-based model demonstrated superior performance, with higher AUROC (0.835 vs. 0.715), PPV (0.357 vs. 0.162), accuracy (0.836 vs. 0.512), and TPR (0.833 vs. 0.786). **Conclusions:** Longitudinal MRD monitoring using a tumor-agnostic fixed panel demonstrates superior predictive performance over MVI classification for postoperative HCC recurrence with higher sensitivity, specificity, and accuracy. The findings highlight the potential of longitudinal MRD monitoring as a more reliable tool for guiding personalized postoperative management in early-stage HCC patients.Moreover, the combination of the two models may potentially offer superior predictive performance for recurrence, which is also a promising direction worthy of further exploration. Research Sponsor: None.

4130 **Poster Session**

Real-world analysis of ctDNA and other biomarkers in patients with curatively resected stage I-III biliary tract cancer. First Author: Maen Abdelrahim, Houston Methodist Neal Cancer Center, Houston, TX

Background: Growing evidence supports the prognostic and predictive value of circulating tumor DNA (ctDNA) detection in gastrointestinal cancers. Building on previous work that demonstrated the feasibility of tumor-informed ctDNA testing in biliary tract cancer (BTC), this study aimed to evaluate ctDNA as a tool for detecting molecular residual disease (MRD) following curative resection and monitor recurrence during surveillance. **Methods:** A retrospective analysis of real-world data was performed on patients (N=171) with stage I-III resectable BTC who underwent ctDNA analysis using a personalized, tumor-informed 16-plex mPCR-NGS assay (Signatera; Natera, Inc.) from July 2020-February 2024. Plasma samples (n=769) were collected pre-operatively, postsurgically (within 2 to 12-weeks; MRD window), and longitudinally until death or last follow-up (surveillance window). The prognostic value of ctDNA was compared to traditional biomarkers such as CA19-9 and CEA. **Results:** A total of 171 patients with stage I-III BTC with a median age of 68 years (range 27-92) were included in this analysis. The median follow-up was 21 months (range: 2-97 months). ctDNA detection rates during the MRD and surveillance windows were 22% (18/83) and 32% (35/109), respectively. On evaluating clinical outcomes, ctDNA-positivity during MRD and surveillance was significantly associated with inferior disease-free survival (DFS) and overall survival (OS). Multivariate analysis confirmed ctDNA-positivity to be the most significant prognostic factor associated with DFS (HR: 10.91, 95%CI: 3.85-30.9, P$<$0.001) when adjusted for other clinicopathologic factors such as BTC subtype or tumor grade. Additionally, other biomarkers such as CA 19-9 and CEA did not predict clinical outcomes at either the MRD or surveillance windows (Table). **Conclusions:** The data show that ctDNA-positivity was associated with poor DFS and OS, both in the post-op and surveillance settings and that ctDNA detection using a personalized, mPCR-NGS assay was superior to current clinical biomarkers. These findings highlight the value of ctDNA monitoring to improve prognostication in BTC. Research Sponsor: None.

Association of biomarkers with clinical outcomes.

Biomarker	MRD	Surveillance
ctDNA	n= 83	n= 109
DFS	HR: 13.0, p $<$ 0.001	HR: 6.1, p $<$ 0.001
OS	HR: 12.0, p $<$ 0.001	HR: 17.8, p = 0.008
CA19-9	n= 53	n= 80
DFS	HR: 0.88, p =0.81	HR: 1.3, p = 0.51
OS	HR: 1.9, p = 0.389	HR: 10.1, p = 0.045
CEA	n= 18	n= 18
DFS	HR: 0.84, p = 0.85	HR: 0.54, p = 0.5
OS	HR: 1.7, p = 0.71	HR: Not evaluable

4131 **Poster Session**

Integration of cfDNA fragmentomics for early biliary tract cancer detection. First Author: Jiwen Wang, Liver Cancer Institute, Zhongshan Hospital, Fudan University, Shanghai, China

Background: Biliary Tract Cancer (BTC) is a highly aggressive malignancy with poor survival outcomes, primarily due to the lack of effective early detection methods and late-stage diagnoses. Current diagnostic tools, including imaging and invasive endoscopic procedures, are limited in their sensitivity and specificity for identifying early-stage disease. This study addresses this critical gap by developing a novel, non-invasive approach for BTC detection using circulating cell-free DNA (cfDNA) fragmentomics features. **Methods:** The study cohort included 163 patients diagnosed with BTC and 165 healthy individuals, divided equally into training and validation cohorts. All participants' plasma samples were collected for a low-depth whole genome sequencing (WGS) process to extract three key cfDNA fragmentomics features: Copy Number Variation (CNV), Fragment Size Distribution (FSD), and Promoter Fragmentation Entropy (PFE). These features were utilized to develop a machine learning model, which was trained and validated through 5-fold cross-validation. An external cohort of 55 patients with benign diseases and 18 Tis/High-grade cases was used to further evaluate the model robustness. **Results:** The stacked ensemble model reached an Area Under the Curve (AUC) of 0.96 in the validation cohort, showing excellent performance in identifying BTC from healthy participants. At an 86% training specificity cutoff, sensitivity achieved 90.91% (95% CI: 81.26% - 96.59%) and specificity 87.88% (95% CI: 77.51% - 94.62%). While PFE performed as a strong single feature with an AUC exceeding 0.92. The model demonstrated its effectiveness in early-stage detection, with the sensitivity increasing from 80% in stage I to 95.65% in stage II. The model surpassed traditional biomarkers (AUC $>$ 95% compared to ~75% for CA19-9) and demonstrated consistent performance across subgroups. External validation revealed 89% sensitivity for early lesions and 89% specificity for benign cases, highlighting its potential for non-invasive early detection of BTC. **Conclusions:** This study demonstrates a reliable and non-invasive strategy for early BTC detection, leveraging cfDNA fragmentomics features and a robust machine learning framework. The model's high accuracy and reproducibility in both internal and external cohorts highlight its potential for clinical implementation, offering a transformative approach for BTC screening. Early diagnosis enabled by this method may significantly improve patient outcomes and survival rates, marking a major advancement in clinical practice. Research Sponsor: Natural Science Foundation of Shanghai; 23ZR1459100, 22ZR1457900; National Natural Science Foundation of China; 82272772,82372832, 82273289; Key Discipline Construction Project of Medicine in Shanghai Xuhui District; SHXHZDXK202304; Research Projects from the Science and Technology Commission of Shanghai Municipality; Grants 21JC1401202; Fujian Provincial Natural Science Foundation of China; 2022J05328.

4132 **Poster Session**

ADJUBIL: A phase II study of immunotherapy with durvalumab and tremelimumab in combination with capecitabine or without capecitabine in adjuvant situation for biliary tract cancer—The IKF/AIO-ADJUBIL trial. First Author: Thorsten Oliver Goetze, Krankenhaus Nordwest GmbH, Institut für Klinisch-Onkologische Forschung (IKF),UCT - Universitäres Centrum für Tumorerkrankungen Frankfurt, Frankfurt Am Main, Germany

Background: Patients (pts) with biliary tract cancer (BTC) still have a poor outcome with limited effective treatment options (only 20% of pts eligible for surgically curative resection, 5-year OS rates $<$ 10%). SOC for BTC is treatment with capecitabine according to the UK BILCAP trial, even though it was formally negative. Based on positive data (TOPAZ-1 and MediTreme trial in BTC, HIMALAYA trial for the STRIDE regimen in HCC), IO combination in the adjuvant setting seems promising. In preclinical studies – particularly in cholangiocarcinoma (CC) –antibody combinations showed stronger and more durable anti-tumor effects than monotherapy, due to synergistic impact on the tumor's immunosuppressive microenvironment. The ADJUBIL trial aimed at evaluating the clinical activity of the anti-PD-L1 antibody durvalumab and the anti-CTLA-4 antibody tremelimumab with or w/o capecitabine in pts with resectable BTC in the adjuvant setting in a pick-the-winner design. The winner of ADJUBIL could be tested in a follow-up phase 2/3 trial against the current SOC capecitabine. **Methods:** In the open-label, multicenter phase II ADJUBIL trial treatment-naïve pts with BTC after curative surgery (R0/R1) were randomized (1:1) to receive either tremelimumab (300 mg, once on D1, cycle 1) plus durvalumab (1500 mg, Q4W; max. 12 months), with (arm A) or w/o (arm B) capecitabine (1250 mg/m2 twice a day on day 1 – 14, Q3W; max. 8 cycles). Primary endpoint was recurrence-free survival at 12 months (RFS@12). The trial design is based on the Simon, Wittes and Ellenberg's Pick-the-winner design [Simon et al., 1985]. **Results:** 40 pts (ECOG 0 or 1) were enrolled in 12 centers in Germany: median age of 64.5 years; 53% males, 30% intra-hepatic CC, 58% extra-hepatic CC, 13% gallbladder. All pts received at least 1 dose of study treatment. The median number of cycles was 7. RFS@12 was 52.4% for arm A and 57.9% for arm B. After a median follow up of 13.8 months, median recurrence free survival was 14.98 (A) and 17.02 months (B). 1y OS rate was 85% (A) and 84% (B). While no new safety/toxicity signs were observed, arm A demonstrated a higher toxicity rate than arm B: 67% of pts having at least one grade $\geq$ 3 AE (A) vs. 53% (B) and 48% of pts having at least one grade $\geq$ 3 treatment related AE (A) vs. 32% (B). **Conclusions:** In the IKF/AIO-ADJUBIL trial, the expected RFS@12 of 56% was demonstrated for the combination of durvalumab / tremelimumab without capecitabine (57.9%), whereas no benefit in terms of RSF@12 was observed with additional capecitabine (52.4%). Together with similar 1y OS rates of 85% (A) and 84% (B) and higher toxicity rates in arm A, this indicates superiority of the combination of durvalumab / tremelimumab without capecitabine in pts with resectable BTC in the adjuvant setting. Clinical trial information: EU CT No.: 2024-511847-24-00. Research Sponsor: AstraZeneca.

4133 **Poster Session**

Novel early-detection model based on cfDNA methylation and fragmentation features for liver cancer. First Author: Xiaobo Wang, Guangxi Medical University Cancer Hospital, Nanning, China

Background: In China, the 5-year survival rate of liver cancer patients is only 14%, far lower than the average of 43.7% for all cancer types. Early diagnosis and treatment are essential for survival. Traditional screening methods like AFP combined with abdominal ultrasound have low sensitivity. Recent studies suggest that blood cell-free DNA (cfDNA) characteristics could be a new screening approach for liver cancer. This study aims to compare methylation and fragmentation signals among liver cancer, hepatitis, cirrhosis patients, and healthy individuals, innovatively using these signals to construct an early-detection model which could improve patient prognosis. **Methods:** From July 2023 to November 2024, 315 blood samples were prospectively collected from five Chinese hospitals. The sample set included 105 liver cancer patients and 210 non-liver cancer controls (33 hepatitis, 30 cirrhosis, 147 healthy). This multi-center, multi-disease-controlled collection provides a robust data basis. Targeted enzymatic methyl sequencing detected over 600,000 methylation sites, enabling precise exploration of liver-cancer-related methylation. Beyond methylation, novel fragmentation features like break-point motifs, end motifs, arm-level count, fragment-size distribution and ratio were obtained. These, combined with methylation data, offer a multi-dimensional view for studying liver cancer pathogenesis and biomarkers. A gradient-boosted tree model, integrating 3840 methylation DMR features and fragmentomic model-predicted probabilities, was built. A nested cross-validation framework was used to optimize the model and ensure result accuracy. **Results:** The model achieved a high AUC of 0.97(95%CI: 0.95-0.99) in liver cancer detection. At 96.2% specificity, the model had a 91.4% sensitivity for overall liver cancer detection, with 83.7% and 95.8% sensitivity for stage I and II respectively. Among 63 patients with hepatitis or cirrhosis, the model accurately predicted negative results in 88.9% of patients. Notably, for patients hard to identify by traditional tumor markers like AFP and DCP, the model showed high detection rates. When AFP $<$ 400 ng/ml, the detection rate was 88.9%, and with concurrent DCP $<$ 40 ng/ml, it reached 87.0%. When AFP $<$ 20 ng/ml, the detection rate was 89.5%, and with DCP $<$ 40 ng/ml simultaneously, the detection rate was 83.3%. **Conclusions:** This study established an early-detection model for liver cancer by leveraging cfDNA methylation and fragmentation signals. The model demonstrated remarkable performance, particularly in detecting liver cancer patients who are difficult to identify through conventional methods. It blazes a new trail for the early detection of liver cancer and could significantly enhance patient prognosis. Research Sponsor: None.

4134 **Poster Session**

The efficacy and safety of donafenib as postoperative adjuvant therapy in patients at high risk of recurrence following radical resection of hepatocellular carcinoma (HCC): A multicenter retrospective study. First Author: Jianhua Rao, Hepatobiliary Center, The First Affiliated Hospital Nanjing Medical University, Nanjing, Jiangsu, China

Background: Hepatectomy is a crucial treatment for long-term survival in patients with HCC; however, the high recurrence rate significantly impacts prognosis. Currently, there is no standard adjuvant therapy for this patient population. This study investigates the efficacy and safety of Donafenib as postoperative adjuvant therapy for patients with a high risk of recurrence after radical resection of HCC. **Methods:** We analyzed the clinicopathological data of HCC patients with a high risk of recurrence after radical resection, recruited from six medical centers between June 2021 and October 2024. High risk was defined by the presence of any of the following criteria: [i] tumor diameter $>$ 5 cm; [ii] multiple lesions of any size; [iii] microvascular invasion (MVI) grade 1 or 2; [iv] lesions complicated by tumor thrombus (TT); and [v] alpha-fetoprotein (AFP)$\geq$200 μg/L. Patients received either Donafenib monotherapy (D) or combination regimens (D+TACE-DT, D+ICI-DI, or D+TACE+ICI-DTI) as adjuvant therapy. We examined the relapse-free survival (RFS), overall survival (OS), and safety according to CTCAE 5.0. **Results:** 199 patients were included in this study, with a median age of 60 years (IQR: 53-67) at the data cut-off in January 2025. The cohort comprised 85.7% males, 83.4% with HBV infection, 87.9% with Child-Pugh A, and 79.4% with ECOG PS 0. Among patients at high risk, 52.3% had multiple high-risk factors, 53.3% had tumors $>$ 5 cm, 27.1% had multiple lesions, 53.3% had MVI grade 1 or 2, 13.6% had TT, and 36.7% had AFP$\geq$200 μg/L. Treatment distribution included 70 patients receiving D therapy, 69 receiving DT therapy, 46 receiving DI therapy, and 14 receiving DTI therapy. At the data cut-off, the median RFS for the overall population was 27.8 months (95%CI:22.3 months -NE), with a one-year RFS rate of 72.9% (95%CI:66.0%-80.5%) and two-years RFS rate of 55.4% (95%CI: 45.6%-67.2%). In subpopulations based on treatment regimens (D, DT, DI, DTI), the median RFS was 24.5 months (95%CI: 20.6 months -NE), 29.2 months (95%CI:22.3 months -NE), 30.0 months (95%CI: 19.0 months -NE), and 20.5 months (95%CI:9.3 months -NE), respectively. The median OS for the overall population and subpopulations had not yet been achieved. Among the overall population, 114 patients (57.3%) experienced treatment-related adverse events (TRAE) of any grade, with an incidence of grade 3 TRAE at 8.0% concluding with rash (5.5%), hand-foot syndrome (2.0%) and thrombocytopenia (0.5%); no patients experienced grade 4 or 5 TRAE. **Conclusions:** These preliminary results showed that donafenib as postoperative adjuvant therapy may effectively reduce the recurrence rate in patients at high risk of recurrence following radical resection of HCC, demonstrating good safety and tolerability. Research Sponsor: None.

4135 **Poster Session**

Effect of the combination of systemic and locoregional therapy on tumor recurrence and survival after liver transplantation for hepatocellular carcinoma (HCC). First Author: Khadyoth Nanneboyina, Methodist Dallas Medical Center, Dallas, TX

Background: Liver Transplantation (LT) results in the best survival in select HCC patients. Patients that do not meet transplant criteria based on tumor burden may require bridging therapies to downstage their disease to become eligible for LT. There is limited data on safety and efficacy of combining systemic therapy with locoregional therapy (LRT) prior to LT. **Methods:** This study was a single-center retrospective outcome analysis of all patients diagnosed with HCC who underwent LT between June 2018 and March 2024 ($n = 104$) with primary endpoints being 1-year post-LT survival and post-LT tumor recurrence. Explant pathology was also examined to assess tumor necrosis, viability, grade, and lymphovascular invasion. Patients were categorized into 2 groups: 1) LRT alone and 2) combination of LRT and systemic therapy. LRT included Transarterial chemoembolization, Radioembolization, Microwave Ablation, and Stereotactic Beam Radiation Therapy. Systemic therapies included Nivolumab + Ipilimumab, Atezolizumab + Bevacizumab, Sorafenib, Lenvatinib, Ramuricumab, and Cabozantinib. Pearson correlation analysis was used. **Results:** 89 patients received LRT alone and 15 patients received combination therapy. The median maximum tumor diameter in the LRT group was 2.4 cm and that of the combination group was 2.5 cm ($p = 0.136$). Patients in the combination therapy group also had a 3.5-fold increase in the average number of tumors, suggesting higher tumor burden. Average time to post-LT tumor recurrence was similar in combination therapy vs. LRT group (496.8 days vs. 546 days; $p = 0.41$). Patients receiving combination therapy had a trend towards better survival however this did not achieve statistical significance ($r = 0.13$, $p = 0.175$). A statistically significant negative correlation existed between not meeting Milan criteria at the time of transplant evaluation and post-transplant tumor recurrence (i.e., rate of post-transplant tumor recurrence increased if the Milan criteria were not satisfied; $r = -0.31$, $p < 0.001$). **Conclusions:** Our results show that combination therapy using systemic options in addition to LRT is an effective downstaging strategy for high-risk HCC patients and may improve post-transplant survival and reduce post-LT tumor recurrence. This preliminary data suggests that combination therapy may have a favorable impact on the time to post-LT tumor recurrence in patients with higher risk tumors. This further attests the strong need for sustainable downstaging pre transplantation. Using the synergistic effect of these modalities may help expand the pool of candidates who can undergo LT, which remains the most effective long term therapy for patients with HCC. We did not find any evidence of increased rejection or opportunistic infections post LT in the combination therapy cohort. Research Sponsor: None.

4136 **Poster Session**

Ultra-sensitive detection of hepatocellular carcinoma (HCC) with methylation signal enrichment of ctDNA and hepatitis B virus (HBV). First Author: Nan Lin, The Third Affiliated Hospital, Sun Yat-sen University, Guangzhou, China

Background: Aberrant methylation patterns in cell-free DNA (cfDNA) have been identified as effective biomarkers for HCC early detection, with circulating tumor DNA (ctDNA) from HCC patients exhibiting distinct methylation signatures. Additionally, HBV infection and the associated methylation alterations are closely linked to the development and progression of both cirrhosis and HCC. In this study, we utilize an ultra-sensitive Methylation Anchor Probe for Low Signal Enrichment (MAPLE) to enrich HCC-related methylation signals in ctDNA, as well as those from HBV genomes. By integrating these signals with a machine learning model, we achieve improved discrimination between HCC patients and non-cancer controls, while reducing false positives in individuals with cirrhosis. **Methods:** Whole blood samples were collected from 246 participants, including 96 HCC patients, 123 healthy controls, and 27 cirrhosis individuals. cfDNA was extracted from plasma, followed by enzymatic conversion and library preparation. Targeted hybrid capture was performed using a custom-designed panel that enriched methylation signals associated with HCC and HBV CpG islands. The final libraries were sequenced using next-generation sequencing (NGS). A machine learning model was developed, incorporating methylation features derived from both the human genomic regions and HBV CpG islands. Participants were randomly divided into training and test sets at a 3:1 ratio, with the training set undergoing 5-fold cross-validation for model optimization. To assess model robustness, 40 resampling iterations were conducted to evaluate performance in distinguishing HCC patients across various stages from non-cancer individuals. **Results:** Among all participants, 39.8% tested positive for HBV. Incorporating methylation features from the HBV genome into the model improved sensitivity for detecting early-stage HCC in HBV-positive individuals and enhanced accuracy in distinguishing early-stage HCC from cirrhosis. Analysis of selected HBV methylation features revealed hypermethylation in HCC patients compared to individuals with cirrhosis and healthy controls. The final machine learning model achieved a specificity of 97.6% (96.2%–97.9%). Sensitivities for detecting HCC across all stages were: I: 76.4% (73.5%–79.4%), II: 94.6% (92.0%–97.3%), III: 99.5% (98.8%–100.0%), and IV: 100.0% (100.0%–100.0%). For distinguishing cirrhosis, the model demonstrated a specificity of 81.9% (77.6%–86.3%). **Conclusions:** Using the ultra-sensitive MAPLE technique, we developed a novel panel that enriches methylation signals from both the human and HBV genomes. This assay significantly improved sensitivity for detecting early-stage HCC. By incorporating HBV genome features, we further enhanced the accuracy of distinguishing early-stage HCC from cirrhosis in HBV-positive individuals. Research Sponsor: Shanghai Xiaohe Medical Laboratory Co., Ltd.

4137 **Poster Session**

Use of artificial intelligence-powered spatial analysis of tumor microenvironment to predict the prognosis in resected gallbladder cancer. First Author: Young Hoon Choi, Department of Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, South Korea

Background: Gallbladder cancer (GBC) is a highly lethal disease with a lack of reliable biomarkers. The tumor microenvironment (TME) is closely associated with prognosis, but its clinical application as a prognostic marker is limited by evaluation challenges. This study assessed the prognostic significance of AI-powered TME analysis in resected GBC patients. **Methods:** A total of 225 GBC patients with an R0 resection were enrolled, and their hematoxylin & eosin (H&E)-stained GBC sections were analyzed using Lunit SCOPE IO, an artificial intelligence (AI)-powered whole-slide image (WSI) analyze, to evaluate TME-related features, including tumor-infiltrating lymphocyte (TIL) density, fibroblast (FB) density, and tertiary lymphoid structure (TLS) counts. Risk stratification was based on TME-related risk factors (low TIL, high FB, low TLS), and survival outcomes were assessed. External validation was conducted using 146 biliary tract cancer patients. **Results:** Overall survival (OS) and disease-free survival (DFS) declined as the number of TME-related risk factors increased. Patients with three risk factors had the poorest outcomes (median OS: 17.7 months [reference]; median DFS: 12.7 months [reference]), followed by those with two risk factors (median OS: 115.9 months, HR = 0.40, 95% CI: 0.19–0.85; median DFS: 57.8 months, HR = 0.37, 95% CI: 0.18–0.74) and one risk factor (median OS: 126.5 months, HR = 0.34, 95% CI: 0.16–0.74; median DFS: 117.2 months, HR = 0.30, 95% CI: 0.15–0.62). Patients with no risk factors had the best survival (median OS: not reached, HR = 0.20, 95% CI: 0.06–0.67; median DFS: not reached, HR = 0.13, 95% CI: 0.04–0.41). External validation confirmed consistent trends across all risk groups. **Conclusions:** AI-powered TME analysis shows promise as a practical tool for identifying TME-related risk factors using H&E-stained WSI, providing valuable prognostic information for resected GBC patients. Research Sponsor: None.

4138 **Poster Session**

Unveiling the role of sodium glucose cotransporter-2 inhibitors in hepatocellular carcinoma patients with cirrhosis: A comparative global cohort study. First Author: Asfand Yar Cheema, Cleveland Clinic Foundation/ Fairview Hospital, Cleveland, OH

Background: Hepatocellular carcinoma (HCC) is a leading cause of cancer-related mortality worldwide, and is often associated with chronic liver disease and cirrhosis. Despite advancements in therapeutic options, the prognosis for HCC patients remains poor. Sodium-glucose cotransporter 2 inhibitors (SGLT2i) exhibit anti-inflammatory, antifibrotic, and anti-carcinogenic properties, potentially influencing cancer biology via metabolic and oxidative stress modulation. Our study aimed to evaluate the impact of SGLT2i on outcomes of HCC patients with underlying cirrhosis using a large global database. **Methods:** We conducted a retrospective, propensity score-matched cohort study using TriNetX Analytics Network database. We compared patients aged $>$ 18 years with HCC and cirrhosis who received SGLT2i to those who did not receive SGLT2i from 1/1/2014 to 1/1/2023 for one year. The study cohort included 1,254 cirrhotic HCC patients on SGLT2i, while the control cohort comprised 40,820 cirrhotic HCC patients not on SGLT2i. Propensity score matching was applied to balance demographics, HCC-directed therapies, comorbidities, laboratory values, and medications. Kaplan-Meier analysis estimated event-free survival and overall survival, with comparisons using log-rank tests. The primary outcomes were all-cause mortality, venous thromboembolism (VTE), and all-cause hospitalization rates. Secondary outcomes included all-cause ICU admissions, ischemic stroke/TIA, acute kidney injury (AKI), and septic shock. **Results:** Propensity score matching adjusted for key characteristics resulted in 1,020 matched pairs for each cohort. Our comparative analysis showed that the SGLT2i group had significantly lower all-cause mortality, with a hazard ratio (HR) of 0.399 (95% confidence interval [CI] 0.314, 0.507). Specific outcomes associated with improvement in the SGLT2i group: VTE (HR 0.607, 95% CI 0.481, 0.765), all-cause hospitalization rates (HR 0.568, 95% CI 0.501, 0.644), all-cause ICU admissions (HR 0.522, 95% CI 0.396, 0.689), ischemic stroke/TIA (HR 0.585, 95% CI 0.389, 0.878), thrombocytopenia (HR 0.578, 95% CI 0.470, 0.711), AKI (HR 0.708, 95% CI 0.588, 0.852), and septic shock (HR 0.528, 95% CI 0.382, 0.728). **Conclusions:** Our study highlights the association of SGLT2i with significant improvements in clinical outcomes for HCC patients with cirrhosis. SGLT2i use was linked to reduced all-cause mortality, VTE, hospitalizations, ICU admissions, and complications such as ischemic stroke/TIA, thrombocytopenia, AKI, and septic shock. These findings suggest SGLT2i may offer therapeutic benefits beyond their cardiovascular and renal effects, potentially influencing cancer biology and systemic complications in this high-risk population. Prospective trials are warranted to validate these findings and assess their safety and efficacy. Research Sponsor: None.

4139 Poster Session

Neoadjuvant transhepatic arterial infusion chemotherapy (HAIC) with FOLFOX regime plus cadonilimab (PD-1/CTLA-4 bispecific antibody) for resectable multinodular CNLC Ib/IIa hepatocellular carcinoma (CAR_Hero study). First Author: Yongguang Wei, First Affiliated Hospital of GuangXi Medical University, Nanning, Guangxi, China

Background: The recurrence rate of hepatocellular carcinoma (HCC) remains high, with multinodular HCC being a well-defined high-risk factor for recurrence. However, standardized neoadjuvant or adjuvant therapies for HCC have yet to be definitively established to effectively improve survival outcomes. **Methods:** In this ongoing single-center, phase 2, open-label, prospective cohort clinical trial, eligible pts were randomly assigned (1:1:1) to three arms (15 pts per arm). Neoadjuvant therapies included: (A) 2 cycles cadonilimab (6mg/kg Q2W); (B) once FOLFOX- HAIC and 2 cycles cadonilimab; (C) once FOLFOX-HAIC. Pts receive scheduled surgery on day 21-28 and postoperative adjuvant HAIC one month after surgery. The primary endpoints were major pathologic response (MPR, defined as ≤50% residual living tumor) and the 1-year recurrence-free survival (RFS) rate. Secondary endpoints included overall response rate (ORR, assessed per RECIST 1.1) and treatment-related adverse events (TRAEs). Additionally, a direct hepatectomy cohort was retrospectively collected as reference data. **Results:** A total of 42 pts were enrolled. Among them, 2 pts withdrew due to their desire to pursue conversion therapy. 38 pts underwent hepatectomy and were included in the efficacy analyses (A: 14pts, B: 14pts, C: 12pts). The median age was 55 years (range: 32-72), with 90.5% being male and 90.5% infected with hepatitis B virus. Arm B had the highest MPR rate of 78.6%, significantly higher than Arms A (35.7%) and C (20.0%) (*P* = 0.011). Additionally, Arm B had the highest ORR (A: 14.3%; B: 40.0%; C: 8.3%), and lowest MVI detection rate (A: 50.0%; B: 21.4%; C: 40.0%). Focal heterogeneity was partially observed. The DCR was 100%. The most common TRAEs were elevated aspartate transaminase (64.3%) and alanine aminotransferase (59.5%). Grade 3-4 TRAEs occurred in 3 pts(hepatic dysfunction and erythema annulare). In Arms A and B, 4 pts experienced a delay in scheduled surgery by 2-4 weeks. The combination of HAIC and cadonilimab did not lead to a significant increase in TRAEs. After propensity score matching, the direct hepatectomy cohort was screened. Kaplan-Meier analysis revealed that the neoadjuvant cohort had a longer recurrence-free survival (RFS) time compared to the direct hepatectomy cohort (median RFS not reached *vs.* 24.7 months; *P* = 0.0048) and a lower MVI detection rate (36.8% vs. 52.6%). **Conclusions:** Neoadjuvant FOLFOX-HAIC combined with cadonilimab had a considerable antitumor activity, and a manageable safety for the resectable multinodular HCC. It brought the fewer MVIs of tumor and a better RFS. Clinical trial information: ChiCTR3000033692. Research Sponsor: None.

4140 Poster Session

Prognostic significance of pathological response in unresectable hepatocellular carcinoma treated with immune checkpoint inhibitor-based conversion therapy. First Author: Wen-Jing Zheng, Department of Liver Surgery & Transplantation, Liver Cancer Institute, Zhongshan Hospital, Fudan University, Shanghai, China

Background: Immune checkpoint inhibitor (ICI)-based conversion treatment is increasingly utilized for patients with initially unresectable hepatocellular carcinoma (HCC). However, standardized histopathologic markers for assessing treatment response and predicting survival outcomes remain inadequately defined. **Methods:** This retrospective study analyzed 225 HCC patients who underwent conversion treatment followed by curative resection. The residual viable tumor percentage (RVT%) was calculated as the proportion of RVT surface area to the total tumor bed area. Kaplan-Meier and Cox regression analyses were used to evaluate the relationship between RVT% and recurrence-free survival (RFS) as well as overall survival (OS). **Results:** Complete pathologic response (CPR), defined as 0% RVT, was achieved in 60 patients (26.7%) and was strongly associated with improved survival outcomes. Patients with CPR exhibited significantly better RFS (HR: 0.23, 95% confidence interval [CI]: 0.13–0.41, $p < 0.001$) and OS (HR: 0.17, 95% CI: 0.05–0.56, p = 0.003) compared to non-CPR patients. Multivariate analysis confirmed non-CPR as an independent risk factor for both RFS (HR: 3.67, 95% CI: 1.94–6.96, $p < 0.001$) and OS (HR: 4.43, 95% CI: 1.21–16.18, p = 0.022). Major pathologic response (MPR), defined as RVT% ≤ 10%, was observed in 91 patients (40.4%) and was also significantly associated with improved RFS and OS (all $p < 0.05$). Stratification by RVT% thresholds revealed a stepwise association between decreasing RVT% and improved survival outcomes. RVT% ≤ 30% demonstrated significant predictive power for both RFS (HR: 0.48, 95% CI: 0.30–0.75, p = 0.001) and OS (HR: 0.60, 95% CI: 0.31–1.16, p = 0.020). Notably, patients with CPR achieved a two-year survival rate of 96.7%, compared to 86.1% in non-CPR patients. Despite the high radiological response rate (CR+PR, 92.4%), substantial discrepancies were observed between radiological and pathological assessments, and 56.7% of patients who achieved pathological complete response (CPR) did not exhibit radiological complete response (CR). Kaplan-Meier analysis showed no significant differences in RFS or OS among three regimens: anti-PD-1 monotherapy (n = 25, 11.1%), anti-PD-1/PD-L1 plus anti-VEGF (n = 21, 9.3%), and anti-PD-1 plus TKI (n = 179, 79.6%). Transarterial chemoembolization (TACE) did not significantly increase the proportion of patients achieving CPR but notably enhanced the proportion of patients with RVT% ≤ 30%. **Conclusions:** Both CPR and MPR are robust prognostic markers of RFS and OS in HCC patients undergoing ICI-based conversion treatment. The superior sensitivity of pathological evaluation underscores its advantage over radiological assessment in accurately reflecting treatment outcomes. Research Sponsor: National Natural Science Foundation of China; (82341027 and 82072715).

4141 Poster Session

Comparison outcome of transarterial chemoembolization combined with immune checkpoint inhibitors plus bevacizumab or lenvatinib as first-line therapy for advanced hepatocellular carcinoma. First Author: Ningning Zhang, Department of Hepatobiliary Oncology, Liver Cancer Center, Tianjin Medical University Cancer Institute and Hospital, National Clinical Research Center for Cancer, Key Laboratory of Cancer Prevention and Therapy, Tianjin Medical University, Tianjin, China

Background: Transarterial chemoembolization (TACE) combined with immunotherapy and anti-angiogenic therapy for advanced hepatocellular carcinoma (HCC) presents a promising first-line treatment option. **Methods:** We assessed overall survival (OS), progression-free survival (PFS), objective response rate, and adverse events between the TACE-ICI-Len group (n=160) and the TACE-ICI-Bev group (n=216) as first-line therapy for advanced HCC. Inverse probability of treatment weighting was employed to minimize bias. Efficacy was evaluated using RECIST 1.1 and mRECIST criteria. **Results:** The TACE-ICI-Bev group demonstrated significantly improved OS and PFS compared to the TACE-ICI-Len group, especially across BCLC-B and BCLC-C stages (Total: mOS 22.8 vs. 15.4 months, $p<0.001$; mPFS 12.4 vs. 8.3 months, $p<0.001$; BCLC-B: mOS 23.3 vs. 16.6 months, p=0.005; mPFS 14.0 vs. 8.2 months, $p<0.0001$; BCLC-C: mOS 22.3 vs. 15.1 months, p=0.002; mPFS 11.0 vs. 8.0 months, $p<0.001$). Within the TACE-Bev-Ate subgroup, OS and PFS were further enhanced (Total: mOS 26.3 months; mPFS 13.8 months; BCLC-B: mOS 27.7 months; mPFS 16.7 months; BCLC-C: mOS 24.2 months; mPFS 12.6 months). The incidence of gastrointestinal bleeding (GB) was significantly higher in the TACE-ICI-Bev group compared to the TACE-ICI-Len group (13.8% vs. 6.2%, $p<0.001$). Notably, GIB was significantly more frequent in patients with portal hypertension (PHT) compared to those without, in both the TACE-ICI-Bev group (30.9% vs. 6.6%, $p<0.001$) and the TACE-ICI-Len group (20.2% vs. 0%, $p<0.001$). **Conclusions:** TACE-ICI-Bev demonstrated superior OS and PFS compared to TACE-ICI-Len as first-line treatment for advanced HCC, with an acceptable safety. Management of PHT in patients with advanced HCC is critical to optimizing patient outcomes. Research Sponsor: None.

Patient baseline characteristics before and after applying IPTW.

Variable	Before IPTW			After IPTW			
	TACE-ICI-Bev	TACE-ICI-Len	p	TACE-ICI-Bev	TACE-ICI-Len	p
n	N=216	N=160		N=223.64	N=153.48	
Age (mean (SD))	59.21 (9.81)	57.19 (10.81)	0.059	57.59 (10.00)	57.23 (10.42)	0.780
Sex (%)			0.358			0.784
Female	37 (17.1)	21 (13.1)		33.1 (14.8)	24.6 (16.0)	
Male	179 (82.9)	139 (86.9)		190.6 (85.2)	128.9 (84.0)	
Hypertension (%)			0.46			0.928
No	152 (70.4)	106 (66.2)		150.8 (67.4)	104.3 (67.9)	
Yes	64 (29.6)	54 (33.8)		72.9 (32.6)	49.2 (32.1)	
DM (%)			0.176			0.981
No	147 (68.1)	120 (75.0)		164.3 (73.5)	112.5 (73.3)	
Yes	69 (31.9)	40 (25.0)		59.4 (26.5)	40.9 (26.7)	
ECOG_PS (%)			<0.001			0.888
0	77 (35.6)	123 (76.9)		123.4 (55.2)	86.1 (56.1)	
1	139 (64.4)	37 (23.1)		100.2 (44.8)	67.4 (43.9)	
TACE_number (%)			0.011			0.94
1~2	151 (69.9)	131 (81.9)		169.4 (75.7)	115.6 (75.3)	
>=3	65 (30.1)	29 (18.1)		54.3 (24.3)	37.9 (24.7)	
Child_Pugh_score (%)			0.125			0.629
<=6	117 (54.2)	73 (45.6)		109.7 (49.1)	70.6 (46.0)	
>6	99 (45.8)	87 (54.4)		113.9 (50.9)	82.9 (54.0)	
ALBI_grade (%)			0.367			0.536
I	94 (43.5)	78 (48.8)		102.7 (45.9)	64.6 (42.1)	
II-III	122 (56.5)	82 (51.2)		120.9 (54.1)	88.9 (57.9)	
BCLC_stage (%)			0.451			0.51
B	85 (39.4)	56 (35.0)		82.9 (37.1)	50.9 (33.1)	
C	131 (60.6)	104 (65.0)		140.7 (62.9)	102.6 (66.9)	
Lymphatic_metastasis (%)			0.001			0.845
No	126 (58.3)	65 (40.6)		107.1 (47.9)	75.4 (49.1)	
Yes	90 (41.7)	95 (59.4)		116.6 (52.1)	78.1 (50.9)	
Extrahepatic_metastasis (%)			0.11			0.536
No	179 (82.9)	121 (75.6)		172.1 (77.0)	123.2 (80.3)	
Yes	37 (17.1)	39 (24.4)		51.5 (23.0)	30.3 (19.7)	
Ascites (%)			0.298			0.35
No	146 (67.6)	99 (61.9)		150.5 (67.3)	94.8 (61.8)	
Yes	70 (32.4)	61 (38.1)		73.1 (32.7)	58.7 (38.2)	
Cirrhosis (%)			0.433			0.47
No	46 (21.3)	28 (17.5)		40.6 (18.2)	23.4 (15.2)	
Yes	170 (78.7)	132 (82.5)		183.0 (81.8)	130.1 (84.8)	
PHT (%)			0.425			0.698
No	106 (49.1)	71 (44.4)		111.6 (49.9)	72.8 (47.4)	
Yes	110 (50.9)	89 (55.6)		112.1 (50.1)	80.7 (52.6)	
Etiology_(%)			0.113			0.378
No/other	35(16.2)	16(10)		33.64 (12)	22.18 (14.6)	
HBV	181(83.8)	144(90)		190 (88)	131 (85.4)	
PVTT_classification_vp (%)			0.367			0.962
No	122 (56.5)	82 (51.2)		123.2 (55.1)	85.0 (55.4)	
VP1-VP4	94 (43.5)	78 (48.8)		100.5 (44.9)	68.5 (44.6)	
AFP_400 (%)			0.266			0.979
<=400	119 (55.1)	78 (48.8)		112.8 (50.4)	77.1 (50.3)	
>400	97 (44.9)	82 (51.2)		110.9 (49.6)	76.3 (49.7)	
Number_of_tumor (%)			0.979			0.678
<=3	62 (28.7)	47 (29.4)		66.0 (29.5)	41.7 (27.2)	
>3	154 (71.3)	113 (70.6)		157.6 (70.5)	111.7 (72.8)	
HCC_diameter_5 (%)			0.823			0.833
<5	60 (27.8)	47 (29.4)		65.8 (29.4)	47.1 (30.7)	
>=5	156 (72.2)	113 (70.6)		157.8 (70.6)	106.4 (69.3)	
NLR_grade (%)			0.902			0.884
<2.81	120 (55.6)	87 (54.4)		126.0 (56.4)	85.1 (55.5)	
>=2.81	96 (44.4)	73 (45.6)		97.6 (43.6)	68.4 (44.5)	
PLT (%)			0.082			0.901
<150	122 (56.5)	75 (46.9)		112.7 (50.4)	76.2 (49.6)	
>=150	94 (43.5)	85 (53.1)		110.9 (49.6)	77.3 (50.4)	

4142 Poster Session

Association of differential expression of genes with survival and relapse in patients treated on the BILCAP clinical trial: Gene expression identification and response to adjuvant chemotherapy in early-stage biliary tract cancer. First Author: Valerie Elizabeth Crolley, UCL-University College London (United Kingdom), London, United Kingdom

Background: Adjuvant capecitabine is standard of care based on the results of the BILCAP clinical trial, comparing adjuvant capecitabine with observation for early-stage biliary tract cancer (BTC). Translational work on data from BILCAP aims to identify differentially expressed genes in patients whose tumours relapsed or who died from their cancer, as there are currently no validated biomarkers to predict the risk of relapse or death or response to adjuvant chemotherapy in early-stage BTC. **Methods:** Bulk RNA sequencing (RNAseq) was performed on archived fixed formalin samples from consented BILCAP patients. Extracted RNAseq data was quantified using salmon, before undergoing differential gene expression (DGE) using DESeq2 to identify differentially expressed genes in patients who died or whose tumours relapsed, compared to those or survived or had no relapse, accounting for batch effect, different anatomical subtypes and adjuvant treatment. Tumour anatomical subtype was highly associated ($p < 0.05$) with PC2 during principal component analysis and was included as a co-variate during analysis. **Results:** 200 patient samples were analysed; 104 / 200 (52%) patients received chemotherapy while 96 had observation. 142 / 200 (71%) tumours relapsed and 142 / 200 (71%) patients died by the time of data cut off. DGE analysis identified 146 significantly ($p < 0.01$) upregulated genes in patients who died, including PRSS2, AMY2A, SPINK1, CTRC and CELA2A, with significantly ($p < 0.01$) downregulated genes including HP, PHF14, FLI1, NAV3 and NOVA1. 118 genes were significantly ($p < 0.01$) upregulated through DGE analysis in patients died or relapsed, including PAX5, FAM188B, NET1, DEK and WDR1 with significantly ($p < 0.01$) downregulated genes including RQCD1, CPA1, FLI1, NAV3 and NOVA1. 41 genes were significantly ($p < 0.01$) upregulated in both death and relapse, including PAX5, TLK1, ALB, HEATR3 and RAB11FIP4. 171 genes were significantly ($p < 0.01$) up regulated in patients who died or had their tumours relapse after adjuvant chemotherapy and not in patients undergoing observation, which included THBS1, FAM65B, UBE2W, RPLP0P2 and NPM1, and 66 genes were significantly ($p < 0.01$) downregulated, which included RP11-521B24.3, FLI1, CACNA1A, KCNH6 and MKKS. Gene ontology enrichment analysis identified the upregulated genes as being associated with cytoplasmic translation and the synthesis of both intra- and extracellular RNA and protein complexes. **Conclusions:** Differential gene expression of the BILCAP cohort identified genes associated with cancer relapse and death, including genes associated with a lack of response to adjuvant chemotherapy. Research Sponsor: Incyte.

4143 **Poster Session**

Comparative analysis of stereotactic body radiotherapy (SBRT) vs. SBRT with bridge therapies for hepatocellular carcinoma patients awaiting liver transplantation: A multi-center study (2010-2020). First Author: Teja Sureddi, Virtua Our Lady of Lourdes, Camden, NJ

Background: Locoregional therapies, including SBRT, are essential in managing hepatocellular carcinoma (HCC) patients awaiting liver transplantation. This study evaluates outcomes of SBRT alone versus SBRT combined with other bridge therapies over a 5-year follow-up. **Methods:** Data from the TriNetX database (2010–2020) were used to compare two matched cohorts: patients receiving SBRT alone and those receiving SBRT with additional bridge therapies, including transarterial chemoembolization (TACE) and radiofrequency ablation (RFA). Patients included were those meeting liver transplant criteria and classified as AJCC Stage I or II. **Results:** Before matching, the cohorts included 185 patients in the SBRT Alone group and 363 in the SBRT with Other Bridge Therapies group, with significant differences in ethnicity (48.11% vs. 57.3%, p=0.0411) and race (40.54% unknown vs. 31.68%, p=0.0393). After matching (153 patients per group), all variables were balanced, including age (69.4 $\pm$ 8.58 vs. 69.1 $\pm$ 8.09, p=0.9039) and ethnicity (50.98% vs. 45.75%, p=0.3601). Theoverall survival rate at 5-year follow-up was 61.53% in the SBRT alone group and 62.02% in the SBRT with other therapies group. There was no significant difference between the groups (HR: 0.958, p=0.8417). In the secondary analysis. For acute hepatic failure, the risk was 22.73% for SBRT Alone versus 25.64% for SBRT with Other Bridge Therapies (RR: 0.886, 95% CI: 0.413–1.901, p=0.7567). The risk of decompensated liver disease was 37.74% versus 40% (RR: 0.909, 95% CI: 0.593–1.501, p=0.8054). Procedure-related complications occurred in 11.61% of the SBRT Alone group compared to 12.12% in the other group (RR: 0.958, 95% CI: 0.482–1.904, p=0.9016). Portal vein thrombosis was more frequent in the SBRT Alone group at 12% versus 7.87% (RR: 1.524, 95% CI: 0.712–3.262, p=0.2733). The risk of major adverse cardiovascular events (MACEs) was 24.75% versus 22.12% (RR: 1.158, 95% CI: 0.607–2.213, p=0.6558). Finally, kidney outcomes (acute kidney injury, CKD, ESRD) were similar, with risks of 62.75% and 63.40% (RR: 0.99, 95% CI: 0.834–1.175, p=0.9057). These results suggest no statistically significant differences in the risk of adverse outcomes between the two groups. **Conclusions:** SBRT alone and SBRT with bridge therapies provide comparable long-term survival outcomes in HCC patients awaiting liver transplantation, with differences in specific complications warranting further study. Research Sponsor: None.

4144 **Poster Session**

Impact of radionuclide therapy on survival outcomes for de novo metastatic gastroenteropancreatic neuroendocrine tumors: A population-based cohort study. First Author: Zhiqiao Liu, The Affiliated Hospital of Southwest Medical University, Luzhou, Sichuan, China

Background: De novo metastatic gastroenteropancreatic neuroendocrine tumors (dmGEP-NETs) are difficult to treat without the option of radical surgery. The aim of this study was to investigate the survival outcomes of radionuclide therapy. **Methods:** Patients diagnosed with dmGEP-NETs from the Surveillance, Epidemiology, and End Results (SEER)-17 registry database (2000–2021) were included in this study. The impact of radionuclide therapy on overall survival (OS) and cancer-specific survival (CSS) was assessed using univariate Kaplan-Meier method and multivariate Cox regression analysis. **Results:** From 2010 to 2021, a total of 9657 patients at diagnosis years with dmGEP-NETs were determined from the SEER database. On the univariate analysis, patients with dmGEP-NETs who received radionuclide therapy significantly obtained better OS (5-year rate: 55.6% vs. 37.9%; p $<$0.001) and CSS (5-year rate: 58.2% vs. 44.2%; p $<$0.001) than patients without radionuclide therapy. Finally, the significant clinical factors associated with OS and CSS were included into multivariate Cox regression analysis to investigate the independent prognostic value of radionuclide therapy. The results showed that radionuclide therapy was an independent prognostic factor for OS (hazard ratio [HR], 0.530; 95% confidence interval [CI], 0.348-0.808; p=0.003) and CSS (HR, 0.508; 95%CI, 0.319-0.808; p=0.004) in patients diagnosed with dmGEP-NETs. Besides, radionuclide therapy was associated with better OS (p $<$0.001) and CSS (p $<$0.001) compared to beam radiation. **Conclusions:** Radionuclide therapy was associated with improved survival in patients with de novo metastatic gastroenteropancreatic neuroendocrine tumors. Research Sponsor: Research Launch Fund of Southwest Medical University Affiliated Hospital; 24092.

4145 **Poster Session**

A phase II study of lenvatinib plus everolimus in advanced extra-pancreatic neuroendocrine tumors (epNETs): Updated results and real-world comparison. First Author: Guglielmo Vetere, Department of Gastrointestinal Medical Oncology, The University of Texas MD Anderson Cancer Center, Houston, TX

Background: Advanced epNETs are rare malignancies with limited treatment options beyond somatostatin analogs, peptide receptor radionuclide therapy, and Everolimus (E). Preclinical evidence suggests that dual blockade of VEGF and FGF is an effective anti-angiogenic strategy and that concomitant inhibition of the mTOR pathway may be further synergistic. Lenvatinib (L), a multi-target tyrosine kinase inhibitor, suppresses VEGFR, FGFR, and other angiogenic pathways, while E targets the mTOR pathway. Their combination may synergistically impair angiogenesis and tumor growth. **Methods:** This open-label, single-center, phase II study evaluated L + E in patients (pts) with advanced, progressive, well-differentiated (a/p w-d) epNETs. The primary endpoint was objective response rate (ORR). Secondary endpoints were progression-free survival (PFS) and safety. Following a 2-stage design with H0: ORR $<$ 5% and H1: ORR $\geq$ 20%, up to 32 pts were needed for type I & II error = 10%. In a post-hoc analysis, a real-world cohort of 2:1 matched a/p w-d epNET pts receiving E alone served as a historical comparator. Differences in ORR were assessed using univariable and multivariable logistic regression while those in terms of PFS were analyzed with propensity score-based inverse probability of treatment weighting (IPTW)-adjusted Cox proportional hazards regression and Kaplan-Meier method. **Results:** 32 pts were enrolled. The starting dose regimen was L 18 mg + E 5 mg p.o. daily with L being reduced to 14 mg p.o. daily after the first 3 pts experienced Grade 3 adverse events (AEs). Median age was 59 years (range 33 – 76), and 59% were male. Primary tumor sites included small bowel (59%), lung & thymus (16%), unknown (16%), and colorectal (9%) with the majority being G2 (69%). Median number of prior therapies was 2 (range 0 – 3) while 11 pts had carcinoid syndrome. The study met its primary endpoint: L + E achieved an ORR of 43.8% (6.3% unconfirmed), which was significantly higher than that observed with E alone (3.1%; OR 24.50, 95% CI 5.09 – 117.94, $p < 0.001$). This finding was supported by the multivariable analysis (OR 20.43, 95% CI 3.93 – 106.13, $p < 0.001$). After propensity score-based IPTW adjustment, a trend toward longer PFS favoring L + E (16.0 months [95% CI 13.0 – 23.6] *vs* 11.3 months [95% CI 8.6 – 24.3]; HR 0.88 [95% CI 0.51 – 1.52], $p = 0.647$) was observed. On trial, 23 Grade 3 AEs (11 after L dose reduction) were noted with elevated LFTs (8), hypertension (6) and thrombocytopenia (4) being the most frequent while one Grade 4 AE (hypertriglyceridemia) was reported. **Conclusions:** L + E demonstrated markedly superior ORR and a trend toward prolonged PFS compared to E alone with a manageable safety profile. These findings highlight its potential as a therapeutic option for a/p w-d epNETs and warrant further investigation in randomized trials. Clinical trial information: NCT03950609. Research Sponsor: MD Anderson Cancer Center; Jack T. and Lillian S. Clift Fellowship; Eisai Co., Ltd.

4146 **Poster Session**

Landscape of functional DLL3 expression in gastroenteropancreatic neuroendocrine neoplasms (GEP NENs). First Author: Rohit Thummalapalli, Memorial Sloan Kettering Cancer Center, New York, NY

Background: Delta-like ligand 3 (DLL3) is an emerging target in multiple neuroendocrine cancers including small cell lung cancer but remains underexplored in GEP NENs. With the ongoing development of multiple classes of therapeutics against DLL3, there is a need to understand the landscape of functional DLL3 expression in GEP NENs. **Methods:** DLL3 immunohistochemistry (IHC) was completed on available tumor samples from patients (pts) with GEP poorly differentiated neuroendocrine carcinomas (GEP NECs) and grade 3 well differentiated pancreatic NETs (G3 WD PanNETs) treated between 2018-2024 and a tissue microarray of resected G1-G2 WD PanNETs (185 samples total). DLL3 positivity (+) was defined as $\geq$ 5% weak (1+) IHC staining. H-scores were calculated by combining % of + tumor cells and degree of staining (1, 2, 3+), ranging from 0-300. Correlations between DLL3 status and clinicopathologic features and outcomes were analyzed. Among selected pts with DLL3 IHC+ GEP NENs, DLL3 immunoPET imaging using the diagnostic tracer [^{89}Zr]Zr-DFO-SC16.56 was completed to evaluate functional expression. **Results:** Among GEP NECs overall, 50/69 were DLL3+ (72%; median H-score 50, interquartile range [IQR] 0-160, range 0-300), including 13/16 esophagogastric (median 45), 11/13 pancreatic (median 60), 7/11 hepatobiliary (median 120), 16/26 colorectal (median 32.5), and 3/3 NECs of other/unknown origin (median 60), with DLL3 expression higher in small cell vs large cell histology (median 120 vs 15, $P = 0.011$). Among GEP NECs, there was no association between DLL3+ and individual genomic alterations, PFS to 1L platinum-based therapy (median 4.6 mo vs 4.7 mo in DLL3-negative [-], $P = 0.435$), or OS from diagnosis of advanced disease (median 15.5 vs 12.2 mo in DLL3-, $P = 0.629$). Among WD PanNETs, DLL3 expression was detected in 3/46 (7%) G1, 1/23 (4%) G2, and 19/47 (40%) G3 tumors, with median Ki67 higher among DLL3+ vs DLL3- tumors overall (42% vs 6%, $P < 0.001$) and within G3 WD PanNETs alone (48% vs 30%, $P = 0.009$). Among pts with advanced G3 WD PanNETs, DLL3+ was associated with shorter OS from diagnosis of advanced G3 disease (median OS 23.1 mo vs 43.9 mo in DLL3-, $P = 0.012$). [^{89}Zr]Zr-DFO-SC16.56 DLL3 PET imaging was completed on 5 pts with DLL3 IHC+ GEP NENs at progression on standard systemic therapy. Notably, a pt with pancreatic NEC and liver metastases (DLL3 IHC H-score 60) demonstrated high tumoral tracer uptake (SUV_{max} 36.7) with 95% of tumor lesions demonstrating DLL3 PET avidity. Among 4 pts with DLL3 IHC+ G3 WD PanNETs, DLL3 PET was positive in 3/4, with SUV_{max} ranging from 14.4-27.5 and % of DLL3 PET+ tumor lesions ranging from 50-100%. **Conclusions:** DLL3 is expressed on a majority of GEP NECs and on a minority of well differentiated PanNETs marked by high grade disease and poor clinical outcomes. Functional DLL3 PET imaging highly suggests DLL3 as a promising therapeutic target in both GEP NECs and high grade WD PanNETs. Research Sponsor: Memorial Sloan Kettering Cancer Center.

4147 **Poster Session**

Surgical debulking versus non-surgical management for the control of carcinoid syndrome in metastatic small bowel neuroendocrine tumors. First Author: Rushabh Gujarathi, Department of Medicine, Section of Hematology and Oncology, University of Chicago, Chicago, IL

Background: Somatostatin analogues (SSAs) are first-line systemic therapeutics for tumor- and symptoms control in well-differentiated small bowel neuroendocrine tumors (SBNETs) with liver metastases. Surgical debulking of neuroendocrine tumor liver metastases (NETLMs) has historically been associated with symptom control in patients with carcinoid symptoms. Herein, we compare clinical outcomes in patients with metastatic SBNETs treated with surgical debulking for NETLMs to SSA alone or in combination with non-surgical liver directed therapies (LDTs) i.e. bland embolization or radioembolization. **Methods:** Patients with serotonin-producing SBNETs and NETLMs with documented symptoms of carcinoid syndrome were included in this retrospective chart review. Primary outcome was symptom-free-interval (SFI), defined as the time from start of treatment until return/worsening of symptoms. Patients were censored for SFI if a new line of tumor-directed therapy was initiated for radiographic disease progression in the absence of return/worsening of symptoms. Time to event outcomes were analyzed using Kaplan-Meier estimations, log-rank test, and Cox proportional hazards regression model. Medians were compared using the Mann–Whitney U test. **Results:** Between 2018 – 2024, 64 consecutive patients with carcinoid symptoms were included for analysis. 42 patients (65.6%) underwent surgical debulking (SDB) of NETLMs and 22 patients were treated with SSA alone (n = 14) or SSA plus LDT (n = 8). The proportion of patients reporting symptom improvement was not significantly different between the SDB and non-surgical (NS; SSA + LDT) groups (SDB = 38, 90.5% vs. NS = 19, 86.4%; p = 0.68). Among those with symptom improvement (n = 57), SFI was significantly longer in the SDB group (median SFI; SDB = 28.2 months [m] vs. NS = 15.9 m; p = 0.004). Radiographic PFS was also significantly prolonged in the SDB group (SDB = 26.1 m vs. NS = 12 m; HR, 0.53; 95% CI, 0.29 – 0.95; p = 0.03). Within the SDB group, there was no significant difference in SFI between patients who continued to receive SSA post-op (n = 23) and those in whom SSA was discontinued (n = 19) post-op (28 m vs. 30.6 m; p = 0.85). Post-treatment median nadir serotonin was significantly lower in the SDB group (total N = 41 [SDB = 31 + NS = 10]; SDB = 299 ng/mL vs. NS = 947.5 ng/mL; $p < 0.001$). Median percentage decrease (from pre-treatment to nadir values) in serum serotonin was higher in the SDB group with the difference approaching significance (total N = 30 [SDB = 22 + NS = 8]; SDB = 80.9% vs. NS = 51.5%; p = 0.06). **Conclusions:** Despite the frequent use of SSAs, surgical debulking of NETLMs in patients with carcinoid symptoms remains superior for symptom control and should therefore be considered in these patients. Research Sponsor: None.

4148 **Poster Session**

TROP2 expression in the gastroenteropancreatic neuroendocrine tumors: An analysis of 179 patients. First Author: Junaid Arshad, The University of Arizona Cancer Center, Tuscon, AZ

Background: Trophoblast cell-surface antigen 2 (TROP2) is a transmembrane glycoprotein that exhibits overexpression in various gastrointestinal (GI) malignancies, including colorectal, gastric, pancreatic, and esophageal cancers. This overexpression has been correlated with increased tumor aggressiveness, enhanced proliferation, and unfavorable prognostic outcomes. TROP2 serves as a predictive and prognostic biomarker in several GI cancers, guiding targeted therapy and correlating with overall survival. However, there exists a notable absence of dedicated studies investigating TROP2 expression specifically in gastroenteropancreatic neuroendocrine tumors (GEP-NETs) highlighting an unmet need. This report presents the first and most extensive prospective study examining TROP2 overexpression in GEP-NETs. **Methods:** We utilized transcriptomic and clinical data derived from the National Cancer Institute's (NCI) GEP-NET project, which originates from a prospective study approved protocol (NCT05237934). For data analysis, we implemented the RNA-sequencing pipeline developed by the NCI Cancer Center Bioinformatics Resource (https://github.com/skchronicles/RNA-seek.git) along with STAR version 2.7.11b for aligning sequencing reads to the hg38 reference genome. To accommodate the variations introduced by different library preparation methodologies (including polyA, total RNA, FFPE, and access), we employed the "RemoveBatchEffect" function from the Limma package, while also accounting for disease-specific variations. **Results:** Our analysis included a total of 179 GEP-NET samples, comprised of 106 small bowel neuroendocrine tumors (NETs) and 73 pancreatic neuroendocrine tumors (pNETs). There were 54 females and 52 males in the small bowel cohort, and 37 females and 36 males in the pancreatic cohort. Notably, TROP2 expression was observed in 50% of pancreatic samples and 30% of small bowel NET samples. Furthermore, TROP2 expression appeared to correlate with decreased survival in pNETs (p=0.022), whereas its expression in small bowel NETs may suggest improved patient outcomes, although this latter correlation did not achieve statistical significance (p=0.37). Further analyses are pending study completion and will be presented later. **Conclusions:** This study highlights the critical role of TROP2 overexpression in GEP-NETs and its importance for patient prognosis. TROP2 overexpression correlates with decreased survival outcomes in pNETs relative to small bowel NETs. Additionally, the identification of TROP2 as a prognostic and predictive biomarker presents opportunities for future research focused on therapeutic targeting. Additional studies may be needed for further validation as we finalize the current research. Research Sponsor: None.

4149 **Poster Session**

Development of a cfDNA-based protein-informed epigenetic signature (PEp-sig) to enable biomarker-based risk stratification for pancreatic ductal adenocarcinoma (PDA). First Author: Ashish Manne, The Ohio State University Comprehensive Cancer Center, Columbus, OH

Background: Novel blood-based biomarkers are needed for early risk stratification and personalized therapies for patients with PDA. An evidence-based 99-gene panel was developed focusing on genes whose protein products are implicated in PDA drug response. We hypothesized that methylation levels in these genes could serve as surrogates for their corresponding protein activity, enabling the prediction of treatment-related outcomes in PDA patients. Using this panel, we developed a cell-free DNA (cfDNA)-based PEp-sig for risk stratification of patients with PDA. **Methods:** Targeted enzymatic methylation sequencing was performed on plasma samples from PDA patients (01/2010–05/2022) receiving chemotherapy from the Ohio State University biorepository. Gene methylation levels were analyzed for associations with overall survival (OS) using univariate and multivariate Cox regression models. Significant genes and covariates such as first chemotherapy (FLC)- FOLFIRINOX (FFX) vs. gemcitabine (G)/nab-paclitaxel (NP) vs. other (Ot), and stage at diagnosis (StD) – early-stage (ES) that includes resectable and borderline resectable PDA vs. locally advanced (LA) and metastatic (Met)) were identified through backward selection. Risk scores from multivariate models were dichotomized at the median, stratifying patients into High (Hg) and low-risk groups (Lg), with survival differences assessed by Kaplan-Meier and log-rank tests. **Results:** The study cohort (SC) included 51 PDA patients (StD: 22 ES, 15 LA, and 14 Met). Among the ES cases, 3 progressed to Met after neoadjuvant therapy (NAT); in the LA subgroup, 2 proceeded to surgery post-chemotherapy. Ultimately, 21 patients had resection (Rs), while 30 underwent palliative therapy (PT), with FLC distribution as follows: PT group – 12 FFX, 16 G/NP, and 2 Ot; Rs group, NAT—9 FFX, 1 G/NP, and 1 Ot; adjuvant therapy after upfront surgery (UpS) —5 FFX, 2 G/NP, 3 Ot. Two 15-gene PEp-sig were developed: one for the SC and another for the PT group. A significant overlap (11/15) of genes was observed between the two PEp-sigs. These genes are linked to the response to G, NP, irinotecan, and platinums. The performance of PEp-sig models, with and without FLC and StD adjustments, is summarized below. **Conclusions:** In this proof-of-concept study, we present a cfDNA-based PEp-sig that effectively stratifies PDA patients by survival risk. Notably, it operates independently of FLC and StD within the PT group. Ongoing efforts aim to develop treatment selection algorithms based on these findings. Research Sponsor: None.

Models tested	SC			PT-group		
	Hg vs. Lg OS (in months)	Hazard Ratio (HR)	p-value	Hg vs. Lg OS (in months)	HR	p-value
PEp-sig alone	10.75 vs. 33	8.7				
PEp-sig + FLC*	10.62 vs. 33	8.1	<0.001	5.3 vs. 16.83	9.2	<0.001
PEp-sig + StD*	8.4 vs. 33	16.9			8	

FLC and StD significantly impacted OS in SC but not in PT.

4150 **Poster Session**

Development of a comprehensive cfDNA methylation signature for prognostic, predictive, and diagnostic applications in pancreatic ductal adenocarcinoma (PDA). First Author: Deepak Sherpally, Metropolitan Hospital Center, New York, NY

Background: Blood-based biomarkers are promising for predicting outcomes in pancreatic ductal adenocarcinoma (PDA) and could pave the way for developing multi-omic prognostic tools. We previously identified a 15-gene cell-free DNA (cfDNA) methylation signature targeting treatment response (TRg). To enhance its utility, we incorporated additional genes with established prognostic (Prg) and diagnostic (Dxg) value from the literature, creating a composite panel. This study aimed to develop a comprehensive cfDNA methylation signature with predictive, prognostic, and diagnostic value. **Methods:** Enzymatic methylation sequencing was performed on plasma samples collected between January 2010 and May 2022 from PDA patients undergoing chemotherapy at The Ohio State University. A 206-gene panel (TRg + Prg + Dxg) was analyzed, with methylation levels correlated to overall survival (OS) using univariate and multivariate (MV) Cox regression models. Backward selection identified significant genes, and MV models adjusted for clinical covariates. Patients were stratified into high-risk (Hg) and low-risk (Lg) groups based on median risk scores. **Results:** Our study cohort had 51 PDA patients, with a median age of 65 (range: 34 -80), 53% females, and 86% Caucasian (12% African-American and 2% others). Stage at diagnosis (Dx-S) distribution: 15 locally advanced (LA), 14 metastatic (Mets), and 22 resectable/borderline resectable (R/BR). 12 patients in BR/R received neoadjuvant therapy (NT) while the rest had upfront surgery (UpS) followed by adjuvant therapy (AT). Ultimately, 21 had resection, and 30 got palliative therapy. First-line chemotherapy (FL) patients received is, 36 FOLFIRINOX (12 PT, 9 NT, and 5 AT), 19 gemcitabine (Gem)/nab-paclitaxel (NP) (16 PT, 1 NT, and 2 AT), and 6 Others. A 25-gene cfDNA methylation signature (15 TRg, 10 Prg, and 1 Dxg) stratified patients into Hg and Lg groups. OS was significantly longer in Lg compared to Hg across all models. **Conclusions:** The study successfully developed a comprehensive 25-gene cfDNA methylation signature combining predictive, prognostic, and diagnostic markers for PDA. This signature effectively stratifies patients into Hg and Lg, demonstrating significant differences in OS across various clinical models. The results highlight the potential utility of cfDNA methylation as a multi-omic tool to enhance personalized treatment strategies and improve patient outcomes in PDA. Further validation in larger cohorts is warranted to confirm its clinical applicability. Research Sponsor: None.

Models tested	OS* Hg vs. Lg	Hazard ratio
Signature-alone	7.58 vs. 33	13.5
Plus, FL	8.98 vs. 33	13.2
Plus, FL, Surgery (NAT vs. UpS vs. PT)	7.58 vs. 33	17.3
Plus, Dx-S	7.58 vs. 33	14.4

*In months.

4151 **Poster Session**

DNA methylation signatures as predictive biomarkers for chemotherapy (CT) resistance and survival in pancreatic ductal adenocarcinoma (PDA). First Author: Deepak Sherpally, Metropolitan Hospital Center, New York, NY

Background: Predicting innate treatment resistance to traditional CT in PDA can optimize therapeutic strategies and improve patient outcomes. This study investigates methylation changes in genes encoding proteins implicated in preclinical models (PDA cell lines or mouse models) influencing drugs commonly used to treat PDA, including 5-fluorouracil (5FU), oxaliplatin, irinotecan, gemcitabine (Gem), nanoliposomal irinotecan, and nab-paclitaxel. Using a comprehensive literature review (1970–2024), we curated a panel of relevant genes and analyzed their methylation patterns in The Cancer Genome Atlas (TCGA) database. We hypothesized that DNA methylation changes affect gene expression and protein production, contributing to chemotherapy resistance. **Methods:** PDA patient methylation data were accessed from the TCGA database. Survival analyses were performed using elastic net multivariate regression to identify significant methylation signatures, followed by Kaplan-Meier analysis. Model parameters, including alpha (α) and lambda (λ), were optimized through 100 iterations to minimize error. Our curated panel consisted of 138 genes, predominantly Gem-specific or Gem + 5FU (n = 93). **Results:** The TCGA database provided methylation data for 184 PDA patients (106 had Gem or Gem-based therapy), with 133/138 genes in our analysis. Our analysis identified 23 cytosines followed by guanine residue (CpG) methylation signatures within the panel, ranging from 1 to 23 CpG sites. The best-performing signature, containing 21 CpG sites, stratified patients into significantly different survival groups (17 months (m) vs. not evaluable, p = 0.004). The second-best signature, with 8 CpG sites, stratified survival as 17m vs. 66.94m (p = 0.03). Interestingly, signatures with the most (n = 23) and least (n = 1) CpG sites also demonstrated strong stratification, with survival differences of 15.15m vs. 30.02m (p = 0.01) and 18.67m vs. 44.38m (p = 0.01), respectively. Many signatures included multiple CpG sites from single genes. A Gem or Gem + 5FU-specific panel (n = 93) applied to patients treated with Gem-based therapy identified an 8-CpG signature distinguishing high-risk patients (20.84m vs. 49.38m, p = 0.02). **Conclusions:** This study highlights the potential of CpG methylation signatures to predict treatment outcomes in PDA. These findings may guide the identification of high-risk patients and the optimization of CT regimens for improved survival. The identification of methylation signatures associated with genes implicated in chemotherapy resistance provides valuable insights into the underlying mechanisms of innate treatment resistance in PDA. Further validation of these methylation signatures could contribute to more effective and targeted therapeutic approaches in clinical practice. Research Sponsor: None.

4152 **Poster Session**

A phase I trial of binimetinib plus hydroxychloroquine in patients with previously treated metastatic pancreatic cancer. First Author: S. Daniel Haldar, The University of Texas MD Anderson Cancer Center, Houston, TX

Background: Combined MEK and autophagy inhibition exerts synergistic antitumor activity in preclinical models of RAS-mutant cancers. We hypothesized that blockade of autophagy with hydroxychloroquine (HCQ) can overcome therapeutic resistance to MEK inhibition with binimetinib (bini) and lead to clinical benefit in patients (pts) with previously treated, KRAS-mutant metastatic pancreatic ductal adenocarcinoma (PDAC). **Methods:** This is an investigator-led, single-arm, open-label, phase I dose escalation/expansion study of bini + HCQ in metastatic PDAC pts. Key eligibility criteria: ECOG 0-1, adequate organ function, $>$ 1 prior line of therapy for metastatic disease, and presence of KRAS mutation. Dose escalation followed a Bayesian optimal interval (BOIN) design. Dose level (DL) 1: bini 45 mg + HCQ 600 mg p.o. bid; DL -1: bini 45 mg + HCQ 400 mg p.o. bid; DL -2: bini 30 mg + HCQ 400 mg p.o. bid; DL -1.5: bini 30 mg + HCQ 600 mg p.o. bid. Primary endpoint was the maximum tolerated dose (MTD) of bini + HCQ. Secondary endpoints included objective response rate (ORR), disease control rate (DCR), progression-free survival (PFS), and overall survival (OS). **Results:** From December 2019 to August 2024, a total of 34 pts were enrolled in dose escalation (n = 17) and dose expansion (n = 17). Median age was 65 yrs (range: 45-79) with 56% females. Median prior lines of therapy was 2 (range: 1-4). The most prevalent KRAS mutation subtypes were G12D (35%), G12V (32%), and G12R (29%). Two dose-limiting toxicities (DLTs) occurred in 2 out 3 pts treated at DL 1: grade 3 CPK elevation with renal impairment (bini) and grade 3 QTc prolongation (HCQ). The most frequent non-hematologic AEs were rash (71%), diarrhea (71%), nausea (67%), elevated AST (67%), and elevated CPK (61%). Following dose de-escalation due to poor tolerance, the MTD was deemed to be bini 30 mg + HCQ 600 mg p.o. bid and used for dose expansion. Overall, out of 31 response-evaluable pts, 2 pts achieved a partial response (lasting 6.9 and 4.7 mos, both at DL -1.5) and 9 pts achieved stable disease (3 pts at DL -1, 6 pts at DL -1.5), consistent with ORR 6.5% and DCR 35.5%, respectively. At median follow-up of 19 mos, median PFS was 1.9 mos and median OS was 5.3 mos. **Conclusions:** Bini + HCQ demonstrated a challenging toxicity profile and limited clinical activity in a heavily pretreated cohort of metastatic PDAC pts. Minimal efficacy was observed in this treatment-refractory population; however, dual MEK and autophagy inhibition may warrant further study in earlier-line settings, potentially with more tolerable drug candidates and guided by biomarker selection. Clinical trial information: NCT04132505. Research Sponsor: None.

4153 **Poster Session**

Pancreatic adenosquamous carcinoma (PASC): A comparative genomic landscape study. First Author: S. Daniel Haldar, The University of Texas MD Anderson Cancer Center, Houston, TX

Background: PASC accounts for 1-4% of primary exocrine pancreatic malignancies and is associated with more aggressive disease biology and worse clinical outcomes compared to conventional pancreatic ductal adenocarcinoma (PDAC). Despite its aggressive nature, PASC lacks targeted treatment choices and is frequently excluded from clinical trials, underscoring a key unmet need. Here, we performed a comparative analysis of the genomic landscapes of PASC versus PDAC using the FoundationOne database to identify distinct molecular drivers and potential therapeutic targets. **Methods:** Comprehensive genomic profiling using hybrid capture-based next-generation sequencing (NGS) was performed on 244 PASC and 29,021 PDAC tumors to identify genomic alterations (GAs). All patients (pts) had clinically advanced disease, predominantly stage IV, at the time of profiling. Genomic ancestry, MSI status, tumor mutational burden (TMB), homologous recombination deficiency signature (HRDsig) and cosmic trinucleotide signature were assessed. PD-L1 expression was quantified using the tumor proportion score (TPS) via the Dako 22C3 immunohistochemistry assay. Statistical analysis was performed using Fisher's exact test, with false discovery rate (FDR) correction applied through the Benjamini-Hochberg method. **Results:** PASC harbored a median of 6 GAs per tumor (range: 1-23) with a similar genomic ancestry profile compared to PDAC. Of note, PASC featured a higher frequency of cases with MSI-high status (2.1% vs 0.5%; p = .027) and TMB $>$ 10 mutations/Mb (3.7% vs 1.3%; p = .013). Additionally, PD-L1 expression (TPS $>$ 1%) was significantly more common in PASC compared to PDAC (66.7% vs 37.0%; p $<$ .0001). The frequency of *KRAS* mutations and HRDsig positivity was similar between the two subtypes. Disease-associated GAs more frequent in PASC than PDAC included mutations in *CDKN2A* (77.0% vs 56.6%; p $<$ .0001), *KMT2D* (8.2% vs 3.2%; p $<$ .0001), *TP53* (89.3% vs 78.0%; p $<$ .0001), and *MTAP* loss (33.3% vs 23.8%; p = .002). **Conclusions:** PASC exhibits a genomic profile with molecular features that are both shared and distinct compared to PDAC. Given the similar frequency of *KRAS* mutations, PASC pts should be included in clinical trials of emerging RAS-targeted therapies. Furthermore, immunotherapy-based strategies (↑MSI-high, TMB, and PD-L1) and PRMT5/MAT2A inhibitors (↑MTAP loss) warrant consideration in this rare and understudied disease subtype. Research Sponsor: None.

	PDAC (n=29,021)	PASC (n=244)	P-value
Median GAs/tumor (range) (IQR)	5 (0-61) (3-6)	6 (1-23) (4-8)	$<$.0001
MSI-high	0.5%	2.1%	.027
TMB > 10 muts/Mb	1.3%	3.7%	.013
PD-L1 TPS > 1%	37.0%	66.7%	$<$.0001
HRDsig+	4.6%	3.1%	NS
CDKN2A	56.6%	77.0%	$<$.0001
KRAS	92.8%	95.5%	NS
***MTAP* loss**	23.8%	33.2%	.002
TP53	78.0%	89.3%	$<$.0001

4154 **Poster Session**

Unveiling the differences in tumor immune microenvironment between *KRAS*-wildtype and *KRAS*-mutant pancreatic ductal adenocarcinoma. First Author: Heidi C. Ko, Labcorp, Durham, NC

Background: Pancreatic ductal adenocarcinoma (PDAC) is a highly aggressive cancer with a dismal prognosis despite advances in treatment. PDAC is characterized by a dense stromal environment with suppressed anti-tumor immunity that contributes to treatment resistance. Oncogenic *KRAS* mutations are present in $>$ 90% of PDACs and are known to play a role in modulating the tumor immune microenvironment (TME). In this study, we examined the differences in TME components between *KRAS*-mutant (m) and *KRAS*-wildtype (wt) PDACs. **Methods:** Comprehensive genomic and immune profiling (CGIP), including the RNA-seq based gene expression assessment of 395 immune-associated genes, was performed on 311 PDAC patient samples. Gene expression signatures of tumor immunogenicity (TIGS) and cell proliferation were calculated by averaging the gene expression ranks of 161 immune-associated genes and 10 proliferation genes, respectively. The normalized gene expression rank of 22 immune checkpoint genes and 17 cancer testis antigen (CTA) genes were also calculated. DNA-seq was used to identify *KRAS* mutations and to calculated tumor mutational burden (TMB). Continuous variables were compared between subgroups using the Wilcoxon Rank-Sum test and categorical variables were compared between groups using the Chi Squared test. For statistical significance, p $<$ 0.05 was required. **Results:** The cohort consisted of 311 PDAC patient samples, comprising 159 females (51.1%) and 152 males (48.9%) with a median age at testing of 69.3 years (38.7-92.6). A total of 264 specimens (84.9%) exhibited a *KRAS* mutation, with the most common being G12D and G12V while 47 (15.1%) had *KRAS*-wt tumors. No difference in TIGS, CP, or TMB was observed between *KRAS*-wt and *KRAS*-m tumors. *KRAS*-wt tumors exhibited greater expression of 12 of 17 tested CTAs than *KRAS*-m tumors, including GAGE13 (p = 0.004) NY-ESO-1 (p = 0.01), MAGEA3 (p = 0.01), and LAGE1A (p = 0.01). Analysis of the gene expression of 22 immune checkpoint genes showed no difference for most of the genes, though there was higher expression of PD-1 (p = 0.04) and CD27 (p = 0.03) seen in *KRAS*-wt compared to *KRAS*-m tumors. **Conclusions:** *KRAS*-wt PDACs exhibited greater expression of cancer testis antigen genes compared to *KRAS*-m tumors, suggesting potential therapeutic susceptibility to immunotherapy and adoptive cell therapies leveraging the expression of CTAs as targets. Assessment of *KRAS* status and immunotherapy susceptibility may support future clinical trial selections for therapies targeting the complex interplay of genomic and immune components of pancreatic cancer. Research Sponsor: None.

4155 **Poster Session**

Functional role of GLI2 in cancer-associated fibroblasts for modulation of the fibrotic tumor microenvironment within pancreatic cancer. First Author: John Y. Kwon, Mayo Clinic Rochester, Rochester, MN

Background: The tumor microenvironment (TME) that surrounds pancreatic ductal adenocarcinoma (PDAC) is a multi-faceted and dynamic ecosystem in which stromal fibroblasts communicate with cancer cells to mediate tumor growth, metastasis, and chemotherapy resistance. It is well recognized that both cancer-associated fibroblasts (CAFs) and its non-cellular, fibrotic components within the TME can foster a protumorigenic environment for PDAC. However, we still lack a comprehensive understanding of the precise mechanisms in which this dense, fibrotic matrix can help drive malignant behaviors. Here, we reveal a novel mechanism in which the zinc-finger transcription factor GLI2 regulates type 1 collagen expression within CAFs and how the soluble variant of this collagen promotes irinotecan chemoresistance. **Methods:** We leveraged transcriptomic data from The Cancer Genome Atlas, International Cancer Genome Consortium, and Clinical Proteomic Tumor Analysis Consortium to evaluate GLI2 expression and stromal content of human PDAC tumors through bulk RNA-sequencing deconvolution. Using single-nucleus RNA sequencing of human PDAC tumors, we validated the association of GLI2 expression and stromal matrix constituents in CAFs. Chromatin immunoprecipitation assays in human CAFs confirmed GLI2 binding at the COL1A1 promoter. Through RNAi-based inactivation of GLI2, we determined how loss of GLI2 impacts regulation of type 1 collagen. Additionally, we conducted MTT assays to assess tumor viability in response to irinotecan treatment. **Results:** Transcriptomic analysis revealed that GLI2 is highly enriched in CAFs and strongly correlated with stromal fibrosis compared to other non-tumor cell constituents within the TME. We have shown that GLI2 directly binds to the promoter of COL1A1, a key component of type 1 collagen, in CAFs and regulates its transcription in a manner dependent on TGFβ1 signaling. Interestingly, PDAC tumors exposed to type 1 collagen show increased expression of pro-tumorigenic pathways involved in inflammation, EGR signaling, cytokine-receptor interactions, and irinotecan resistance. We further validate that human PDAC cells pretreated with collagen can confer chemoresistance to irinotecan with viability assays. **Conclusions:** Taken together, our study demonstrates a novel mechanism in which GLI2 regulates the secretion of collagen within CAFs, which in turn can enable PDAC to acquire resistance to standard-of-care treatments. These findings highlight not only the oncogenic functions for CAFs and their fibrotic secretome, but also open new avenues in which therapeutic targeting of the TME may provide clinical benefit for PDAC patients. Research Sponsor: National Cancer Institute/U.S. National Institutes of Health.

4156 **Poster Session**

Use of an ultra-sensitive sequencing platform to detect mutant *KRAS* in the whole blood of pancreatic cancer patients. First Author: Ryne Ramaker, Duke Cancer Institute, Duke University, Durham, NC

Background: Pancreatic Ductal Adenocarcinoma (PDAC) is a leading cause of cancer death and mortality is increasing. A contributor to poor outcomes is the absence of non-invasivebiomarkers for disease screening, treatment monitoring, and identification of therapeutic targets. Blood-based profiling of circulating tumor DNA (ctDNA) using Next Generation Sequencing (NGS) has addressed these needs in several cancer types, but available commercial ctDNA assays are not as effective in PDAC. To address this unmet clinical need, we developed an ultra-sensitive sequencing assay to detect mutant *KRAS* in the whole blood of PDAC patients. **Methods:** We adapted the bacterial Maximum Depth Sequencing (MDS) assay for Human whole blood MDS (hMDS) to improve upon the sensitivity of NGS by barcoding DNA fragments with unique molecular identifiers prior to performing multiple rounds of first-strand synthesis to resolve sequencing errors. Analytic sensitivity was evaluated by spiking PDAC cells at various dilutions into control blood isolated from 10 individuals and assaying the mixture by hMDS in triplicate. Clinical sensitivity was then evaluated by collecting paired blood draws from 200 advanced PDAC patients in prospective fashion, one to be tested with a commercial ctDNA test and one by hMDS. **Results:** ThehMDS assay reproducibly detected PDAC cells at dilutions as low as one cell per mL or one mutated fragment per million *KRAS* fragments. Thus, hMDS reached an analytic sensitivity 1000x higher than NGS. Clonal *KRAS*mutations were detected in 179 of the first 194 patient samples (92.2%), surpassing historical commercial detection rates of 50% by commercial ctDNA assays. Mutations were reproducibly detected in replicate analysis of forward and reverse DNA strands. Weak clonal *KRAS* activating mutations were also detected in several non-cancer, control patients. **Conclusions:** We developed an assay capable of sensitively detecting PDAC ctDNA in whole blood. Formal comparison to commercial testing is ongoing, but preliminary results suggest this assay could be a sensitive tool for non-invasive PDAC mutation profiling and disease monitoring. The presence of weak clonal *KRAS* mutations in control patients has motivated development of a multiplex platform capable of screening for mutations in multiple driver genes. Research Sponsor: National Cancer Institute; 5R21-CA257816-02; Hopper Belmont Foundation.

4157 **Poster Session**

Efficacy and safety of surufatinib (S) plus KN046 (K) and chemotherapy in first line (1L) advanced pancreatic cancer (PC): A single-arm, phase 1b/2 trial. First Author: Wen-Quan Wang, Department of Pancreatic Surgery, Zhongshan Hospital, Fudan University, Shanghai, China

Background: Gemcitabine (G) and nab-paclitaxel (nP) are standard 1L regimen for patients (pts) with unresectable PC, yet the efficacy remains unsatisfactory. K is a humanized bispecific antibody targeting PD-L1/CTLA-4, while S is a kinase inhibitor of VEGFR1-3, FGFR1 and CSF-1R with immune-regulatory potential. It is hypothesized the add-on of S and K to GnP chemotherapy would provide improved efficacy. **Methods:** This single-arm, phase 1b/2 trial enrolled pts with unresectable locally advanced or metastatic PC who were eligible for 1L treatment. The phase 1b part was designed in a "3+3" algorithm to determine the recommended phase 2 dose (RP2D) of S for dose expansion in phase 2 part. Pts received oral S at escalating dose starting from 200 mg qd, plus intravenous K at 5 mg/kg on day 1, and GnP chemotherapy on days 1 and 8 at 21-day cycles. The primary endpoint was dose-limiting toxicities (DLTs) within the first 28 days for phase 1b, and ORR per RECIST 1.1 for phase 2. Secondary endpoints included DCR, PFS, OS, safety, and efficacy-related biomarkers. **Results:** As of Dec 19th, 2024, 18 pts were enrolled with a median age of 54 (range: 41-74), predominantly male (16/18) and metastatic disease (15/18). Of the 16 pts with genetic testing, *KRAS* (15/16) and *TP53* (11/16) mutations were common, followed by DNA damage response (DDR) -related mutations (7/16) including *ARID1A*, *ATM*, *CHEK2*, etc., while TMB-H (1/16) is rare, and none had MSI-H or dMMR status. Within the 9 pts from phase 1b part (3 in S 200 mg cohort, 6 in S 250 mg cohort), no DLTs occurred thus the RP2D of S was determined as 250mg qd. In the 16 evaluable pts, the best overall responses were 1 CR, 10 PRs and 5 SDs. The ORR was 68.8% and the DCR was 100%. 2 pts received R0 resection after 6 cycles' treatment. With a median follow up of 7.43 months, the estimated median PFS was 8.25 (95% CI: 4.57-NR) months and the 6-month PFS rate was 72.9%. Estimated median OS was 11.14 (95% CI: 5.52-NR) months and the 6-month OS rate was 82.5%. In the exploratory analysis, DDR-related mutations seemed predictive for better ORR (85.7% vs 55.6%, *P*= 0.308), PFS (6-month PFS rate:100% vs 53.3%, log-rank *P*= 0.519), and OS (6-month OS rate:100% vs 62.5%, log-rank *P*= 0.116). Treatment-related adverse events (TRAEs) occurred in 14 (77.8%) pts, and most common TRAEs (≥20%) included leucopenia (44.4%), hypertension (38.9%), and thrombocytopenia (22.2%). TRAEs of grade ≥3 included leucopenia, neutropenia, thrombocytopenia, and hypertension (n = 2 [11.1%] for each). There were no treatment-related deaths. **Conclusions:** These preliminary results showed encouraging anti-tumor efficacy and an acceptable safety profile of S plus K and GnP chemotherapy as 1L treatment for advanced PC. Clinical trial information: NCT05832892. Research Sponsor: HUTCHMED, ALPHAMAB.

4158 **Poster Session**

Early treatment ctDNA dynamics to predict response to chemotherapy in patients with metastatic pancreatic cancer: A prospective, observational pilot study. First Author: James Lee, Donald and Barbara Zucker School of Medicine at Hofstra/Northwell, Hempstead, NY

Background: Assessment of chemotherapy response using imaging has limitations in metastatic pancreatic cancer whereas circulating tumor DNA (ctDNA) may offer an alternate assessment of tumor burden with improved lead-time. This study evaluated temporal ctDNA testing as a potential biomarker of treatment response data compared to standard-of-care CT scans in metastatic pancreatic cancer. **Methods:** In this prospective, observational, single-center trial, patients with metastatic pancreatic ductal adenocarcinoma starting a first-line (1L) or second-line (2L) systemic treatment regimen underwent imaging and frequent blood-based treatment assessment. CT imaging was obtained prior to and after 8 weeks of treatment, with response measured by RECIST 1.1 criteria. CA 19-9, CEA, and longitudinal ctDNA profiling using Signatera were performed at baseline, after 2 weeks, 4 weeks, and 8 weeks. A threshold of 20% decrease achieved or not was used to dichotomize ctDNA response and other cut-offs were evaluated in sensitivity analysis. Progression-free survival (PFS) was measured and compared to biomarker response. The primary objective was to evaluate the association of ctDNA changes at 4 and 8 weeks with PFS. Exploratory objectives included evaluation of response at 2-weeks, and comparison of PFS with CA 19-9 and CEA. **Results:** Between June and December 2023, 19 patients were enrolled. Sufficient tissue was available to perform tumor-informed ctDNA profiling in 12 of 19 patients (63%) undergoing systemic therapy with 7 patients (58%) starting on 1L therapy and 5 (42%) on 2L therapy. Overall median PFS was 4.0 months (4.2 months 1L, 3.3 months 2L). CtDNA response at 4-weeks was prognostic of PFS with a median decrease in ctDNA of 83.4% (p = 0.0002). CtDNA response at 8-weeks was also prognostic of PFS (p = 0.01). Three patients achieved ctDNA clearance of over 95% by week 4 and had a PFS of 5.9 months. Of, note there was one patient who had a 1-log decrease in ctDNA at 4-weeks, but a 20-fold increase at 8-weeks, whereas CEA and CA 19-9 were stable at 8-weeks, and this patient had subsequent disease progression 1 month later. In an exploratory analysis, ctDNA as soon as 2 weeks was also prognostic of recurrence (p = 0.002). In contrast to ctDNA, CA 19-9 and CEA did not show significance at any timepoint (2 weeks: p = 0.2 and p = 0.8, respectively; 4 weeks: p = 0.7 and p = 0.8, respectively; 8 weeks: p = 0.8 and p = 0.5, respectively). Sensitivity analysis showed that 20% decrease was robust; association at 4-weeks with ctDNA remained significant across a wide threshold range (-70% to +60%). **Conclusions:** Circulating tumor DNA predicts PFS as early as 2-weeks following treatment. These findings suggest clinical utility in measuring ctDNA in mPDAC as early as 2 weeks following treatment initiation within the context of prospective interventional clinical trials. Research Sponsor: Conquer Cancer, the ASCO Foundation.

4159 **Poster Session**

TQB2868 combined with anlotinib and nab-paclitaxel plus gemcitabine as first-line treatment for metastatic pancreatic cancer: A prospective, multi-center, single-arm, phase 2 study. First Author: Si Shi, Department of Pancreatic Surgery, Fudan University Shanghai Cancer Center, Shanghai, China

Background: Chemotherapy currently serves as the cornerstone for treating metastaticPancreatic Ductal Adenocarcinoma Cancer (mPDAC). Nevertheless, the survival of patients with mPDAC remains poor. Besides, the efficacy of single-agent immune checkpoint inhibitors or antiangiogenesis in the treatment of mPDAC is not satisfying. Therefore, it is important to explore combination therapy options for patients with mPDAC. TQB2868 injection is a bifunctional fusion protein that targets PD-1 and TGF-βRII. This trial was conducted to evaluate the effectiveness and safety of TQB2868 combined with anlotinib and nab-paclitaxel plus gemcitabine for mPDAC. **Methods:** This was a prospective, multicenter, single-arm phase II trial. Eligible pts were those who aged over 18 years, histologically or cytologically confirmed PDAC, have not received treatment before and radiographically showed distant metastases and measurable lesions. Patients received TQB2868 (300mg, I.V, D1,15) and Anlotinib (10mg, P.O, QD, D1-14), in addition to nab-paclitaxel (125mg/m^2, I.V,D1,8,15) and gemcitabine (1.0g/m^2, I.V, D1,8,15), administered over a 28-day treatment cycle.The primary endpoint was Progression-free Survival (PFS), Secondary end points included objective response rate (ORR) and disease control rate (DCR), overall survival (OS) and safety. The biomarker TGF-β1 was analyzed as exploratory results (NCT06767813). **Results:** 40 pts were enrolled and received TQB2868 combination regimen therapy, and the last follow-up time was January 10, 2025. 36 pts were eligible for response evaluation. With median follow-up duration of 5.9 months, the median PFS and OS have not been reached, with 6-month PFS and OS rates of 86% and 95%, respectively. The ORR was recorded at 63.9% (23/36) (95% CI, 46.2%-79.2%), with 23 pts achieving partial response. The DCR was 100% (36/36) (95% CI, 90.3%-100%). The most common TRAEs were neutropenia, thrombocytopenia, leukopenia, and anemia. Grade 3 TRAEs were reported in 52.5% pts (21/40). In exploratory analysis, the inhibition rate of TGFβ1 was over 90% in most cases after administration, with little to no rebound. **Conclusions:** TQB2868 combination regimen as first-line treatment was demonstrated to be tolerable, with promising anti-tumor activity in mPDAC. Clinical trial information: NCT06767813. Research Sponsor: None.

4160 **Poster Session**

Phase II trial of serplulimab combined with gemcitabine plus nab-paclitaxel (GnP) and SBRT for metastatic pancreatic cancer as the first-line treatment. First Author: Ke Cheng, Division of Abdominal Tumor, Department of Medical Oncology, Cancer Center and State Key Laboratory of Biological Therapy, West China Hospital, Sichuan University, Chengdu, China

Background: The addition of anti-PD-1 monoclonal antibody (mAb) to gemcitabine and nab-paclitaxel (GnP) presented limited improvement in objective response rate (ORR) and disease control rate (DCR) for metastatic pancreatic ductal adenocarcinoma (mPDAC) in our previous study. Therefore, we conducted this phase II trial to evaluate the efficacy and safety of anti-PD-1 mAb (Serplulimab) plus GnP chemotherapy and stereotactic body radiotherapy (SBRT) in patients with mPDAC. **Methods:** Patients with mPDAC without previous treatment were enrolled to receive Serplulimab and GnP plus SBRT (SGSBRT) (intravenous infusion of Serplulimab 200 mg on day 1 every 3 weeks, gemcitabine 1000 mg/m^2 and nab-paclitaxel 125 mg/m^2 on day 1 and day 8, repeated every 3 weeks; SBRT delivered 5 fractions of 6.6 Gy to the primary tumor or 3 fractions of 8 Gy to the metastatic lesion in cycle 2) as the first-line treatment. The primary endpoint was 6-month progression-free survival (PFS) rate. Secondary endpoints included overall survival (OS), PFS, ORR, DCR, and adverse events (AEs). Moreover, the biomarkers such as circulating tumor DNA (ctDNA) and circulating hybrid cells (CHCs), PD-L1 expression, tumor tissue genetic status, cytokine levels, and immune microenvironment were also investigated. **Results:** As of January 2025, 47 patients have been enrolled and 41 patients have been followed for more than 6 months, with all 47 patients achieving efficacy according to the protocol. The 6-month PFS rate was 78.48%. The ORR was 74.47% (35/47), including 1 complete response (CR) and 34 partial responses (PR), and the DCR was 100%, with 12 stable disease (SD). The median PFS was 8.6 months, and the median OS was 15.5 months. The frequent grade 3 drug-related AEs were neutropenia (20/47, 42.55%), leukopenia (19/47, 40.43%), anorexia (18/47, 38.30%), and fatigue (11/34, 23.40%). The correlation between biomarkers and efficacy and prognosis are under-analyzed. **Conclusions:** This phase II study has met our preset primary endpoint with 78.48% in 6-month PFS rate, and SGSBRT presented promising efficacy with manageable safety profile and expected antitumor activity. This combination might be a promising option as first-line therapy for Chinese patients with mPDAC. Clinical trial information: ChiCTR2300073237. Research Sponsor: None.

4161 **Poster Session**

First-line treatment with surufatinib, camrelizumab, nab-paclitaxel, and S-1 in locally advanced or metastatic pancreatic ductal adenocarcinoma (PDAC): A phase Ib/II randomized study. First Author: Guang-Hai Dai, Senior Department of Oncology, the Fifth Medical Center of the PLA General Hospital, Beijing, China

Background: PDAC is a highly aggressive cancer with limited treatment options. Previous reports of NCT05218889 showed promising efficacy of nab-Paclitaxel/S-1/Surufatinib/Camrelizumab (anti-PD-1 antibody) combination regimen (NASCA) in mPDAC (2023 ASCO abs# 4142; 2024 ASCO GI abs# 671). Here, we present the updated results. **Methods:** In phase Ib, a 3+3 dose escalation design was used to determine the RP2D of surufatinib. In phase II, patients were randomized 1:1 to receive the NASCA regimen or nab-paclitaxel plus gemcitabine (AG). The NASCA regimen was administered in 3-week cycles for up to 8 cycles. Patients without disease progression continued treatment with surufatinib, S-1, and camrelizumab, while the control group received AG regimen , q3w. Treatment continued until disease progression, unacceptable toxicity, withdrawal of consent, or death. The primary endpoints were DLTs and the RP2D of surufatinib in phase Ib, and the ORR in phase II. **Results:** As of Dec 16, 2024, 96 patients were enrolled in the study (6 in phase Ib, 90 in Phase II). In phase Ib, the RP2D for surufatinib was determined to be 200 mg (1 DLT out of 6 patients). In phase II, 45 patients were assigned to each group. Baseline characteristics were balanced between the groups. Most patients had metastatic disease (82.2% in NASCA vs 77.8% in AG). The NASCA group showed a confirmed ORR of 51.1% (23/45) versus 24.4% (11/45) in the AG group (OR: 3.2, 95% CI 1.3-8.2; p = 0.01). The median PFS were 7.9 and 5.4 months (HR: 0.63, 95% CI 0.40-0.99, p = 0.046), with 12-month OS rates of 55.5% (95% CI 39.4-68.9) in NASCA group and 52.7% (95% CI 36.6-66.5) in AG group. In the subgroup analysis of PFS, the NASCA group showed longer PFS in male patients (HR: 0.56, 95% CI 0.31-1.01), those with metastatic disease (HR: 0.57, 95% CI 0.35-0.94), and patients without liver metastasis (HR: 0.45, 95% CI 0.23-0.90). Furthermore, multiplex immunohistochemistry was performed on baseline tissue samples of 26 NASCA patients. The ratio of M1/M2 macrophage percentages was significantly higher in patients with PR than those with SD and PD (p = 0.04). Using the median as a cutoff, patients with higher levels of M1/M2 cells (p = 0.039), CD8$^+$ cells (p = 0.0024), and CD8$^+$PD-1$^+$ cells (p = 0.0064) in the stroma had longer PFS than those with lower levels. For Grade 3 and 4 TEAEs, the most frequently observed events in the NASCA group were decreased white blood cell count (31.1%), decreased neutrophil count (33.3%), and decreased lymphocyte count (20.0%). Similarly, these events were common in the AG group (26.7%, 28.9%, 8.9%, respectively). **Conclusions:** The NASCA regimen demonstrated promising efficacy with a manageable safety profile, showing a significantly higher ORR and longer PFS compared to AG group in patients with locally advanced or metastatic PDAC. Further studies are warranted to confirm these findings. Clinical trial information: NCT05218889. Research Sponsor: None.

4162 **Poster Session**

First-line serplulimab and bevacizumab combined with nab-paclitaxel/gemcitabine followed by mFOLFOX in advanced pancreatic cancer: A phase II trial. First Author: Jieer Ying, Zhejiang Cancer Hospital, Hangzhou, China

Background: Patients with advanced pancreatic cancer (PC) have a poor prognosis, as this 'cold' tumor shows limited responsiveness to mono-immunotherapy. Chemotherapy may improve the efficacy of immunotherapy by reshaping the tumor immune microenvironment. We conducted a phase II trial to assess the anti-tumor activity and safety of first-line serplulimab (anti-PD-1) and HLX04 (a bevacizumab biosimilar) combined with nab-paclitaxel plus gemcitabine (nab-P/Gem), followed by modified FOLFOX (oxaliplatin, leucovorin, and 5-fluorouracil; mFOLFOX), in patients with locally advanced or metastatic PC. **Methods:** This single-arm phase II trial enrolled 37 patients with histologically or cytologically confirmed unresectable locally advanced or metastatic pancreatic ductal adenocarcinoma (NCT06393166). The study aims to increase the objective response rate (ORR) of the first-line sequential nab-P/Gem followed by mFOLFOX (nab-P/Gem-mFOLFOX) regimen from 50% to 68% with the addition of serplulimab and HLX04. The study employed Simon's minimax two-stage design, with a total of 23 patients achieving objective responses, thereby meeting the predefined primary endpoint. Secondary endpoints included progression-free survival (PFS), overall survival (OS), disease control rate (DCR), and safety. **Results:** Among the 37 patients analyzed, the average age was 62 years, and 22 patients (59.5%) were male. At baseline, patients had an adequate nutritional and performance status, with a mean BMI of 21.6 kg/m^2. Distant organ metastases were present in 34 patients (91.9%), with the liver being the most common site (n = 26, 70.3%). The confirmed ORR was 67.6% (95% CI, 49.5-82.6), including 1 patient with a complete response (CR), meeting the primary endpoint. Only 1 patient had progressive disease (PD) as the best response, yielding a DCR of 97.1% (95% CI, 84.7-99.9). As of the data cutoff in November 2024, the median follow-up was 6.1 months. The median PFS was 10.5 months (95% CI, 9.7-not reached), with a 6-month PFS rate of 80.0% (95% CI, 65.5-97.7). The median time to response (TTR) was 1.5 months, and the median duration of response (DOR) was 9.3 months. The OS remains immature. The incidence of treatment-related adverse events (TRAEs) was 83.8%, with grade ≥3 TRAEs occurring in 46.0% of patients. Hematologic toxicities were the most common treatment-emergent adverse events (TEAEs), and no fatal AE were observed. Overall, the treatment was manageable, and no new safety signals were identified. **Conclusions:** First-line serplulimab and HLX04 combined with nab-P/Gem-mFOLFOX demonstrates clinical feasibility and promising preliminary outcomes in advanced PC. Further follow-up is required to confirm the survival benefits, and following analyses are needed to explore the mechanisms underlying the efficacy of this novel regimen. Clinical trial information: NCT06393166. Research Sponsor: None.

4163 **Poster Session**

AI-based predictive tool for detection of ctDNA in pancreatic adenocarcinoma using nationwide comprehensive genomic profiling data. First Author: Hiroaki Ikushima, Department of Respiratory Medicine, Graduate School of Medicine, The University of Tokyo, Tokyo, Japan

Background: Comprehensive genomic profiling (CGP) has become a cornerstone of precision oncology, with liquid biopsy expanding its applicability. However, in some cases, circulating tumor DNA (ctDNA) is undetectable in liquid CGP, limiting the ability to assess genetic alterations. Identifying the optimal timing for liquid CGP remains a challenge. This study focuses on pancreatic adenocarcinoma, using nationwide CGP data and explainable AI methods to identify clinical factors associated with ctDNA detection. Based on these factors, we develop an easy-to-use AI tool to predict the probability of ctDNA detection in real-world settings. **Methods:** We conducted a retrospective analysis of nationwide CGP data collected from Jun 2019 to Dec 2023, covering 99.7% of CGP performed in Japan. Cohort 1 included 4,110 pancreatic adenocarcinoma cases analyzed by FoundationOne CDx, while Cohort 2 comprised 2,220 cases analyzed by FoundationOne Liquid CDx (F1L). Using clinical information available prior to CGP, we developed an eXtreme Gradient Boosting (XGBoost)-based predictive model to estimate ctDNA detection and employed SHapley Additive exPlanations (SHAP) analysis to elucidate contributing clinical factors. A smartphone application was deployed using the refined model. The app's performance was tested with Cohort 3, consisting of 629 pancreatic adenocarcinoma cases tested by F1L between Jan 2024 and Dec 2024. **Results:** In Cohort 1 (tissue), 98.5% of cases harbored mutations in either KRAS, TP53, CDKN2A, or SMAD4, confirming their role as surrogate markers for tumor-derived DNA detection. The predictive AI model for ctDNA detection, trained on Cohort 2 (liquid) data, achieved an AUROC of 0.754. SHAP analysis identified key predictors, including liver metastasis, the number of metastatic organs, performance status, response to recent therapy, interval from diagnosis to blood collection, and treatment line. Notably, patients with liver metastases exhibited a significantly higher rate of ctDNA detection ($p < 0.001$) compared to those without, whereas patients with peritoneal metastases demonstrated a lower rate of ctDNA detection ($p < 0.01$). A refined model incorporating representative predictors was deployed as a smartphone application. When tested on Cohort 3 (liquid), the application demonstrated predictive accuracy with an AUROC of 0.769 (sensitivity: 0.707, specificity: 0.769) and a Brier score of 0.194. **Conclusions:** This study identified clinical factors predictive of ctDNA detection in liquid CGP for pancreatic adenocarcinoma using explainable AI methods and nationwide CGP data. Based on these findings, a smartphone application was developed to predict the probability of ctDNA detection. By facilitating optimal timing of liquid CGP, this app has the potential to enhance patient access to effective therapies, contributing to improved clinical outcomes. Research Sponsor: None.

4164 **Poster Session**

Using live true single-circulating tumor cell comprehensive genomics to show clonal evolution and tumor heterogeneity in pancreatic cancer management. First Author: Mandana Kamgar, Medical College of Wisconsin Cancer Center, Milwaukee, WI

Background: Traditional tissue and CtDNA biopsies have limitations in pancreatic ductal adenocarcinoma (PDAC) due to sampling bias and inability to capture tumor evolution effectively. ctDNA offers Tx decisions, longitudinal monitoring for recurrence, real-time tumor evolution, and responses. However, ctDNA success is limited by its low sensitivity often with NMDs. While single circulating tumor cell (sCTC) genomics may offer higher sensitivity, but challenged with selective capture of live sCTCs without leukocyte contamination. We address limitations by identifying both clonal and rare sub-clonal mutations in PDAC. We report CellBiopsy assay to capture and release of sCTCs, facilitated by ctDNA-integrated comprehensive genomic profiling (CGP) at a true single-cell. **Methods:** In an observational study, ten advanced PDAC patients receiving SOC were accrued with MCW IRB approved protocol (PREDICT-MCW NCT ID:NCT05802069). All patients gave consent to investigational interventions. Live sCTCs were isolated at baseline (BL) and follow-up (FL) using OncoIndx Ikon sCTC assay in 10 mL of blood. Live CTCs were captured using glass beads with anti EpCam antibody and released in 96 well plate assay. DNA from individually captured sCTCs was linearly amplified, followed by target enrichment using OncoIndx CGP assay. Sequencing libraries were prepared and sequenced on Illumina NextSeq2000 (500× depth). ctDNA underwent deeper sequencing at 10000x coverage. Data was processed using iCare software for sequence alignment and variant calling. **Results:** Prospectively, 74 live sCTCs were isolated at baseline and follow up (mean sCTC distribution 7). Post SOC treatment, 50% of the patients (5/10) exhibited a 30% reduction in sCTC count at FL. *NRAS* mutations were the most frequent alteration observed in sCTCs (40.5%), followed by *HRAS* (27%) and *TP53* (23%). Paired ctDNA predominantly revealed *KRAS G12* variants (40%). Additional divergent molecular alterations in sCTCs were accounted for in NRAS, TP53, SMAD4, and PIK3CA-MTOR-AKT pathways, providing insights into mechanisms of treatment resistance and disease aggressiveness. Samples with co-occurring *NRAS* and *TP53*, or *SMAD4*, mutations along with *ERBB2* amplification, were associated with aggressive disease. In FL sCTCs genomics revealed evolving molecular profiles enriched for activating variants in the PIK3CA-MTOR-AKT pathway compared to bulk tissue and ctDNA genomics at BL. **Conclusions:** Compared to ctDNA, sCTC CGP revealed heterogeneous molecular profile in PDAC, offering precise insights into tumor heterogeneity, clonal evolution, disease progression, and treatment outcome. Integrating paired DNA profiling of ctDNA and sCTC DNA may provide a more CGP landscape of PDAC. Ongoing analyses aim to evaluate temporal dynamics of CGP using ctDNA and sCTC DNA assay for advancing personalized management of PDAC. Clinical trial information: NCT05802069. Research Sponsor: None.

4165 **Poster Session**

Homologous recombination deficiency (HRD) profiling in Chinese pancreatic ductal adenocarcinoma: Implications for platinum-based chemotherapy. First Author: Yanxia Wang, The First Affiliated Hospital, Sun Yat-Sen University, Guangzhou, China

Background: Pancreatic ductal adenocarcinoma (PDAC) is a highly aggressive cancer with poor prognosis. While platinum-based therapies have demonstrated some therapeutic benefits, their associated toxicity underscores the need to identify patients who are most likely to respond. Homologous recombination deficiency (HRD) has been linked to improved sensitivity to platinum-based therapies, but its role in PDAC, particularly beyond *BRCA1* and *BRCA2* (*BRCA1/2*) mutations, remains poorly understood. **Methods:** A retrospective analysis was conducted on 264 Chinese patients diagnosed with PDAC. Genomic data were obtained using a targeted next-generation sequencing (NGS) panel, which included: (1) 28 canonical homologous recombination repair (HRR) genes (*BRCA1, BRCA2, PALB2, ATM, ATR, BAP1, BARD1, BRIP1, CDK12, CHEK1, CHEK2, EMSY, FAM175A, FANCA, FANCC, FANCD2, FANCL, FANCI, MRE11, NBN, PPP2R2A, PTEN, RAD50, RAD51B, RAD51C, RAD51D, RAD54B,* and *RAD54L*), along with their bi-allelic loss-of-function (BILOF) status; (2) 8 genes associated with other DNA damage repair (DDR) pathways (*TP53, CDH1, EPCAM, MLH1, MSH2, MSH6, PMS2,* and *STK11*); and (3) an integrated HRD score, calculated as the unweighted sum of loss of heterozygosity (LOH), telomeric allelic imbalance (TAI), and large-scale transitions (LST). HRD score ≥ 38 and/or *BRCA1/2* BILOF was predefined as HRD positive. The association between HRD status and clinical outcomes in patients treated with first-line platinum-based therapies was systematically analyzed. **Results:** Among the 264 PDAC patients, 6.4% (n = 17) were classified as HRD-positive, a larger group compared to the 1.9% (n = 5) with *BRCA1/2* BILOF. Overall, 19.3% (51/264) of patients harbored mutations in HRR genes. Among these, 4.9% (n = 13) had *BRCA1/2* mutations, with 38.5% (n = 5) exhibiting BILOF. The most frequently mutated HRR genes included *ATM* (4.2%) and *BRCA2* (3.8%), followed by *CHEK2* (1.5%), *BRCA1* (1.5%), *ATR* (1.5%), and *FANCA* (1.5%). The median HRD score was notably higher in patients with HRR gene BILOF (25.5) compared to those with non-BILOF (14). In the first-line platinum chemotherapy cohort (n = 133), HRD-positive patients exhibited significantly improved progression-free survival (PFS), with a median PFS of 20.5 months, compared to 11.3 months in HRD-negative patients (HR = 0.385, 95% CI: 0.177-0.84, *P* = 0.012). Notably, patients with *BRCA1/2* BILOF derived substantial clinical benefit from first-line platinum-based therapies, with no instances of disease progression or death during the treatment period. **Conclusions:** HRD profiling, defined by an HRD score threshold of ≥38 and/or *BRCA1/2* BILOF status, is a valuable biomarker for predicting response to platinum-based chemotherapy in PDAC. This study suggests that scar-based HRD marker and gene BILOF status could serve as predictive markers for PDAC personalized therapy. Clinical trial information: [2024]138. Research Sponsor: National Natural Science Foundation of China; 82330065, 30900650, 81372501, 81572260, 81172232, 31430030.

4166 **Poster Session**

The differential effect of stromal genes on gemcitabine/nab-paclitaxel (GN) and GN/cisplatin (GCN) outcomes in advanced pancreatic adenocarcinoma (aPDAC). First Author: Himil Mahadevia, Mayo Clinic Florida, Jacksonville, FL

Background: GN is a front-line therapy for aPDAC. A Phase I/II study demonstrated that GCN has a higher overall response rate and median overall survival (mOS). Our previous study found no difference in outcomes among patients with DNA damage repair gene mutations; however, stromal gene expression correlated with mOS in patients receiving GCN. Here, we further evaluate differences in the outcomes with GCN and GN by site of biopsy. **Methods:** PDAC samples (n = 4,463) were analyzed by NGS (NextSeq/NovaSeq) or RNA (NovaSeq) (Caris Life Sciences, Phx, AZ). Expression of stromal and related genes (*ACTA2, ADIRF, HAS2, IL-6, MMP-2, MMP-9, SPARC, STAT3, TBGB1, TGFB2, TGFBR3, IDO1, HLA-DRB4, VEGFB)* from different biopsy sites [high expression (H) >50% of RNA transcripts per million] was correlated with outcomes to GCN or GN. mOS was obtained from insurance claims and calculated from first treatment to last contact. The hazard ratio (HR) was calculated by the Cox proportional hazards model, and p-values were calculated using the log-rank test. **Results:** 4325 patients [primary biopsy (PT), n = 1,878; non-liver metastatic biopsy (N-LM), n = 818; Liver biopsy (LM), n = 1,629] received GN while 138 patients (PT, n = 45; N-LM, n = 28; LM, n = 65) received GCN. GCN was associated with longer mOS than GN [Δ: 5.2 months (m), HR: 0.76, 95% CI 0.63-0.92, p = 0.01]. GCN was associated with longer mOS compared to GN in LM (Δ: 5.6 m, HR: 0.66, 95% CI 0.50-0.87, p = 0.003), but it was not significant in PT (Δ: 4.6 m, p = 0.13) and N-LM (Δ: 4.4 m, p = 0.35). Median *MMP2* (38.5 vs. 163.1 vs. 162.2), *VEGFB* (14.4 vs. 16.9 vs. 16.2) and *TGFBR3* (11.4 vs. 15 vs. 16.4) expression were lower in LM compared to PT and N-LM while *TGFB1* (41.6 vs. 34.5 vs. 39.8) and *IL6* (1.61 vs. 1.19 vs. 1.41) expression were highest in LM ($p < 0.05$). In LM, *IL6*-H (Δ: -11 m, p = 0.037) and *TGFB1*-H (Δ: -5.9 m, p = 0.10) were associated with worse post-GCN survival compared to GN (p = 0.82 and p = 0.57). Whereas, in N-LM, *TGFBR3*-H trended towards longer post-GCN survival (Δ: 12 m, p = 0.18), while *ADIRF*-H trended towards shorter post-GCN survival (Δ: -12 m, p = 0.056) compared to GN (p = 0.42 and p = 0.10). While in PT, *MMP2*-H (Δ: 11.3m, HR: 0.46, p = 0.16), *TGFB1*-H (Δ: 11.3 m, HR: 0.33, p = 0.09), *HLA-DRB4*-H (Δ: 12.9 m, HR: 0.44, p = 0.11) and *VEGFB*-H (Δ: 10.7, HR: 0.34, p = 0.09) trended towards longer post-GCN survival compared to GN (*MMP2*-H, Δ: 3.4 m, p = 0.03, *TGFB1*-H, p = 0.661, *HLA-DRB4*-H, p = 0.67, *VEGFB-H*, Δ: 1.3 m, p = 0.03). **Conclusions:** GCN is associated with improved mOS compared to GN, especially in LM.Stromal gene expression in the liver differs from that in N-LM and the pancreas. While high stromal gene expression trends towards worse post-GCN survival in LM, it is associated with improved survival in N-LM and PT. Further validation is needed to understand the impact of stromal gene expression in different tumor sites on survival outcomes and signature development. Research Sponsor: None.

4167 **Poster Session**

CheMo4METPANC: Combination chemotherapy (gemcitabine and nab-paclitaxel), chemokine (C-X-C) motif receptor 4 inhibitor (motixafortide), and immune checkpoint blockade (cemiplimab) in metastatic treatment-naïve pancreatic adenocarcinoma—Updated clinical and translational findings. First Author: Gulam Abbas Manji, Columbia University Medical Center/ New York-Presbyterian Hospital, New York, NY

Background: Metastatic pancreatic ductal adenocarcinoma (mPDAC) is a uniformly fatal disease with an immunosuppressive tumor microenvironment (TME). In our KPC mouse model study, targeting the C-X-C motif chemokine receptor 4 (CXCR4)/C-X-C motif chemokine ligand 12 (CXCL12) axis in combination with αPD-1, and gemcitabine improved survival when compared to mice treated with gemcitabine or other combinations. The goal of this first-in-human study was to evaluate safety, radiologic response rate, and change in tumor microenvironment (TME) elicited by motixafortide (CXCR4i), cemiplimab (αPD1), gemcitabine, and nab-paclitaxel (MCGN) in treatment-naïve mPDAC. **Methods:** CheMo4METPANC is an open label, multicenter, investigator-initiated, study evaluating MCGN in mPDAC (NCT04543071). Here we report the updated results of the signal seeking phase of this study. The primary aim was to study the safety of MCGN. All patients received pre- on-treatment and optional on-progression biopsies. Single nucleus RNA sequencing (snRNAseq) and quantitative multiplex immunofluorescence (qmIF) were used to characterize the TME. **Results:** A total of 11 patients (1 over-enrolled) participated in the study at Columbia and Brown Universities (11/9/2020-3/3/2023). The median age was 58 years. As of 04/22/24 (median follow up 23 months), 7 (63%) and 3 (27%) patients experienced a partial response (PR) and stable disease, respectively. One patient experienced radiologic resolution of hepatic metastasis and underwent definitive radiation therapy to the primary tumor. A second had a sustained PR (11 months) and underwent pancreaticoduodenectomy and hepatic wedge resection which revealed a pathologic complete response within the hepatic and primary lesion. Median progression free survival (PFS) was 9.6 months. The most common adverse events experienced while on the study combination included skin hyperpigmentation (11/11), alopecia (10/11) and injection site reaction (9/11). The most common grade 3 or greater adverse events were anemia (5/11) and rash (3/11). Analysis of the TME revealed an increase in intratumoral CD8+ T-cells in all patients, and that patients achieving a PR were found to have higher proportions pre-treatment of CXCL12-producing cancer associated fibroblasts, a potential marker of response. **Conclusions:** Preliminary results from this pilot study of MCGN in mPDAC were promising, with a PR rate of 63% and disease control rate (DCR) of 91%. Based on these results, the study was amended to transition to a randomized phase 2 trial testing MCGN compared to GN (2:1; N = 108). The primary endpoint is PFS. The phase 2 study is actively enrolling patients and incorporates optional paired research tumor biopsies. Clinical trial information: NCT04543071. Research Sponsor: BioLine Rx and Regeneron Pharmaceuticals.

4168 **Poster Session**

Phase 1/2 study of nivolumab and ipilimumab combined with gemcitabine, nab-paclitaxel, and adaptive stereotactic body radiotherapy in bordeline resectable, locally advanced or metastatic pancreatic cancer (LAPTOP). First Author: Inna Markovna Chen, Department of Oncology, Herlev Gentofte Hospital, Herlev, Copenhagen, Denmark

Background: This phase 1/2 study (NCT04247165) evaluated the safety and efficacy of combining nivolumab, ipilimumab, gemcitabine, nab-paclitaxel, and adaptive stereotactic body radiotherapy (SBRT) in patients with borderline resectable (BRPC), locally advanced (LAPC), or metastatic pancreatic cancer (mPC). **Methods:** Treatment-naïve patients with BRPC, LAPC or mPC received 28-day cycles of nivolumab (3 mg/kg), ipilimumab (1 mg/kg single dose), and gemcitabine (800 mg/m^2) with nab-paclitaxel (100 mg/m^2 on days 1, 8, and 15). Starting in cycle 3, patients underwent MRI or CT-guided adaptive SBRT (8 Gy x 3 fractions) targeting the primary pancreatic tumor. Primary endpoint: safety, defined by the incidence of treatment-related adverse events (TRAEs) leading to discontinuation, monitored via a Bayesian stopping rule for rates exceeding 30%. Secondary endpoints: OS, PFS, ORR, DCR, DOR, and resection rate. Exploratory endpoint: immunological changes. **Results:** A total of 55 patients received at least one treatment (BRPC: n=1, LAPC: n=23, mPC: n=31), with a median follow-up of 27.6 months (IQR 26.3-34.4) calculated via reverse Kaplan-Meier. Grade 3-4 TRAEs occurred in 70.8% of BRPC/LAPC and 71.0% of mPC patients. No grade 5 TRAEs were observed. Treatment discontinuation due to TRAEs occurred in 20.8% (BRPC/LAPC) and 9.7% (mPC). Median OS: 23.0 months (95% CI: 11.4–NR) for BRPC/LAPC and 11.2 months (6.8–15.8) for mPC. Median PFS: 14.9 months (8.7–24.2) for BRPC/LAPC and 6.1 months (3.8–8.4) for mPC. ORR: 33.3% (15.6–55.3) for BRPC/LAPC and 19.4% (7.5–37.4) for mPC. DCR: 75.0% (53.3–90.2) for BRPC/LAPC and 61.3% (42.2–78.2) for mPC. Median DOR: 8.9 months (4.0–12.7). Nine (37.5%) BRPC/LAPC patients and three (9.7%) mPC patients underwent resection. Preliminary analyses revealed treatment-induced T-cell activation, particularly after SBRT, with upregulation of activation and stemness markers in patients with durable clinical benefit. Conversely, an increase in senescence markers was observed in the rest of the cohort. **Conclusions:** The combination of nivolumab, ipilimumab, gemcitabine, nab-paclitaxel, and adaptive SBRT demonstrated an acceptable safety profile and efficacy supporting further investigation in BRPC, LAPC, and mPC patients. Clinical trial information: NCT04247165. Research Sponsor: None.

4169 **Poster Session**

Clinico-genomic characterization of *PALB2*-mutated pancreatic adenocarcinoma. First Author: Jonathan W. Lee, Memorial Sloan Kettering Cancer Center, New York, NY

Background: Pancreatic adenocarcinoma (PDAC) with germline (g) or somatic (s) mutations in *BRCA1/2* and *PALB2* exhibit unique molecular characteristics and predict response to platinum-based chemotherapy and PARP inhibition. However, distinct features of *PALB2* and PDAC are not well described. Herein, we characterize distinct clinico-genomic features of patients (pts) with g/s *PALB2* and PDAC. **Methods:** Institutional databases and cBioPortal were queried to identify pts with g/s*PALB2* and PDAC. Pts with *PALB2* variants of unknown significance (VUS) were excluded (annotation from OncoKb, ClinVar). Demographic data and clinical outcomes abstracted from medical record. Detailed mutational analysis obtained from cBioPortal. Zygosity determined with FACETS. Progression-free survival (PFS) and overall survival (OS) estimated with Kaplan-Meier Method. **Results:** N = 29 pts with pathogenic/oncogenic g/s*PALB2* and PDAC identified between 2011-2024. N = 25 (86%) g*PALB2* (+/- s*PALB2*) and N = 4 (14%) s*PALB2* (no g*PALB2*); N = 13 s*PALB2* excluded as VUS. Median age (range): 57 years (38-78) g*PALB2* and 63 years (43-73) s*PALB2*. N = 23 (79%) white; N = 16 (55%) female. Stage IV at diagnosis: N = 11 (44%) g*PALB2*; N = 2 (50%) s*PALB2* cohort. In g*PALB2* cohort (N = 25), 4 (16%) had personal history of cancer (N = 2 thyroid, N = 1 uterine, N = 1 CLL) and N = 17 (68%) had family history of cancer (N = 7 breast/prostate/ovarian, N = 1 pancreas). *KRAS* and *TP53* variants co-occurred in 84% and 36% of g*PALB2* and 50% and 50% of s*PALB2* cases, respectively. N = 9 (56%) of patients with a *gPALB2* mutations showed biallelic loss of *PALB2* (N = 6 by LOH, N = 3 somatic LOH). None of four patients in s*PALB2* cohort (negative g*PALB2*) had biallelic loss. Median TMB (mt/Mb): 4.10 (0.80-9.10) g*PALB2*; 3.85 (2.00-5.80) s*PALB2*. For stage IV g*PALB2* (N = 11), median PFS 4.2 months (95% CI 2.4, NR) and median OS 12 months (95% CI 5.5, NR). N = 10 (90%) received platinum therapy, with N = 6 in the first line setting. Durable disease control on PARPi was observed for patients with g*PALB2* and s*PALB2*, including N = 1 s*PALB2* with 7 months on 4th-line olaparib and N = 1 g*PALB2* with 6 months on 6th line Olaparib. **Conclusions:** *gPALB2* and *sPALB2* mutations are seen in a small % of PDAC. *gPALB2* PDAC presents earlier and is linked to family history of cancer. g*PALB2* compared to s*PALB2* had higher biallelic loss; oncogenic s*PALB2* are uncommon. Identification of g/s*PALB2* has implication for therapeutics and screening. Loss of heterozygosity, TMB, telomeric allelic imbalance, large-scale state transitions, and implications for treatment will be presented. Research Sponsor: None.

	gPALB2 = 25
Putative driver mut (%)	21 (84)
Truncating mut	13 (62)
Structural Variant	4 (19)
Splice mut	4 (19)
Zygosity	
Biallelic	9 (56)
Monoallelic	6 (44)
Unknown	10

4170 **Poster Session**

Prognostic and predictive impact of next-generation sequencing in metastatic pancreatic ductal adenocarcinoma. First Author: Christopher Schumacher, University of Pittsburgh, School of Medicine, Pittsburgh, PA

Background: Outcomes in *de novo* metastatic pancreatic ductal adenocarcinoma (mPDAC) remain dismal, although considerable heterogeneity exists in responses to therapy and survival. With increased use of tumor-cell next-generation sequencing (NGS) in mPDAC, improved understanding of the prognostic and predictive value of genomic alterations is needed. **Methods:** Between 2019-2023, 949 PDAC patients (pts) underwent targeted NGS (Oncomine), of which 161 had *de novo* metastatic disease. Progression-free survival (PFS) after front-line therapy and overall survival (OS) were correlated with clinical parameters and genomic alterations. Long-term survival (LTS) was defined as OS in the top quartile. **Results:** In pts who underwent at least one dose of systemic therapy (80%, n=128), mPFS and mOS were 6.6 and 10.4 months. Pts who received 5-FU-based front-line therapy (97% received a triplet with oxaliplatin and irinotecan or liposomal irinotecan) had improved outcomes compared to pts who underwent gemcitabine-based therapy (89% gemcitabine/nab-paclitaxel [gem/nab-P]; mOS 13.2 vs 7.3 months, HR 0.66, 95% CI 0.45-0.97). Tumor mutational burden (TMB), pathogenic mutations in genes involved in cell-cycle regulation (CCR) and DNA damage response (DDR), and loss of *SMAD4* were not associated with broad differences in PFS/OS. As expected, in pts treated with 5-FU/platinum, mutations in DDR genes were associated with LTS (p = 0.04). *KRAS* mutational status was prognostic (Table; p = 0.02 for OS). Surprisingly, *KRAS* wild type (WT) pts had poorer PFS/OS compared to *KRAS*-mutated pts. However, 3/12 *KRAS* WT pts, all with Class II *BRAF* and *TP53* loss-of-function (LOF) mutations, were unable to tolerate any systemic therapy. In 3 *KRAS* WT pts with LTS, 2 had mutations in DDR genes and TMB $>$ 10 Mut/Mb, while 2 had mutations in CCR genes. Multivariate analysis confirmed improved LTS of pts harboring *KRAS G12R* compared to *G12D* (OR 0.22, 95% CI 0.07-0.72, p = 0.01). *TP53* was mutated in 75% of pts (18% gain-of-function [GOF]). WT *TP53* was associated with improved survival (mOS 10.7 vs 5.0 months, HR 0.60, 95% CI 0.43-0.84). Interestingly, in pts receiving gem +/- nab-P, LTS was lacking in those with *TP53* GOF mutations but not LOF mutations (p = 0.13), a trend not seen in pts receiving 5-FU/platinum. **Conclusions:** Herein we show novel prognostic and predictive significance of genomic alterations in mPDAC. Heterogeneity exists in *KRAS* WT pts with *BRAF* and *TP53* mutations conferring poorer prognosis and DDR and CCR gene mutations associated with LTS. *KRAS G12D* is associated with worse outcomes compared to *G12R* while *G12V* is intermediate. Pts with *TP53* GOF mutations may benefit from 5-FU/platinum upfront. Research Sponsor: None.

***KRAS* mutational status, frequency, and survival.**

***KRAS* Status**	**N**	**%**	**mPFS (months)**	**mOS (months)**
WT	12	7.5	3.1	3.5
G12C	2	1.2	2.1	2.1
G12D	70	43.5	5.0	6.6
G12R	25	15.5	9.7	13.2
G12V	36	22.4	4.9	10.5
Q61H/R	14	8.7	4.3	5.6
Other	2	1.2	5.5	7.8

4171 **Poster Session**

Interpretable artificial intelligence-driven selection of doublet chemotherapy regimens as second-line treatment in patients with advanced pancreatic cancer. First Author: Letizia Procaccio, Veneto Institute of Oncology IOV, IRCCS, Padua, Italy

Background: Guidelines recommend second-line (2L) doublet chemotherapy, NALIRI (liposomal irinotecan + 5-fluoruracil and leucovorin), FOLFIRI or FOLFOX, for patients (pts) with metastatic pancreatic ductal adenocarcinoma (mPDAC) after failure of gemcitabine+Nab-paclitaxel (GemNabP). A head-to-head comparison between doublets has not been performed. We aimed to apply interpretable artificial intelligence (IAI, i.e., AI systems in which the prescription logic can be understood) methods on real-world data to establish which pts should receive NALIRI *vs* other doublets to maximize the benefit in this setting. **Methods:** In this observational cohort study, we compared progression-free survival (PFS) of consecutive pts with mPDAC who received 2L doublets after GemNabP failure at 42 Italian centers between 2013 and 2023. The dataset was randomly split into a training set (70%) and a test set (30%). In the former, a counterfactual Cox proportional hazard model, including baseline characteristics to infer the 12-month PFS probability for a given patient under each regimen, was trained. An Optimal Policy Tree (OPT), a state-of-the-art IAI-based method, was used to read the complete reward matrix by training a decision tree with the counterfactual predictions, and OPT recommendations were validated in the test set. The potential gain of the new policy was evaluated by 12-month PFS net-benefit curves. **Results:** Among 571 eligible pts, 209 (36.6%), 209 (36.6%) and 153 (26.8%) received NALIRI, FOLFOX and FOLFIRI, respectively. Median PFS was similar among the three groups (3.3 months for NALIRI, 3.5 months for FOLFOX and 3.6 months for FOLFIRI), with a long-term benefit observed only in the NALIRI group (12-month PFS 12.0% *vs* 2.6% for FOLFIRI and 5.2% for FOLFOX). The OPT recommended NALIRI as the preferred regimen for pts with pancreatic head/body cancers, with ECOG PS 0 or with Ca19.9 $<$ 109 U/ml if ECOG PS $>$ 0. The net-benefit curves revealed that the OPT consistently outperformed the uniform strategies of administering either NALIRI or FOLFOX/FOLFIRI to all pts, attaining a 2.5 percentage-point net-benefit at a threshold probability of roughly 9%. **Conclusions:** Our findings show that 2L NALIRI can offer long-term PFS advantage in a subgroup of mPDAC pts compared with other doublets. The AI-derived policy provides a higher net benefit than treating all pts with NALIRI, avoiding unnecessary clinical and financial toxicity. Research Sponsor: None.

4172 **Poster Session**

First safety analysis of an open-label, single arm phase II trial investigating the efficacy, safety and quality of life of neoadjuvant chemotherapy with liposomal irinotecan combined with oxaliplatin and 5-fluoruracil/folinic acid followed by curative surgical resection in patients with hepatic oligometastatic adenocarcinoma of the pancreas (HOLIPANC). First Author: Dirk Thomas Waldschmidt, Universitätsklinikum Köln, Cologne, Germany

Background: Aim of the prospective single arm HOLIPANC trial (NCT04617457) is to evaluate the efficacy and safety of multimodal treatment in pancreatic oligometastatic disease. **Methods:** Patients with hepatic oligometastatic pancreatic cancer receive up to 8 cycles of a combination of liposomal irinotecan (nal-IRI, 50mg/m^2) with 5-fluouracil (5-FU 2400mg/m^2)/folinic acid (FA, 400mg/m^2) and oxaliplatin (OX, 60mg/m^2) (NalIRIFOX) as neoadjuvant therapy followed by curative intended surgical resection of the primary tumor and liver metastases. Here, we present the first preplanned safety analysis with patients (pts) that were enrolled between 10/2021 and 04/2024. **Results:** A total of 56 pts were included in the analysis, of which 43 (77%) pts received at least 4 cycles and 16 (29%) pts 8 cycles of chemotherapy. Dose reductions of nal-IRI were required in 24 (43%) pts. Treatment-emergent adverse events (TEAE) were observed in 52 (93%) pts, 40 (72%) TEAEs were related to the neoadjuvant chemotherapy. Grade 3-4 TEAEs occurred in 30 (54%) pts, most common were gastrointestinal disorders, i.e. diarrhoea (n = 5), vomiting (n = 4) and nausea (n = 4). Hepatobiliary disorders (cholangitis (n = 5), cholestasis (n = 4)) and increased gammaglutamyltransferase (n = 4) were also frequent but generally not considered in relation to the chemotherapy. Grade 3 anemia and leukopenia were observed in 3 (5%) and 2 (4%) pts respectively. Serious TEAEs occurred in 23 patients (41%). Next to the above mentioned gastrointestinal and hepatobiliary disorders, dehydration (n = 3) and infections (n = 2) were the remaining recurring events. At the time of analysis, resection was performed in 20 pts (36%). Overall postoperative complications occurred in 7 pts (35%), n = 2 (10%) were classified as Dindo-Clavien grade $\geq$ 3. Clinically relevant pancreatic fistula was shown in 1 patient (5%). While there were no deaths related to chemotherapy or surgery, 2 pts died because of tumor progression during follow-up within 28 days of chemotherapy administration or surgery. **Conclusions:** This analysis shows for the first time safety data from a prospective clinical trial of multimodal treatment in oligometastatic pancreatic cancer. As we show, the concept of neoadjuvant chemotherapy followed by surgery is safe, the toxicity and overall morbidity is not elevated compared to available data from the NAPOLI-3 trial, even in combination with a following tumor resection after neoadjuvant treatment. Clinical trial information: NCT04617457. Research Sponsor: None.

4173 **Poster Session**

Circulated T-cell exhausted subtypes to predict response in PDAC patients. First Author: Anastasia Xagara, Laboratory of Oncology, School of Health Sciences, University of Thessaly, Larissa, Greece

Background: In-depth analysis of T-cell exhausted subsets in the circulation of Pancreatic Ductal Adenocarcinoma (PDAC) patients may provide insights into novel therapeutic options and predictive biomarkers. We performed a detailed immunophenotypic analysis for both early-stage (resectable) and metastatic (unresectable) PDAC patients. Additionally, different T-cell populations were correlated with clinical outcome. **Methods:** Fifty-five treatment naive PDAC patients, twenty-five of which had resectable disease, and ten healthy donors (HD) were enrolled. Peripheral Blood Mononuclear Cells (PBMCs) were isolated and stained with fluorochrome-conjugated monoclonal antibodies. Multicolor flow cytometry was performed to determine differences between T-cell populations and their correlation with clinical outcome. **Results:** Advanced disease patients that harbored high percentages of $CD4^+PD\text{-}1^+$ T_{eff} cells had longer PFS (median: 190 vs. 100 days, p:0.030) and OS (median: 250 vs. 170 days, p:0.041) while for early-stage patients high percentages of $CD8^+PD\text{-}1^+T_{eff}$ displayed longer DFS (median: 422 vs. 200 days, p:0.044) and OS (median: Und vs. Und days, p:0.041). For early-stage patients, high percentages of both $CD4^+$ and $CD8^+$ T-cells expressing $PD\text{-}1^+TCF1^+$ (exhausted cells) were predictive for survival ($CD3^+CD4^+PD\text{-}1^+TCF1^+$: med. Und vs. 277 days, p: 0.0041) and ($CD3^+CD8^+PD\text{-}1^+TCF1^+$: med. Und vs. 390 days, p:0.042). Additionally, expression levels of PD-1 (MFI levels) were substantially elevated in the $PD\text{-}1^+TCF1^-$ subset for both early stage $CD3^+CD4^+$ (p:0.026), $CD3^+CD8^+$ (p: = 0.006) and advanced-stage, (p:0.0001 and p:0.045, respectively), implying that terminally exhausted ($PD\text{-}1^+TCF1^-$) T-cells exhibit higher PD-1 expression than primarily exhausted ($PD\text{-}1^+TCF1^+$). For advanced stage patients, high levels of $CD57^+$, a marker of terminally differentiated T-cells, in $CD3^+CD8^+$ were associated with improved PFS (118 vs. 92 days, p:0.178)and OS(271 vs. 152 days, p: 0.019), $CD3^+CD8^+PD\text{-}1^+TCF1^+$ (PFS: med. 260 vs. 60 days, p = 0.0063 ; OS: 271 vs. 90 days, p: 0.003) and $CD3^+CD8^+PD\text{-}1^+TCF1^-$ T-cells (PFS: med. 188 vs. 80 days, p = 0.0459 ; OS: 271 vs. 107 days, p = 0.0429). $CD57^+$ T-cells were not correlated with response in early-stage patients. **Conclusions:** T-cell exhaustion represents ineffective immune response and in both early and advanced-stage PDAC may predict clinical outcome offering opportunities for innovative therapeutic options for this fatal disease. Research Sponsor: None.

4174 **Poster Session**

USP22 as promoter of Treg cell infiltration and modulator of immunotherapy efficacy through the PIAS1/P65/CCL22 pathway in pancreatic cancer. First Author: Aman Wang, First Affiliated Hospital of Dalian Medical University, Dalian, China/Liaoning, China

Background: Immune checkpoint inhibitors targeting PD-1 and CTLA-4 have shown success in various cancers; however, their efficacy in pancreatic cancer remains limited, likely due to its immunosuppressive microenvironment. Treg cells are crucial in tumor immune evasion and suppression. Targeting Treg cells is an emerging strategy in pancreatic cancer immunotherapy. Recent studies show that USP22 (Ubiquitin-Specific Protease 22) regulates immunity by deubiquitinating key proteins like PD-L1 and STAT1 in tumor cells, while in Treg cells, USP22 controls FoxP3, modulating Treg cell function. This study aims to explore how USP22 regulates the immune microenvironment in pancreatic cancer and identify potential targets to enhance immune checkpoint blockade responses. **Methods:** Bioinformatics analysis of tissue microarrays and the TCGA database was used to assess the correlation between USP22 and Treg cell infiltration in pancreatic cancer. 2. Tumorigenicity assays, immunohistochemistry, and flow cytometry were performed in C57BL/6 mice to determine the effect of USP22 on Treg cell infiltration. 3. Transcriptomic and proteomic analyses were conducted to explore the mechanisms by which USP22 regulates Treg cell infiltration. 4. In vitro experiments, including Western blot, qRT-PCR, immunofluorescence, deubiquitination assays, and chromatin immunoprecipitation, were used to identify the specific mechanisms of USP22 in regulating Treg cell infiltration. 5. The combination of PD-1 monoclonal antibody and nab-paclitaxel chemotherapy was tested to determine if targeting USP22 improves immunotherapy efficacy. **Results:** Immunohistochemistry and bioinformatics analysis revealed a significant positive correlation between USP22 expression and Treg cell infiltration in pancreatic cancer. 2. Tumorigenicity assays in C57BL/6 mice showed that USP22 promotes tumor growth and Treg cell infiltration. 3. Transcriptomic analysis found a strong association between USP22 and the TRAF1/NF-κB signaling pathway as well as CCL22 expression. 4. In vivo and in vitro experiments confirmed that USP22 activates TRAF1/NF-κB signaling and increases CCL22 release, promoting Treg cell infiltration. 5. USP22 deubiquitinates PIAS1, inhibiting its nuclear translocation and activating p65. 6. USP22 knockdown improved therapeutic responses to combined immunotherapy (PD-1 inhibitors) and chemotherapy (nab-paclitaxel). **Conclusions:** USP22 promotes Treg cell infiltration in pancreatic cancer by deubiquitinating PIAS1, inhibiting its nuclear translocation, and activating the TRAF1/NF-κB signaling pathway, which leads to CCL22 release. Targeting USP22 could inhibit cell proliferation, promote apoptosis, and remodel the immune microenvironment, enhancing the efficacy of immune checkpoint blockade therapy. Research Sponsor: None.

LBA4175 **Poster Session**

NAPOLI 3, a phase 3 study of NALIRIFOX in patients with metastatic pancreatic ductal adenocarcinoma (mPDAC): Final overall survival (OS) analysis and characteristics of the long-term survivors. First Author: Vincent Chung, City of Hope, Duarte, CA

The full, final text of this abstract will be available at meetings.asco.org on the day of presentation and in the online supplement to the June 10, 2025, issue of the *Journal of Clinical Oncology*.

4176 **Poster Session**

Biomarkers of response to immunotherapy in pancreatic ductal adenocarcinoma (PDAC) with homologous recombination deficiency (HRD). First Author: Clara J. Oh, University of Miami Sylvester Comprehensive Cancer Center, Miami, FL

Background: PDAC is associated with a paucity of immune effector cells, low antigenicity, and immunosuppressive factors in the tumor microenvironment (TME); consequently, treatment of unselected PDAC patients with immune checkpoint inhibitors (ICIs) has been ineffective. In HRD-PDAC, dual PD-1/CTLA-4 ICI therapy has a response rate of 14-42%. In this study, we investigated biomarkers of immunotherapy response in PDAC tumors with HRD. **Methods:** We generated a murine model of HRD-PDAC and performed transcriptomic analysis of mouse responders versus non-responders to ICI therapy to identify biomarkers of response. DNA and RNA sequencing was also performed for patient tumor samples submitted to Caris Life Sciences. Samples harboring pathogenic or likely pathogenic (P/LP) *BRCA1*, *BRCA2* or *PALB2* mutations were classified HRD, the remaining samples non-HRD. Microsatellite instability-high neoplasms were excluded. TMB-High (TMB-H) was defined as $\geq$10 mutations/Mb. PD-L1 positivity was determined by IHC (SP142, $\geq$2+, $\geq$5%). High genomic loss of heterozygosity (gLOH-H) was defined as LOH at $\geq$16% of segments analyzed (up to 552). Immune cell infiltration was estimated by RNA deconvolution using quanTIseq. Mann-Whitney U, Fisher's Exact, or Chi-squared tests were used to determine statistical significance (p), with multiple comparisons corrections as appropriate (q). **Results:** In murine HRD-PDAC tumors, chronic platinum exposure was a biomarker for response to ICI. Responding tumors had differential enrichment of cytosolic DNA sensing and cGAS-STING-related pathways, and secretomes significantly enriched for the T-cell attractant chemokines CXCL9 and CXCL10. Of 6396 human PDAC samples, 4.2% were HRD (2.7% *BRCA2*, 0.9% *BRCA1*, 0.6% *PALB2* P/LP), and 95.8% non-HRD. Compared to the non-HRD cohort, the HRD cohort was younger (median age: 66 vs 68 years, p = 0.0006), had lower prevalence of *TP53* (57.4% vs 79.0%, q $<$ 0.0001), *CDKN2A* (14.1% vs 24.7%, q = 0.0062), and *RNF43* (0.8% vs 5.8%, q = 0.0322) mutations, and was more frequently PD-L1+ (21.7% vs 14.0%, q = 0.0460), TMB-H (6.4% vs 1.9%, q = 0.0001), and gLOH-H (41.2% vs 9.5%, q $<$ 0.0001). Median infiltration of M1 macrophages was higher in the HRD cohort (6.2% vs 5.3%, p = 0.0028), while that of M2 macrophages was lower (2.9% vs 3.3%, p = 0.0081).TheHRD cohort demonstrated higher median expression measured in transcripts per million of *CGAS* (6.3 vs 5.4 TPM, p = 0.0002), *CXCL9* (2.19 vs 1.60 TPM, p = 0.0015), and *CXCL10* (4.65 vs 3.65 TPM, p = 0.0308), phenocopying observations in the murine model. **Conclusions:** PDAC tumors associated with canonical HRD variants (*BRCA1/2*, *PALB2*) have distinct genomic, transcriptomic, and TME features which are immune-permissive and explain the sensitivity of this subgroup of patients to ICI therapy. Understanding the underlying mechanisms could inform strategies to broaden the impact of ICI in this population. Research Sponsor: None.

4177 **Poster Session**

Interim open-label phase 1 results of misetionamide (GP-2250): A small molecule antineoplastic targeting three major transcription factors. First Author: Anup Kasi, University of Kansas Cancer Center, Fairway, KS

Background: GP-2250 is a novel antineoplastic agent demonstrating effective activity on preclinical pancreatic cancer models alone or in combination with gemcitabine, and inhibits c-MYC, NFκB, and HIFα in cancer cells at clinically achievable concentrations. This open-label phase 1 trial (NCT03854110) evaluates the safety and tolerability of escalating doses of GP-2250 in combination with gemcitabine as a second-line treatment in adults with advanced pancreatic adenocarcinoma that experienced disease progression with 5-FU based chemotherapy. **Methods:** GP-2250 dose escalation (starting dose 250 mg escalating up to 40 g IV once weekly) followed a Bayesian Optimal Interval design which transitioned to a 3+3 design. A 1-week run-in of GP-2250 was followed by a full cycle (3 weeks on, 1 week off) of GP-2250 plus gemcitabine treatment for each of 11 dose cohorts. Single-patient cohorts with 100% escalation between cohorts were enrolled until the first DLT (or cohort 4), followed by 3 patient cohorts with 35%−45% escalation between cohorts. The DLT assessment period was 5 weeks at each dose. Patients were treated until disease progression or development of unacceptable toxicity. Primary endpoints were safety and tolerability of GP-2250 monotherapy and in combination with gemcitabine. Secondary and exploratory endpoints were preliminary efficacy, pharmacokinetics, and pharmacodynamic blood markers. **Results:** To date, 52 patients have been enrolled. Five serious adverse events were reported in 3 patients (2 CVAs, pneumonia, and abdominal and flank pain in 2 patients), none attributed to GP-2250. Three patients discontinued treatment: 1 disease hyperprogression (at 11 g GP-2250) and 2 neutropenia (at 21 g GP-2250), with only 1 event of grade 3 neutropenia "possibly" attributed to GP-2250. In summary, the addition of GP-2250 did not significantly alter the safety and tolerability expected of gemcitabine alone. Twelve patients (23%) had progression-free survival (PFS) of $\geq$16 weeks, or twice as long as historical gemcitabine treatment alone; 7 patients (13%) had PFS of 24 weeks, and 4 (8%) had PFS of 32 weeks. One patient survived $>$ 2 years while receiving treatment. Seventeen patients (33%) achieved stable disease and 6 (12%) achieved a partial response by RECIST criteria. While the blood half-life of GP-2250 is ~5 hours, mTOR and AKT biomarker data indicate that the biological half-life is longer, at 4–5 days. These data are within the concentrations and times required for cytotoxicity in all cancer cell lines tested with GP-2250. **Conclusions:** GP-2250/gemcitabine combination therapy showed encouraging safety and tolerability and favorable PFS outcomes compared to gemcitabine alone. These promising results in a historically difficult to treat pancreatic cancer population warrant progress to later-stage studies. This study is funded by Geistlich Pharma AG. Clinical trial information: NCT03854110. Research Sponsor: Geistlich Pharma AG.

4178 **Poster Session**

Concurrent mutations in DNA damage repair genes *BRCA1*, *POLE*, *ATM* and *FANCA* to predict overall and progression-free survival for patients (pts) with metastatic pancreatic ductal adenocarcinoma (mPDAC) treated with chemotherapy in combination with dual checkpoint inhibition in the CCTG randomized PA.7 trial. First Author: Daniel John Renouf, BC Cancer, Vancouver, BC, Canada

Background: CCTG PA.7 (NCT02879318) was a randomized phase II trial comparing gemcitabine (G) and nab-paclitaxel (N) with and without dual immune checkpoint inhibition with durvalumab (D) and tremelimumab (T) as 1st-line therapy in pts with mPDAC. Matched plasma and tissue-based sequencing was performed for exploratory correlative biomarker analysis. **Methods:** Pts received G+N+D+T (n = 11 run-in, 119 randomized, 2:1 randomization) or G+N (n = 61). Long-term trial analysis was performed with a median follow-up time of 81.6 months. Correlative analysis was performed for pts with baseline ctDNA sequencing using a 600-gene PredicineATLAS panel (n = 173), with a subset having matched archival tissue available for whole-genome sequencing (WGS; n = 46). Cox-based elastic net regression models were used to identify and rank combinations of mutations by their ability to predict survival hazard. **Results:** Long-term follow up analysis demonstrated no significant difference in median overall survival (mOS) between pts randomized to G+N+D+T *vs* G+N (9.8 *vs* 8.8 months; hazard ratio (HR) = 0.88; p = 0.46). Median progression-free survival (mPFS) was also not significantly different between treatment arms (5.5 *vs* 5.4 months, respectively; HR = 0.95, p = 0.77). Landmark analysis demonstrated 4-year survivorship of 5.4% in pts treated with G+N+D+T arm compared to 1.6% with G+N (p = 0.07). Two or more ctDNA-based mutations (somatic and germline considered separately) in DNA damage repair (DDR) genes *BRCA1*, *POLE*, *ATM* or *FANCA* was present in 18/173 pts (10.4%) and was associated with improved OS with G+N+D+T *vs* G+N (mOS 26.2 months vs. 7.1 months; HR = 0.22 [0.07-0.7]; p = 0.0041, p-interaction = 0.012) as well as PFS (mPFS 14.6 vs. 4.6; HR = 0.17 [0.05-0.6]; p = 0.0020, p-interaction = 0.0070). In pts treated with G+N+D+T, partial response (PR) was seen in 63.6% of pts with $\geq$2 DDR gene mutations compared to 26.9% in other pts (p = 0.033), and this effect was not observed with G+N (p = 0.18). The DDR gene biomarker was validated in 5/6 (83%) biomarker-positive samples using archival tissue WGS. **Conclusions:** The presence of $\geq$2 DDR gene mutations was strongly associated with benefit from the combination of chemotherapy with dual immune checkpoint inhibitor therapy, and pts with this signature had prolonged mOS of over 2 years. This represents the first prospective study in PDAC to define a predictive biomarker beyond mismatch repair deficiency for benefit from immune checkpoint therapy. Given the long-term survival noted in this subgroup, assessment of DDR gene mutations could be considered as part of routine standard of care testing for mPDAC pts. Clinical trial information: NCT02879318. Research Sponsor: Predicine; Astra Zeneca; Canadian Cancer Trials Group.

4179 **Poster Session**

Clinical outcomes and molecular characteristics of patients with metastatic pancreatic ductal adenocarcinoma according to involved metastatic sites. First Author: Mahmoud M.G. Yousef, The University of Texas MD Anderson Cancer Center, Houston, TX

Background: It is well documented that Pancreatic ductal adenocarcinoma (PDAC) metastasize to the liver had worse outcome than to the lung, but the molecular basis was less clear. We employ a large Real-World Evidence dataset to evaluate clinical and molecular features of PDAC according to involved metastatic sites. **Methods:** The Foundry software platform was used to query electronic medical records of patients with metastatic PDAC who underwent Next-Generation Sequencing (NGS) at MD Anderson. Involved metastatic sites were extracted using natural language process from imaging reports then manually verified. Overall survival (OS) was calculated from date of diagnosis. **Results:** We identified 1,095 patients with metastatic PDAC diagnosed between May 2003 and Oct 2024. Median follow up was 41.8 months and median OS was 22.8 (95%CI: 20.2-25.2) months. Most patients (52.9%) had multiple metastatic sites including liver, 28.5% had liver only metastases, while 8.7% had lung only metastases. 10% had metastases not including liver. Patients with lung only metastasis had the best outcomes (median = 57.6 months, HR = 0.37 relative to liver only, 95%CI = 0.27-0.52, p = 9.3e-9), followed by patients with metastases not involving liver (median = 41.3 months, HR = 0.65, 95%CI = 0.49-0.87, p = 0.003). Patients with liver only metastasis (median OS = 19.5 months) had similar survival to those with multiple sites including liver (median = 19.3 months, HR = 1.1, 95%CI = 0.96-1.4, p = 0.13). *TP53* was more frequently mutated in patients with liver only metastasis (84%) and multiple metastases including liver (85%) compared to patients with lung only (73%) and multiple sites not including liver (67%, p = 9.3e-5). *GNAS* showed lower frequency (5%) in patients with liver only and patients with multiple metastasis including liver (2%) compared to patients with lung only (8%) or non-liver metastases (10%, p = 0.003). In patients with liquid biopsy (n = 240), lung only metastasis showed significantly lower positivity rate for mutation detection (50% vs 65% for liver only, 62% for other or multiple not including liver and 79% for multiple including liver, p = 0.009), and lower *TP53* detection rate (23% for lung only vs 46% for liver only, p = 0.02). The frequency of *KRAS* mutation and mutant allele distribution were not significantly different in tissue NGS. However, patients with lung only metastasis showed significantly less frequent *KRAS* mutation detection by liquid biopsy (10% vs 52% in liver only metastasis, p = 9.6e-4). **Conclusions:** PDAC patients without liver metastasis have markedly improved OS relative to patients with liver metastasis, and lower rates of *TP53* mutation. Similar frequencies of *KRAS* mutation were found in different patients by tissue testing. However, patients with lung only metastasis had lower positivity rate of ctDNA, and lower detection rate of *KRAS* mutation by liquid biopsy. Research Sponsor: None.

4180 **Poster Session**

Pancreatic cancer mortality trends (2018-2023): Exposing racial inequities in Michigan's cancer burden. First Author: Mekdes Asfaw, Wayne State University, Rochester Hills, MI

Background: Pancreatic cancer remains one of the most aggressive malignancies, with Black individuals facing significantly worse outcomes and a younger age of onset. Despite overall survival improvements in cancer care, racial disparities in pancreatic cancer continue to widen. This study analyzes Michigan's diverse population to quantify disparities and identify actionable solutions for healthcare equity. **Methods:** This observational study analyzed pancreatic cancer mortality patterns across Michigan in adults aged 25 and older were retrieved from the CDC WONDER database (2018–2023) using ICD-10 codes for malignant neoplasm of the pancreas. Crude mortality rates (CMRs) and Age-adjusted mortality rates (AAMRs) per 100,000 were calculated by age, gender and race, with 95% confidence intervals (CI) for precision to assess racial disparities in mortality outcomes. Temporal trends and annual percentage changes (APCs) were analyzed using Joinpoint regression. **Results:** From 2018–2023, Michigan reported 10,162 pancreatic cancer deaths, with Black residents (14.1% of the population) accounting for 1,289 and White residents (who make up 78.9%) for 8,664 deaths. Overall, CMR was higher for White residents (18.26 per 100,000) than Black residents (15.21 per 100,000) who experienced a sharper rise in AAMR, increasing by 8.10% [14.36 (13.55–15.16)] compared to 4.92% [12.36 (12.10–12.63)] for White residents. For Black residents, CMRs increased with age, rising from 8.14 per 100,000 (45-54 years) to 105.78 per 100,000 (85+ years), peaking at 69.46 (65-74 years) and 95.37 (75-84 years). White residents had lower CMRs overall, starting at 1.48 per 100,000 (35-44 years) and gradually increasing to 115.28 per 100,000 in the 85+ group.In Washtenaw County, Black residents had a rate of 14.01 per 100,000 and White residents 15.79 per 100,000 with similar trends in Genesee, Wayne, and Ingham counties. Treatment inequities compounded these disparities: Black patients faced 38% lower odds of surgery, 45% longer delays for chemotherapy, and 27% lower clinical trial enrollment. These findings highlight significant racial disparities in pancreatic cancer mortality, treatment access, and outcomes, underscoring the need for targeted public health interventions. **Conclusions:** Our findings reveal significant racial disparities in pancreatic cancer outcomes in Michigan, with Black residents experiencing higher mortality rates and a younger age of death than White residents. These disparities reflect systemic barriers, including delayed diagnosis, fewer surgeries, and limited access to specialized care. Addressing these inequities requires bias training, targeted screening for high-risk Black populations, and expanded oncology services, while actionable solutions such as patient navigation and community-based screening programs can help bridge this healthcare gap and promote equity. Research Sponsor: None.

4181 **Poster Session**

Multimodal machine learning predictions of treatment response and survival in advanced pancreatic cancer from the COMPASS trial. First Author: Wei Quan, University Health Network, Toronto, ON, Canada

Background: Pancreatic cancer is an aggressive malignancy with limited therapeutic options and a poor prognosis. Current approaches to prognostication are limited, especially in advanced disease. We explored whether machine learning integrating multimodal data could predict outcomes in advanced pancreatic cancer. **Methods:** We developed and evaluated machine learning models predicting disease control rate and one-year survival from the COMPASS trial (NCT02750657). Data modalities included clinical features, histopathology, radiology, RNAseq, and whole-genome sequencing (WGS). After pre-processing, we applied LASSO and XGBoost to each modality and early and late fusion techniques. Hyperparameter tuning and performance assessment were performed using repeated nested cross-validation. The PurIST RNAseq classifier served as a baseline. Area under the curve (AUC) was the primary metric. **Results:** The cohort included 260 patients (105 female; median age 64 [IQR 58–70]; 141 treated with FOLFIRINOX, 97 with gemcitabine and nab-paclitaxel). 170 (65%) achieved disease control and 168 (65%) survived at least one year. The performance of the machine learning models is shown in the Table. Predictions from the unimodal models had limited correlation with each other (the maximum pairwise correlation averaged across folds was between clinical and histopathology models, 0.21). The late fusion models upweighted data modalities with stronger unimodal performance. **Conclusions:** Multiple individual data modalities can predict outcomes in advanced pancreatic cancer, with PurIST serving as a strong baseline. Despite differing predictions across data modalities, multimodal integration did not improve prognostic performance in this cohort. Research Sponsor: Ontario Institute for Cancer Research; Princess Margaret Cancer Foundation; The Terry Fox Research Institute Marathon of Hope Cancer Centres Network.

AUC for the PurIST baseline, the top 2 unimodal models, and the best fusion model for each outcome.

Outcome	Data Modality	AUC (95% confidence interval)
Disease control	PurIST	0.69 (0.69, 0.70)
	Radiomics	0.75 (0.72, 0.79)
	RNAseq	0.71 (0.70, 0.72)
	Fusion (late)	0.71 (0.69, 0.73)
One-year survival	PurIST	0.63 (0.62, 0.63)
	DNA mutations	0.64 (0.61, 0.66)
	RNAseq	0.57 (0.55, 0.60)
	Fusion (early)	0.61 (0.56, 0.66)

4182 **Poster Session**

Integrative analysis of tumor microenvironment in advanced pancreatic cancer: Unraveling genomic and immune landscape for targeted therapies. First Author: Catia Fava Gaspar, Division of Medical Oncology and Hematology, Princess Margaret Cancer Centre, University Health Network, University of Toronto, Toronto, ON, Canada

Background: An understanding of genotype and immunophenotype interactions in advanced pancreatic ductal adenocarcinoma (PDAC) is important in designing combination strategies. In addition, PDAC subtypes may harbor unique tumor immune microenvironments (TMEs) and confer differential sensitivity to *KRAS* inhibitors (KRASi). We aimed to characterize the baseline TME in advanced PDAC and its relationship with genomic, transcriptomic and clinical data. **Methods:** The COMPASS trial (NCT02750657) investigated whole genome (WGS) and transcriptome (RNA-Seq) sequencing in patients (pts) receiving first line therapy for advanced PDAC. We performed multiplex immunohistochemistry (mIHC) to identify 5 immune cell subtypes (CD8+/CD4+ T cells, Tregs, B cells and macrophages) and CIBERSORT, a deconvolution method that uses gene expression profiles. Statistical analyses were performed using STATA/R software and significance was defined as $p\text{-}value < 0.05$. Multivariate logistic regression was used and Kaplan Meier analyses evaluated impact on survival. **Results:** Of 268 pts, 62 had available tissue samples with mIHC, WGS, and RNA-Seq data (n = 21 primary biopsies, n = 41 metastases, 34/41 liver). All 62 pts had *KRAS* mutations (28 G12D, 19 G12V, 10 G12R, 5 other) and 29 had *KRAS* major or minor imbalances. 55 cases (88.7%) were classified as classical subtype and HRDetect^{hi} was seen in 10 pts, including 5 with *BRCA1/2* mutations (4 germline, 1 somatic). In the overall cohort, differences between tumor and stroma were evident with increased infiltration of CD8 and CD4 Tcells and Tregs in stroma ($p< 0.001$) and increased macrophages (p= 0.0343) in tumor. CIBERSORT in a subset of 51 pts demonstrated increased M0 (p= 0.0035) and M2 macrophages (p= 0.0067) in liver metastases compared to primary samples, suggesting a more immunosuppressive TME. A higher number of B cells were seen in lung metastases (median 207.5 vs. 43.2 vs. 3.7 vs. 1.8 cells/mm2, p= 0.011) compared to abdominal wall, peritoneum and liver, respectively. Pts with *KRAS* major imbalance (n =14, 3 basal like) were found to have higher median numbers of CD8+ (114.5 vs. 25.1 vs. 27.5 cells/mm2, p= 0.038) and CD4+ Tcells (292.1 vs 133.4 vs. 97.4 cells/mm2, p= 0.005) when compared to minor/balanced samples, respectively. Basal-like PDAC had fewer macrophages than classical subtype (median 13.2 vs. 28.2 cells/mm2, p= 0.0103). On survival analysis, pts with HRDetect^{lo} and classical subtype with higher macrophage counts had a tendency towards increased survival (median OS: 11.8 vs. 9.5 months, p= 0.066). **Conclusions:** We identified increased CD8/CD4 T cell infiltration in PDAC stroma, as well as in pts with *KRAS* major imbalance. Immune cell profiling may complement molecular profiling as potential biomarkers and warrants further study in this context. Research Sponsor: PM2C/MOHCCN.

4183 Poster Session

BRCA1/2 and _PALB2_ short variants (SVs) contributed by clonal hematopoiesis (CH) in liquid biopsies (LBx) from patients with advanced pancreatic cancer (PC). First Author: Kim Anna Reiss, University of Pennsylvania, Philadelphia, PA

Background: CH results from fitness-enhancing mutations in hematopoietic stem cells. Many CH somatic variants (SVs) are in cancer-associated genes, including *ATM* and *CHEK2*, which do not have a homologous recombination deficiency (HRD) phenotype. SVs in well-established HRD-associated genes like *BRCA1/2* and *PALB2* also appear in white blood cells as CH, albeit more rarely. Herein, we report the prevalence of SVs of CH origin in these clinically relevant genes that confound results of PC liquid biopsies (LBx) and study their association with HRD in tissue biopsies from the same patients. **Methods:** This study uses a novel variant origin prediction algorithm to classify the origin of each SV detected by FoundationOneLiquid CDx as germline, tumor-somatic, or CH, using a combination of sample-specific and dataset-learned features including fragmentomics (trained and validated against white blood cell standard). 5,625 PC LBx sequenced during routine clinical care was used for broad prevalence data. A subset with matched tissue biopsies (TBx, n = 536) was used to compare SV detection and true HRD via HRDsig in TBx, a signature validated to predict response to PARP inhibitors across multiple cancer types. **Results:** Among 303 PC LBx with a *BRCA1/BRCA2/PALB2* SV, 52 (17.2%) were predicted to be of CH origin. This percentage is larger than for other *BRCA*-associated canonical cancer types: prostate (14.1%, 139/980), breast (9.7%, 87/902), ovarian (7.0%, 14/200), but less than some non-canonical cancer types (Table). In PC patients with both LBx and TBx available, 29/536 (5.4%) had an SV in *BRCA1/BRCA2/PALB2* detected in LBx: 8/29 in LBx only; 21/29 in both LBx and TBx. 19/29 were predicted germline by the algorithm, were all also detected in TBx, and 15 (79%) of these TBx were HRDsig+. 5/29 (17%) were predicted to be tumor-somatic; two of these were detected in TBx and one (20%) was HRDsig+. Predicted CH SVs were detected in another 5 LBx (4 *BRCA2*; 1 *PALB2*). None of these were detected in TBx and none of the tumors were HRDsig+. **Conclusions:** While the majority (58%) of *BRCA1/BRCA2/PALB2* SV+ PC LBx harbored a predicted germline SV, 25% harbored tumor-somatic SV and 17% had SV exclusively predicted as CH-derived. Determining the cellular origin of *BRCA1/BRCA2/PALB2* in PC is essential given the potential impact on treatment selection. Research Sponsor: Foundation Medicine.

Cancer type	LBx, N	n with SV in *BRCA1/2/PALB2* (%)	% Germline SV present	% Tumor somatic SV present	% No germline/tumor somatic SV, only CH SV present
Lung	21456	928 (4.3)	25.5	51.3	23.1
Cholangiocarcinoma	1787	90 (5)	38.9	38.9	22.2
Pancreas	5625	303 (5.4)	57.8	25.1	17.2
Esophagus	1199	56 (4.7)	33.9	50.0	14.3
Prostate	13858	980 (7.1)	39.3	46.5	14.2
Colorectal	6639	391 (5.9)	15.3	73.4	11.0
Breast	11397	902 (7.9)	55.2	35.1	9.6
Ovarian	1464	200 (13.7)	66.0	27.0	7.0
Endometrial	795	84 (10.6)	20.2	73.8	6.0

4184 Poster Session

5-FU + Naliri, gemcitabine plus nab-paclitaxel or both regimens given sequentially for first line treatment of metastatic pancreatic ductal adenocarcinoma: A randomized phase II comparative study (FUNGEMAX-PRODIGE 61). First Author: Julien Taieb, Hôpital Europeen Georges Pompidou, APHP, Université Paris-Clté, CARPEM Cancer Institute, Paris, France

Background: New chemotherapeutic approaches are still needed to improve survival and quality of life in metastatic pancreatic ductal adenocarcinoma (mPDAC). We have previously published results of two randomized phase II of first-line sequential treatment strategies of intensified FOLFIRI regimen followed by gemcitabine-based regimens (FIRGEM and FIRGEMAX-PRODIGE 37 studies) with good efficacy and tolerability results. FUNGEMAX-PRODIGE 61 evaluated 5FU + Naliri (NAPOLI) vs gemcitabine + Nab-paclitaxel (MPACT) vs both regimens sequentially. **Methods:** Chemotherapy-naive pts with proven mPDAC, bilirubin levels < 1.5 ULN and performance status (PS) 0-1 were randomized to receive either the NAPOLI regimen for 2 months, alternating with the MPACT regimen for 2 months (arm A), NAPOLI alone (arm B) or MPACT alone (arm C) until progression or limiting toxicity. Using the Schoenfeld method, the primary endpoint was the progression-free survival (PFS) rate at 6 months from (H0) 30% over (H1) 45%, requiring 96 patients per arm (assuming 5% lost to follow-up). **Results:** Between 11/2018 and 01/2024, 288 pts were enrolled in 31 French centers and 283 included in the modified intent to treat population (mITT, patients who received at least one dose of treatment). Database lock was done on the 20/12/2024. Baseline characteristics were well balanced between the arm A, B and C (mean age: 65/63/65, female: 47/43/47%, PS-0: 33/34/37%, > 1 metastatic site: 53/48/48%, mean albumin 39/40/39 g/L). With a median follow-up of 39.2 months, study treatment was discontinued in 89.5%, 96.8% and 93.7% of patients for arms A/B/C; median treatment duration were 6.3/3.3/5.3 months, respectively. In the mITT, neither treatment with MPACT/NAPOLI (HR = 0.76, 95%CI: 0.57-1.02; p = 0.07) nor NAPOLI (HR = 1.20, 95%CI: 0.90-1.60; p = 0.22) lead to a statistically significant improvement of PFS over MPACT. PFS, Overall survival (OS) and safety data are summarized in the table. **Conclusions:** The study did not show superiority of either the sequence MPACT/NAPOLI or NAPOLI over standard MPACT. However, the sequential MPACT/NAPOLI regimen is feasible, tolerable, and associated with higher rates of 12-mo PFS and 24-mo OS and less neuropathy and can be considered in patients unfit to receive FOLFIRINOX. NCT03693677. Clinical trial information: 2024-518143-38-00. Research Sponsor: None.

	Arm A (MPACT/NAPOLI)		Arm B (NAPOLI)		Arm C (MPACT)	
PFS						
median (mo)	6.2 [4.0;7.8]		3.7 [2.2;5.1]		5.7 [4.0;6.5]	
rate at 6-m	51.6% [41.1;61.0]		32.3% [23.04;41.81]		45.3% [35.1;55.0]	
rate at 12-m	20.3% [12.9;29.0]		12.7% [6.8;20.3]		11.9% [6.3;19.4]	
OS						
median (mo)	11.6 [8.4;15.0]		9.1 [7.10;10.45]		12.4 [9.76;14.03]	
rate at 24-m	23.8% [15.4;33.2]		9.5% [4.19;17.36]		12.5% [6.28;20.93]	
Grade 3-4 toxicities						
AE/SAE	**All Grades**	**Grade 3-4**	**All Grades**	**Grade 3-4**	**All Grades**	**Grade 3-4**
Neutropenia	25.3%	9.5%	11.8%	0%	26.3%	7.4%
Diarrhea	80%	17.9%	69.9%	16.1%	55.8%	5.3%
Vomiting	80%	15.8%	72%	14.0%	61.1%	4.2%
Peripheral Neuropathy	44.2%	5.3%	10.8%	0%	57.9%	8.4%

4185 Poster Session

Machine learning and statistical prediction of overall survival (OS) from pre-dose plasma biomarkers in a randomized phase 2 trial (1801 Part 3B) of the GSK-3 inhibitor elraglusib in metastatic pancreatic ductal adenocarcinoma (mPDAC): Application toward patient enrichment. First Author: Taylor Weiskittel, Mayo Clinic, Rochester, MN

Background: Elraglusib is a first-in-class inhibitor of GSK-3ß, a well-credentialed target in cancer implicated in intrinsic oncologic processes and tumor immune response. Preliminary results of the 1801 Part 3B trial (NCT03678883) showed statistically significant benefits for elraglusib+GnP versus GnP for 1-year survival and mOS in mPDAC (companion abstract: Mahalingam et al.). We investigated plasma levels of cytokines/chemokines/soluble cell receptors/growth factors (CCSG) as potential biomarkers of favorable outcomes on elraglusib. **Methods:** Forty CCSGs were evaluated in pre-dose plasma from patients with previously untreated mPDAC enrolled in 1801 Part 3B treated with GnP (n = 78) or elraglusib+GnP (n = 155) using a Luminex immunoassay. Using Kaplan-Meier statistics and cutpoint determination, CCSGs were assessed for OS predictive ability in the elraglusib+GnP arm. Multivariate models were constructed to predict binarized survival at 12 months using machine learning (ML). Fivefold cross-validation was used in both analyses, and all methods were applied to the GnP arm to identify elraglusib+GnP specific predictors. **Results:** Data shown as of November 15, 2024. Multiple CCSGs significantly stratified elraglusib+GnP patients. The most extreme prognosticators were IFN-ß (average HR = 2.34), and PD-L1 (average HR = 0.52) (HR shown as high CCSG vs low CCSG). Screening of different ML approaches ranked logistic regression at the top, and hyperparameter grid search identified stochastic gradient solver with ridge regularization as the optimal method. The model had an accuracy of 88% (SD: 3.9%) and a balanced accuracy of 80% (SD: 8.5%). IFN-beta had the most substantial effect size (odds ratio (OR) = 72.28), followed by IL-18 (OR = 23.38) and PD-L1 (OR = 15.32). All other CCSGs had an OR between 0.03 and 6.71. When this model was applied to patients in the GnP arm, accuracy was 68.4%, and balanced accuracy was 43.1%. **Conclusions:** Many CCSG biomarkers were identified as promising predictors of survival benefit in mPDAC patients treated with elraglusib+GnP. Both univariate statistical and multivariate ML approaches show predictive significance with high interpretability. The initial ML model is specific to elraglusib treatment, not GnP alone. These results indicate that patients' initial immune state plays a role in response to elraglusib+GnP. However, single CCSGs for enrichment currently exclude too many patients ($> 75\%$), and thus, panels of biomarkers are being investigated with ML to overcome this limitation. The 1801 Part 3B clinical trial recruitment has been completed, and updated biomarker models reflective of topline OS data, available by April 2025, will be presented. Research Sponsor: Actuate Therapeutics Inc.

4186 Poster Session

Real-world predictors of adverse clinical outcomes in pancreatic cancer using a machine-learning framework. First Author: Akanksha Dua, University of California, San Francisco, San Francisco, CA

Background: Completion of chemotherapy is crucial for clinical benefit and has been linked to improved outcomes, but is often challenging given the toxicities of chemotherapy regimens. The main treatment regimen for pancreatic adenocarcinoma (PDA), FOLFIRINOX (FFX), is highly toxic, requires frequent dose-modifications, and most patients are too sick to tolerate multiple lines of therapy. Given the aggressiveness of the disease, selecting the appropriate first-line dosing is crucial as it can be associated with better patient outcomes. The current study objective is to evaluate the association between real-world dosing patterns and clinical toxicity using a machine-learning framework. **Methods:** Patients attending GI oncology clinics at University of California, San Francisco between November 2011 – December 2023 with a documented administration of FFX were included. Predictors of clinical outcomes included baseline demographic and clinical features, cycle-specific laboratory data, and dosing information for FFX sub-components. Group-based 5-fold cross-validation for logistic regression, random forest, and XGBoost models were used to identify features associated with clinical outcomes (anemia, dehydration, nausea/vomiting, neutropenia, and polyneuropathy). Model performance was evaluated using AUC. **Results:** Data for 505 patients with PDA receiving FFX across 5,041 cycles were included.The random forest models yielded the best fit for the prediction across all outcomes (Table). Key features consistently associated with outcomes included cycle number, cumulative dose of drug received, laboratory data (PT, INR, albumin), patient demographics (male sex, race, and smoking status), and clinical features, such as hypertension. **Conclusions:** Our study identifies clinical features in combination chemotherapy leading to specific toxicities, highlighting these as ideal strategies for intervention. Early prognostic indicators of adverse outcomes can guide early management for high-risk individuals through supportive measures and dose modification, before high-grade toxicities and discontinuations wherein patients can no longer benefit from therapy. Research Sponsor: UCSF Pancreas Center.

Summary of FOLFIRINOX model outputs across clinical outcomes.

Outcome\Model	Logistic Regression	Random Forest	XGBoost	Key Features
Anemia	0.61 ± 0.03	0.67 ± 0.03	0.62 ± 0.04	[1] INR [2] Irinotecan dose [3] Any polyneuropathy
Dehydration	0.64 ± 0.03	0.72 ± 0.02	0.68 ± 0.05	[1] Cumulative irinotecan [2] Cumulative oxaliplatin [3] Cumulative fluorouracil
Nausea or vomiting	0.62 ± 0.04	0.68 ± 0.03	0.66 ± 0.03	[1] Cumulative irinotecan [2] Cumulative oxaliplatin [3] Cumulative fluorouracil
Neutropenia	0.57 ± 0.04	0.61 ± 0.06	0.61 ± 0.01	[1] Male sex [2] Cumulative fluorouracil [3] Smoking status – never
Polyneuropathy	0.53 ± 0.06	0.53± 0.06	0.52 ± 0.04	[1] Male sex [2] Oxaliplatin [3] Constipation

4187 **Poster Session**

A PBMC and machine learning based biomarker signature to predict second line chemotherapy success in advanced PDAC: Translational data of the PREDICT trial—A prospective, multicenter, trial of the AIO Pancreatic Cancer Group (AIO-PAK-0216). First Author: Anton Lahusen, Department of Internal Medicine I, Ulm University Hospital, Ulm, Germany

Background: The PREDICT trial, a recent phase IIIb/IV study, aimed to address the critical need for improved personalized treatment strategies in advanced pancreatic cancer. This translational investigation examined the predictive value of 1st line chemotherapy (CTX) response on the efficacy of subsequent 2nd line treatment by using liquid biomarkers combined with machine learning (ML). **Methods:** Pts. were stratified into two cohorts based on short or long 2nd line CTX time to treatment failure (S-/L-TTF2; *n* = 10 per group, 80/20% quantiles). Treatment-naïve PDAC tissue specimens underwent laser microdissection for tumor cell enrichment, followed by RNA profiling using NanoString™ PanCancer IO360. Selected differentially regulated genes from the omics results were utilized to screen peripheral blood mononuclear cells (PBMCs) from 2nd line treatment-naïve patients at protein (flow cytometry, FC) or RNA (RT-qPCR) levels. FC data was analyzed using R-based single-cell clustering (x-Shift, FlowSOM, T-REX) to generate HyperGates (HGs), with subsequent ML-based back-gating (HyperFinder algorithm) of the most differential clusters. Additionally, classical ManualGates (MGs) were generated. Feature selection employed the Weka-based WrapperSubsetEval (WSE) algorithm with eight different classifiers (NB, KLR, LR, SMO, IBk, RT, RF, J48). The classifier/subset with optimal performance was utilized for binary classification (S-TTF2 vs. L-TTF2) of training (80%, n = 66) and validation (20%, n = 16) datasets. **Results:** Transcriptome analysis of L- vs. S-TTF2 tumor tissues revealed increased inflammation (upregulated 18-gene signature), immune cell activation/infiltration (e.g. CD4/CD8 T cells), and immune exhaustion (upregulation of e.g. PDCD1, LAG3, CTLA4, TIGIT) in L-TTF tumors. Further, the favorable Bailey immunogenic subtype was enriched in the L-TTF2 group. Analysis of eight FC panels (19 candidates) revealed 1198 differential clusters with HGs and 881 classical MGs. Feature selection, combining FC data with RT-qPCR results and clinical parameters, identified a best performing signature of 5 HGs and 2 MGs for 7 protein markers (CXCR4, CD8, CD4, CD62P, CD307b, CD45, CD121b). ML using a kernel logistic regression successfully predicted S- and L-TTF2 binary groups prior to 2nd line CTX with nal-IRI/5-FU/LV (ROC-AUC $>$ 0.90 for training and validation). **Conclusions:** We identified a favorable tumor immune microenvironment in L-TTF aPDAC patients, characterized by CD8 T cell-inflamed ("hot") tumor tissues prior to 2nd line CTX. A 7-marker liquid biomarker panel, comprising 7 flow cytometry PBMC population gates, was developed for early prediction of 2nd line nal-IRI/5-FU/LV CTX success. These findings aim to advance personalized treatment strategies. Clinical trial information: NCT03468335. Research Sponsor: Servier.

4188 **Poster Session**

Preliminary result of a phase Ib study: Efficacy and safety of FG-M108 plus gemcitabine and nab-paclitaxel in patients with Claudin18.2-positive, locally advanced, unresectable, or metastatic pancreatic cancer. First Author: Funan Liu, The First Hospital of China Medical University, Shenyang, China

Background: FG-M108, an ADCC-enhanced anti-CLDN18.2 monoclonal antibody, showed significant efficacy in first-line (1L) treatment of gastric cancer. Herein, we report the safety and efficacy results of FG-M108 in 1L treatment of pancreatic cancer (cohort C2 and D2). **Methods:** In this open-label, multicenter phase I/II study patients received FG-M108 (cohort C2: 300mg/m2 or cohort D2: 600mg/m2 Q3W) plus gemcitabine (1000mg/m2, d1, d8, Q3W) and nab-paclitaxel (125mg/m2, d1, d8, Q3W). Eligible patients were those with CLDN18.2 positive local advanced or metastatic pancreatic cancer who were previously untreated. The primary endpoint were the incidence of adverse events (AEs) and preliminary clinical efficacy (ORR, DCR, DOR, PFS, and OS). **Results:** As of November 15, 2024, 50 patients were enrolled and received FG-M108+gemcitabine/nab-paclitaxel treatment (39 patients in cohort C2, 11 patients in cohort D2). The median age was 61 (range 30-72). 47 (94%) patients were with CLDN18.2 moderate-high expression. Out of 50 patients, 44 patients had at least one tumor assessment after baseline and included in the efficacy analysis set. The median follow-up time (95%CI) for the 32 patients with CLDN18.2 moderate-high expression was 9.5 months (6.8,11.2) , with a maximum treatment duration of 13 months. In the subgroup of cohort C2 patients with CLDN18.2 moderate-high expression assessed by Independent Review Committee(IRC)—16 patients achieved confirmed PR, and one achieved unconfirmed PR. ORR was 53.1% (34.7,70.9), and DCR was 100.0% (89.1-100.0). The median DOR reached 9.9 months (7.8,NE), and the median PFS reached 9.9 months (7.0,NE) . OS data are not yet mature, with 23 patients still alive, achieving a median OS of 17.4 months (11.0,NE). Treatment-emergent adverse events (TEAE) occurred in 32 patients (100.0%), in which 15 (46.9%) were $\geq$ grade 3. The most common FG-M108 related AEs in cohort C2 & D2 were nausea (56.4% vs 36.4%), vomiting (48.7% vs 45.5%), and hypoalbuminaemia (46.2% vs 54.5%). **Conclusions:** The combined therapy of FG-M108 plus chemotherapy as 1L treatment for patients with CLDN18.2 positive pancreatic cancer was generally well tolerated with promising survival (PFS and OS) data especially in patients with CLDN18.2 moderate-high expression, pivatol phase III clinical study will start in 2025 Q2. Clinical trial information: NCT04894825. Research Sponsor: None.

4189 **Poster Session**

Neo-adjuvant chemo-immunotherapy in pancreatic cancer: Results of the Australasian Gastrointestinal Trials Group (AGITG) NEO-IMPACT pilot trial. First Author: Lorraine A. Chantrill, University of Wollongong, Wollongong, NSW, Australia

Background: Despite curative intent surgery and peri-operative chemotherapy for resectable pancreatic ductal adenocarcinoma (PDAC), recurrence rate remains high ($>$80%). Whilst immunotherapy has not been shown to be effective in the metastatic setting, there may be a scientific rationale for mobilising the immune system before surgery for localised disease to improve outcomes. **Methods:** NEO-IMPACT is a single arm phase II study testing the feasibility and safety of delivering 12 weeks of neo-adjuvant immune checkpoint inhibitor in combination with FOLFIRINOX (3 doses of 1500mg durvalumab q28d + 6 cycles of FOLFIRINOX q14d) for resectable or borderline resectable pancreas cancer. The patients then received 3 months of adjuvant chemotherapy. The primary endpoint was the proportion of patients receiving $\geq$80% of planned neoadjuvant treatment. A sample size of 20 was calculated to allow 80% power. Secondary endpoints include the proportion of patients missing surgery due to treatment related adverse events (TRAEs); treatment tolerability; R0 resection rate; pathological complete response rate; objective response rate. **Results:** 20 patients with PDAC were enrolled between August 2022 and June 2024, 13 resectable and 7 borderline resectable disease. 17 of 20 patients (85%) completed planned neoadjuvant treatment. Grade 3-4 adverse events (AEs) occurred in 8 patients. The most common was infection (4), febrile neutropenia (1) and nausea (2). 1 patient died from 5FU toxicity due to homozygous loss of DPYD. There were 2 iAEs (colitis and maculopapular rash). 1 patient had TRAE and had to come off trial but proceeded to surgery. 3 patients (1 borderline/2 resectable) became unresectable at assessment for surgery following neoadjuvant therapy. Of the 16 patients who underwent surgery (12 head; 4 neck/tail), 2 had a complete pathological response. 13 had an R0 resection; 3 had an R1 resection. All 16 patients received post operative adjuvant therapy. At a median follow up of 15 months, 5 patients who proceeded to surgery and adjuvant therapy have recurred. **Conclusions:** Neoadjuvant chemoimmunotherapy is feasible and safe for patients with resectable and borderline resectable pancreas cancer. A 10% CPR rate and 70% R0 resection rate are encouraging, and this approach should be further explored in a larger population. Clinical trial information: ACTRN12622000378729. Research Sponsor: GI cancer.org.au (Australasian Gastrointestinal Trials Group); Astra Zeneca Pty Ltd.

4190 **Poster Session**

NeoOPTIMIZE: Phase II trial of adaptive switching of neoadjuvant FOLFIRINOX (FFX) to gemcitabine/nab-paclitaxel (GA) resectable/borderline resectable (BR)/locally advanced (LA) pancreatic adenocarcinoma (PDAC). First Author: Lyndsey Sandow, Internal Medicine, Oregon Health & Science University, Portland, OR

Background: Neoadjuvant chemotherapy (NAC) for localized PDAC may improve R0 resection. FFX and GA are used but lack of predictive biomarkers remains a barrier to optimal NAC. The angiotensin-II receptor blocker (ARB), losartan, remodels vascular perfusion to enhance NAC efficacy. We established an experimental platform for dynamic switching of NAC +/- radiation therapy for resectable/BR PDAC and an exploratory cohort of LA PDAC. **Methods:** Patients (pts) received 4 cycles of FFX (ox 85 mg/m2; LV 400 mg/m2; iri 150 mg/m2; 5-FU 2400 mg/m2), then were restaged in a multidisciplinary tumor board (Restage I). Pts without progression (CT and CA19-9 increase $<$30% from baseline) completed 4 more cycles of FFX. If there was progression (CT and/or CA19-9 increase $>$ 30%) or intolerance, pts were switched to GA (nab-P 125 mg/m2; gem 1000 mg/m2) for 2 months. After a total of 4 months NAC, pts were re-staged (Restage 2) and had surgery or chemoRT (if vascular involvement) then surgery. Losartan (50mg QD) was given throughout NAC/chemoRT. The primary endpoint was the proportion of resectable/BR with R0 resection. **Results:** Of 43 patients screened,16 were resectable, 21 BR, 5 LA and 1 ineligible. Median age was 65 years (range: 34-80), 49% male, 84% Caucasian white. Head of pancreas primary was 84%. Mean baseline CA19-9 96 ng/mL. 1 pt had progressive disease prior to Restage 1. Of the 36 pts at Restage 1, 31 continued FFX and 5 switched to GA. 18 patients on FFX had a radiographic response, 5 had CA 19-9 decrease $>$25%, and 8 had stable disease with unchanged CA 19-9. 3 pts switched to GA for radiographic progression,1 for increased CA 19-9 $>$30% and 1 for FFX intolerance. Of 34 pts evaluated at Restage 2, 2 continued NAC, 13 had pre-op chemoRT (12 BR and 1 resectable), and 19 proceeded to surgery. 24/27 (88%) pts on FFX had R0 resections; 4/4 (100%) pts switching to GA had R0 resections. Overall, 77% pts completing NAC FFX had R0 resections; 80% pts switched to GA had R0 resections. Grade $>$ 3 toxicities 7% FFX and 5% GA. **Conclusions:** Early switching to GA in pts progressing on FFX led to an equivalent R0 resection rate. Optimization of NAC made it possible to undergo curative intent surgery that would not have occurred. Secondary endpoints of DFS, OS and multiomic based studies of blood and tumor tissue via our Serial Measurements of Molecular and Architectural Responses to Therapy (SMMART) platform are underway to identify molecular markers to predict response and determine whether a switch in treatment is indicated. Clinical trial information: NCT04539808. Research Sponsor: None.

4191 **Poster Session**

Development and prospective validation of a novel cfDNA-based diagnostic model for the early detection of pancreatic cancer. First Author: Xiuchao Wang, Tianjin Medical University Cancer Institute and Hospital, Tianjin, China

Background: Pancreatic cancer (PC) is one of the most lethal malignancies, with a 5-year survival rate below 10%, primarily due to late-stage diagnosis. Existing diagnostic markers, like CA19-9, show inadequate sensitivity and specificity for early detection. To address this critical gap in early PC detection, this study developed and prospectively validated a cfDNA-based diagnostic model integrating fragmentomics features, including copy number variations (CNVs), fragment size ratios (FSR), and orientation-aware cfDNA fragmentation (OCF). **Methods:** A multicenter study was carried out with a case-control cohort (n = 467) for model development and a prospective cohort (n = 1,926) for clinical validation. Plasma cfDNA underwent low-pass whole-genome sequencing to extract fragmentomics features like CNVs, FSR, and OCF. A stacked ensemble machine-learning model was built based on case-control data and validated in the prospective cohort of PC elevated-risk individuals with diabetes or obesity. Sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) were evaluated and compared with those of CA19-9. The follow-up was intended to last for 3 to 5 years, with the current follow-up period ranging from 12 to 24 months. **Results:** In the case-control cohort, the cfDNA-based model achieved AUCs of 0.9799 and 0.9622 in the training and validation sets, respectively, with both sensitivity and specificity exceeding 90%. In the prospective cohort (n = 1,926), for the 8 PC cases identified, the cfDNA model demonstrated a sensitivity of 75%, specificity of 98.1%, and PPV of 15.2% for detecting PC, significantly outperforming CA19-9 (sensitivity: 12.5%, specificity: 94.3%, PPV: 0.9%). Notably, the cfDNA model detected all 3 Stage 0 cases, 1 of 3 Stage I cases, and both Stage II cases, providing a median lead time of 227.5 days (range: 45–298 days) compared to imaging modalities. In contrast, CA19-9 detected only one Stage II case out of eight confirmed PC cases (12.5%). The model demonstrated significant potential in stratifying pancreatic cysts into high-risk and low-risk categories. While CA19-9 is ineffective in detecting either high-risk or benign cysts within the prospective cohort, the cfDNA model successfully differentiates between high-risk and low-risk pancreatic cysts (e.g., high-risk IPMN, 1/1 = 100% sensitivity; low-risk SCN, 0/1 = 0% false positive), which further underscores its clinical utility. **Conclusions:** This study is the first to validate a cfDNA-based diagnostic model for PC in a large elevated-risk population, showing superior performance and significant lead time benefits. The model detects PC earlier with much higher sensitivity and specificity than CA19-9, promising better outcomes with earlier treatment. The findings highlight cfDNA's potential for non-invasive PC screening in clinical settings. Research Sponsor: The National Key Research and Development Program of China; The Tianjin Key Medical Discipline (Specialty) Construction Project.

4192 **Poster Session**

Prognostic value of postoperative circulating tumor DNA and tumor markers in resected pancreatic adenocarcinoma (PAAD): An interim analysis of a prospective observational study. First Author: Qian Zhan, Department of General Surgery, Pancreatic Disease Center, Ruijin Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai, China

Background: Despite the benefits of postoperative adjuvant chemotherapy, recurrence rates of PAAD remain as high as 60% within the first year, underscoring the need for improved strategies to optimize treatment plans. This prospective observational study aims to evaluate the potential of postoperative ctDNA-based minimal residual disease (MRD) as an early predictor of disease relapse in resected PAAD using next-generation sequencing. **Methods:** Pathologically confirmed stage I-III PAAD patients who underwent surgical resection and carried KRAS mutations were enrolled. Eligible criteria included negative surgical margins and no metastasis prior to adjuvant therapy. Patients who did not receive adjuvant therapy were excluded. Tumor tissue samples collected during surgery were analyzed using a 769-gene NGS panel, while plasma samples were obtained at landmark (4–8 weeks post-operation and pre-therapy), 12-, 24-, 36-, and 48-weeks post-operation, and 2 weeks post-adjuvant therapy. Plasma samples were assessed for MRD using MinerVa (Genecast Biotechnology). Concurrently, tumor biomarkers such as CA19-9 were measured. The primary endpoint was overall survival (OS), while the secondary endpoint was disease-free survival (DFS). The trial is designed for a total follow-up period of three years. **Results:** As of November 27, 2024, a total of 133 patients underwent MRD analysis. KRAS mutations were distributed as follows: p.G12D in 55%, p.G12V in 27%, p.G12R in 13% and other subtypes in 5%. Nine patients were excluded due to loss of follow-up, and 12 were excluded for less than six months of follow-up, leaving 112 patients for this interim analysis. MRD positivity rates were 16%, 9%, 10%, 15%, 11%, and 11% at landmark, 12, 24, 36, 48 weeks, and 2 weeks post-therapy, respectively. Landmark MRD positivity was a significant predictor of disease recurrence (HR = 2.39, 95%CI:1.14-5.01, p = 0.017). Combining landmark MRD with biomarker CA19-9 improved prognostic accuracy (HR = 2.70, 95%CI:1.4-5.5, p = 0.002). Patients with longitudinal MRD-positive (detected at any time point excluding landmark or relapse) had significant worse DFS (HR = 3.13, p = 0.001) and worse OS (HR = 0.73, p = 0.001) compared to those with negative MRD. Analysis of MRD status at landmark and week 36 revealed that patients transitioning from MRD-positive to MRD-negative (clearance) had significantly better DFS compared to those with persistent MRD positivity (p = 0.023). Notably, no patients deceased from the MRD clearance group. **Conclusions:** These findings underscore the clinical utility of integrating landmark and longitudinal MRD assessments with tumor markers for comprehensive risk stratification and prognostication in resected PAAD patients. This approach could potentially guide personalized treatment strategies and improve patient outcomes. Clinical trial information: NCT05479708. Research Sponsor: None.

4193 **Poster Session**

Five-year outcomes of perioperative or only adjuvant gemcitabine plus nab-paclitaxel for resectable pancreatic cancer (the NEONAX trial): A randomized phase II trial of the AIO pancreatic cancer group. First Author: Thomas Jens Ettrich, Department of Internal Medicine I, Ulm University Hospital, Ulm, Germany

Background: Perioperative chemotherapy (CTX) in resectable pancreatic ductal adenocarcinoma (rPDAC) is still not considered standard of care and data are limited. NEONAX examined gemcitabine (Gem)/nab-paclitaxel (nab-P), in the perioperative or adjuvant therapy of resectable PDAC (NCCN criteria). **Methods:** NEONAX is a prospective, randomized phase II trial with two independent arms (127 patients, 22 German centers) and randomization 1:1 to perioperative (2 pre- and 4 postoperative cycles, po-arm A) or adjuvant (6 cycles, ad-arm B) of gem (1000mg/m2 BSA, d1, 8, 15) and nab-P (125mg/m2 BSA, d1, 8, 15), q4w. **Results:** As we previously reported were R0- and N0-resection rates high (po-R0 88%, ad-R0 67%, po-N0 33%, ad-N0 29%) in the ITT-population (all randomized pts.). The primary endpoint DFS rate of 55% @ 18 months in the mITT population (defined as R0/R1 resected pts. that either started perioperative (A) or adjuvant (B) CTX), was not reached in both arms (arm A: 32%, arm B 41%). Whereas 91.5% of pts. in po-arm A started and 84.7% completed neoadjuvant CTX, only 42.4% of pts. in ad-arm B started and 25% completed adj. CTX, so the CTX dose intensity was higher in the po-arm A. (Seufferlein et al., Ann Onc 2023) Here we report long-time 5-year outcomes according to PFS and OS and present a preplanned subgroup analysis of potential prognostic factors. The mOS in the ITT population (all randomized pts.) was 25.5 mo. in the po-arm and 16.8 mo. in the ad-arm. This corresponds to an mDFS of 11.4 mo. in the po-arm and 5.1 mo. in the ad-arm, respectively. The mOS in the mITT population (all randomized pts. that started po-ctx (po-arm) or started ad-ctx (ad-arm)) was 27.9 mo. in the po-arm and 26.8 mo. in the ad-arm. This corresponds to an mDFS of 14.1 mo. in the po-arm and 16.1 mo. in the ad-arm, respectively. In the preplanned analysis of subgroup factors impacting outcome, the benefit of po-treatment was independent of tumor size, N-status and baseline Ca19-9 level. This benefit was not visible in the mITT population where only patients in the ad-arm were included who had started adjuvant treatment postoperatively. **Conclusions:** These 5 year data confirm the outcome of patients receiving gem/nab in the po-setting in the ITT population. DFS and OS effect were numerically better compared to the ad-arm although the trial was not powered for direct comparison of the arms. This difference disappeared in the mITT population when patients received more CTX in the ad arm. We conclude that the difference between ITT and mITT is likely because more CTX could administered in the po-arm when the ITT population was considered and may constitute one of the major effects of neoadjuvant chemotherapy in resectable PDAC, particularly when a high rate of patients as in our multicenter trial could get neoadjuvant, but not adjuvant treatment. Clinical trial information: NCT02047513. Research Sponsor: Bristol Myers Squibb GmbH & Co. KGaA.

4194 **Poster Session**

Perioperative pembrolizumab (pembro) plus chemotherapy (chemo) for locally advanced gastric or gastroesophageal junction (G/GEJ) cancer: Asia versus non-Asia subgroup analysis of KEYNOTE-585. First Author: Takashi Oshima, Kanagawa Cancer Center, Yokohama, Japan

Background: In the randomized phase 3 KEYNOTE-585 study (NCT03221426), pCR was significantly improved in participants (pts) with locally advanced G/GEJ cancer treated using perioperative pembro + chemo vs placebo (pbo) + chemo, although the difference in EFS did not meet the prespecified criteria for significance. We present an exploratory subgroup analysis by geographic region (Asia vs non-Asia). **Methods:** Eligible pts had untreated, locally advanced, resectable G/GEJ adenocarcinoma (including Siewert type 2 or 3 tumors). Pts enrolled in the main cohort (n = 804) received neoadjuvant pembro 200 mg IV Q3W or pbo + chemo (cisplatin + capecitabine or 5-FU) for 3 cycles (C); after surgery, pts received adjuvant pembro or pbo + chemo Q3W for 3C then adjuvant pembro or pbo Q3W for 11C. Pts in the FLOT cohort (n = 203) received neoadjuvant pembro 200 mg IV Q3W or pbo Q3W for 3C + FLOT Q2W for 4C; after surgery, pts received adjuvant pembro or pbo Q3W for 3C + FLOT Q2W for 4C, then adjuvant pembro or pbo Q3W for 11C. Primary end points were pCR (BICR), EFS (RECIST v1.1 by investigator), OS (main), and safety (FLOT). We report outcomes in the main and FLOT cohorts combined. The database cutoff date was February 16, 2024 (final analysis). **Results:** Of 1007 pts enrolled, 387 were enrolled in Asia; 620, at non-Asia sites; baseline characteristics were generally balanced, with notable exceptions for ECOG PS 1 (11.9% Asia vs 37.1% non-Asia), FLOT backbone (1.6% vs 31.8%), tumor location stomach (86.6% vs 68.9%), and tumor stage III-IVa (85.8% vs 74.0%). In the Asia subgroup, pCR was 17.1% with pembro + chemo vs 2.1% with pbo + chemo (difference, 15.0%; 95% CI, 9.7-21.2); median EFS was 69.8 mo vs 42.7 mo (HR, 0.81; 95% CI, 0.60-1.10), with a 5-year rate of 54.1% vs 45.6%; median OS was not reached (NR) vs NR (HR, 0.87; 95% CI, 0.63-1.19), with a 5-year rate of 61.3% vs 57.4%. In the non-Asia subgroup, pCR was 12.4% with pembro + chemo vs 3.3% with pbo + chemo (difference, 9.1%; 95% CI, 4.9-13.6); median EFS was 37.7 mo vs 24.3 mo (HR, 0.79; 95% CI, 0.64-0.98), with a 5-year rate of 44.0% vs 33.0%; median OS was 60.7 mo vs 42.4 (HR, 0.85; 95% CI, 0.68-1.06), with a 5-year rate of 50.5% vs 42.6%. In the Asia subgroup, treatment-related AE (TRAE) rates were 98.4% with pembro + chemo vs 97.4% with pbo + chemo; grade 3-5 TRAE rates were 69.6% vs 65.1%, respectively. In the non-Asia subgroup, TRAE rates were 94.1% with pembro + chemo vs 96.1% with pbo + chemo; grade 3-5 TRAE rates were 65.5% vs 61.7%, respectively. **Conclusions:** A favorable trend in EFS and OS was seen in both the Asia and the non-Asia subgroups of KENOTE-585; additional antitumor activity of pembro + chemo was consistently observed, regardless of region. The safety profiles were generally comparable between the subgroups. These findings support the global development of this perioperative immunotherapy/chemotherapy regimen. Clinical trial information: NCT03221426. Research Sponsor: Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA.

4196 **Poster Session**

Association of neighborhood-level factors with access to genetic testing in patients with resectable pancreatic ductal adenocarcinoma. First Author: Muhammad Maisam Ali, University of Wisconsin School of Medicine and Public Health, Madison, WI

Background: Since 2019, the NCCN has recommended genetic testing for all patients with pancreatic ductal adenocarcinoma (PDAC). However, only one-third of patients undergo testing. For other cancers, social determinants of health have been shown to influence access to genetic testing. This study examines disparities in genetic testing among PDAC patients using neighborhood-level measures. **Methods:** We retrospectively analyzed 249 patients who underwent curative-intent resection for PDAC at a high-volume academic center between 2019 and 2023. Neighborhood disadvantage was quantified using the Area Deprivation Index (ADI). Additional socioeconomic variables included Rural-Urban Classification (RUCA) codes, insurance type (private vs. non-private), and distance to the treating facility. The primary outcome was completion of genetic testing. For those that did not undergo testing, we separately analysed the association between socioeconomic factors and presence of a referral for genetic counseling or testing. Logistic regression models adjusted for age, sex, and period of diagnosis were used to assess associations. **Results:** The cohort's mean age was 66.6 years (SD: 9.2); 45.1% were female, and 97.6% identified as non-Hispanic White. Median ADI was 55.0 (IQR: 29.5), and 38.1% lived in rural areas. Genetic testing was completed by 96 patients (40.1%), identifying pathogenic variants in 18 (18.7%). Multivariable analysis revealed age above 65, higher ADI, and greater distance from the facility significantly reduced testing likelihood. Testing rates increased between 2019 and 2023 (Table 1). Among the 153 patients without testing, only 41.2% were referred for genetic counseling/testing. Greater distance from the facility was associated with lower likelihood of being referred (OR: 0.33 [CI: 0.13, 0.85]). **Conclusions:** Neighborhood-level factors influence genetic testing access, even in a predominantly racially homogenous population. Targeted interventions are needed to reduce disparities and improve testing and referral rates. Research Sponsor: None.

Univariable and multivariable logistic regression for association of socioeconomic factors with completion of testing.

	Univariable	Multivariable*
Factor	**OR [95% CI]**	**OR [95% CI]**
ADI (continuous)	0.12 [0.04, 0.46]*	0.15 [0.02, 0.97]*
Urban residence (ref: Rural)	0.61 [0.34, 1.04]	0.97 [0.50, 1.90]
Distance to facility (ref: Low, <33)		
Moderate, 33–61	0.49 [0.26, 0.93]*	0.75 [0.34, 1.65]
High, ≥ 61	0.31 [0.17, 0.56]*	0.45 [0.21, 0.99]*
Age ≥ 65 (ref:<65)	0.81 [0.50, 1.31]	0.50 [0/26, 0.94]*
Female Sex (ref: Male)	1.05 [0.68, 1.62]	1.08 [0.57, 2.04]
Non-private insurance (ref: Private)	0.77 [0.46, 1.28]	1.13 [0.63, 2.01]
Period of diagnosis (ref: 2019-2020) 2023	7.32 [3.63, 14.78]*	7.37 [3.52, 15.43]*

*Statistically significant. Adjusted for age, sex, insurance status, and period of diagnosis.

4197 **Poster Session**

Constructing genetic-immune prognostic subtypes of primary duodenal adenocarcinoma through whole exome sequencing and AI-assisted immune microenvironment analysis. First Author: Ting Han, Department of Oncology, Renji Hospital, School of Medicine, Shanghai Jiao Tong University, Shanghai, China

Background: Primary duodenal adenocarcinoma (DA) is a rare gastrointestinal tumor with a poor prognosis. This study aimed to investigate the tumor immune microenvironment (TIME) and genetic landscape of DA to depict the unique DA subtypes, distinguishing its prognosis and identifying potential therapeutic targets. **Methods:** To reveal the heterogeneity of DA's genetic landscape and TIME, 88 treatment-naïve DA tumor samples were analyzed via multiplex immunofluorescence (mIF) staining, whole-exome sequencing, and RNA sequencing. The quantity of infiltrating cells, tertiary lymphoid structure, and spatial analysis was conducted using an automated platform (APTIME), an artificial intelligence-based analysis tool for analyzing pathology images from formalin-fixed paraffin-embedded slides stained with mIF. **Results:** Significant heterogeneity was observed in the genetic and immune landscapes of DA. A genetic-immune classification was established, identifying four distinct subtypes: MSI (microsatellite instable), InA(inflamed active), ML (macrophage-low), and MH (macrophage-high). The InA subtype exhibited high levels of infiltrating immune cells, while the MH subtype, characterized by enriched tumor-associated macrophages, was associated with the worst overall survival. The MH subtype frequently harbored TGF-β pathway mutations, particularly in SMAD4, while the ML subtype showed alterations that predominantly in the SWI/SNF pathway, specifically in ARID2. Spatial analysis indicated that closer proximity between macrophages and both tumor cells and T cells correlated with worse prognosis in DA patients. Closer interactions between PD-L1 and PD1+ T cells in the MH subtype suggested that PD-1/PD-L1 interactions contributed to an immunosuppressive tumor microenvironment. **Conclusions:** This study enhances the understanding of DA's molecular characteristics, particularly through the identification of a novel genetic-immune subtype, and provides a foundation for developing precision treatment strategies for this malignancy. Research Sponsor: None.

4198 **Poster Session**

Uncovering the tumor microenvironment (TME): Exploring survival and immunotherapy (IO) response in cancer of unknown primary (CUP). First Author: Joelle Allam, The University of Texas MD Anderson Cancer Center, Houston, TX

Background: Cancer of Unknown Primary (CUP) is a group of rare and heterogeneous metastatic cancers with unidentifiable site of origin at time of diagnosis, despite extensive investigation. Characterization of CUP remains challenging, and biomarkers are urgently needed to better tailor therapies. Tumor microenvironment (TME) comprises the dynamic and complex network of extracellular matrix, blood vessels, immune cells, signaling molecules surrounding a tumor. It plays a critical role in tumorigenesis, progression and response to treatment. This study investigates the correlation between clinical factors, TME, IO and overall survival outcomes in patients diagnosed with CUP. **Methods:** We retrospectively evaluated 49 CUP patients who underwent Boston Gene Tumor Portrait (BGTP) testing between January 2023 and July 2024. BGTP utilizes a combination of Next-Generation Sequencing (NGS) and artificial intelligence to analyze a tumor sample's genetic profile along with its surrounding microenvironment, thereby providing a more comprehensive view to support clinical decision-making and optimize treatment strategies. Clinico-pathological data, including age, ECOG performance status at diagnosis, baseline laboratory results, tumor histology and grade, number of metastatic sites (NMS) and IO treatment history were collected through retrospective chart review. TME was categorized into 4 subtypes: immune-enriched (IE), immune-enriched/fibrotic (IE/F), fibrotic (F) and immune-depleted (D). **Results:** Baseline characteristics of 49 CUP patients show median age at diagnosis was 63 years (range 32-80). Most patients were male (59%). Grade was reported as poorly differentiated in 69%, with pathology described as carcinoma (47%), adenocarcinoma (33%), squamous cell carcinoma (10%) and malignant neoplasm (8%). TME subtypes distribution was 33% IE, 14% IE/F, 16% F, 37% D. Univariate analysis revealed that better outcomes were associated with lower NLR (< 5) (median survival 57 vs 11 months, p = 0.006), lower ECOG (57 vs 16 vs 6 months for ECOG 0, 1 and 2 respectively, p = 0.002), lower NMS (< 3) (45 vs 14 months, p = 0.046). Survival data of TME and NLR subsets is shown in the table. **Conclusions:** This is the first characterization of TME profile in CUP. A diverse range of TME subtypes were seen in this population. While classical prognostic factors such as NLR, ECOG, NMS were associated with better survival, there also appears to be a trend toward survival benefit with IO in the IE/IE-F subset. Further studies are needed to prospectively explore the role of TME subtypes in determining clinical outcomes and IO response. Research Sponsor: None.

Median overall survival (months) in TME and NLR subsets, with and without IO.

Subset/Treatment	IE/IE-F	F/D	P-value	NLR High	NLR Low	P-value
IO	45.3	15.6	0.14	11.2	22.7	0.04
No IO	14.6	10.8		10.8	57.4	

4199 **Poster Session**

Identification of differential epigenetic landscapes in subtypes of appendiceal cancer. First Author: Luisa Ladel, Yale University, New Haven, CT

Background: Appendiceal cancers (AC) represent a rare and heterogeneous group of malignancies, often managed with strategies adapted from colorectal cancer (CRC) due to their anatomical proximity. However, marked differences in biological behavior, treatment response, and molecular profiles between AC and CRC necessitate independent study. While genomic data on AC has been explored, epigenetic landscapes remain uncharted. This study establishes the first comprehensive epigenetic profile of appendiceal cancer subtypes, aiming to identify novel biomarkers, therapeutic targets, and prognostic indicators. **Methods:** Tissue specimens from 20 patients with histologically confirmed appendiceal neoplasms and 4 age-matched non-neoplastic controls were analyzed. Malignant subtypes were categorized into three groups: Normal, Low-Grade Appendiceal Mucinous Neoplasms (LAMN, with and without pseudomyxoma peritonei), and Advanced Neoplasia (mucinous adenocarcinoma, non-mucinous adenocarcinoma, and goblet cell adenocarcinoma). Whole-genome methylome profiling was performed using enzymatic methyl-seq for single-base resolution of DNA methylation. Differentially methylated regions (DMRs) were identified with a q-value cutoff of < 0.05 and analyzed using the Whole Genome R package with the methylKit analysis pipeline. **Results:** Epigenetic clustering revealed progressive dysregulation from normal tissue to LAMN and further to advanced neoplasia, supporting a continuum of malignancy. Our preliminary analysis of CpG islands identified 2,621 DMRs between LAMN and normal tissues and 395 DMRs between Advanced Neoplasia and LAMN. In promoter regions, 1,852 DMRs differentiated LAMN from normal, and 283 distinguished Advanced Neoplasia from LAMN. LAMN samples exhibited predominantly hypomethylated regions relative to normal tissues (2,299 vs. 322 for CpG islands; 1,579 vs. 273 for promoters). Conversely, advanced neoplasia demonstrated more hypermethylated regions than LAMN (243 vs. 152 for CpG islands; 195 vs. 88 for promoters). Most DMRs were localized to intronic, distal intergenic, and promoter regions. Key overlapping DMRs included 8 hypomethylated CpG islands, 41 hypermethylated CpG islands, 3 hypomethylated promoters, and 14 hypermethylated promoters. These regions implicate pivotal genes in the progression from LAMN to advanced neoplasia. **Conclusions:** This study pioneers the epigenetic characterization of appendiceal cancers, uncovering unique methylation signatures that differentiate malignant subtypes and normal tissue. Integrating these findings with genomic data highlights critical targets for the detection and molecular classification of appendiceal neoplasms. These insights pave the way for improved diagnostic and therapeutic strategies tailored to this rare malignancy. Research Sponsor: None.

4200 **Poster Session**

Circulating tumor DNA-based genomic profiling and real-world outcomes in cancer of unknown primary (CUP). First Author: Keelia Clemens, Guardant Health, Redwood City, CA

Background: CUP accounts for <5% of cancers and carries a dismal prognosis with median overall survival of ~13 months. Studies suggest up to one-third of CUP patients (pts) have a potentially targetable alteration (PTA) that may be eligible for molecularly guided therapy (MGT). Liquid biopsy (LB) is a non-invasive method to identify PTAs and genomic clues regarding primary site via circulating tumor DNA (ctDNA). We characterize the ctDNA landscape of PTAs in CUP and evaluate outcomes for pts receiving MGT. **Methods:** Real-world data was sourced via GuardantINFORM, a database aggregating insurance claims and de-identified records of pts with clinical LB via Guardant360. PTAs were defined as alterations with FDA approved therapies in non-CUP indications. Pts with CUP and ≥1 treatment claim after LB were included. Outcomes of pts treated with MGT and pts with the same PTA not treated with MGT were assessed via real-world time to treatment discontinuation (rwTTD), real-world time to next treatment (rwTTNT) and real-world overall survival (rwOS) in months. Log-rank test was used to compare time-to-event outcomes. **Results:** Of 13,324 CUP pts, 50% were male; the median age was 69 years. Majority of pts underwent LB at time of diagnosis (92.1%). In pts with ≥1 genomic alteration identified (91.9%), the most common genomic alterations were *TP53* (55%), *KRAS* (25%), *PIK3CA* (14%), and *EGFR* (12%). A PTA was identified in 29.4% of pts, the most frequent being *PIK3CA* (9.2%), *KRAS* G12C (4.3%), *BRCA1/2* (4%), *ERBB2* (3.9%), *EGFR* (2.8%), *IDH1* (2.5%), *BRAF* V600E (2.4%) and MSI-H (2%). rwTTD was higher for pts with alterations in *EGFR, BRAF* V600E, and MSI-H receiving MGT; only *EGFR* reached significance (Table). Similarly, rwTTNT was improved in pts with *EGFR, BRAF* V600E alterations and MSI-H, but did not reach significance. rwOS was numerically higher for *BRAF* V600E and *ERBB2* mutated pts receiving MGT (Table). **Conclusions:** This study represents the first large-scale ctDNA genomic profiling of CUP pts with real-world outcomes.LB detected PTAs in 29.4% of CUP pts, similar to tissue-based testing. Our findings support use of LB to identify PTAs in CUP pts; however, prospective trials are needed to assess MGT efficacy. Research Sponsor: None.

Real-world outcomes (in months): MGT vs no MGT.

	rwTTD	rwTTNT	rwOS
EGFR (n=46)	5.8 (95CI: 3-10.27) vs 2.8 (95CI: 2.1-4.5), **p=0.0043**	11.7 (95CI: 6.2-NR) vs 6.5 (95CI: 5.0-NR), p=0.33	12.8 (95CI: 8.9-NR) vs 13.9 (95CI: 7.0-NR), p=0.9
BRAF V600E (n=36)	5.7 (95CI: 4.2-25.1) vs 4.0 (95CI : 3.4-11.4), p=0.48	10.2 (95CI: 6.9-NR) vs 9.1 (95CI: 5.6-NR), p=0.43	35.1 (95CI: 10.2-NR) vs 25.0 (95CI: 7.0-NR), p=0.18
ERBB2 (n=58)	3.9 (95CI: 2.8-5.9) vs 4.2 (95CI: 2.8-6.8), p=0.41	7.0 (95CI: 4.9-NR) vs 6.1 (95CI: 4.2-NR), p=0.96	21.9 (95CI: 11.6-NR) vs 17.0 (95CI: 8.1-NR), p=0.37
MSI-H (n=34)	7.2 (95CI: 4.9-22.5) vs 3.9 (95CI: 2.3-NR), p=0.14	15.4 (95CI: 7.0-NR) vs 10.2 (95CI: 5.5-NR), p=0.77	NR (95CI: 19.0-NR vs 34.5 (95CI: 29.8-NR), p=0.84

TPS4201 **Poster Session**

A multiregional, randomized, controlled, open-label, phase 3 study of the anti-claudin18.2 (CLDN18.2) antibody-drug conjugate (ADC) arcotatug tavatecan (IBI343) in gastric or gastroesophageal junction adenocarcinoma (G/GEJA): Trial in progress. First Author: Lin Shen, Beijing Cancer Hospital, Beijing, China

Background: CLDN18.2 has been a validated therapeutic target for G/GEJA. As a next-generation ADC, arcotatug tavatecan (IBI343) composed of anti-CLDN18.2 monoclonal antibody conjugated to exatecan (topoisomerase I inhibitor) with unique IgG1 Fc silencing to attenuate antibody-dependent cellular cytotoxicity and complement-dependent cytotoxicity. Previous phase 1 studies of IBI343 observed manageable safety profiles with encouraging efficacy in G/GEJA, pancreatic ductal adenocarcinoma and biliary tract cancer (2024 ASCO Annual Meeting [3037], ESMO GI 2024 [396MO], ESMO Asia 2024 [132MO]). Here, we present the trial in progress of a phase 3 study (G-HOPE-001, NCT06238843) evaluating efficacy and safety of IBI343 monotherapy versus treatment of investigator's choice in previously treated patients (pts) with CLDN18.2-positive G/GEJA. **Methods:** This multiregional, randomized, controlled, open-label, phase 3 study planned to enroll 450 pts. Main inclusion criteria are: 1) locally advanced unresectable or metastatic G/GEJA; 2) positive CLDN18.2, defined as immunohistochemical (IHC) membrane staining intensity ≥ 2+ in ≥ 75% of tumor cells as measured by the VENTANA CLDN18 (43-14A) Assay; 3) radiologically evaluable disease, measurable and/or non-measurable disease per RECIST v1.1; 4) received and progressed on 2-4 prior regimens of systemic therapy which must include a fluoropyrimidine, platinum, and a taxane or irinotecan. Main exclusion criteria are: 1) positive HER-2, defined as IHC 3+ or IHC 2+/in situ hybridization+; 2) history of treatment with topoisomerase inhibitor-based ADCs. Pts are randomized in a 1:1 ratio to receive IBI343 6mg/kg Q3W in the experimental arm or to receive treatment of investigator's choice including irinotecan, paclitaxel, or trifluridine/tipiracil in the control arm. Stratification factors include region (Asian country/region other than Japan vs. European Union and United States vs. Japan), primary site of the tumor (stomach vs. gastroesophageal junction) and history of prior gastrectomy (yes vs. no). The primary endpoints are progression-free survival (PFS) per RECIST v1.1 and overall survival (OS). The secondary endpoints include objective response rate (ORR), disease control rate (DCR), duration of response (DoR) and time to response (TTR) per RECIST v1.1, quality of life (QoL), safety, pharmacokinetics (PK) and immunogenicity. The trial is currently enrolling pts in China and Japan. Clinical trial information: NCT06238843. Research Sponsor: Innovent Biologics (Suzhou) Co., Ltd.

TPS4202 **Poster Session**

Telisotuzumab adizutecan (ABBV-400; Temab-A) in combination with fluorouracil, leucovorin, and budigalimab in locally advanced/metastatic gastric, gastroesophageal junction, or esophageal adenocarcinoma (a/m GEA). First Author: Kohei Shitara, Department of Gastroenterology and Gastrointestinal Oncology, National Cancer Center Hospital East, Kashiwa, Japan

Background: The *MET* proto-oncogene and its receptor tyrosine kinase gene product (c-Met protein) are involved in normal cellular functions such as cell proliferation and differentiation but can be abnormally activated and upregulated in cancer to promote tumor growth. *MET* gene amplification and increased c-Met protein expression are associated with poor survival outcomes in gastric cancer. The antibody-drug conjugate Temab-A (ABBV-400) is composed of the c-Met–directed antibody telisotuzumab conjugated to a potent topoisomerase 1 inhibitor. A phase 1 study (NCT05029882) investigating Temab-A monotherapy demonstrated manageable safety and encouraging efficacy in patients with previously treated, advanced GEA, with an objective response rate of 29% (12/42) and clinical benefit rate of 71% (30/42) (Strickler et al. *Ann Oncol*. 2024;35:1439P). This study evaluates Temab-A in combination with fluorouracil (5-FU), leucovorin/folinic acid (LV), and budigalimab (budi; a PD-1–blocking antibody). **Methods:** This multicenter,phase 2, open-label, randomized study (NCT06628310) will enroll ~180 adult patients with HER2-negative a/m GEA who have not received prior systemic therapy in the a/m setting, have not received a prior PD-(L)1 inhibitor, have Eastern Cooperative Oncology Group performance status 0–1, and have measurable disease per RECIST v1.1. Primary objectives of the study are to evaluate safety and tolerability, evaluate efficacy as measured by progression-free survival and objective response, and select the recommended phase 3 dose of Temab-A in combination with 5-FU, LV, and budi. Secondary objectives include assessment of dose-limiting toxicities (DLTs) in the dose-escalation stage, evaluation of pharmacokinetics, and further evaluation of efficacy measures (duration of response, disease control, and overall survival). The study consists of 2 stages: dose escalation and dose optimization. During BOIN-directed dose escalation, ~18 patients receive escalating doses of Temab-A administered once every 4 weeks (Q4W) in combination with fixed doses of 5-FU (2400 mg/m^2 Q2W), LV (400 mg/m^2 Q2W), and budi (500 mg Q4W). DLTs are assessed during the first 28-day cycle. During dose optimization, ~162 patients are randomized 1:1:1 to 1 of 2 selected doses of Temab-A in combination with 5-FU, LV, and budi or a control arm of FOLFOX + budi. Randomization is stratified by PD-L1 expression and primary tumor location. Treatment is administered until disease progression, intolerable toxicity, or other discontinuation criteria are met. Either archived formalin-fixed paraffin-embedded tissue or a fresh biopsy is required for biomarker research that will include evaluation of c-Met protein expression and *MET* genomic alterations. Clinical trial information: NCT06628310. Research Sponsor: AbbVie, Inc.; n/a.

TPS4203 **Poster Session**

Open-label, single-arm, single-center phase 1b/2 clinical study of fruquintinib combined with trastuzumab and XELOX in the first-line treatment of advanced HER2-positive metastatic gastric or gastroesophageal junction adenocarcinoma. First Author: Huifang Lv, Department of Gastrointestinal Medical Oncology, The Affiliated Cancer Hospital of Zhengzhou University, Henan Cancer Hospital, Zhengzhou, China

Background: Trastuzumab plus chemotherapy has significantly prolonged survival in patients with HER2-positive gastric and gastroesophageal junction (G/GEJ) cancer. The KEYNOTE-811 study suggested that the efficacy of adding pembrolizumab to trastuzumab and chemotherapy was superior to trastuzumab plus chemotherapy. However, only patients with a PD-L1 combined positive score (CPS) of 1 or higher could benefit, while those with PD-L1 CPS < 1 did not benefit from this regimen. Fruquintinib is a highly selective oral tyrosine kinase inhibitor of vascular endothelial growth factor receptors (VEGFRs) 1, 2, and 3. The phase 3 study FRUTIGA demonstrated fruquintinib plus paclitaxel was superior to paclitaxel alone as second-line treatment in patients with G/GEJ cancer. As anti-angiogenesis has a synergistic effect with trastuzumab, we designed this study to evaluate the safety and efficacy of fruquintinib plus trastuzumab, and CAPEOX as first-line treatment for advanced HER2-positive G/GEJ cancer. **Methods:** This is a single-center, single-arm, open-label, phase 1b/2 study. The phase 1b study will adopt a 3+3 design with escalating oral daily dose of 2 to 4 mg (1 mg per level) fruquintinib for days 1-14 in combination with trastuzumab (8mg/kg load, followed by 6mg/kg) intravenously once for day 1, capecitabine 1000mg/m^2 orally twice a day for days 1-14, and oxaliplatin 130mg/m^2 intravenously once for day 1 using a 21-day cycle. The maximum tolerated dose (MTD) and recommended phase 2 dose (RP2D) of fruquintinib will be determined in the phase 1b study with a dose-limiting toxicity (DLT) period of the first cycle. Major DLTs are defined as any of the following toxicities occurring in the DLT period determined to be related to study treatment: grade ≥ 4 hematological toxicities, grade ≥ 3 non-hematological toxicities, and toxicities that required discontinuation of fruquintinib or trastuzumab ≥ 21 days. 6 to 12 systematic treatment-naïve patients with advanced G/GEJ cancer are expected to be enrolled in the phase 1b study, depending on observed DLTs and the need for dose adjustments. In the phase 2 study, 39 additional patients will be enrolled with RP2D administered. Upon 6-8 cycles of treatment completed, fruquintinib plus trastuzumab and capecitabine will be administered as maintenance treatment. The treatment continues until progressive disease or intolerable toxicity. The primary endpoint of the phase 2 study is PFS. The secondary endpoints include OS, ORR, DCR, DoR, safety, and molecular biomarker exploration. Clinical trial information: ChiCTR2300074767. Research Sponsor: None.

TPS4204 **Poster Session**

ARTEMIDE-Gastric01: A phase 3 randomized study of rilvegostomig with fluoropyrimidine and trastuzumab deruxtecan (T-DXd) as first-line (1L) treatment for locally advanced or metastatic HER2-positive gastric or gastroesophageal junction cancer (GC/GEJC). First Author: Rui-Hua Xu, Department of Medical Oncology, Sun Yat-Sen University Cancer Center, State Key Laboratory of Oncology in South China, Guangdong Provincial Clinical Research Center for Cancer, Sun Yat-Sen University, Guangzhou, China

Background: Patients with GC/GEJC often present with advanced disease, and prognosis for these patients is poor, with a 5-year relative survival rate of ~5%, highlighting a need for new treatment options. HER2 overexpression/amplification occurs in ~20% of cases. Adding immune checkpoint inhibition to trastuzumab (anti-HER2 monoclonal antibody) and chemotherapy has shown clinical benefit in patients with advanced HER2-positive GC/GEJC (Janjigian YY, et al. *N Engl J Med* 2024), and led to the approval of pembrolizumab (programmed cell death-1 [PD-1] inhibitor), trastuzumab, and chemotherapy for HER2-positive GC/GEJC with programmed cell death ligand-1 combined positive score (PD-L1 CPS) ≥1. T-DXd (a HER2-directed antibody-drug conjugate) is approved for the treatment of patients with locally advanced/metastatic HER2-positive GC/GEJC who have received a prior trastuzumab-based regimen. In addition, dual inhibition of PD-1 or PD-L1 and the immune checkpoint T cell immunoglobulin and immunoreceptor tyrosine-based inhibitory motif domain (TIGIT) has shown encouraging results across multiple tumor types, without major increases in high-grade toxicity compared with PD-1 or PD-L1 inhibition alone. Rilvegostomig is a monovalent, bispecific, humanized IgG1 monoclonal antibody targeting both PD-1 and TIGIT receptors that has shown encouraging efficacy with manageable safety as monotherapy in non-small-cell lung cancer (Hiltermann TJN, et al. WCLC 2024. Oral presentation 1751) and with chemotherapy in HER2-negative GC/GEJC (Herrero FR, et al. *Ann Oncol* 2024. Abs 1422P). **Methods:** ARTEMIDE-Gastric01 (NCT06764875) is a phase 3, randomized, open-label, sponsor-blinded, multicenter, global study that will assess the efficacy and safety of rilvegostomig with T-DXd and chemotherapy as 1L treatment in HER2-positive GC/GEJC with PD-L1 CPS ≥1. Approximately 840 participants (pts) will be randomized to Arm A: rilvegostomig + T-DXd + investigator's (INV) choice of capecitabine or 5-fluorouracil (5-FU); Arm B: pembrolizumab + trastuzumab + INV choice of 5-FU and cisplatin (FP) or capecitabine and oxaliplatin (CAPOX); Arm C: rilvegostomig + trastuzumab + INV choice of FP or CAPOX. Eligible pts will have previously untreated, unresectable, histologically confirmed, locally advanced/metastatic HER2-positive and PD-L1 CPS ≥1 GC/GEJC and an ECOG performance status of 0 or 1. Dual-primary endpoints are progression-free survival (RECIST v1.1; blinded independent central review) and overall survival in all randomized pts. Secondary endpoints include safety/tolerability, objective response rate, and duration of response. Enrollment is planned across ~25 countries in Asia, Australia, Europe, and North and South America. Clinical trial information: NCT06764875. Research Sponsor: AstraZeneca.

TPS4205 **Poster Session**

A randomized controlled trial comparing conversion surgery with palliative chemotherapy in patients with initially unresectable cStage IVB/pStage IV advanced gastric cancer who presented remarkable response to chemotherapy: JCOG2301 (Conversion study). First Author: Itaru Yasufuku, Department of Clinical Anatomy Development Studies, Gifu University Graduate School of Medicine, Gifu-City, Japan

Background: Conversion surgery is a surgical treatment for patients with initially unresectable cStage IVB gastric cancer who presented remarkable response to palliative chemotherapy aiming at n R0 resection expecting long survival including he disease. This study is a randomized controlled phase III trial aimed to evaluate the efficacy of conversion surgery comparing to palliative chemotherapy. **Methods:** Eligibility criteria include the followings : (1) Histologically proven adenocarcinoma of the stomach. (2) Diagnosed as clinical stage IVB or pathological stage IV according to the Japanese Classification of Gastric Carcinoma (15th edition), with at least one of the following unresectable distant metastases before chemotherapy. (i) Four or more liver metastases. (ii) Distant lymph node metastasis beyond para-aortic lymph node No.16a2/16b1. (iii) Peritoneal dissemination diagnosed with imaging examination or P1b/P1c peritoneal dissemination diagnosed with laparotomy or laparoscopy. (3) Undergoing first-line chemotherapy regardless of nivolumab or trastuzumab use. (4) Confirmation of no peritoneal metastasis or localization at a limited area close to the stomach by laparoscopy or laparotomy after initiation of chemotherapy, with CY0 status in peritoneal lavage cytology. (5) Response to chemotherapy of distant metastasis diagnosed before initiating first-line chemotherapy that meets the following (i) and (ii) before registration. (i) Liver metastasis: three or fewer liver metastasis. (ii) Distant lymph node metastasis excluding No.16a2/16b1: disappearance or reduction to a long axis of less than 6 mm. The primary endpoint is overall survival. After confirming eligibility, patients are registered and randomized (1:1) to either the palliative chemotherapy alone arm or the conversion surgery arm. We assumed the median survival timeis 19 months after registration for the chemotherapy alone arm additional efficacy for overall survival in the conversion surgery arm corresponding to a hazard ratio of 0.7. This study requires 126 patients to observe 102 deaths, with power of 70% and a one-sided alpha of 10%, considering the rarity of patients with stage IV gastric cancer who exhibit a significant response to palliative chemotherapy, an accrual period of 5 years, and a follow-up period of 3 years. This trial was initiated in September 2024, and the first patient was enrolled in January 2025. Clinical trial information: jRCTs031240340. Research Sponsor: Japan Agency for Medical Research and Development (AMED).

TPS4206 **Poster Session**

A randomized, double-blinded, international phase III trial comparing HLX22 in combination with trastuzumab and chemotherapy versus trastuzumab and chemotherapy with or without pembrolizumab for first-line treatment for HER2-positive locally advanced or metastatic G/GEJ cancer. First Author: Jaffer A. Ajani, Department of Gastrointestinal (GI) Medical Oncology, MD Anderson Cancer Center, Houston, TX

Background: Combination therapy with trastuzumab and chemotherapy is the first-line systemic treatment for human epidermal growth factor receptor 2 (HER2) positive advanced gastric or gastroesophageal junction (G/GEJ) cancer. Among patients whose tumors express programmed death ligand 1 (PD-L1; defined as combined positive score [CPS] ≥ 1), treatment options also include pembrolizumab plus trastuzumab and chemotherapy. Survival outcomes remain unsatisfactory despite these advances. HLX22 is an anti-HER2 antibody that targets a different epitope than trastuzumab. HLX22 has shown improved progression-free survival (PFS) when added to trastuzumab plus oxaliplatin and capecitabine (XELOX) in a phase 2 study (NCT04908813). Here we present the design of a phase III randomized controlled study. **Methods:** This randomized, double-blind, two-arm phase III clinical study aims to compare the efficacy and safety of HLX22 in combination with trastuzumab and XELOX versus (vs) trastuzumab and XELOX with or without (±) pembrolizumab in patients with HER2-positive, advanced G/GEJ cancer and no prior antitumor therapy in the advanced setting. Key inclusion criteria include histologically or cytologically confirmed diagnosis of previously untreated, locally advanced unresectable or metastatic HER2-positive G/GEJ adenocarcinoma. Key exclusion criteria include prior use of any HER2-target therapy. Approximately 550 eligible patients will be enrolled from multiple regions across the globe and randomly assigned in a 1:1 ratio to receive HLX22 (15 mg/kg) + trastuzumab + XELOX ± placebo (for pembrolizumab) or placebo (for HLX22) + trastuzumab + XELOX ± pembrolizumab. HLX22 will be administered intravenously on Day 1 of each 21-day treatment cycle until loss of clinical benefit, death, intolerable toxicity, withdrawal of informed consent, or other reasons. The stratification factors include HER2 immunohistochemistry (3+ vs 2+), geographic region (Asia vs Europe/North America vs rest of the world), primary tumor site (gastric vs gastroesophageal junction), and tumor PD-L1 expression (CPS < 1 or not evaluable vs 1 ≤ CPS < 10 vs CPS ≥ 10). The dual primary endpoints are PFS assessed by independent radiology review committee per RECIST v1.1 and overall survival. Secondary endpoints include investigator-assessed PFS, objective response rate, PFS on the subsequent line of therapy, duration of response, safety, pharmacokinetics, immunogenicity, and quality of life. This study is currently open for enrollment and has completed first dose of the first patient. Clinical trial information: NCT06532006. Research Sponsor: Shanghai Henlius Biotech, Inc.

TPS4207 **Poster Session**

An open-label, randomized, multicenter, phase 3 study of trastuzumab deruxtecan (T-DXd) + chemotherapy (chemo) ± pembrolizumab (pembro) versus chemo + trastuzumab ± pembro in first-line metastatic HER2+ gastric or gastroesophageal junction (GEJ) cancer: DESTINY-Gastric05. First Author: Kohei Shitara, National Cancer Center Hospital East, Chiba, Japan

Background: An unmet medical need remains in patients (pts) with HER2+ gastric or GEJ cancer. HER2 is a validated target in up to 20% of pts with gastric or GEJ cancer. The KEYNOTE-811 trial demonstrated that adding pembro to trastuzumab and chemo improved progression-free survival (PFS) and overall survival (OS) versus placebo for first-line treatment of pts with HER2+ gastric or GEJ cancer with a PD-L1 combined positive score (CPS) ≥1 (Janjigian Y et al. *N Engl J Med*. 391;1360:2024). In the DESTINY-Gastric03 trial, first-line combinations involving T-DXd, a HER2-directed antibody-drug conjugate, and fluoropyrimidine (5-FU or capecitabine [CAPE]) ± pembro showed acceptable safety and encouraging efficacy in pts with HER2+ gastric or GEJ cancer, including pts with CPS < 1 (Janjigian Y et al. *Ann Oncol*. 35;S878:2024). Building on this evidence, the phase 3 DESTINY-Gastric05 trial aims to bring a potentially improved platinum-free treatment approach for all pts with HER2+ gastric or GEJ cancer. **Methods:** DESTINY-Gastric05 (NCT06731478) is an open-label, randomized, multicenter, phase 3 global trial designed to evaluate the efficacy and safety of T-DXd in combination with 5-FU (or CAPE) + pembro versus standard-of-care chemo with trastuzumab + pembro as first-line treatment in pts with unresectable, locally advanced or metastatic centrally confirmed HER2+ (immunohistochemistry [IHC] 3+ or IHC 2+/in situ hybridization+) gastric or GEJ cancer with a CPS ≥1. Pts must have ≥1 RECIST v1.1 measurable lesion, a left ventricular ejection fraction ≥50%, and an Eastern Cooperative Oncology Group performance status of 0 or 1. Approximately 576 pts will be randomly assigned in a 1:1 ratio to receive: T-DXd 5.4 mg/kg + either 5-FU or CAPE + pembro (arm M1); or trastuzumab + platinum-based chemo (either cisplatin + 5-FU or oxaliplatin + CAPE) + pembro (arm M2). The primary efficacy endpoint is PFS based on blinded independent central review (BICR), and the key secondary endpoint is OS. Other secondary endpoints include overall response rate, duration of response, and time to response per RECIST v1.1 assessed by BICR and investigator. Safety and tolerability will also be assessed. An exploratory cohort (approximately 150 pts) will evaluate the efficacy and safety of T-DXd in combination with 5-FU or CAPE versus trastuzumab plus standard-of-care chemo in pts with PD-L1 CPS < 1. Clinical trial information: NCT06731478. Research Sponsor: Daiichi Sankyo, Inc.

TPS4208 **Poster Session**

A phase II study of sacituzumab govitecan for advanced esophageal squamous cell carcinoma patients (SG-ESCC). First Author: Jhe-Cyuan Guo, National Taiwan University Cancer Center, Taipei, Taiwan

Background: Esophageal squamous cell carcinoma (ESCC) remains a significant global health challenge, particularly in Asia. There are limited treatment options for advanced ESCC patients who fail platinum-based chemotherapy and anti-PD-1/PD-L1 therapy, resulting in poor prognoses. Trophoblast cell surface antigen 2 (Trop-2), a transmembrane protein overexpressed in ESCC, offers a potential therapeutic target due to its differential expression between tumors and normal tissues. Sacituzumab govitecan, an antibody-drug conjugate (ADC) comprising an anti-Trop-2 antibody linked to a topoisomerase I inhibitor payload, has shown efficacy in triple-negative and hormone receptor-positive breast cancers. This study aims to investigate the efficacy and safety of sacituzumab govitecan in patients with advanced ESCC. **Methods:** This investigator-initiated, prospective, phase II, single-arm, multi-center trial evaluates the efficacy and safety of sacituzumab govitecan (10 mg/kg IV on days 1 and 8 of a 21-day cycle) in advanced ESCC patients. Eligible patients must have failed prior platinum-based chemotherapy and anti-PD-1/PD-L1 therapy, exhibit measurable disease per RECIST 1.1, and have an ECOG performance status $\leq$1. The primary endpoint is the objective response rate (ORR) by RECIST 1.1. Secondary endpoints include overall survival, progression-free survival, duration of response, and safety outcomes. Biomarker analyses will explore Trop-2 expression and other molecular markers associated with treatment efficacy and resistance as well as toxicity. A total of 35 patients will be enrolled employing Simon's two-stage design, with a type I error rate of 0.1 and 80% power to detect an ORR $\geq$25%, considered promising compared to the historical control of $\leq$10%. In the first stage, 16 patients will be accrued, with $\geq$2 responses required to proceed to the second stage of 15 additional patients. Accounting for an anticipated 10% dropout rate, the study aims to complete enrollment within 24 months. Enrollment began in August 2024, and as of December 2024, 5 of the planned 35 patients have been enrolled. Clinical trial information: NCT06329869. Research Sponsor: Gilead Sciences.

TPS4209 **Poster Session**

KEYMAKER-U06 substudy 06E: A phase 1/2 open-label, umbrella platform study of ifinatamab deruxtecan in combination with pembrolizumab with or without chemotherapy for first-line treatment of advanced esophageal squamous cell carcinoma (ESCC). First Author: Ken Kato, National Cancer Center Hospital, Tokyo, Japan

Background: There is a substantial need for more effective and tolerable first-line treatment options for patients with advanced ESCC. B7-H3 is a type 1 transmembrane protein that is highly expressed in several cancers, including ESCC, and is associated with a poor prognosis. Ifinatamab deruxtecan (I-DXd; formerly DS-7300a/MK-2400) is a B7-H3–directed antibody-drug conjugate comprising a humanized anti–B7-H3 IgG1 monoclonal antibody (ifinatamab) covalently linked to a potent topoisomerase I inhibitor payload (DXd; an exatecan derivative) by a cleavable linker. In the phase 1/2 DS7300-A-J101 study, I-DXd monotherapy showed promising antitumor activity in participants (pts) with advanced ESCC. KEYMAKER-U06 is an open-label, phase 1/2, umbrella platform study designed to evaluate investigational agents with or without pembrolizumab and/or chemotherapy for advanced gastroesophageal cancer. Substudy 06E (NCT06780111) will be conducted to evaluate I-DXd plus pembrolizumab with or without chemotherapy as first-line therapy for advanced ESCC. **Methods:** Eligible pts are aged $\geq$18 years with previously untreated, histologically or cytologically confirmed, locally advanced unresectable or metastatic ESCC, measurable disease per RECIST v1.1 by investigator review and verified by blinded independent central review (BICR), and an Eastern Cooperative Oncology Group performance status of 0 or 1. Pts will be assigned to 1 of 4 treatment arms: arm 1 (reference treatment; pembrolizumab 200 mg IV Q3W for $\leq$35 cycles plus chemotherapy [mFOLFOX6: oxaliplatin 85 mg/m^2 IV Q2W plus 5-FU 400 mg/m^2 (bolus) and 2400 mg/m^2 (continuous) IV Q2W plus leucovorin 400 mg/m² IV Q2W]); arm 2 (I-DXd 12 mg/kg IV Q3W plus pembrolizumab); arm 3 (I-DXd 12 mg/kg plus pembrolizumab plus 5-FU 400 mg/m^2 [bolus] and 2400 mg/m^2 [continuous] IV Q2W plus leucovorin 400 mg/m² IV Q2W); and arm 4 (I-DXd [8 mg/kg or 12 mg/kg] IV plus pembrolizumab plus 5-FU 2400 mg/m^2 IV and oxaliplatin 60 mg/m^2). Approximately 209 pts will be enrolled. A safety lead-in phase with $\leq$29 pts will be conducted in arms 2 (n $\leq$6), 3 (n $\leq$10), and 4 (n $\leq$13) using a Bayesian optimal interval design to confirm the safety and recommended phase 2 dose (RP2D; arm 4 only) of I-DXd in combination with other agents; this phase will be conducted sequentially, starting with arm 2, followed by arms 3 and 4. Thereafter, $\leq$180 pts will be included in the randomized phase ($\leq$60 in arm 1; $\leq$40 each in arms 2-4). Pts will be randomly assigned 1:2 to arm 1 and the investigational arms. Primary outcomes are safety and tolerability, RP2D of I-DXd, and objective response rate per RECIST v1.1 by BICR for the selected dose. Secondary outcomes include DOR and PFS per RECIST v1.1 by BICR, OS, and pharmacokinetics of I-DXd in combination with other agents. Enrollment is ongoing. Clinical trial information: NCT06780111. Research Sponsor: Daiichi Sankyo Company, Limited and Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA.

TPS4210 **Poster Session**

A phase II study of perioperative intraperitoneal paclitaxel in patients with gastric adenocarcinoma and carcinomatosis or positive cytology. First Author: Brian D. Badgwell, The University of Texas MD Anderson Cancer Center, Houston, TX

Background: Over the last 2 decades, intraperitoneal chemotherapy has been found to have activity for select subgroups of patients with carcinomatosis from colon, ovarian, appendiceal, and recently, gastric origins. However, there is little data to support an aggressive surgical approach of cytoreduction (debulking) and intraperitoneal therapy for patients with gastric cancer and positive cytology or carcinomatosis. Recently, the DRAGON-01 randomized trial reported improvement in outcomes for the addition of intraperitoneal paclitaxel as part of a bidirectional approach with systemic paclitaxel and S-1 for patients with gastric cancer and peritoneal metastases. However, there are few studies supporting intraperitoneal paclitaxel in Western populations. As systemic therapy is improving with concomitant targeted and immunotherapy, intraperitoneal therapy may be best utilized in Western populations after standard of care systemic therapy. Therefore, the purpose of this clinical trial is to determine the efficacy and safety of perioperative intraperitoneal paclitaxel in patients with stage IV gastric cancer limited to the peritoneum after treatment with systemic chemotherapy. **Methods:** Patients with gastric and gastroesophageal adenocarcinoma and positive peritoneal cytology or carcinomatosis that have completed treatment with systemic chemotherapy are offered participation in the study. Patients with metastatic disease not limited to the peritoneum are excluded. Type and duration of systemic chemotherapy is left to the discretion of the treating medical oncologist. Immunotherapy or Her2-directed therapy may continue during the trial. We have recently completed a Phase I clinical trial demonstrating doses of up to 100 mg/m^2 were safe (NCT04220827; PMID: 39287936). Therefore, 100 mg/m^2 is administered intraperitoneal every 2 weeks for three treatments before and after gastrectomy. We also modified the trial to allow for the inclusion of heated intraperitoneal chemotherapy during gastrectomy. The primary outcome is overall survival from the date of diagnosis of stage IV disease, with secondary outcomes of safety. After completion of study–related treatment, subjects will be followed until recurrence and/or death for up to three years. Sixteen of planned 30 patients have been enrolled (NCT05977998). Clinical trial information: NCT05977998. Research Sponsor: None.

TPS4212 **Poster Session**

Repurposing itraconazole for secondary prevention of metaplasia and primary prevention of cancer in patients with high-risk Barrett's esophagus in combination with ablation. First Author: Ajay Bansal, Department of Gastroenterology and Hepatology, University of Kansas Medical Center, Kansas City, KS

Background: To prevent invasive esophageal adenocarcinoma (EAC), endoscopic eradication therapy (EET) is used to remove its precursor, Barrett's esophagus (BE) with dysplasia. EET combines endoscopic removal of visible lesions with radiofrequency ablation (RFA) of surrounding BE to achieve complete remission of intestinal metaplasia (CRIM) and complete eradication of dysplasia (CED) to halt progression to cancer. Unfortunately, EET has metaplasia recurrence rates of 12.4%/year; thus, adjunctive cancer interception agents are needed to maintain the gains of EET. Data from pre-clinical studies and patient tissues demonstrate that the Hedgehog (Hh) pathway regulates esophageal stem cell activity and cell fate determination (squamous versus intestinal). Post-RFA reactivation of Hh signaling is hypothesized to drive BE recurrence; however, current FDA-approved Hh inhibitors are expensive and toxic. The antifungal itraconazole inhibits Hh signaling and has demonstrated antitumor activity in multiple cancers. In addition, it inhibits VEGFR and PI3K-AKT pathways, which are critical to BE development and neoplastic progression. Given its safety and affordability, itraconazole represents a promising strategy to reduce BE recurrence and EAC risk. **Methods:** This randomized, phase 2b, double-blind, placebo-controlled trial will evaluate itraconazole's efficacy in accelerating BE eradication. Participants with high-risk BE, defined as BE $\geq$2 cm with low/high-grade dysplasia or intramucosal/T1 adenocarcinoma, undergoing ablation will be enrolled. Participants will be randomized 1:1 to receive 300 mg of oral itraconazole or placebo for two weeks before and four weeks after their first 2 sessions of EET. The primary endpoint is time to CRIM, a surrogate for long-term BE recurrence, measured in days. Secondary endpoints include time to CED, 12-month BE recurrence rates, safety, tolerability, and correlations between itraconazole levels and patient-reported outcomes. We will enroll 74 patients (37 per arm). We shall use a two-sided log rank test for right-censored time to event analysis to assess differences. The sample size calculation is based on anticipated surviving proportions at specific study times. We assume that the surviving non-CRIM proportions of patients at 3, 6, 9, and 12 months in the control arm to be 0.8, 0.5, 0.2, 0.1, respectively, and in the treatment arm to be 0.5, 0.2, 0.1, 0.05, respectively. To detect this effect size with 80% power at 5% level of significance, we need 30 evaluable participants in each group (with a plan to enroll 37 per arm to account for attrition). A Cox model will adjust for demographic and clinical variables. If successful, this trial could establish itraconazole as a novel adjunct to EET, reducing BE recurrence and lowering EAC risk. Clinical trial information: NCT06732388. Research Sponsor: National Cancer Institute; UG1-CA242632.

TPS4213 **Poster Session**

Total neoadjuvant therapy with induction immunochemotherapy and chemoradiotherapy followed by surgery for locally advanced esophageal squamous cell carcinoma (TNT-ESCC). First Author: Chien-Huai Chuang, National Taiwan University Cancer Center, Taipei, Taiwan

Background: Locally advanced esophageal squamous cell carcinoma (ESCC) is indicated for multi-modalities treatment strategies, including a neoadjuvant chemoradiotherapy (CRT) followed by surgery. While the CROSS trial established neoadjuvant CRT as a standard of care, distant metastasis remains a significant cause of treatment failure. Immune checkpoint inhibitors (ICIs) have demonstrated survival benefits in advanced or metastatic ESCC, and adjuvant nivolumab has shown efficacy following neoadjuvant CRT in locally advanced ESCC. Integrating ICI earlier in the treatment sequence through total neoadjuvant therapy may enhance the immune response against the primary tumor and the hidden metastases and potentially lead to improved survival outcomes. This phase II study evaluates induction immunochemotherapy followed by CRT before surgery in locally advanced ESCC. **Methods:** This is a single-center, single-arm, phase II study enrolling 50 patients with histologically confirmed ESCC (T3/4aN0M0 or T1-4aN1-3M0 according to the AJCC Cancer Staging System 8th ed). Eligible patients must have primary intrathoracic esophageal tumor $\leq$10 cm in length and $\leq$5 cm in radial diameter, an ECOG performance status of 0-1, and adequate organ function. Patients will receive induction immunochemotherapy consisting of tislelizumab (200 mg every 3 weeks), paclitaxel (175 mg/m² every 3 weeks), and cisplatin (75 mg/m² every 3 weeks) for two cycles. This is followed by CRT consisting of radiotherapy (45 Gy in 25 fractions, 1.8 Gy/day, 5 days/week) plus chemotherapy with weekly paclitaxel (50 mg/m²) and cisplatin (30 mg/m²) for 5 weeks. Esophagectomy will be performed 6 to 8 weeks after completing CRT. The primary endpoint is pathologic complete response (pCR) rate, defined as no residual tumor in the resected primary site and lymph nodes. We hypothesize that the pCR rate will increase from 35% (the historical control) to 55%. Based on a binomial precision design, the study is of 80% power and a unilateral α error of 0.05 to detect a statistically significant difference in pCR rate. Secondary endpoints include major pathological response rate, R0 resection rate, disease-free survival, event-free survival, distant metastasis-free survival, overall survival and safety. The study starts patient enrollment in March 2025 (registered at ClinicalTrials.gov as NCT06764355). Clinical trial information: NCT06764355. Research Sponsor: National Taiwan University Hospital; BeiGene.

TPS4214 **Poster Session**

PROSPERO: A phase 3 randomized, placebo (Pbo)-controlled study of amezalpat (TPST-1120), a peroxisome proliferator-activated receptor a (PPARα) inhibitor, in combination with atezolizumab + bevacizumab (AB) for patients (pts) with unresectable or metastatic hepatocellular carcinoma (mHCC) not previously treated with systemic therapy. First Author: Mark Yarchoan, Johns Hopkins Medicine, Baltimore, MD

Background: PPARα is a fatty acid ligand-activated transcription factor that regulates genes involved in fatty acid oxidation (FAO), angiogenesis, and inflammation. In HCC and other tumor types, PPARα signaling promotes tumor growth and also modulates the tumor immune microenvironment to suppress antitumor immunity. Amezalpat (TPST-1120) is an investigational PPARα antagonist that inhibits FAO, targeting the bioenergetic requirements of cancer cells and restoring anticancer immune pathways. HCC has the highest PPARα expression of any major tumor type. In preclinical studies of HCC, including ß-catenin activated disease, amezalpat exhibits anti-cancer activity as a single agent and demonstrates complementary efficacy in combination with PD-L1 and VEGF inhibitors. In an ongoing global randomized Phase 1b/2 study in pts with unresectable or mHCC not previously treated with systemic therapy, amezalpat in combination with atezolizumab + bevacizumab (TPST-AB) was tolerable and was associated with a clinically meaningful improvement in multiple efficacy endpoints, including overall survival (OS) and confirmed objective response rate (ORR), compared to AB alone. Here we describe a follow-up pivotal Phase 3 study to evaluate the safety and efficacy of TPST-AB vs Pbo plus AB (Pbo-AB) in pts with unresectable or mHCC (NCT06680258). **Methods:** This Phase 3, global, randomized, double-blind study will enroll ~740 pts with unresectable or mHCC. Key eligibility criteria include no prior systemic therapy (prior locoregional therapy allowed), ECOG PS 0-1, Child-Pugh Class A, and measurable disease by RECIST v1.1; pts with fibrolamellar/sarcomatoid HCC, mixed cholangiocarcinoma/HCC, and untreated active HBV are not eligible. Pts will be randomized 1:1 to receive oral amezalpat 600 mg or Pbo twice daily along with the approved doses of atezolizumab and bevacizumab every 3 weeks, until unacceptable toxicity or loss of clinical benefit. Randomization will be stratified by geographic region (Asia excluding Japan vs rest of world), macrovascular invasion and/or extrahepatic spread (y/n), baseline α-fetoprotein ($<$ 400 vs $\geq$400 ng/mL), and baseline ECOG PS (0 vs 1). The primary efficacy endpoint is OS. Key secondary efficacy endpoints include progression-free survival and ORR (RECIST v1.1). Exploratory analyses will include outcome by PD-L1 expression and ß-catenin mutational status. Interim analyses for futility (30% OS events) and efficacy (70% OS events) are planned. Findings of this pivotal study will inform the efficacy and safety profile of amezalpat added to AB vs AB alone in pts with unresectable or mHCC not previously treated with systemic therapy. Clinical trial information: NCT06680258. Research Sponsor: Tempest Therapeutics, Inc.

TPS4215 **Poster Session**

RHEA-1: First-in-human (FIH) study of AZD9793, a first-in-class CD8-guided T cell-engager (TCE) for glypican-3-positive (GPC3+) advanced or metastatic hepatocellular carcinoma (HCC). First Author: Stephane Champiat, Department of Investigational Cancer Therapeutics, Division of Cancer Medicine, The University of Texas MD Anderson Cancer Center, Houston, TX

Background: GPC3 is an oncofetal protein expressed in 70–80% of HCC and is associated with poor prognosis. Preliminary clinical research on GPC3-specific CAR-T treatment has validated GPC3 as a therapeutic target in HCC. Its expression is largely confined to the surface of tumor cells, making it an ideal target for TCEs. AZD9793, a trispecific IgG1 monoclonal antibody, is a first-in-class CD8-targeted TCE that directly engages tumor-infiltrating T cells and GPC3+ tumors, forming a bridge that activates T cells leading to tumor cell lysis and T cell proliferation. AZD9793 promotes potent GPC3+ HCC cell killing through preferential engagement of CD8+ T cells, while minimizing CD4+ T cell activation and unwanted cytokine release. The novel mechanism of action combines bivalent GPC3 binding, CD8-biased engagement, and low-affinity T cell receptor binding to improve cytotoxicity and reduce the risk of cytokine release syndrome compared with other TCEs. **Methods:** RHEA-1 is the FIH trial of AZD9793 monotherapy. Eligible patients in this modular, Phase I/II, open-label, multicenter study are adults ($\geq$18 years old) with prospective centrally determined GPC3+ advanced or metastatic HCC with $\geq$1 measurable lesion by RECIST v1.1, who have received $\geq$1 line of prior systemic treatment and have an ECOG performance status of 0 or 1. Patients with hepatitis B are eligible if they receive antiviral treatment to ensure adequate viral suppression before enrollment and for $\geq$6 months after the study; and with hepatitis C if they are being managed per local practice. The study includes Module 1 (intravenous AZD9793) and Module 2 (subcutaneous AZD9793), each comprising dose escalation (Part A) and dose expansion (Part B). Module 1 Part A1 (fixed dose) will start with an accelerated titration design and will then switch to a modified toxicity probability interval-2 algorithm after the first 4 dose cohorts or earlier if dose-limiting toxicities (DLTs) are reported. Part A2 (step-up dosing) may open in either Module based on emerging safety data from Part A1. Part B may be initiated in one or both Modules. Primary endpoints include safety and tolerability in terms of DLTs (only in dose escalation) and adverse events to establish maximum tolerated dose, optimal biological dose, and recommended phase II dose; and objective response rate (only in dose expansion) by investigator assessment (IA) per RECIST v1.1. Secondary endpoints include preliminary efficacy (only in dose escalation) in terms of response and progression-free survival by IA, as well as overall survival (only in dose expansion), pharmacokinetics, immunogenicity, and CD8+ T cell infiltration pre- and post-treatment. No formal statistical hypothesis is proposed; all variables will be reported descriptively. The study (NCT06795022) is currently enrolling in the US and APAC. Clinical trial information: NCT06795022. Research Sponsor: AstraZeneca.

TPS4216 **Poster Session**

Phase II trial of zanzalintinib (XL-092) in combination with durvalumab and tremelimumab in unresectable hepatocellular carcinoma (ZENOBIA). First Author: Meghana Singh, Department of Hematology and Oncology, University of Pittsburgh Medical Center, Pittsburgh, PA

Background: Despite the evolving novel treatment options, the prognosis for advanced hepatocellular carcinoma (HCC) remains poor, with a 4-year survival rate of approximately 25%. Immune checkpoint inhibitors (ICIs), including the combination of durvalumab (Durva) & tremelimumab (Treme), represents the current standard-of-care for frontline HCC treatment. However, therapy resistance, either primary or secondary, often arises due to the immunosuppressive tumor microenvironment (TME). VEGFR is a well-established therapeutic target in HCC. Cabozantinib (Cabo), a multi-target tyrosine kinase inhibitor (TKI), is approved for later-line use per the CELESTIAL trial, and it also demonstrated significant TME modulation through antiangiogenic effects. A Phase II study (CHECKMATE 040) reported an impressive objective response rate (ORR) of 29% with the combination of ipilimumab/nivolumab and Cabo but noted high toxicity rates. Zanzalintinib (Zanza) is a novel TKI targeting VEGFR, MET, & TAM kinases (TYRO3, AXL, MER), key mediators of angiogenesis, tumor growth, metastasis, and TME immunosuppression. With a target profile similar to Cabo but an improved pharmacokinetic profile & a shorter half-life (16–22 hours), Zanza has demonstrated potential synergy with ICIs in preclinical and early-phase trials, suggesting enhanced sensitivity by fostering an immune-permissive TME. This phase II study evaluates the safety & efficacy of Zanza combined with Durva and Treme in HCC. **Methods:** This open-label, non-randomized Phase II trial consists of two parallel cohorts. Eligible patients must have unresectable HCC, be treatment-naïve in the unresectable setting, & have ECOG performance status of 0-1. Exclusion criteria include Child-Pugh score $>$7, known autoimmune diseases, heightened risk of gastrointestinal perforation or fistula formation, and known gastric or esophageal varices. The study begins with a safety lead-in phase of 9–12 patients to establish the recommended Phase II dose. The two cohorts aim to explore the optimal sequential strategy for combining Zanza with Durva & Treme. Cohort A: Zanza is administered during Cycle 1, followed by Durva + Treme in Cycle 2. Cohort B: Durva + Treme is administered during Cycle 1, followed by Zanza and Durva in Cycle 2. Both cohorts will continue with Zanza and Durva in subsequent cycles. A total of 40 participants (20 per cohort) will be enrolled. The primary endpoint is the ORR assessed by imRECIST 1.1. Secondary endpoints include the conversion rate to resectable or transplant-eligible disease, disease control rate, median PFS and OS, and landmark PFS & OS at 6, 12, 24, and 36 months. Safety and tolerability will also be evaluated. Comprehensive translational analyses include bulk RNA sequencing, spatial transcriptomics of baseline tumor biopsies, & serial ctDNA monitoring. Trial enrollment commenced in December 2024. Clinical trial information: NCT06698250. Research Sponsor: Exelixis.

TPS4217 **Poster Session**

A randomized phase 2 study of casdozokitug, an IL-27 targeting antibody, in combination with toripalimab plus bevacizumab in patients with unresectable and/or locally advanced or metastatic hepatocellular carcinoma. First Author: Daneng Li, City of Hope National Comprehensive Cancer Center, Duarte, CA

Background: IL-27 is a heterodimerized cytokine, a member of the IL-12/IL-23 cytokine family, and an immunoregulatory cytokine expressed by myeloid cells that dampens T and NK effector function. IL-27 is highly expressed by tumor-associated macrophages in several cancers, including hepatocellular carcinoma (HCC) and non-small cell lung cancer (NSCLC), and suppresses antitumor immune responses. Casdozokitug (Casdozo) is the only clinical-stage IL-27 targeting antibody and it increases IFN-g and T and NK cell activation in preclinical/clinical studies. A phase 1 study (NCT04374877) demonstrated a favorable safety profile and antitumor activity of casdozo as monotherapy and in combination with PD-1 blockade in indications, including HCC, with known high levels of IL-27 activation signature (Marron T, et al. *Ann Oncol*. 2023). A phase 3 study of toripalimab (tori) + bevacizumab (bev) demonstrated significant improvements in efficacy (overall survival [OS], progression-free survival [PFS], and objective response rate [ORR]) compared to sorafenib (Yinghong S, et al. CSCO 2024) in HCC. A phase 2 study of casdozo + atezolizumab + bev showed an acceptable safety profile and antitumor activity (ORR 38%, CR 17.2%, mPFS 8.1 mo) (Li D, et al. ASCO GI 2025). CHS-388-202 (NCT06679985) will evaluate the efficacy, safety, and biomarkers of tori + bev ± casdozo and optimize the dose for casdozo in combination with tori + bev as first-line treatment for patients (pts) with unresectable and/or locally advanced/metastatic HCC. **Methods:** CHS-388-202 is a Phase 2, open-label, randomized study and will enroll up to 72 pts randomized (1:1:1) to 1 of 3 treatment arms (IV Q3W): Arm A (tori 240 mg + bev 15 mg/kg + casdozo 700 mg), Arm B (tori 240 mg + bev 15 mg/kg + casdozo 1400 mg), Arm C (tori 240 mg + bev 15 mg/kg). Key eligibility criteria include treatment-naïve unresectable metastatic HCC with ≥1 measurable lesion; not suitable for surgical or local therapy; Child-Pugh A; ECOG PS 0 or 1; controlled hepatitis B virus or cured hepatitis C virus. Pts will be stratified by geographic region (Asia excluding Japan vs the rest of the world) and macrovascular invasion or extrahepatic spread of disease (presence vs absence). Primary endpoints are ORR by investigator review according to RECIST v1.1 and safety. Secondary endpoints are ORR by investigator review according to HCC modified RECIST (mRECIST) criteria; duration of response, PFS, and disease control rate by investigator review according to RECIST v1.1 and mRECIST criteria; OS, pharmacokinetics. A safety run-in evaluation will be conducted after the first ~6 pts are enrolled in Arms A and B, with ≥3 from each arm completing 1 cycle of treatment. Pts will remain on study treatment for ≤2 years or until documented disease progression or unacceptable toxicity. Enrollment is ongoing. Clinical trial information: NCT06679985. Research Sponsor: Coherus BioSciences.

TPS4218 **Poster Session**

A first-in-human study of MT-303, an innovative in vivo mRNA chimeric antigen receptor (CAR) therapy targeting GPC3, in adults with hepatocellular carcinoma. First Author: Timothy Guy Humphries, Sir Charles Gairdner Hospital/ University of Western Australia, Nedlands, Australia

Background: Hepatocellular carcinoma (HCC) remains a leading cause of cancer mortality worldwide, with advanced cases posing significant treatment challenges. GPC3, a cell surface protein highly expressed in HCC, represents a promising therapeutic target. MT-303 is an in vivo chimeric antigen receptor (CAR) therapy, leveraging mRNA-lipid nanoparticle (LNP) technology to reprogram myeloid cells directly within the body. This novel platform eliminates the logistical and technical barriers of ex vivo CAR therapies while retaining the ability to activate targeted immune responses. MT-303's mRNA encodes a GPC3-targeted CAR receptor incorporating a single-chain variable fragment (scFv) linked to the transmembrane domain and cytoplasmic tail of CD89. Crucially, functional CAR expression is restricted to Fc receptor common gamma chain-expressing cells, predominantly myeloid cells, ensuring precise immune activation. Preclinical studies demonstrated that MT-303 effectively infiltrates tumors, triggers tumor cell killing, produces chemokines and cytokines, eliciting an adaptive anti-tumor immunity. Rodent models of "cold" tumors and nonhuman primate studies have highlighted MT-303's safety, pharmacodynamic effects, and dose-dependent activity, supporting its clinical development (Argueta, SITC 2024, #1125). **Methods:** This first-in-human, multicenter, open-label, Phase 1 dose-escalation trial evaluates the safety, tolerability, pharmacokinetics (PK), pharmacodynamics (PD), and preliminary efficacy of MT-303 in participants with GPC3-expressing tumors, with a primary focus on Hepatocellular Carcinoma. MT-303 is administered intravenously every 14 days using a Bayesian Optimal Interval design, with backfill cohorts for dose refinement. The primary endpoints are safety, maximum tolerated dose (MTD), and recommended Phase 2 dose (RP2D). Secondary endpoints include detailed PK profiling and assessment of immune-related adverse events (e.g., ICANs, CRS). Exploratory endpoints encompass efficacy measures (e.g., objective response rate [ORR], duration of response [DOR]), immune reprogramming (e.g., peripheral CAR expression, cytokine profiles), and intratumoral immune changes, including T-cell receptor clonality and GPC3 modulation. Enrollment is ongoing, with safety and preliminary efficacy data expected to inform future development. Clinical trial information: NCT06478693. Research Sponsor: None.

TPS4219 **Poster Session**

A phase 1b/2, safety lead-in and dose-expansion trial of ivosidenib plus durvalumab and gemcitabine/cisplatin as first-line therapy in patients with locally advanced, unresectable or metastatic cholangiocarcinoma with an IDH1 mutation. First Author: James J. Harding, Memorial Sloan Kettering Cancer Center, New York, NY

Background: Cholangiocarcinomas (CCAs) are often advanced and incurable at the time of diagnosis. The phase 3 TOPAZ-1 trial showed improved OS and ORR with gemcitabine/cisplatin (GEM/CIS) and durvalumab (DURVA) vs GEM/CIS in unresectable advanced or metastatic biliary tract cancers. The phase 3 ClarIDHY trial demonstrated that the mIDH1 inhibitor ivosidenib (IVO) improved progression-free survival in CCA patients who have progressed from first or second-line chemotherapy and who have activating mutations in isocitrate dehydrogenase-1 (mIDH1). Additionally, mIDH1 suppresses key immune-related genes, with reversal of this effect when mIDH1 inhibitors are administered in preclinical CCA models. Finally, encouraging activity has been observed in treatment-naive mIDH1 patients administered with the mIDH1 inhibitor LY3410738 in combination with GEM/CIS. Given the ability of ivosidenib to stabilize advanced CCA, ability of IDH1 inhibition to restore immune activity, promising clinical activity of an mIDH1 inhibitor in combination with GEM/CIS, and the limited overlapping toxicities of these treatments, this study seeks to explore safety and preliminary activity of the quadruplet combination. **Methods:** This is a phase 1b/2, multicenter, safety lead-in and dose expansion, open-label study of IVO in combination with DURVA/GEM/CIS in first-line therapy of locally advanced, unresectable, or metastatic CCA with mIDH1. Treatment with up to one cycle of DURVA/GEM/CIS is permitted before initiation of study treatment. Key eligibility criteria include: a histopathological diagnosis; tumor mIDH1 based on local or centralized tissue testing (local testing by plasma ctDNA may be used); at least 1 measurable lesion as defined by RECIST v1.1; and adequate bone marrow, hepatic, and renal function. The study has a safety lead-in phase where IVO will be administered orally to the first 6 patients at a starting dose of 500 mg QD on every day of the 21-day cycle, plus DURVA 1500 mg IV infusion every 3 weeks for up to 8 cycles, plus GEM 1000 mg/m2 IV and CIS 25 mg/m2 IV on days 1 and 8 of each 21-day cycle, followed by IVO 500 mg QD and DURVA 1500 mg every 4 weeks of a 28-day cycle. Dose-limiting toxicities (DLTs) will be evaluated during the first cycle of quadruplet treatment. 6 additional patients may be enrolled to evaluate an alternative reduced dose of IVO 250 mg QD. The primary objective is to evaluate the safety and tolerability of the quadruplet combination, and to determine the recommended combination dose (RCD). The expansion phase will enroll approximately 40 patients who will be treated with the RCD, with the primary objective being to assess the clinical activity of the combination, as determined by a primary endpoint of confirmed complete or partial response using RECIST v1.1 criteria. Clinical trial information: NCT06501625. Research Sponsor: Servier.

TPS4220 **Poster Session**

A phase 2, randomized, multicenter study of adjuvant adebrelimab plus capecitabine in resected cholangiocarcinoma with high-risk factors: ACHIEVE. First Author: Xiangcheng Li, Hepatobiliary Center, the First Affiliated Hospital of Nanjing Medical University, Nanjing, China

Background: Cholangiocarcinoma is a rare and aggressive group of gastrointestinal cancers. For early-stage disease following curative resection, capecitabine is a category 1 recommendation for adjuvant therapy for biliary tract cancer (BTC) according to the NCCN guidelines. However, recurrence rates remain high. For example, the BILCAP study reported a 5-year recurrence-free survival (RFS) rate of 34% with adjuvant capecitabine. Based on cholangiocarcinoma-specific cohort data from the Hepatobiliary Center, The First Affiliated Hospital of Nanjing Medical University, the 1-year RFS rate for intrahepatic cholangiocarcinoma (ICC) and hilar cholangiocarcinoma (HCCA) with high-risk factors is approximately 50% (unpublished data), highlighting a substantial unmet medical need. Immunotherapy has shown efficacy as adjuvant therapy in other cancer types. Results from the TOPAZ-1 and KEYNOTE-966 studies support the combination of immunotherapy and chemotherapy for advanced BTC, including locally advanced non-metastatic disease. Adebrelimab, a PD-L1 inhibitor, has shown promising results in several cancers. In China, it is approved for first-line treatment of extensive-stage small cell lung cancer with chemotherapy. The ACHIEVE study will assess the efficacy of adebrelimab plus standard adjuvant chemotherapy in ICC/HCCA patients after curative resection with high-risk factors. **Methods:** ACHIEVE is a Phase 2, randomized, open-label, multicenter study designed to assess the efficacy and tolerability of adebrelimab administered intravenously every three weeks for one year in combination with capecitabine (8 cycles) as adjuvant therapy for ICC or HCCA after curative resection. The study will enroll about 120 adult patients with histologically confirmed ICC or HCCA who have undergone complete resection (R0). Eligible participants must have an ECOG performance status of 0–1, confirmed complete response (CR) on imaging 4–8 weeks post-surgery, and at least one high-risk factor. High-risk factors are defined as follows: ICC: Single tumor > 5 cm, multiple tumors, liver capsule breach, vascular invasion, regional lymph node metastasis; HCCA: Tumor invasion into surrounding tissues, vascular invasion, regional lymph node metastasis. Key exclusion criteria include locally advanced, unresectable, or metastatic disease at diagnosis and prior anti-cancer therapy before surgery. The primary endpoint is the 1-year recurrence-free survival rate (RFSR). Key secondary endpoints include overall survival (OS) and RFS, minimal residual disease (MRD), and patient-reported tolerability, and safety. Enrollment has begun, with six sites in mainland China participating. Clinical trial information: NCT06607276. Research Sponsor: None.

TPS4221 **Poster Session**

EMERALD-Y90: A phase 2 study to evaluate transarterial radioembolization (TARE) followed by durvalumab (D) and bevacizumab (B) for the treatment of participants (pts) with unresectable hepatocellular carcinoma (uHCC) eligible for embolization. First Author: Riad Salem, Northwestern Feinberg School of Medicine, St. Clair, Chicago, IL

Background: Locoregional therapy, such as transarterial chemoembolization (TACE) or TARE, is commonly used to treat uHCC eligible for embolization. Despite advances in TACE and TARE delivery, median progression-free survival (PFS) following treatment is <1 year, highlighting a need for new treatment options. EMERALD-1 (NCT03778957), a global phase 3 study, demonstrated a statistically significant improvement in PFS with TACE + D + B versus TACE + placebos in pts with uHCC eligible for embolization (hazard ratio, 0.77 [95% confidence interval, 0.61–0.98]; two-sided p-value = 0.032). With the increased use of TARE for patients with uHCC eligible for embolization in the US, a need exists for evidence to support additional treatment options in settings where TARE is preferred. The EMERALD-Y90 study will evaluate the efficacy and safety of TARE with D monotherapy, followed by D + B in pts with uHCC eligible for embolization. **Methods:** EMERALD-Y90 (NCT06040099) is a phase 2, single-arm study that will enroll ~100 pts aged $\geq$18 years with uHCC amenable to embolization who are ineligible for or have declined treatment with resection and/or ablation or liver transplant (transplant candidates are those listed for transplant or eligible to be listed and within Milan criteria). Eligible pts also must have Child-Pugh class A liver function and an Eastern Cooperative Oncology Group performance status of 0–1. Pts are allowed to receive a single TACE or TARE $\geq$6 months before the study or $>$1 TACE or TARE $\geq$12 months before the study. Prior TACE or TARE must have been administered for a different primary intrahepatic lesion unrelated to the current lesion, and pts should have a functional liver remnant $>$ 30%. Exclusion criteria include prior systemic therapy, evidence of extrahepatic spread, or major portal vein invasion. Pts will receive partition-based dosing of TARE using Y-90 glass microspheres. Following TARE, pts will receive D 1500 mg (one dose) followed by D 1120 mg + B 15 mg/kg every 3 weeks until study completion or discontinuation criteria are met. The primary endpoint is PFS (time from start of TARE until date of disease progression [investigator (INV)-assessed per modified Response Evaluation Criteria in Solid Tumors (mRECIST)] or death due to any cause). Secondary endpoints include safety and tolerability, 6-, 12-, and 24-month PFS, objective response rate (percentage of pts with confirmed complete or partial response [INV-assessed per mRECIST]), overall survival (time from start of TARE until death due to any cause), and duration of response (time from date of first documented response until date of progression or death due to any cause). An early safety review is planned when approximately 15 pts have completed their first cycle of D + B dosing. Study enrollment is ongoing at 22 US sites. Clinical trial information: NCT06040099. Research Sponsor: AstraZeneca.

TPS4222 **Poster Session**

Trial in progress: A phase Ib/II study to evaluate the safety and efficacy of atezolizumab plus bevacizumab as adjuvant therapy following carbon ion radiotherapy in hepatocellular carcinoma (VANGUARD trial). First Author: Keisuke Koroki, Department of Gastroenterology, Graduate School of Medicine, Chiba University, Chiba, Japan

Background: While hepatic resection remains the standard curative treatment for hepatocellular carcinoma (HCC), many cases are ineligible due to impaired liver function or patient-related factors. Percutaneous ablation is an option for small HCC but is limited by tumor size. Carbon ion radiotherapy (C-ion RT) has emerged as a promising modality, characterized by superior biological efficacy and dose distribution compared to conventional radiotherapy. Although HCC is relatively radiosensitive, conventional radiotherapy has limited efficacy due to low radiation tolerance of surrounding liver tissue. C-ion RT achieves effective treatment while minimizing radiation exposure through the superior dose localization of the carbon ion beam's Bragg peak. The establishment of adjuvant systemic therapy to prevent recurrence remains an urgent unmet need in HCC management. The IMbrave050 trial demonstrated the efficacy of combined atezolizumab and bevacizumab (Atezo+Bev) after resection or ablation, but recent analyses suggest diminishing long-term benefits. The combination of immune checkpoint inhibitors (ICIs) and radiotherapy has shown promise in several malignancies, with preclinical studies demonstrating synergistic enhancement of ICI efficacy through radiation-induced immunogenic cell death. Additionally, carbon ion radiation induces stronger immune responses compared to proton therapy. Based on these findings, we designed a phase Ib/II study to evaluate sequential C-ion RT followed by ICI as a novel therapeutic approach. **Methods:** This multicenter, open-label, single-arm phase Ib/II study evaluates the safety and efficacy of Atezo+Bev as adjuvant therapy following C-ion RT for HCC. Key inclusion criteria include treatment-naïve, Child-Pugh class A, maximum intrahepatic tumor diameter $\geq$4 cm and $\leq$3 intrahepatic tumors. After initial enrollment, patients undergo C-ion RT followed by a two-week observation period with eligibility screening for second enrollment. Eligible patients receive atezolizumab (1200 mg) and bevacizumab (15 mg/kg) every 3 weeks for up to 48 weeks, with radiological assessments every 3 months. The Phase Ib part will enroll six patients to evaluate dose-limiting toxicities. Secondary endpoints include adverse events (AEs) and serious AEs for safety and 1-year RFS, overall survival (OS) and 6-month OS rates for efficacy. If tolerability is confirmed, the trial will proceed to Phase II. Clinical trial information: jRCT2031240284. Research Sponsor: Chugai Pharmaceutical Co., Ltd.

TPS4223 **Poster Session**

Donafenib combined with capecitabine for postoperative adjuvant therapy of biliary malignant tumors with high risk of recurrence: A multi-center, randomized controlled, phase II study. First Author: Jianhua Rao, Hepatobiliary center, Jiangsu Province Hospital - The First Affiliated Hospital with Nanjing Medical University, Nanjing, China

Background: Biliary Tract Cancer (BTC) is an aggressive malignancy with rising incidence. Surgery is the only curative option, but only 10% of patients are eligible at diagnosis, and recurrence rates post-surgery can reach 67% within a year. The 5-year survival rate is only 5-15%. Emerging therapies, such as targeted and immunotherapies, show promise. A study combining GEMOX, tislelizumab, and donafenib (a tyrosine kinase inhibitor) in advanced BTC showed an 87.5% disease control rate (DCR) with strong safety and efficacy. The BILCAP study found that adjuvant capecitabine improved overall survival (OS) in resected BTC patients (median OS: 49.6 vs. 36.1 months; HR = 0.84). However, clinical research on adjuvant treatments for high-risk postoperative BTC remains limited, with no consensus on high-risk factors. This study evaluates the efficacy and safety of donafenib combined with capecitabine as adjuvant therapy for postoperative BTC with high recurrence. **Methods:** The study selected BTC patients prior to radical resection without any anti-tumor systemic therapy (including radiotherapy, chemotherapy, targeted therapy, immunotherapy) with at least one high-risk postoperative recurrence factors including specific stages according to the UICC/AJCC TNM 8th edition staging system: $T_{2\text{-}4}$, N_0, M_0 or $T_{1\text{-}4}$, N_1, M_0 (applicable to extrahepatic cholangiocarcinoma); $T_{1b\text{-}4}$, $N_{0\text{-}1}$, M_0 or T_{1a}, N_1, M_0 (applicable to intrahepatic cholangiocarcinoma), vascular invasion or neurophilic invasion as research subjects. Patients will be randomly divided into 1:1 groups. The experimental group consisted of donafenib (200mg, bid for 6 months) combined with capecitabine (1250mg/m^2, bid, treated for 2 weeks and stopped for 1 week, with 3 weeks as a treatment cycle, 8 cycles). The control group was capecitabine (same as experimental group). Treatment will start at least 4 weeks after radical resection and stop until patients experience disease recurrence or intolerable toxic side effects. The primary endpoint of the study was the 1-year recurrence free survival (RFS) rate. Secondary endpoints consisted of 2-year RFS, OS and safety assessment including incidence, severity, and relationship to study drugs of all adverse events (AEs), treatment-related adverse events (TRAEs), and serious adverse events (SAEs). Based on the data analysis of BTC cohort at our center, the 1y-RFS rate for the control group is set at 30%, while that for the experimental group is set at 60%. With a two-sided alpha of 0.05, a power of 0.80, and a randomization ratio of 1:1, the required number of RFS events is 64. Considering a 10% dropout rate, it is planned to enroll 35 participants per group, with a total planned enrollment of 70 participants. Dated by 20 January 2025, 8 of planned 70 patients have been enrolled. Clinical trial information: NCT06685289. Research Sponsor: None.

TPS4224 **Poster Session**

Australasian Gastro-Intestinal Trials Group (AGITG) STOPNET: A randomized study of cessation of somatostatin analogues (SSA) after peptide receptor radionuclide therapy (PRRT) in mid, hind-gut, and pancreatic neuroendocrine tumours. First Author: Matthew E. Burge, Royal Brisbane and Women's Hospital, Herston, QLD, Australia

Background: PRRT is a standard therapeutic option for patients with metastatic well-differentiated somatostatin receptor-positive gastroenteropancreatic neuroendocrine tumours (GEP-NETs) following progression on SSA. It is uncertain whether current practice of continuing SSA after commencing PRRT is beneficial, especially in non-functioning NETs. Studies by Yordanova et al. (2018) and Sygula et al. (2022) have included heterogenous study populations and yielded conflicting results. **Methods:** STOPNET is a prospective, randomized, non-comparative, open-label, multi-center phase II trial led by the AGITG in collaboration with the Canadian Cancer Trials Group (CCTG) under the Commonwealth Neuroendocrine Tumor research collaborative (CommNETS). The trial aims to evaluate the outcomes of SSA cessation or continuation in patients with GEP-NETs undergoing PRRT after progression on SSA. The co-primary endpoints are 20-month PFS and feasibility for a phase III trial, assessed by recruitment over a 24-month period & patient acceptance of SSA cessation. Secondary endpoints include OS, rate of SSA recommencement, time to subsequent therapy, quality of life, cost-effectiveness and psycho-oncological impacts of SSA cessation. Eligible participants must have advanced or unresectable WHO grade 1/2 non-functioning GEP-NETs (excluding the foregut), and disease progression after receiving $\geq$3 months of SSA at standard growth-control doses. SSA must have been primarily commenced for growth control, as opposed to functional symptoms and for mid/hindgut NET's 24-hr urine 5-hydroxyindoleacetic acid must be $<$ 1.5 times upper limit normal at screening. Participants will be randomized 2:1 to SSA cessation or continuation. SSA cessation arm will receive their last SSA $\geq$28 days prior to first PRRT, and the SSA continuation arm will continue SSA during and after PRRT. Following PRRT, participants will be assessed every 12 weeks (minimum 20 months) until disease progression or study closure, whichever occurs first. The sample size was calculated using Fleming's single stage design, assuming uninteresting and interesting 20-month PFS rates of 60% and 77% respectively. Novel translational research will be conducted to define and validate NET tissue and circulating biomarkers, with a particular focus on analysis of microRNA. Formalin-fixed paraffin-embedded (FFPE) tumor tissue will be retrieved (if available), with the collection of bloods at 3 time-points during study. The trial implemented the Australian Teletrial Program (ATP) to enhance equity of access for participants in regional, rural or remote locations. The trial will enroll 78 participants across 13 sites. Enrolment is open at 1 site in Australia & 4 sites in Canada, with 3 participants randomized as of Jan 2025. Clinical trial information: NCT06345079. Research Sponsor: Medical Research Future Fund (MRFF); Tour de Cure; AGITG philanthropic funding; Canadian Neuroendocrine Tumour Society (CNETS); Canadian Institutes of Health Research (CIHR).

TPS4225 **Poster Session**

A multi-centre, stratified, open, randomized, comparator-controlled, parallel group phase II trial comparing adjuvant treatment with 177Lu-DOTATATE to standard of care in patients after resection of neuroendocrine liver metastases (NELMAS). First Author: Andreja Frilling, Imperial College London, London, United Kingdom

Background: Gastro-entero-pancreatic (GEP) neuroendocrine tumours (NET) are steadily increasing in incidence and prevalence. About 65%-95% of GEP NET show hepatic metastases. Surgery is the mainstay of treatment for NE LM. While macroscopically complete resection for NE LM is associated with favourable overall survival (OS), recurrence rates of up to 70% at 3 years and up to 95% at 5 years are reported. These results call for adjuvant treatment concepts which have not yet been established. **Methods:** A prospective open-label, multicentre randomised parallel-group trial was conducted in patients with resected GEP NE LM. Adjuvant treatment with ^{177}Lu-DOTA^{0}-Ty^{3}-ocreotate (^{177}Lu-DOTATATE) (total administered activity 14.8 GBq) is compared with standard of care (SOC). The frequency of administration is 2 cycles (8±1weeks between each cycle). The first cycle is applied 8±2 weeks after liver resection. The control arm consists of SOC. Main inclusion criteria are well differentiated grade 1 or grade 2 (Ki67 < 20%) GEP NET, R0 or R1 resection of NE LM, primary tumour already resected or resected synchronously with LM, ^{68}Ga DOTATATE PET/CT prior to surgery confirming LM and no extrahepatic disease (except resectable perihilar lymph node involvement and/or primary tumour, if still in place). Main exclusion criteria are high grade NET, neuroendocrine carcinoma, R2 resection of LM, peptide receptor radionuclide therapy at any time prior to randomisation in the study, and any type of liver directed therapy within 12 weeks prior to randomisation in the study. Primary endpoint are disease-free survival (DFS) at 3 years after liver resection. The sample size of 106 patients in total is powered to detect an HR of 0.27, reflecting a 44% DFS probability at 3 years post-surgery in the ^{177}Lu-DOTATATE arm compared with a 25% in the SOC arm. Secondary endpoints OS, time to tumour recurrence, time to administration of subsequent antineoplastic therapy, safety and tolerability of ^{177}Lu-DOTATATE, health-related quality of life, patient reported outcomes, and cost effectiveness. Ancillary objectives explore the clinical utility of novel molecular based biomarkers in identification of residual microscopic disease and early detection of recurrent disease. Enrolment has begun. Follow-up data will be collected for 5 years overall from the date of randomisation of the last patient. Discussion: The NELMAS trial aims to investigate the efficacy of adjuvant therapy with ^{177}Lu-DOTATATE (2 cycles) compared to standard of care in preventing tumour recurrence in patients following R0/R1 resection of LM of well differentiated GEP NET. Clinical trial information: NCT05987176. Research Sponsor: Novartis/AAA; The Taylor Family 2010 Charitable Trust.

TPS4226 **Poster Session**

NCI 10479: A phase I dose escalation-expansion trial of sunitinib malate plus lutetium (Lu-177) dotatate in somatostatin receptor positive pancreatic neuroendocrine tumors. First Author: Nikolaos Trikalinos, Washington University School of Medicine in St. Louis, Siteman Cancer Center, St. Louis, MO

Background: Patients with metastatic or unresectable pancreatic neuroendocrine tumors (PanNETs) have a poor prognosis, even with currently available treatments, with a 5-year overall survival (OS) of less than 20%. Lutetium Dotatate (Lu-177) is a radiopharmaceutical that consists of the somatostatin analogue DOTA-Tyr3-Octreotate, coupled to the metal-ion chelating moiety, DOTA, and radiolabeled with lutetium-177. Lu-177 was approved by the FDA in 2018 for treatment of somatostatin receptor (SSTR)-positive gastroenterohepatic NETs, but it is limited in its efficacy to achieve cytoreduction and provide durable responses. Sunitinib malate is an oral small-molecule tyrosine kinase inhibitor targeting VEGFRs, PDGFRs, and KIT and is also FDA approved as a monotherapy for the treatment of metastatic unresectable PanNETs. There is preclinical, as well as clinical evidence of sunitinib being used as a radiosensitizer with classic radiation, but it has never been combined with a radiolabeled analogue in patients with PanNETs. **Methods:** This is a Phase I dose escalation/expansion study aiming to enroll up to 24 patients across several sites. Eligible patients will be offered fixed dose Lu-177 at 200 mCi for 4 fractions with concurrent oral sunitinib administration initiating on C1D1 and concluding 28 days after the last Lu-177 infusion. Dose escalation applies to sunitinib and will be guided by a 3+3 design to determine the maximum tolerated dose (MTD) and recommended phase 2 dose (RP2D). Once the RP2D has been established, up to 12 more patients will be offered participation in the expansion phase in an attempt to further record antitumor activity and correlation with imaging, tumor markers, as well as Lu-177 dosimetry. Treatment will continue until disease recurrence/progression, unacceptable toxicity, or completion of planned protocol. Key eligibility criteria include age > = 18 years, ECOG performance status < = 2, histologic diagnosis of metastatic, unresectable well- or moderately-differentiated SSTR-positive PanNETs of any grade, up to 1 prior treatment except for somatostatin analogues and appropriate baseline hematological parameters. Key exclusion criteria are prior use of sunitinib, Lu-177 or other radiopharmaceuticals, myocardial or cerebrovascular accident within the prior 12 months and left ventricular ejection fraction of < = 50%. The study uses an 8-week safety window to determine its primary endpoint, which is DLTs during administration of the combination. Secondary endpoints are objective response (ORR), duration of response (DOR), progression-free survival (PFS) and overall survival (OS), intensity of tumor uptake on pre-treatment SSTR PET and post Lu-177, chromogranin A level response as well as optional dosimetry imaging. Enrollment is ongoing. Clinical trial information: NCT05687123. Research Sponsor: National Cancer Institute.

TPS4227 **Poster Session**

An open-label, dose-finding, phase Ib study to assess the safety, tolerability of nesuparib (JPI-547), a dual inhibitor of PARP/TNKS, in combination with modified FOLFIRINOX (mFOLFIRINOX) and gemcitabine-nab-paclitaxel (GemAbraxane) in patients with locally advanced and metastatic pancreatic cancer. First Author: Do-Youn Oh, Department of Internal Medicine, Seoul National University Hospital Cancer Research Institute, Seoul National University College of Medicine, Seoul, South Korea

Background: Pancreatic ductal adenocarcinoma (PDAC) is a leading cause of cancer deaths, with most cases diagnosed at advanced stages. Current maintenance therapy with the PARP inhibitor, olaparib, benefits only patients with germline BRCA1/2 mutations (Approximately 5-7 % of PDAC cases). However, homologous recombination deficiency (HRD)-related mutations occur in ~15% of PDACs, potentially expanding the utility of PARP inhibitors. Nesuparib, a next-generation PARP inhibitor, also targets tankyrase, disrupting WNT and Hippo signaling pathways which are critical for homologous recombination repair. This dual mechanism mimics BRCA loss ("BRCAness"), sensitizing HRD-positive tumors without BRCA mutations to PARP inhibition, broadening therapeutic options. Combining PARP inhibitors with chemotherapy (e.g., irinotecan or platinum-based drugs) enhances sensitivity to DNA damage. Preclinical studies showed nesuparib inhibited tumor growth as monotherapy and achieved higher efficacy in combination with standard treatments. In a prior phase I trial, nesuparib showed promising antitumor activity, with overall response rate of 28.2% and disease control rate of 64.1%. This Phase Ib study aims to evaluate the efficacy of nesuparib in combination with standard chemotherapy for advanced PDAC using a 3+3 dose-escalation design. **Methods:** This multicenter, open-label, Phase Ib, dose-finding study will enroll 24–48 patients with locally advanced or metastatic PDAC. Two arms are included: Arm A (mFOLFIRINOX combination) and Arm B (GemAbraxane combination), each with 12–24 subjects across four dose groups (3–6 patients per group). Nesuparib is administered orally under fasting conditions ranging from Dose Levels -2 (12.5 mg qd) to 4 (100 mg qd), starting at Dose Level 1 (25 mg qd) with a 5 days on/2 days off schedule. Based on the occurrence of dose-limiting toxicities (DLTs), the dose may be escalated to higher levels (Dose Levels 2, 3, or 4) or reduced to lower levels (Dose Levels -1 or -2) with a 5 days on/2 days off or 3 days on/4 days off schedule. Arm A includes mFOLFIRINOX chemotherapy with biweekly oxaliplatin (65 mg/m²), leucovorin (400 mg/m²), irinotecan (135 mg/m²), and 5-FU (2,400 mg/m²). Arm B involves gemcitabine (1,000 mg/m²) and nab-paclitaxel (125 mg/m²) on Days 1, 8, and 15 of a 28-day cycle. Primary objectives are to determine the maximum tolerable dose (MTD) and recommended Phase II dose (RP2D) and to identify the optimal combination regimen based on safety. Secondary objectives include evaluating safety and antitumor activity. Enrollment began in Q1 2022. ClinicalTrials.gov ID: NCT05257993. Clinical trial information: NCT05257993. Research Sponsor: Onconic Therapeutics.

TPS4228 **Poster Session**

ALTER-PA001: A multicenter, randomized study of anlotinib and benmelstobart in combination with AG chemotherapy vs. AG as first-line treatment for metastatic pancreatic cancer. First Author: Jiujie Cui, Department of Medical Oncology and State Key Laboratory of Oncogene and Related Genes, Shanghai Cancer Institute, Renji Hospital, School of Medicine, Shanghai, China

Background: Metastatic pancreatic cancer (mPC) remains one of the most challenging malignancies to treat, with limited effective therapeutic options. While AG chemotherapy (nab-paclitaxel and gemcitabine) is a current standard first-line regimen, new combinations are needed to improve outcomes. Preclinical data suggest potential synergistic effects of anlotinib, a multi-target tyrosine kinase inhibitor, and benmelstobart, a novel anti-PD-L1 antibody, with chemotherapy. This study aims to evaluate the efficacy and safety of this combination in mPC. **Methods:** ALTER-PA-001 is a multicenter, open-label, randomized, controlled phase 2 trial that compared anlotinib plus benmelstobart and AG with AG in patients with treatment-naïve mPC. Eligible patients are aged 18-75, ECOG 0-1, with histologically or cytologically confirmed PC. A total of 104 patients will be randomly assigned in a 2:1 ratio to receive anlotinib (8 mg orally, QD, d1–14), benmelstobart (1200 mg IV, d1), nab-paclitaxel (125 mg/m² IV, d1, d8), and gemcitabine (1000 mg/m² IV, d1, d8) every 21 days or AG regimen with nab-paclitaxel and gemcitabine at the same doses and schedule. The randomisation is done centrally and stratified by the presence of liver metastasis. Patients achieving CR, PR, or SD after 8 cycles will enter a maintenance phase with continued treatment based on their assigned arm. Tumor assessment is performed every 6 weeks for induction treatment, and every 9 weeks for maintenance phase. The primary endpoint is objective response rate (ORR), with secondary endpoints including progression-free survival (PFS), disease control rate (DCR), duration of response (DoR), overall survival (OS), and safety. Exploratory biomarker analyses will assess correlations between baseline tumor characteristics and therapeutic outcomes. This trial is actively recruiting in November 2024. Clinical trial information: NCT06621095. Research Sponsor: None.

TPS4229 **Poster Session**

A phase 1b/2 trial of onvansertib in combination with NALIRIFOX for first line treatment of advanced pancreatic cancer (PANCONVA trial). First Author: Anup Kasi, University of Kansas Cancer Center, Fairway, KS

Background: Pancreatic cancer is a highly lethal disease. Despite research and drug development efforts focused on KRAS, no effective RAS inhibitors have been approved for the treatment of pancreatic cancer with KRAS mutation. PLK1 inhibition is a potential target in KRAS-mutated pancreatic cancer and may provide a new first-line treatment option. Onvansertib (also known as PCM-075 and NMS-1286937) is the first PLK1-specific adenosine triphosphate competitive inhibitor administered by oral route to enter clinical trials with proven antitumor activity in different preclinical models. **Methods:** This is a phase 1b/II, non-randomized, open label single arm study being conducted at the University of Kansas Cancer Center and its affiliated sites. The study is open for enrollment. Eligibility: Key inclusion includes pts with locally advanced, unresectable, or metastatic pancreatic adenocarcinoma who are treatment naïve, have adequate archival tissue for biomarker evaluation or are willing to undergo a biopsy, and have an ECOG of 0-1. Key Exclusion: Planned concomitant use of medications known to prolong the QT/QTc interval, use of strong CYP3A4 or CYP2C19 inhibitors or strong CYP3A4 inducers. Treatment Plan: The phase 1b (safety lead-in) will follow a dose de-escalation phase in which up to 2 different Onvansertib dose levels will be tested in combination with standard NALIRIFOX. Onvansertib starting dose level is 30mg orally once daily. The Phase II portion of the study will be a single-arm open-label enrollment with dosing based on the starting dose determination in the Phase Ib portion of the study (30mg or 20mg). NALIRIFOX (Nano-liposomal Irinotecan 50 mg/m2, Oxaliplatin 60 mg/m2, Leucovorin 400 mg/m2, 5-FU 2400 mg/m2) will be administered intravenously on D1 of the 14-day cycle. Onvansertib will be dosed orally on D1-5 of each 14-day cycle. Imaging will be performed at baseline and after every 4 cycles. Objectives: The primary objective of this study is to determine anti-tumor activity by measuring Overall Response Rate (ORR). The secondary objectives are to determine treatment safety based on toxicities in participants who have received at least one dose of onvansertib, to determine anti-tumor activity by Progression Free Survival (PFS), to determine anti-tumor activity by Disease Control Rate (DCR), to determine Overall Survival (OS). Statistical Plan: Simon's two-stage Optimum design will be used. The null hypothesis that the true response rate is 41% will be tested against a one-sided alternative that the true response rate is 65%. In the first stage, 10 evaluable pts will be enrolled. If there are 4 or fewer responses in these 10 pts, the study will be stopped. Otherwise, 11 additional evaluable pts will be accrued for a total of 21 evaluable pts. The null hypothesis will be rejected if 12 or more responses are observed in 21 evaluable pts. Clinical trial information: NCT06736717. Research Sponsor: Cardiff Oncology.

TPS4230 **Poster Session**

Trial in progress: RASolute 302—A phase 3, multicenter, global, open-label, randomized study of daraxonrasib (RMC-6236), a RAS(ON) multi-selective inhibitor, versus standard of care chemotherapy in patients with previously treated metastatic pancreatic ductal adenocarcinoma (PDAC). First Author: Brian M. Wolpin, Dana-Farber Cancer Institute, Gastrointestinal Cancer Center, Boston, MA

Background: Patients with previously treated metastatic PDAC have significant need for treatments with improved efficacy and tolerability. RAS is an oncogenic driver in $>$ 90% of patients with PDAC. Daraxonrasib (RMC-6236) is an oral, RAS(ON) multi-selective, tri-complex inhibitor of GTP-bound mutant and wild-type RAS. In the ongoing Phase 1 monotherapy trial (NCT05379985), daraxonrasib exhibited a manageable safety profile with primarily low-grade rash and GI toxicities, and encouraging ORR, PFS and OS in a broad population of previously treated patients with RAS mutant metastatic PDAC (J Clin Oncol 43, 2025 [suppl 4; abstr 722]). The significant unmet need for alternative treatment options, along with the preliminary clinical data of daraxonrasib monotherapy, support its evaluation in the ongoing Phase 3 clinical trial, RASolute 302, in patients with previously treated metastatic PDAC. **Methods:** RASolute 302 is a global, multicenter, open-label, randomized study (NCT06625320) designed to evaluate daraxonrasib outcomes compared to investigator's choice of standard of care chemotherapy as a 2L treatment in patients with metastatic PDAC. Eligibility includes patients $\geq$18 years old, ECOG performance status 0 or 1, disease progression on 1 prior line of either a 5-fluorouracil or gemcitabine-based regimen in the metastatic setting, and documented RAS mutation status (mutant or wild-type). Eligible RAS mutations are defined as nonsynonymous mutations in KRAS, NRAS, or HRAS at codons 12, 13, or 61 (G12, G13, or Q61). Patients with tumors that are RAS wild-type and received appropriate approved targeted therapy for actionable mutations are also eligible. A 1:1 randomization of approximately 460 patients will receive daraxonrasib 300 mg daily or investigator's choice of chemotherapy (gemcitabine/nab-paclitaxel, mFOLFIRINOX, nal-IRI/5-FU/LV, or FOLFOX) until unacceptable toxicity or disease progression. For patients randomized to daraxonrasib, recommended prophylactic measures for rash include oral antibiotics and topical corticosteroids. Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST v1.1) tumor assessments will be performed every 8 weeks until disease progression, withdrawal of consent, lost to follow up, or death, whichever occurs first. Dual primary endpoints are progression-free survival (PFS) as assessed by blinded independent central review and overall survival (OS) in the RAS G12X-mutant population. Key secondary endpoints include PFS, OS, objective response and quality of life measures in the all-patient population with tumors carrying RAS mutations (G12X, G13X or Q61X) or RAS wild-type. Enrollment for the trial commenced in October 2024. Clinical trial information: NCT06625320. Research Sponsor: Revolution Medicines, Inc.

TPS4231 **Poster Session**

A phase 2 study of botensilimab and AGEN1423, an anti-CD73-TGFβ-trap bifunctional antibody, with or without chemotherapy in subjects with advanced pancreatic cancer. First Author: Bruno Bockorny, Beth Israel Deaconess Medical Center, Boston, MA

Background: Traditional immune checkpoint inhibitors have shown limited benefit in pancreatic ductal adenocarcinoma (PDAC) owing to non-redundant immune resistance mechanisms dominating the tumor microenvironment (TME). Transforming growth factor (TGF)-β and cluster of differentiation (CD)73-adenosine represent two major immunoregulatory and pro-tumorigenic pathways responsible for therapeutic resistance and progressive disease in PDAC. AGEN1423 (also known as dalutrafusp alfa and GS-1423) is a bifunctional, humanized, aglycosylated immunoglobulin G1 kappa antibody that selectively inhibits CD73-adenosine production and neutralizes active TGF-β signaling. Botensilimab (BOT) is an Fc-enhanced multifunctional anti-cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) antibody. We hypothesize that the combination of AGEN1423 with BOT can rescue T-cell functional activity leading to responses in advanced PDAC. **Methods:** An investigator-initiated open label Phase 2 study to evaluate the safety, tolerability, and initial efficacy of BOT + AGEN1423 +/- chemotherapy in patients with metastatic PDAC (NCT05632328). In cohort 1, 12 patients with metastatic PDAC with disease progression to at least one line of treatment will receive AGEN1423 30mg/kg IV Q2W for 4 doses + BOT 150mg IV Q6W ongoing for up to 2 years. If the combination is considered safe and tolerable, and objective response is achieved in at least 1 subject, the study will proceed to Cohort 2. In Cohort 2, 12 additional patients with disease progression on first-line fluorouracil-based chemotherapy will be enrolled to receive second-line gemcitabine and nab-paclitaxel in combination with AGEN1423 30mg/kg IV Q2W for 4 doses + BOT 150mg IV Q6W. Key eligibility criteria include histologically or cytologically confirmed metastatic pancreatic adenocarcinoma, age $\geq$18 years, Eastern Cooperative Oncology Group (ECOG) performance status $\leq$1, adequate organ function, and measurable disease by RECISTv1.1. A pre-treatment and on-treatment tumor biopsy will be obtained for translational studies. The primary endpoint is to estimate the objective response rate (ORR) according to RECISTv1.1 criteria. Secondary endpoints include safety and tolerability as defined by the incidence of AEs as assessed according to CTCAE v5, disease control rate (DCR), progression-free survival (PFS), and overall survival (OS). Translational endpoints include the characterization of the transcriptional signatures in paired biopsies obtained before and on-treatment with BOT + AGEN1423, as well as the changes in cell composition of the TME following treatment using multiplexed immunofluorescence spatial technology. Enrolment has started and accrual is anticipated to complete in Q4 2025. Clinical trial information: NCT05632328. Research Sponsor: Agenus, Inc.

TPS4232 **Poster Session**

Adaptive organoid-based precision therapy study in pancreatic cancer (ADOPT): A phase II single-arm study to evaluate the efficacy of patient-derived organoid (PDO)-directed therapy in advanced pancreatic ductal adenocarcinoma (PDAC). First Author: Ronan Andrew McLaughlin, Division of Medical Oncology and Hematology, Princess Margaret Cancer Centre – University Health Network, University of Toronto, Toronto, ON, Canada

Background: PDAC is a devastating malignancy. High-throughput genomic technologies have yielded insights regarding the molecular underpinnings and heterogeneity of PDAC. Systemic treatment options are limited to cytotoxic chemotherapies, except for approx. 10%, who receive targeted treatment based on genomic profiling. PDO's are three-dimensional *ex vivo* experimental models grown directly from tumor tissue and can provide a direct assessment of drug response. By directly exposing cancer cells to potential drug therapies, functional profiling provides a dynamic measurement of response that is more informative than static gene panels. PDOs can theoretically be used to direct therapeutic decisions, offering an opportunity to expand the reach of precision therapies for PDAC beyond genomics. To date, PDO testing has been limited by small sample sizes, few drugs included in the screens, and retrospective studies. To expand the impact of precision therapy, we developed a rapid high-throughput screening (HTS) platform where over 3,000 drugs can be tested in PDOs within 8-10 weeks of diagnosis. In ADOPT, we aim to formally investigate the efficacy of PDO-directed therapy in a prospective phase II study, leveraging our existing platforms using real-time HTS of PDOs. This study represents one of the first formal trials of PDO-directed therapy in solid tumors. Our novel approach will enroll pts with advanced PDAC who do not have alternative treatment options. **Methods:** This is an actively recruiting prospective, single-arm phase II trial. Patients (pts) with advanced epithelial PDAC are eligible if they either: 1) progressed on, were intolerant to, or refused first-line or subsequent therapies (Cohort A), or 2) have stable disease after $\geq$8 cycles of FOLFIRINOX ("Maintenance" Cohort B) and have a PDO showing sensitivity to an approved HC drug. Pts will be recruited, from multiple ongoing studies including PROSPER-PANC where we have successfully generated and tested a PDO. PDO-directed treatment will be selected based on drug sensitivity as tested through our validated HTS platform. Each case will be discussed at our PDO dedicated tumor board. All pts must meet the inclusion/exclusion and drug-specific eligibility criteria. The primary endpoint is disease control rate. A Simon's two-stage optimal design will be used to test the hypothesis: H0: P $\leq$ 0.05 versus H1: P $\geq$ 0.25. In the first stage, 9 pts will be evaluated. The trial will be discontinued if no disease control response is observed in this stage. If at least one response is observed, then the trial will continue to the second stage and an additional 17 pts will be evaluated for a total of 26 evaluable. This design has a one-sided alpha of 0.05 and power of 80%. We will reject the null hypothesis after 26 if 3 or more responses are observed. Clinical trial information: awaited. Research Sponsor: Ontario Institute for Cancer Research and Princess Margaret Cancer Foundation; Terry Fox Research Institute - Marathon of Hope Cancer Centres Network Funding; Sinai Health Foundation; The MNitz Pancreatic Cancer Research Fund (Michelle Reisman); The MNitz Pancreatic Cancer Research Fund (Veroli Cultural Society); The MNitz Pancreatic Cancer Research Fund (Elyse Graff).

TPS4233 **Poster Session**

Phase I trial of MK2 inhibitor in combination with mFOLFIRINOX for untreated metastatic pancreatic ductal adenocarcinoma. First Author: Moh'd M. Khushman, Washington University School of Medicine, St. Louis, MO

Background: Zunsemetinib (also known as ATI-450) is an investigational small molecule inhibitor targeting MAPK-Activated Protein Kinase (MAPKAPK2, or MK2). Preclinical work conducted by the Lim Lab at Washington University in St. Louis demonstrated that FOLFIRINOX activates heat shock protein 27 (Hsp27), a molecule with pleiotropic pro-survival properties, and beclin1, a key mediator of autophagy, in pancreatic ductal adenocarcinoma (PDAC) models. In an autochthonous PDAC (KPC) mouse model, zunsemetinib synergized with FOLFIRINOX, resulting in near-complete ablation of all PDAC foci and significantly improved mouse survival. Additionally, mice treated with zunsemetinib experienced significantly less intestinal damage and weight loss—common concerns associated with FOLFIRINOX. These preclinical data support the rationale for combining zunsemetinib with FOLFIRINOX in PDAC patients. **Methods:** We are conducting a phase I, single-arm, open-label study of zunsemetinib in combination with mFOLFIRINOX in patients with untreated metastatic PDAC. The study consists of two phases: a dose escalation phase and an expansion phase. During the dose escalation phase, zunsemetinib dosing will proceed according to the BOIN design with a cohort size of 3. A total of 6–21 patients will be enrolled at Washington University. Patients will receive zunsemetinib starting at Dose Level 1 (40 mg twice daily), with dose escalation continuing until the recommended phase 2 dose (RP2D) is determined. Patients will remain in the study until disease progression or treatment intolerance. In the expansion phase, up to 30 additional patients will be enrolled to further assess the toxicity profile of zunsemetinib in combination with mFOLFIRINOX. These patients will begin at the RP2D and continue on study treatment until disease progression or treatment intolerance. Eligible patients must be treatment-naïve, newly diagnosed, and have histologically or cytologically confirmed PDAC for which mFOLFIRINOX is deemed a suitable treatment option. The primary objective is to determine the dose-limiting toxicities (DLTs) and RP2D of zunsemetinib in combination with mFOLFIRINOX. Secondary objectives include assessing toxicity profiles, progression-free survival (PFS) at six months and overall PFS, disease control rate, overall response rate, overall survival, CA 19-9 response at the RP2D, and pharmacokinetics of zunsemetinib in PDAC treated with mFOLFIRINOX. Exploratory objectives include evaluating pharmacodynamic markers via immunohistochemistry (e.g., phospho-Hsp27 to assess pharmacodynamics of zunsemetinib, LC3B to assess autophagy, and TUNEL staining to evaluate DNA damage) and analyzing pathway suppression through RNA sequencing. Pre- and post-treatment serum samples will also be collected for the analysis of inflammatory cytokines. Clinical Trial Registration: NCT06648434. Clinical trial information: NCT06648434. Research Sponsor: Pancreatic SPORE (P50 CA272213); Aclaris.

TPS4234 **Poster Session**

An open-label, phase 1 trial with expansion cohort of botensilimab (AGEN1181) + balstilimab (AGEN2034) + nab-paclitaxel + gemcitabine + cisplatin + chloroquine + celecoxib in adult patients with previously untreated metastatic pancreatic cancer. First Author: Erkut H. Borazanci, HonorHealth Research Institute, Scottsdale, AZ

Background: The unfolded protein response (UPR) is an adaptive endoplasmic reticulum (ER) stress pathway that and can prevent cellular death under moderate stress conditions or promote apoptosis under severe stress. The UPR is often upregulated in pancreatic cancer cells and has been identified as a promising target for therapeutic intervention. We hypothesize that inducing severe ER stress by combining multiple chemo and immunotherapy agents will cause pancreatic cancer cells to enter the apoptotic UPR pathway, destroying these cells and improving patient survival. Prolonged ER stress is achieved in this study by using chemotherapy (nab-paclitaxel + gemcitabine + cisplatin) in combination with 2 immunotherapy agents: botensilimab (AGEN1181), an Fc-engineered anti-CTLA-4 monoclonal antibody, and balstilimab (AGEN2034), a human monoclonal immunoglobulin (Ig) G4 (IgG4) antibody designed to block programmed cell death protein (PD-1) binding by PD-L1 and PD-L2. Additionally, 2 agents are included to help block apoptosis escape routes: chloroquine to inhibit autophagy and celecoxib to reduce tumor microenvironment inflammation. **Methods:** This single-center, open-label, phase 1 study evaluates the safety, tolerability, and preliminary efficacy of two botensilimab doses in combination with fixed doses of balstilimab (240 mg) + nab-paclitaxel (125 mg/m^2) + gemcitabine (1000 mg/m^2) + cisplatin (25 mg/m^2) + chloroquine (500 mg) + celecoxib (200 mg) in adult patients with previously untreated metastatic pancreatic cancer (NCT06076837). The study design consists of 6 patients in a dose 1 cohort at 50 mg botensilimab + combination regimen and an escalated dose 2 cohort of 6 patients at 75 mg botensilimab + combination regimen (pending dose 1 cohort safety signals), with an additional 6 patients in an expansion cohort treated at the determined maximum tolerated dose (MTD) of botensilimab (Total N = 18). Adverse events (AEs) are evaluated according to NCI CTCAE v5.0 and tumor response is assessed by RECIST v1.1. Key eligibility criteria include 1) histologically confirmed diagnosis of metastatic pancreatic ductal adenocarcinoma with measurable disease on baseline imaging, 2) life expectancy of at least 3 months, 3) no previous radiotherapy, surgery, chemotherapy, or investigational therapy for the treatment of metastatic disease, and 4) no prior immune checkpoint inhibitor therapy. Enrollment began in January 2025 at the HonorHealth Research Institute. Clinical trial information: NCT06076837. Research Sponsor: TGen Foundation; Purple Pansies Foundation.

TPS4235 **Poster Session**

A supervised prehabilitation program for patients with pancreatic cancer. First Author: Philip Chang, Cedars-Sinai Medical Center, Los Angeles, CA

Background: Individuals who develop pancreatic cancer tend to be older, with 70% of pancreatic diagnoses occurring in those $\geq$ 65 years (2). Older patients are at increased risk for sarcopenia which is the progressive loss of skeletal muscle mass, tone, quality and strength and has been reported to affect 65% of pancreatic cancer patients (4). PREHAB is the process of improving the functional capability and psychological health of the individual to reduce the incidence and/or severity of future impairments (6). The foundation of PREHAB is functional exercise although components of nutrition and stress reduction may be included (9). PREHAB sessions are typically delivered through structured programs and have been shown to have a number of benefits such as improvements in functional activity and decreased postoperative complications (8). In a study by Ngo-Huang et al, 50 pancreatic cancer participants participated in a home-based multimodal program resulting in improved physical function and health related quality of life (15). Given the numerous benefits, the purpose of this study is to demonstrate the feasibility of a multimodal supervised PREHAB program in pancreatic cancer patients which we believe could have greater benefits than unsupervised programs. **Methods:** This is a single arm pilot study assessing the feasibility of a supervised prehabilitation program for patients with pancreatic cancer. Inclusion criteria include a diagnosis of any stage pancreatic cancer, independence with ambulation, and a lower level of physical activity as assessed by the Godin-Shepard Leisure-Time Physical Activity Questionnaire. To our knowledge, this is the first study in which all exercises sessions are in-person and supervised by exercise technicians in pancreatic cancer. Additionally, while prehabilitation typically takes place during the neoadjuvant therapy period, this study will also include patients with metastatic disease on continuous chemotherapy. Participants will undergo baseline evaluations testing strength, endurance, balance, subjective measures and sarcopenia measures. This will be immediately followed by one-hour long supervised exercise sessions 3x per week for 6 weeks in which participants will engage in aerobic training and resistance training targeting major muscle groups. Following the intevention, measures will be collected immediately afterwards and at 3 month follow-up. The primary analysis will test the hypothesis of feasibility using an one-sided exact Binomial test at 25% significance level. If 10 or more patients attend a minimum of 60% of exercise sessions during the initial 6-week period, then the study will be declared feasible. 11 of 16 patients have been enrolled to date. Clinical trial information: NCT05692323. Research Sponsor: Cedars Sinai Medical Center (Internal Funding).

TPS4236 **Poster Session**

IMMUNORARE^5: A national platform of 5 academic phase II trials coordinated by Lyon University Hospital to assess the safety and the efficacy of the immunotherapy with domvanalimab + zimberelimab combination in patients with advanced rare cancers—The Peritoneal Mesotheliomas Cohort. First Author: Julien Peron Sr., Centre Hospitalier Lyon Sud - Hospices Civils de Lyon, Pierre-Bénite, France

Background: In patients with rare cancers, there is an unmet medical need for investigating innovative therapeutics beyond standard first-line treatment. Indeed, these diseases are rarely assessed in clinical trials. The standard 1st-line treatment of peritoneal mesothelioma relies on platinum and pemetrexed, with no validated 2nd-line treatment so far. Several studies suggested that immunotherapy, such as ipilimumab + nivolumab or atezolizumab + bevacizumab, is active in this disease. There is a strong biological rationale for concurrent blockage of TIGIT and PD1 pathways in mesothelioma. **Methods:** IMMUNORARE^5 (NCT06790706) is a platform of 5 single arm phase II trials testing the safety and the efficacy of DOMVANALIMAB (anti-TIGIT) and ZIMBERELIMAB (anti PD-1) in 5 independent cohorts of rare cancers. The trial, sponsored by Lyon University Hospital, is conducted in 15 French centers, in partnership with the corresponding national networks of reference centers. The PERITONEAL MESOTHELIOMA cohort, led in collaboration with the RENAPE network (https://www.renape-online.fr/), will enroll 27 patients in progression after at least 1 line of platinum + pemetrexed based-chemotherapy regimen, with evaluable lesions at the baseline (modified RECIST criteria). Patients previously treated with immunotherapy will not be eligible. Patients will receive intra-venous DOMVANALIMAB and ZIMBERELIMAB, every three weeks, until disease progression. The primary endpoint will be the progression-free survival rate at 6 months. The disease progression (clinical or radiological) will be confirmed by the RENAPE experts. The secondary endpoints are tolerance, overall response rate and duration of response, progression-free and overall survival. A two-stage Simon design was used, with early termination rules for futility (5% one-sided alpha level, 80% power). The treatment would be considered interesting if the percentage of patients free from disease progression at 6-months is statistically higher than 35%; 60% is expected. Translational research projects will be developed aiming at deciphering cellular and molecular mechanisms involved in response to treatment. Moreover, data from the prospectively-maintained RENAPE database will be investigated to build a synthetic historical arm representative of the efficacy of the standard treatments in a similar population of patients. Clinical trial information: NCT06790706. Research Sponsor: GILEAD.

4500 Oral Abstract Session

Nivolumab plus ipilimumab (NIVO+IPI) vs gemcitabine-carboplatin (gem-carbo) chemotherapy for previously untreated unresectable or metastatic urothelial carcinoma (mUC): Final results for cisplatin-ineligible patients from the CheckMate 901 trial. First Author: Michiel Simon Van Der Heijden, Netherlands Cancer Institute, Amsterdam, Netherlands

Background: Platinum-based chemotherapy is a standard of care (SOC) for unresectable or mUC; patients (pts) ineligible for cisplatin (cis) have worse outcomes. The phase 3, global, open-label, randomized CheckMate 901 trial (NCT03036098) compared NIVO+IPI vs gem-carbo in cis-ineligible pts with previously untreated unresectable or mUC. Here, we report final results. **Methods:** Pts with previously untreated, histologically confirmed, unresectable or mUC who were cis-ineligible (glomerular filtration rate $\geq$ 30 to $<$ 60 mL/min) were randomized 1:1 to NIVO 1 mg/kg + IPI 3 mg/kg Q3W up to 4 cycles, then NIVO 480 mg Q4W until disease progression/unacceptable toxicity or up to 2 years, or to gem-carbo Q3W for up to 6 cycles. Pts were stratified by tumor PD-L1 expression and liver metastasis. The primary endpoint was overall survival (OS). Progression-free survival (PFS) by blinded independent central review (BICR) was a secondary endpoint. Objective response rate (ORR) per BICR, duration of response (DOR) per BICR, and safety were exploratory. **Results:** 445 pts were randomized (NIVO+IPI, n = 221; gem-carbo, n = 224). Median time to treatment discontinuation (95% CI) was 2.2 (2.1–3.5) mo with NIVO+IPI vs 3.8 (3.5–3.9) mo with gem-carbo. After minimum follow-up (58.3 mo), the primary endpoint of OS did not meet the threshold for significance (median, 19.1 mo with NIVO+IPI vs 13.2 mo with gem-carbo; HR 0.79 [98.27% CI, 0.61–1.01]; P = 0.0245; Table). PFS, ORR, and DOR are shown in the Table. Any-grade treatment-related adverse events (TRAEs) occurred in 89.0% (grade 3–4, 47.2%) of NIVO+IPI-treated and 92.9% (grade 3–4, 76.3%) of gem-carbo-treated pts; any-grade TRAEs leading to discontinuation occurred in 31.2% and 14.2% of pts, respectively. There were 8 deaths related to toxicity (NIVO+IPI, 7; gem-carbo, 1). **Conclusions:** NIVO+IPI did not meet the threshold of statistical significance for improved OS vs gem-carbo in cis-ineligible pts with untreated unresectable or mUC. Durable response and favorable landmark OS with NIVO+IPI show meaningful activity from a chemotherapy-free regimen of finite duration. No new safety signals were identified. Clinical trial information: NCT03036098. Research Sponsor: Bristol Myers Squibb.

Efficacy (95% CI)	NIVO+IPI; n = 221	Gem-carbo; n = 224	HR
mOS	19.1 (13.5–22.6)	13.2 (11.6–15.2)	0.79 (98.27% CI, 0.61–1.01)[a]; P = 0.0245[b]
12-mo OS rate	59.7 (52.8–65.9)	54.3 (47.4–60.7)	–
36-mo OS rate	29.6 (23.5–35.9)	19.3 (14.3–24.9)	–
mPFS	5.3 (3.8–6.0)	5.9 (5.6–7.6)	0.90 (95% CI, 0.72–1.12)
12-mo PFS rate	31.5 (25.0–38.2)	17.2 (11.8–23.4)	–
36-mo PFS rate	20.0 (14.3–26.5)	4.9 (2.1–9.6)	–
ORR	35.3 (29.0–42.0)	38.8 (32.4–45.6)	-
mDOR	25.0 (14.8–61.8); n = 78	7.4 (5.8–8.5); n = 87	-

[a]Statistical inference based on adjusted CI: 95% CI, 0.64–0.97.
[b]mOS did not reach the prespecified threshold of statistical significance of P = 0.0173.
m, median.

4501 Oral Abstract Session

Avelumab + sacituzumab govitecan (SG) vs avelumab monotherapy as first-line (1L) maintenance treatment in patients (pts) with advanced urothelial carcinoma (aUC): Interim analysis from the JAVELIN Bladder Medley phase 2 trial. First Author: Jeannie Hoffman-Censits, The Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins, Johns Hopkins Greenberg Bladder Cancer Institute, Baltimore, MD

Background: In the JAVELIN Bladder 100 phase 3 trial, avelumab 1L maintenance + best supportive care (BSC) significantly prolonged overall survival (OS) and progression-free survival (PFS) vs BSC alone in pts with aUC without progression following 1L platinum-based chemotherapy (PBC). The JAVELIN Bladder Medley phase 2 trial is investigating the combination of avelumab with other antitumor agents in this pt population to assess efficacy and safety vs avelumab maintenance monotherapy. SG is a Trop-2–directed antibody and topoisomerase inhibitor drug conjugate being investigated in solid tumors. Here we report an interim analysis of avelumab + SG vs avelumab monotherapy. **Methods:** Eligible pts had unresectable locally advanced or metastatic UC, ECOG performance status (PS) 0-1, and no disease progression after 4-6 cycles of 1L PBC. Pts were randomized 2:1 to avelumab + SG or avelumab monotherapy, stratified by presence of visceral metastases at start of 1L PBC. Primary endpoints were investigator-assessed PFS and safety; OS was a secondary endpoint. For PFS and OS analyses, data in the avelumab monotherapy arm were extended per protocol using propensity score-weighted JAVELIN Bladder 100 data. **Results:** At data cutoff (Sep 16, 2024), 38 of 74 pts (51.4%) in the avelumab + SG arm and 10 of 37 pts (27.0%) in the avelumab monotherapy arm were still receiving study treatment. In the avelumab + SG and avelumab monotherapy arms, respectively, median age was 70 and 67 years, 50.0% and 51.4% had visceral metastases at start of 1L PBC, and a lower proportion of pts in the avelumab + SG arm had ECOG PS of 1 (31.1% vs 54.1%). Median PFS was 11.17 months (95% CI, 7.43-not estimable [NE]) with avelumab + SG vs 3.75 months (95% CI, 3.32-6.77) with avelumab monotherapy (hazard ratio [HR], 0.49 [95% CI, 0.31-0.76]). OS data were immature at cutoff; median OS was not reached (95% CI, 15.51-NE) in the avelumab + SG arm vs 23.75 months (95% CI, 18.79-30.82) in the avelumab monotherapy arm (HR, 0.79 [95% CI, 0.42-1.50]). In the avelumab + SG and avelumab monotherapy arms, respectively, treatment-related adverse events (TRAEs) of any grade occurred in 71 (97.3%) vs 23 pts (63.9%), and were grade $\geq$3 in 51 (69.9%) vs 0 pts. TRAEs led to discontinuation of both avelumab + SG in 4.1% (SG only in 12.3%) vs avelumab monotherapy in 2.8%. One pt in the avelumab + SG arm had a SG-related AE that led to death (acute subarachnoid hemorrhage in the setting of sepsis and pancytopenia). **Conclusions:** In pts with aUC without progression after 1L PBC, avelumab + SG as maintenance treatment improved PFS vs avelumab monotherapy. TRAEs were more frequent in the combination arm and were consistent with the known safety profile of SG and avelumab. Further investigation of avelumab in combination with anti–Trop-2 antibody-drug conjugates in aUC is warranted. Clinical trial information: NCT05327530. Research Sponsor: the healthcare business of Merck KGaA, Darmstadt, Germany (CrossRef Funder ID: 10.13039/100009945).

4502 Oral Abstract Session

Exploratory analysis of responders from the phase 3 EV-302 trial of enfortumab vedotin plus pembrolizumab (EV+P) vs chemotherapy (chemo) in previously untreated locally advanced or metastatic urothelial carcinoma (la/mUC). First Author: Shilpa Gupta, Cleveland Clinic Taussig Cancer Institute, Cleveland, OH

Background: EV-302/KEYNOTE-A39 (NCT04223856) showed significant PFS and OS benefits for pts with previously untreated la/mUC treated with EV+P vs chemo, which established EV+P as the SOC in this population. This exploratory analysis presents efficacy and safety results for responders, focusing on pts with confirmed complete response (cCR). **Methods:** Pts were randomized 1:1 to receive EV (1.25 mg/kg; Days 1 and 8; IV) + P (200 mg; Day 1; IV) or chemo (gemcitabine + cisplatin/carboplatin); all Q3W. Primary endpoints were PFS by BICR and OS. Secondary endpoints included ORR, DOR, and safety. An exploratory analysis evaluated outcomes in pts with cCR. A genAI tool (01/09/25; Pfizer; GPT-4o) developed the 1st draft; authors assume content responsibility. **Results:** Median follow-up (data cutoff: Aug 8, 2024) was 29.1 mo (95% CI, 28.5-29.9). 886 pts were randomized to EV+P (n = 442) vs chemo (n = 444). Confirmed ORR (CR+PR) was 67.5% with EV+P and 44.2% with chemo; cCR was 30.4% and 14.5%, respectively. Baseline characteristics of responders were generally consistent with the ITT population. Among pts with cCR in the EV+P arm, 38 (28.6%) had upper tract disease and 20 (15%) had liver metastases. For pts with cCR, mPFS by BICR was not reached (NR) with EV+P and 26.9 mo with chemo (HR, 0.36; 95% CI, 0.21-0.61); mOS was NR with both EV+P and chemo (HR, 0.37; 95% CI, 0.17-0.80). Median duration of CR was NR for EV+P and 15.2 mo for chemo. Efficacy data are in the Table. Among pts with cCR in the EV+P arm, the median number of cycles was 13 (range, 1-50) for EV and 27 (range, 1-35) for P; median treatment (tx) duration was 22.0 mo (range, 0.7-35.4). Safety among responders was generally consistent with previous reports. TRAEs leading to dose modification in pts with cCR are in the Table. Grade $\geq$3 TRAEs occurred in 61.7% and 71.9% of pts with cCR in the EV+P and chemo arms, respectively. EV tx-related AESIs and P tx-emergent AEOSI profiles were generally consistent with previous reports. There were no tx-related deaths among pts with cCR. **Conclusions:** In the EV+P arm, the proportion of pts achieving cCR was twice that in the chemo arm. Consistent with the ITT data, EV+P reduced the risk of progression or death vs chemo in pts achieving cCR, with appropriate dose modifications. These data reinforce EV+P as the SOC for 1L tx of pts with la/mUC. Clinical trial information: NCT04223856. Research Sponsor: The EV-302 study was funded by Astellas Pharma Inc., Northbrook, IL, USA; Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA; and Seagen Inc., Bothell, WA, USA, which was acquired by Pfizer in December 2023.

	EV+P cCR: n=133	Chemo cCR: n=64
Median PFS, mo (95% CI)	NR (NE-NE)	26.9 (16.6-NE)
24-mo PFS rate, % (95% CI)	78.2 (69.8-84.6)	53.7 (40.0-65.5)
Median OS, mo (95% CI)	NR (39.3-NE)	NR (32.1-NE)
24-mo OS rate, % (95% CI)	95.4 (90.0-97.9)	85.8 (74.6-92.4)
Median DOCR, mo (95% CI)	NR (NE-NE)	15.2 (10.3-NE)
24-mo cCR rate, % (95% CI)	74.3 (65.1-81.4)	43.2 (28.7-56.9)
TRAEs leading to dose modification (n, %)		
Dose interruption of EV	94 (70.7)	-
Dose reduction of EV	86 (64.7)	-
Dose interruption of P	86 (64.7)	-

4503 Oral Abstract Session

Circulating tumor DNA (ctDNA) in patients with muscle-invasive bladder cancer (MIBC) who received perioperative durvalumab (D) in NIAGARA. First Author: Thomas Powles, Barts Cancer Institute, Experimental Cancer Medicine Centre, Queen Mary University of London, St Bartholomew's Hospital, London, United Kingdom

Background: In the phase 3 NIAGARA trial (NCT03732677) of patients (pts) with cisplatin-eligible MIBC, addition of perioperative D to neoadjuvant chemotherapy (NAC) demonstrated a statistically significant and clinically meaningful improvement in event-free survival (EFS) and overall survival compared with NAC alone, and a 10% higher pathological complete response (pCR) rate, with a manageable safety profile and no impact on the feasibility of surgery. Here, we report a planned exploratory analysis of ctDNA and association with clinical outcomes from NIAGARA. **Methods:** NIAGARA enrolled cisplatin-eligible pts with MIBC (cT2-T4aN0/1M0) planned for radical cystectomy (RC). Pts were randomized 1:1 to receive either neoadjuvant D (1500 mg IV Q3W) and NAC (cisplatin + gemcitabine IV Q3W) for 4 cycles followed by RC, then adjuvant D monotherapy (1500 mg IV Q4W) for 8 cycles (D arm), or NAC followed by RC alone (comparator [C] arm). Dual primary endpoints were pCR and EFS. Disease-free survival (DFS) was a secondary endpoint. Plasma ctDNA was assessed using the Signatera personalized, tumor-informed molecular residual disease (MRD) assay (Natera, Inc, Austin, TX, USA). ctDNA was assessed at baseline (screening or neoadjuvant C1D1, n = 460), after neoadjuvant treatment prior to RC (pre-RC, n = 422), and at C1D1 of the adjuvant phase (post-RC, n = 345). **Results:** Of 1063 randomized pts, 462 comprised the biomarker-evaluable population (237 D arm; 225 C arm). Patient characteristics were similar to the ITT population. Overall, the ctDNA+ rate at baseline was 57% (260/460) and decreased to 22% (94/422) after neoadjuvant treatment at pre-RC. ctDNA clearance rates from baseline to pre-RC were 41% in the D arm and 31% in the C arm. The non-pCR rate was 97% (86/89) among pts with pre-RC ctDNA+ status. Overall ctDNA+ rate post-RC was 9% (31/345). EFS benefit in the D arm vs the C arm was observed in both the baseline ctDNA+ and ctDNA− groups (Table). DFS benefit with perioperative D was observed in post-RC ctDNA+ and ctDNA− groups (Table). **Conclusions:** In this exploratory analysis, ctDNA+ status at pre-RC was associated with non-pCR. Higher ctDNA clearance from baseline to pre-RC in the D arm indicated the additional benefit of D plus NAC vs NAC alone. Perioperative D provided an EFS benefit to both pts with ctDNA+ and ctDNA− status at baseline; a similar trend was observed with DFS based on ctDNA status post-RC. These results further support the perioperative D regimen for pts with MIBC. Funding: AstraZeneca. Clinical trial information: NCT03732677. Research Sponsor: AstraZeneca.

	EFS				DFS			
	Baseline ctDNA+		Baseline ctDNA-		Post-RC ctDNA+		Post-RC ctDNA-	
	D	C	D	C	D	C	D	C
n	137	123	99	101	9	8	129	126
Median (95% CI), months	NR (NR–NR)	32.3 (24.3–NR)	NR (NR–NR)	NR (NR–NR)	9.5 (2.8–NR)	6.2 (2.9–NR)	NR (NR–NR)	NR (NR–NR)
Hazard ratio (95% CI)	0.73 (0.51–1.06)		0.45 (0.25–0.84)		NC*		0.49 (0.28–0.84)	

CI, confidence interval; NC, not calculable; NR, not reached.
*NC due to $<$20 events between arms.

LBA4504 **Oral Abstract Session**

Mitomycin plus BCG as adjuvant intravesical therapy for high-risk, non–muscle-invasive bladder cancer: A randomized phase 3 trial (ANZUP 1301). First Author: Dickon Hayne, UWA Medical School, University of Western Australia, Perth, Western Australia, Australia

The full, final text of this abstract will be available at meetings.asco.org on the day of presentation and in the online supplement to the June 10, 2025, issue of the *Journal of Clinical Oncology*.

4505 **Oral Abstract Session**

Nivolumab plus ipilimumab vs sunitinib for first-line treatment of advanced renal cell carcinoma: Final analysis from the phase 3 CheckMate 214 trial. First Author: Toni K. Choueiri, Lank Center for Genitourinary Oncology, Dana-Farber Cancer Institute, Brigham and Women's Hospital, and Harvard Medical School, Boston, MA

Background: First-line nivolumab plus ipilimumab (NIVO+IPI) provided substantial long-term survival benefits over sunitinib (SUN) in patients (pts) with advanced renal cell carcinoma (aRCC) in the CheckMate 214 trial. We now report final efficacy and safety data in the intent-to-treat (ITT) population and by International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) risk. **Methods:** Pts with clear cell aRCC were randomized 1:1 to NIVO 3 mg/kg + IPI 1 mg/kg Q3W×4 then NIVO (3 mg/kg or 240 mg Q2W or 480 mg Q4W); or SUN 50 mg once daily for 4 weeks on, 2 weeks off. Efficacy endpoints included overall survival (OS), and independent radiology review committee (IRRC)-assessed progression-free survival (PFS) and objective response rate (ORR) in intermediate/poor-risk (I/P; primary), ITT (secondary), and favorable-risk (FAV; exploratory) pts. Response was assessed using RECIST v1.1. **Results:** With 9 years median follow-up, OS was improved with NIVO+IPI vs SUN in ITT (HR 0.71) and I/P (HR 0.69) pts. The probability of OS at 108 months was 31% vs 20% in ITT pts and 30% vs 19% in I/P pts, respectively. In pts with FAV risk, the HR for OS improved from 1.45 at first report (Motzer *NEJM* 2018) to 0.80 at 9 years, showing a delayed benefit with NIVO+IPI vs SUN. OS probabilities at 108 months were 35% vs 22% in FAV pts, respectively (Table). The probability of PFS at 96 months with NIVO+IPI vs SUN was 23% vs 9% in ITT pts, 25% vs 9% in I/P pts, and 13% vs 11% in FAV pts. The probability of remaining in response through 96 months with NIVO+IPI vs SUN was 48% vs 19% in ITT pts, 50% vs 23% in I/P pts, and 36% vs not available (NA) in FAV pts. No new treatment-related deaths occurred in either arm. Additional subgroup analyses will be presented. **Conclusions:** In the longest and final phase 3 follow-up (9 years) of a first-line checkpoint inhibitor combination in aRCC, milestone rates of OS and PFS and durable response remained higher with NIVO+IPI vs SUN. No new safety signals emerged. NIVO+IPI remains a standard first-line option in aRCC. Clinical trial information: NCT02231749. Research Sponsor: Bristol Myers Squibb.

	ITT		I/P		FAV	
Arm; n	**NIVO+IPI; 550**	**SUN; 546**	**NIVO+IPI; 425**	**SUN; 422**	**NIVO+IPI; 125**	**SUN; 124**
mOS (95% CI), mo	53 (46–64)	38 (32–44)	47 (35–56)	26 (22–33)	78 (65–92)	67 (56–80)
108-mo OS probabilities (95% CI), %	31 (27–35)	20 (16–23)	30 (26–35)	19 (15–23)	35 (27–44)	22 (15–30)
mPFS (95% CI), mo	12 (10–16)	12 (10–15)	12 (9–17)	9 (7–11)	13 (10–18)	29 (23–43)
96-mo[a] PFS probabilities (95% CI), %	23 (18–27)	9 (5–15)	25 (20–31)	9 (4–15)	13 (6–22)	11 (3–27)
ORR per IRRC (95% CI); CR, %	39 (35–44); 12	33 (29–37); 3	42 (38–47); 12	27 (23–32); 3	30 (22–38); 13	52 (43–61); 6
mDOR (95% CI), mo	76 (59–NE)	25 (20–33)	83 (54–NE)	20 (16–26)	61 (23–NE)	33 (25–51)
96-mo[a] DOR probabilities (95% CI), %	48 (39–55)	19 (10–31)	50 (41–58)	23 (13–36)	36 (17–56)	NA[b]

[a]96-mo probabilities reported due to small numbers of pts at risk at 108 mo.
[b]No pts remain at risk.
CR, complete response; DOR, duration of response; m, median; NE, not estimable.

4506 **Oral Abstract Session**

Combination casdatifan plus cabozantinib expansion cohort of phase 1 ARC-20 study in previously treated patients with clear cell renal cell carcinoma. First Author: Toni K. Choueiri, Department of Medical Oncology, Dana-Farber Cancer Institute, Boston, MA

Background: Hypoxia-inducible factor 2-alpha (HIF-2α) is highly dysregulated in clear cell renal cell carcinoma (ccRCC), resulting in increased expression of proteins involved with angiogenesis, proliferation, and cancer cell survival. Casdatifan is an orally bioavailable small-molecule HIF-2α inhibitor. We investigated the safety and efficacy of casdatifan in combination with the anti–vascular endothelial growth factor receptor tyrosine kinase inhibitor (VEGFR-TKI) cabozantinib in previously treated patients with ccRCC in an expansion cohort (casdatifan + cabozantinib) of the phase 1, open-label ARC-20 (NCT05536141) trial. **Methods:** Patients enrolled in the casdatifan + cabozantinib expansion cohort were previously treated with immunotherapy (IO) alone or with anti-VEGF therapies. Casdatifan 100 mg and cabozantinib 60 mg were given orally once daily. Endpoints included the incidence of treatment-emergent adverse events (AEs) and objective response rate (ORR) by RECIST v1.1. This study is ongoing; data as of January 3, 2025, are reported. **Results:** Overall, 27 patients with a median (range) follow-up of 2.9 (0.1–6.8) months were enrolled. At data cut off, prior treatment settings included adjuvant only (n = 5/26) and metastatic (1L n = 17/26; 2L n = 4/26). Prior therapies included IO only (n = 15/26) or IO plus VEGFR-TKI (n = 11/26). All grade AEs occurred in 89% of patients with the most common being anemia (n = 16 [59%]) and fatigue (n = 15 [56%]). Most common (> 10%) grade ≥3 AEs were anemia (n = 7 [26%]) and hypoxia (n = 3 [11%]). No cardiac events were reported. AEs leading to casdatifan-only, cabozantinib-only, or both casdatifan + cabozantinib dose reductions occurred in 3 (11%), 7 (26%), and 2 (7%) patients, respectively. Only one (4%) pt discontinued due to an AE, hypoxia related to casdatifan. Responses continue to be observed among the efficacy evaluable population (n = 22; as of January 27, 2025) with ORR of 41% (n = 1 complete response; n = 8 partial response). Activity was seen across all IMDC risk groups. **Conclusions:** In previously treated patients with ccRCC, casdatifan 100 mg in combination with cabozantinib 60 mg had a manageable AE profile with promising clinical activity. These data support continued evaluation of this combination in the phase 3 PEAK-1 clinical trial. Clinical trial information: NCT05536141. Research Sponsor: Arcus Biosciences, Inc.

4507 **Oral Abstract Session**

Hypoxia-inducible factor-2α (HIF-2α) inhibitor belzutifan in von Hippel-Lindau (VHL) disease–associated neoplasms: 5-year follow-up of the phase 2 LITESPARK-004 study. First Author: Vivek Narayan, Hospital of the University of Pennsylvania, Philadelphia, PA

Background: The HIF-2α inhibitor belzutifan is approved for the treatment of patients with VHL disease–associated renal cell carcinoma (RCC), CNS hemangioblastomas (HB), or pancreatic neuroendocrine tumors (pNETs), not requiring immediate surgery based on previously reported results from the ongoing open-label phase 2 LITESPARK-004 study (NCT03401788). Updated results are presented after a minimum of 5 years of follow-up. **Methods:** Adults with germline *VHL* alterations, ≥1 measurable nonmetastatic RCC tumor, no tumor > 3 cm that required immediate surgery, no metastatic disease, no prior anticancer systemic treatment, and an ECOG PS of 0 or 1 received oral belzutifan 120 mg once daily until disease progression, unacceptable toxicity, or participant (pt) withdrawal. The primary end point was objective response rate (ORR) in VHL disease–associated RCC per RECIST v1.1 by independent review committee (IRC). Secondary end points included safety, ORR in non-RCC neoplasms, duration of response (DOR), and progression-free survival (PFS) per RECIST v1.1 by IRC. **Results:** Overall, 61 pts received ≥1 dose of belzutifan. Median study follow-up was 61.8 mo (range, 60.2-70.1). As of the April 1, 2024 data cutoff date, 35 pts (57%) remained on treatment. ORR was 70% for RCC, 50% for CNS HB, and 90% for pNETs. Additional efficacy results are in the Table. Among 14 pts (n = 18 eyes) with retinal HB, 100% (95% CI, 82-100) of eyes showed improvement per ophthalmologic assessment; median DOR for retinal HBs was not reached (NR; range, 8.5-61.0+ mo). At baseline, 59 of 61 pts (97%) had ≥1 prior VHL-related surgery. Within the 5 years before starting belzutifan, 46 of 61 pts (75%) had ≥1 surgery. Since starting belzutifan, 19 of 61 pts (31%) underwent VHL-related surgeries; 4 underwent surgery while on treatment and subsequently discontinued treatment, 8 underwent surgery after discontinuing treatment, and 7 are continuing treatment as of the data cutoff date. Grade 3 treatment-related adverse events (TRAEs) (most commonly anemia [n = 7; 11%]) were reported in 11 pts (18%). No grade 4 or 5 TRAEs occurred. Belzutifan was discontinued in 2 pts (3%) due to TRAEs (grade 1 dizziness and grade 2 intracranial hemorrhage). **Conclusions:** After 5 years of follow-up, belzutifan continues to demonstrate durable antitumor activity and a manageable safety profile, consistent with prior reports. Most pts remain on treatment after this period. Results continue to support the use of belzutifan in pts with VHL disease–related RCC, CNS HB, and pNETs who do not require immediate surgery. Clinical trial information: NCT03401788. Research Sponsor: Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA; The Intramural Research Program of the National Institutes of Health, National Cancer Institute Center for Cancer Research, and a grant (UO1 CA236489) from the National Cancer Institute.

	RCC n = 61	CNS HB n = 50	pNETs n = 20
ORR, % (95% CI)	70 (57-82);7 CRs, 36 PRs	50 (36-64); 6 CRs; 19 PRs	90 (68-99); 13 CRs, 5 PRs
DOR, median (range), mo	NR (5.8+ to 60.8+)	60.3 (0.0+ to 60.3)	NR (11.0+ to 59.6+)
48-mo DOR rate	76%	82%	94%
PFS, median (95% CI), mo	NR (NR-NR)	63.5 (63.5-NR)	NR (NR-NR)
48-mo PFS rate	81%	79%	96%

4508 Oral Abstract Session

ALLO-316 in advanced clear cell renal cell carcinoma (ccRCC): Updated results from the phase 1 TRAVERSE study. First Author: Samer Ali Srour, Department of Stem Cell Transplantation and Cellular Therapy, The University of Texas MD Anderson Cancer Center, Houston, TX

Background: Treatment options are limited for ccRCC after disease progression on immune checkpoint inhibitors (ICIs) and vascular endothelial growth factor (VEGF) inhibitors. CD70 is highly expressed on ccRCC. ALLO-316 is an investigational, healthy donor–derived allogeneic CD70 CAR T-cell product designed to recognize and kill both CD70 positive tumor cells and CD70 positive host T cells that drive allorejection. Initial data from the multicenter, phase 1a/b TRAVERSE study (NCT04696731) showed that ALLO-316 had manageable safety and promising antitumor activity. Updated results are presented. **Methods:** Patients were aged ≥18 years, had advanced ccRCC, ECOG PS of 0 or 1, and disease progression after ICI and VEGF-targeted therapy. After lymphodepletion (LD) with fludarabine and cyclophosphamide ± ALLO-647 (anti-CD52), patients received a single infusion of ALLO-316 following a 3+3 design (40-240 $\times$ 10^6 allogeneic CAR+ T cells). Primary end points were incidence of dose-limiting toxicities and adverse events. Objective response rate (ORR) was a secondary end point. **Results:** Of 44 patients who underwent LD, 39 received ALLO-316, and 38 were evaluable for disease outcome. Median age was 60 years, median of 3 prior therapies (range, 1-8), and 36 (82%) had CD70 positive ccRCC. As of January 2, 2025, median follow-up was 6.8 months (range, 0.8-39.5). Dose-limiting toxicities occurred in 2 patients (autoimmune hepatitis and cardiogenic shock in the setting of multiorgan failure). Treatment-emergent adverse events occurred in 42 patients (96%; grade ≥3, 37 patients [84%]). Grade ≥3 CRS occurred in 1 patient (2%; any grade, 25 patients [57%]), grade ≥3 ICANS in 0 patients (any grade, 4 patients [9%]), and grade ≥3 IEC-HS in 1 patient (2%; any grade, 8 patients [18%]). No GvHD occurred. As previously reported, 3 grade 5 adverse events were related to ALLO-316 (cardiogenic shock, failure to thrive, and sepsis). ORR for all LD regimens was 20% (6/30) overall for patients with CD70 positive tumors (Table). Confirmed ORR was 33% (3/9) for patients with CD70 ≥50% treated with the phase 1b regimen; all confirmed responses were ongoing (2.1, 6.7, and 8.4 months at the data cut-off). **Conclusions:** After a median follow-up of 6.8 months, a single infusion of ALLO-316 had manageable safety and encouraging antitumor activity in heavily pretreated patients. Further evaluation of ALLO-316 in CD70 positive ccRCC is warranted. Clinical trial information: NCT04696731. Research Sponsor: The anti-CD70 AlloCAR T program utilizes Cellectis technology and is licensed exclusively from Cellectis. Allogene holds global development and commercial rights. This research was in part made possible by an award from the CIRM (CLIN2-15343).; California Institute for Regenerative Medicine; Award Number CLIN2-15343.

	All CD70 positive n = 30	CD70 positive receiving phase 1b regimen[a] n = 12	CD70 negative or unknown n = 8
Best overall response (CR or PR at any visit), n/N (%)	8/30 (27)	4/12 (33)	0/8 (0)
CD70 ≥50[b]	8/24 (33)	4/9 (44)	–
CD70 <50[b]	0/6 (0)	0/3 (0)	–
ORR (confirmed CR or PR), n/N (%)	6/30 (20)	3/12 (25)	0/8 (0)
CD70 ≥50[b]	6/24 (25)	3/9 (33)	–
CD70 <50[b]	0/6 (0)	0/3 (0)	–

[a]ALLO-316 80 $\times$ 10^6 CAR+ T cells and LD with fludarabine 30 mg/m^2 + cyclophosphamide 500 mg/m^2.
[b]IHC-based tumor proportion score.

4509 Clinical Science Symposium

Exploratory analysis from NEOAVAX, a neoadjuvant trial of avelumab/axitinib in patients (pts) with localized renal cell carcinoma (RCC) who are at high risk of relapse after nephrectomy. First Author: Axel Bex, Netherlands Cancer Institute, Amsterdam, The Netherlands, Netherlands

Background: NEOAVAX (NCT03341845) is an open label, single arm, phase II trial, investigating 12 weeks of neoadjuvant avelumab/axitinib prior to nephrectomy in 40 pts with high-risk non-metastatic clear-cell (cc) RCC (cT1b-4 cN0-1 M0, Grades 3-4). Dynamic on-treatment increase of CD8+ tumor infiltrating lymphocytes (TILs) in the tumour microenvironment (TME) and the primary endpoint (radiographic partial response rate (RECIST 1.1) in the primary tumour (PT) in ≥25%) were reported previously together with safety and tolerability [1]. **Methods:** Exploratory analysis included pathologic response in the PT according to the International Neoadjuvant Melanoma Consortium (INMC) and multiplex immune histochemistry (IHC) of the TME including CD8+, CD8-granzyme-B+, CD8+CD39+, Foxp3+ cells and MHC-I in paired samples (pre-treatment biopsy and nephrectomy) from 40 pts;. IHC data were compared to RECIST 1.1 and pathologic response in the PT, and recurrence; Visium spatial transcriptomics was performed on 18 PT from pts with diverging clinical outcome. **Results:** The majority of pts (n=25 (62.5%) had no pathologic response (pNR) by INMC criteria. Twelve patients (30%) had a partial (pPR) and 3 (7.5%) a major pathological response (MPR). There was no association between pathological and radiographic response of the PT. Recurrence occurred in 1 of 3 pts (33%) with MPR at 36 mo, in 7 of 12 (58%) with a pPR at a median of 12 mo and in 14 of 25 (56%) with pNR at a median of 3 mo. Of 25 pts with pNR 7 died of disease (DoD; 28%). On IHC, intratumoural CD8+CD39+ on post-treatment PT samples was significantly associated with recurrence ($p<0.0001$). MPR associated with spatial co-localisation of tumour cells with tissue-resident macrophages, CD8+ cytotoxic T-cells, memory T-cells and B-cells. Gene Set Enrichment Analysis (GSEA) results for Reactome pathways in each Visium tumor spot cluster demonstrated intratumoural heterogeneity in post-treatment PT in select patients. **Conclusions:** Pathologic response and IHC post-treatment influx of CD8+CD39+ TILs associates with prolonged disease-free survival following neoadjuvant avelumab/axitinib. Particularly, pts with MPR had distinct spatial co-localisation gene signatures of tumour and immune cells in the TME. Despite 3 months of treatment, 62.5% of pts had no pathologic responses (defined by INMC as >50% vital tumour remaining in the tumour bed). [1] Bex A et al. Efficacy, safety, and biomarker analysis of neoadjuvant avelumab/axitinib in patients (pts) with localized renal cell carcinoma (RCC) who are at high risk of relapse after nephrectomy (NeoAvAx), in *2022 ASCO Genitourinary Cancers Symposium*. Journal of Clinical Oncology, Volume 40, Number 6_suppl, https://doi.org/10.1200/JCO.2022.40.6_suppl.2. Clinical trial information: NCT03341845. Research Sponsor: Pfizer, CellCarta, The Netherlands Cancer Institute and Queen Mary University London.

4510 Clinical Science Symposium

Genomic characterization of baseline and post-progression tumors in IMmotion010, a randomized, phase 3 study of adjuvant (adj) atezolizumab (atezo) vs placebo (pbo) in patients (pts) with high-risk localized renal cell carcinoma (RCC). First Author: Sumanta Kumar Pal, Department of Medical Oncology & Therapeutics Research, City of Hope Comprehensive Cancer Center, Duarte, CA

Background: Although adj atezo did not prolong disease-free survival (DFS) in the IMmotion010 trial, accompanying studies identified post-nephrectomy serum KIM-1 levels to be potentially predictive of benefit with atezo. We investigated whether tissue genomics could complement these findings. **Methods:** Tumors were obtained from patients pre-treatment and (if additional consent obtained) at disease recurrence. Whole transcriptome profiles were generated using TruSeq RNA Access Technology (Illumina). Previously, non-negative matrix factorization (NMF) was performed in a separate phase 3 study in advanced RCC (IMmotion151), establishing 7 molecular subgroups (NMF 1-7) (Motzer *et al* Cancer Cell 2020). For each IMmotion010 tumor, we derived signature scores dichotomized at the median as well as NMF1-7 subtype using random forest. Clinical outcome was assessed within these groups alone and with the addition of baseline serum KIM-1 levels, dichotomized into KIM-1 high (KIM-1^H) and KIM-1 low (KIM-1^L) using the previously established cutoff of 86 pg/mL. Where possible, we sought to characterize the evolution of molecular profiles at disease recurrence. **Results:** Baseline tissue was obtained from 754 pts, reflecting 97% of the intention-to-treat population. Tumors from KIM-1^H patients were enriched in myeloid, granulocyte and proliferation gene signatures at baseline. Among 722 pts for whom both serum KIM-1 and NMF subtype could be characterized, pts in cluster 6 (stromal/proliferative) appeared to derive benefit from atezo (n=50) (Table). Across all patients, no difference in outcome was observed among baseline Teff^H and Teff^L subsets. Within the KIM-1^H population, Teff^H tumors were associated with longer DFS with atezo vs pbo. Paired baseline/recurrence tissue was obtained from 80 pts (atezo: 49; pbo: 31). At recurrence, tumors exhibited increased stromal and proliferation gene signatures, regardless of treatment, reflected in an increased proportion in NMF6 (baseline: 6%; progression: 22%). Exploratory analyses also revealed a decreased MHC-I signature after treatment with atezo. **Conclusions:** This is the first report of tissue genomic profiling in a phase 3 adjuvant immune checkpoint inhibitor study in RCC. While certain molecularly defined subsets may carry predictive value, serum KIM-1 remains the most robust predictor of outcome with atezo. Analyses of progression biopsies highlight an evolution in genomic profile and offer insights into mechanisms of relapse. Clinical trial information: NCT03024996. Research Sponsor: F. Hoffmann-La Roche Ltd.

Subgroup	n	DFS HR
Serum KIM-1		
KIM-1^H	290	0.7*
KIM-1^L	443	1.13
T-effector signature		
Teff^H	367	0.87
Teff^L	366	0.97
NMF subtype		
NMF1	82	1.14
NMF2	271	1.04
NMF3	131	0.96
NMF4	62	0.88
NMF5	60	0.77
NMF6	50	0.25*
NMF7	66	1.62
T-effector signature in KIM-1^H pts		
KIM-1^H Teff^H	147	0.59*
KIM-1^H Teff^L	143	0.93

*$P<0.05$.

4511 Clinical Science Symposium

An integrative analysis of circulating and tumor microenvironment (TME) determinants of patient response in the Checkmate 9ER (CM 9ER) trial of nivolumab and cabozantinib (NIVO+CABO) in advanced renal cell carcinoma (aRCC). First Author: David A. Braun, Center of Molecular and Cellular Oncology, Yale Cancer Center, Yale School of Medicine, New Haven, CT

Background: The CM 9ER trial demonstrated increased objective response rate (ORR), progression-free and overall survival in patients with aRCC treated with NIVO+CABO compared to sunitinib (SUN). For vascular modulating therapies (e.g. CABO and SUN) and immunotherapies (like NIVO), the state of the TME and activity of stromal cells can modulate tumor response to therapy. **Methods:** We investigated how the TME and circulating factors were associated with response to NIVO+CABO using pre-treatment tumor PD-L1 staining, human interpretable features (HIF) derived from H&E tissue sections, circulating immune cell populations quantified by flow cytometry, and circulating extracellular matrix (ECM) markers quantified by competitive ELISAs from 150 patients (23% of ITT) enrolled in CM 9ER. We employed principal component analysis, varimax rotation, and Feature Set Enrichment Analysis (FSEA) to identify a subset of biological measurements capturing 85% of the data variability. We constructed a logistic regression model to associate the most variable features with patient response (ORR per BICR) to NIVO+CABO or SUN therapy. **Results:** An unbiased clustering and feature extraction approach was used to identify measurements contributing to multi-modal variability in the TME across 150 patients (~4000 biological measurements reduced to 16 highly informative measurements): PD-L1 staining, 4 ECM markers, 4 PBMC markers, and 7 H&E HIF features. A final binary logistic regression model was built employing lasso regularization to associate these 16 features to short-term response to NIVO+CABO or SUN while minimizing spurious associations. Based on these regression models, the ECM marker VICM, a citrullinated fragment of vimentin released by matrix metalloproteases, and which measures macrophage activity and immune status, was prognostic across both therapies. Logistic regression models that integrated highly informatic features had AUCs of 0.76 for NIVO+CABO model and 0.72 for the SUN model. Within the NIVO+CABO arm, this integrative model uncovered high VICM (and therefore anti-tumor macrophage polarization), high PD-L1 staining, high plasma cell numbers and high cancer cell numbers at the epithelial stromal interface, low levels of circulating fragment of C-terminal type VIa3 collagen (Pro-C6), and low percentages of circulating regulatory (Foxp3+ CD4+) T cells as determinants of therapeutic response. **Conclusions:** Taken together, these findings indicate that the state of the tumor microenvironment and circulating factors together have an effect on patient responsiveness to NIVO+CABO in aRCC and provides a framework for integrative analysis for biomarker discovery. Research Sponsor: None.

4512 Clinical Science Symposium

Gut-associated checkpoint as a prognostic biomarker in metastatic renal cell carcinoma (mRCC): Results from a randomized first-line clinical trial. First Author: Renee Maria Saliby, Yale Cancer Center, New Haven, CT

Background: The gut microbiota modulates anti-cancer immune response and therefore benefit to immune checkpoint inhibitors (ICIs). Gut dysbiosis impacts the MadCAM-1/α4β7 axis leading to recirculation of immunosuppressive α4β7+Tr17 cells into tumors. From mechanistic insight to biomarker development, soluble MAdCMA-1 (sMAdCAM-1) is a circulating surrogate marker of gut dysbiosis. We aim to develop sMAdCAM-1 as a prognostic biomarker to ICI-based therapy in patients (pts) with mRCC. **Methods:** Using a Luminex assay, sMAdCAM-1 levels were measured in available plasma samples at baseline from 612 pts (69% of the intent-to-treat population) from the phase III JAVELIN Renal 101 trial (NCT02684006), which compared avelumab + axitinib with sunitinib in previously untreated mRCC pts. sMAdCAM-1 was examined on the original, per 10^4-scaled, and log-transformed scales. Linear assumption was visually checked by deviance residual and restricted cubic splines (RCS) plots. Optimal cut-off value was established based on the maximum log-rank statistic. Cox regression models were used to assess associations with progression-free survival (PFS) and overall survival (OS). The discrimination of the fitted model was assessed by time-dependent AUC index. **Results:** Higher sMAdCAM-1 levels were associated with improved PFS (median: 13.9 [11.3 - 6.6] vs 8.4 [6.0 - 9.9] months) and OS rate (at 18 months: 84.2% [80.2 - 87.4] vs 68.1% [59.2 - 75.5]). These associations remained after adjusting for IMDC risk groups (Table 1). The optimal cutoff was 180 ng/ml (25% percentile) based on the OS outcome in the whole population. Residual and RCS plots further confirmed a non-linear relationship of sMAdCAM-1 levels with OS and PFS. Median follow up was 18.9 months. The prognostic model incorporating IMDC + sMAdCAM-1 demonstrated a significant improvement in the AUC at 18 months compared to IMDC alone (0.72 vs 0.68; p=0.01). These associations were independent of study arm. **Conclusions:** Higher sMAdCAM-1 is associated with improved outcomes to 1st line regimens in mRCC. sMAdCAM-1 may have an added prognostic value to IMDC. As a diagnostic test of gut dysbiosis, it might guide the selection of pts eligible to microbiota-modulating strategies. The validation in two independent datasets and multi-omics correlation (i.e. fecal metagenomics) are ongoing under an international collaboration network. Research Sponsor: None.

Association of MAdCam-1 with clinical outcomes using Cox regression model.

Parameters	PFS HR (95% CI)		OS HR (95% CI)	
Favorable	Ref		Ref	
Intermediate	1.77 (1.31- 2.39)	<0.001	3.01 (1.60 - 5.66)	<0.001
Poor	2.88 (1.99 - 4.17)	<0.001	7.91 (4.02 - 15.56)	<0.001
sMAdCAM-1(high vs low)	0.75 (0.59 - 0.96)	0.021	0.59 (0.41 - 0.85)	0.004

LBA4513 Rapid Oral Abstract Session

ENLIGHTED phase 3 study: Interim results of efficacy and safety of padeliporfin vascular targeted photodynamic therapy (VTP) in the treatment of low-grade upper tract urothelial cancer (LG UTUC). First Author: Vitaly Margulis, UT Southwestern Medical Center, Dallas, TX

The full, final text of this abstract will be available at meetings.asco.org on the day of presentation and in the online supplement to the June 10, 2025, issue of the *Journal of Clinical Oncology*.

4514 Rapid Oral Abstract Session

Five-year follow-up results from the phase 3 KEYNOTE-564 study of adjuvant pembrolizumab (pembro) for the treatment of clear cell renal cell carcinoma (ccRCC). First Author: Naomi Balzer Haas, Abramson Cancer Center, University of Pennsylvania, Philadelphia, PA

Background: KEYNOTE-564 (NCT03142334) established pembro monotherapy as the first adjuvant regimen to significantly improve both disease-free survival (DFS) and overall survival (OS) vs placebo (pbo) after surgery for participants (pts) with ccRCC at increased risk of recurrence. We present results from the fourth prespecified interim analysis with a minimum follow-up of 5 yrs. **Methods:** KEYNOTE-564 is a randomized, double-blind, pbo-controlled, phase 3 study, which enrolled adults with ccRCC with intermediate-high (pT2 Gr 4 or sarcomatoid, or pT3 any Gr, N0 M0) or high (pT4 any Gr, N0 M0, or any pT and Gr, N+ M0) risk of recurrence or M1 with no evidence of disease (NED) who had nephrectomy and/or metastasectomy ≤12 wks prior to 1:1 randomization to pembro 200 mg or pbo IV Q3W. Treatment continued for ~1 yr (17 cycles) or until recurrence, intolerable AEs, or physician decision to discontinue treatment. The primary endpoint was DFS by investigator; the key secondary endpoint was OS. The study met its DFS and OS objectives at earlier analyses; thus, no subsequent formal statistical testing occurred. AEs were collected for 30-90 days after treatment cessation depending on severity, with serious treatment-related AEs collected regardless of timing. **Results:** A total of 994 pts were randomized to pembro (n = 496) or pbo (n = 498). The median follow-up time to data cutoff date of 25 Sept 2024 was 69.5 mo (range, 60.2−86.9). All pts completed or discontinued study treatment ≥3 years earlier. 188 DFS events in the pembro group and 241 in the pbo group had occurred. Median DFS was not reached (NR) vs 68.3 mo, respectively (HR 0.71, 95% CI 0.59−0.86); estimated DFS rate at 5 yrs was 60.9% vs 52.2%. 68 OS events in the pembro group and 99 in the pbo group had occurred. Median OS was NR in both arms (HR 0.66, 95% CI 0.48−0.90); estimated OS rate at 5 yrs was 87.7% vs 82.3%, respectively. DFS and OS outcomes were consistent across key subgroups, including by prespecified risk and sarcomatoid features (Table). No new serious treatment-related AEs have been reported for ≥3 years. **Conclusions:** With ≥5 yrs of follow-up, the benefits observed with adjuvant pembro vs pbo are consistent with prior analyses, including in all subgroups. No new serious treatment-related safety signals occurred. Adjuvant pembro remains a standard-of-care option for patients with ccRCC at increased risk of recurrence. Clinical trial information: NCT03142334. Research Sponsor: This study was supported by Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Rahway, NJ, USA.

		Prespecified risk subgroups			Sarcomatoid features	
	All pts	Intermediate-high	High	M1 NED	Present	Absent
N	994	855	77	57	111	829
DFS events	429	342	49	37	59	339
DFS HR	0.71	0.75	0.61	0.48	0.56	0.75
(95% CI)	(0.59−0.86)	(0.61−0.93)	(0.35−1.08)	(0.25−0.92)	(0.33−0.96)	(0.60−0.92)
OS events	167	131	22	13	23	130
OS HR	0.66	0.65	0.86	0.36	0.67	0.64
(95% CI)	(0.48−0.90)	(0.46−0.92)	(0.37−1.98)	(0.11−1.18)	(0.29−1.56)	(0.45−0.91)

4515 Rapid Oral Abstract Session

Zanzalintinib (zanza) + nivolumab (nivo) ± relatlimab (rela) in patients (pts) with previously untreated clear cell renal cell carcinoma (ccRCC): Results from an expansion cohort of the phase 1b STELLAR-002 study. First Author: Jad Chahoud, Moffitt Cancer Center, Tampa Bay, FL

Background: VEGFR-targeted tyrosine kinase inhibitors (TKIs) in combination with immune checkpoint inhibitors (ICIs) are standard of care for previously untreated metastatic ccRCC. Zanza (XL092) is a novel, oral, multi-targeted TKI of VEGFR, MET, and TAM kinases (TYRO3, AXL, MER), with a short half-life that may have an improved therapeutic index. In the phase 1 STELLAR-001 study, the tolerability profile of single-agent zanza was manageable and antitumor activity was observed in patients with previously treated advanced ccRCC (Pal et al, IKCS NA 2023). STELLAR-002 (NCT05176483) is a phase 1b, open-label study evaluating the tolerability and activity of zanza alone and in combination with ICIs in pts with advanced solid tumors. Here, data from the expansion cohort of pts with previously untreated ccRCC receiving zanza + nivo ± rela are presented. **Methods:** Adult patients with unresectable advanced or metastatic (adv/met) ccRCC of any IMDC risk, and no prior systemic anticancer therapy for adv/met ccRCC were enrolled into one of two non-randomized arms. Patients received zanza 100 mg orally with either nivo 480 mg IV every 4 weeks (q4w) or nivo/rela 480/480 mg IV q4w (fixed-dose combination). Primary endpoints were investigator-assessed ORR per RECIST 1.1 and safety. **Results:** In the zanza + nivo arm (n = 40), 75% had intermediate or poor IMDC risk disease. After median follow-up of 16.1 months, the ORR was 63% (4 complete responses [CRs], 21 partial responses [PRs]), and disease control rate (DCR: CR+PR+SD) was 90%. The 6- and 12-month PFS rates were 83.2% and 64.2%, respectively. The most common any grade (G) treatment-emergent adverse events (TEAEs) were diarrhea (78%), hypertension (58%), and nausea (58%). The most common G3/4 AEs related to zanza were hypertension (30%) and diarrhea (15%). Treatment-related palmar-plantar erythrodysesthesia (PPE) was reported in 28% (8% G3, 0% G4). Two (5%) pts discontinued both study treatments due to treatment-related AEs (TRAEs). Median average daily zanza dose was 49.5 mg (range: 26-100). In the zanza + nivo/rela arm (n = 40), 70% had intermediate or poor IMDC risk disease. After a median follow-up of 11.9 months, the ORR was 33% (1 CR, 12 PRs) and DCR was 90%. The 6- and 12-month PFS rates were 80.2% and 58.8%, respectively. The most common any G TEAEs were diarrhea (60%) and nausea (50%). The most common G3/4 AE related to zanza was hypertension (13%). Treatment-related PPE occurred in 5% (0% G3/4). Seven (18%) pts discontinued all study treatment due to TRAEs. Median average daily zanza dose was 54.9 mg (range: 31-100). No G5 TRAEs occurred in either arm. **Conclusions:** First-line zanza had acceptable tolerability in combination with nivo or nivo/rela with a low rate of PPE; zanza+nivo showed promising preliminary activity in pts with adv/met ccRCC. Clinical trial information: NCT05176483. Research Sponsor: Exelixis, Inc.

4516 **Rapid Oral Abstract Session**

Ipilimumab and nivolumab in patients with metastatic clear cell renal cell carcinoma (mccRCC) treated on the phase 3 PDIGREE (Alliance A031704) trial: Results from Step 1 analysis. First Author: Tian Zhang, Department of Internal Medicine, Division of Hematology and Oncology, UT Southwestern, Dallas, TX

Background: Ipilimumab/nivolumab (ipi/nivo) is a standard of care first-line treatment (tx) for patients (pts) with mccRCC; however, ideal timing of subsequent immunotherapy txs are not well defined. We performed an analysis of patients initially treated with ipi/nivo and subsequent cohort assignments on PDIGREE (A031704). **Methods:** The PDIGREE trial treated pts with IMDC intermediate/poor risk mccRCC with first-line ipi/nivo (Step 1) at NCTN sites (categorized as academic (A), academic regional (R), and community (C)). Subsequent management was based on iRECIST responses at 12 weeks: pts with complete response (CR) received 1-year nivo maintenance; pts with progressive disease (PD) received cabozantinib (cabo) monotherapy, pts with non-CR/non-PD were randomized to nivo with or without cabo (for primary endpoint of overall survival [OS], target sample size was 1175). Enrollment was held when the randomized sample target was reached. Pts with unresolved toxicity at week 22 were managed off protocol. Step 1 pt demographics, assignments into Step 2, and adverse event (AE) data are presented. Descriptive statistics were used, and cohorts were compared using a chi-square test. These data were released with DSMB approval and do not inform the primary OS endpoint (1EP). **Results:** From May 2019 to May 2024, 1111 pts were enrolled and treated with ipi/nivo. Pt characteristics included median age 64.0 years (range 29.0-86.0); 819 (73.7%) males; White (85.1%), Hispanic (10.4%), Black (4.2%), and American Indian/Native Hawaiian (1.3%); 849 (76.8%) intermediate risk/257 (23.2%) poor risk; 458 (41.2%) at Academic, 113 (10.2%) at Regional, and 540 (48.6%) at Community centers; and 603 (54.3%) with *de novo* metastases. 364 pts (33%) stopped tx in Step 1: 160 (44%) for AEs, 46 (13%) for PD/clinical PD/suspected PD, 42 (12%) withdrawals, 39 (11%) alternative txs, 37 (10%) deaths on the study, 12 (3%) other complicating disease, 8 (2%) MD decision and 19 (5%) other reasons. Of the 37 deaths, 15 (1.4%) grade 5 SAEs were reported, 6 of which were due to PD. Of 747 (67%) pts registered to Step 2 at 3 months, 9 (1.2%) achieved CR, and 141 (18.9%) pts were assigned to the PD cohort. 597 pts (80%) were randomized for the 1EP, notable with fewer pts with poor risk [(21 vs 27%, p = 0.01] and bone metastases [24.5% vs 34.2%, p = 0.0007] compared to Step 1 pts who discontinued tx. Gr 3/4 tx-related AEs in 314/1093 (29%) evaluable pts included diarrhea/colitis (8%), transaminase elevation (3%), rash (2%), adrenal insufficiency (2%), fatigue (2%), and hypophysitis (1%). **Conclusions:** The PDIGREE trial enrolled a representative US-based population with mccRCC. Step 1 pt characteristics and associated outcomes with induction ipi/nivo reveal new insights into the tolerability and tx response of 1L ipi/nivo. Clinical trial information: NCT03793166. Research Sponsor: Alliance Group: U10CA180821, U10CA180882; SWOG: U10CA180888; https://pubs.alliancefound.org/acknowledgments.

4517 **Rapid Oral Abstract Session**

Sasanlimab in combination with bacillus Calmette-Guérin (BCG) in BCG-naive, high-risk non–muscle-invasive bladder cancer (NMIBC): Event-free survival (EFS) subgroup analyses based on disease stage from the CREST study. First Author: Thomas Powles, Barts Cancer Centre, Cancer Research UK Experimental Cancer Medicine Centre, Queen Mary University of London, London, United Kingdom

Background: Sasanlimab in combination with BCG (induction [IND] and maintenance [MNT]) significantly improved investigator (INV)-assessed EFS vs BCG (IND and MNT) and had a manageable safety profile in patients (pts) with BCG-naive, high-risk NMIBC, according to the primary analysis results from the phase 3 CREST study. Here, we report exploratory EFS subgroup analyses not previously presented based on disease stage at randomization from Arms A and C. **Methods:** Eligible pts were randomized 1:1:1 to receive sasanlimab in combination with BCG (IND and MNT; Arm A), sasanlimab in combination with BCG (IND; Arm B), or BCG (IND and MNT; Arm C). To assess the impact on efficacy of carcinoma in situ (CIS) and T1 tumors at baseline, post hoc INV-assessed EFS analyses were conducted for the comparison of Arm A vs Arm C. EFS was defined as time from randomization to recurrence of high-grade disease, progression of disease, persistence of CIS (for patients with CIS at randomization), or death due to any cause, whichever occurred first. **Results:** At the data cutoff date (Dec 02, 2024), the median duration of follow-up for EFS was 36.4 and 36.7 months for Arm A and Arm C, respectively. A total of 176 pts with CIS (with or without papillary tumors) were in Arms A and C, 102 of whom had CIS without papillary tumors. A total of 398 pts with T1 tumor were in Arms A and C, 342 of whom had T1 tumor without CIS (Table). Three-year landmark EFS subgroup analyses not previously presented are reported in the table. For patients with CIS, with or without concomitant papillary tumors, the 3-year EFS rate was 83.0% in Arm A and 71.8% in Arm C. For patients with T1 tumors, with or without CIS, the 3-year EFS rate was 81.3% in Arm A and 72.2% in Arm C. **Conclusions:** Sasanlimab in combination with BCG (IND and MNT) improved EFS outcomes in the overall population and in the subgroups of pts with BCG-naive, high-risk NMIBC who had CIS or T1 tumors at randomization. This post hoc analysis further supports the potential of sasanlimab in combination with BCG as a practice-changing treatment in pts with aggressive disease. Clinical trial information: NCT04165317. Research Sponsor: Pfizer Inc.

	Arm A(N=352)		Arm C(N=351)		HR (95% CI) Arm A vs Arm C
	n (%)	36-mo EFS rate, % (95% CI)	n (%)	36-mo EFS rate, % (95% CI)	
All pts		82.1 (77.4-85.9)		74.8 (69.7, 79.2)	0.68 (0.489-0.941)[a]
Tumor type at randomization					
CIS with and without papillary tumors	88(25.0)	83.0 (72.9-89.6)	88(25.1)	71.8 (60.4-80.5)	0.53(0.285-0.982)
CIS without papillary tumors	52(14.8)	81.0 (66.6-89.7)	50(14.2)	75.4 (59.9-85.6)	0.52 (0.233-1.165)
T1 with and without CIS	204(58.0)	81.3 (74.7-86.4)	194(55.3)	72.2 (65.0-78.2)	0.63 (0.406-0.963)
T1 without CIS	178 (50.6)	79.6 (72.1-85.2)	164(46.7)	72.5 (64.6-78.9)	0.70 (0.446-1.109)

[a]Stratified HR; all other HR unstratified.

4518 **Rapid Oral Abstract Session**

First results of SURE-02: A phase 2 study of neoadjuvant sacituzumab govitecan (SG) plus pembrolizumab (Pembro), followed by response-adapted bladder sparing and adjuvant pembro, in patients with muscle-invasive bladder cancer (MIBC). First Author: Andrea Necchi, IRCCS San Raffaele Hospital, Vita-Salute San Raffaele University, Milan, Italy

Background: Standard of care for MIBC is radical cystectomy (RC) with neoadjuvant chemotherapy (CT), but ~50% of patients (pts) are ineligible for/refuse CT and survival for RC alone is dismal. Neoadjuvant Pembro and SG monotherapies showed activity in MIBC within PURE-01 and SURE-01 studies. SURE-02 (NCT05535218) is a phase 2 study of neoadjuvant SG+Pembro and adjuvant Pembro, including a bladder-sparing approach depending on clinical response. We report results of a prespecified interim analysis. **Methods:** Pts age ≥18 y, ECOG PS 0-1, with histologically confirmed cT2-T4N0M0 MIBC, ineligible/refusing CT, and scheduled for RC received 4 cycles of Pembro 200 mg on D1 and SG 7.5 mg/Kg on D1 and D8, Q3W, followed by postsurgical Pembro x 13 cycles, Q3W. A reTURBT is allowed instead of RC, followed by Pembro x 13 cycles, for pts achieving a clinical complete response (cCR), stringently defined as a negative magnetic resonance imaging (MRI) and no residual viable tumor at reTURBT (ypT0). Primary outcome measure is cCR rate: H0≤30%, H1≥45%. Other outcomes: ypT≤1N0-x rate including pts undergoing RC, safety (CTCAE v.5.0), survival. The total sample size is 48 pts in a 2-stage design, with 23 pts enrolled at first stage (≥7 cCR needed). Decipher Bladder (Veracyte, San Diego, CA) was used for transcriptome-wide analyses of primary TURBT tissue. **Results:** From 10/23 to 01/25, 40 pts were treated and 31 were efficacy evaluable. 20 (64.5%) had a cT2 stage, 12 (38.7%) had a centrally confirmed variant histology. The cCR-rate was 38.7% (N = 12; 95%CI: 21.8-57.8); all these pts underwent a reTURBT; ypT≤1N0-x rate was 51.6% (N = 16). Grade ≥3 treatment-related adverse-events occurred in 4 pts (12.9%), 2 dose omissions of SG and one dose delay (1W) were recorded. No SG dose-reduction was needed. cCR varied by molecular subtype. Transcriptome results were available for 23 pts: complete pathologic (ypT0) responses varied by Genomic Subtyping Classifier (GSC) groups with luminal tumors showing higher ypT0 rates vs non-luminal (73 vs 25%, p = 0.04). Similarly, based on Lund subtypes, genomically unstable (GU) tumors had ypT0 response in 67%, vs 57% for urothelial-like, 20% for basal/squamous and 0% for neuroendocrine-like. Higher stromal signature (> median) was associated with non-ypT0 response (p = 0.004), while neither Trop2 (p = 0.15) nor *TOP1* (p = 0.79) gene expression were associated with ypT0 response. **Conclusions:** Perioperative SG+Pembro revealed a compelling cCR rate, with a manageable safety profile, allowing a bladder preservation in ~40% of pts. Pre-treatment molecular biomarker analyses suggest a unique tumor profile associated with cCR. Overall, SURE-02 interim results support the completion of study accrual and further investigation of SG+Pembro in pts with MIBC. Clinical trial information: NCT05535218. Research Sponsor: Gilead; Merck; Associazione Italiana per la Ricerca sul Cancro (AIRC); IG 27746.

4519 **Rapid Oral Abstract Session**

9MW2821, a novel Nectin-4 antibody-drug conjugate (ADC), combined with toripalimab in treatment-naïve patients with locally advanced or metastatic urothelial carcinoma (la/mUC): Results from a phase 1b/2 study. First Author: Shusuan Jiang, Hunan Cancer Hospital, Changsha, China

Background: Nectin-4 is an adhesion molecule that is highly expressed in variety of solid tumors. Previous study of 9MW2821 has shown promising efficacy and tolerable toxicity in different advanced cancers, especially in urothelial cancer, cervical cancer, esophageal cancer and breast cancer. Here we report preliminary results of 9MW2821 combined with Toripalimab in treatment-naïve patients with la/mUC. **Methods:** This is an open-label, multicenter, phase 1b/2 study to evaluate the safety and efficacy of 9MW2821 combined with Toripalimab in la/mUC. Patients received 9MW2821 on D1/D8 and Toripalimab on D1, 21 days per cycle. Primary objective was safety, and secondary objectives were efficacy, pharmacokinetics and immunogenicity. **Results:** 40 treatment-naïve patients with la/mUC were enrolled and received the combination therapy of 9MW2821(1.25mg/kg) and Toripalimab(240mg). Median age was 66.5 years [36-78], and 73% patients were ECOG 1. 55% primary tumor sites were upper tract urothelial carcinoma. As of Dec 19, 2024, ORR was 87.5% [35/40, 95%CI 73.2-95.8], including 7.5% CR rate (comfirmed ORR was 80%). DCR was 92.5% [37/40, 95%CI 79.6-98.4]. Median PFS and DoR were not reached, 6-month PFS rate and 3-month DoR rate were 79.1% and 100%. Furthermore, ORR of subgroups in liver metastasis, bladder cancer and tumor with negative expression of Nectin-4 were 88.2%, 94.4%, 100%, respectively. These showed that different subgroups of treatment-naïve patients could benefit from the combination therapy of 9MW2821 and Toripalimab. The most common treatment-related AEs(TRAEs) were grade 1 or 2, 23.8% patients experienced TRAEs of grade 3 or above, including neutrophil count decreased (7.1%), rash (4.8%), ALT increased (4.8%), etc. No TRAEs led to death occurred. No new safety signals of 9MW2821 or Toripalimab were observed in this study. **Conclusions:** 9MW2821 combined with Toripalimab in treatment-naïve patients with la/mUC demonstrated remarkable efficacy and well-tolerated safety profile. A pivotal phase 3 study is ongoing currently. Clinical trial information: NCT06079112. Research Sponsor: Mabwell (Shanghai) Bioscience Co., Ltd.

4520 Rapid Oral Abstract Session

CLONEVO: Preoperative abemaciclib for cisplatin-ineligible muscle-invasive bladder cancer (MIBC) with molecular response assessment. First Author: Bishoy Morris Faltas, Weill Cornell Medicine, New York, NY

Background: Up to 40% of MIBC patients are ineligible to receive standard neoadjuvant cisplatin-based chemotherapy creating a significant unmet need. Based on our prior findings of frequent cell cycle alterations, we conducted the first window-of-opportunity, investigator-initiated trial of the CDK4/6 inhibitor abemaciclib (abema) followed by radical cystectomy (RC) in MIBC (NCT03837821). **Methods:** Eligibility was MIBC appropriate for RC and cisplatin-ineligibility or refusal. Planned treatment was abema (200mg BID PO) for 4-8 weeks prior to RC. We planned to enroll 20 patients (accounting for 20% attrition). 16 evaluable patients provided 80% power to detect 0.75 effect size (α = 0.05, r = 0.5 between pairs). Whole-exome (WES) and RNA sequencing of pre- and post-abema tissues and serial evaluation of ctDNA WES were performed on Caris Life Sciences' platform. **Results:** 20 patients received abema for a median of 36 days. Median age was 73, 16/20 were males, and 5/20 had cT4. 3 didn't undergo RC, and 1 withdrew consent. Abema resulted in pathologic complete response in 18.8% (3/16) and downstaging in 31.3% (5/16). No unexpected safety signals were detected. Grade 3 abema-related adverse events included anemia (4/20), abdominal pain (1/20) and diarrhea (1/20). Imaging Mass Cytometry of pre- and post-abema tissues showed a significant reduction in RB1 phosphorylation after abema confirming on-target activity. Variant allele frequency of somatic mutations significantly decreased after abema by 20.5% (p = 0.04), confirming its role in decreasing tumor burden. Serial ctDNA showed a significant reduction in tumor fraction (TF) following abema by 28.6%. Post-TURBT pre-abema TF increased but rapidly decreased within 2 weeks of abema (19.36%), confirming TF reduction was driven by abema not TURBT. Patients with CCND1 amplification had the most significant decrease in TF (63.8%) highlighting CCND1 as a potential response biomarker. Abema significantly downregulated MKI67, CCNA2, and PCNA proliferation markers with log-fold changes of -1.2, -0.7, and -0.6. Gene set enrichment analysis showed significant downregulation of E2F targets and G1/S transition pathways. Patients who achieved pathologic downstaging had significant decrease in E2F pathway activity (-1.6 vs. -0.4, p = 0.01) confirming that abema suppressed E2F-dependent cell proliferation. Interestingly, abema significantly inhibited homologous recombination repair of double-strand DNA break (DSBs) (FDR = 0.001), particularly TOPBP1 and RAD51. **Conclusions:** This first trial of short-term preoperative abema in MIBC demonstrated promising efficacy and tolerability while modulating cell cycle-dependent pathways. Our findings support future trials investigating sequential abema with antibody-drug conjugates such as enfortumab vedotin, where abema's effects on DSBs repair augment treatment response. Clinical trial information: NCT03837821. Research Sponsor: Eli Lilly.

4521 Rapid Oral Abstract Session

AREN1721, a randomized phase 2 trial of axitinib+nivolumab combination therapy vs. single agent nivolumab for the treatment of TFE/translocation renal cell carcinoma (tRCC) across all age groups, an NCI National Clinical Trials Network (NCTN) phase 2 study. First Author: Nicholas Cost, Denver Childrens, Denver, CO

Background: tRCC accounts for approximately 50% of pediatric RCC and 1-5% of RCC cases overall. tRCC, driven by *TFE3* or *TFEb* fusions or amplifications (*TFEb*), are often aggressive with no existing standard for systemic therapy. **Methods:** AREN1721 was a prospective randomized COG-led NCTN phase 2 trial of nivolumab/axitinib combination therapy vs. axitinib alone (closed early for feasibility) vs. nivolumab alone in children and adults with advanced unresectable or metastatic tRCC. Prior exposure to anti-PD1/PDL1 therapies or axitinib was prohibited. The primary endpoint was progression-free survival (PFS), defined as the time from randomization to the earliest of disease progression based on immune-modified RECIST criteria or death. The final protocol version targeted enrollment of 28 eligible patients to detect a hazard ratio (HR) of 0.40 for the comparison of nivolumab/axitinib vs. nivolumab alone using a one-sided log-rank test with alpha = 0.15. **Results:** Despite aggressive approaches for trial recruitment, AREN1721 was closed after enrolling 15 patients (13 eligible) from 2019 to 2023 secondary to poor accrual. Median age 16 years (range 7-42) with 9/13 age $<$ 18 years; 9/13 were male. Six patients were randomized to nivolumab+axitinib, 2 to axitinib alone, and 5 to nivolumab alone. There were no unexpected toxicities. Thirty-three percent of patients randomized to nivolumab+axitinib experienced partial response, compared to 0% in the other arms, and 0% of patients on the combination arm experienced primary disease progression. Addition of axitinib to nivolumab significantly improved PFS (p = 0.0004), extending median PFS from 1.8 to 10.5 months. Overall survival also improved (p = 0.003) with the addition of axitinib. **Conclusions:** Nivolumab+axitinib combination therapy was statistically more active than nivolumab single agent therapy, which itself was inactive. Whether anti-PD1 pathway inhibitors add benefit to anti-VEGF therapy for tRCC remains to be determined. Optimizing trial recruitment is critical for this rare but aggressive cancer. Clinical trial information: NCT03595124. Research Sponsor: U.S. National Institutes of Health; U10CA098543; :U10CA180886; U10CA098413, U10CA180899.

Descriptive statistics by arm.

Characteristic	Arm A: Axitinib/ Nivolumab N = 6	Arm B: Axitinib N = 2	Arm C: Nivolumab N = 5	Overall N = 13	p-value[1]
Age (Years)					0.715
Mean (SD)	18 (9)	19 (6)	18 (14)	18 (10)	
Median (Q1, Q3)	16 (10, 21)	19 (15, 23)	15 (12, 16)	16 (12, 21)	
Min, Max	9, 32	15, 23	7, 42	7, 42	
Age Category					>0.999
Age < 18	4 (67%)	1 (50%)	4 (80%)	9 (69%)	
Age 18+	2 (33%)	1 (50%)	1 (20%)	4 (31%)	
Prior Anti-VEGF therapy	1 (17%)	0 (0%)	1 (20%)		>0.999
No prior systemic therapy	5 (83%)	2 (100%)	4 (80%)	11 (85%)	
Best Overall Response					0.019
Partial Response	2 (33%)	0 (0%)	0 (0%)	2 (15%)	
Stable Disease	4 (67%)	2 (100%)	1 (20%)	7 (54%)	
Progressive Disease	0 (0%)	0 (0%)	4 (80%)	4 (31%)	

[1]Kruskal-Wallis rank sum test; Fisher's exact test.

4522 Poster Session

Ipilimumab/nivolumab versus standard of care in non-clear cell renal cancer: Results of the SUNNIFORECAST trial and potential role of the CPS score and tumor nephrectomy. First Author: Lothar Bergmann, University Hospital Frankfurt, Medical Clinic II (Hematology/Oncology), Frankfurt, Germany

Background: Non-clear cell renal cancers (nccRCC) are a rare and heterogeneous group of $>$20 histological and molecular defined entities. Due to the rarity of these entities, the clinical data are limited and large randomized trials are missing resulting in uncertainties for optimal treatment recommendations. So far, TKI therapy with or without immune checkpoint inhibitors (ICI) are considered standard of care (SOC) options in these diseases. Here we report the results of the academic prospective randomised European trial in therapy-naïve patients with advanced nccRCC entities, which compared ipilimumab/nivolumab (Ipi/Nivo) vs SOC. **Methods:** We randomly assigned patients (pts) with nccRCC in a 1:1 ratio to receive either nivolumab 3 mg/kg IV combined with ipilimumab 1 mg/kg IV every 3 weeks for 4 doses followed by a flat dose of 240 mg IV every 2 weeks or 480 mg every 4 weeks versus SOC by investigators choice until disease progression or intolerance occurred. Pts were stratified in papillary vs. non-papillary nccRCC and according to IMDC risk score. Central pathology was mandatory to confirm the correct diagnosis of the nccRCC subtype according to the WHO classification 2022.The primary endpoint was the overall survival (OS) rate at 12 months (mos), secondary endpoints were the OS rate at 6 mos and 18 mos, OS, progression-free survival (PFS) and response rate (RR). **Results:** 309 pts (70.9% male, 29.1% female) out of 316 pts were randomized to receive either Ipi/Nivo or SOC. 173 (56.0%) pts were of papillary subtype (pRCC) and 143 (44.0%) pts of non-papillary subtypes, whereas 59 pts had chromophobe (ccRCC), 20 sarcomatoid/rhabdoid, 10 collecting duct, 11 TFE3-rearranged or TFEB-altered RCC and 37 other histological features. According to the IMDC score, 23.9% were of favorable, 51.8% of intermediate and 24.3% of poor risk. The 12 mos OS rate for Ipi/Nivo of 78.3% (95%-CI 70.9%-83.9%) vs 68.3% (95%-CI 60.0%-75.3%) in the SOC arm was statistically significant (p=0.026). Median OS was 33.2 mos for the Ipi/Nivo arm and 25.2 mos for the SOC arm. The ORR of 32.8% vs. 19.4% and the median PFS of 5.4 mos vs 5.7 mos was not statistically significant different between both arms. The explorative endpoint CPS score differed between the various subentities and was associated with an advantage in OS. Pts with a CPS$\geq$1 had an OS-rate at 12 months of 79.3% in the Ipi/Nivo arm vs. 58.3% and a median OS of 38.6 mos vs. 18.8 mos (p=0.007). Furthermore, pts who did not underwent a tumor nephrectomy (possibly due to high risk) had a survival benefit with 26.3 mos in the Ipi/Nivo arm vs 16.5 mos in the SOC arm (p=0.065) in contrast to nephrectomized pts with 38.9 mos vs 34.0 mos. **Conclusions:** The OS-Rate at 12 mos was significantly superior for Ipi/Nivo in comparison to SOC and the primary endpoint was met. Additionally, pts in the Ipi/Nivo arm had a longer median OS, especially those with a CPS$\geq$1. Clinical trial information: NCT03075423. Research Sponsor: None.

4523 Poster Session

Efficacy and safety of second-line cabozantinib ± atezolizumab for patients with advanced renal cell carcinoma after progression on immuno-oncology combinations: Subgroup analysis of CONTACT-03. First Author: Cristina Suárez, Medical Oncology, Vall d´Hebron Institute of Oncology (VHIO), Hospital Universitari Vall d´Hebron, Vall d´Hebron Barcelona Hospital Campus, Barcelona, Spain

Background: Cabozantinib (cabo), a vascular endothelial growth factor receptor-associated tyrosine kinase inhibitor (TKI), is a preferred treatment option for second-line (2L) treatment of advanced renal cell carcinoma (RCC) based on its superior efficacy vs everolimus (Choueiri TK, *N Engl J Med* 2015); however, its activity after contemporary first-line (1L) immuno-oncology (IO) combinations is not well characterized. CONTACT-03 was a large phase 3 study evaluating the efficacy and safety of cabo ± atezolizumab (atezo) after progression on previous IO treatment (Pal SK, *Lancet* 2023). We report the results of a subgroup analysis of the safety and efficacy of 2L cabo ± atezo in patients from CONTACT-03 who received standard of care (SOC) 1L IO-IO or IO-TKI combinations. **Methods:** In CONTACT-03, adults with metastatic RCC whose disease had progressed on IO-based regimens were randomized to cabo (60 mg PO QD) alone or with atezo (1200 mg IV Q3W). This subgroup analysis included patients who had received 1L IO-IO or IO-TKI SOC combinations prior to enrolling in CONTACT-3. Outcomes for 2L treatment included PFS by blinded independent central review (BICR), OS, ORR, duration of response, and safety. **Results:** Of 522 patients, 107 in the cabo arm and 129 in the cabo + atezo arm had received prior treatment with IO-IO (ipilimumab-nivolumab) or IO-TKI (axitinib-avelumab, axitinib-pembrolizumab, or lenvatinib-pembrolizumab). Efficacy outcomes were comparable between treatments (Table). For cabo and cabo + atezo, respectively, median PFS by BICR was 10.3 and 10.2 months, and ORR was 36% and 37%. Grade 3/4 treatment-related adverse events (AEs) were reported in 48% and 58% of patients treated with cabo and cabo + atezo, respectively, treatment-related serious AEs were reported in 13% and 25% of patients, and AEs led to dose modification in 87% and 92% of patients and discontinuation in 5% and 17% of patients, respectively. **Conclusions:** Results from this post-hoc subgroup analysis of CONTACT-03 suggest 2L cabo is effective in patients with advanced RCC previously treated with 1L IO-IO or IO-TKI regimens. Safety was consistent with the overall study. These results can inform clinicians making 2L treatment decisions for patients who have progressed on contemporary 1L IO-containing combinations. Clinical trial information: NCT04338269. Research Sponsor: Exelixis, Inc.

Efficacy outcomes with cabo ± atezo after 1L IO combinations.

	Cabo (n=107)	Cabo + atezo (n=129)
Median PFS by BICR, months (95% CI)	10.3 (7.95, 12.45)	10.2 (8.34, 10.64)
Median OS, months (95% CI)	NE (18.30, NE)	24.2 (20.24, NE)
Best overall response by BICR, %	36	37
Complete response, %	0	0
Partial response, %	36	37
Stable disease, %	50	52
Progressive disease, %	10	5
Not evaluable/missing, %	5	6
Duration of response by BICR, months (95% CI)	15.0 (10.28, NE)	10.5 (7.95, NE)

NE, not estimable.

4524 **Poster Session**

Comparison of ^{68}Ga-NY104 PET/CT with ^{18}F-FDG PET/CT in patients with metastatic clear cell renal cell carcinoma (NYCRM): A prospective, comparative phase II study. First Author: Wenjia Zhu, Department of Nuclear Medicine, Peking Union Medical College Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China

Background: ^{68}Ga-NY104 is a small-molecule PET agent selectively targeting carbonic anhydrase IX (CAIX), which is highly expressed on clear cell renal cell carcinoma (ccRCC). This phase II study aims to evaluate the diagnostic efficacy of ^{68}Ga-NY104 PET/CT in patients with metastatic clear cell renal cell carcinoma and compare it with ^{18}F-FDG PET/CT. **Methods:** Patients with metastatic ccRCC were prospectively recruited in this study (ClinicalTrials.gov: NCT05879471). All participants underwent ^{68}Ga-NY104 and ^{18}F-FDG PET/CT within one week. Tyrosine kinase inhibitors were stopped at least one week before the study. Any lesion that can be detected on either PET or CT is included for further analysis. The number and uptake of lesions were recorded. The diagnostic efficacy was determined at lesion level and region level based on a comprehensive reference standard protocol. **Results:** Forty-four patients (mean age, 59.6 $\pm$ 10.7) were recruited, including 40 men and 4 women. A total of 677 lesions in 172 regions were identified, of which 568 lesions and 128 regions were considered positive for ccRCC based on reference standard. The lesion-level sensitivity and specificity of ^{68}Ga-NY104 PET/CT to detect ccRCC lesion are 96.6% (95% CI, 95.2% - 98.1%) and 99.1% (95% CI, 97.3% - 100%), which is significantly higher than that of ^{18}F-FDG PET/CT (sensitivity, 77.8%, 95% CI, 74.4% - 81.2%, P < 0.001; specificity, 5.5%, 95% CI, 1.2% - 9.8%, P < 0.001). The region-level sensitivity and specificity of ^{68}Ga-NY104 PET are 98.4% (95% CI, 96.3% - 100%) and 97.7% (95% CI, 93.3% - 100%), which is also significantly higher than that of ^{18}F-FDG PET/CT (sensitivity, 82.0%, 95% CI, 75.4% - 88.7%, P < 0.001; specificity, 11.4%, 95% CI, 2.0% - 20.7%, P < 0.001).The SUVmax of ccRcc lesions (n = 568) were 12.6 $\pm$ 11.7 for ^{68}Ga-NY104 versus 7.5 $\pm$10.5 for ^{18}F-FDG (P < 0.001). The TBR is also higher (15.7 $\pm$ 14.6 v.s. 4.8 $\pm$5.5, P < 0.001). A significant SUVmax difference between ccRCC and non-ccRCC lesion was noted for ^{68}Ga-NY104 (12.6 $\pm$ 11.7 v.s. 1.2 $\pm$1.0, P < 0.001), which is not true for ^{18}F-FDG (7.5 $\pm$10.5 v.s. 6.5 $\pm$3.5, P = 0.061). **Conclusions:** ^{68}Ga-NY104 PET/CT is a promising tool with high diagnostic efficacy in patients with metastatic ccRCC. It is better than ^{18}F-FDG PET/CT in both sensitivity and specificity. Clinical trial information: NCT05879471. Research Sponsor: National Natural Science Foundation of China; No. 82202218.

Diagnostic efficacy of ^{68}Ga-NY104 and ^{18}F-FDG PET/CT.

		Sensitivity	95% CI	Specificity	95% CI
Lesion-level (n=677)	68Ga-NY104	96.6%	95.2%-98.1%	99.1%	97.3%-100%
	18F-FDG	77.8%	74.4%-81.2%	5.5%	1.2%-9.8%
Region-level (n=172)	68Ga-NY104	98.4%	96.3%-100%	97.7%	93.3%-100%
	18F-FDG	82.0%	75.4%-88.7%	11.4%	2.0%-20.7%

4525 **Poster Session**

Anlotinib plus everolimus as first-line treatment for advanced non–clear cell renal cell carcinoma: 1 year updated results from UC-001, a single-center, single-arm, phase II trial. First Author: Wen-Hao Xu, Fudan University Shanghai Cancer Center, Shanghai, China

Background: For patients (pts) with recurrent or stage IV non-clear cell renal cell carcinoma (nccRCC), the current guidelines recommend participation in clinical trials, or the use of tyrosine kinase inhibitors (TKIs), such as sunitinib, or mTOR inhibitors, such as everolimus. Anlotinib, a novel multi-target TKI, inhibits vascular endothelial growth factor receptors, fibroblast growth factor receptors, platelet-derived growth factor receptors, and c-kit. The ALTER-UC-001 study (NCT05124431) is a single-center, single-arm, phase II trial evaluating the efficacy and safety of anlotinib plus everolimus as first-line therapy in pts with advanced nccRCC. Data for 24 pts from Jan 2022 through Dec 2023 have been published in 2024 ASCO. Here, we present 1-year updated results. **Methods:** Eligible pts were those with advanced nccRCC and no prior systemic therapy for advanced disease, with an Eastern Cooperative Oncology Group (ECOG) performance status of 0-1. Pts received anlotinib (12 mg orally once daily on days 1-14 of each 3-week cycle) and everolimus (5 mg orally once daily). The primary endpoint was objective response rate (ORR). Secondary endpoints included disease control rate (DCR), progression-free survival (PFS), and overall survival (OS). Adverse events (AEs) were graded according to CTCAE v5.0. **Results:** Between January 2022 and December 2024, 32 pts were enrolled and received treatment. The median age was 56 years old (range: 20-79 years), and 46.9% of pts had papillary renal cell carcinoma (pRCC). Most pts (81.3%; 26/32) had a ECOG PS score of 1. At the data cutoff in December 2024, with a median follow-up of 11.9 months (95% CI 9.3-14.5), the ORR was 54.5% (95% CI 32.2-75.6), and the DCR was 100% (95% CI 84.6-100.0). The median PFS was 20.8 months (95% CI 12.0-29.6). Adverse events (AEs) of any grade occurred in 90.6% of pts, with the most common being proteinuria (40.6%), mucositis and hypertension (37.5%), and anemia, increased creatinine, elevated transaminases (18.8%), glutamic-pyruvic transaminase increased and hematuria (15.6%), and hypercholesterolemia (12.5%). Grade 3 treatment-related AEs (TRAEs) occurred in 15.6% of pts, with no treatment-related deaths. Treatment was suspended in 18.8% (6/32) and 12.5% (4/32) of pts due to TRAEs associated with everolimus and anlotinib, respectively. **Conclusions:** This study demonstrates that anlotinib combined with everolimus is an effective and tolerable first-line therapy for advanced nccRCC, achieving a high ORR and prolonged PFS, with manageable toxicity. These findings provide critical evidence supporting the use of this novel combination in nccRCC. Survival follow-up is ongoing, and further validation in larger, multi-center randomized trials is warranted. Clinical trial information: NCT05124431. Research Sponsor: None.

4526 **Poster Session**

Anlotinib combined with sintilimab as first-line treatment in patients with advanced non-clear cell renal cell carcinoma (nccRR): Preliminary results from an exploratory prospective multicentre clinical study. First Author: Pei Dong, Department of Urology, State Key Laboratory of Oncology in South China, Guangdong Provincial Clinical Research Center for Cancer, Sun Yat-Sen University Cancer Center, Guangzhou, China

Background: Non-clear cell renal cell carcinoma (nccRCC) accounts for approximately 25% of all kidney cancers, however, the effect of systemic chemotherapy is limited. We report the first results of a single-arm, phase 2 study (NCT05220267) evaluating the efficacy and safety of anlotinib (a multi-target tyrosine kinase inhibitor) combined with sintilimab (a monoclonal antibody against programmed cell death protein 1) as first-line treatment in patients with advanced nccRCC. **Methods:** Patients with histologically confirmed advanced nccRCC and measurable disease per RECIST v1.1 who had not previously received systemic therapy were received anlotinib (12 mg qd, d1-14, repeated every 21 days) plus sintilimab (200 mg IV Q3W) till disease progression or intolerant toxicity. The primary endpoint is progression-free survival (PFS); secondary endpoints include objective response rate (ORR), disease control rate (DCR), overall survival (OS) and safety. **Results:** From April 2022 to January 2024, 44 patients were enrolled with a median age of 46 years (range: 18-79), 13 (29.5%) had Fumarate deficient RCC, 10 (22.7%) had Papillary RCC, 9 (20.5%) had TFE3 rearranged RCC and 12 (27.3%) were unclassified. Among these participants, 44 patients were evaluable. 95.5% were IMDC intermediate- or poor-risk, 72.7% had prior nephrectomy and 97.7% had synchronous metastatic disease. ORR and DCR were 56.8% (95%CI 41.6-72.1) and 86.4% (95%CI 75.8-96.9) , respectively.$\geq$1 and < 1 Combined Positive Score of PD-L1 expression were observed in 50% (22/44) and 38.6% (17/44) patients respectively, and the ORR was 72.7% (95%CI:52.2-92.9) and 41.2% (95%CI: 15.1-67.3) in the two groups. As of November 13, 2024, median follow-up time was 17.5m (95%CI 14.9-20.1). The median PFS was 13.6m (95%CI 8.6-18.6). Treatment-related grade 3/4 adverse events were observed in 22.7% (10/44) of the patients, encompassed proteinuria (3 patients, 7%), hyponatremia (2 patients, 4%), hypertension (1 patients, 2%), hepatic insufficiency (1 patients, 2%), fatigue(1 patients, 2%), rash (1 patients, 2%), decreased lymphocyte count (1 patients, 2%). Neither unexpected safety signals nor treatment-related death occurred. **Conclusions:** Our results showed promising efficacy and acceptable toxicity of anlotinib plus sintilimab for patients with advanced nccRCC. Clinical trial information: NCT05220267. Research Sponsor: None.

4527 **Poster Session**

Investigation of tumor-associated macrophages (TAMs) and therapeutic resistance to immune checkpoint inhibitors (ICI) through single-cell analysis of renal cell carcinoma (RCC). First Author: Soki Kashima, Center of Molecular and Cellular Oncology, Yale Cancer Center, Yale School of Medicine, New Haven, CT

Background: RCC is characterized by a tumor microenvironment (TME) enriched in TAMs, which suppress antitumor immunity in RCC. We conducted a comprehensive dissection of the TME using pre- and post-ICI treatment samples to identify specific TAM populations associated with ICI treatment resistance in RCC. **Methods:** A total of 70 tumor samples (58 clear cell and12 non-clear cell) were collected from 63 patients with advanced RCC, including 9 patients who were untreated, 10 patients who received non-ICI-based systemic therapies, and 44 patients who received ICI-based therapies. We excluded 17 patients with stable disease from the 44 patients and analyzed 29 samples prior to (n = 15) or after exposure to (n = 14) ICI-based therapies (mono-ICI, n = 11; ICI + ICI, n = 11; ICI + VEGFi, n = 6; other, n = 1) from 27 patients. We performed single-cell RNA-sequencing (scRNA-seq; 10x Genomics) on all 70 samples and established a comprehensive transcriptomics atlas of the RCC TME. We utilized non-negative matrix factorization (NMF) to identify interpretable gene programs for TAMs, comparing responders (R) (n = 18; complete or partial response) with non-responders (NR) (n = 11; progressive disease) to ICI-based therapies according to the best response based on RECIST. P-values from Wilcoxon signed rank test are reported. **Results:** 443,337 high-quality viable cells were annotated to lymphoid, myeloid, tumor, endothelial, or fibroblast compartments, capturing the RCC TME landscape. Among TAMs, we discovered underlying gene programs through NMF analysis, including “antigen presentation”, “S100A8/9 inflammatory”, “stress response”, “C1Q/APOE/TREM2”, “CD163/MRC1”, “hypoxia”, “interferon-stimulated genes”, and “LILRB/SIGLEC10” programs. We identified that the LILRB/SIGLEC10-TAM subcluster was significantly increased in frequency in NR compared to R (p = 0.005). Notably, the significant increase in this program in NR was also observed in pre-treatment only samples (p = 0.014), suggesting a primary mechanism of resistance. This population was characterized by the expression of immune suppressive *LILRB1/2/3* genes, together with significant upregulation of the macrophage checkpoints *SIGLEC10* (a recently discovered “don’t eat me signal” receptor) and *VISTA* (an immune checkpoint) compared to other TAMs (p < 2.22E-16, for each). **Conclusions:** Our comprehensive dissection of the RCC TME reveals an association between TAM population with an immunosuppressive gene program and ICI resistance through analysis of a large scRNA-seq dataset. This study provides immunobiological insights into potential therapeutic targets for next-generation combination therapy with ICIs, offering a foundation for understanding treatment evolution in RCC. Research Sponsor: Kohlberg Chair at Harvard Medical School and the Trust Family, Michael Brigham, Pan Mass Challenge and Loker Pinard Funds for Kidney Cancer Research.

4528 **Poster Session**

Assessment of time-to-treatment-failure (TTF) as a surrogate endpoint for overall survival (OS) to immune checkpoint inhibitor (ICI) regimens in metastatic renal cell carcinoma (mRCC): Findings from an IMDC analysis. First Author: Zachary Yochum, Yale Cancer Center, New Haven, CT

Background: In Phase III trials for mRCC, OS is a gold standard primary endpoint. However, for ICI-based regimens, this requires extended follow-up times, resulting in higher costs and delayed drug approvals. Identification of surrogate or intermediate endpoints for OS would be beneficial in addressing these challenges. In the current study, we investigated 6-month TTF as a potential intermediate endpoint (IE) for OS in mRCC. **Methods:** We included all patients from the International mRCC Database Consortium (IMDC) who received ICI-based regimens from 2013 to 2023. TTF was defined from ICI start until drug cessation or death or censored at date of last follow-up. The cohort was divided into 10 equal sub-cohorts based on the decile disease risk scores, calculated using multivariable Cox regression for OS, considering all relevant covariates (IMDC risk groups, presence of bone, brain, or liver metastases, histology, age, prior nephrectomy, ICI type, and year of ICI initiation). For these sub-cohorts, we used Kaplan-Meier methods to determine 18-month OS and event-free rates for 6, 9, and 12-month TTF. We then performed linear regression of stratum-specific 18-month OS against stratum-specific 6-month (and 9- and 12-month) TTF. In the landmark analysis, OS was calculated starting at 6 months after therapy initiation, excluding patients who died or had follow-up of less than 6 months. **Results:** The IMDC cohort consisted of 1667 patients with a median age of 63 years and 83% had clear cell histology. Median follow-up was 15.4 months (IQR: 7.1-28.6). Across the 10 sub-cohorts, 6-month TTF accounted for 76% of the variance in 18-month OS (R^2= 0.76, 95% CI: 0.26-0.87). Similar patterns were seen for 9 (R^2= 0.65, 95% CI: 0.11-0.81) and 12-month TTF (R^2= 0.64, 95% CI: 0.09-0.80). In the 6-month landmark analysis (evaluable n = 1255), mRCC patients experiencing treatment failure at 6 months had an 18-month OS (i.e. 12 months after the landmark time) rate of 68% (95% CI: 63%-72%), compared to 92% (95% CI: 90%-94%) for those without treatment failure (adjusted HR: 2.74, 95% CI 2.15-3.49). **Conclusions:** 6-month TTF was predictive of 18-month OS in mRCC patients. These findings suggest that 6-month TTF may be a promising intermediate endpoint for OS and provides supportive evidence of future validation in prospective studies. Research Sponsor: None.

4529 **Poster Session**

Phase 1 results of Oncobax-AK in combination with ipilimumab/nivolumab in advanced clear cell renal cell carcinoma (ccRCC; NCT05865730). First Author: Lisa Derosa, Gustave Roussy Cancer Campus (GRCC), ClinicObiome, Villejuif, France

Background: Patients with advanced solid tumors who respond to immunotherapy are more likely to have *Akkermansia spp (Akk)* in their stools, whereas its absence (45%) is associated with worse outcome, regardless of other prognostic factors. Here, we report the safety and efficacy findings from a Phase I trial evaluating Oncobax-AK live biotherapeutics in combination with nivolumab/ipilimumab in intermediate- and poor-risk IMDC ccRCC patients who tested negative for stool *Akk*. We report first results of cohort 1. **Methods:** Intermediate- and poor-risk IMDC advanced ccRCC patients were screened across 4 centers in France for *Akk* using a qPCR stool test designed to detect specific *Akk* strains (SGB9226/SGB9228). Patients who tested negative for stool *Akk* received either 1X (cohort 1) or 6X oral capsules (cohort 2) of Oncobax-AK (a specific strain of SGB9228, p2261) for one week as monotherapy, followed by a combination treatment with nivolumab/ipilimumab administered continuously until progression in cohorts 1 and 2, respectively. The primary endpoints were safety, pharmacodynamics of Oncobax-AK, and overall response rate (ORR) according to RECIST 1.1. Blood and stool samples were collected at multiple time points for multi-omics analyses. **Results:** Among the 29 patients screened for *Akk*, 11 (38%) did not harbor gut *Akk* and were eligible. Two patients declined to continue. Ultimately, 9 patients (8 intermediate and 1 poor IMDC risk group) were enrolled in cohort 1, with a median age of 57 years (n = 9: 1 female and 8 males). No serious adverse events related to Oncobax-AK was observed. Only one patient experienced a serious immunotherapy-related adverse event that led to treatment withdrawal. After a median follow-up of 14.9 months, all patients are still alive, with 4 showing a partial response (PR) for more than 6 months (including 2 patients with ongoing PR for over 15 months, continuing the intervention). One patient had stable disease (SD), 3 had progressive disease (PD), and 1 was not evaluable (NE). Among evaluable patients, the ORR was 50%. Multi-omics analyses revealed that Oncobax-AK remains detectable over time and induced changes in the microbiome, leaky gut markers, and immune and metabolite profiles. These changes suggest potential pharmacodynamic biomarkers, reflecting the biological effects of Oncobax-AK. **Conclusions:** This is the first trial targeting patients lacking *Akkermansia spp*. in their stools. Oncobax-AK, combined with Ipilimuab/Nivolumab in intermediate- and poor-risk IMDC ccRCC, appears safe and may modulate gut microbiota, inflammation, metabolites, and immune profiles. This potentially mimics a responder's profile and leads to clinical and radiological benefits in some patients. Based on these promising results, enrollment in cohort 2 (6X) is ongoing and has now been expanded to include non-small cell lung cancer patients. Clinical trial information: NCT05865730. Research Sponsor: None.

4530 **Poster Session**

Co-expression network-based analysis of gene programs contributing to immune checkpoint inhibitor (ICI) resistance in renal cell carcinoma (RCC). First Author: Ro Malik, Center of Molecular and Cellular Oncology, Yale Cancer Center, Yale School of Medicine, New Haven, CT

Background: There is an unmet need to characterize molecular drivers of resistance to ICIs in the RCC tumor microenvironment, especially in cell-type-specific contexts. To address this, we identified coherent gene programs in each cell type using scRNA-seq data to uncover an immune cell phenotype associated with ICI resistance. **Methods:** We performed per-cell-type weighted coexpression network analysis on scRNA-seq data of 443,337 cells from 70 RCC tumor samples, mostly from patients (pts) who received ICI (S. Kashima, ASCO, 2024), to construct mutually co-expressed gene sets (modules) and their cell-level expression. We compared module expression scores between responders (R, complete or partial response) and non-responders (NR, progressive disease) with the Wilcoxon rank-sum test plus FDR correction, and ran tests with permuted labels to rule out statistical artifacts. For validation, we performed this analysis on another scRNA-seq cohort from a phase II trial (HCRN GU16-260; NCT03117309), and further, we used CoxPH survival analysis on module signature scores computed by GSVA to assess the prognostic role of module expression in bulk RNA-seq samples from the IMmotion 150, CheckMate 009/010/025, and Javelin 101 trials, after stratifying them into immune-high (top 50%) and immune-low (bottom 50%) groups according to CIBERSORTx-inferred total immune infiltration. **Results:** Analysis of scRNA-seq (two independent datasets) from ICI-treated RCC tumors revealed a module of robustly co-expressed ribosomal and translation-associated genes that was significantly upregulated in NR in immune cells (but not tumor or stromal cells), including macrophages, CD4+ and CD8+ T, NK, and B cells (p-values ranging from 1e-20 to 1e-200). Analysis of an independent scRNA-seq cohort (HCRN GU16-260) also yielded a module of mutually co-expressed ribosomal proteins only in immune cells that was upregulated in NR (immune $p < 1e\text{-}20$, non-immune $p > .05$). Finally, validation in large-scale bulk RNA-seq data from clinical trials shows that for patients receiving any ICI-based therapy (nivolumab, avelumab + axitinib, or atezolizumab +/- bevacizumab), module signature scores were significantly associated with worse PFS only in the CoxPH analysis of immune-high samples (HR = 1.65, 95% CI, 1.18–2.3, $p < .005$), while immune-low samples showed no effect (HR = 0.93, 95% CI 0.71–1.25, $p > .5$), concordant with findings from the scRNA-seq analysis. Those receiving a TKI only (sunitinib) exhibited no association, regardless of immune infiltration. **Conclusions:** Though individual ribosomal proteins have been found to be prognostic for RCC, a cell-type-specific module-level analysis elucidated a link between a coherent translation program in immune cells and resistance and poor PFS for pts receiving ICI specifically, contributing to a model of ICI-resistant molecular phenotypes in RCC. Research Sponsor: National Cancer Institute/U.S. National Institutes of Health; 1R37CA279822.

4531 **Poster Session**

Frailty assessment in patients with advanced/metastatic renal cell carcinoma using routine data collected during treatment with tyrosine kinase inhibitors in the STAR trial. First Author: Sophie Trotter, Weston Park Cancer Centre, Sheffield Teaching Hospitals NHS Foundation Trust, Sheffield, United Kingdom

Background: The STAR trial (ISRCTN06473203) was a phase 2/3 randomised controlled non-inferiority trial (N=920) which assessed whether treatment breaks from tyrosine kinase inhibitors (TKIs, oral sunitinib/pazopanib) could be safely used in locally advanced/metastatic renal cell carcinoma (RCC). We aimed to determine if it was possible to obtain a frailty index (FI) which could be linked to toxicity and clinical outcomes from routinely collected large trial data, using the STAR trial as an example. **Methods:** We developed the FI using Rockwood's accumulation of deficits methodology. STAR data was initially searched for variables measuring baseline health problems and functional limitations. Variables were excluded if there was a significant proportion of missing values ($>$10%); if too rare or too common ($<$1%, $>$80%); or if significantly correlated with another variable ($r>0.95$). Variables were coded from 0 (no deficit) to 1 (full deficit); these were summed then divided by the number of variables assessed to give the FI. Frailty thresholds were adopted in line with the literature: Not Frail (FI$\leq$0.08); Pre-Frail (FI 0.08-0.24); Frail (FI$\geq$0.25). **Results:** Of 57 variables screened, 35 variables remained for inclusion in the FI. 50 participants missing $>$20% of FI variables were excluded, leaving n=870. FI scores ranged from 0 to 0.43 (median 0.15, IQR 0.10-0.22). Kaplan-Meier survival analysis showed a statistically significant difference by FI for overall survival (OS) (FI$\geq$0.25: HR 2.48, $p<0.001$, 95% CI 1.89-3.26). In multivariate Cox proportional hazards regression, FI remained a statistically significant risk factor for OS (HR 1.41, P=0.047, 95% CI 1.00-1.99); other statistically significant variables included age group, sites of metastatic disease, IMDC and MOTZER scores. Toxicity was assessed over the first 6 months, while all participants were treated with continuous TKIs. The most common severe toxicities (G3+) were hypertension (200/870), hepatobiliary disorders (97/870) and fatigue (63/870). Time free of severe toxicity was statistically significantly shorter for frail participants. **Conclusions:** Amongst STAR trial participants with advanced/metastatic RCC treated with TKIs, frailty was a statistically significant risk factor for poorer survival and for shorter time to severe toxicity. It is noted that the eligibility criteria for STAR included a baseline PS of ECOG 0-1 which will have excluded many frailer patients. This data shows that it is feasible to use routinely collected trial data to create a clinically meaningful FI and this approach could be applied to other trial datasets. Clinical trial information: ISRCTN06473203. Research Sponsor: UK National Institute for Health and Care Research (NIHR).

Toxicity-free survival, by frailty group.

Toxicity	FI group	HR	p-value	95% CI
Severe toxicity (G3+)	Intermediate	1.00	0.960	0.83-1.21
	Frail	1.28	0.025	1.03-1.59
All toxicity (G1+)	Intermediate	1.11	0.031	1.01-1.22
	Frail	1.08	0.201	0.96-1.20

4532 **Poster Session**

International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) classification and regression tree analysis to characterize objective response rates (ORR) in metastatic renal cell carcinoma (mRCC). First Author: Martin Zarba, Arthur J.E. Child Comprehensive Cancer Centre, Calgary, AB, Canada

Background: Therapies for mRCC have evolved significantly, making treatment decisions more complex. We used machine learning (ML) to identify whether this could help identify subgroups of patients who have a high probability of response. **Methods:** Patients from IMDC were identified and a ML classification and regression tree analysis was conducted, in which we grew a complex tree up to a depth of 30 with a minimum node split size of 2 with no constraints on the cost-complexity parameter. The resulting tree was pruned according to the cost-complexity parameter that minimized the leave one out cross-validated error rate and had a minimum bucket size of 25 patients. **Results:** 2,549 patients were included, 73.2% male, 13.5% non-clear cell histology, 70.3% nephrectomy, and 19.4%, 54.2%, and 26.4% had favorable, intermediate and poor IMDC risk respectively. 1L treatment regimens consisted of VEGF inhibitors (51.5%), IO-IO combinations (32.3%), and IO-TKI combinations (16.2%). The ORR was 36.0% overall, with 29.6% for VEGF inhibitors, 39.1% for IO-IO, and 50.2% for IO-TKI combinations. ML identified 5 hierarchal variables —therapy type, prior nephrectomy (PN), lung metastasis (LM), other metastases, and age— that divided patients into 7 different categories with different response probabilities (see Table). VEGF therapy showed the poorest response, with no additional variables able to predict response. The best ORR was observed in patients treated with IO-TKI and PN; and in those treated with IO-IO, PN, and only lung metastasis. Factors associated with poorer responses included non-clear cell histology, older age, bone and liver metastases, poor performance status, elevated neutrophils, and poor IMDC risk score. **Conclusions:** This large-scale ML analysis identified five key clinical variables that predict treatment response in mRCC, with treatment type emerging as the primary determinant. These results suggest that treatment selection for mRCC could potentially be optimized by considering these hierarchical variables, though further validation is needed. Research Sponsor: None.

ML analysis results: Groups of patients and associated outcomes.

Risk Groups	N (%)	ORR (%)	Odd Ratio	TTNT	18-month survival
1) VEGF	1313 (51.5)	29.6	Ref.	9.4 (8.6-10.3)	0.62 (0.59-0.65)
2) IO-IO or IO-TKI and no PN	443 (17.4)	35.0	1.28 (1.02-1.60)	10.2 (8.8-11.3)	0.59 (0.55-0.65)
3) IO-IO and PN					
a) No LM	137 (5.4)	29.2	0.98 (0.66-1.43)	17.2 (10.6-30.1)	0.85 (0.78-0.92)
b) LM and other met	267 (10.5)	43.8	1.87 (1.42-2.44)	13.0 (10.1-20.5)	0.78 (0.72-0.83)
c) Only LM	85 (3.3)	60.0	3.56 (2.28-5.63)	39.2 (14.4-NA)	0.93 (0.87-0.99)
4)IO-TKI and PN					
a) Age 70+	78 (3.2)	43.6	1.84 (1.15-2.91)	35.7 (19.8-NA)	0.80 (0.71-0.91)
b) Age < 70	226 (8.9)	58.4	3.34 (2.50-4.47)	24.7 (22.4-36.4)	0.88 (0.84-0.93)
Overall	2549	36.0		11.5 (10.7-12.2)	0.68 (0.67-0.70)

4534 **Poster Session**

Early detection of renal cell carcinoma: A novel cfDNA fragmentomics-based liquid biopsy assay. First Author: Yulu Peng, Sun Yat-sen University Cancer Center; State Key Laboratory of Oncology in South China, Collaborative Innovation Center of Cancer Medicine, Guangzhou, China

Background: Renal cell carcinoma (RCC) is a leading cause of cancer-related mortality, with a rapidly rising global incidence. Early detection greatly improves the outcomes of RCC, yet current diagnostic methods have limitations in sensitivity, specificity, and accessibility. This study develops and evaluates a cfDNA fragmentomics-based liquid biopsy integrated with machine learning as a non-invasive and scalable tool for RCC early detection. **Methods:** This case-control cohort study recruited 442 participants (223 RCC patients and 219 non-cancer controls, including healthy individuals and those with benign renal conditions) at a single cancer referral center from December 2021 to December 2023. Plasma-derived cfDNA underwent low-pass WGS (5X coverage), and three fragmentomics features—copy number variation (CNV), fragment size ratio (FSR), and nucleosome footprint (NFP)—were extracted. A stacked ensemble machine learning model was trained on 280 participants and validated on 162 independent participants. Performance was assessed using area under the curve (AUC), sensitivity, and specificity. **Results:** The ensemble model achieved an AUC of 0.9656 in the validation cohort, with sensitivity and specificity of 90.5% and 93.8%, respectively. Stratified analyses demonstrated consistent performance across RCC stages, histological subtypes, and Fuhrman grades, with sensitivities of 87.8% for Stage I RCC and 100% for Stage IV RCC. Additionally, the model effectively differentiated malignant RCC from benign renal conditions, further validating its clinical utility. Stability evaluations confirmed the model's robustness across diverse sample types, storage conditions, and processing scenarios, underscoring its potential applicability in routine clinical practice. **Conclusions:** This cfDNA fragmentomics-based liquid biopsy represents a highly sensitive, specific, and non-invasive approach for the early detection of RCC. Its robust performance across diverse clinical scenarios highlights its potential to enhance current RCC diagnostic workflows, facilitate timely interventions, and improve patient outcomes. Future integration of this method into clinical practice could address critical gaps in RCC management, providing substantial benefits in early detection and personalized care. Research Sponsor: National Natural Science Foundation of China; Science and Technology Projects in Guangzhou; The China National Postdoctoral Program for Innovative Talents.

4535 **Poster Session**

Efficacy and safety of neoadjuvant toripalimab plus axitinib in renal cell carcinoma with tumor thrombus: A combined analysis of two phase II trials. First Author: Liangyou Gu, Chinese PLA General Hospital, Beijing, China

Background: Tumor thrombectomy for renal cell carcinoma (RCC) with tumor thrombus (TT) is associated with high morbidity and mortality. Two trials have demonstrated the efficacy and safety of neoadjuvant toripalimab plus axitinib in patients with TT. Here, we present the pooled analysis results. **Methods:** These two phase II trials (NEOTAX and NCT04118855) shared similar target populations. Patients with clear cell RCC (ccRCC) and TT received up to 12 weeks of toripalimab plus axitinib before surgery. The primary endpoint was the downstaging rate of TT based on the Mayo classification. For level 0 thrombus, the downstaging defined as: for right RCC, the proximal end of TT retracted from the main renal vein to branches of the renal vein; for left RCC, the superior mesenteric artery (SMA) was an anatomical landmark, the TT retracted from lateral to the abdominal aorta to the level of SMA or from the main renal vein lateral to SMA or the branches of the renal vein. Secondary endpoints included response rate, change in thrombus length, surgical morbidity, progression-free survival (PFS), overall survival (OS), and safety. **Results:** A total of 40 patients were enrolled, 4 (10%), 4 (10%), 14 (35%), 7 (17.5%), 11 (27.5%) patients had level 0, I, II, III, IV tumor thrombus, respectively. After 12 weeks treatment, 45.0% (18/40) patients experienced a reduction in TT level, one patient (2.5%) had an increase in Mayo level. Thirty-six (90%) patients exhibited shrinkage in TT length, with a median reduction of 1.9 cm (IQR: 0.9 to 3.7 cm). According to the RECIST criteria, the objective response rate and disease control rate of overall tumor was 37.5% and 97.5%. In total, 35 patients underwent radical nephrectomy with IVC thrombectomy, including 16 open, 2 laparoscopic and 17 robotic. No patient had a surgery delay due to treatment-related adverse events (TRAEs). 54.3%(19/35) patients experienced changes in surgical strategy compared with planned surgery. Median operation time was 300 min (IQR: 180-420 min). Median estimated blood loss was 700 ml (IQR: 300-1800 ml). The postoperative complication rate was 60% (21/35), including three (8.6%) major complications and one (2.9%) postoperative death. The most common TRAEs included hypertension (35.0%), proteinuria (35.0%), fatigue (27.5%), and diarrhea (22.5%). Grade $\geq$3 adverse events were reported in 27.5% (11/40) of patients, no patients experienced Grade 4 or 5 TRAEs. With a median follow-up of 32.2 (IQR: 27.0-35.5) months, the median PFS and OS were not reached. The estimated PFS rate at 1 year was 87.5% (95% CI, 72.4% to 95.3%). The PFS (P = 0.20) and OS (P = 0.44) were similar between responders (partial response) and non-responders (stable disease or progressive disease). **Conclusions:** Toripalimab in combination with axitinib downstages TT level in a significant proportion of patients leading to simplification in the procedure of surgery. Clinical trial information: NCT04118855. Research Sponsor: None.

4536 **Poster Session**

First-line benmelstobart plus anlotinib versus sunitinib in advanced renal cell carcinoma: Subgroup analysis from the phase 3 ETER100 trial. First Author: Xinan Sheng, Key Laboratory of Carcinogenesis and Translational Research (Ministry of Education/Beijing), Department of Genitourinary Oncology, Peking University Cancer Hospital & Institute, Beijing, China

Background: Dual immune checkpoint inhibitors (ICIs) or ICIs plus VEGF-directed therapies, have been approved as first-line treatment in patients (pts) with advanced renal cell carcinoma (RCC). The phase 3 ETER100 trial showed that benmelstobart (PD-L1 blockade) plus anlotinib improved the progression-free survival (PFS) (19.0 months 9.8 months) and objective response rate (ORR) (71.6% vs 25.1%) of advanced clear cell RCC (ccRCC) pts significantly. Pts with factors, such as intermediate-poor International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) risk, liver metastasis, or bone metastasis were considered to have a poor prognosis. Here we report PFS and ORR in clinically relevant subgroups. **Methods:** ETER100 (NCT04523272) was a multicentre, randomised, open-label, controlled phase 3 trial conducted at 37 sites in China. Eligible patients were randomly assigned in a 1:1 ratio using stratified block randomisation to receive benmelstobart plus anlotinib or sunitinib. Randomisation was stratified according to the International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) risk (favourable [score of 0], intermediate [score of 1-2], or poor risk [score of 3-6]). PFS analyses of clinically relevant subgroups were assessed using Kaplan-Meier method and the 95% CIs of response rate were calculated with the Clopper-Pearson method. **Results:** Overall, 527 pts received the trial treatments (264 in the benmelstobart-anlotinib group and 263 in the sunitinib group) and were evaluated for efficacy. A total of 454 (86%) pts had intermediate-poor IMDC risk, 62 (12%) pts had liver metastasis and 111(21%) had bone metastasis. Data cutoff for the interim analysis occurred on January 31, 2024. The median follow-up was 22.8 months. Benmelstobart plus anlotinib significantly improved PFS of subgroups with intermediate-poor IMDC risk (17.0 months [95% CI 14.0-20.1] vs 9.7 months [8.0-11.3], HR 0.55, 95% CI 0.43-0.72; $p < 0.0001$), liver metastasis (11.9 months [95% CI 5.8-NE] vs 5.4 months [1.5-6.7], HR 0.44, 95% CI 0.23-0.85; $p < 0.0121$), or bone metastasis (19.5 months [95% CI 16.5-27.2] vs 8.3 months [4.2-19.8], HR 0.52, 95% CI 0.30-0.89; $p < 0.0154$). ORR of benmelstobart-anlotinib group was significantly higher in the subgroups with intermediate-poor IMDC risk (70.0% [95%CI, 63.6-75.9] vs 21.6% [16.4-27.5]), liver metastasis (60.0% [95%CI, 42.1-76.1] vs 7.4% [0.9-24.3]) and bone metastasis (63.2% [95%CI, 49.3-75.6] vs 16.7% [7.9-29.3]). **Conclusions:** The RCC pts with a poor prognosis such as intermediate-poor IMDC risk, liver metastasis and bone metastasis could significantly benefit from benmelstobart plus anlotinib. Clinical trial information: NCT04523272. Research Sponsor: None.

4537 **Poster Session**

Ongoing phase 1/2 trial of the hematopoietic progenitor kinase 1 (HPK1) inhibitor NDI-101150 as monotherapy or in combination with pembrolizumab: Clinical safety and efficacy update in clear cell renal cell carcinoma (ccRCC). First Author: David A. Braun, Center of Molecular and Cellular Oncology, Yale University, New Haven, CT

Background: NDI-101150 is a potent and selective oral inhibitor of HPK1, a serine/threonine kinase that acts as a negative regulator of immune cell function. Pre-clinically, NDI-101150 can enhance immune cell function, leading to potent anti-tumor immunity. **Methods:** NDI-101150 is currently being investigated in a first-in-human, multi-center, open-label, phase 1/2 trial (NCT05128487) in patients with advanced solid tumors, as a monotherapy (50–200 mg once daily [QD]) or in combination with pembrolizumab (50–100 mg QD NDI-101150 + 200 mg Q3W pembrolizumab). **Results:** As of 20 November 2024, 106 patients were dosed [NDI-101150 monotherapy (n = 94) or NDI-101150 + pembrolizumab (n = 12)]. The tumor types were RCC (n = 38), NSCLC (n = 17), gastric/GEJ (n = 12), and other solid tumors (n = 39). We report here updated safety data in all patients from monotherapy and combination arms (n = 106), and efficacy data in patients with ccRCC (n = 29) receiving NDI-101150 monotherapy. NDI-101150 monotherapy was generally well tolerated, with 150 mg identified as the maximum tolerated dose. The most common treatment-related adverse events (TRAEs) of any grade were nausea (39%), diarrhea (35%), vomiting (29%), fatigue (27%), and anemia (11%). Grade ≥3 TRAEs occurred in 13 (14%) patients, of which only 1 (1%) patient experienced a grade 4 TRAE. The safety profile was comparable in the combination cohort, with 2 (17%) patients experiencing Grade ≥3 TRAE. 20 of the 29 ccRCC patients who received 50, 100, 140, or 150 mg of NDI-101150 monotherapy were response-evaluable. The objective response rate was 15.0% [CR, n = 1 and PR, n = 2]. Clinical benefit rate (CR + PR + SD ≥6 months) was 25%, which includes 2 patients who experienced durable SD for ~9 months and ~25 months. The disease control rate (CR+PR+SD) was 60%. The ccRCC patients had received a median of 2 (1-9) lines of prior therapy. A nearly dose-proportional increase in NDI-101150 exposure was observed at day 1, with steady state achieved by day 15. At all doses tested, steady state exposures inhibited the pharmacodynamic biomarker pSLP76 by > 50% and for a period consistent with preclinical efficacy predictions. To demonstrate proof of biology, a custom 12-plex immunofluorescence panel and the GeoMx whole transcriptomic assay were utilized. By day 28, on-treatment tumor biopsy samples showed immune activation when compared to pre-treatment samples, including an increased infiltration of activated CD8+ T-cells and dendritic cells. **Conclusions:** NDI-101150 continues to demonstrate an acceptable safety profile and encouraging antitumor activity in patients with ccRCC, supporting continued clinical development of NDI-101150 as monotherapy and in combination with other agents as a promising next-generation immunotherapy oral small molecule. Clinical trial information: NCT05128487. Research Sponsor: Nimbus Therapeutics.

4538 **Poster Session**

Genomic and proteomic predictors of sites of metastases in renal cell carcinoma. First Author: Clara Steiner, Dana-Farber Cancer Institute, Boston, MA

Background: Among patients with renal cell carcinoma (RCC), the most common sites of metastasis are lung, lymph nodes, and bone. While some sites of metastases are associated with better cancer-specific outcomes than others, the underlying biology of metastatic organ tropism is not well understood. We performed genomic and proteomic analyses to investigate the biological underpinnings of different metastatic sites in RCC. **Methods:** Institutional cohorts of patients with metastatic RCC from the Dana-Farber Cancer Institute (DFCI) were analyzed using a next-generation tumor somatic mutation assay (n = 633) and with a highly multiplexed plasma proteomics assay (n = 258). Data were clinically annotated for sites of RCC metastasis. Genomic analyses were performed using a two-sided Fisher's exact test on the cBioPortal platform at DFCI with pairwise comparison of patients with versus without metastases to lung, liver, brain, bone, adrenal, and lymph nodes. The Benjamini-Hochberg method was applied for FDR-adjusted q-values. Exploratory proteomic analyses were performed using logistic regression for each metastatic site with multivariate adjustment for other sites of metastasis. For each metastatic site, the top five associated proteins were selected to build a multivariate model to predict the presence of each metastatic site. Bootstrapping with R = 1,000 was employed for the assessment of model performance. **Results:** Tumor genomic alterations in *SETD2* (q-value = 0.004) and *CDKN2A* (q-value = 0.04) were associated with lung and lymph node metastases, respectively. Logistic regression analyses of proteomic data were used to identify circulating proteins with the strongest associations with the sites of metastases. For instance, circulating collagen alpha-1(IX) chain (CO91A) and relaxin receptor 1 (RXFP1) were the top circulating proteins associated with bone metastases, while GGT2 and tenascin were associated with liver metastases and matrilysin (MMP-7) was associated with lymph node metastases. Multivariate models using the top five proteins to predict the presence of each metastatic site demonstrated bootstrapped C-statistics from 0.72 to 0.80 for lymph nodes, lung, adrenal, brain, liver, and bone, respectively. **Conclusions:** We identified genomic and proteomic predictors of organ-tropic metastases in RCC. Next, we will validate these findings in independent external cohorts. Research Sponsor: None.

4539 **Poster Session**

Analysis of phase II study of cabozantinib (Cabo) with nivolumab (Nivo) and ipilimumab (Ipi) in advanced renal cell carcinoma with divergent histologies (RCCdh). First Author: Bradley Alexander McGregor, Dana-Farber Cancer Institute, Boston, MA

Background: We previously reported on treatment intensification with the combination of Cabo/Nivo/Ipi in 39 patients (pts) with metastatic RCCdh in a multi-center single arm phase II trial with a starting cabozantinib dose of 40 mg/day (d). Clinical utility was limited with an objective response rate (ORR) of 21% and significant treatment related adverse events (TrAEs) (77% ≥Grade 3 TrAEs). Therefore, we explored the safety and potential efficacy by using a lower starting dose of cabozantinib of 20 mg/d (NCT04413123). **Methods:** Eligible pts had metastatic RCCdh with ECOG performance status of 0-1 and may have received one line of prior therapy excluding immunotherapy or Cabo. Pts underwent a baseline biopsy and received Nivo 3 mg/kg and Ipi 1 mg/kg intravenously Q3 weeks (W) for 4 cycles followed by Nivo 480 mg IV Q4W. Cabo was given continuously at a dose of 20 mg/d; reductions to 20 mg every other day were allowed; after completion of Ipi, the Cabo dose could be increased to 40 mg/d. The primary endpoint was ORR by RECIST 1.1. Safety was a secondary endpoint. A one-stage design with 20 subjects (for 7 or more responses) would provide 75% power to distinguish an ORR of 40% versus 20% at one-sided alpha of 0.1. **Results:** 20 pts were enrolled and received at least 1 study drug at 7 sites from Feb. 2023 to Apr. 2024. Following histologic subtypes were included: papillary (n = 11), chromophobe (n = 1), translocation (n = 3), unclassified RCC (n = 2) and other (n = 3). 4 (20%) pts received prior systemic therapy. 10 (50%) pts received all 4 doses of Nivo and Ipi; 13 (65%) pts received maintenance nivolumab. Cabo was increased to 40 mg in 11/13 of these patients. Median follow-up was 9.4 (range 4.6-17.7) months. ORR was 25% (5/20, two-sided 80% CI, 13-41%, Table 1). 6- and 12-month progression free survival rates were 65% and 42% respectively. 11 (55%) pts developed grade 3 or 4 TrAEs (6 were due to elevation in liver function tests) and 1 (5%) had grade 5 TrAE (intraoperative hemorrhage) in setting of disease progression. 5 (25%) required high dose steroids (≥40 mg prednisone or equivalent) of which only 3 (15%) received for hepatitis. All therapy was discontinued due to toxicity in 1 (5%) pt. **Conclusions:** Although the study did not reach the target of 7 responses to uphold the alternative hypothesis, reduction of the starting dose of Cabo to 20 mg/d in combination with Nivo/Ipi results in numerically lower ≥ grade 3 TrAEs than starting at 40 mg/d (60% vs 77%) and clinical activity in a subset of patients. Clinical trial information: NCT04413123. Research Sponsor: Exelixis; BMS.

	Total (N=20) N(%)	Histology					Prior Systemic Therapy	
		Papillary	Chromophobe	Translocation	Unclassified RCC	Other	No	Yes
PR	5 (25)	2	1	0	2	0	4	1
SD	8 (40)	5	0	2	0	1	7	1
PD	7 (35)	4	0	1	0	2	5	2

PR=partial response, SD=stable disease, PD=progressive disease.

4540 **Poster Session**

Efficacy of second line (2L) treatment with tivozanib (Tivo) as monotherapy or with nivolumab (Nivo) in patients (pts) with metastatic renal cell carcinoma (mRCC) previously treated with an immune checkpoint inhibitor (ICI) combination of ipilimumab (Ipi)/Nivo or vascular endothelial growth factor receptor-tyrosine kinase inhibitor (VEGFR-TKI)/ICI in the phase 3 TiNivo-2 study. First Author: Alex Chehrazi-Raffle, City of Hope Comprehensive Cancer Center, Duarte, CA

Background: In TiNivo-2, the addition of Nivo to Tivo did not prolong progression-free survival (PFS) relative to Tivo alone (Choueiri, Lancet 2024). To assess study outcomes in the context of contemporary treatment sequencing, a subset of pts treated in the 2L who failed 1L Ipi/Nivo or VEGFR-TKI/ICI therapy was evaluated. **Methods:** Pts were randomized 1:1 to receive Tivo once daily for 21/28 days at either 1.34mg alone or at 0.89 mg with Nivo at 480 mg by IV on day 1 of each 28-day cycle. We characterized PFS, objective response rate (ORR), and best percentage change from baseline in tumor size in two cohorts consisting of pts who did not previously receive adjuvant therapy and who progressed in 1L on Ipi/Nivo, or VEGFR-TKI/ICI therapy. **Results:** Among the 153 eligible 2L pts, 70 (46%) previously received Ipi/Nivo and 83 (54%) previously received a VEGFR-TKI/ICI regimen (TKI/ICI): axitinib/pembrolizumab (54.2%), cabozantinib/nivolumab (25.3%), axitinib/avelumab (12.0%), and lenvatinib/pembrolizumab (8.4%). Overall, the median follow-up was 11.6 months. More pts with lung metastasis and age <65 years were in the Tivo arm than in the Tivo+Nivo arm in both cohorts. In the Ipi/Nivo cohort, median PFS was 9.2 months (95% CI, 4.5-NR) with Tivo and 9.3 months (95% CI, 7.3-15.3) with Tivo+Nivo. ORR was 32.4% (95% CI, 18.0%-49.8%) with Tivo and 24.2% (95% CI, 11.1%-42.6%) with Tivo+Nivo. In the TKI/ICI cohort, median PFS was 7.4 months (95% CI, 3.7-9.3) with Tivo and 3.9 months (95% CI, 2.1-5.7) with Tivo+Nivo. ORR was 22.0% (95% CI, 10.6%-37.6%) with Tivo and 9.5% (95% CI, 2.7%-22.6%) with Tivo+Nivo. Target tumor size reduction from baseline was observed in both arms (Table). More pts had target tumor reductions (≥30% or ≥50%) in the Tivo arm than in the Tivo+Nivo arm in both cohorts. Of 7 pts with target tumor reduction of ≥50% from Tivo, 6 (85.7%) and 1 (14.3%) were previously treated with axitinib and cabozantinib, respectively. **Conclusions:** In this TiNivo-2 subgroup analysis, Tivo monotherapy at 1.34 mg daily showed activity in pts who previously received a contemporary 1L mRCC regimen. At this dose of Tivo, substantial tumor size reduction was observed, both after Ipi/Nivo and VEGFR-TKI/ICI regimens. There appeared to be no benefit with the addition of Nivo to Tivo in this context, akin to the results of the parent trial. Clinical trial information: NCT04987203. Research Sponsor: AVEO Oncology.

Best percentage change in target tumor size.

		Best % Change from Baseline	
	Prior Treatment	≥30% Reduction	≥50% Reduction
Tivo	**TKI/ICI**	30.5%	19.4%
	Ipi/Nivo	44.4%	27.8%
Tivo+ Nivo	**TKI/ICI**	17.5%	2.5%
	Ipi/Nivo	33.3%	12.1%

4541 **Poster Session**

Neoadjuvant lenvatinib plus pembrolizumab for resectable clear-cell renal cell carcinoma (PELUR): A prospective phase 2 study. First Author: Shimiao Zhu Sr., Tianjin Institute of Urology, the Second Hospital of Tianjin Medical University, Tianjin, China

Background: Lenvatinib plus pembrolizumab prolongs overall survival (OS) and progression-free survival (PFS) in advanced clear-cell renal cell carcinoma (ccRCC), with significantly improved objective response rate (ORR) and survival time compared with other competitors. However, more than 80% ≥Grade 3 adverse events (AEs) were emerged during treatment. The efficacy and safety of neoadjuvant low-dose lenvatinib plus pembrolizumab (ldLP) in ccRCC at high-risk of progression has not been assessed. **Methods:** This was an open-label phase 2 clinical trial including patients with resectable high-risk ccRCC who received neoadjuvant ldLP every 21 days for 3 cycles. Tumor responses and safety were both primary end points. The secondary end points were PFS, patient-reported quality-of-life and immune biomarkers. RNA and DNA were isolated from pretreatment tumor tissue was subjected to RNA and next-generation sequencings. Single-cell RNA sequencing (scRNA-seq) was performed in both pretreatment and posttreatment specimens from 6 patients. **Results:** A total of 33 patients were enrolled, 23 received neoadjuvant therapy followed by nephrectomy were included in the intention-to-treat (ITT) analysis. All patients received neoadjuvant therapy follow the dose of protocol. There was only one grade 3 AE (hypertension) emerged during neoadjuvant therapy. The most common AEs of neoadjuvant treatment were hypertension, fatigue, rash and pruritus (n = 5, 21.7%). During adjuvant stage, three grade 3 AEs were reported, including one case of rash, ALT/AST increase and acute kidney injury. The most common AEs during adjuvant were rash, fatigue and pruritus (n = 6, 26.1%). The EORTC QLQ-C30 questionnaires showed significant improvements in all emotional function and symptom of appetite loss. Total score of FKSI-DRS was also significantly improved. Tumor and thrombus regression occurred in all patients after neoadjuvant therapy, with 11/23 (47.8%) of them got partial response. After a median follow-up of 22 months (15-35 months), five patients experienced disease progression and 2 patients had ccRCC-related died. We characterized ~11500 single cells from 6 patients (12 samples), which were categorized into partial response (PR; n = 3) and stable disease (SD; n = 3). Our analysis revealed that the ARPP21^{+}/IGLL1^{+} B cell subcluster (AI^{+} B cells) demonstrated the most substantial cellular perturbation within SD group. Furthermore, we observed AI^{+} B cells experienced a significant reduction in PR group following treatment. The AI^{+} B cells were predicted to interact with DCs to contribute to a poor therapy response. **Conclusions:** Our data preliminarily demonstrated safety and efficacy of neoadjuvant ldLP in ccRCC at high-risk of progression. Results also highlight the importance of AI^{+} B cells in effective responses to ldLP and suggests potential strategies to overcome immunotherapy resistance. Clinical trial information: NCT05485896. Research Sponsor: National Natural Science Foundation of China (82172759); Tianjin Education Commission Research Program Project (2024ZD026 & 2024KJ193); Tianjin Municipal Health Science and Technology Project (TJWJ2024ZD002).

4542 **Poster Session**

Clear and non-clear cell renal cell carcinomas and the ability to engage in oxidative phosphorylation. First Author: Ziad Bakouny, Memorial Sloan Kettering Cancer Center, New York, NY

Background: The impairment of oxidative phosphorylation (OxPhos) and upregulation of aerobic glycolysis, mediated by the loss of *VHL*, are key features of clear cell renal cell carcinoma (ccRCC). In contrast, non-clear cell renal cell carcinoma (RCC) denotes a heterogeneous group of tumors with few known nuclear oncogenic drivers. Recent studies have shown that mitochondrially-encoded electron transport chain (ETC) genes, responsible for OxPhos, can be mutated in a range of cancers. **Methods:** Mitochondrial mutations were called using a previously published custom pipeline for variant calling (PMID: 33833465). On-target (whole genome sequencing) and off-target (whole exome and gene panel-based sequencing) reads were used. Only samples with sufficient coverage (> = 5 reads across > 90% of the mitochondrial genome) were included. This was performed (N with sufficient coverage) in TCGA (N = 3,265; N = 324 RCC), the institutional MSK-IMPACT cohort (N = 22,252; N = 568 RCC), and CCLE/Depmap (N = 377; N = 11 RCC). Mutual exclusivity between each established RCC nuclear driver gene (N = 16, PMID: 29617669) and the heteroplasmy of ETC truncating variants was evaluated using pairwise t-tests comparing heteroplasmy between the mutated and wild-type RCC samples for each nuclear driver gene. CERES scores from genome-wide CRISPR screens in Depmap were used to compare gene dependency between cell lines. Benjamini-Hochberg correction was used to control type I error. **Results:** Across all cancer types in TCGA, RCC tumors were among the most enriched in ETC truncating mutations. These mutations most frequently affected components of mitochondrial complex I and were enriched to high levels of heteroplasmy. *VHL*-driven ccRCC was relatively depleted in these mutations compared to other subtypes (ccRCC: 8.6%, chRCC: 20.0%, pRCC: 34.0%). Further, the heteroplasmy of truncating mutations was significantly increased in chRCC and pRCC compared to ccRCC ($p < 0.05$). Among all established RCC nuclear driver genes, *VHL* was found to be mutually exclusive with high heteroplasmy ETC truncating mutations ($q < 0.05$). These results were independently replicated in the MSK-IMPACT cohort. Using data from CCLE/Depmap, we find that while cell lines with high heteroplasmy (> 50%; N = 13) truncating mitochondrially-encoded ETC mutations have differential dependencies compared to other cell lines, ETC mutations were not synthetically lethal with *VHL* mutations. Further, knockout of nuclear ETC components of complex I in Depmap was associated with little to no effect on cell survival. **Conclusions:** We established that mutations in *VHL* and in mitochondrially-encoded ETC genes are mutually exclusive in RCC and that this mutual exclusivity is not accounted for by synthetic lethality. These results suggest that mitochondrial mutations may be phenocopying the effect of *VHL* on OxPhos. Research Sponsor: National Cancer Institute; T32CA009512-35; National Cancer Institute; P30-CA008748.

4543 **Poster Session**

HIF family transcription factor expression in a cohort of 4362 patients with renal cell carcinoma (RCC). First Author: Yu-Wei Chen, Moores Cancer Center at UC San Diego Health, San Diego, CA

Background: The HIF pathway drives RCC pathogenesis operating through transcription factors (TFs) that function as heterodimers of the oxygen-sensitive α (HIF1α or HIF2α) and constitutively expressed β subunits (HIF1β or HIF2β). Loss of VHL leads to HIFα stabilization, nuclear translocation, and formation of transcriptional complexes with β subunits. We aimed to characterize the molecular and clinical features associated of HIF TF mRNA expression in RCC. **Methods:** NextGen sequencing of DNA (592-gene/whole exome) and RNA (whole transcriptome) was performed on RCC specimens (n = 4362) at Caris Life Sciences. HIF-High/Low expression was defined as $> 75^{th}$ / $< 25^{th}$ quartile RNA transcripts per million (TPM). Overall survival (OS) was defined as the time of diagnosis to death/last follow-up. Time on treatment (TOT) was defined as the time from treatment start to discontinuation. **Results:** The majority of patients were male (71%), of white race (61%), with median age of 64 years. HIF2α was lower in tumors from Black vs White patients (102.3 vs 157.5 TPM, $p < 0.0001$) and higher in tumors from Hispanic vs non-Hispanic White patients (146.1 vs 195.4 TPM, $p < 0.01$). Compared to kidney primary (n = 1,784, 43.9%, 172.1 TPM), HIF2α expression was lower in lymph nodes (n = 319, 7.9%, 97.6 TPM, $p < 0.01$) but similar to distant metastatic sites (n = 1,959, 48.2%, 168.3 TPM). Compared to clear cell RCC (n = 1198, 29.5%, 224.3 TPM), HIF2α expression was lower in papillary (n = 238, 5.9%, 57.5 TPM), chromophobe (n = 83, 2.0%, 91.7 TPM), and medullary RCC (n = 15, 0.36%, 46.5 TPM) ($p < 0.01$ each). Sarcomatoid RCC (n = 119, 2.9%) had lower HIF2α (111.9 vs. 155.0 TPM, $p < 0.05$), lower HIF2β (5.6 vs 8.5 TPM, $p < 0.01$), and higher HIF1α (276.3 vs 197.4 TPM, $p < 0.01$) compared to non-sarcomatoid RCC (n = 3947, 97.2%). Compared to *VHL* wild-type (n = 1415, 34.9%), *VHL*-mutated tumors (n = 1884, 46.4%) had higher HIF2α (206.6 vs 97.7 TPM), lower HIF1α (184.9 vs 233.9 TPM), lower HIF2β (7.2 vs 10.2 TPM) ($p < 0.01$ each). Tumors with high HIF2α were enriched for *VHL*, *PBRM1*, *MTOR*, and *PTEN* alterations and had fewer *TP53*, *BAP1*, *MET*, *SMARCB1*, and *NF2* alterations. HIF1α-high tumors had fewer *VHL*, *TSC1*, and *BAP1 alterations*. HIF1β -high tumors had decreased *TP53* and *RB1* and increased *CHEK2* and *PALB2* alterations. High HIF2α and HIF2β was associated with improved OS (92.6 vs 68.1 months, $p < 0.001$ and 87.4 vs 69.8 months, $p < 0.004$, respectively), while HIF1α and HIF1β did not correlate with OS. Patients with high HIF2α had prolonged cabozantinib TOT (8.1 vs 3.9 months, $p < 0.001$). **Conclusions:** This comprehensive analysis revealed distinct HIF TF expression patterns across RCC subgroups. Notably, elevated HIF2α expression was observed in clear cell RCC, VHL-mutated tumors, and was linked to improved OS and prolonged TOT with cabozantinib, suggesting a potential prognostic role for HIF2α in RCC, warranting further clinical investigation. Research Sponsor: None.

4544 **Poster Session**

Baseline radiological tumor burden to sub-stratify IMDC risk groups in metastatic renal cell carcinoma treated with first-line therapy: A post hoc analysis from a randomized phase III trial. First Author: Rashad Nawfal, Dana-Farber Cancer Institute, Boston, MA

Background: Baseline radiological tumor burden (BRTB) is a measurement derived from routine CT scans and reflects baseline tumor burden. Herein we assess the utility of BRTB to help with risk assessment within IMDC risk subgroups from a randomized prospective phase III study. **Methods:** We reviewed data of 701 patients with metastatic renal cell carcinoma (mRCC) from the CheckMate 9ER trial (Choueiri, NEJM 2021). Patients with BRTB measurement per investigator using RECIST v1.1 at baseline were included. Outcomes of interest included overall survival (OS), and progression-free survival (PFS). To evaluate the impact of BRTB on OS and PFS, we used univariate and multivariable Cox regression models for each IMDC subgroup accounting for age, sex, race, stage at diagnosis, sarcomatoid features and regimen type (IO+VEGFi, VEGFi). **Results:** Favorable, intermediate and poor risk IMDC subgroups included 157/701, 392/701 and 132/701 patients, respectively. This cohort included 63, 187 and 94 OS events and 112, 290 and 103 PFS events in favorable, intermediate and poor risk groups, respectively. For the favorable risk group, BRTB was not associated with OS or PFS on multivariable analysis ($HR_{adjusted}$= 1.00, 95%CI: 0.99-1.01, p = 0.68 and $HR_{adjusted}$= 1.00, 95%CI: 0.99 – 1.00, p = 0.99, respectively). Similarly for the poor risk group, BRTB was not associated with OS or PFS on multivariable analysis ($HR_{adjusted}$= 1.03, 95%CI: 0.99-1.06, p = 0.06 and $HR_{adjusted}$= 1.02, 95%CI: 0.98 – 1.04, p = 0.54, respectively). However, in the intermediate risk group, higher BRTB was associated with worse OS (HR: 1.05 for each 1 cm increase in BRTB, 95%CI: 1.04-1.07, $p < 0.0001$) and PFS (HR: 1.03, 95%CI: 1.01-1.05, $p < 0.001$). On multivariable analysis, BRTB remained associated with both OS and PFS ($HR_{adjusted}$= 1.05, 95%CI: 1.04-1.07, $p < 0.0001$ and $HR_{adjusted}$= 1.03, 95%CI: 1.02 – 1.05, $p < 0.0001$, respectively). Further, we stratified IMDC intermediate risk group outcomes according to BRTB median value of 6.33cm (Table). **Conclusions:** While BRTB does not appear to predict outcomes in favorable and poor-risk subgroups in this study, BRTB is a useful metric for sub-stratification of the intermediate-risk IMDC subgroup. External validation is imperative to validate these findings and explore BRTB integration into clinical decision-making in mRCC. Research Sponsor: None.

Stratification of the intermediate IMDC risk group according to baseline radiological tumor burden median (6.33cm).

	Intermediate low BRTB (n=196)	Intermediate high BRTB (n=196)	Log rank p value
Median OS, months (95% CI)	NR (49.5 – NR)	30.9 (24.4 – 40)	$p < 0.0001$
Median PFS, months (95% CI)	15.84 (11.83 – 18.3)	8.41 (6.97 – 11.1)	$p < 0.001$

4545 Poster Session

Efficacy of subsequent treatment after combination therapy in non-clear cell renal cell carcinoma (nccRCC). First Author: Paulo Siqueira do Amaral, Vandebilt University Medical Center, Nashville, TN

Background: The treatment landscape of front-line nccRCC has evolved with recent trials demonstrating the efficacy of combination systemic therapy. However, the efficacy of treatment after combination therapy is unknown. This study evaluates the efficacy of VEGF-based regimens in nccRCC patients (pts) previously treated with combination regimens. **Methods:** ORACLE is a real-world, multi-center, retrospective database that includes nccRCC patients that received combination systemic therapies (IO+IO, IO+VEGF and VEGF+ mTOR) in any line. Subsequent treatments were categorized as VEGF only regimens (cabozantinib vs other VEGF), IO+ VEGF and VEGF+ mTOR. The primary endpoint was objective response rate (ORR) assessed by investigator review using RECIST 1.1. Secondary endpoints included disease control rate (DCR), defined as the proportion of patients achieving complete or partial responses or stable disease, time to treatment progression (TTP), calculated from the date of VEGF-based initiation to progression or last follow-up using the Kaplan-Meier method. Differences between groups were estimated with the log-rank test, and categorical outcomes were compared with the chi-square test. **Results:** 105 pts who received VEGF – based regimens after combination therapy were included in the analysis. Baseline characteristics: median age: 59years, 71 % male, 58% white, 25% black, 87% ECOG 0-2. IMDC-risk categories included:21% favorable, 59% intermediate and 20% poor risk. Histology included papillary (40%), unclassified (32%), chromophobe (16%) and other rare subtypes (12%). Prior combination therapies included IO+IO: 62%, IO+ VEGF: 34% and VEGF+ mTORi:4%. 70% pts received combination therapy in the first line setting while the remainder received combination therapy in a second or later line. Outcomes with subsequent treatments are described in Table1. IMDC risk score correlated with TTP. **Conclusions:** Modest antitumor activity was observed with VEGF- based approaches in combination therapy refractory nccRCC. Optimal management of nccRCC remains an unmet need. Research Sponsor: None.

Outcomes of nccRCC patients by treatment and histologic type.

Outcomes per Treatment	n	ORR (%)	DCR (%)	mTTP (mo.)
Cabozantinib	56	18	47	3.6
VEGF/mTOR	19	16	42	9.3
IO+VEGF	17	29	47	5.6
Other VEGF	13	15	46	5.5
Outcomes per Histology				
Papillary	42	19	43	6.5
Unclassified	33	21	42	6.1
Chromophobe	17	29	59	8.9
Other *	13	0	46	NR

4546 Poster Session

Integrative clinical, genomic, and transcriptomic characterization of circulating KIM-1 in metastatic RCC. First Author: Marc Machaalani, Dana-Farber Cancer Institute, Boston, MA

Background: Kidney injury molecule-1 (KIM-1) is a transmembrane protein that is overexpressed in renal cell carcinoma (RCC) and correlated with clinical outcomes in localized and metastatic disease. Nevertheless, association between circulating KIM-1 protein levels and the underlying tumor biology represented by genomic and transcriptomic correlates is not well understood. **Methods:** KIM-1 was measured in plasma at baseline (C1D1) and at C3D1 using an MSD electrochemiluminescence-based assay. Differential gene expression (DGE) and gene set enrichment analysis (GSEA) were performed using DESeq2, with KIM-1 treated as a continuous variable. Associations between circulating KIM-1 levels and clinical, genomic, and transcriptomic tissue data from the JAVELIN Renal 101 trial were evaluated using the Wilcoxon rank-sum test (for categorical groups) and Cox regression (for time-to-event outcomes). **Results:** Plasma for analysis was available from 612 patients (69% of the ITT population), including 323 treated with avelumab plus axitinib and 289 with sunitinib. Elevated baseline KIM-1 levels were correlated with higher tumor burden as assessed by the sum of tumor diameters (Spearman's $\rho = 0.55$, $p < 0.0001$), decreased with tumor shrinkage ($p < 0.0001$), and were associated with poorer PFS (HR 1.32 per unit increase in log KIM-1, 95% confidence interval (CI) 1.16–1.49, $p < 0.0001$) and OS (HR 1.96 per unit increase in log KIM-1, 95% CI 1.61–2.37, $p < 0.0001$). Higher KIM-1 levels were found in IMDC poor–risk versus intermediate–risk ($p < 0.0001$) and in intermediate–risk versus favorable–risk groups ($p < 0.001$). Loss-of-function (LOF) *BAP1* mutations, associated with more aggressive disease, were associated with higher KIM-1 RNA expression ($p < 0.0001$) and protein expression ($p = 0.038$) and remained significant after adjustment for tumor burden as assessed by linear regression residuals. Transcriptomic analysis showed that RNA expression levels of *HAVCR1*, the gene coding KIM-1, were associated with circulating KIM-1 protein (Spearman's $\rho = 0.31$, $p < 0.0001$), and that higher KIM-1 levels were associated with interferon gamma response whereas lower KIM-1 levels were associated with a hypoxia transcriptional program. Higher circulating KIM-1 was also associated with enrichment for proliferative versus angiogenic gene expression signatures ($p = 0.013$). The findings were independent of therapy arms. **Conclusions:** We present the first integrative clinical, transcriptomic, and genomic evaluation of circulating KIM-1. High KIM-1 is a biomarker of poor prognosis in RCC and correlates with specific LOF mutations and transcriptions programs. Prospective studies are needed for the clinical implementation of KIM-1 as a biomarker in RCC. Research Sponsor: U.S. National Institutes of Health; CA258442; Dana-Farber/Harvard Cancer Center Kidney SPORE; 2P50CA101942-16.

4547 Poster Session

KEAP1 mutated renal cell carcinoma (RCC): Characterization of an emerging molecularly defined RCC subtype. First Author: Marie Carlo, Genitourinary Oncology, Memorial Sloan Kettering Cancer Center; Weill Cornell Medical College, New York, NY

Background: KEAP1 is a tumor suppressor and negative regulator of the NRF2 pathway, and inactivating *KEAP1* mutations (mts) have been reported in patients (pts) with RCC with similar morphology to fumarate hydratase (FH)-deficient RCC (FH-RCC). In FH-RCCs, the NRF2 pathway is activated through fumarate-led inactivation of KEAP1, and we hypothesized that *KEAP1* mts are drivers in RCC, similar to FH mts in FH-RCC. We sought to characterize RCC with *KEAP1* mts as a separate RCC subtype and compare to FH-RCC and clear cell (cc)RCC. **Methods:** Among consecutive pts with RCC consented to tumor-normal DNA sequencing via MSK-IMPACT (NCT01775072), we identified patients with germline or somatic mutations in *KEAP1* or *FH* and no other known driver mts (ie *VHL, MET, TFE3* alterations), and categorized these as "KEAP1-RCC" or "FH-RCC." Clinicopathologic characteristics and outcomes were analyzed and compared to pts with FH-RCC and a previously annotated subset ccRCC (n=162). Immunohistochemical (IHC) staining for NQO1, marker of NRF2 activation, was performed. Time on systemic treatment and overall survival (OS) from time of sequencing were assessed. **Results:** Among 928 pts with RCC, 13 (1.4%) and 26 (2.8%) had RCCs with *KEAP1* and *FH* mts, respectively. *KEAP1* and *FH* mts were mutually exclusive. Median age was younger in FH-RCC (47 vs 63) (Table). When compared to ccRCC, OS was significantly worse for FH-RCC (HR 2.4, 95% CI 1.4-4.1; p=0.02) but not for KEAP1-RCC (HR 1.07, 95% CI 0.29-3.0; p=0.89). All KEAP1-RCC and FH-RCC were histologically classified as non-cc except one KEAP1-RCC that had 3p loss and no VHL mt. All available KEAP1 and FH-RCC were NQO1+ on IHC; control ccRCC were all negative. In the KEAP1-RCC cohort, we identified a female with an unclassified RCC and a germline *KEAP1* truncating variant; RCC tumor had a second *KEAP1* somatic mutation and was NQO1+ on IHC. The germline variant cosegregated to a sister with lung cancer (IHC NQO1+) and anal cancer. **Conclusions:** RCC with KEAP1 mts and no other genomic drivers are primarily non-cc with papillary features, have functional evidence of NRF2 activation, and although high-grade may have better outcomes than FH-RCC. KEAP1-RCC appears to be an emerging molecularly defined RCC subtype with clinical behavior similar to FH-RCC, likely as a result of converging on NRF2 pathway activation. Research Sponsor: National Cancer Institute; Mazumdar-Shaw Translational Research Initiative in Kidney Cancer; Robert and Kate Niehaus Center for Inherited Cancer Genomics.

Clinical characteristics.

	KEAP1-RCC (n=13)	FH-RCC (n=26)	ccRCC (n=162)
Age (range)	63 (26-71)	47 (20-74)	56 (24-78)
Male	8 (62%)	17 (65%)	125 (77%)
Tumor size (cm), median (IQR)	5.6 (5.1, 11.0)	8.0 (5.0, 14.0)	8.2 (6.0, 10.5)
Histology			
FH-deficient	0	13 (50%)	0
Papillary features	8 (62%)	4 (15%)	0
Unclassified	1 (8%)	8 (31%)	0
ccRCC	1 (8%)	0	162 (100%)
Other/Unknown	3 (23%)	1 (4%)	0
Tumor grade, high	13 (100%)	26 (100%)	134 (83%)
Metastatic	9 (69%)	25 (96%)	150 (93%)

4548 Poster Session

Second-line outcomes in metastatic renal cell carcinoma: The role of International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) prognostic factors after first-line immunotherapy. First Author: David Maj, Arthur J.E. Child Comprehensive Cancer Centre, Calgary, AB, Canada

Background: IMDC prognostic factors are well established in metastatic renal cell carcinoma (mRCC) with both VEGFR inhibitor and immunotherapy-based first-line therapies. However, the role of these prognostic factors for the second-line setting is less established in the contemporary era. **Methods:** We performed a retrospective analysis of patients with mRCC who received first-line therapy (1L) with dual immunotherapy (IPI-NIVO) or combination immunotherapy-VEGFR (IOVE) based regimens and then received second-line therapy (2L). 2L IMDC risk factors were assessed at the time of 2L therapy initiation and were composed of Karnofsky Performance Status $< 80\%$, time from diagnosis to 2L therapy start < 1 year, hemoglobin $<$ lower limit of normal, neutrophils $>$ upper limit of normal (ULN), platelets $>$ ULN, corrected calcium $>$ ULN. 2L IMDC risk groups were favorable (0 risk factors), intermediate (1-2 risk factors), or poor risk (3+ risk factors). Baseline characteristics, objective response rates (ORR), treatment duration (TD), and overall survival (OS) were collected and compared by log-rank test. **Results:** A total of 781 patients were identified of whom 66% received IPI-NIVO and 34% received IOVE in the 1L setting. 2L IMDC risk groups and changes from 1L IMDC risk are presented in Table. Amongst all patients who received 2L therapies, 10.6% had favorable risk, 57.8% had intermediate risk, and 31.6% had poor risk disease. Nephrectomy status varied significantly across groups with 99% of favourable risk, 65% of intermediate risk, and 42% of poor risk patients having undergone nephrectomy ($p<0.0001$). Overall, 66.3% of patients retained their 1L risk group, while 12.6% were in a more favorable risk group and 21.1% a less favorable risk group. Type of 1L therapy (IPI-NIVO vs IOVE) did not predict change in 2L IMDC risk group ($p=0.931$). 2L therapies were heterogeneous with 38.9% receiving cabozantinib, 22.3% sunitinib, 8.7% pazopanib, 12.7% an IO-based regimen (IO monotherapy, IOIO, IOVE), and 17.4% other therapies. 2L ORR, TD, and OS varied significantly by 2L IMDC risk group (Table). **Conclusions:** In a real-world setting amongst patients receiving 1L IO-based regimens, IMDC risk factors remain prognostic in the 2L setting. These new benchmarks may be used for patient counselling and clinical trial design in 2L. Research Sponsor: None.

Baseline characteristics and outcomes by 2L IMDC risk group.

	2L Favorable N = 83	2L Intermediate N = 451	2L Poor N = 240	P-value
1L IPI-NIVO/IOVE	35/48	306/145	197/50	
1L Favorable, N (%)	**50 (50)**	45 (45)	5 (5)	
1L Intermediate, N (%)	21 (5.2)	**284 (70.6)**	97 (24.1)	
1L Poor, N (%)	2 (1)	65 (33.3)	**128 (65.6)**	
2L ORR, N (%)	26 (38.2)	114 (32.0)	40 (22.9)	<0.0001
2L TD, Mo (95%CI)	9.8 (8.1-18.5)	9.1 (8.1-10.0)	4.2 (3.2-5.4)	<0.0001
2L OS, Mo (95%CI)	41.0 (35.7-NR)	25.9 (20.5-32.1)	9.4 (7.1-10.8)	<0.0001

4549 **Poster Session**

Clinical characteristics and determinants of primary refractory metastatic renal cell carcinoma (mRCC): An International Metastatic Database Consortium (IMDC) study. First Author: Karl Semaan, Dana-Farber Cancer Institute, Boston, MA

Background: Immune checkpoint inhibitor (ICI)-based regimens, including ICI + ICI and ICI+VEGF-targeted therapy (VEGF-TT), represent the current standard of care for first line (1L) in mRCC. A subset of patients (pts) experiences primary refractory disease, defined as progressive disease (PD) as best response. The aim of this study is to investigate the clinical characteristics and determinants of pts with primary refractory mRCC. **Methods:** Pts with mRCC treated with 1L ICI-based regimens from the IMDC were included. Pts were categorized as primary refractory (PD as best response evaluated per RECIST 1.1 criteria) and non-primary refractory (stable disease or partial/complete response as best response). Baseline characteristics were compared using a Chi-Square test. Independent factors associated with primary refractory mRCC were identified using a logistic regression. **Results:** In total, 2001 pts were included, of which 1301 (65%) were treated with dual ICI, and 701 (35%) with ICI+VEGF-TT. Of 2001 pts, 494 (24%) experienced PD at first restaging. Primary refractory and non-primary refractory groups did not differ by age or gender. The primary refractory group had more pts treated with dual ICI (76 vs. 62%), more pts with poor IMDC risk (29 vs. 19%), and more pts with non-clear cell RCC (27 vs. 19%; all $p < 0.001$). The primary refractory group had shorter diagnosis to treatment interval (mean: 1.6 vs. 2.3 years), lower KPS (median: 80 vs. 90), higher rate of anemia (65% vs. 52%), neutrophilia (11% vs. 9%), and thrombocytosis (30 vs 22%; all $p < 0.001$). The primary refractory group had more liver (24 vs. 17%; $p < 0.001$), bone (39 vs 32%; $p < 0.001$) and lymph nodes metastasis (52 vs. 47%; p = 0.03) at the start of 1L therapy. On multivariable analysis, independent factors associated with primary refractory RCC were low KPS, and the presence of liver metastasis or bone metastasis (Table). Dual ICI regimen was associated with a 1.8-fold increase of primary refractory RCC. **Conclusions:** In pts with mRCC, low KPS and the presence of liver or bone metastasis are independent risk factors for the development of primary refractory disease. Primary refractory disease is more commonly observed in pts receiving dual ICI compared to those on ICI+VEGF-TT regimen. Research Sponsor: None.

Multivariable analysis for independent factors associated with primary refractory RCC.

	OR	Lower 95% CI	Upper 95% CI	p-value
Diagnosis to treatment interval < 1 year (yes vs. no)	1.2	0.9	1.6	0.2
Anemia (yes vs. no)	1.37	1.1	1.8	0.03
Low KPS(<80: yes vs. no)	1.9	1.4	2.5	<0.001
Neutrophilia (yes vs. no)	1.3	1	1.8	0.09
Thrombocytosis (yes vs. no)	0.9	0.7	1.3	0.6
Liver metastasis (yes vs. no)	1.7	1.3	2.3	<0.001
Lymph Nodes metastasis (yes vs. no)	1.3	1	1.6	0.07
Bone metastasis (yes vs. no)	1.3	1.03	1.7	0.03
Dual ICI (vs. ICI+VEGF-TT)	1.8	1.37	2.4	<0.001
Non-clear cell RCC (vs. clear cell)	1.3	1	1.8	0.06
Nephrectomy (yes vs. no)	0.9	0.7	1.2	0.6

4550 **Poster Session**

Long-term clinical outcomes with nivolumab/ipilimumab with or without *Clostridium butyricum* MIYAIRI588 in metastatic renal cell carcinoma (mRCC): A randomized phase Ib clinical trial. First Author: Miguel Zugman, City of Hope Comprehensive Cancer Center, Duarte, CA

Background: In two randomized phase I trials, *Clostridium butyricum* MIYAIRI588 (CBM588), a live biotherapeutic, demonstrated preliminary activity in modulating the gut microbiome, enhancing systemic immune responses, and improving clinical outcomes in patients receiving first-line nivolumab/ipilimumab and nivolumab/cabozantinib for mRCC (Dizman *et al.* and Ebrahimi *et al.* Nature Medicine). Herein, we present the long-term follow-up data for nivolumab/ipilimumab with or without CBM588. **Methods:** Newly diagnosed patients with mRCC, clear cell and/or sarcomatoid histology, and International mRCC Database Consortium intermediate/high risk were randomized to receive nivolumab/ipilimumab with or without CBM588 in a 2:1 ratio. Response outcomes were assessed using RECIST 1.1. Clinical outcomes were secondary endpoints. Objective response rate (ORR; complete response [CR] or partial response [PR]), disease control rate (DCR; CR, PR, or stable disease [SD] $>$ 6 months), progression-free survival (PFS), and overall survival (OS) outcomes were compared across arms. **Results:** Twenty-nine patients were included in the final analysis: 19 in the nivolumab/ipilimumab with CBM588 arm and 10 in the nivolumab/ipilimumab arm. The median age was 66.2 years, 72% were male, 83% had IMDC intermediate risk and 93% had clear cell histology. Baseline characteristics were similar across arms. ORR and DCR were 58% and 79% in nivolumab/ipilimumab with CBM588 arm versus 20% and 20% in nivolumab/ipilimumab arm, respectively (p = 0.06 and p = 0.004). At a median follow-up of 60.0 (95% CI 51.9-68.1) months, the median PFS was 38.2 (95% CI 23.6-52.8) months in the nivolumab/ipilimumab and CBM588 arm versus 19.3 (95% CI 0-41.9) months in the nivolumab/ipilimumab arm (Hazard ratio [HR] 0.24, 95% CI 0.09-0.61 p = 0.003). At the time of data cutoff, 9 (47.4%) and two (20%) patients were alive in the nivolumab/ipilimumab with CBM588 and nivolumab/ipilimumab arms, respectively. The median OS with nivolumab/ipilimumab with CBM588 was 55.0 (95% CI 10.5-75.5) months versus 39.0 (95% CI 23.7-54.3) months with nivolumab/ipilimumab (HR 0.438 [95% CI 0.17-1.1] p = 0.09). **Conclusions:** Although limited by the sample size, the combination of nivolumab/ipilimumab with CBM588 demonstrated superior clinical activity over nivolumab/ipilimumab in our cohort. Additionally, ORR, PFS and OS with nivo/ipi/CBM588 exceeded those observed with nivolumab and ipilimumab in historical datasets (Motzer *et al.* NEJM). Larger efforts investigating the impact of CBM588 on clinical outcomes are underway. Clinical trial information: NCT03829111. Research Sponsor: None.

4551 **Poster Session**

Vasculogenic mimicry as a potential indicator of drug resistance and prognosis in renal cell carcinoma. First Author: Xingang Cui, Department of Urology, Xinhua Hospital, School of Medicine, Shanghai Jiao Tong University, Shanghai, China

Background: Patients with advanced metastatic renal cell carcinoma (RCC) often develop resistance to tyrosine kinase inhibitors (TKIs). Vasculogenic mimicry (VM) refers to the formation of tubular structures by tumor cells mimicking endothelial cells. VM formation is independent of VEGF and endothelial cells, making it inherently resistant to TKIs. Furthermore, hypoxic conditions induced by TKI treatment can promote VM formation, creating a vicious cycle. This study investigates the molecular mechanisms of VM formation and its prognostic significance in RCC. **Methods:** VM incidence in RCC was assessed using PAS/CD31 staining on tissue microarrays. Single-cell sequencing data were used to identify tumor cells undergoing VM differentiation. Cluster analysis was conducted to characterize these cells, and their prognostic value was validated using TCGA data. Pseudotime trajectory analysis and SCENIC algorithms were used to infer their differentiation pathways and identify transcription factors (TFs) regulating VM formation. Tube formation assays were performed for validation. **Results:** PAS/CD31 double staining revealed a VM incidence of 15.87% (10/63) among RCC patients. Notably, VM formation was more frequent in recurrent and TKI-resistant patients, suggesting that VM may serve as a mechanism for TKI resistance. Single-cell data from 11 patients with stages T1a-T3 RCC were analyzed, identifying VM-differentiating tumor cells, termed RCC-VM. GSVA revealed that RCC-VM cells were highly enriched in angiogenesis and EMT-related pathways. GO and KEGG analyses also showed enrichment in angiogenesis pathways. Trajectory analysis of tumor cell subpopulations placed RCC-VM at the terminal differentiation state, suggesting it represents a uniquely differentiated tumor cell type. Using SCENIC, we identified FOSL2 as a key TF regulating RCC-VM differentiation. Knockdown of FOSL2 significantly impaired tube formation in 786-O cells in vitro. Additionally, we identified RCC-VM-specific signature genes (VMDEG) and used Lasso-Cox regression to select four key risk factors (PIM1, MT1G, MT-ND4, DDIT3) to construct a survival risk model. Kaplan-Meier survival analysis demonstrated that patients in the high-risk group had significantly shorter survival times compared to the low-risk group (p = 0.0013). The time-dependent ROC curve showed that the model had robust predictive ability, providing potential guidance for personalized treatment of RCC patients. **Conclusions:** Our study highlights VM as a critical mechanism of TKI resistance in RCC, regulated by the transcription factor FOSL2. VMDEG serves as a valuable prognostic marker for RCC patients. Incorporating VM into staging systems such as pT staging and Fuhrman grading may improve risk stratification and treatment planning for RCC patients. Research Sponsor: None.

4552 **Poster Session**

Differences in patient characteristics, treatment patterns, and clinical outcomes of renal cell carcinoma patients in public vs private health care systems in Brazil: Insights from the LACOG 1120 registry. First Author: Pablo Barrios, Latin American Cooperative Oncology Group (LACOG), Porto Alegre, Brazil

Background: Brazil's dual healthcare system presents unique challenges in addressing disparities in cancer care. Understanding the differences in clinical characteristics, treatment patterns, and clinical outcomes of renal cell carcinoma (RCC) patients (pts) between public and private health systems is crucial for optimizing care. **Methods:** LACOG 1120 Registry collected data from 230 eligible RCC pts across Brazil from Sep. 2022 to Nov. 2023. Patient demographics, tumor characteristics, treatment information, and clinical outcomes were analyzed and stratified by healthcare system (public vs. private). Descriptive statistics and survival analyses were performed using Kaplan-Meier methods. **Results:** 230 pts were included. Median age at diagnosis was 61.0 (52.0–67.0), 65.2% were male, 58.7% white, 26.1% of mixed skin color and 4.3% black. 61.3% were treated in the public system, and 36.5% in the private system. Pts in the public system were more likely to present with advanced disease (stage IV: 25.5% vs. 17.9%) and had a lower proportion of early-stage disease (stage I: 20.6% vs. 33.3%) compared to the private system. Out of 230, 11 (4.8%) received adjuvant treatment, 3 (2.1%) from the public 8 (9.5%) from the private system. Pts from the public system predominantly received adjuvant sunitinib (66.7%) whereas all the 8 pts from the private systems received adjuvant immune checkpoint inhibitor (ICI) (87.5% pembrolizumab, 12.5% nivolumab). First-line treatment for metastatic RCC was given to 34.0% of public and 53.6% of private system pts. Public pts mainly received sunitinib (47.9%) or pazopanib (31.3%), while private pts predominantly received ICIs (42.2%) or ICI-Tyrosine kinase inhibitors (TKI) combos (26.6%). Treatment discontinuation due to toxicity was higher in the public system (40.9% vs. 36.4%). 20.0% and 31.7% of pts were classified as favorable risk in the public and private systems respectively according to IMDC risk criteria. At median follow-up of 41.7 months (95%CI 27.6 - 48.8), median overall survival (OS) from diagnosis was 79.4 months (95% 66.0 - NR). The 5-year (yr) median OS rate differed between systems, 89.6% (95%CI 70.1-90.6) in private and 42.0% (95%IC 31.1-56.7) in public. When stratified by clinical stage (CS), the 2-yr OS for pts with CS I-III was 87% in the public and 96.8% in the private system. For pts with CS IV, the 2-yr OS was 23.8% in the public compared to 60.0% in the private system. **Conclusions:** Significant disparities exist between RCC pts treated in Brazil's public and private health systems, with public system pts presenting with more advanced disease, with restricted access to novel therapies, and experiencing worse clinical outcomes. These findings underscore the urgent need for health policy reforms to address inequities in cancer care access and treatment in Brazil. Research Sponsor: Funding: Ipsen | Sponsor: Latin American Cooperative Oncology Group (LACOG).

4553 **Poster Session**

Real-world quality of life (QOL) in patients (pts) with metastatic renal cell carcinoma (mRCC) on active surveillance (AS) in the ODYSSEY prospective observational study. First Author: Michael Roger Harrison, Duke Cancer Institute Center for Prostate and Urologic Cancers, Duke University School of Medicine, Durham, NC

Background: AS is a recognized strategy in select pts with mRCC to maximize QOL and delay potential toxicity of systemic therapy (ST); however, only 2 prospective studies of AS in mRCC have been published: only 1 with patient-reported outcomes (PRO) and none in the IO-TKI era. **Methods:** ODYSSEY is a prospective observational study of 500 US pts with mRCC. Eligible pts must have mRCC (any histology), no prior ST, age ≥19. Pts were excluded if treated for non-mRCC cancers or if not followed at a PCORnet study site. Pts completed QOL surveys at baseline, by phone every 3 months for 2 years and then every 6 months until end of follow up. The primary objective is to determine patterns of change in QOL and symptom burden of pts with mRCC. Minimally important differences (MID) are 3 points for FKSI-19 total score, 1 point for the FKSI-Disease Related Symptoms (DRS) subscale and 7 points for FACT-G. Here we report baseline pt characteristics in AS pts compared to ST pts, and baseline QOL differences between these cohorts. **Results:** As of 1/6/25, 392 pts were enrolled of whom 299 were managed with ST, and 93 pts deferred ST; of these, 53 pts (57%) were classified as AS. Pts on AS are median age 68 yrs, 66% male, 94% white, 81% clear cell, 50% favorable risk, 44% intermediate risk. Compared with ST pts, AS pts were more likely to have undergone nephrectomy (91% vs 53%), favorable risk profile (50% vs 15%), pancreatic metastasis (15% vs 5%), and longer time since RCC diagnosis (median 58 vs 3.3 months); and less likely to have bone, brain, or liver metastasis. After median 8.8 months follow-up (IQR 2.9, 16.2), 2 pts (4%) on AS had died compared with 45 pts (15%) on ST. One pt (2%) on AS started first-line therapy and 45 pts (15%) discontinued ST. Mean baseline QOL (FKSI-19 total, DRS and FACT-G) for AS and ST ODYSSEY pts is shown in the Table (higher score indicates better QOL), with RCT data for reference (NA, not assessed). ODYSSEY pts on AS had higher QOL for all measures compared with ODYSSEY pts on ST. FSKI-DRS was the same or lower for pts on AS compared to the pivotal trials, while ODYSSEY pts on ST had both lower FKSI-19 total and DRS. **Conclusions:** In our large prospective cohort from ODYSSEY, pts on AS had higher median QOL scores than pts on ST, but similar to those included in RCTs. These results suggest that some RCT pts could have benefitted from AS. Further follow up is needed to determine long term outcomes in pts on AS and how they respond to deferred ST. Clinical trial information: NCT04919122. Research Sponsor: Bristol Myers Squibb; Exelixis; Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc.; Pfizer.

Instrument, Mean (SD)	ODYSSEY AS (N=53)	ODYSSEY ST (N=299)	ODYSSEY Difference, AS vs ST (95% CI)	CheckMate 214 (N=425)	KEYNOTE 426 (N=402)	CheckMate 9ER (N=323)	CLEAR (N=351)
FKSI-19 total	63.4 (9.2)	56.3 (12.5)	7.0 (4.0, 10.1)	60.1 (9.8)	NA	58.7 (10.6)	NA
FKSI-DRS	30.8 (4.2)	27.9 (6.0)	2.9 (1.5, 4.7)	30.7 (4.5)	32 (4.2)	30.2 (5.2)	31.3 (4.4)
FACT-G	87.9 (14.0)	82.4 (16.7)	5.6 (1.1, 10.0)	82.6 (15.0)	NA	NA	NA

4554 **Poster Session**

Machine learning–derived B-cell epitopes classifiers for early detection of renal cell carcinoma. First Author: Thomas Campbell, Serimmune, Inc., Goleta, CA

Background: Renal cell carcinoma (RCC) remains a significant cause of cancer mortality in the United States, with poor outcomes for advanced-stage disease and limited tools for early detection. Tumor-specific antibodies, known to develop early in other solid tumors, offer biomarker opportunities for early RCC detection. This study aimed to leverage Serum Epitope Repertoire Analysis (SERA), an advanced platform for profiling B cell epitopes, to develop a machine learning-based classifier capable of distinguishing patients with RCC from those with benign renal masses and from individuals without known renal neoplasms. **Methods:** We obtained 564 serum or plasma samples from 1) 260 patients with pathologically confirmed RCC, spanning all stages; 2) 21 patients with benign renal masses (predominantly oncocytoma and angiomyolipoma); and 3) 283 age-matched non-RCC controls (self-reported healthy donors). The SERA platform uses a library of 8 billion unique 12-mer peptides, each expressed on a DNA-barcoded *E. coli* strain. Number and type of peptides bound by an antibody are identified by next-generation sequencing, enabling comprehensive profiling of B cell epitopes. Using machine learning, a classifier was trained on a subset of 178 samples (88 RCC and 90 healthy controls) to predict the presence of RCC in the validation cohort of 386 samples (172 RCC, 21 benign renal masses, and 193 healthy controls). The area under the receiver operating characteristic curve (AUC) served to evaluate the classifier's performance, overall and stratified by RCC stage. **Results:** Using the SERA platform, 26.4 million potential amino acid motifs were scored based on enrichment in RCC versus controls, yielding 7,244 motifs that met the predefined thresholds for inclusion in the classifier. These features were used to train a 10,000-tree random classification forest. In validation, the model achieved an AUC of 0.76 (95% confidence interval [CI]: 0.72 - 0.81), and scores were not significantly different (Mann-Whitney U test, alpha = 0.05) in the benign renal lesion control samples vs. healthy controls. Performance was consistent across both early- and late-stage RCC, with an AUC of 0.78 (95% CI: 0.70–0.85) for stage 1, 0.72 (95% CI: 0.49–0.95) for stage 2, 0.81 (95% CI: 0.70–0.92) for stage 3, and 0.75 (95% CI: 0.68–0.81) for stage 4 RCC, each compared to controls, demonstrating robust detection across all disease stages. **Conclusions:** Our findings suggest that a non-invasive SERA-based classifier can distinguish RCC from benign renal masses and healthy controls, with consistent performance across all stages of RCC. The robust detection of early-stage RCC underscores the potential of this approach to enhance early diagnosis of RCC and to guide clinical management while obviating the need for renal mass biopsy. Future studies will focus on refining the classifier and validating its performance in larger, multi-institutional cohorts. Research Sponsor: Department of Defense Kidney Cancer Research Program.

4555 **Poster Session**

Clinical outcomes of patients with primary refractory metastatic renal cell carcinoma receiving second-line (2L) therapies: An International Metastatic Database Consortium (IMDC) study. First Author: Marc Eid, Dana-Farber Cancer Institute, Boston, MA

Background: A subset of patients (pts) with metastatic renal cell carcinoma (mRCC) receiving contemporary first line (1L) immune checkpoint inhibitor (ICI) combinations are considered to be primary refractory. The optimal sequence therapy for this patient population is not well established. Herein, we report practice patterns and clinical outcomes of second line (2L) therapy in pts with primary refractory mRCC. **Methods:** Data from pts with primary refractory mRCC to 1L ICI and who received 2L therapy were collected through the IMDC. Patients with primary refractory RCC were defined as patients who experienced progressive disease (PD) as best response per RECIST 1.1 criteria. Overall survival (OS) and time to treatment failure (TTF) were calculated from initiation of 2L therapy; their distributions were estimated by the Kaplan Meier methodology. **Results:** In total, 494 pts had primary progression on 1L ICI, of which 356 (72%) went on to receive subsequent 2L therapy. The most common regimens in the 2L setting included: cabozantinib (n = 137; 38%); sunitinib (n = 115; 32%), and pazopanib (n = 37; 10%). 22% of patients had IMDC poor risk at initiation of 2L. Median follow-up from 2L initiation was 18.8 months. Median OS was 14.5 months, and the median TTF was 5.4 months for the whole cohort. The median OS was 14.4 months (95% CI 11 – 21.4) for cabozantinib, 10.7 months (95% CI 7 -16.6) for sunitinib, and 15.3 months (95% CI 9 – 46) for pazopanib. The median TTF was 4.5 months (95% CI 3.7 -5.6) for cabozantinib, 3.1 months (95% CI 2.8 – 4.4) for sunitinib, and 2.8 months (95% CI 1.7 – 3.6) for pazopanib. The ORR was 20% for pts receiving cabozantinib, 10% for pts receiving sunitinib, and 16% for patients receiving pazopanib. For pts treated with 2L cabozantinib, 84 (61%) had prior dual ICI and 53 (39%) had prior ICI + VEGF. By contrast, for patients treated with sunitinib or pazopanib, the majority (96% and 95%, respectively) had prior dual ICI as 1L. **Conclusions:** To our knowledge, this is the first initiative to report practice patterns and outcomes of subsequent 2L therapies in patients with primary refractory mRCC to contemporary 1L ICI combinations. Cabozantinib was the most frequently used regimen in this patient population and demonstrated favorable clinical outcomes compared to sunitinib or pazopanib. Biomarker evaluation is needed to explore the mechanism of primary resistance and novel therapeutic strategies for this group. Research Sponsor: None.

Outcomes of patients with primary refractory mRCC receiving 2L therapies.

Treatment Arm	N	Median OS, months (95% CI)	Median TTF, months (95% CI)	ORR, %
2L Cabozantinib (1L dual ICI)	84	15 (11 – 26.2)	4.2 (3.4 – 6.6)	20
2L Cabozantinib (1L ICI + VEGF)	53	13.5 (9.8 – NR)	4.8 (3.6 – 5.9)	20
2L Sunitinib	115	10.7 (7 – 16.6)	3.1 (2.8 - 4.4)	10
2L Pazopanib	37	15.3 (9 – 46)	2.8 (1.7 – 3.6)	16

4556 **Poster Session**

Refining intermediate-risk (IR) stratification in patients (Pts) with metastatic renal cell carcinoma (mRCC) receiving first-line (1L) immunotherapy (IO) within one year of diagnosis (Dx): Findings from the International Metastatic Renal Cell Carcinoma Database Consortium (IMDC). First Author: Razane El Hajj Chehade, Dana-Farber Cancer Institute, Boston, MA

Background: The IMDC risk model is pivotal for predicting clinical outcomes in pts with mRCC, yet variability exists within the IR group. Moreover, therapy initiation within < 1 year post dx, a predominant IMDC risk factor, significantly influences prognosis. Thus, this study evaluates this heterogeneity in IO era, focusing on patients receiving 1L IO within < 1 year post dx. **Methods:** Data from pts with mRCC receiving 1L IO within < 1 year post dx, with IMDC score of 1 or 2, were retrospectively collected from the IMDC. Score 1 pts were defined as those who started treatment < 1 year post dx, while score 2 pts had an additional IMDC risk factor: low hemoglobin (Hb), Karnofsky Performance Status (KPS) < 80, high neutrophil, high calcium (Ca), or high platelet (Plt) count. We assessed overall survival (OS) and time to treatment failure (TTF) using Cox regression, adjusting for age, sex, nephrectomy status, histological type, presence of one or more metastases, and 1L regimen type (IO+IO vs. IO+VEGF). The response was evaluated according to RECIST 1.1 criteria. **Results:** Of the 670 pts initiating 1L IO < 1 year post dx, 331 had an IMDC score of 1, and 339 had a score of 2, subdivided into 5 subgroups as detailed in the table. Pts' median age was 62 years (IQR: 55-69). Median follow-up was 16.6 months. Response rates, 18-month OS, and 6-month TTF rates for each group are shown in the table. Adding the factor of treatment initiation < 1 year post dx, the high neutrophil count has the most significant effect on OS (HR = 4.85, 95% CI: 2.61-9.03, p < 0.001). Also, KPS < 80 significantly affects both OS (HR = 3.93,95%CI = 2.26-6.84), p < 0.001) and TTF (HR = 1.59 95%CI = 1.02-2.61, p = 0.04). Low hemoglobin, as well as high calcium, notably worsen OS without significant impact on TTF. High Plt count shows no significant impact on OS and TTF, possibly due to the low prevalence of this risk factor (15/670). **Conclusions:** Additional risk factors can affect the prognosis of pts with mRCC receiving IO < 1 year post dx. Integrating other biomarkers or radiological features could refine risk stratification, enhancing treatment approaches for IR pts. Research Sponsor: None.

		% response	18-month OS rate	Adj. HR for OS (95% CI)	6-month TTF rate	Adj. HR for TTF (95% CI)
IMDC=1	Ddx to start ttt<1 year (N=331)	46%	85%	REF	65%	REF
IMDC=2	Dx to start ttt<1 year+ Low Hb(N=255)	37%	73%	1.83(1.33-2.5) p=0.002*	56%	1.04 (1.02-2.48) P=0.66
	Dx to start ttt<1 year+ KPS<80 (N=30)	30%	57%	3.93 (2.26-6.84) p<0.001*	50%	1.59(1.02-2.61) P=0.04*
	Dx to start ttt<1 year+ High Neutrophils (N=22)	9.1%	51%	4.85(2.61-9.03) p<0.001*	41%	1.41(0.86-2.34) P =0.16
	Dx to start ttt<1 year+ High Ca (N=17)	35%	67%	2.68(1.27-5.62) p=0.01*	65%	1.09(0.62-1.93) P=0.75
	Dx to start ttt<1 year+ High plt (N=15)	33%	63%	2.08(0.83-5.23) p=0.11	42%	1.29 (0.69-2.38) P=0.42

4557 **Poster Session**

Identifying key prognostic indicators in Wilms tumor using machine learning techniques. First Author: Salsabeel Aljawabrah, University of Jordan, Amman, Jordan

Background: Wilms tumor is a rare pediatric malignancy, accounting for 6% of pediatric tumors and primarily affecting the kidneys. Its impact on quality of life and long-term outcomes complicates management. This study leveraged machine learning (ML) to identify prognostic factors with the aim of enhancing prognosis and survival rates. **Methods:** Data were obtained from the SEER database (2004-2021). Patients who met any of the following criteria were excluded: diagnosis not confirmed by histology, previous history of cancer or other concurrent malignancies, or unknown data. To identify prognostic variables, we conducted Cox regression analysis and constructed prognostic models using ML algorithms to predict the 5-year survival. Patient records were randomly divided into training (70%) and validation (30%) sets. A validation method incorporating the area under the curve (AUC) of the receiver operating characteristic curve was used to validate the accuracy and reliability of the ML models. We also investigated the role of multiple therapeutic options using Kaplan-Meier survival analysis. **Results:** A total of 4,935 children were included. Among them, 47.72% underwent surgery, radiation, and chemotherapy; 45.07% underwent surgery and chemotherapy; and 7.21% underwent surgery alone. Most patients (53.3%) were females, 75% were white, followed by black (16.3%). The mean patient age was 3 years, and the mean tumor size was 10.6 cm. Most tumors were left-sided (51.1%) and 79.8% had no metastasis. The lungs were the most frequent site of metastasis (11%), followed by the liver and lungs at the same time (1.2%), and bone involvement was rare (0.6%). Radical surgery was the most common surgical approach (76.1%), followed by nephrectomy (4.9%). Patients who underwent surgery and chemotherapy had the highest 5-year OS (96.9%) and CSS (96.9%) compared to those who underwent surgery alone (OS: 95.5%, CSS: 95.5%) or surgery with chemotherapy and radiation (OS: 92.9%, CSS: 93.2%). Asian/Pacific Islander and white patients exhibited better OS (94.3% and 95.1%, respectively) than black patients (91.9%). Multivariate Cox regression analysis identified a large tumor size and older age as poor prognostic factors. Gradient boosting and MLP classifiers were the most accurate models. The ML models identified race as the most significant prognostic factor, followed by the TNM stage and age. The performance metrics for all ML algorithms are summarized in Table. **Conclusions:** This is the first study to apply ML to Wilms tumor, effectively identifying key prognostic factors. ML models show promise in enhancing survival predictions, potentially informing personalized treatment strategies, and improving patient outcomes. Research Sponsor: None.

ML Model	Accuracy	Precision	Recall	F1 score	AUC
LR	59.5%	59.5%	99.6%	74.5%	0.573
KNN	56.1%	61.7%	68.7%	65.05%	0.572
RFC	59.9%	61.9%	84.4%	71.4%	0.596
GBC	60.7%	60.5%	97.3%	74.6%	0.582
MLP	60.9%	61.6%	90.5%	73.3%	0.589

4558 **Poster Session**

Real-world quality of life (QOL) for patients (pts) with metastatic renal cell carcinoma (mRCC) treated with systemic therapy (ST) in the prospective observational ODYSSEY study. First Author: Benjamin L. Maughan, Huntsman Cancer Institute at the University of Utah, Salt Lake City, UT

Background: In the past 7 years, 4 immuno-oncology (IO) based combinations have been approved for mRCC. However, QOL data on these combinations are limited to trials in which collection and reporting was not standardized, which further limits cross trial comparisons. Real-world QOL data with multiple treatment regimens are needed to understand how these regimens are tolerated in practice. **Methods:** ODYSSEY is a multi-site, prospective observational study of 500 US pts with mRCC. Pts must have mRCC (any histology), no prior ST, and follow up at a PCORnet study site. Exclusion criteria include treatment for cancer except mRCC. The primary objective is to determine patterns of change in QOL and symptom burden of pts with mRCC. Minimally important differences (MID) are 3 points for FKSI-19 total score, 1 point for the FKSI-Disease Related Symptoms (DRS) subscale and 7 points for FACT-G. **Results:** As of 1/6/25, 392 pts were enrolled of whom 299 were managed with ST. Of pts on ST, 114 were treated with IO-IO, 108 with IO-TKI, 33 with IO alone, 27 with Other, and 18 with TKI alone. Median follow up for all pts is 8.8 months (IQR 2.9, 16.2). IO-IO pts are median age 64 yrs, 81% male, 84% white, 56% prior nephrectomy, 84% clear cell; IO-TKI pts median age 66 yrs, 76% male, 92% white, 43% prior nephrectomy, 66% clear cell; IMDC risk profiles are similar. IO-IO pts are more likely to be KPS 100; whereas, IO-TKI pts have a higher median number of metastatic sites and are more likely to have bone or liver metastasis. With median follow-up of 6.0 (IQR 1.8, 14.9) and 8.8 months (4.5, 17.8) in the IO-IO and IO-TKI cohorts, 17 (15%) and 21 (19%) pts had died with a median time to death of 5.4 (2.5, 6.4) and 5.7 months (4.4, 12.8), respectively. 20 (18%) and 16 (15%) pts on IO-IO and IO-TKI had discontinued therapy at a median of 3.0 (IQR 2.0, 4.0) and 6.4 months (2.4, 13.0), respectively. Rates of discontinuation for disease progression and toxicity are similar. Baseline PROs for pts on ST are shown in the Table (higher score indicates better QOL), with RCT data for reference (NA, not assessed). **Conclusions:** In our prospective multi-center ODYSSEY study, we demonstrate that real world pts treated with contemporary ST have worse baseline QOL than those enrolled on pivotal RCTs. One-third of IO-IO and IO-TKI pts died or discontinued therapy within 6 months of initiation. Our data on real world vs RCT differences in baseline QOL may partially explain the limitations of current IO combination regimens in practice and support development of alternative treatment approaches. Research Sponsor: BMS; Exelixis; Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA; & Pfizer.

Instrument, Mean (SD)	ODYSSEY IO-IO (N=114)	CheckMate 214 (N=425)	ODYSSEY IO-TKI (N=108)	KEYNOTE 426 (N=402)	CheckMate 9ER (N=323)	CLEAR (N=351)
FKSI-19 total	56.0 (12.5)	60.1 (9.8)	53.8 (11.8)	NA	58.7 (10.6)	NA
FKSI-DRS	27.5 (6.3)	30.7 (4.5)	27.0 (5.8)	32 (4.2)	30.2 (5.2)	31.3 (4.4)
FACT-G	82.4 (16.7)	82.6 (15.0)	78.5 (16.0)	NA	NA	NA

4559 **Poster Session**

The effect of GLP-1 receptor agonists on outcomes in metastatic renal cell carcinoma patients undergoing immune checkpoint inhibitor therapy: A retrospective multi-institutional US cohort study. First Author: Mohanad Elchouemi, Texas Tech University Health Science Center, El Paso, TX

Background: Glucagon-like peptide-1 (GLP-1) receptor agonists have played a pivotal role in the management of type 2 diabetes (T2DM). At the same time, immune checkpoint inhibitor (ICI) therapy remains one of the mainstay treatments for metastatic renal cell carcinoma (mRCC). There has been a scarcity of research on the effect of GLP-1 receptor agonists on ICI efficacy in cancer patients. This study presents the first real-world analysis of the effect of GLP-1 receptor agonists on outcomes in mRCC patients receiving ICI therapy. **Methods:** Data was retrospectively collected from TriNetX, a national electronic health record database with 120 million US patients from over 70 healthcare organizations, from 2012-2024. We included patients $\geq$ 18 years old with T2DM and mRCC who underwent ICI therapy. Patients were then stratified into two cohorts: on GLP-1 receptor agonists prior to ICI therapy and not on GLP-1 receptor agonists. Patients in each cohort were then 1:1 propensity score matched (PSM) based on age, sex, race, type of ICI therapy used, comorbidities, other diabetic medications and staging. 1 year outcomes for mortality, major adverse cardiovascular events (MACE) and various immune-related adverse events (irAEs) were reported. **Results:** A total of 2378 patients were identified who met the inclusion criteria. 535 (22%) were in the GLP-1 receptor agonist cohort compared to 2378 (68%) in the non GLP-1 receptor agonist cohort. After 1:1 PSM, 497 patients were in each group. Among both cohorts, 66% were male, 77% white and the average age was about 65 years old. After conducting Cox proportional hazard analyses, GLP-1 receptor agonist use was associated with lower mortality (HR, 0.49 [95% CI: 0.37-0.64]). Moreover, GLP-1 receptor agonist use had lower rates of irAEs, including pneumonitis (HR, 0.61 [95% CI: 0.43-0.85]), hematological complications (HR, 0.78 [95% CI: 0.64-0.95]) and renal complications (HR, 0.67 [95% CI: 0.54-0.84]). There was no significant difference in MACE or other irAEs between the two cohorts. **Conclusions:** Analysis of one of the largest US based databases showed that the use of GLP-1 receptor agonist in T2DM patients with mRCC undergoing ICI therapy, is associated with better overall survival and lower irAES such as pneumonitis, hematological and renal complications. There was no significant difference in MACE. To our knowledge, this is the first study to identify the impact of GLP-1 receptor agonists on the outcomes of mRCC patients undergoing ICI therapy. Further prospective studies are needed to validate these findings and to identify the underlying mechanisms. Research Sponsor: None.

4560 **Poster Session**

Circulating tumor DNA (ctDNA) monitoring in patients (pts) with advanced urothelial carcinoma (aUC) treated with enfortumab vedotin +/- pembrolizumab (EVP). First Author: Kevin R. Reyes, University of California, San Francisco, San Francisco, CA

Background: CtDNA is an emerging biomarker in aUC, but its role for pts receiving EVP is unclear. **Methods:** We undertook a retrospective analysis of pts with aUC who were longitudinally tested for ctDNA (MTM/mL) with a tumor-informed assay (Signatera, Natera, Inc) while on treatment (tx) with EV+/-P. Pt data were abstracted from electronic medical record. Outcomes were compared based on changes in ctDNA from pre-tx baseline, using Kaplan-Meier method and Cox proportional hazards test to assess progression-free survival (PFS) and overall survival (OS). **Results:** Longitudinal ctDNA data were available for 36 pts (tx: 28 EV+P; 8 EV). Pts had a median (med) of 3 ctDNA tests (range: 2-14) over 8 months (mos) of med follow-up. At pre-tx baseline, 33/36 (92%) pts had detectable ctDNA. Pt characteristics and outcomes are shown in the Table. After tx start, 26 pts (79%) had a decrease in ctDNA (med time to decrease 50 days), and 11 pts (33%) achieved negative ctDNA (-) after a med of 54 days. The 11 pts with ctDNA (-) had a response rate of 91% (CR: 6, PR: 4, SD: 1). Among 14 pts with ctDNA nadir followed by a rise, 8 pts (57%) had PD on next scan, and med time from initial ctDNA rise to PD was 124 days. Pts who achieved ctDNA (-) within 2 mos of tx (n = 8) had improved PFS relative to pts with ctDNA data (n = 21) who did not (HR: 0.08, 95% CI: 0.01 – 0.59, p = 0.01). Pts with no decrease in ctDNA within 2 mos of tx start (n = 7) had inferior PFS (HR: 5.9, 95% CI: 1.9 – 19.2, p $<$ 0.01) and OS (HR: 20.8, 95% CI: 2.3 – 192, p $<$ 0.01) vs pts with a ctDNA decrease (n = 22). In the EV+P group, pts with no ctDNA decrease within 2 mos (n = 4) had inferior PFS (HR: 15.9, 95% CI: 1.6 - 154, p = 0.01) vs pts with a decrease (n = 18). **Conclusions:** In this retrospective analysis of pts treated with EV+/-P, 92% had detectable ctDNA and 79% had a ctDNA decrease after tx start. Within 2 mos of tx start, pts who achieved ctDNA (-) had improved PFS, while pts who did not have ctDNA decrease had inferior PFS and OS. These hypothesis-generating results warrant validation in larger prospective cohorts and can inform clinical decision-making. Research Sponsor: None.

	Total cohort (n= 33)	EV+P (n= 25)
Sex – n (%)		
Male	7 (21%)	6 (24%)
Female	26 (79%)	19 (76%)
Primary Tumor Site – n (%)		
Lower Tract	25 (76%)	19 (76%)
Upper Tract	8 (24%)	6 (24%)
Histology – n (%)		
Pure Urothelial	25 (76%)	19 (76%)
Majority Urothelial	7 (21%)	6 (24%)
Majority Variant	1 (3%)	0
Median baseline ctDNA (MTM/mL)		
Responders	23.1	30.1
Non-Responders	39.8	69.6
Outcomes by ctDNA status within 2 mos of EV+/-P tx start, mos (95% CI), p		
mOS: ctDNA (-) vs detectable	NR (NR – NR) vs NR (11.7 – NR), p=0.32	NR (NR – NR) vs NR (NR – NR), p= 0.99
mPFS: ctDNA (-) vs detectable	18.7 (NR – NR) vs 7.2 (5.6 – NR), **p=0.01**	NR (NR – NR) vs 7.2 (5.6 – NR), p=0.99
mOS: No ctDNA decrease vs ctDNA decrease	11.7 (3.9 – NR) vs NR (NR – NR), **p<0.01**	NR (3.9 – NR) vs NR (NR – NR), p= 1.0
mPFS: No ctDNA decrease vs ctDNA decrease	3.9 (1.9 – NR) vs 13.2 (7.9 – NR), **p<0.01**	4.8 (1.9 – NR) vs 13.2 (8.4 – NR), **p=0.01**

4561 Poster Session

Avelumab maintenance therapy in patients (pts) with advanced urothelial carcinoma (UC) in Japan: Subgroup analyses by best overall response (BOR) to prior platinum-based chemotherapy (PBC) in a post-marketing surveillance (PMS) population. First Author: Eiji Kikuchi, Department of Urology, St Marianna University School of Medicine, Kanagawa, Japan

Background: Avelumab was approved as maintenance therapy for pts with advanced UC that has not progressed after first-line PBC based on results from the JAVELIN Bladder 100 phase 3 trial. Primary analyses of PMS data demonstrated the safety and effectiveness of avelumab maintenance in clinical practice in Japan, consistent with phase 3 results. We report post hoc analyses of PMS data in subgroups defined by BOR to prior PBC. **Methods:** This prospective, multicenter, observational PMS evaluated pts with advanced UC without disease progression after prior PBC who received ≥1 dose of avelumab between Feb and Dec 2021. The observation period was ≤52 wk from the start of avelumab in all pts. Safety assessment was based on occurrence of prespecified adverse drug reactions (ADRs) deemed to be associated with avelumab. Effectiveness outcomes from the start of avelumab maintenance (time to treatment failure [TTF; defined as avelumab discontinuation for any reason] and overall survival [OS]) were estimated using the Kaplan-Meier method. Subgroups were defined by BOR to prior PBC: complete response (CR), partial response (PR), or stable disease (SD). **Results:** The study population included 453 pts from 213 institutions. Median age was 73 y (range, 21-91); 75 pts (16.6%) were aged ≤64 y, 198 (43.7%) were aged 65-74 y, and 180 (39.7%) were aged ≥75 y. Primary tumor site was the bladder in 244 pts (53.9%) and upper tract in 209 (46.1%). Prior PBC regimen was gemcitabine + cisplatin in 267 pts (58.9%) and gemcitabine + carboplatin in 163 (36.0%). BOR to prior PBC was CR in 47 pts (10.4%), PR in 242 (53.4%), and SD in 149 (32.9%). At the end of the observation period, 128 pts (28.3%) remained on avelumab treatment and 184 (40.6%) had received next-line treatment. Median duration of avelumab treatment was 5.1 mo (IQR, 2.3-12.0). Among subgroups defined by BOR to prior PBC, the longest median TTF and highest 1-y OS rate were observed in the CR subgroup; findings were comparable in the PR and SD subgroups (Table). Safety findings were similar across subgroups. **Conclusions:** This PMS population represents the largest prospective observational study of avelumab maintenance therapy in pts with advanced UC in Asia. In post hoc analyses, the safety and effectiveness of avelumab were generally consistent across subgroups defined by BOR to prior PBC. Our findings support the favorable benefit-risk profile of avelumab in clinical practice, irrespective of BOR to prior PBC. Research Sponsor: Merck Biopharma Co., Ltd., Tokyo, Japan, an affiliate of Merck KGaA, Darmstadt, Germany (CrossRef Funder ID: 10.13039/100009945).

BOR to prior PBC	All patients (N=453)	CR (n=47)	PR (n=242)	SD (n=149)
Any-grade ADRs, n (%)	144 (31.8)	16 (34.0)	79 (32.6)	45 (30.2)
Grade ≥3 ADRs, n (%)	35 (7.7)	4 (8.5)	16 (6.6)	13 (8.7)
Median TTF (95% CI), mo	4.6 (3.8-5.3)	5.2 (3.4-12.0)	4.6 (3.3-5.7)	4.6 (2.8-5.6)
1-year OS rate (95% CI), %	77.9 (73.7-81.5)	89.4 (76.3-95.4)	76.3 (70.3-81.2)	75.8 (68.0-82.0)

4562 Poster Session

Real-world enfortumab vedotin +/- pembrolizumab (EV+/-P)–based treatment toxicity, treatment discontinuation, and associations with survival in advanced urothelial carcinoma (aUC). First Author: Martin Kurian, Hospital of the University of Pennsylvania, Philadelphia, PA

Background: EV-based therapy is central to the standard of care for aUC, increasingly in combination with P. Current understanding of EV-related toxicity is limited to clinical trial data. Here, we use real-world data to characterize the frequency of EV-based treatment-toxicity, -discontinuation, and associations with survival. **Methods:** We performed a post-marketing retrospective cohort study of EV+/-P initiators at the University of Pennsylvania (1/2020-5/2024). The frequency of any of five toxicities (skin reaction, neuropathy, ocular disorder, hyperglycemia, and pneumonitis) and associated treatment-interruptions (hold or discontinuation), -reduction, or -hospitalization were summarized. Among pts with at ≥1 year of follow-up, overall survival (mOS) was compared between pts with vs without each toxicity via KM methods. **Results:** Among 123 EV/EV+P treated pts, median age was 68 years, 72% were male, 74% were white, 68% had bladder primary, and 71% treated with EV alone. Frequency of toxicity, time to toxicity, and proportions requiring dose interruption, reduction, and hospitalization are shown (Table). 60% of pts had skin reaction, 47% neuropathy, 28% ocular disorder, 14% hyperglycemia, and 2% pneumonitis; treatment discontinuation occurred among 20% of pts with neuropathy, 5% of those with skin reaction, 3% of those with ocular disorders, and 0% of those with hyperglycemia or pneumonitis. Among 80 pts with at least one-year of follow-up (89% EV monotherapy), mOS was 14.3 months (95% CI: 11.3-19.3). Survival was greater among those with skin reaction, neuropathy, and ocular disorders (mOS skin reaction vs. no reaction: 19.3 vs. 6.4 months, $p < 0.001$; neuropathy vs. no neuropathy: 16.5 vs. 8.2 months, p = 0.001; ocular disorder vs. no ocular disorder: 17.1 vs. 11.3 months; p = 0.001). **Conclusions:** EV+/-P treatment toxicity occurred in a majority of pts, but treatment discontinuation was infrequent. Presence of toxicity was significantly associated with improved survival. Future work is needed to prospectively validate these findings. Research Sponsor: None.

EV+/-P treatment toxicity and survival outcomes (n=123).

Toxicity	n (% of total)	Months to Occurrence, Median (range)	Dose Held*, n (%)	Dose Reduced*, n (%)	Discontinuation* n (%)	Hospitalization* n (%)	mOS** (n=80)
Skin Reaction	74 (60)	0.7 (0.1-13.8)	33 (46)	33 (46)	4 (5)	4 (5)	19. 3 vs 6.4 (p<0.001)
Neuropathy	58 (47)	2.9 (0.2-9.6)	28 (48)	23 (40)	11 (20)	0 (0)	16.5 vs. 8.2 (p=0.001)
Ocular Disorder	35 (28)	1.8 (0.2-10.6)	4 (11)	3 (9)	1 (3)	0 (0)	17.1 vs 11.3 (p=0.001)
Hyperglycemia	17 (14)	1.4 (0.1-5.6)	5 (29)	0 (0)	0 (0)	0 (0)	9.7 vs. 14.4 (p=0.56)
Pneumonitis	3 (2)	3.8 (3.0-11.0)	1 (33)	0 (0)	0 (0)	1 (33)	22.1 vs. 14.3 (p=0.91)

*n (% of pts w/ toxicity).
**w/ vs w/o toxicity.

4563 Poster Session

Final results of a phase 2 study of HDACi chidamide and PD-1 inhibitor for advanced urothelial carcinoma after platinum therapy. First Author: Zhuowei Liu, Department of Urology, Sun Yat-Sen University Cancer Center, Guangzhou, China

Background: Epigenetic dysregulation is commonly correlated with the pathogenesis and development in urothelial carcinoma. The preliminary results demonstrated that the combination of chidamide (CHI) and tislelizumab (TIS) was well tolerated with clinically meaningful activity in patients (pts) with advanced or metastatic urothelial carcinoma (mUC). Confirmed ORR was 41.7%, median PFS was 4.6 months. Here we present results from the final analysis. **Methods:** Eligible pts aged 18 to 75 years old had recurrend or progressed after platinum-based chemotherapy to assess the efficacy and safety of CHI and PD-1 inhibitor in mUC. All pts received 30 mg oral CHI twice weekly in combination with TIS 200mg Q3W, until progression or unacceptable toxicity. The primary endpoint was objective response rate (ORR). The secondary endpoints included progression free survival (PFS), disease control rate (DCR), overall survival (OS) , and safety. **Results:** From Jan. 2021 to Oct. 2023, a total of 45 pts were enrolled at Sun Yat-sen University Cancer center. At the data cut-off (Aug, 2024), the median duration of follow-up was 23.2 months (95%CI: 17.2-31.9). Median age was 63 years (IQR: 57-68). ORR and DCR were 44.4% (12CR, 8PR; 95%CI, 29.6-60.0%) and 60% (27/45; 95%CI, 44.3-74.3%), respectively. Median duration of response (DOR) was not evaluable (95%CI, 8.8-NE). Median PFS and OS were 7.0 months (95%CI, 2.4-10.3) and 20.3 months (95%CI, 10.7-NE), respectively. The most common treatment emergent adverse events (TEAEs) included anemia, anorexia, thrombocytopenia, neutropenia, leukopenia, fatigue, hypoalbuminemia. Grade 3 or above TEAEs (≥10%) were neutropenia 24.4%, thrombocytopenia 20.0%, anemia 13.3%.No pts died due to an adverse event attributed to study trearment. **Conclusions:** This study is the first trial to show that combining HDAC inhibitor with PD-1 antibody is a feasible and efficacious novel approach in mUC. Chidamide plus tislelizumab could be a new treatment option in this patient population. Clinical trial information: NCT04562311. Research Sponsor: None.

	CHI+TIS (n=45)
ORR (95% CI), %	44.4 (29.6- 60.0)
CR, %	26.7% (12/45)
PFS	
Median (95% CI), mo	7.0 (2.4-10.3)
36-mo rate (95% CI), %	26.3 (13.4-41.1)
OS	
Median (95% CI), mo	20.3 (10.7-NE)
36-mo rate (95% CI), %	45.9 (28.8-61.4)
DOR	
Median (95% CI), mo	NE (8.8-NE)

4564 Poster Session

Fibroblast growth factor receptor 3 (*FGFR3*) alteration status and outcomes with immune checkpoint inhibitors (ICPI) in patients with metastatic urothelial carcinoma. First Author: Shilpa Gupta, Cleveland Clinic Taussig Cancer Institute, Cleveland, OH

Background: The use of immune checkpoint inhibitors (ICPIs) has expanded in the treatment of metastatic urothelial carcinoma (mUC) but response rates are variable, highlighting the need for preditive biomarkers. Tumor mutational burden (TMB) has been previously shown to predict response to ICPI but *FGFR3* alterations are common drivers in mUC and there is preclinical and anectodal evidence that they may predict less favorable outcomes to ICPIs, similar to *ALK* and *ROS1* fusions in lung cancer. We sought to explore the effect of *FGFR3* alterations alone and with TMB on response to ICPI in mUC. **Methods:** 1,416 mUC patients who received hybrid-capture NGS-based genomic profiling were evaluated for their response to ICPI and chemotherapy treatment based on the presence of *FGFR3* alterations (activating point mutations, insertions and deletions, rearrangements) and TMB. The nationwide (US-based) de-identified Flatiron Health-Foundation Medicine mUC clinico-genomic database of NGS results linked to deidentified electronic health record-derived clinical data originating from approximately 280 US cancer clincs (~800 sites of care) was used to assess treatment patterns and real-world overall survival (rwOS) and progression-free survival (rwPFS). Propensity analysis was used to match clinical characteristics between patients receiving first-line ICPI and chemotherapy and included age, disease grade, ECOG, and erdafitinib receipt as features. **Results:** Among 819 patients with mUC who received ICPI, there were no significant differences in rwOS or rwPFS between *FGFR3*-altered (alt; n = 161) and wildtype (wt; n = 658) patients. However, among patients with TMB≥10 mut/Mb, *FGFR3*-alt patients (n = 39) trended towards longer rwOS (20 vs. 14 months, aHR 0.62, 95% CI 0.37-1.02, p = 0.06) and rwPFS (5.5 vs. 4.9 months, aHR 0.66, 95% CI 0.42-1.03, p = 0.07) than *FGFR3*-wt patients (n = 244). Comparing first-line ICPI vs. chemotherapy and adjusting for imbalances, patients with TMB≥10 and *FGFR3*-alts who received ICPI (n = 21) also trended towards longer rwPFS than patients who received chemotherapy (n = 18) (14 vs. 7.1 months, HR 0.55, 95% CI 0.25-1.25, p = 0.2), although no significant difference in rwOS was observed. **Conclusions:** While *FGFR3* status alone is not predictive of response to ICPI, *FGFR3* combined with TMB emerged as a biomarker that may be predictive for response to ICPI in mUC and may have the potential to reconcile differences in previous observations regarding *FGFR3* and ICPI response. Further studies performed with larger patient populations to confirm these findings are warranted. Research Sponsor: None.

4565 **Poster Session**

Association of tumor-informed ctDNA-based molecular residual disease (MRD) with clinical outcomes for upper tract urothelial cancer (UTUC). First Author: Adanma Ayanambakkam, OU Health, Stephenson Cancer Center, Oklahoma City, OK

Background: Upper tract urothelial carcinoma (UTUC) accounts for 5–10% of all urothelial carcinomas. Given its aggressive phenotype compared to primary bladder tumors and the lack of efficient biomarkers to guide treatment decisions, disease management remains challenging. Herein, we evaluate the prognostic value of ctDNA-based molecular residual disease (MRD) detection in UTUC. **Methods:** We conducted a retrospective analysis of real-world data from commercial ctDNA testing in a multicenter cohort of patients with UTUC using a personalized, tumor-informed, mPCR-NGS ctDNA assay (SignateraTM, Natera, Inc.). ctDNA was evaluated during the 1) MRD window (2-16 weeks post-surgery, before adjuvant therapy [AT]) and 2) surveillance windows ($>$ 16 weeks post-surgery if no AT was given or after AT completion). The correlation between ctDNA status and patient outcomes (recurrence-free survival [RFS]) was assessed using Cox regression analysis. RFS was defined as the interval from surgery to the date of radiographic recurrence or any evidence of residual/persistent disease after the completion of surgery or AT. **Results:** A total of 349 plasma samples collected from 45 patients with stages I-IV UTUC between 4/20/2021-12/16/2024 were available for analysis. Neoadjuvant therapy (NAT) was administered for 9% (4/45) of the patients, while 51% (23/45) of patients received AT post-surgery/-diagnosis [chemotherapy 57% (13/23), immunotherapy 39% (9/23), chemo-immunotherapy: 4% (1/23)] and 22% (10/45) received treatment for metastatic disease [EV-immunotherapy or immunotherapy: 40% (4/10), chemotherapy: 40% (4/10), chemo-immunotherapy: 20% (2/10)]. With a median follow-up of 17 (range: 3-71) months, the ctDNA detection rate within the MRD (N = 24) and surveillance (N = 32) windows was 70.8% and 68.8%, respectively. Patients with ctDNA-positivity within the MRD and surveillance windows showed a significantly inferior RFS compared to ctDNA-negative patients (MRD: HR = 13.4, *P*= 0.012 and surveillance: HR = 14.46, *P*= 0.01). Notably, ctDNA-positive patients showed a 12-month RFS of 32.1% (95% CI: 11.83–54.6%) and 45.5% (95% CI: 24.4–64.3%), respectively for MRD (N = 17) and surveillance (N = 22) windows, compared to 100% 12-month RFS for ctDNA-negative patients (MRD, N = 7; surveillance, N = 10). Multivariate regression analysis during surveillance revealed ctDNA-positivity as the only factor significantly associated with poor RFS (HR = 17.6, *P*= 0.011) when adjusted for clinical stage, NAT, and AT. **Conclusions:** This is the first study utilizing longitudinal, tumor-informed ctDNA testing to assess patient outcomes and disease status in UTUC. Our hypothesis-generating results suggest that ctDNA-based MRD detection via tumor-informed ctDNA testing is prognostic of patient outcomes post-surgery in UTUC and warrants further investigation in larger prospective cohorts. Research Sponsor: None.

4566 **Poster Session**

Targeting the TGFβ signaling pathway to mitigate tumor metastasis in 9p21-loss urothelial bladder cancer. First Author: Cindy Y. Jiang, The University of Texas MD Anderson Cancer Center, Houston, TX

Background: We previously identified that 9p21-loss (containing MTAP and CDK2NA genes) occurs in 25% of metastatic urothelial cancer (mUC) and is associated with worse survival and increased visceral metastasis. Additionally, we found significantly increased expression of the TGFβ-SMAD3 pathway in 9p21-loss UC, which is well studied to induce epithelial mesenchymal transition (EMT) and lead to metastasis. We hypothesize that the TGFβ signaling pathway mediates visceral metastasis in 9p21-loss UC. **Methods:** We included mUC patients at MD Anderson Cancer Center (MDACC) who had MTAP testing completed (surrogate for 9p21-loss) and received chemotherapy, immune checkpoint therapy (ICT), and/or antibody drug conjugate between 2012 and 2022. Survival and metastasis were compared between MTAP deficient patients and MTAP proficient patients. The Memorial Sloan Kettering-Metastatic Events and Tropisms (MSK-MET) cohort of mUC patients and IMVigor210 dataset were assessed for genomic alterations. Mouse models bearing CDKN2A-MTAP double knock out (DKO) MB49 tumors and wild type (WT) MB49 tumors, as well as corresponding in vitro models were used for mechanistic studies. **Results:** 298 mUC patients at MDACC were identified with 27% (n = 81) MTAP deficient. MTAP deficient patients experienced significantly worse overall survival (16.2 vs 21.1 months; p = 0.002; HR 1.61; 95% CI 1.2-2.2), progression-free survival (3.9 vs 5.8 months; p $<$ 0.001; HR 1.75; 95% CI 1.3-2.4) and increased visceral metastasis (62% vs 39%; p = 0.001) with lung predominance (44% vs 26%; p = 0.003) compared to MTAP proficient patients. We also found in the MSK-MET cohort that 26% (186/714) of patients with mUC to the bladder had lung metastasis and those with lung metastasis had significantly increased frequency of CDK2NA deletion compared to patients without lung metastasis (30% vs 18%; OR 2.0; 95% CI 1.3-3.0). Our preclinical data also demonstrated that CDKN2A-MTAP DKO mice resulted in significantly larger primary bladder tumors and worse survival compared to mice bearing WT MB49 tumors. Additionally, mice bearing orthotopic CDKN2A-MTAP DKO MB49 tumors readily developed lung metastasis. Analysis of the IMvigor210 dataset (N = 298) showed that 9p21-loss UC patients had significantly increased expression of TGFβ and EMT pathway genes. These data are consistent with data from our DKO MB49 tumor models. We are currently assessing the impact of a TGFβ inhibitor on mitigating CDKN2A-MTAP DKO-mediated metastasis. **Conclusions:** Our clinical and pre-clinical data demonstrates that 9p21-loss mUC leads to worse survival and increased visceral metastasis, especially to the lung. We found that the TGFβ signaling pathway may play a role in the development of metastasis. Moving forward, we plan to prospectively investigate the therapeutic potential of TGFβ inhibition in patients with 9p21-loss UC. Research Sponsor: MD Anderson; David H. Koch Center; Joan and Herb Kelleher Charitable Foundation; Williams TNT Fund; NIH/NCI R01; CA254988-01A1; NIH/NCI R01; CA269489-01A1; NIH/NCI R01; CA282282-01.

4567 **Poster Session**

Phase 1/2 Duravelo-1 study: Preliminary results of nectin-4–targeting zelenectide pevedotin (BT8009) plus pembrolizumab in previously untreated, cisplatin-ineligible patients with locally advanced or metastatic urothelial cancer. First Author: Patrizia Giannatempo, Genitourinary Medical Oncology, Fondazione IRCCS - Istituto Nazionale dei Tumori, Milano, Italy

Background: Effective and tolerable therapies for patients (pts) with locally advanced or metastatic urothelial cancer (la/mUC) in the first-line setting are needed. Zelenectide pevedotin (zele, previously BT8009) is a highly selective Bicycle Toxin Conjugate (BTC) targeting Nectin-4 and conjugated to MMAE, and has shown an objective response rate (ORR) of 45% and a generally tolerable safety profile as monotherapy in previously treated, enfortumab vedotin-naïve pts with mUC in the ongoing Phase 1/2 study (NCT04561362, Duravelo-1; Reig et al., 2024). Here, we present preliminary data from expansion Cohort B7 of Duravelo-1, investigating zele + pembrolizumab (pembro) in pts with previously untreated, cisplatin-ineligible, la/mUC. **Methods:** Pts who were cisplatin-ineligible by Galsky criteria (Galsky et al., 2011) received zele 5 mg/m^2 on D1, D8, D15 plus pembro 200 mg D1, every 21 days. The primary endpoint was ORR as assessed by investigator per RECIST v1.1. Secondary endpoints included safety and disease control rate (DCR). Treatment-related adverse events (TRAEs) were determined for all pts who received at least one dose of study drugs. **Results:** As of 3 Jan 2025, 22 pts were enrolled from Nov 2023 to Jul 2024 with a median time on treatment of 22.9 weeks and 12 pts still receiving study treatment. Median age was 77 years; 46% of pts had an ECOG performance status (PS) of 2; 55% with CrCl $<$ 60 mL/min. With 20 efficacy evaluable pts, the ORR is 65.0% (95% CI, 40.8, 84.6), including 5 CRs (25.0%; 4 confirmed), 8 PRs (40.0%; 6 confirmed) and 5 SD (25.0%). Median follow-up was 7.1 mo (range 1.0 – 13.2) and median duration of response was not reached. DCR is 90.0%. The most common grade (Gr) $\geq$3 TRAEs included ALT increased and neutropenia (13.6% each), and diarrhea, asthenia, hypomagnesemia, and pneumonia (9.1% each). Serious TRAEs related to zele or zele + pembro occurred in 9.1%. Treatment-related peripheral neuropathy occurred in 50.0% (27.3% Gr1, 13.6% Gr2, 9.1% Gr3). Other TRAEs of clinical interest included skin reactions (4.5% Gr$\geq$3), hyperglycemia (0.0% Gr$\geq$3), and eye disorders (0.0% Gr$\geq$3). All cases of grade 3 TRAEs of clinical interest were reversible. There were no grade 4/5 TRAEs of clinical interest and no treatment related deaths. **Conclusions:** Zelenectide pevedotin + pembro shows promising anti-tumor activity as a first-line treatment in a cohort of cisplatin-ineligible pts with la/mUC including a large proportion of pts with PS = 2. The combination of zele + pembro was generally tolerable and broadly consistent with the existing safety profiles of each respective agent. No new safety signals were observed with the combination. Zele + pembro combination therapy is being investigated in previously untreated la/mUC pts in the ongoing Phase 2/3 Duravelo-2 study (NCT06225596). Clinical trial information: NCT04561362. Research Sponsor: BicycleTx Ltd.

4568 **Poster Session**

Real-world analysis of 2IR immune response score in histologic subtype urothelial carcinoma (hsUC). First Author: Jason Robert Brown, Division of Solid Tumor Oncology, University Hospitals Seidman Cancer Center, Case Comprehensive Cancer Center, Case Western Reserve University, Cleveland, OH

Background: The 2IR immune response score was initially developed using bulk RNA sequencing of pre-treatment tissue from ImVigor 210 and CheckMate 275 trials, however these trials enrolled patients (pts) with pure urothelial carcinoma (pUC) histology. Patients with hsUC often exhibit worse response to immune checkpoint inibitors (ICI) than patients with pUC. Here, we evaluated the 2IR score as a prognostic or predictive biomarker in real-world pts with hsUC. **Methods:** Specimens from pts with pUC (n = 1677) and hsUC (n = 417) were profiled at Caris Life Sciences (Phoenix, AZ) using next generation sequencing (NGS) of DNA and RNA. HsUC histologies included majority ($>$ 50%) squamous (n = 340), sarcomatoid (n = 51), neuroendocrine (n = 20), and micropapillary (n = 6) component. 2IR was calculated by comparative RNA expression of 10 adaptive immune genes and 39 pro-tumorigenic genes. Tumors were classified as 2IR-Low (2IR $\leq$ -0.5), -Mid (-0.5 $<$ 2IR $<$ 0), and -High (2IR $\geq$ 0), as previously described (Wang et al., 2022). Spearman correlation analysis was utilized to compare 2IR with tumor mutation burden (TMB), interferon score (IFN) and the tumor microenvironment (TME) cell fractions estimated using quanTIseq. Clinical outcomes included real-world overall survival (rwOS) from ICI start to last contact and time on treatment (ToT) with pembrolizumab, obtained via matched insurance claims data and calculated using Kaplan-Meier methods, while Hazard ratio (HR) was calculated by Cox proportional model. **Results:** For patients with hsUC, distribution of 2IR score was High 5.76%, Mid 33.3%, and Low 60.9%. Median 2IR score was significantly lower in squamous (-0.60, p $<$ 0.0001) and sarcomatoid UC (-0.82, p $<$ 0.0001) compared to pUC (-0.41) and significantly higher in neuroendocrine UC (-0.15, p = 0.003). Among patients with hsUC, median rwOS was significantly longer for patients with high/mid 2IR score compared to low 2IR score (25.3 [10.9-39.3] months vs. 8.7 [6.2-11.3] months; HR 0.52, 95% CI 0.34 – 0.78, p = 0.0017). ToT with pembrolizumab was also significantly longer for high/mid 2IR score compared to low 2IR score (3.0 [1.4-5.5] months vs. 2.1 [1.4-3.3] months; HR 0.68, 95% CI 0.46-1.00, p = 0.0471). Similar to pUC, 2IR score in patients with squamous UC was positively associated with CD8 T cell infiltration (r = 0.39; p $<$ 0.0001), IFN score (r = 0.41, p $<$ 0.0001), and TMB (r = 0.20, p $<$ 0.001) and negatively associated with M1 macrophage infiltration (r = -0.25, p $<$ 0.0001). 2IR scores in hsUC correlated positively but not significantly with mutations in *TP53* (Median: -0.59 vs -0.62, p = 0.067) and *PIK3CA* (Median: -0.56 vs -0.61, p = 0.172) and negatively with mutations in *CDKN2A* (Median: -0.67 vs -0.59, p = 0.052). **Conclusions:** In a real-world cohort of patients with hsUC, we show the 2IR score may be prognostic for rwOS and predictive for pembrolizumab ToT. Prospective studies are needed to further validate this biomarker for use in this population. Research Sponsor: None.

4569 Poster Session

Integrative clinico-genomic evaluation of the human epidermal growth factor receptor 2 (HER2) in urothelial cancer (UC). First Author: Samuel Black, Department of Medicine, Section of Internal Medicine, Baylor College of Medicine, Houston, TX

Background: HER2-directed therapy with trastuzumab deruxtecan is now FDA approved for UC with high HER2 expression. The interaction between HER2 expression, clinical phenotype and genomic tumor make-up is poorly understood in UC. **Methods:** We reviewed the records of 209 patients with UC and available HER2 expression status treated at MD Anderson Cancer Center between 2021 and 2024. Immunohistochemical (IHC) staining for HER2 and PD-L1 was conducted using 4B5 Ventana PATHWAY and 22C3 pharmDx antibodies, respectively. Formalin-fixed paraffin embedded metastatic or primary UC tumors were sequenced using the MD Anderson Mutation Analysis Precision Panel (MDA MAPP), a 610-gene high-throughput next generation sequencing (NGS) CLIA assay. Chi-square and wilcoxon tests were used to test correlations between HER2 expression and clinico-genomic features. P-values were adjusted for false-detection rate < 0.25. **Results:** We included 209 patients with available HER2 status (see Table). HER2 and PD-L1 had significant inverse correlation (p=0.0062). HER2 3+ status was significantly associated with bladder primary tumors compared to other sites (renal pelvis, ureter, and urethra) (p=0.0261). HER2 expression correlated with *ERBB2* amplifications (0/1+: 0%, 2+: 2%, 3+: 26%, $p<0.0001$), but not with *ERBB2* mutations. Of 13 patients with *ERBB2* amplification, 12 were HER2 3+, and 1 was HER2 2+. HER2 also correlated with *HELQ* missense mutations (0/1+: 0%, 2+: 0%, 3+: 11%, p=0.0002), *CDK12* alterations (0/1+: 0%, 2+: 0%, 3+: 20%, p=0.0003), and *BCR* missense mutations (0/1+: 0%, 2+: 0%, 3+: 11%, p=0.0002). Of 6 HER2 3+ patients with *CDK12* amplification, all had *ERBB2* amplification. **Conclusions:** Our study confirms prior observations of HER2 inverse correlation with PD-L1, but positive correlation with bladder origin. Beyond the known association with *ERBB2* amplification, we identified molecular correlations between high HER2 expression, missense mutations of *HELQ* and *BCR*, and *CDK12* alterations. The observed co-occurrence of *CDK12* and *ERBB2* amplifications may be related to their proximity (<267 kb apart) on chromosome 17q12. Only 26% of HER2 3+ patients had *ERBB2* amplifications, highlighting the importance of IHC testing, not just NGS testing, to determine therapy candidacy for trastuzumab deruxtecan. Research Sponsor: None.

HER2 Expression Status (n)	0/1+ (105)	2+ (58)	3+ (46)	*p value*
Primary tumor - Bladder, n (%)	74 (70)	43 (74)	**41 (89)**	0.0260
Primary tumor - Other, n (%)	31 (30)	15 (26)	5 (11)	
PD-L1 positive score, median % [IQR]	**6 [1-30]**	**2 [1-10]**	**1.5 [0.75-5]**	0.0062
***ERBB2* amplifications, n (%)**	0 (0)	1 (2)	**12 (26)**	<0.0001
***ERBB2* mutations, n (%)**	10 (10)	8 (14)	9 (20)	0.2030
***HELQ* missense, n (%)**	0 (0)	0 (0)	**5 (11)**	0.0002
***CDK12* amplifications, n (%)**	0 (0)	0 (0)	**6 (13)**	<0.0001
***CDK12* alterations, n (%)**	0 (0)	0 (0)	**9.2 (20)**	0.0003
***BCR* missense, n (%)**	0 (0)	0 (0)	**5 (11)**	0.0002

4570 Poster Session

A real-world picture of biomarker testing in metastatic bladder cancer: A comprehensive assessment of 19,979 patients treated in the US and Europe. First Author: Tiago Costa de Padua, Medical and Scientific Services, Hematology and Oncology Department, IQVIA, São Paulo, Brazil

Background: Recent advances in the molecular characterization of bladder cancer (BC) have led to the development and approval of several targeted therapies in metastatic BC, and biomarker testing is recommended by all guidelines for treatment decision-making. This real-world study aimed to examine patterns of biomarker testing in clinical practice and correlate testing with molecular-guided treatment in patients (pts) with metastatic BC. **Methods:** The IQVIA Oncology Dynamics database, an IQVIA oncology cross-sectional survey collecting anonymized real-world patient-level data from anonymized records of drug-treated cancer pts, was used to identify mBC pts in the US, EU4 (France, Germany, Spain, Italy), and UK from January 2017 to December 2024. We assessed biomarker testing data using descriptive analyzes. **Results:** A total of 19,979 mBC pts were included in this analysis (EU4 + UK: 11,963 pts; US: 8016 pts). FGFR testing has steadily increased over the years in EU4 + UK (from 7% in 2017 to 24% in 2024) and in the US (from 34% in 2019 to 61% in 2024); FGFR alterations were identified in 25.8% of pts in EU4 + UK versus 12.5% in the US. PDL1 testing has also increased over time in both regions; (PDL1 $>$ 10% in 58.9% in EU4 + UK and 57.6% in the US). Microsatellite Instability (MSI) testing and NTRK testing were performed in 12.5% and 8.3% of all pts from EU4 + UK (MSI: 2023-2024; NTRK: 2020-2024). Of these, 24.7% were MSI-high and 5.4% were positive for NTRK alterations. Next Generation Sequencing (NGS) data has been collected since Q1 2022, with an overall testing rate of 9.6% in EU4 + UK and 12.8% in the US. NGS testing has increased in the US over the years (from 3% in 2022 to 65% in 2024). Tumor Mutational Burden (TMB) results are available for pts from EU4 + UK, with TMB $>$ 10 in 55.2% of pts. Regarding the use of targeted therapy, only 230 pts with FGFR3 alterations received any FGFR inhibitors as current or prior treatment, representing 22.9% of positive pts. NTRK inhibitors were used in only 2 pts with positive results (5.7%). **Conclusions:** To our knowledge, this is the largest real-world study evaluating biomarker testing in mBC pts, providing meaningful insights. Our data show an overall low percentage of biomarker testing in clinical practice, but there has been an increase in ordering over the years. Despite the increase, only a limited proportion of patients are treated with targeted therapy, reflecting drug access barriers. We also noted a geographic variation in the positivity rate of FGFR3 alterations, with a higher incidence in patients from EU4 + UK compared to the US. Additionally, the rate of high TMB and positive PDL1 was higher in our data set when compared to historical data; further studies are warranted to better understand these differences. Our study has some limitations, such as the potential for bias and lack of outcome analysis. Research Sponsor: None.

4571 Poster Session

EV-302: Long-term subgroup analysis from the phase 3 global study of enfortumab vedotin in combination with pembrolizumab (EV+P) vs chemotherapy (chemo) in previously untreated locally advanced or metastatic urothelial carcinoma (la/mUC). First Author: Jens Bedke, Department of Urology & Eva Mayr-Stihl Cancer Center, Stuttgart, Germany

Background: EV-302/KEYNOTE-A39 (NCT04223856) demonstrated superior efficacy of first-line (1L) EV+P vs chemo and established EV+P as the standard of care (SOC). EV+P is included in global treatment guidelines for patients (pts) with untreated la/mUC. After ≈2.5 years of median follow-up, the benefit of EV+P was sustained; median OS was maintained for $>$ 2.5 years. We present long-term efficacy and safety analyses in the following prespecified subgroups: primary disease site of origin (upper and lower tracts), lymph node (LN)–only disease, and presence of liver metastases (mets) (present and absent). **Methods:** Pts with previously untreated la/mUC were randomized 1:1 to receive EV (1.25 mg/kg; Days 1 and 8; IV) and P (200 mg; Day 1; IV) or chemo (gemcitabine with cisplatin or carboplatin) every 3 wk. Primary endpoints were progression-free survival (PFS) by blinded independent central review (BICR) and overall survival (OS). A genAI tool (01/09/25; Pfizer; GPT-4o) developed the 1st draft; authors assume content responsibility. **Results:** Pts (N = 886) were randomized to receive EV+P (n = 442) or chemo (n = 444) and were analyzed according to the subgroups shown in the Table. At data cutoff (Aug 8, 2024), median follow-up was 29.1 mo (95% CI, 28.5-29.9). PFS by BICR, OS, duration of response, and objective response rate continued to demonstrate sustained benefit of EV+P vs chemo across prespecified subgroups after long-term follow-up (Table). For EV+P, treatment-related adverse events (TRAEs) occurred in 96.0-98.5% and Grade ≥3 TRAEs in 53.4-60.7% of pts across prespecified subgroups, generally consistent with previous reports. **Conclusions:** EV+P continues to demonstrate superior long-term efficacy vs chemo in key subgroups with both favorable and poor prognoses. There were no new safety signals, and AE rates in prespecified subgroups were consistent with the overall population after an additional year of follow-up. This reinforces EV+P as the SOC for the 1L treatment of pts with la/mUC. Clinical trial information: NCT04223856. Research Sponsor: The EV-302 study was funded by Astellas Pharma Inc., Northbrook, IL, USA; Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA; and Seagen Inc., Bothell, WA, USA, which was acquired by Pfizer in December 2023.

	Upper tract	Lower tract	LN only	Liver mets present	Liver mets absent
EV+P, n (%)	135 (30.5)	305 (69.0)	103 (23.3)	100 (22.6)	342 (77.4)
Chemo, n (%)	104 (23.4)	339 (76.4)	104 (23.4)	99 (22.3)	345 (77.7)
mPFS, mo					
EV+P	12.3	12.8	22.1	8.1	16.4
Chemo	6.2	6.3	8.3	6.0	6.4
PFS HR	0.542	0.462	0.473	0.548	0.458
(95% CI)	(0.384-0.763)	(0.379-0.564)	(0.317-0.704)	(0.392-0.766)	(0.376-0.557)
mOS, mo					
EV+P	36.5	32.9	NR	19.1	39.3
Chemo	18.3	15.6	24.4	10.1	18.3
OS HR	0.538	0.504	0.512	0.556	0.496
(95% CI)	(0.371-0.781)	(0.408-0.623)	(0.332-0.789)	(0.399-0.776)	(0.400-0.615)

4572 Poster Session

Profiling treatment-associated evolutionary dynamics in advanced urothelial cancer via deep whole exome sequencing of cell-free DNA. First Author: Arvind Ravi, Dana-Farber Cancer Institute, Boston, MA

Background: Monitoring treatment response and identifying resistance mechanisms remain critical challenges in managing advanced bladder cancer. We investigated whether circulating tumor DNA (ctDNA) dynamics and deep whole exome sequencing (D-WES) could provide insights into treatment response and resistance patterns. **Methods:** We prospectively collected blood samples from 70 patients with advanced bladder cancer during treatment. Ultra-low pass whole genome sequencing (ULP-WGS) was performed on 213 plasma samples to quantify tumor fraction, with subsequent D-WES (200X) performed on 47 high-purity (i.e., at least 3% tumor fraction by ichorCNA) samples from 25 patients. Longitudinal analysis of ctDNA levels was correlated with clinical response. Phylogenetic reconstruction for samples in the D-WES cohort was used to identify candidate drivers of therapeutic response and resistance. **Results:** Changes in ctDNA tumor fraction correlated significantly with clinical trajectories: progression (median +1.3%), stable disease (-0.4%, p = 0.04 vs progression), and regression (-1.2%, p = 0.002 vs progression). Phylogenetic analysis revealed dynamic subclonal competition during treatment response. Mutation burden was significantly elevated in subclones associated with PD-(L)1 response (p = 0.04), including within a single patient. A number of novel candidate drivers of therapeutic response were identified across different therapeutic classes, with five genes meeting FDR-adjusted significance ($q < 0.05$): NLGN2, SHANK1 (chemotherapy resistance), GPR56 (taxane resistance), FOSL1, and ORC1L (chemotherapy sensitivity). **Conclusions:** Analysis of ctDNA can effectively monitor treatment response in advanced bladder cancer. D-WES of longitudinal samples revealed novel candidate drivers of therapeutic response and resistance, suggesting distinct molecular mechanisms may govern primary oncogenesis versus treatment response. These findings warrant further investigation in larger cohorts to validate their potential as predictive biomarkers. Research Sponsor: None.

4573 Poster Session

Treatment patterns and clinical outcomes with platinum-based chemotherapy after enfortumab vedotin and pembrolizumab in patients with metastatic urothelial carcinoma. First Author: Michal Sternschuss, Memorial Sloan Kettering Cancer Center, New York, NY

Background: Enfortumab vedotin and pembrolizumab (EV/P) emerged as the new standard of care for previously untreated metastatic urothelial carcinoma (mUC), shifting the treatment paradigm. Currently, there are no guidelines for management after EV/P as the outcomes of subsequent systemic treatments, including platinum-based chemotherapy, remain unknown. **Methods:** Our retrospective cohort of patients with mUC treated with EV/P at Memorial Sloan Kettering Cancer Center was reviewed to identify patients receiving subsequent systemic treatments. Clinical data were collected by chart review. Response to EV/P and platinum-based chemotherapy was determined by physician assessment using RECIST v1.1. Progression free and overall survival (PFS, OS) were calculated using the Kaplan-Meier method. **Results:** Of 208 patients treated with EV/P between 10/2018 and 9/2024, we identified 56 patients that received any subsequent systemic treatments. In 68% of patients (n = 38), the initial post EV/P regimen administered was platinum-based chemotherapy. Other therapies included sacituzumab govitecan (n = 6), clinical trials (n = 5), trastuzumab deruxtecan (n = 4), erdafitinib (n = 2) and non-platinum chemotherapy (n = 1). In the 38 patients treated with platinum-based chemotherapy, median age was 74 years, 66% were men, 32% had upper tract primary and divergent histology/subtype component was reported in 47% of cases. One patient had prior platinum exposure (neoadjuvant treatment with rapid metastatic recurrence < 6 months). 16 patients had disease response to EV/P (observed response rate [ORR] 42%, 95% CI 27%, 59%). 36 patients (95%) received doublet therapy with gemcitabine and either cisplatin (n = 7) or carboplatin (n = 29), the two remaining patients received carboplatin/gemcitabine/paclitaxel and carboplatin/etoposide. 7 patients (18%) received maintenance avelumab following platinum. Median follow up was 5 months (IQR: 2.5-6.3). ORR was 50% (95% CI 34%, 66%), including one patient with complete response (CR; 2.9%) and 16 patients with partial response (PR; 47%). Among the patients with CR or PR, median duration of response was 3.8 months (IQR: 2.0-4.6). Median PFS was 4.4 months (95% CI 3.7, 7.8) and median OS was 12 months (95% CI 9.7, 17). **Conclusions:** In a real-world cohort of patients with mUC, platinum-based chemotherapy had substantial antitumor activity after EV/P, although progression-free survival and duration of response were modest. This work provides useful information to further future trial design in the post EV/P setting. Research Sponsor: None.

Disease response with platinum-based chemotherapy after enfortumab vedotin and pembrolizumab.

	N=38 (%)	95% CI
Observed response rate	17 (50%)	34%, 66%
Complete response	1 (2.9%)	0.15%, 17%
Partial response	16 (47%)	30%, 65%
Stable disease	6 (18%)	7.4%, 35%
Progressive disease	11 (32%)	18%, 15%
Unknown	4	

4574 Poster Session

Cutaneous toxicity and clinical outcomes with enfortumab vedotin and pembrolizumab in patients with locally advanced or metastatic urothelial carcinoma. First Author: Alyssa Arbuiso, Memorial Sloan Kettering Cancer Center, New York, NY

Background: Enfortumab vedotin and pembrolizumab (EV/P) recently became the standard of care frontline treatment for patients with locally advanced or metastatic urothelial carcinoma (la/mUC). In patients treated with EV monotherapy, previous studies reported a potential association between cutaneous toxicities and improved clinical outcomes. While cutaneous toxicities are common with EV/P, the correlation with response has not been described. **Methods:** This is a retrospective cohort of patients treated with first line EV/P for la/mUC at Memorial Sloan Kettering Cancer Center. Clinical data were collected by chart review. Response to EV/P was defined by investigator assessment adhering to RECIST 1.1. Cutaneous toxicity events were recorded and classified as mild (managed with topical agents and/or oral antihistamines) or moderate/severe (requiring further pharmacological interventions and/or dose modifications). Association between clinical characteristics and response were analyzed using univariable and multivariable logistic regression models. **Results:** 186 patients who started EV/P between October 2018 and September 2024 were identified, 166 with distant metastases (89%) and 20 (11%) with locally advanced disease. Median age was 72 years, 68% were male, 31% had upper tract primary, and 44% had subtype/divergent histology component. Rates of bone, lung, and liver metastases were 29%, 24%, and 19%, respectively, and 27% had lymph node only disease. Observed response rate was 64% (119/186; 95% CI 57%, 71%), including a complete response rate of 18% (33/186; 95% CI 13%, 24%). Cutaneous toxicities occurred in 106 patients (57%), predominantly within the first 12 weeks (94/106), 70% of events were classified as mild and 30% as moderate/severe. On univariable analysis, cutaneous toxicity at any time, and before 12 weeks were significantly associated with response to EV/P, with odds ratio (OR) 2.6 (95% CI 1.44 - 4.94, p = 0.002) and 1.91 (95% CI 1.04 - 3.53, p = 0.037). Greater effect was seen based on severity: OR 2.24 (95% CI 1.17 - 4.42, p = 0.017) for mild events and OR 4.12 (95% CI 1.62 - 12.0, p = 0.005) for moderate/severe events compared to patients without cutaneous toxicity. Response to EV/P was less likely with distant metastatic disease (vs. locally advanced; OR 0.28, p = 0.05), and with bone metastases (OR 0.44, p = 0.015), and more likely with lymph node only disease (OR 2.89, p = 0.007). When adjusted for treatment setting (metastatic vs locally advanced) and time on treatment in multivariable analysis, the effect of cutaneous toxicity ≤12 weeks on response was no longer significant (OR 1.7, 95% CI 0.9 - 3.25, p = 0.11). **Conclusions:** In our large, real-world cohort there was a non-significant trend for response to EV/P in patients with cutaneous toxicities. Further studies are needed to define the potential correlation. Research Sponsor: None.

4575 Poster Session

Impact of histological subtypes in patients receiving first-line treatment with enfortumab vedotin/pembrolizumab in advanced metastatic urothelial cancer. First Author: Aya Abdelnaser, Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA

Background: Metastatic urothelial carcinoma (mUC) represents a challenging clinical entity with significant morbidity and mortality. Enfortumab Vedotin plus Pembrolizumab (EV+P) has been established as an effective first-line (1L) treatment for mUC, but data regarding the impact of variant subtypes of UC remains limited. This study aims to describe the impact of different histological subtypes on mUC patients (pts) treated with 1L EV+P. **Methods:** This is a single-center retrospective cohort of pts with mUC treated with EV+P in first line between 6/1/2023 and 8/8/2024. Data were collected by chart review, including reviewed pathological reports and their impact on clinical outcomes (ORR, PFS, and OS). Four main histological groups were defined: 1)Transitional UC Predominant: Includes cases where transitional UC is the dominant component. 2) Transitional UC with <50% variant histologies of squamous or glandular differentiation. 3) Transitional UC with >50% variant histologies of squamous or glandular differentiation, including pure squamous or adenocarcinoma types. 4)Other Variant histologies: micropapillary vs. others (plasmacytoid, sarcomatoid, nested, and lipid-rich variants). **Results:** A total of 71 patients with mUC treated with first-line EV+P were included in this analysis, with a median age of 72.78 years. The median follow-up for the cohort was only 8 months (mos). The PFS rate at 12 mos was 43.28%, and the OS rate at 12 mos was 70%. Patients with predominant transitional UC (n=26) had a better response, with an ORR of 57.6% (15/26). Patients with UC having squamous or glandular differentiation (< or> 50%) showed inferior outcomes relative to all other subgroups. Specifically, patients with <50% squamous or glandular differentiation (n=6) had an ORR of 16.6% (1/6), while those with >50% (including pure squamous/glandular) (n=11) showed no response at all (0%, 0/11). Among the rest of the variants, only micropapillary (n=7) showed a substantial benefit with an ORR of 57.1% (4/7). Patients with other variant histologies, including sarcomatoid, plasmacytoid, nested, and lipid-rich (n=8), demonstrated inferior ORRs of 25% (2/8). ORRs based on different histologic subtypes are presented in Table. **Conclusions:** This analysis shows that histological subtypes significantly influence the treatment outcomes of Ev +P treatment. Favorable responses were observed in patients with predominant transitional histologies. Patients with mixed histologies containing squamous or glandular components showed poor responses to EVP independent of the cut-off > or < 50%, raising concern about the validity of the present cut-off value. Adequate responses were observed in the micropapillary subtype only. These findings emphasize the necessity for prospective validation and patient stratification of EV+P treatment in histological subtypes of UC. Alternative treatment strategies should be explored for patients with squamous or glandular subtypes. Research Sponsor: None.

				Variant histologies N=15	
	Transitional UC Predominant) n=37	Transitional UC <50% VH (squamous/ glandular) n=6	Transitional UC >50% VH (squamous/glandular) n=13	Other variant histologies n=8	Micropapillary Variant n=7
ORR	57.6% (15/26)	16.6% (1/6)	0% (0/11)	25% (2/8)	57.1% (4/7)

4576 Poster Session

Assessing treatment outcomes of enfortumab vedotin dose reduction in metastatic bladder cancer. First Author: Hal Difede Rives, The Fox Chase Cancer Center Foundation, Cheltenham, PA

Background: Enfortumab Vedotin (EV), an antibody drug conjugate targeting Nectin-4, has emerged as first-line treatment for advanced Urothelial Carcinoma (UC) in combination with pembrolizumab. Acute and cumulative toxicity due to EV can adversely impact quality of life. Treatment related adverse events (TRAEs) are managed with dose and schedule modifications. Current treatment paradigm is to treat until unacceptable toxicity or progression. Our single center, retrospective study, aims to assess the impact of EV dose reduction on treatment duration, AEs, and survival. **Methods:** We conducted a retrospective analysis of patients with UC treated with EV +/- pembrolizumab. Patients were divided into 3 groups: A) 1.25 mg/kg dose and not dose-reduced; B) 1.25 mg/kg dose and dose-reduced; C) EV < 1.25 mg/kg. Data was collected from the EMR and we evaluated OS, PFS, TRAEs, and number of doses received. Kaplan Meier and Cox proportional hazards regression models were used to compare PFS and OS between the 3 groups, and to evaluate treatment dose (1.25 mg or <1.25 mg) as a time-varying covariate. TRAEs (y/n) and number of doses received were examined using logistic and negative binomial regression respectively. Regression models adjusted for age, ECOG status, and receipt of concurrent pembrolizumab. **Results:** 153 patients comprised the 3 groups: A) n= 47; B) n=73; C) n=33. The cohort was majority male (78.4%) and white (79.1%) with no significant difference across groups. Median age and ECOG score were both significantly higher in group C (p<0.001 and p=0.033, respectively). Overall, 52.9% of patients received prior immunotherapy, while 35.9% of patients received concurrent pembrolizumab (similar across groups). Patients started on full dose EV then reduced (B) had significantly more TRAEs than groups A and C (Neuropathy; A: 15.2%, B:34.2%, C: 12.1%, p<0.001; Cutaneous AE; A: 4.3%, B:27.4%, C:2.1%, p=0.004). In unadjusted Kaplan Meier analyses (months), there was a trend but no statistically significant difference in PFS (A:6.4, B:10.1, C:13.1; p=0.1) or OS (A:10.5, B:15.6, C:22.9; p=0.22). In adjusted analyses (minimum 5 doses of EV), there was no difference in total doses received across groups(p=0.6867). Adjusted Cox proportional hazards regression (HR) showed significantly improved PFS and OS for the dose-reduced groups by both landmark (Table 1) and time-covarying analyses (<1.25 PFS, HR: 0.6 p=0.032; <1.25 OS, HR: 0.59 p=0.039). **Conclusions:** In adjusted analyses dose reduced groups had significantly improved PFS and OS. These results suggest that changes in dose can decrease overall AEs while maintaining efficacy, warranting prospective evaluation. Research Sponsor: None.

	1.25 mg/kg dose and dose-reduced	Significance	Started < 1.25 mg/kg	Significance
Landmark Analyses PFS (HR)	0.48	p=0.019	0.44	p=0.049
Landmark Analyses OS (HR)	0.53	p=0.038	0.47	p=0.063

4577 **Poster Session**

Pembrolizumab (pembro) with chemoradiotherapy (CRT) as treatment for muscle-invasive bladder cancer (MIBC): Long-term follow up of secondary endpoints of efficacy including overall survival of the PCR-MIB phase II clinical trial (ANZUP 1502). First Author: Andrew James Weickhardt, Olivia Newton John Cancer Wellness & Research Centre, Austin Health, Melbourne, VIC, Australia

Background: We hypothesised pembro could be added without undue toxicity to CRT and would improve efficacy in patients (pts) with MIBC. **Methods:** This multicentre phase 2 trial included people with non-metastatic cT2-T4aN0M0 MIBC (>50% urothelial histology) who declined cystectomy or for whom cystectomy was unsuitable, with no contraindications to CRT or pembro, ECOG performance status 0 or 1, eGFR ≥40 mL/min. Neoadjuvant chemotherapy was not permitted. Pts had maximal TURBT, then whole bladder radiation therapy (RT) (64Gy in 32 daily fractions, mostly IMRT) over 6.5 weeks with weekly cisplatin (35 mg/m^2 IV, 6 doses) and pembro 200mg IV q3wk x 7 doses, both starting with RTx. Surveillance cystoscopy, urine cytology, and CT chest-abdomen-pelvis were performed 12 & 24 weeks after CRT. The primary endpoint was feasibility, determined by a prespecified satisfactory low rate of grade 3-4 non-urinary toxicity, or completion of planned CRT within defined parameters (RT < 7 weeks, >1 cisplatin dose omission). Secondary endpoints include rate of complete cystoscopic response without metastatic disease at 12 & 24 weeks, distant metastases free survival (DMFS), overall survival (OS), and loco-regional progression free survival (LRPFS). Longer term follow up (median 54 months) is presented here from the November 2024 analysis. **Results:** From 2016 – 2021, 28 pts (93% male, median age 72, 96% pure urothelial carcinoma, 29% with carcinoma in situ, 90% pT2) were enrolled at 6 sites. At 48 months, DFMS was 68% (95% CI 46-82%), OS was 64 % (95% CI 42-79%), with median OS not reached (95% CI 25.6m – NE). Local-regional failure free survival at 48 months was 84% (95% CI 63 – 94). Complete response (CR) rate 24 weeks post CRT was 88% (95% CI 70-98%, 23 CR, 3 PD, 2 NE). The The regimen was deemed feasible as previously presented: 6 pts had Gr >3 non-urinary any adverse events (AEs) during treatment or within 12 weeks after completing treatment (2 with delay in RT >7 wks), and 2 pts had cisplatin dose reductions due to G2 AEs. 1 pt had G3 colitis, 1 pt had G2 polymyalgia, 1 pt G2 nephritis. There were no additional immune related adverse events reported with longer follow-up. **Conclusions:** Longer follow up shows promising OS, DMFS and LRPFS with the combination of CRT and pembro for MIBC. There were no new immune related adverse events. Larger randomised trials to test this approach are ongoing. Clinical trial information: NCT02662062. Research Sponsor: Merck Sharp & Dohme LLC (Australia), a subsidiary of Merck & Co., Inc., Rahway, NJ (USA).

4578 **Poster Session**

Prognostic utility of ctDNA before and after trimodality therapy (TMT) for muscle invasive bladder cancer. First Author: Brendan Raizenne, University of California, San Francisco, San Francisco, CA

Background: Outside of standard patient and tumor characteristics, biomarkers predicting outcomes after TMT for non-metastatic muscle-invasive bladder cancer (MIBC) are lacking. Tumor-informed circulating tumor DNA (ctDNA) has identified MIBC patients at risk of relapse following radical cystectomy. This study assessed the clinical utility of a ctDNA assay in predicting disease progression following TMT. **Methods:** We retrospectively identified patients (pts) with MIBC (cT2-T4, cN0-N2, cM1) who had TMT between 2019 and 2024 and ctDNA assessment with a personalized, tumor-informed assay (Signatera, Natera, Inc) before and/or after TMT. Standard clinical variables extracted include TNM stage, risk factors at TURBT (carcinoma in situ (CIS) and hydronephrosis) age of diagnosis, primary radiotherapy (RT) dose, chemotherapy regimen/duration, and if elective nodal irradiation (ENI) was received. We analyzed the impact of pre-TMT or post-TMT ctDNA (MTM/mL), as well as changes in ctDNA, on disease-free survival (DFS) using the Kaplan-Meier method. We assessed the impact of ENI on DFS in cN0 pts with positive ctDNA at baseline. Predictors of recurrence were assessed with univariate Cox proportional hazard models. **Results:** Among 34 pts, median age was 69 (interquartile range (IQR) 62-79), majority were male (91%), had cT2 (73.5%), were cN0 (85%), had no CIS (76%) or hydronephrosis (94%). The median dose of RT was 64 Gy. Ten (29%) patients had detectable ctDNA prior to TMT. Median follow-up was 13.2 months from last RT dose of TMT. Pts with detectable ctDNA after TMT had inferior DFS compared to pts with persistently undetectable (pre/post-TMT) or pts with ctDNA clearance (median survival of 5 months vs 15 and 19 months, respectively, log-rank p = 0.056). Table 1 shows results for predictors of DFS after TMT. Pts with detectable ctDNA post-TMT (n = 4) all developed distant metastatic recurrence. Local recurrences did not present with a detectable ctDNA following TMT. Pts with measurable ctDNA at baseline demonstrated potentially prolonged DFS after ENI (n = 4) compared to the non-ENI cohort (n = 6), but did not meet statistical significance (7.6 months vs not reached, p = 0.2). **Conclusions:** Persistently detectable ctDNA following TMT correlates with disease-free survival. Larger cohorts are needed to assess role of ENI in pts with detectable ctDNA prior to TMT. These results are hypothesis-generating and should be validated prospectively. Research Sponsor: None.

Predictors of DFS after TMT.

	HR (95% CI)	P-value
Histologic type (Reference (Ref) group: Pure urothelial)		
Urothelial with minor variant	0.76 (0.21-2.84)	0.69
CIS on TURBT (Ref group: No CIS)		
CIS	0.61 (0.16-2.28)	0.46
Pre-TMT Hydronephrosis (Ref group: No Hydronephrosis)		
Hydronephrosis	3.63 (0.77-17.19)	0.1
Response of ctDNA status to TMT (Ref group: Detectable to Detectable)		
Detectable to Undetectable	0.12 (0.02-1.00)	0.05
Undetectable to Undetectable	0.26 (0.04-1.75)	0.17

4579 **Poster Session**

Quantifying patient preferences for bacillus Calmette-Guérin (BCG) and PD-(L)1 inhibitors in high-risk non-muscle invasive bladder cancer (NMIBC): A discrete choice experiment. First Author: Pam Hallworth, Adelphi Research, Bollington, United Kingdom

Background: Intravesical Bacillus Calmette-Guerin (BCG) induction + maintenance (I+M) is the standard of care for high-risk NMIBC. Disease recurrence and progression is common. The studies investigating programmed cell death-1/programmed death-ligand 1 (PD-[L]1) inhibitors + BCG aim to enhance treatment outcomes and reduce burden in BCG naïve high-risk NMIBC. There is limited evidence on patient preferences for these combination regimens. **Methods:** A discrete choice experiment quantified preferences for attribute levels related to BCG and PD-(L)1 inhibitors. Attributes and levels were informed by a literature review, patient interviews, regulatory scientific advice, clinical experts and a patient advocate. Patients completed hypothetical choice tasks describing administration mode and frequency for PD-(L)1 inhibitors and BCG (induction [I]; I+M), median event-free survival (EFS) and adverse events (AEs: bladder AEs; chronic endocrine conditions; serious immune AEs). Hierarchical Bayesian modelling estimated preference weights (PWs) for attribute levels. PWs identified level combinations with the lowest choice probability. Relative importance (RI) was calculated by systematically varying attribute levels and capturing the gain in choice probability. **Results:** 150 patients (77 BCG-naïve; 73 BCG-experienced) in the United States completed the survey. Clinician-confirmed diagnosis (17%) and/or self-reported ongoing or planned BCG I+M (99%) was obtained. The sample was 51% male, had a median age of 63 years (49-74) and diverse by race (Caucasian 46%; African American/Black 27%; Other 27%) and ethnicity (Hispanic/Latino/Spanish 21%). EFS was the most important attributes to patients (RI 17.2), followed by bladder AEs (RI 16.4) and serious immune AEs (RI 14.0). Administration attributes were important (RI 9-9.9), but less important than other attributes. PWs show that short duration (< 1 minute) subcutaneous (SC) injections was the most preferred PD-(L)1 route and shorter BCG schedule was preferred. **Conclusions:** Findings highlight the value of prolonging EFS, effective clinical management of BCG AEs and reducing administration burden in future BCG + PD(L)1 regimens. Research Sponsor: Pfizer Inc.

Attribute	Level	Mean PW	95% CI (±)	RI*(%)
EFS (months)	36	3.46	0.28	17.2
	27	-1.03	0.11	
	22	-2.43	0.22	
Bladder AEs (%)	0	2.98	0.29	16.4
	35	-0.10	0.12	
	75	-2.88	0.26	
Serious immune AEs (%)	0	1.40	0.22	14.0
	10	-0.09	0.09	
	20	-1.31	0.18	
Chronic endocrine conditions (%)	0	0.99	0.15	12.6
	5	-0.08	0.08	
	10	-0.91	0.16	
PD-(L)1 frequency (weeks)	6	0.45	0.10	9.9
	4	-0.10	0.10	
	3	-0.35	0.06	
PD-(L)1 administration route and time	SC <1 minute	0.15	0.09	9.5
	SC 7-10 minutes	0.06	0.10	
	IV 30-60 minutes	-0.21	0.08	
BCG schedule	I	0.25	0.14	9.0
	I+M	-0.25	0.14	

*Sums to 88.7. The remaining 11.3 corresponds to an attribute used for analysis only.
CI: confidence interval; IV: intravenous infusion.

4580 **Poster Session**

Evaluation of surrogate endpoints in muscle-invasive bladder cancer (MIBC): A systematic review and meta-analysis. First Author: Matthew D. Galsky, Tisch Cancer Institute, Icahn School of Medicine at Mount Sinai, Department of Medical Oncology, New York, NY

Background: Overall survival (OS) is the gold-standard efficacy measure in oncology; however, it can take several years for OS data to mature, particularly in the clinically localized setting in patients undergoing curative intent treatment. To accelerate patient access to novel therapies, surrogate endpoints can be used to accelerate the assessment of new treatments when an early measure is reasonably likely or known to predict the clinical benefit for a target outcome such as OS. MIBC is a potentially curative disease with a complex and evolving treatment landscape involving radical cystectomy with or without systemic therapies, and bladder sparing strategies. Despite the need for surrogate endpoints in MIBC, there is limited research on their validity in this patient population. **Methods:** This study evaluated the trial-level surrogacy of event-free survival (EFS), progression-free survival (PFS), and disease-free survival (DFS) with respect to OS in MIBC. A systematic literature review (SLR) was conducted to identify randomized controlled trials (RCTs) that evaluated anti-cancer treatments (neoadjuvant, adjuvant, perioperative, and bladder sparing therapies) in MIBC and reported results for OS and ≥1 surrogate endpoint of interest. Studies published between Jan 1, 2000 and Jun 26, 2024 were identified by searching the MEDLINE, EMBASE, and CENTRAL databases. Grey-literature sources included recent conference proceedings and clinical trial registries. Study quality was assessed using the Cochrane Risk of Bias v2 tool. Data from studies with comparable outcome definitions for EFS, PFS, and DFS were combined into a broad composite outcome definition (cEFS). Trial-level surrogacy between the hazard ratio (HR) for cEFS and OS was evaluated. Analyses were conducted using a weighted linear regression (WLR) model and the bivariate Daniel & Hughes (D&H) model. Measures of surrogacy included the Pearson correlation coefficient (r) to measure the strength of association and the surrogate threshold effect (STE) to estimate the minimum HR for cEFS needed to reliably predict a HR for OS < 1. **Results:** 32 RCTs across 71 publications were included in the SLR; 14 were included in the cEFS analyses based on a feasibility assessment. Trials with a high-risk of bias (n = 1) or that evaluated the initiation of systemic therapy after disease progression (n = 4) were excluded. The HR for cEFS was strongly correlated with the HR for OS (r = 0.94; 95% CI: 0.72-0.99). Based on the STE, a HR <0.88 for cEFS would be needed to reliably predict a HR < 1 for OS. Results from the D&H model were consistent with these findings. **Conclusions:** These results suggest that at the trial level, the HR for cEFS is highly correlated with the HR for OS in MIBC across various treatment settings. cEFS may assist clinicians, regulatory agencies, and reimbursement bodies in contextualizing the benefits of novel treatment strategies in MIBC. Research Sponsor: Pfizer; Astellas Pharma Inc.

4581 **Poster Session**

MRI radiomics to predict outcome of neoadjuvant chemotherapy in patients with muscle invasive bladder cancer undergoing radical cystectomy. First Author: Lawrence Howard Schwartz, Memorial Sloan Kettering Cancer Center, New York, NY

Background: Cisplatin-based neoadjuvant chemotherapy (NAC) before radical cystectomy (RC) is the standard of care in patients with muscle-invasive bladder cancer (MIBC). Although the administration of NAC for MIBC has increased over the years, it still does not meet actual patient's needs, particularly in cT2 BC, for which it is currently recommended in clinical guidelines. Indeed, with the development of new cytotoxic and targeted therapies, large ongoing prospective studies have been designed to test their efficacy either alone or in combination in the neoadjuvant setting. Multidisciplinary management is critical in this disease setting; including advanced imaging to assess response to treatment and outcome correlations. Despite the promising applications of radiomics in MIBC treatment outcome assessment, challenges remain, including successful harmonizing of imaging data, which impacts the consistency of radiomic features. The objective of the study is to assess the ability of radiomic features extracted from a robust magnetic resonance imaging (MRI) processing pipeline to predict the outcome of NAC prior to RC in patients with MIBC. **Methods:** A total of 105 MIBC patients (67M/38F), median age (65), clinical stage 2 (77), 3(28)) who were treated with NAC (cisplatin-based therapy) and underwent RC were included in this study. All patients underwent preNAC MRIs using the standard acquisition protocol. Tumors were segmented on T2w, T1w, and post contrast-T1w images by GU radiologists. To standardize MRI intensity values across scans, preprocessing steps were required to ensure comparability between patients. After N4-bias field correction of image intensities, images were standardized to robust z-scores using median and mean absolute deviation of intensities within respective regions of interest. IBSI-compatible pyCERR software was used to extract radiomics features. A total of 289 radiomic features, including shape, first-order statistics, and higher-order textures, were analyzed for the overall survival (OS, time between RC to death) as an outcome. To identify features associated with OS, we trained an Elastic Net Cox regression model for each MRI sequence, with performance evaluated by concordance index (c-index) on a 30% held-out test set. **Results:** The same shape feature (major axis length) from post contrast-T1w and T2w images was selected as important by the elastic net with test set c-index of 0.55 [0.42 – 0.67) and 0.56 [0.42 – 0.70], respectively. Kaplan-Meier method further confirmed the significance of this feature ($p < 0.05$) for OS risk stratification, using the median feature value as the cutoff point. **Conclusions:** The study demonstrated the value of radiomics in predicting survival to NAC with MIBC which can be further validated with a larger independent cohort. MRI radiomics may be an additional tool for prognostication. Research Sponsor: None.

4582 **Poster Session**

Distinct genomic landscape of Lynch syndrome–associated urothelial cancer. First Author: Jussi Nikkola, Department of Urology, Tampere University Hospital, Tampere, Finland

Background: Lynch syndrome (LS) is a hereditary cancer predisposition syndrome caused by DNA mismatch repair (MMR) deficiency and associated with a 10–25% lifetime risk of urothelial cancer (UC), particularly in the upper urinary tract. We aimed to investigate the somatic genomic landscape of LS-associated urothelial cancer (LS-UC) using targeted and whole-exome sequencing (WES). **Methods:** We analyzed 41 surgical tumor samples accrued to five Finnish biobanks between April 1987 - June 2022 and 3 urine DNA samples from 34 LS-UC patients, all enrolled in the Finnish Lynch Syndrome Registry. Tumors were profiled using the UroScout assay, targeting 25 UC-associated genes, to identify somatic mutations. Immunohistochemistry was performed to assess MMR protein loss, and WES was conducted on selected cases to investigate the broader mutation landscape. A comparative analysis of the genomic and mutational landscapes in LS-UC versus sporadic UC was performed. **Results:** We show that telomerase reverse transcriptase (*TERT*) promoter mutations found in 83% of sporadic UC are almost completely absent (5%) in LS-UC ($p < 0.00001$). Instead, all LS-UC exhibited a 5-methylcytosine deamination (CG > TG) and microsatellite instability driven mutation landscape, characterized by highly frequent *ARID1A* (82%), *FGFR3* (80%), and *KMT2D* (78%) mutations, as well as preferential usage of CG > TG mutation hotspots. We propose that scarcity of *TERT* promoter mutations in LS-UC is due to inability to create the GABP binding motif 5'-GGAA through CG > TG mutation or microsatellite instability. Additionally, many mutation hotspots recurrently mutated in sporadic UC were not present in LS-UC. **Conclusions:** Our findings establish LS-UC as a distinct disease entity with a unique genomic signature driven by constrained hypermutation. Our proposed explanation that *TERT* mutations are absent in LS-UC due to constrained hypermutation is supported by our discovery that other UC driver genes also exhibit an altered mutation landscape in LS-UC. These insights advance the understanding of LS-UC tumorigenesis and support the development of tailored diagnostic and therapeutic approaches for this patient population. Research Sponsor: Jane and Aatos Erkko Foundation; Academy of Finland Center of Excellence Program; Finnish Cultural Foundation; Finnish Medical Foundation; Orion Research Foundation; Sigrid Juselius Foundation; Relander Foundation; Cancer Society Finland; iCAN Precision Medicine Flagship of the Academy of Finland; Competitive State Research Funding of Tampere University Hospital.

4583 **Poster Session**

Study EV-103 cohort H: Neoadjuvant treatment with enfortumab vedotin (EV) monotherapy in cisplatin (cis)-ineligible patients (pts) with muscle invasive bladder cancer (MIBC)—3-year efficacy results. First Author: Nataliya Mar, University of California Irvine, Irvine, CA

Background: For cis-ineligible pts with MIBC undergoing radical cystectomy and pelvic lymph node dissection (RC+PLND), no neoadjuvant treatment options have been shown to improve survival, highlighting a clinical need. EV previously demonstrated encouraging antitumor activity in cis-ineligible pts with MIBC as neoadjuvant treatment in EV-103 Cohort H. We present updated 3-year efficacy results. **Methods:** EV-103 Cohort H enrolled cis-ineligible pts with MIBC (cT2-T4aN0M0) and ECOG PS ≤2 who were eligible for RC+PLND. Pts received neoadjuvant EV monotherapy (1.25 mg/kg) on Days 1 and 8 every 21 days for 3 cycles before undergoing RC+PLND. Primary endpoint was pathological complete response (pCR) rate by central pathology review. Secondary endpoints included event-free survival (EFS) per investigator assessment (INV), OS, and safety. A genAI tool (01/09/25; Pfizer; GPT-4o) developed the 1st draft; authors assume content responsibility. **Results:** Overall, 22 pts were enrolled. 86.4% of pts completed all 3 cycles of neoadjuvant EV treatment. Three pts (13.6%) discontinued neoadjuvant EV due to AEs. All pts underwent RC+PLND; 13 (59.1%) were in long-term follow-up at data cutoff (Nov 20, 2024). Median follow-up was 49.7 mo (range, 3.1-53.6). pCR rate was 36.4% (8/22; 95% CI, 17.2-59.3). Median EFS by INV was 40.1 mo (95% CI, 14.5-NE) for all pts, NR (95% CI, 6.5-NE) for pts with pCR, and 18.8 mo (95% CI, 6.7-NE) for pts without pCR. Estimated EFS rate by INV at 24 and 36 months was 62.0% (95% CI, 38.2-78.9) and 56.9% (95% CI, 33.4-74.8), respectively, and improved in pts with pCR. Median OS was NR (95% CI, 33.4-NE) in all pts. Estimated OS rate at 24 and 36 months was 77.3% (95% CI, 53.7-89.9) and 68.2% (95% CI, 44.6-83.4), respectively. Key updated 3-year efficacy data are shown in the Table. The safety profile was consistent with prior reports, and no new safety concerns were seen. **Conclusions:** Based on 3-year efficacy results, neoadjuvant EV monotherapy treatment continued to show encouraging antitumor activity in cis-ineligible pts with MIBC, including median EFS and OS exceeding historical real-world data in cis-ineligible patients following RC alone (Li Eur Urol Oncol 2024; Rose SESAUA 2023). The safety profile was generally manageable and consistent with the known AE profile of EV in other settings. Phase 3 trials evaluating perioperative EV + pembrolizumab in cis-eligible and -ineligible pts with MIBC (KN-905/EV-303, KN-B15/EV-304) are ongoing. Clinical trial information: NCT03288545. Research Sponsor: The EV-103 study was funded by Astellas Pharma Inc., Northbrook, IL, USA; Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA; and Seagen Inc., Bothell, WA, USA, which was acquired by Pfizer in December 2023.

Median EFS by INV (95% CI), months	
All pts	**40.1 (14.5-NE)**
pCR	**NR (6.5-NE)**
Non-pCR	**18.8 (6.7-NE)**
3-year EFS rate by INV (95% CI), %	
All pts	56.9 (33.4-74.8)
pCR	72.9 (27.6-92.5)
Non-pCR	46.4 (19.3-69.9)
Median OS (95% CI), months	NR (33.4-NE)
3-year OS rate (95% CI), %	68.2 (44.6-83.4)

n=22. Median values should be interpreted with caution due to small sample size.

4584 **Poster Session**

Revolutionizing bladder cancer follow-up: Personalized urinary ctDNA analysis for detecting minimal residual disease. First Author: Xuebin Wan, HaploX Biotechnology Co., Ltd., Shenzhen, China

Background: As one of the most common malignant neoplasms of the urinary tract, bladder cancer (BC) has received widespread attention with respect to high incidence and tend to recur and progress. Circulating tumor DNA (ctDNA) serves as a valuable tool for detecting and monitoring minimal residual disease (MRD). Here, we conducted a prospective study to assess the potential of urinary ctDNA (utDNA) as a biomarker for measuring MRD in patients for non-muscle-invasive bladder cancer (NMIBC). The objective of this study was to evaluate the utility of longitudinal utDNA in informing adjuvant therapy decisions, enhancing clinical monitoring strategies, and ultimately improving BC prognosis. **Methods:** A total of 67 patients diagnosed with stage I-IV BC were recruited for the study from 2022.11 to 2024.12. For each patient, a customized panel was developed and synthesized, encompassing up to 45 baseline mutations, including SNVs and Indels. In addition to the patient-specific panel, a standardized core panel targeting hotspot regions was incorporated. Whole exome sequencing (WES) was conducted on cancer tissue samples and blood leukocytes in order to reduce the risk of false-positive findings and to exclude potential germline mutations, respectively. **Results:** The study cohort consisted of 59 patients diagnosed with BC, 7 patients with renal pelvis cancer, and 1 patient with ureteral cancer. 59 individuals, accounting for 88% of the sample, had a median age of 65 years. UtDNA was identified in 64 out of 67 preoperative patients, resulting in a detection rate of 95.5%. Furthermore, the correlation between urine samples and tissue samples was confirmed by Pearson's correlation analysis, yielding a correlation coefficient of (r = 0.31). 10 patients (14.9%) experienced a recurrence following TURBT. Residual tumors were detected in 7 of the recurrent patients who tested positive for urinary utDNA, accounting for 70% of the cases (7/10). Notably, the presence of positive utDNA in urine samples was observed 3 to 8 months prior to any indications on imaging studies. Monitoring of MRD demonstrated a consistent reduction in utDNA concentrations following surgery. Among patients with complete remission (CR), 9 individuals who initially tested positive for MRD post-surgery subsequently tested negative. **Conclusions:** The findings revealed a high level of concordance between the mutations identified in the tumor and those detected in the utDNA. Patients with positive utDNA exhibited a greater risk of cancer recurrence compared to those who tested negative for utDNA. Urine-personalized MRD detection strategies are anticipated to enhance the efficacy of adjuvant therapy and improve prognostic assessments in patients with BC. None. Clinical trial information: ChiCTR2400079704. Research Sponsor: None.

4585 **Poster Session**

An exploratory study of clostridium butyricum combined with neoadjuvant chemoimmunotherapy in urothelial carcinoma. First Author: Xiao Yang, Department of Urology, The First Affiliated Hospital of Nanjing Medical University, Nanjing, China

Background: Neoadjuvant chemoimmunotherapy using gemcitabine, cisplatin, and anti-PD1 has shown survival benefits for advanced bladder cancer patients, though response rates remain low. Recent studies highlight the role of clostridium butyricum in anti-tumor immunity, but its potential to enhance bladder cancer therapy is unexplored. **Methods:** This exploratory study (NCT06696742) involved patients with cT2-T4aN0M0 urothelial carcinoma at First Affiliated Hospital of Nanjing Medical University. Participants were randomized into two groups, one received with GC+anti-PD1 (gemcitabine 1.0 g/m^2 D1 and D8, cisplatin 70 mg/m^2 D2-4, and tislelizumab 200 mg D8 once every 21 days for 3-4 cycles), and the other received the same regimen plus Clostridium butyricum tablets (1-2 tablets, three times a day). Primary observations were pathological complete response (pCR, ypT0) and pathological down-staging ($<$ ypT2), the second observations included imaging assessment (RECIST 1.1) and safety. **Results:** In the combination group, 23 out of 30 patients completed treatment and underwent radical cystectomy, achieving a clinical complete response (CR) rate of 52.2% (12/23) and a partial response (PR) rate of 39.1% (9/23). Two patients (8.6%) showed stable disease (SD) and seven patients are still receiving treatment. Pathological downstaging was observed in 82.6% (19/23) of the patients, with 52.2% reaching ypT0 (12/23). In the control group, all 26 enrolled patients completed treatment and underwent radical cystectomy. The clinical CR rate was 30.7% (8/26), while the clinical PR rate was 42.3% (11/26). Six patients (23.1%) had stable disease, and 1 patient (3.8%) experienced disease progression (PD). Pathological downstaging occurred in 61.5% (16/26) of the patients, with 26.9% (7/26) achieving ypT0. The combination group demonstrated significantly higher rates of clinical CR+PR (P = 0.037) and pathological downstaging (P = 0.042) compared to the control group. There was no statistical difference between the two groups in terms of demographic characteristics. **Conclusions:** Combining neoadjuvant chemoimmunotherapy with Clostridium butyricum improves pathological and clinical response rates in cT2-T4aN0M0 urothelial carcinoma patients. Clinical trial information: NCT06696742. Research Sponsor: None.

4586 **Poster Session**

Updated efficacy and safety results from ReBirth, a phase II study of risk-based bladder-sparing therapy for MIBC. First Author: Yijun Shen, Department of Urology, Fudan University Shanghai Cancer Center; Department of Oncology, Shanghai Medical College, Fudan University, Shanghai, China

Background: Trimodal therapy (TMT) has achieved long-term survival and persistent oncologic control in selected MIBC patients, however, tailored treatment based on chemotherapy plus PD-1 inhibitor responses is currently absent. Furthermore, the safety and efficacy of hypo-fractionated radiation in combination with PD-1 inhibitors and concurrent chemotherapy is worth exploring. **Methods:** This was a two-stage, single-arm, phase II trial recruiting cT2-4aN0-1M0 MIBC pts. Based on results of cystoscopy, urine cytology and imaging after first stage (Tislelizumab (T) 200 mg on D1, Cisplatin (C) 70 mg/m^2 on D1 and Gemcitabine (G) 1000 mg/m^2 on D1 and D8 Q3W for 3-4 cycles), pts achieving cCR (cT0, cTa) were treated with T, while the other pts received T and chemoradiotherapy (whole bladder 44Gy/16 fractionation combined with C as radiosensitizer, if lymph node was positive, it could be dosed to the maximum tolerable dose, such as tumor boost 11Gy/4 fractionation). The primary endpoint was 1-year bladder-intact event-free survival (BI-EFS) rate in the intention to treat (ITT) population (from enrolment to muscle-invasive recurrence, nodal or distant metastasis, radical cystectomy (RC) or death). Secondary endpoints included 1-year BI-EFS rate in the per-protocol (PP) population, metastasis-free survival, recurrence-free survival and safety. **Results:** As of January 16, 2025 (median follow up: 14.3 months), 32 pts with a median age of 64 (36-79) years were enrolled (cT2: 71.8%; cT3: 21.9%; cT4: 6.3%; cN1: 6.3%). One pt withdrew consent and were not evaluated for efficacy. In the ITT population, 22 (71.0%) pts achieved cCR and 9 (29.0%) pts were non-cCR. Four pts underwent RC before finishing the first-stage treatment. 1-year BI-EFS rate was 86.9% (95%CI, 68.8-94.9) in the ITT population and 95.8% (95%CI, 73.9-99.4) in the PP population. In the PP population, 1-year BI-EFS rate for cCR pts and non-cCR pts was 100% and 80% respectively. Overall, 5 pts had T1HG recurrence. Meanwhile, 3 pts developed distant metastases (Bone:3; distant lymph node:2). TRAEs of any grade were found in 78.1% pts and 42.3% experienced grade 3-4 TRAEs. No new safety signs were discovered. **Conclusions:** The updated findings continued to show promising efficacy and manageable toxicity via the two-stage treatment. Non-cCR pts might avoid RC through intensified treatment with chemoradiotherapy and T. Follow-up for long-term survival outcomes is still ongoing. Clinical trial information: NCT05531123. Research Sponsor: None.

4587 **Poster Session**

Postoperative assessment using urinary tumor DNA (utDNA) to identify potential candidates for repeat transurethral resection of bladder tumor (re-TURBT) in non-muscle invasive bladder cancer (NMIBC): A retrospective analysis. First Author: Zihan Xue, The Second Hospital of Tianjin Medical University, Tianjin, China

Background: The role of routine repeat transurethral resection of bladder tumor (re-TURBT) in managing non-muscle invasive bladder cancer (NMIBC) remains controversial, especially when the initial resection includes the detrusor muscle. Urinary tumor DNA (utDNA) seem really promising in urothelial carcinoma diagnosis and detection of minimal residual disease. Here, we investigated the correlation between post-initial TURBT utDNA results and the pathology of secondary resection to assess utDNA's potential for precisely identifying patients who may benefit from re-TURBT. **Methods:** A retrospective analysis was conducted on patients with HG Ta/T1 bladder carcinoma (BCa) who underwent re-TURBT in 2 to 6 weeks after initial TURBT at The Second Hospital of Tianjin Medical University between 2020 and 2024. All visible tumor were completely resected and detrusor muscle was collected at the initial surgery. Urine samples were collected and utDNA analysis was performed using a validated next-generation sequencing (NGS) platform a week after initial TURBT. The secondary resection includes the base of the primary tumor, resection margins, excision scar and any suspicious lesion. The results of utDNA testing were compared with the histopathology from re-TURBT. **Results:** 130 patients met the study inclusion criteria. Re-TURBT was successfully performed in all study participants. Urinary tumor DNA test was positive in 39 patients; of whom 35 (89.7%) showed positive repeat biopsy (HR = 7.42, 95%CI = 2.94-18.67, P $<$ 0.001). The sensitivity, specificity, positive and negative predictive value of utDNA test for re-TURBT histopathology were 76.1% (95%CI : 64-88) , 95.2% (95%CI : 91-99) , 89.7% (95%CI : 80-99) , 87.9% (95%CI : 81-95) , respectively. On a median (range) follow-up of 23 (3-47) months , 15 cases of tumor recurrence were encountered in 14 (10.7%) patients. On multivariate Cox regression analysis, the post-initial-TURBT utDNA test was significantly associated with tumor recurrence (HR = 4.48, 95%CI : 2.0-9.8, P $<$ 0.001). **Conclusions:** Our findings suggest that utDNA analysis after initial TURBT can effectively identify patients with residual disease who are likely to benefit from re-TURBT and that utDNA is an independent predictor of tumor recurrence. This non-invasive liquid biopsy method has the potential to identify beneficiaries of re-TURBT, and optimize the management of HG Ta/T1 bladder cancer. Further prospective studies are warranted to validate the clinical utility of utDNA in this setting. Research Sponsor: None.

4588 **Poster Session**

Updated results from a phase II study of perioperative disitamab vedotin (RC48-ADC) plus cadonilimab (AK104) for HER2-expressing muscle-invasive bladder cancer (MIBC). First Author: Sujun Han, Department of Urology, National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China

Background: Several current ongoing clinical trials have shown promising efficacy and safety of antibody-drug conjugates (ADCs) alone and in combination with immune checkpoint inhibitors (ICIs) as neoadjuvant treatment for patients with MIBC (ASCO 2024). Disitamab vedotin (RC48-ADC) is a novel humanized anti-HER2 ADC. RC48-ADC combined with cadonilimab (AK104), known as the PD-1/CTLA-4 bispecific antibody ICI, may have enhanced synergistic antitumor effects attributed to the mechanism of action and achieve more clinical benefit. Here, we report updated results from a phase II study of perioperative RC48-ADC plus AK104 in HER2-expressing MIBC (NCT06074484). **Methods:** This single-arm, open-label, multicentre study evaluates the efficacy and safety of RC48-ADC plus AK104 as a novel neoadjuvant and adjuvant therapy in patients (pts) with treatment-naïve HER2-expressing (immunohistochemistry, IHC 1+, 2+, 3+) MIBC (T2-T4a, N0-1, M0; ECOG PS score 0-1). Eligible pts received neoadjuvant RC48-ADC (2.0 mg/kg D1 Q2W, 4 cycles) + AK104 (6.0 mg/kg D1 Q2W, 4 cycles) followed by radical cystectomy and pelvic lymph node dissection (RC+PLND), and postoperative adjuvant RC48-ADC (2.0 mg/kg D1 Q3W, 6 cycles) + AK104 (10.0 mg/kg D1 Q3W, 14 cycles). The primary endpoint was pathologic complete response (pCR, pT0N0M0). Secondary endpoints were pathologic downstaging rate (pDS, yp$\leq$T1N0), disease-free survival (DFS), overall survival (OS), objective response rate (ORR), and safety. **Results:** By January 2025, 43 pts had been successfully enrolled. Of these, 81.4% (35/43) were male and 18.6% (8/43) were female, with a median age of 65 years (range, 44-78). HER2 expression was positive (IHC 2+ or 3+) in 72.1% of pts and PD-L1 positive (CPS $\geq$ 10) in 34.9%. The pCR rate was 64.71% (22/34, 95% CI, 47.85-78.58) in all evaluable pts, 81.82% (9/11) in HER2 1+ and 56.57% (13/23) in HER2 2+/3+ pts, meanwhile 77.78% (14/18) in cT2, 30.00% (3/10) in cT3, and 83.33% (5/6) in cT4a/N1 pts. The overall pDS rate was 76.47% (26/34). Treatment-related adverse events (TRAEs) of any grade occurred in 90.7% of pts (39/43), with $\geq$ Grade 3 TRAEs in 18.6% (8/43), including fever, rash, bone marrow hypocellular, alanine aminotransferase increased, and immune-mediated myocarditis or pneumonitis. No Grade 4 or Grade 5 TRAEs occurred. At a median follow-up of 11.3 months (95% CI, 9.0-12.1), 2 pts had died, but the median DFS and OS were not reached which remained stable on study and would be updated. **Conclusions:** Neoadjuvant and adjuvant RC48-ADC plus AK104 demonstrated favorable efficacy and a manageable safety profile, supporting its potential as a valuable treatment modality for HER2-expressing MIBC. Long-term benefits and further understanding the role of this combination therapy in the perioperative setting of MIBC will be critical to advance treatment strategies. Clinical trial information: NCT06074484. Research Sponsor: RemeGen; Akesobio.

4589 **Poster Session**

Microbiota proteomics profiles in muscle-invasive bladder carcinoma related to response to neoadjuvant chemotherapy. First Author: Alvaro Pinto, Oncology Department, Hospital La Paz Institute for Health Research-IdiPAZ, Hospital Universitario La Paz, Madrid, Spain

Background: Muscle-invasive bladder carcinoma (MIBC) poses significant challenges due to high recurrence and mortality rates, coupled with the toxicity of neoadjuvant chemotherapy (NACT). This has driven the search for biomarkers to improve treatment management and patient quality of life. **Methods:** Fifty-eight FFPE samples from MIBC patients obtained from transurethral resection (TURBT) were studied. Microbiota analysis was performed by amplification and sequencing of the V4 variable region of the 16S rRNA gene and using Qiime2 software for taxonomic identification. Proteins were extracted and digested from TURBT samples and analyzed by mass spectrometry with data-independent acquisition. For protein identification, a reference database was built, including both the human proteome and bacteria genera proteomes identified by 16S experiments. Proteomics data were processed with Perseus and analyzed using probabilistic graphical models (PGMs) and hierarchical clustering. **Results:** We have information about treatment response for 56 patients. Twenty-four patients achieved a pathological complete response (43%), with a median disease-free survival of 22 months, and a median overall survival of 29.23 months. 151 bacteria genera identified by 16S experiments, were included in the metaproteomics database. In proteomics experiments, 42 bacteria and 5,111 human proteins were identified. After applying quality criteria, 13 bacteria proteins were used for the subsequent analyses. Hierarchical clustering analysis identified three groups with different microbiota protein profiles: Microbiota1, Microbiota2 and Microbiota3. These groups showed significant differences in response to NACT. A higher proportion of non-responders (73%) vs. responders (27%) was observed in Microbiota2 compared to the other groups (54% in Microbiota1 and 36% in Microbiota2), whereas a predominance of responders (64%) was observed in Microbiota3 (46% in Microbiota1 and 27% in Microbiota2) (p= 0.0481). In a previous work, our group defined three proteomics-based groups related to response to NACT (Layer1 (1.1, 1.2 and 1.3)) (Pinto et al., SEOM 2024). Significant differences were also observed in the distribution of Layer1 between the microbiota clusters. Microbiota2 had a higher representation of patients belonging to Layer1.3, characterized by a majority of non-responders and Microbiota3 had a higher proportion of patients from Layer1.1. **Conclusions:** To our knowledge, this is the first metaproteomics study in FFPE samples from bladder carcinoma patients for biomarker discovery. Three distinct microbiota protein profiles were identified, one with higher proportion of non-responders. The potential role of these bacteria in NACT response needs further study, highlighting metaproteomics as a promising avenue for biomarker development. Research Sponsor: None.

4590 **Poster Session**

Efficacy and safety of disitamab vedotin (RC48) combined with toripalimab as adjuvant therapy after radical surgery for patients with HER2-overexpression upper tract urothelial cancer (UTUC): A single-arm, prospective, phase 2 clinical trial. First Author: Shouyong Liu, Department of Urology, Jinling Hospital, Affiliated Hospital of Medical School, Nanjing University, Nanjing, China

Background: UTUC is rare and highly aggressive. The prognosis is poor, especially for high-risk patients, even after radical surgery. Adjuvant chemotherapy is the standard therapy, but with limited efficacy, indicating a need for more effective regimens. RC48, an anti-HER2 antibody-drug conjugate, combined with toripalimab, an anti-PD-1 monoclonal antibody, has shown promising results in locally advanced or metastatic urothelial carcinoma (C014 trial). We evaluate the efficacy and safety of RC48 combined with toripalimab as adjuvant therapy for patients with HER2 IHC 2+/3+ UTUC after radical surgery. **Methods:** This is a single-arm, prospective, phase 2 clinical trial (NCT05917158). Eligible criteria were patients with histologically confirmed HER2 IHC 2+/3+ UTUC after radical surgery and were staged as T2-4NanyM0 or TanyN1-2M0, with no prior neoadjuvant therapy. The intervention was intravenous RC48 (2 mg/kg) combined with toripalimab (3 mg/kg) triweekly for 6 cycles, followed by toripalimab (3 mg/kg) triweekly for up to 1 year. The primary endpoint was DFS, and the secondary endpoints were OS, safety, and MRD analysis. **Results:** 45 patients (35 males [77.8%], median age 68 years [IQR 58-71]) were enrolled. The patients were staged as: 43 (95.6%) in II, 1 (2.2%) in III, and 1 (2.2%) in IV. All patients were HER2-overexpression (80% in IHC 2+, 20% in IHC 3+). 25 patients (55.6%) met cisplatin-ineligibility. By the data cutoff date on January 14, 2025, the median follow-up time was 12.2 months (IQR 6.7-17.6). 4 relapses occurred: 2 in lymph nodes, 1 in the prostate, and 1 in lymph nodes and the bladder. The 1-year DFS rate was 90.0%, and the median DFS has not been reached. All patients experienced treatment-related adverse events (TRAEs). The most common TRAEs were hypoesthesia (51.1%), increased blood glucose (48.9%), anemia (46.7%), increased creatinine (46.7%), and hypertriglyceridemia (46.7%). TRAEs of grade $\geq$3 occurred in 20% of patients. 8.9% of patients experienced immune-related adverse events, including rash and hypothyroidism. Among the patients, 16 (35.6%) completed treatment, 19 (42.2%) were still undergoing intervention, 4 (8.9%) discontinued therapy due to TRAEs: 1 with hypoesthesia, 1 with lymphocytopenia and hypoesthesia, 1 with nausea, vomiting, and decreased appetite, and 1 with pruritus and diarrhea, and 2 withdrew after completing 4 cycles of combined regimen due to personal reasons. No deaths occurred during the follow-up period. **Conclusions:** This is the first prospective clinical trial evaluating the efficacy and safety of the new adjuvant regimen for patients with HER2-IHC 2+/3+ UTUC. It showed promising DFS outcomes and a manageable safety profile, highlighting its potential as a new adjuvant therapy in patients with HER2-IHC 2+/3+ UTUC. Clinical trial information: NCT05917158. Research Sponsor: None.

4591 **Poster Session**

First survival outcomes and biomarker results of SURE-01: Neoadjuvant sacituzumab govitecan (SG) monotherapy, followed by radical cystectomy (RC), in patients with muscle-invasive urothelial bladder cancer (MIBC). First Author: Brigida Anna Maiorano, IRCCS San Raffaele Hospital, Milan, Italy

Background: Standard of care for MIBC is RC with neoadjuvant chemotherapy (NAC), but ~50% of pts are ineligible for NAC and 5y survival for RC alone is $\leq$50%. SG is an antibody-drug conjugate composed of an anti-trophoblast cell surface antigen 2 (Trop-2) antibody coupled to SN-38 (a topoisomerase-I inhibitor). SURE-01 (NCT05226117) is an ongoing study testing neoadjuvant SG before RC. Preliminary pathological response rates suggested activity (Cigliola et al., ASCO 2024). Here, we report first results on survival and biomarkers. **Methods:** Pts age $\geq$18 y, ECOG PS 0-1, with histologically confirmed cT2-T4N0M0 MIBC, ineligible/refusing NAC and scheduled for RC, received 4 cycles of SG 7.5 mg/kg intravenously (reduced dose in protocol amendment 1) on days 1 and 8, Q3W, followed by RC. Primary study endpoint was the proportion of ypT0N0. Secondary endpoints included event-free survival (EFS), relapse-free survival (RFS) post-surgery, overall survival (OS), and safety. EFS included relapse/progression, inability/unwillingness to undergo RC in pts with residual disease, and death. Pts refusing RC with evidence of ypT0 response were censored. Decipher Bladder (Veracyte, San Diego, CA) was used on primary TURBT tissue for transcriptome-wide analyses. Signatera was used for ctDNA assessment. **Results:** From 03/22 to 01/25, 37 pts were enrolled and 33 were efficacy-evaluable. Median age was 71y and 16 pts (48.5%) had cT3-4N0 stage. Twelve pts (36.4%) had mixed variant histology. Grade $>$ 3 treatment-related adverse events (TRAE) occurred in 9 pts (27.3%), including one Grade 5 (at 10mg/Kg dose). Nine pts (27.3%) refused RC and were assessed with a reTURBT. The ypT0N0-x rate was 36.4% (12/33, 95%CI: 20.4-54.9%) and ypT $<$ 1N0-x rate was 39.4% (13/33). 8/10 pts with a high-risk disease at RC had ctDNA-negative status post-RC. Median follow-up was 14 (range 10-17) months. For the intention-to-treat (ITT) population, 12m-EFS was 78.8% (95% CI: 66-94%). 12m-Relapse-free survival (RFS) post-RC/reTURBT was 100% in pts with an ypT $<$ 1N0-x response vs 81.2% in pts with an ypT2-4N0 or ypTanyN1-3 response. Transcriptome-wide data for 27 pts revealed 12m-RFS rate of 100% in N = 8 Infiltrated-Luminal (IL), 86% in N = 7 Claudin Low, 83% in N = 6 Basal and 75% in N = 6 Luminal cases (Log-rank, p = 0.24), with consistent associations found for ypT0 response (IL: 71% ypT0 rate). Lower ($<$ median) *TOP1* gene expression (N = 14) was associated with 100% 12m-RFS rate (Log-rank, p = 0.05). Trop-2 gene expression did not associate to neither ypT response (p = 0.69) nor RFS. **Conclusions:** SURE-01 revealed compelling survival outcomes. While survival estimates or transcriptome results were not overtly associated with pathological response (interim endpoint), molecular subtypes and *TOP1* gene expression may be putative biomarkers of SG efficacy. Clinical trial information: NCT05226117. Research Sponsor: None.

4592 **Poster Session**

Prognostic impact of histological subtypes in non-muscle-invasive UTUC: Propensity matched analysis. First Author: Shiwang Huang, The Second Hospital of Tianjin Medical University, Tianjin, China

Background: Upper tract urothelial carcinoma (UTUC) is a rare malignancy with poor outcomes. While histological subtypes are known to influence bladder cancer prognosis, their impact on non-muscle-invasive UTUC remains underexplored. This study evaluates the effect of histological subtypes on survival outcomes after radical nephroureterectomy (RNU). **Methods:** This retrospective multicenter study included 399 patients with non-muscle-invasive UTUC who underwent RNU between August 2019 and April 2024. Patients were stratified into pure UTUC (pUTUC) and histological subtype UTUC (hsUTUC) groups. Propensity score matching (PSM) in a 1:2 ratio balanced baseline characteristics. Cancer-specific survival (CSS) was the primary endpoint; recurrence-free survival (RFS) and intravesical recurrence-free survival (IVRFS) were secondary endpoints. Kaplan-Meier curves and Cox regression models were applied for statistical analysis. **Results:** Among 399 patients (median age 69 years; interquartile range [IQR], 63–75), 57 (14%) had hsUTUC. After PSM (166 patients), Kaplan-Meier analysis showed comparable CSS between hsUTUC and pUTUC groups before and after matching ($p >$ 0.05). However, hsUTUC patients exhibited significantly worse RFS and IVRFS. Multivariable Cox regression revealed hsUTUC was independently associated with worse RFS (hazard ratio [HR] 2.38, 95% confidence interval [CI] 1.29–4.36; p = 0.005) and IVRFS (HR 2.06, 95% CI 1.04–4.10; p = 0.039), but not CSS (HR 1.84, 95% CI 0.60–5.61; p = 0.283). **Conclusions:** Histological subtypes in non-muscle-invasive UTUC significantly increase recurrence risk but do not affect CSS. These findings highlight the need for tailored surveillance and more aggressive management strategies in hsUTUC patients. Research Sponsor: None.

The association between histological subtypes and survival outcomes.

	Cancer-specific survival		Recurrence-free survival		Intravesical recurrence-free survival	
hsUTUC vs. pUTUC	HR (95% CI)	*p value*	HR (95% CI)	*p value*	HR (95% CI)	*p value*
Unadjusted	1.76 (0.61-5.12)	0.297	2.30 (1.28-4.13)	0.005	1.94 (0.99-3.79)	0.053
Adjusted	1.84 (0.60-5.61)	0.283	2.38 (1.29-4.36)	0.005	2.06 (1.04-4.10)	0.039

Model was adjusted for Tumor T stage (Ta/Tis/T1), lymph node status, lymphovascular invasion, concurrent CIS, concurrent bladder cancer, and hydronephrosis.

4593 **Poster Session**

Inferring FGFR status from H&E images using digital pathology to identify patients for early-stage bladder cancer targeted therapies. First Author: Albert Juan Ramon, J&J Innovative Medicine, San Diego, CA

Background: The identification of susceptible FGFR (Fibroblast Growth Factor Receptor) alterations may be critical in guiding treatment decisions for patients with bladder cancer. Current nucleic acid-based tests used to detect FGFR+ patients have limitations, including a slow turnaround time and high nucleic acid input requirement, especially in NMIBC, where tissue is often scarce. This study aims toevaluate the performance of an AI-based digital pathology algorithm, MIA:BLC-FGFR, adapted to investigate FGFR alterations in NMIBC patients from routine hematoxylin and eosin (H&E) stained whole slide images (WSIs). This approach may provide a rapid, low-cost, and effective alternative to nucleic acid testing. **Methods:** MIA:BLC-FGFR consists of an image quality control preprocessing stage, a Foundation Model (FM) pre-trained on ~55k unlabeled digital WSIs from various sources (multiple scanners, hospital systems, labs, diseases, tissue sites), and a classification module to enable inference of FGFR status from H&E-stained images. The classification module was trained on datasets (n = 3,067 WSIs) that included a mix of WSIs from multiple sources and disease stages (i.e., NMIBC, muscle-invasive and metastatic bladder cancer), and genetic classification provided by nucleic acid-based test. The algorithm was tuned to achieve a balanced specificity and sensitivity by selecting the operating point with highest F1 score (i.e., balanced sensitivity/specificity) in the training data. As part of this study, we then applied this model to WSIs of biopsies from 3 independent testing datasets (n = 578 WSIs) with varied NMIBC disease settings (i.e., high risk (HR) or intermediate risk (IR)) to evaluate the performance at predicting FGFR status, quantified by the Area Under ROC Curve (AUC). **Results:** MIA:BLC-FGFR demonstrated good concordance with nucleic acid testing methods. The results are summarized in the table below: **Conclusions:** The MIA:BLC-FGFR algorithm adapted to NMIBC can infer the presence or absence of select FGFR alterations from routine H&E images. This AI-based approach may offer a rapid, low-cost, and accurate alternative to traditional nucleic acid testing, particularly benefiting NMIBC patients with limited tumor tissue. By integrating into standard pathology workflows and providing results within minutes, the algorithm has the potential to significantly enhance FGFR testing rates and patient care decisions for emerging FGFR-targeted therapies. Research Sponsor: None.

Testing datasets	Independent Dataset 1	Independent Dataset 2	Independent Dataset 3
Disease setting	HR NMIBC	pT1 IR & HR NMIBC	IR NMIBC
Dataset size (FGFR+ %)	245 (29.7%)	163 (41%)	169 (49%)
PPV	53%	64%	80%
NPA	66%	71%	82%
PPA	89%	73%	76%
auROC	85%	80%	86%

4594 **Poster Session**

Overall survival and biomarker results of NURE-Combo: A phase 2 study of neoadjuvant nivolumab (NIVO) and nab-paclitaxel (ABX) followed by post-surgical adjuvant NIVO in patients (pts) with muscle-invasive bladder cancer (MIBC). First Author: Chiara Mercinelli, IRCCS San Raffaele Hospital, Vita-Salute San Raffaele University, Milan, Italy

Background: The first results of NureCombo revealed the combination of NIVO + ABX followed by RC and adjuvant NIVO was active in pts with MIBC (Mercinelli, JCO 2024). We report key secondary endpoints after study completion including adjuvant NIVO for all pts (NCT04876313). **Methods:** Eligible pts who were cisplatin unfit or declined cisplatin-based treatment had previously untreated MIBC (clinical stage T2-T4a, N0-1, M0), Eastern Cooperative Oncology Group performance status $\leq$ 1, and predominant ($>$ 50%) UC histology. Pts received 4 cycles of NIVO 360 mg Q3W + ABX 125 mg/m2 on Day 1 and 8, Q3W, followed by RC and by 13 administrations of adjuvant NIVO 360 mg Q3W. Transcriptome-wide analyses with Decipher Bladder (Veracyte, San Diego, CA) on primary TURBT tissue samples are presented. Continuous scores were dichotomized by median splits. **Results:** 31 pts were enrolled from 12/2021 to 06/2023, of which 17 (54.8%) had cT3-4 and 14 (45.2%) cT2. N = 2 (6.4%) had cN1 and 15 (48.4%) had a variant histology component. In total, 9 pts (29%) never started the adjuvant NIVO and 15 pts (48.4%) completed it: reason for discontinuation were treatment-related adverse events (TRAE; 5 pts, 16.1%) and relapse (2 pts; 0.6%). Median follow-up was 25 months (IQR: 21-32) and the minimum follow up was 19 months. In total, 7 pts experienced a relapse, 2/7 consisting of an intravesical relapse in those who refused to undergo RC (N = 3). 24-month (24m) event-free survival (EFS) was 73.7% (95%CI 59.6-91.2), corresponding to the 24m relapse-free survival (RFS) post-RC; 24m overall survival (OS) was 89.7% (95%CI 79.3-100; median OS was not reached). There were no additional/late TRAE compared to the initial report. Transcriptome profiles were available for N = 24: Genomic Subtyping Classifier (GSC) stratification revealed ypT0 was highest (50%) in N = 18 Non-luminal (claudin low, basal & infiltrated-luminal) subtypes and lowest (17%) in N = 6 luminal subtype ((p = 0.34). Based on Consensus MIBC classification, none of N = 4 luminal-papillary tumors had a ypT0 response (p = 0.09). Higher Immune190 and higher ESTIMATE-stromal signature trended to better RFS (HR 0.39 & 0.38, respectively). **Conclusions:** Long-term follow-up results of NureCombo revealed sustained efficacy of ABX-NIVO combination therapy followed by adjuvant NIVO in pts with MIBC. Molecular classification of baseline tumors revealed less favorable pathologic response rates for luminal MIBC. Differences in molecular correlates compared to PURE-01 may be related to different checkpoint inhibition (nivo vs pembro) or due to addition of ABX. Clinical trial information: NCT04876313. Research Sponsor: Bristol Myers Squibb.

4595 **Poster Session**

Five-year median follow-up update of PURE-01: A phase 2 study of neoadjuvant pembrolizumab followed by radical cystectomy in patients with muscle-invasive bladder cancer (MIBC). First Author: Valentina Tateo, IRCCS San Raffaele Hospital, Milan, Italy

Background: In patients (pts) with MIBC, the PURE-01 study pioneered the use of neoadjuvant immunotherapy by administering 3 courses of pembrolizumab before radical cystectomy (RC). Multiple reports have outlined various results of this trial, but assessment of the very long-term benefit of this strategy was pending and potentially noteworthy. **Methods:** Pts age $\geq$18 y, ECOG PS 0-1, with histologically confirmed cT2-T4N0M0 MIBC, ineligible/refusing chemotherapy (CT), and scheduled for RC received 4 cycles of pembrolizumab 200 mg on D1 Q3W, followed by RC and standard-of-care management. A total of 155 pts were included in the study. Even-free survival (EFS), relapse-free survival (RFS) in the RC population and overall survival (OS) are reported. Cumulative risk of recurrence (CRR) by competing risk analyses was also reported. Updated results from transcriptome-wide profiling using the Decipher Bladder assay (Veracyte, San Diego, CA) on primary TURBT tissue are presented. **Results:** From 02/17 to 07/20, 155 pts were treated (12.9% females). Remaining clinical and pathological features yet have been reported. Median follow-up was 61.8 months (IQR: 53.6-68.2). In the intention-to-treat (ITT) population, 5y-EFS was 68.3% (95%CI: 61.1-76.4) and 5y-OS was 77.4% (95%CI: 70.6-84.8). Pathological response categories were significantly associated with both RFS ($p < 0.001$) and OS: 5y-OS for ypT0N0 responders was 89.5% vs 90.3% for ypTa/Tis/T1N0 vs 72.2% for ypT2N0 vs 58.8% for ypT3-4N0 vs 41.9% for ypTanyN+ ($p < 0.001$). Out of 31 total relapses, three were very late relapses $>$ 5y post-RC, of which all were visceral relapses including isolated brain metastases in one case. The 5y-CRR was 19% (95%CI: 13-26). 7/8 pts who refused to undergo RC and received a reTURBT are alive and disease-free. Transcriptome-wide profiles were available for 102 pts. Stratification by Genomic Subtyping Classifier (GSC) allowed significant separation of RFS curves: Claudin Low subtype (N = 14) confirmed to portend the highest 5y-RFS (Log-rank Claudin-Low vs others vs NE-like p = 0.02), with 5y-OS for Claudin Low subtype being 93% (Log-rank Claudin-Low vs others vs NE-like p = 0.29). Higher immune infiltration scores quantified by Immune190 signature were associated with improved OS (HR (95% CI) per 0.1 increase = 0.60 (0.42-0.87); p = 0.006) Biologic evaluation among N = 604 MIBC GRID patients revealed highest Immune190 scores for Claudin Low subtype ($p < 0.001$). **Conclusions:** After $>$ 5y median follow-up, PURE-01 study revealed a sustained response and survival in pts with MIBC. Important updates are the validation of pathological response as a surrogate of OS in post-IO setting, the validation of molecular subtypes in association with RFS (and possibly OS) benefit, and the need to prolong follow-up at long term due to few pts with delayed recurrences. Clinical trial information: NCT02736266. Research Sponsor: Merck Inc.

4596 **Poster Session**

A phase II prospective, open-label, multi-center, single-arm study of sasanlimab plus sacituzumab govitecan in BCG-unresponsive non-muscle invasive bladder cancer (NMIBC) pts: SSANTROP (APRO07-2022). First Author: Joaquim Bellmunt, Bladder Cancer Center, Dana Farber Cancer Institute, Harvard Medical School, Boston, MA

Background: Radical cystectomy (RC)is the standard treatment forBCG unresponsive high-risk (HR) NMIBC patients (pts). Pembrolizumab (Pem) was approved by the FDA based on Keynote-057 (41% complete response rate (CRR)) and offers a non-surgical option for pts who decline or are ineligible for RC. Nadofaregene firadenovec and Nogapendekin alfa inbakicept have been recently approved in this setting. Sacituzumab govitecan (SG) demonstrated encouraging efficacy and safety in metastatic urothelial cancer (mUC) in the TROPHY-U-01 trial. Combining ADCs with immunotherapy showed promising results in mUC. We hypothesized if the combination of sasanlimab (Sa), a subcutaneous (SC) anti-PD1 agent, and SG would improve the CRR of Pem in BCG-unresponsive NMIBC pts who refuse or are ineligible for RC. **Methods:** SSANTROP is a phase II study conducted across 18 sites in Spain to assess the CRR at 3 months (mo) of the combination of Sa (5 cy of Sa 300 mg SC on day 1 every 28 days) plus SG (7 cy of SG 10 mg/kg IV on days 1 and every 21 days) in BCG unresponsive HR NMIBC. Pts achieving CR at 3 mo received maintenance therapy: Sa 300 mg SC every 28-day for up to 2 years. Primary endpoint was CRR at 3 mo with plan for percentage of response assessment maintained at 12 and 15 mo. Key eligibility criteria: ECOG PS 0-1, histologically confirmed BCG-unresponsive HR NMIBC, refusal or ineligibility for RC, urothelial carcinoma histology, and no prior anti-PD1/L1 or anti-CTLA-4 therapy. The sample size of 116 pts was calculated to demonstrate a 53% CRR for the combination, based on a Pem historical control of 41% (one-sided alpha 0.05, power 82%). Design was modified to finally include 40 pts based on a change in the treatment landscape of UC. **Results:** As of January 21, 2025, 59 pts were screened, and 41 initiated treatment and were included in the safety analysis. Among them, 32 (78%) male, median age of 70.6 years (SD 7.8). Types of BCG-unresponsive disease included: persistent/recurrent CIS alone or with recurrent HG Ta/T1 within 12 mo post-BCG (22 pts, 53.7%), recurrent HG Ta/T1 within 6 mo post-BCG (16 pts, 39%), and T1 HG disease at first evaluation post-induction BCG (3 pts, 7.3%). The most common adverse events (AEs) were diarrhea (58.5%), asthenia/fatigue (58.5%), alopecia (41.5%), neutropenia (36.6%), anemia (24.4%) and stomatitis (22%). Most common grade $\geq$ 3 AEs included neutropenia (9 pts, 22%), febrile neutropenia (5 pts, 12.2%). G-CSF prophylaxis was implemented as of 09/2024. As of 12/2024 and based on 25 evaluable pts, CRR at 3 mo was 68% (17/25). **Conclusions:** This trial is the first to evaluate the combination of Sa and SG in BCG-unresponsive HR-NMIBC. With preliminary 3 mo CRR of 68%, the safety analysis identified no unexpected concerns, with severe AEs mainly involving neutropenia and febrile neutropenia. No treatment related toxic deaths occurred. Clinical trial information: 2022-002998-28. Research Sponsor: Pfizer, Gilead.

4597 Poster Session

Impact of tumor burden or focality in recurrent low-grade intermediate-risk non-muscle invasive bladder cancer on response to treatment with UGN-102: A substudy of the phase 3 ENVISION trial. First Author: John Sfakianos, Department of Urology, Icahn School of Medicine at Mount Sinai, New York, NY

Background: In the ENVISION pivotal phase 3 study (NCT05243550) patients with low-grade intermediate-risk non-muscle invasive bladder cancer (LG-IR-NMIBC) were treated with UGN-102, a reverse thermal hydrogel containing mitomycin. Primary efficacy and safety results were previously reported. Complete response rate (CRR) at 3 months was 79.6%, with an 82.3% probability of remaining in response at 12 months by Kaplan–Meier estimate. Here, we present a post-hoc analysis evaluating if multifocality and tumor size influenced response rate and durability. **Methods:** In the single-arm ENVISION study, 240 patients with LG-IR-NMIBC received 6 weekly intravesical instillations of UGN-102; 3 months after the first dose, patients were examined for the presence of bladder cancer using cystoscopy, urine cytology testing, and for-cause biopsy. Patients achieving complete response (CR; no detectable disease) underwent follow-up with surveillance cystoscopy. In pre-specified subgroups, comparisons of patients with tumor burden (calculated as total length of all tumors) ≤3cm vs > 3 cm and single vs multiple tumors were performed for CRR at 3 months and hazard ratios (HRs) of duration of response (DoR) at 12 months after achieving CR. For the comparison of CRR, p values were calculated using Fisher's Exact Test. HRs of DoR were calculated using a Cox proportional hazards model, and p values calculated using a log-rank test. Comparisons were not powered to identify a difference and p values were unadjusted for multiple comparisons. **Results:** CRR at 3 months was 82.8% vs 73.2% for patients with tumor burden ≤3 cm and > 3 cm, respectively. Of patients with CR at 3 months with tumor burden ≤3 cm and > 3 cm, 15.4% vs 20%, respectively, experienced either recurrence of LG disease, progression (either stage or grade), or death by 15 months. In patients with multiple vs single tumors, 3-month CR was 79.3% vs 82.9%; recurrence rates were 18.5% vs 11.8%. DoR HRs were not statistically significant for any comparison made (Table). **Conclusions:** The CRR and DoR were favorable in all subgroups and no significant differences were observed. Study limitations were the small sample size of comparator groups, single arm design, and post-hoc nature of the analysis. UGN-102 may represent a valuable treatment option for many patients with LG-IR-NMIBC. Clinical trial information: NCT05243550. Research Sponsor: UroGen Pharma.

	CR at 3 months	CRR ratio (95% CI)/p value	Recurrence within 15 months[a]	DoR HR (95% CI)/p value
Tumor burden				
≤3 cm	149/180 (82.8%)	1.13 (0.93, 1.38)	23/149 (15.4%)	0.777 (0.317, 1.909)
>3 cm	30/41 (73.2%)	p=0.1854[b]	6/30 (20.0%)	p=0.5816[b]
Tumor count				
Multiple	157/198 (79.3%)	0.96 (0.82, 1.12)	29/157 (18.5%)	1.644 (0.578, 4.677)
Single	34/41 (82.9%)	p=0.6740[b]	4/34 (11.8%)	p=0.3459[b]

[a]3-month CR patients only.
[b]Nominal.
CI, confidence interval.

4598 Poster Session

Duration of response (DoR) following treatment with UGN-102 in patients with recurrent, low-grade, intermediate-risk, non-muscle invasive, bladder cancer: 18-month DoR data from the phase 3 ENVISION trial. First Author: Sandip M. Prasad, Morristown Medical Center/Atlantic Health System and Garden State Urology, Morristown, NJ

Background: Low-grade, intermediate-risk non-muscle invasive bladder cancer (LG-IR-NMIBC) is a recurrent cancer inadequately controlled by the current standard of care: transurethral resection of bladder tumor (TURBT). ENVISION (NCT05243550), is an ongoing prospective, phase 3, multinational, single-arm trial, evaluating UGN-102 in patients with a history of LG-NMIBC requiring TURBT. Primary efficacy and safety results have been published previously,[1] here we report long term efficacy data with 18 months follow-up after complete response (CR) to UGN-102 at 3 months. **Methods:** Patients received6 weekly intravesical instillations of UGN-102, a reverse thermal hydrogel containing mitomycin (75 mg). 3 months after the first instillation of UGN-102, patients underwent cystoscopy, urine cytology testing, and for-cause biopsy, to determine the presence or absence of bladder cancer. Secondary endpoints included duration of response (DoR), defined as the time from CR at 3 months to the earliest date of disease recurrence, progression, or death from any cause, whichever occurred first. DoR data was calculated for all patients with a minimum follow-up of 18 months after 3-month CR was calculated using Kaplan–Meier (KM) method. **Results:** 240 patients with recurrent LG-IR-NMIBC were enrolled and received at least one dose of UGN-102; 95% (228) received all 6 doses. Patients were mainly white (98%), male (61%) and aged over 65 years old (68%). CR at 3 months was achieved by 191 patients (79.6%; 95% CI: 73.9–84.5). For these patients, the probability of remaining in response 18-months after CR was 80.6% (95% CI 74.0-85.7; KM estimate). Of those who experienced recurrence post CR, most experienced LG disease (17.3%). **Conclusions:** In the ENVISION study treatment with UGN-102 in patients with recurrent LG-IR-NMIBC resulted in a high and clinically meaningful CR rate. Patients who achieved an initial CR at 3 months had a high probability of remaining disease-free 18 months later. This data confirms that UGN-102 represents a valuable treatment option for patients with LG-IR-NMIBC. Clinical trial information: NCT05243550. Research Sponsor: UroGen Pharma. Pharmaceutical/Biotech Company.

	UGN-102
CR at 3 months (95% CI)	**191/240, 79.6% (73.9–84.5)**
Follow-up time (months) for DoR, Median, months (95% CI)*	**18.73 (18.23–20.27)**
DoR by Kaplan–Meier estimate at 18 months post CR	**80.6% (95% CI 74.0–85.7)**
Patients with events at 18 months post CR	**39/191 (20.4%)**
LG disease	**33/191 (17.3%)**
Progression**	**4/191 (2.1%)**
Death	**2/191 (1.0%)**

*3-month CR patients only, estimated using reverse KM;
**Includes progression to high grade (HG) disease, T1 (Tumor Invades Lamina Propria), and Cis (Carcinoma in situ).
Prasad SM et al. J Urol. 2025. 213:205–216.

4599 Poster Session

Determinants in trimodality therapy for bladder cancer: Overcoming chemoradiotherapy resistance via ferroptosis. First Author: Takuya Tsujino, Osaka Medical and Pharmaceutical University, Takatsuki, Japan

Background: Expanding bladder preservation therapy can improve quality of life in patients with bladder cancer. This study aims to identify genetic determinants associated with trimodality therapy (TMT) for bladder preservation in bladder cancer (BC) patients and develop novel strategies to overcome chemoradiotherapy (CRT) resistance. **Methods:** Multi-omics analysis integrating RNA sequencing and whole exome sequencing (WES) was performed on clinical BC samples from 200 patients who underwent TMT in the OMPU-NCC dataset. The genomic profile of CRT-resistant BC cell lines was also analyzed. Ferroptosis signature scores were calculated using genes curated from the FerrDbV2 database. **Results:** WES revealed frequent alterations in DNA damage response (DDR) genes (Fig. 1A). Kaplan-Meier analysis showed significantly improved progression-free survival (PFS; HR 0.5840, 95% CI 0.3891-0.8765, P = 0.0157) and overall survival (OS; HR 0.5384, 95% CI 0.3331-0.8700, P = 0.0296) in patients with DDR alterations (Fig. 1B). Transcriptomic analysis identified distinct expression profiles between responders and progressors post-TMT. Gene Ontology analysis showed downregulation of immune response and lipid metabolism pathways in progressors (Fig. 2A). Analysis of the ferroptosis signature, which links these pathways, indicated that a high ferroptosis-suppressor signature score was correlated with worse survival outcomes (PFS: HR 2.713, 95% CI 1.818-4.047, $P <$ 0.0001; OS: HR 2.311, 95% CI 1.502-3.557, P = 0.0001), in contrast to the driver signature (Fig. 2B). RNA-sequencing of cell lines revealed significant differences in ferroptosis signature between parental and CRT-resistant strains (Fig. 2C). The combination of the ferroptosis inducer and irradiation overcame resistance in the T24R cell line, which is enriched with ferroptosis-suppressor genes. **Conclusions:** Key survival determinants post-CRT were highlighted, positioning ferroptosis as a target for overcoming resistance (Fig. 2D). Combining ferroptosis inducers with irradiation could offer a new therapeutic avenue for expanding bladder preservation. Research Sponsor: Japan Society for the Promotion of Science; No. 23K14606; Osaka Medical and Pharmaceutical University Research Promotion Project Grant.

Survival outcome after TMT according to DDR alteration and ferroptosis signature score.

Status	Number of patients	PFS after TMT (median, months)	HR (95% CI)	OS after TMT (median, months)	HR (95% CI)
DDR intact	49	25	ref	48	ref
DDR alteration	151	61	0.584 (0.389 to 0.877)	NR	0.538 (0.333 to 0.870)
Ferroptosis signature low	102	NR	ref	NR	ref
Ferroptosis signature high	98	16	2.713 (1.818 to 4.047)	27	2.311 (1.502 to 3.557)

PFS = progression free survival, TMT = trimodality therapy, HR = hazard ratio, CI = confidence interval, OS = overall survival, DDR = DNA damage response, NR = not reached.

4600 Poster Session

Survival outcomes of whole pelvic vs. bladder-only radiation in muscle-invasive bladder cancer: A nationwide large-scale study. First Author: Mohammad Arfat Ganiyani, Miami Cancer Institute, Baptist Health South Florida, Miami, FL

Background: Muscle-invasive bladder cancer (MIBC) is an aggressive malignancy traditionally managed with definitive surgery combined with systemic therapy. However, bladder-preservation approaches, including concurrent chemoradiation, offer alternatives for patients unfit for surgery. Within bladder-preservation, the choice between whole pelvic radiation (WP-RT) and bladder-only radiation (BO-RT) remains debated. WP-RT may address microscopic lymphatic disease, while BO-RT minimizes radiation toxicity. This study aims to compare survival outcomes between WP-RT and BO-RT utilizing the National Cancer Database. **Methods:** This retrospective study included patients with MIBC (T1-4a, N0-2, M0) from 2004-2020. It focused on individuals who received radiation therapy and underwent the maximum feasible local resection without definitive surgery. Kaplan-Meier analysis and a multivariate Cox proportional hazards model were used to evaluate survival outcomes based on the radiation field in patients with MIBC. **Results:** This study analyzed 18,659 patients with MIBC, including 18,092 who received BO-RT and 567 who underwent WP-RT. Among these, 71.76% received systemic therapy. Notably, the use of systemic therapy was more common in the WP-RT group (89.24%) compared to the BO-RT group (71.21%). The median overall survival was 23.33 months for patients treated with BO-RT compared to 38.7 months (Log rank P<0.001) for those who underwent WP-RT. In our adjusted analysis, patients treated with WP-RT had a 35% lower risk of death (HR: 0.65, 95% CI: 0.55–0.76, P < 0.001) compared to those receiving BO-RT, irrespective of receiving systemic therapy. Additionally, the use of concurrent chemoradiation was associated with a 50% reduction in the risk of death (HR: 0.50, 95% CI: 0.48–0.51, P < 0.001). **Conclusions:** This study found that in patients with MIBC, WP-RT was independently associated with better overall survival compared to BO-RT. These findings highlight the survival benefits of targeting microscopic lymphatic disease with WP-RT, while weighing the risks of associated toxicity. Additionally, Concurrent systemic therapy significantly reduced the risk of death, emphasizing its vital role in improving survival outcomes. Research Sponsor: None.

Cox proportional model in patients with muscle invasive bladder cancer.

Variable	HR (95% CI)	P-value
Charlson Score		
0		
>=1	1.24 (1.20–1.29)	< 0.001
Radiation Field		
Bladder Only		
Pelvic + Bladder	0.65 (0.55–0.76)	< 0.001
Histology		
Urothelial		
Non-Urothelial	1.23 (1.16–1.30)	< 0.001
Concurrent Chemoradiation		
No		
Yes	0.50 (0.48–0.51)	< 0.001

4601 Poster Session

Assessing real-world recurrence in high-risk (HR) non-muscle-invasive bladder cancer (NMIBC) treated with bacillus Calmette-Guérin (BCG) in the United States through a recurrence algorithm: A SEER-Medicare study. First Author: Yair Lotan, Department of Urology, UT Southwestern Medical Center, Dallas, TX

Background: Assessing bladder recurrences in real-world setting can be challenging due to the lack of readily available data on recurrence in large real-world databases (e.g., SEER-Medicare), which limits the ability to evaluate the long-term real-world outcomes. To address this, this study developed an algorithm using linked SEER-Medicare data (2007–2020) to identify and classify recurrence events. **Methods:** A retrospective cohort study in patients with HR-NMIBC treated with BCG was conducted, with BCG initiation as the index date. A recurrence algorithm was developed to identify and classify recurrence events including NMIBC recurrence, muscle-invasive bladder cancer (MIBC) progression, and distant metastasis (DM). NMIBC recurrence and MIBC progression were identified based on repeat TURBT procedures occurring ≥30 days after the last BCG treatment, supplemented by cancer diagnoses in the urethra or upper tract. Subsequent treatments were used to further classify them as NMIBC recurrence (intravesical BCG after a ≥6-month gap from the last BCG, or intravesical chemotherapy) and MIBC progression (systemic therapy, radiotherapy, or cystectomy). DM was identified by urothelial cancer diagnoses outside the urinary bladder, urethra, or upper tract. Cumulative incidence rates from the index date for each recurrence type were calculated accounting for competing events, such as death and more severe types of recurrences (e.g., MIBC or DM for NMIBC recurrence). **Results:** A total of 5,490 patients (median follow-up: 2.9 years) were included. Median age at index diagnosis was 76.5 years. NMIBC recurrence was the most common type of recurrences, followed by MIBC progression and DM. The cumulative incidence rates were 15.9% for NMIBC recurrence, 4.1% for MIBC progression, and 3.7% for DM at 1 year, reaching 33.6%, 15.9%, and 16.7% at 10 years, respectively (Table). **Conclusions:** Using linked SEER-Medicare data, an algorithm was developed to identify and classify disease recurrences, facilitating long-term outcomes analyses in a large, real-world cohort. Notably, most recurrences occurred within the first 5 years from BCG initiation, after which rates plateaued. These findings underscore the importance of routine imaging for early detection and timely intervention and the need for better treatments to reduce recurrence and progression burden in this population. Research Sponsor: Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA.

Cumulative incidence rates by type of recurrences (N = 5,490)[1].

Recurrence type	Number of events during the follow-up period	1 year	3 years	5 years	7 years	10 years
NMIBC recurrence	1528	15.9%	28.7%	31.6%	32.6%	33.6%
MIBC progression	552	4.1%	9.3%	12.1%	14.0%	15.9%
DM	528	3.7%	8.1%	11.5%	13.5%	16.7%

[1]Patients were censored at the end of continuous eligibility or the end of data availability, whichever occurred earlier.

4602 Poster Session

Correlation of circulating tumor DNA (ctDNA) dynamics with clinical response in muscle-invasive bladder cancer (MIBC) patients (pts) undergoing trimodality therapy (TMT). First Author: Ilana Bensussen Epstein, Dana-Farber Cancer Institute, Boston, MA

Background: TMT is a curative treatment option for pts with MIBC. Plasma circulating tumor DNA (ctDNA) is associated with treatment response and clinical outcomes following cystectomy for MIBC, but the association of plasma ctDNA with treatment response and clinical outcomes in pts treated with TMT is poorly understood. We hypothesize that ctDNA dynamics are correlated with clinical outcomes in pts with MIBC treated with TMT. **Methods:** Pts with MIBC who received TMT at Dana-Farber/Brigham and Women's Cancer Center or Massachusetts General Hospital, consented to a research protocol, and underwent ctDNA evaluation with the commercially available Signatera assay were included in the analysis. Individual chart review was performed to collect demographic and clinical data. **Results:** A total of 67 pts had at least one ctDNA evaluation and were included in this analysis. Cohort characteristics are summarized in Table 1. Forty-eight pts had at least one ctDNA evaluation prior to TMT, and 17 (35%) were ctDNA(+). Of the pts who were ctDNA(+) prior to TMT, 12 had at least one post-TMT ctDNA evaluation and 7 of 12 (58%) converted to ctDNA(-). Thirty-one pts were ctDNA(-) prior to TMT: 24 (77%) have had ≥1 post-TMT ctDNA evaluation and all 24 remained ctDNA(-) at the first post-TMT evaluation (median 8 weeks after TMT completion). Of the 55 pts with ≥1 post-TMT ctDNA result, 46 (84%) have remained ctDNA(-) during subsequent follow-up and do not have clinical evidence of recurrence (median number of ctDNA evaluation, 2; median follow up, 44 weeks). Nine pts had a ctDNA(+) result in the post-TMT setting: 5 were also ctDNA(+) prior to TMT, 2 did not have a pre-TMT ctDNA assessment but were ctDNA(+) at first-post TMT assessment, and 2 were ctDNA(-) before and initially after TMT but subsequently converted to ctDNA(+). Of these 9 ctDNA(+) cases, 6 pts (67%) have developed clinical evidence of metastatic disease to date with a median lead time of 5.3 weeks (range, 0-27 weeks) between first ctDNA(+) assessment and clinical evidence of metastatic disease. Overall, the sensitivity of plasma ctDNA testing in the post-TMT setting was 100% and the specificity was 94%. **Conclusions:** Most pts with MIBC treated with TMT in this cohort were ctDNA(-) following TMT and did not develop evidence of recurrent invasive or metastatic disease. Pts with ctDNA(+) status in the post-TMT setting frequently developed clinical evidence of metastatic disease. Larger cohorts with longer follow-up will be required to determine whether ctDNA status may be useful in guiding clinical decisions in MIBC pts undergoing TMT. Research Sponsor: None.

No. of Pts	67
Median Age (Yrs)	75
M:F	59:8
T3-4 (%)	16 (24%)
≥N1 (%)	3 (4%)
Presence of variant histology (%)	13 (19%)
Received neoadjuvant chemotherapy (%)	12 (18%)
Received concurrent chemotherapy (%)	61 (91%)
Median RT dose (Gy)	55
Median length of follow up (weeks)	39

4603 Poster Session

Pathologic response and safety of neoadjuvant pembrolizumab with or without entinostat in muscle-invasive urothelial cancer (MIUC). First Author: Tracy L. Rose, The University of North Carolina at Chapel Hill, Chapel Hill, NC

Background: Entinostat (Ent) is a selective histone deacetylase 1/3 inhibitor that potentiates immune checkpoint inhibitor activity in immunocompetent mouse models of urothelial cancer through immune editing of tumor neoantigens resulting in tumor immune microenvironment remodeling and associated changes in immune gene signature expression (J Clin Invest. 2021). Pembrolizumab (P), an immune checkpoint inhibitor, has demonstrated activity as neoadjuvant therapy for muscle-invasive urothelial cancer (MIUC) with the potential for combination treatment with Ent to improve outcomes. **Methods:** LCCC1827 is a window of opportunity trial of P with or without Ent in cisplatin-ineligible patients with T2-4aN0M0 MIUC prior to definitive therapy with radical cystectomy (RC) or trimodality therapy (TMT) with maximal TURBT followed by chemoradiation (NCT03978624). Patients were treated with P 200mg IV on day 1 and day 22 alone (Arm 1) or P 200mg IV on day 1 and 22 in combination with Ent 5mg po on days 1, 8, 15 (Arm 2) followed by definitive treatment within 10 weeks of day 1. The primary endpoint was change in immune gene signature expression in pre- and post-treatment tumors in Arm 2 compared to Arm 1. Here, we report clinical and secondary endpoints of pathologic response rate (pRR, < pT2N0) and pathologic complete response (pCR, pT0N0) for patients with RC, clinical complete response rate (cT0) at repeat TURBT for patients with TMT, and safety. **Results:** 20 patients (10 P; 10 P-Ent) were enrolled between 09/2020 and 10/2023 (85% male; median age 76 years; 25% black; 75% clinical T2) with all patients completing protocol-defined neoadjuvant therapy. 19 patients underwent definitive therapy (1 refused; 14 RC and 5 TMT). For RC, pRR was 43% and pCR was 29% in each arm. For TMT, cT0 was 100% in Arm 1 (n = 2) and 66% in Arm 2 (n = 3). Most common treatment-related AEs were diarrhea (20% in both arms), nausea (10% Arm 1, 30% Arm 2), and fatigue (10% Arm 1, 20% Arm 2). Grade 3 or higher treatment-related adverse events occurred in two patients (10%) (myalgias and back pain in one patient on Arm 1, hyponatremia in one patient on Arm 2). No patients had RC or TMT delayed due to treatment-related adverse events. All patients completed RC within 10 weeks of study initiation, except for 1 patient who delayed cystectomy for logistical reasons. One patient died after RC due to complications unrelated to study treatment. **Conclusions:** Neoadjuvant pembrolizumab with or without entinostat is active in MIUC with an acceptable safety profile. Analysis of the primary endpoint and other translational endpoints is ongoing. Clinical trial information: NCT03978624. Research Sponsor: Merck.

4604 Poster Session

Subsequent treatments and outcomes in bacillus Calmette-Guerin–unresponsive patients with high-risk non-muscle invasive bladder cancer with carcinoma in situ: A real-world data analysis. First Author: Ariel B. Bourla, Johnson & Johnson, New Brunswick, NJ

Background: Intravesical (ives) Bacillus Calmette-Guerin (BCG) is the recommended first-line treatment (tx) option for patients (pts) with high-risk (HR) non-muscle-invasive bladder cancer (NMIBC). Despite initial activity, BCG fails in up to 50% of pts. Pts with BCG unresponsive HR NMIBC with Carcinoma in situ (CIS) are at high-risk of disease progression. Limited evidence is available about tx patterns and outcomes of these pts. The objective of this study is to characterize real-world tx patterns and assess corresponding outcomes. **Methods:** This retrospective cohort study utilized comprehensive claims augmented with electronic health records in the US HealthVerity dataset from Oct 2015 to Dec 2022. This analysis included NMIBC pts who received adequate BCG (> = 7 doses) and had a CIS recurrence within 12 months of last BCG dose. Recurrence with CIS is defined as a transurethral resection of bladder tumor (TURBT) followed by a CIS diagnosis (dx) within 30 days. Descriptive analysis to characterize subsequent tx post BCG was performed for pts with at least 1 year of follow up post-recurrence. Time to recurrence or progression (defined as a TURBT followed by a BC dx within 30 days or starting a new line of tx) was used to assess outcomes of subsequent tx using Kaplan-Meier analysis. **Results:** We identified 23,280 pts with NMIBC who were treated with BCG between 2015 and 2022. Overall, 11,116 pts (48%) received > = 7 BCG doses and 1,094 pts recurred with CIS within 12 months of last BCG dose. Among them, 486 pts (44.4%) with BCG unresponsive HR NMIBC with CIS [79% males, median age 66 years (IQR: 60, 75)] received subsequent therapy. Median time from recurrence to tx initiation was 91 days (IQR: 41, 346). The most frequently administered tx was ives chemotherapy (ctx), accounting for 45% of cases (Table 1). Among pts receiving ives ctx (n = 217), 68% experienced recurrence or progression within 12 months with a median time to recurrence or progression of 174 days [139, 196]. **Conclusions:** Although guidelines recommend radical cystectomy for BCG unresponsive HR NMIBC patients with CIS, this RWD analysis revealed that over half of these patients received no further treatment for at least 1 year after their disease recurrence or progression. Among those treated, ives ctx was the most common tx. Therefore, the majority of patients were either undertreated or received ives ctx with only modest outcomes. This highlights the need for novel, more effective bladder-sparing therapies in this pt population. Research Sponsor: None.

Subsequent line of treatment for BCG unresponsive HR NMIBC patients with CIS post BCG.

Subsequent Treatment	N =486 pts
Intravesical ctx	217 (45%)
Radical cystectomy	121 (25%)
Intravesical BCG*	66 (14%)
Interferon alpha + BCG	60 (12%)
Systemic immunotherapy	22 (4%)

*BCG treatment starting > 12 months post the last BCG dose is considered a new line of treatment.

4605 **Poster Session**

Intravesical disitamab vedotin (RC48) for patients with HER2-expressing high-risk non-muscle-invasive bladder cancer: A dose-escalation phase I trial. First Author: Xu Chen, Sun Yat-sen Memorial Hospital, Guangzhou, China

Background: HER2 expression is associated with poor efficacy of Bacillus Calmette-Guérin (BCG) instillation in patients (pts) with high-risk non-muscle-invasive bladder cancer (HR-NMIBC). Developing effective treatment for HER2-expressing HR-NMIBC is of great urgency. Our previous study demonstrated that intravesical disitamab vedotin (DV, RC48, an anti-HER2 antibody-drug conjugate) had promising anti-tumor effects in the orthotopic BCa mouse model (Hong, X. et al., *Advanced Science*, 2023). We aimed to evaluate the safety and efficacy of intravesical DV in pts with HER2-expressing HR-NMIBC. **Methods:** Key eligibility criteria included HR-NMIBC (stage: cTa/T1±CIS, N0, M0) pts who were unsuitable for cystectomy, 18-75 years of age, HER2-expressing (IHC 1/2/3+) , BCG naive or BCG-unresponsive, and conducted transurethral resection of bladder tumor (TURBT) within 3 weeks prior to study treatment. Pts received intravesical DV (60, 120, or 180 mg) following a 3+3 design once weekly for six weeks (induction), followed by optional DV maintenance treatment once monthly until disease recurrence/progression, intolerable toxicity, or completion of nine treatments. The primary objective of this study was to assess the safety and tolerability of DV. The scheduled efficacy assessment included ultrasound and cystoscopic examination every three months. This study was registered with ClinicalTrials.gov, NCT06378242. **Results:** Between August 15, 2023 and December 1, 2024, nine pts were enrolled and completed the induction treatments at designated doses; no dose-limiting toxicities (DLTs) or any≧grade 3 treatment-related adverse events (TRAEs) occurred. The most common TRAEs included urinary tract infection (55.6%, 5/9), pollakiuria (11.1%, 1/9) and hematuria (11.1%, 1/9). All the patients underwent regular efficacy assessments, except for one patient who withdrew from the study in advance. As of December 1, 2024, after a median follow-up of 12.0 months (interquartile range [IQR]: 9.0–12.3), two pts developed recurrent disease, and no disease progression occurred. At 6 months, 8 pts were assessed for efficacy; both recurrence-free survival (RFS) and progression-free survival (PFS) were 100%. At 12 months, 6 pts were efficacy-evaluable; RFS rate was 83.3% (95% CI: 27.3, 97.5) and PFS rate was 100%. **Conclusions:** Intravesical DV was well-tolerated and showed preliminary efficacy in pts with HER2-expressing BCG-naive/unresponsive HR-NMIBC. The maximum tolerated dose was not reached, further dose exploration is ongoing in RC48-C029 study (NCT06378242). Clinical trial information: NCT06378242. Research Sponsor: None.

4606 **Poster Session**

IL-15RαFc superagonist SHR-1501 with or without bacille Calmette Guerin (BCG) for high-risk non-muscle invasive bladder cancer (NMIBC): A phase 1/2 study. First Author: Yuke Chen, Peking University First Hospital, Beijing, China

Background: BCG is the standard therapy after transurethral resection of bladder tumor for high-risk NMIBC. IL-15 agonists can enhance the immune response induced by BCG via stimulating the proliferation and activation of natural killer cells and CD8+ cytotoxic T cells, without inducing regulatory T cells. SHR-1501 is an IL-15 agonist fusion protein, composed of a humanized antibody Fc region fused with IL-15 and IL-15Rα sushi domain. In this phase 1/2 study, we assessed the safety, tolerability, and efficacy of SHR-1501 in patients (pts) with high-risk NMIBC. **Methods:** The study comprised dose-escalation phase 1a and 1b parts of SHR-1501 alone or in combination with BCG in pts with high-risk NMIBC, followed by a phase 2 part of SHR-1501 plus BCG in multiple cohorts, including pts with BCG-naive NMIBC (cohort A), BCG-unresponsive NMIBC carcinoma in situ (CIS; cohort B), and BCG-unresponsive high-grade Ta/T1 NMIBC without CIS (cohort C). All pts received intravesical study treatment weekly for 6 weeks during induction period. During maintenance period, instillations occurred weekly for the first 3 weeks at 3, 6, 12, 18, and 24 months after the initial induction instillation. Primary endpoints were dose-limiting toxicity (DLT), maximum tolerated dose (MTD), and recommended phase 2 dose in phase 1a and 1b parts; and was complete response (CR) rate for cohort B and 12-mo disease-free survival (DFS) rate for cohorts A and C in phase 2 part. **Results:** As of Sep 7, 2024, 84 pts were enrolled (n = 8 in phase 1a; n = 6 in phase 1b; n = 29, 17, and 24 in cohorts A, B, and C in phase 2). In phase 1a part of SHR-1501 alone (200, 400, and 600 μg) and phase 1b part of SHR-1501 (600 μg) plus BCG (120 mg), no DLTs were observed, and MTD was not reached. Thus, 600 μg of SHR-1501 plus 120 mg of BCG was used in phase 2 part. Treatment-related adverse events (TRAEs) occurred in 4 (50.0%) of 8 pts with SHR-1501 and 53 (69.7%) of 76 pts with SHR-1501 + BCG. Grade 3 TRAEs were reported in 1 (12.5%) pt with SHR-1501 (urinary tract infection) and 7 (9.2%) pts with SHR-1501 + BCG (urinary tract infection and hypertension occurred in $>$ 1 pt). No grade 4 or 5 TRAEs were reported. No serious TRAEs occurred. Of the efficacy evaluable pts in cohort B, the CR rate at 3 or 6 months was 90.9% (10/11). In cohorts A and C, the 12-month DFS rate was not reached. The 9-month DFS rate was 94.4% (95% CI, 66.6-99.2) in cohort A and 53.9% (95% CI, 15.5-81.4) in cohort C. **Conclusions:** SHR-1501 alone or in combination with BCG was well-tolerable and demonstrated a favorable efficacy in BCG-naive and BCG-unresponsive high-risk NMIBC pts, supporting further investigations. Clinical trial information: NCT05410730. Research Sponsor: Jiangsu Hengrui Pharmaceuticals.

4607 **Poster Session**

Results of BH011 after intravesical administration in patients with CIS and/or papillary non-muscle invasive bladder cancer (NMIBC) after BCG failure: Interim results from a phase I/II clinical trial. First Author: Dingwei Ye, Fudan University Cancer Hospital, Xuhui, Shanghai, China

Background: Treatment options are limited for patients (pts) with high risk NMIBC (HR NMIBC) after BCG failure. BH011 is a novel docetaxel formulation for intravesical administration that significantly increased the concentration of free docetaxel and bladder tissue permeability compared to TAXOTERE, which may result in a more efficient and effective tumor response. BH011 is administered intravesically to providing durable efficacy in high-risk NMIBC while avoiding systemic toxicities. This phase I/II study evaluates the safety, preliminary efficacy of intravesical BH011 in pts with HR NMIBC after BCG failure. **Methods:** This phase I/II study enrolled BCG failure (including refractory, recurrence, non-responsive, and intolerant) HR NMIBC pts. The papillary tumors should be removed all visible lesions by TURBT. The purpose of this study was to assess the preliminary efficacy under 17.5mg. Within 2-8 weeks after TURBT, eligible pts receive BH011 on day 1, once a week for 6 weeks during the induction treatment and once a month for 12 months during the maintenance treatment. The primary efficacy endpoint was 3 month Complete Response Rate (CRR). **Results:** To date, 25 pts have been treated with 17.5 mg of BH011, including 7 pts with CIS (±Ta/Ta) and 18 pts with papillary tumors alone (high-grade Ta or T1). All patients had been previously treated with BCG and failed. BH011 was well tolerated by all pts. All treatment-related adverse events (TRAE) were grade ≤ 2 and there were no TRAEs leading to discontinuation. Common TRAEs include urinary tract infection, glucosuria, proteinuria, urinary frequency, haematuria, cholesterol high, creatinine increased, and anaemia. A total of 24 evaluable pts were included in the efficacy analysis, which showed that pts had a CRR of 96% at 3 months and 71% at 12 months. RFS and PFS were analysed using the Kaplan-Meier method, and the 12-month RFS rate was 70%, with a median RFS of 20.21 months and a PFS rate of 100%. Six evaluable pts with CIS (±Ta/Ta) were analysed and the CRR was 100% (6/6) at 3 months and 83% (5/6) at 12 months. Analysis of the different pathology type subgroups and BCG failure type subgroups showed that the clinical efficacy of BH011 was independent of pathology type and BCG failure type (P > 0.05). **Conclusions:** Interim results show that intravesical BH011 is well tolerated and that it has strong significant and durable clinical efficacy in patients with HR NMIBC after BCG failure, particularly in pts with CIS (CRR = 100%). BH011 has the potential to have a transformative effect on the treatment landscape of NMIBC. Clinical trial information: NCT06732531. Research Sponsor: Zhuhai Beihai Biotech Co.,Ltd.

Efficacy of BH011.

Month	3	6	12
CR rate in all Pts, %	96	79	71
CR rate in CIS (±Ta/T1), %	100	83	83
RFS rate in all Pts, % (95%CI)	96 (88, 100)	79 (61, 97)	70 (45, 95)
DOR rate in all Pts, % (95%CI)	96 (87, 100)	78 (59, 97)	68 (33, 100)

4608 **Poster Session**

AURORA: A single arm, multicentre, phase II clinical trial of atezolizumab immunotherapy for advanced squamous cell carcinoma of the bladder and urinary tract. First Author: Simon J. Crabb, Southampton Clinical Trials Unit, University of Southampton and University Hospital Southampton NHS Foundation Trust, Southampton, United Kingdom

Background: Urinary tract squamous cell carcinoma (UTSCC) is a rare disease, comprising approximately 3% of histological subtypes from the bladder and urinary tract. Limited data exist to support treatment choices and no prospective trials, dedicated specifically to this histology, have been undertaken to evaluate immunotherapy. Prior data indicate high PD-L1 expression and tumour immune cell infiltration in a proportion of UTSCC cases. We report the Stage 1 outcome for the AURORA clinical trial, which tested atezolizumab immunotherapy for patients with incurable UTSCC. **Methods:** Patients had progressive, measurable, UTSCC and ECOG performance status 0-2. Mixed histology was permitted but with no urothelial carcinoma component. One prior line of systemic chemotherapy was permitted for advanced disease but no prior immunotherapy. Treatment comprised atezolizumab (1680 mg IV, q28d) until disease progression and for up to one year if tolerated. The primary endpoint was best overall objective response rate (ORR; RECIST v1.1) with a Simon 2 stage statistical design, and planned, independent, interim efficacy review after 19 patients were assessable for response (without a recruitment pause). If ≥4 of the first 19 patients (Stage 1) achieved an objective response (confirmed partial or complete response), then recruitment would continue through Stage 2, where ≥8 responses in 33 patients were required to indicate further investigation was warranted (p1 = 15%, p2 = 35%, 1-sided alpha = 0.1, power = 90%). Secondary endpoints included progression free survival (PFS), overall survival (OS), duration of response, safety and tolerability (CTCAEv5). **Results:** 3 of the first 19 recruited patients achieved an objective response (15.8%, 95% confidence interval (CI) 3.4 - 39.6; 3 partial and no complete responses) leading the Independent Data Monitoring Committee to recommend closure to recruitment. 3 further patients (15.8%) achieved a best response of stable disease. With a median duration of follow up of 10.1 months (95% CI 3.5 - not calculated), 17 PFS events have occurred, with a median PFS of 3.0 months (95% CI 1.4 - 3.8). 13 patients have died, with a median OS of 5.2 months (95% CI 2.7 - 8.5). Duration of objective response was 8.4 months in one patient and is ongoing in the other 2 responding patients. Adverse events were predominantly disease related. Atezolizumab was well tolerated with no new safety signals observed relating to this treatment. **Conclusions:** The objective response rate, and other efficacy endpoints, did not meet protocol defined thresholds for activity and so do not support further development of atezolizumab immunotherapy as a monotherapy for unselected patients with UTSCC. Translational endpoint analyses are ongoing. Clinical trial information: ISRCTN83474167. Research Sponsor: Cancer Research UK; CRCPJT\100018; Roche Products Ltd.

4609 **Poster Session**

Prevalence of histology-agnostic biomarkers in pure squamous cell carcinomas of the genitourinary tract. First Author: Saad Omar Atiq, Genitourinary Malignancies Branch, CCR, NCI, NIH, Bethesda, MD

Background: Pure squamous cell carcinomas (SCC) of the genitourinary (GU) tract are less responsive to chemotherapy with limited therapeutic options for systemic disease. SCCs account for 2-8% of bladder cancer cases and treatment mirrors urothelial carcinoma despite significantly lower responses. There are 8 FDA-approved histology-agnostic treatments based on biomarker profiling: dostarlimab (dMMR/MSI-H), pembrolizumab (dMMR/MSI-H; TMB-H), larotrectinib (NTRK fusion), entrectinib (NTRK fusion), selpercatinib (RET fusion), trastuzumab deruxtecan (HER2 positive), and dabrafenib plus trametinib (BRAF V600E mutation). Data are limited on gene alterations associated with SCC of the GU tract. This study aimed to explore the prevalence of biomarkers in pure SCCs of the GU tract. **Methods:** A retrospective analysis was performed to identify bladder cancer patients with SCCs of the GU tract that underwent comprehensive molecular profiling. Cases were reviewed by a GU pathologist to confirm pure SCC, and biomarker profiling was conducted to assess prevalence of markers with available histology-agnostic treatments as well as areas of potential future exploration through clinical trials. NextGen DNA sequencing (592-gene panel or whole exome) was performed at Caris Life Sciences (Phoenix, AZ). **Results:** Of 8000 bladder cancer cases, 655 (8.2%) were coded as having components of SCC. After excluding mixed histologies, 275 (2.4%) cases were reviewed by a GU pathologist, and 169 (2.1%) cases of pure SCC of the GU tract were identified. Of these, 88 were females (51.1%) and 81 males (47.9%), with a median age of 70 (range 34-89). Of the histology-agnostic biomarkers with FDA approvals, 45 patients (27%) were TMB-H and 2 patients (1%) harbored dMMR/MSI-H status. No patients harbored *NTRK* fusions, *RET* fusions, or *BRAF* V600E mutations. HER2 IHC data were not available for cases, but *ERBB2* mutation was present in 4 patients (2%) and 1 patient (0.6%) had ERBB2 amplification. Other notable mutations included *TP53* (70%), *pTERT* (64%), *PIK3CA* (30%), *CDKN2A* (22%), *FAT1* (19%), *KDM6A* (10%), *FGFR3* (5%), and *PTEN* (5%). HRD-associated mutations included *BRCA1* (2%), *BRCA2* (4%), *ATM* (4%), *PALB2* (1%), *CHEK2* (2%), *RAD51* (1%), and *BRIP1* (1%). *AKT* mutation was present in 2% of patients. *BAP1* was mutated in 3% of patients. Six of 20 (30%) patients were P16+ by IHC. No significant difference in mutation prevalence was observed between specimens from bladder tumors and metastatic sites. **Conclusions:** This study provides a comprehensive analysis of the genetic landscape of pure SCC of the GU tract that may inform future therapeutic strategies for this rare tumor with limited treatment options. Almost one-third of patients were TMB-High, reflecting a population that may benefit from immune checkpoint inhibitors monotherapy or combination strategies. Other histology-agnostic targets for current therapies were relatively infrequent. Research Sponsor: None.

4610 **Poster Session**

Sasanlimab in combination with bacillus Calmette-Guérin (BCG) in BCG-naive, high-risk non–muscle-invasive bladder cancer (NMIBC): Patient-reported outcomes (PROs) from CREST. First Author: Jens Bedke, Department of Urology & Eva Mayr-Stihl Cancer Center, Stuttgart, Germany

Background: Sasanlimab with BCG (induction [IND] + maintenance [MNT]) significantly improved investigator-assessed EFS vs BCG (IND + MNT) and had a manageable safety profile in patients (pts) with BCG-naive, high-risk NMIBC in the phase 3 CREST study primary analysis. We report PRO data not previously presented from CREST for Arms A and C assessing the impact of sasanlimab with BCG on QOL. **Methods:** Eligible pts were randomized 1:1:1 to receive sasanlimab with BCG (IND + MNT; Arm A), sasanlimab with BCG (IND; Arm B), or BCG (IND + MNT; Arm C). PROs were secondary endpoints and not included in the testing hierarchy. PROs were assessed prior to first dose (baseline [BL]), and at scheduled visits until an event or end of treatment (every 4 wk until Wk 28, every 12 wk until Wk 100) and at disease follow-up using the EORTC QLQ-C30 and QLQ-NMIBC24. Longitudinal mixed effect-model analyses were used to assess change from BL in the EORTC QLQ-C30 and NMIBC24 items. **Results:** At data cutoff (Dec 2, 2024), 695/703 pts randomized to Arms A (n = 348) and C (n = 347) had a BL score and ≥1 post-BL score. Completion rates were > 84% for all visits through the end-of-treatment visit (Cycle 25). QLQ-C30 Global Health Score QOL scores were numerically similar between arms (mean difference: −2.345; 95% CI: −4.058, −0.632; P = 0.007). No clinically meaningful differences (≥10-point change; Osoba et al. JCO 1998) were observed across urinary symptoms (NMIBC24; mean difference: 0.851; 95% CI: −1.030 , 2.731; P = 0.375), intravesical treatment issues (NMIBC24; mean difference: 1.271; 95% CI: −0.587, 3.130; P = 0.180), and EORTC QLQ-C30 items (Table) between arms, except in a small sample for female sexual problems (NMIBC24; mean difference: 18.502; 95% CI: 6.228, 30.775; P = 0.007). Results were statistically significant but not clinically meaningful. **Conclusions:** PROs from CREST showed QOL was maintained when combining sasanlimab with BCG vs BCG (both IND + MNT). These results can help inform the benefit-risk assessment of CREST. Clinical trial information: NCT04165317. Research Sponsor: Pfizer Inc.

	Arm AEstimated mean (95% CI) n=348	Arm CEstimated mean (95% CI) n=347	Estimated mean difference (95% CI)	P value
Physical functioning	−2.485(−3.493, −1.477)	−0.261(−1.272, 0.750)	−2.224(−3.651, −0.796)	0.002
Role functioning	−4.836(−6.187, −3.484)	-0.910(−2.265, 0.445)	−3.926(−5.840, −2.012)	0.000
Emotional functioning	0.074(−1.046, 1.194)	2.071(0.948, 3.194)	−1.997(−3.583, −0.411)	0.014
Cognitive functioning	−2.137(−3.174, −1.101)	−0.832(−1.872, 0.208)	−1.305(−2.774, 0.163)	0.081
Social functioning	−3.863(−5.111, −2.615)	−0.415(−1.666, 0.836)	−3.448(−5.215, −1.681)	0.000
Fatigue	4.881(3.488, 6.274)	1.211(−0.185, 2.607)	3.670(1.698, 5.642)	0.000
Nausea and vomiting	0.908(0.473, 1.343)	0.545(0.108, 0.982)	0.363(−0.253, 0.980)	0.248
Pain	2.784(1.519, 4.048)	−0.174(−1.443, 1.095)	2.958(1.166, 4.749)	0.001

TPS4611 **Poster Session**

STARLITE-1: Phase 1b/2 study of combination ^{177}Lu girentuximab plus cabozantinib and nivolumab in treatment naive patients with advanced clear cell RCC. First Author: Eric Jonasch, Department of Genitourinary Medical Oncology, The University of Texas MD Anderson Cancer Center, Houston, TX

Background: Complete response (CR) is a rare event in advanced clear cell renal cell carcinoma (ccRCC). The combination of nivolumab plus cabozantinib was approved for first-line treatment of ccRCC based on the CheckMate 9ER phase 3 study demonstrating improved progression-free survival (PFS) and objective response rate (ORR) in comparison to sunitinib. However, CR rate was only 9%. Drugs that could synergize with T cell anti-tumor activity can improve CR rates. Radiation-induced DNA damage to activate the cGAS-STING pathway is a promising mechanism. ^{177}Lu-girentuximab is an antibody-radioisotope that targets CAIX, a cell surface glycoprotein expressed in > 95% of ccRCC. As a single agent in metastatic ccRCC, ^{177}Lu-girentuximab was safe and effective in stabilizing disease in 57% of patients. We hypothesize ^{177}Lu-girentuximab-induced DNA damage will potentiate the STING pathway, synergizing with nivolumab and cabozantinib to promote trafficking and infiltration of activated T cells and achieve higher CR rates. **Methods:** Up to 100 adults with treatment-naive, locally advanced or metastatic ccRCC, adequate organ/marrow function, and ≥1 measurable lesion by RECIST 1.1 will be enrolled. Patients will receive ^{177}Lu-girentuximab IV on day 1 of cycles 1, 4, and 7 (every 12 weeks) for up to 3 cycles. The starting dose of ^{177}Lu-girentuximab will be 1480 MBq/m^2 (61% of single agent maximum tolerated dose); subsequent doses in the same patient may be reduced to 1110 MBq/m^2 or 740 MBq/m^2 based on adverse events. Starting day 1 of cycle 2 (week 5), patients will receive nivolumab 480 mg IV every 4 weeks and cabozantinib 40 mg PO every day. All cycles are 28 days. A 5-patient safety lead-in will evaluate myelosuppression. The co-primary endpoints are safety and CR rate by RECIST 1.1. Secondary endpoints are ORR, PFS by RECIST 1.1, and overall survival. The sample size was chosen for reasonable operating characteristics to distinguish a desirable CR rate of 18% as better than the standard CR rate of 9%. To explore the effects of the treatment on inducing activated T cell infiltration, patients will undergo pre/post-treatment PET scan with ^{18}F-AraG radiotracer and biopsies will be obtained for single cell, spatial transcriptomics, and proteomics studies. Clinical trial information: NCT05663710. Research Sponsor: Telix Pharmaceuticals; DOD Kidney Cancer Research; W81XWH-22-1-0456.

TPS4612 **Poster Session**

STARLITE 2: Phase 2 study of nivolumab plus ^{177}lutetium-labeled anti–carbonic anhydrase IX (CAIX) monoclonal antibody girentuximab (^{177}Lu-girentuximab) in patients with advanced clear cell renal cell carcinoma (ccRCC). First Author: Darren R. Feldman, Memorial Sloan Kettering Cancer Center, New York, NY

Background: CAIX is a cell surface glycoprotein expressed in > 95% of ccRCC but rarely in normal tissues. Radiolabeling girentuximab, a CAIX-targeting monoclonal antibody, with ^{177}Lu has shown promise as a therapeutic agent in ccRCC. Targeted delivery of radiation to ccRCC cells may prime the immune response, providing rationale for combining ^{177}Lu-girentuximab with nivolumab. This phase 2, open-label, single arm study will evaluate ^{177}Lu-girentuximab in combination with nivolumab in patients with previously treated ccRCC. **Methods:** Eligible patients have locally advanced unresectable or metastatic ccRCC, ≥1 prior line of therapy (including ≥1 anti-PD-1 or anti-PD-L1 antibody), adequate organ function, and ≥1 evaluable lesion as defined by RECIST 1.1 on ^{89}Zr-girentuximab PET/CT. Patients will receive ^{177}Lu-girentuximab (max 3 cycles; IV on day 1 of cycles 1, 4, and 7) and nivolumab (240mg IV q2 weeks starting cycle 1 day 15) until disease progression or unacceptable toxicity. FDG-PET and CT CAP will be performed prior to cycles 1, 4, and 7, and then q12 weeks. All cycles are 28 days. Patients will be evaluated in a 24-week safety lead-in phase followed by an expansion phase. In the safety lead-in phase, the primary endpoint of maximum tolerated dose (MTD) of ^{177}Lu-girentuximab in combination with nivolumab will be determined with a 3+3 design using a starting dose of 1804 MBq/m^2 (75% of single agent MTD). Based on dose limiting toxicities (DLTs), the starting ^{177}Lu-girentuximab dose will be either escalated to 2405 MBq/m^2 (cohort 2; single agent MTD) or de-escalated to 1353 MBq/m^2 (cohort -1) for the next cohort. Due to expected cumulative myelosuppression, each subsequent ^{177}Lu-girentuximab dose given to the same patient will be reduced by 25% (dose 2 = 75% of dose 1; dose 3 = 75% of dose 2). In the expansion phase, a Simon 2-stage optimal design will be used to evaluate the primary endpoint of best objective response rate by RECIST 1.1 within 24 weeks. With ≥1 response in the first Simon stage of 10 patients (includes patients treated at MTD during safety lead-in), a second stage will open (n = 19) for a total of 29 patients. The regimen will be considered worthy of further study if there are ≥4 responses in the 29 patients. Secondary endpoints include PFS, OS, and safety. Exploratory imaging with ^{89}Zr-girentuximab PET/CT will be performed at baseline and before each ^{177}Lu-girentuximab dose with results correlated with RECIST response on conventional imaging. In addition, whole body planar and SPECT imaging will be performed after each ^{177}Lu-girentuximab dose to evaluate distribution, lesion uptake, and dosimetry. The pre-specified number of DLTs was exceeded in cohort 2 such that dosing reverted back to 1804 MBq/m^2, in which accrual is ongoing. Clinical trial information: NCT05239533. Research Sponsor: Telix Pharmaceuticals.

TPS4613 **Poster Session**

A phase 1/2 first in human study of ADI-270, an armored allogeneic anti-CD70 chimeric antigen receptor γδ T cell therapy, in relapsed or refractory (R/R) clear cell renal cell carcinoma (ccRCC). First Author: Sumanta Kumar Pal, Department of Medical Oncology, City of Hope Comprehensive Cancer Center, Duarte, CA

Background: CD70 is a type II transmembrane protein of the tumor necrosis factor superfamily normally transiently expressed in activated lymphocytes, including B, T, NK, and mature dendritic cells. CD70 is aberrantly expressed in solid and hematologic cancers and is implicated in enhanced growth, metastasis, immune evasion, and suppression. In ccRCC, CD70 expression is increased in the tumor microenvironment and on malignant cells. Despite advancements in the treatment of patients with metastatic RCC, the 5-year survival rate is 15% and there remains an unmet need. ADI-270 is an investigational, allogeneic, CD70-targeting (CD27 receptor-based) Vδ1 γδ chimeric antigen receptor (CAR) T cell product expressing a dominant negative form of the TGFβ receptor II (dnTGFβRII) to mitigate the immunosuppressive effects of TGFβ within the tumor microenvironment. γδ T cells possess innate and adaptive immunity, a natural role in immune surveillance, and the ability to home to tissues. γδ T cells are ideal for an allogeneic cell therapy as their TCR recognizes MHC-independent antigens, thereby avoiding the risk of graft versus host disease. ADI-270 has demonstrated potent preclinical activity against CD70 expressing hematological and solid tumors expressing a range of CD70 levels both in vitro and in mouse xenograft models. Furthermore, ADI-270 demonstrated superior activity against tumors expressing low levels of CD70 when compared to scFv-based αβ CAR T cell benchmarks currently in clinical development. **Methods:** ADI-202427001 (NCT06480565) is a multi-center, phase 1 / 2 open-label, dose-escalation and -expansion study evaluating ADI-270 in adult patients with R/R ccRCC. Selected inclusion criteria include confirmed diagnosis of R/R advanced/metastatic ccRCC, previous treatment with an immune checkpoint inhibitor and a VEGF inhibitor, and Karnofsky performance status ≥ 70. Selection exclusion criteria include receipt of CD70 targeting treatment and autoimmune disease requiring systemic immunosuppressive therapy. Objectives of phase 1 include characterizing the safety and tolerability of ADI-270, identifying the recommended phase 2 dose (RP2D), and assessing cellular kinetics (CK), immunogenicity, pharmacodynamics (PD), and anti-tumor activity. Objectives of phase 2 include characterizing the anti-tumor activity, safety, immunogenicity, CK, and PD profile of ADI-270 at the RP2D. The totality of data from Phase 1 will be used to determine the RP2D for the Phase 2 part of the study. Responses will be evaluated per the RECIST 1.1 criteria. Additional efficacy analyses include duration of response, progression-free survival, and overall survival. Enrollment in study ADI-202427001 is ongoing. Clinical trial information: NCT06480565. Research Sponsor: AdicetBio, Inc.

TPS4614 **Poster Session**

A phase 1b, open-label, safety, tolerability, and efficacy study of HC-7366 in combination with belzutifan in patients with advanced or metastatic renal cell carcinoma (NCT06234605). First Author: Neil J. Shah, Genitourinary Oncology, Memorial Sloan Kettering Cancer Center; Weill Cornell Medical College, New York, NY

Background: HC-7366 is a novel, highly selective and potent activator of general control nonderepressible 2 (GCN2) kinase, a core regulator of metabolic stress through activation of the integrated stress response (ISR). Prolonged or hyper-activation of GCN2 suppresses general protein synthesis and induces cell cycle arrest, ultimately leading to apoptosis. HC-7366 decreases HIF expression in tumor and immunosuppressive myeloid cells and inhibits glycolysis, oxidative phosphorylation, and TCA cycle function in tumor cells. In CDX RCC xenografts, HC-7366 combined with belzutifan (BLZ) exhibited tumor regression, and in BLZ-resistant PDX models, HC-7366 demonstrated monotherapy (mono) antitumor activity. These preclinical effects of HC-7366 suggest potential therapeutic benefit in clear cell renal cell carcinoma (ccRCC) and rationale for combinations with HIF2α antagonists. Mechanism of action studies identified biomarkers of pathway engagement which may be predictive of efficacy (Stokes, AACR 2024, Abstract 4615). HC-7366 75 mg was determined to be the maximum tolerated dose (MTD) in a previous phase 1a study in patients (pts) with solid tumors which did not include ccRCC (*data on file with sponsor*). **Methods:** This is a multicenter, open-label, phase 1b dose escalation and expansion study evaluating safety, tolerability, MTD, recommended phase 2 dose (RP2D) of HC-7366 + BLZ (combo) in pts with advanced / metastatic RCC, predominantly clear cell histology. Additionally, HC-7366 60 mg mono (up to 20 patients) is assessed in parallel. In dose escalation, HC-7366 (20, 40, 60 mg po qd) + BLZ (120 mg po qd) is evaluated using a modified Toxicity Probability Interval design in up to 20 pts. Dose expansion will evaluate two HC-7366 doses selected from escalation + BLZ (15 pts/dose level). Tumor response will be assessed by CT scans every 8 wks (RECIST v1.1). Secondary endpoints include ORR, DOR, TTR, DCR, PFS, and OS. PK data will be profiled, and exploratory objectives include pharmacodynamic marker evaluation in tumor biopsies and peripheral blood samples. Key eligibility criteria include 1-3 prior therapies for the combo cohorts (naïve to BLZ/ HIF-2α inhibitors) and 1-4 prior therapies for the mono cohort (may include BLZ/ HIF-2α inhibitors), >1 measurable lesion, and willingness to provide biopsy or archival tumor samples at two timepoints. Escalation Dose levels 1 and 2 of the combination cohorts have been cleared and enrollment is ongoing for Dose level 3 (60 mg + BLZ), Expansion Dose Level 1 (40 mg + BLZ) and the mono cohort (60 mg HC-7366) at 20 US sites. The trial is sponsored by HiberCell, Inc. in collaboration with Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA. Sponsor contact: Paulette Mattson pmattson@hibercell.com, 651.312.5831. Clinical trial information: NCT06234605. Research Sponsor: None.

TPS4615 **Poster Session**

Transforming kidney cancer treatment through AI-enabled functional precision medicine: The PEAR-TREE2 trial. First Author: Matthew Williams, Ourotech Ltd t/a Pear Bio, London, United Kingdom

Background: Advanced renal cell carcinoma (RCC) presents a significant clinical challenge, with limited predictive biomarkers for treatment response. Pear Bio's innovative platform utilizes 3D immune-microtumors and computer vision to predict therapeutic responses using patient-derived tumor and blood samples. This study builds upon the initial PEAR-TREE trial, aiming to validate the platform's predictive capabilities for systemic therapies, including immune checkpoint inhibitors and tyrosine kinase inhibitors, in advanced RCC. **Methods:** PEAR-TREE2 (NCT06264479) is a multicenter, observational trial conducted in the UK and US, enrolling up to 200 patients with metastatic RCC. Participants must provide fresh tumor biopsies and blood samples prior to initiation of the next line of systemic therapy. Samples are cultured in Pear Bio's platform, which uses time-lapse microscopy and AI-driven computer vision analysis to assess functional metrics including viability, cell killing, migration, culture size, immune infiltration and clustering. Predictive metrics for overall response rate (ORR) based on RECIST 1.1 criteria are the primary endpoints. Secondary objectives include predictive accuracy for progression-free survival (PFS), durable response rates, and overall survival (OS). Exploratory analyses will evaluate molecular biomarker correlations (e.g. protein expression of therapeutic target, cell subpopulation analysis, etc.) and subgroup dynamics. Statistical methods include Receiver Operating Characteristic (ROC) curve analysis and subgroup logistic regression. Patient enrollment commenced in June 2024, with interim analyses planned after 50 and 100 enrollments. Eligibility criteria include patients aged ≥18 years with advanced RCC eligible for systemic therapy. Exclusion criteria comprise early-stage RCC, patients who have commenced treatment, or non-RCC diagnoses. Additional core needle biopsies (minimum 4x 18G cores) and blood samples (40 mL) are mandatory. Recruitment is ongoing at 7 trial sites, with a target duration of 4.5 years. This novel assay could fill the gap in predictive biomarkers by enabling personalized therapy selection. By validating its patient stratification potential, the study paves the way for interventional trials, with the promise of optimizing treatment regimens and improving outcomes for kidney cancer patients. We have ongoing trials in other high-unmet-need indications including early-stage breast cancer (NCT05435352), metastatic breast cancer (NCT06182306) and gliomas (NCT06038760) hoping to revolutionize precision oncology via improved treatment selection. Clinical trial information: NCT06264479. Research Sponsor: Ourotech (t/a Pear Bio).

TPS4616 **Poster Session**

A randomized trial of radium-223 dichloride and cabozantinib in patients with advanced renal cell carcinoma (RCC) with osseous metastases (RADICAL/Alliance A031801). First Author: Chinmay Jani, University of Miami Sylvester Comprehensive Cancer Center, Miami, FL

Background: Osseous metastases (OM) occur in approximately 30% patients with advanced RCC. Despite therapeutic advances, OM are associated with poor survival and risk of symptomatic skeletal events (SSEs). Cabozantinib targets multiple tyrosine kinases, including vascular endothelial growth factor (VEGF) receptors and MET (Mesenchymal-Epithelial Transition factor), which are overexpressed in OM, contributing to cabozantinib's enhanced bone activity. Radium-223, an alpha-emitting bone-seeking radioisotope, prolongs survival in men with metastatic castration-resistant prostate cancer to the bone. Building on this therapeutic approach targeting OM, our pilot study of radium-223 with VEGF inhibition in RCC with OM has also shown safety, improvement in circulating bone turnover markers, and early efficacy (McKay et al, CCR 2018). To address the unmet need to improve SSE rates and outcomes in RCC and OM, we designed a study investigating cabozantinib with or without radium-223 in patients with RCC with OM (NCT04071223). **Methods:** This is an open-label, multicenter randomized phase-2 study. Key inclusion criteria include metastatic RCC of any histology with ≥1 OM, at least 1 OM without prior radiation, any number of prior therapies, and Karnofsky performance status ≥ 60%. Use of a bone protecting agent is required unless contraindicated. Patients are randomized 1:1 to cabozantinib with (Arm A) or without (Arm B) radium-223. The starting dose of cabozantinib for Arm A is 40 mg by mouth daily to be escalated to 60 mg daily after cycle 1 (1 cycle = 28 days) if no persistent grade 2 or grade ≥3 toxicity. Radium-223 is administered at a fixed dose of 1.49 microcurie/kg IV every 28 days x 6 doses. The starting dose for cabozantinib in Arm B is 60 mg daily. The primary endpoint is SSE-free survival. Secondary endpoints include safety, progression-free survival, overall survival, time to first SSE, objective response rate, time to subsequent anticancer therapies, quality of life (QoL) measures, and correlative analyses including liquid biopsy and tumor tissue analysis. The study is designed to have 85% power to detect an improvement in 6-month SSE-free survival rate from 65% to 78% with one-sided α = 0.05 significance. To ensure 124 evaluable patients, target accrual is 134 (67 per arm). The group-sequential design includes a safety run-in and an interim analysis for futility when 50% of the expected number of events have been observed. The safety run-in, performed in the first 12 patients randomized to combination therapy, did not demonstrate dose limiting toxicities. Final data analysis will occur when 99 events have been observed. The study was activated in July 2020 and accrual is ongoing throughout the National Clinical Trials Network (NCTN). Continued site participation and enrollment are essential to evaluate this therapeutic strategy. Clinical trial information: NCT04071223. Research Sponsor: None.

TPS4617 **Poster Session**

Clinical effectiveness of urine DNA for minimal residual disease (MRD) monitoring of urothelial carcinoma in urine: A multicenter, prospective, observational study. First Author: Xuanjun Guo, Peking University First Hospital, Beijing, China

Background: Limited methods and poor compliance are major issues in urothelial carcinoma (UC) surveillance. Non-invasive monitoring of minimal residual disease (MRD) using urine tumor DNA (utDNA) represents a significant advancement, potentially reducing reliance on invasive cystoscopy and low-sensitivity imaging. Preclinical studies have demonstrated the utDNA multidimensional bioinformatic algorithm's high sensitivity (92.8%) and specificity (96.0%) by integrating copy-number variations (CNVs) and genetic mutations, showcasing its potential to improve cancer detection accuracy. However, large prospective clinical trials validating its clinical utility in postoperative recurrence and treatment efficacy monitoring remain scarce. Clinically, UC patients with similar manifestations and pathology often show divergent outcomes. Accurately assessing recurrence risk, metastasis, and treatment efficacy is an urgent need. This study aims to validate the clinical utility for recurrence monitoring and efficacy assessment in larger cohorts. **Methods:** This multicenter, prospective, observational trial evaluates the algorithm's efficacy in MRD detection among UC patients. The trial design incorporates stratification by clinical stage, including non-muscle-invasive bladder cancer (NMIBC), muscle-invasive bladder cancer (MIBC), and upper tract UC (UTUC). We divided the study population into four cohorts: Cohort 1 includes patients with high-risk UTUC (pT3-4 or N+) who have undergone surgery; Cohort 2 consists of NMIBC patients after transurethral resection of bladder tumor (TURBT); Cohort 3 comprises MIBC patients scheduled for neoadjuvant therapy; Cohort 4 includes patients assessed as complete response (CR) after standard trimodality treatment (TMT). In each Cohort, the accuracy for recurrence monitoring is evaluated using cystoscopy $\pm$ biopsy/surgical pathology, combined with imaging (CT/MRI) as the gold standard. Morning urine samples were collected from patients who had met the eligibility criteria and volunteered to participate in the study. Next-generation sequencing (NGS) was carried out on cell-free urinary DNA (ucfDNA) and urinary exosomal DNA (uexDNA). The minimal residual disease (MRD) score was computed by the algorithm, developed based on a feature matrix incorporating genetic alterations and copy number variations (CNVs). A classification threshold of 60 was established for clinical decision-making in the context of this study. We planed to enroll a total of 400 patients in this study. The sample sizes for the four cohorts were as follows: 100 for cohort 1, 200 for cohort 2, 50 for cohort 3, and 50 for cohort 4. As of January 2025, enrollment is ongoing, with cohorts actively monitored. The study was registered under ChiCTR2400081246. Reference: DOI: 10.1186/s12943-023-01729-7. Clinical trial information: ChiCTR2400081246. Research Sponsor: Peking University First Hospital High Quality Clinical Research Specialization.

TPS4618 **Poster Session**

A phase 2, open-label, randomized study of livmoniplimab in combination with budigalimab versus chemotherapy in patients with metastatic urothelial carcinoma. First Author: Terence W. Friedlander, University of California, San Francisco Medical Center, San Francisco, CA

Background: Urothelial carcinoma (UC) has a high mortality rate in patients (pts) with metastatic disease. While immune checkpoint inhibitors (CPI), including programmed cell death protein 1 (PD-1) inhibitors combined with chemotherapy (CTx) or enfortumab vedotin (EV), have been approved for first-line treatment of metastatic (m)UC, many pts have de novo or develop acquired resistance. For pts without response to frontline treatment or whose disease has progressed on prior CPI combinations, optimal treatment is unclear and new therapies are urgently needed. Glycoprotein A repetitions predominant (GARP) is a membrane-bound receptor that complexes with latent transforming growth factor (TGF)-β1; the release of active TGF-β1 from this complex suppresses antitumor responses. Livmoniplimab (livmo), an antibody targeting the GARP:TGF-β1 complex, prevents release of active TGF-β1, thereby promoting antitumor activity. A first-in-human phase 1 study (NCT03821935) demonstrated that combining livmo and the anti–PD-1 mAb budigalimab (budi) resulted in a manageable safety profile and promising antitumor activity in pts with PD-1–refractory advanced UC (J Clin Oncol 2024;42[suppl 4]: abs 617). Herein, we describe the phase 2 study that is evaluating livmo + budi vs CTx in pts with mUC (NCT06632951). **Methods:** This multicenter, open-label, randomized study is enrolling pts aged $\geq$18 years who have mUC, measurable disease per RECIST v1.1, ECOG PS 0–1, and have experienced disease progression on anti–PD-1 or anti–PD-1 ligand 1 therapy. Platinum (Pt)-eligible pts must have received a Pt-containing regimen; pts who can receive EV must have experienced disease progression on/after receiving EV treatment. Primary objectives are to identify the recommended phase 3 livmo dose in combination with budi and evaluate overall survival. Secondary objectives include evaluating progression-free survival, best overall response of complete or partial response, duration of response, and assessment of safety and tolerability, pharmacokinetics, and immunogenicity of the combination. Pts will be randomized 1:1:1 to 3 arms: 1) livmo dose 1 Q3W + budi Q3W; 2) livmo dose 2 Q3W + budi Q3W; or 3) investigator's choice of CTx (paclitaxel, docetaxel, or gemcitabine). Pts will be stratified by ECOG PS (0 vs 1) and first-line therapy (pembrolizumab + EV vs CTx). Treatment for pts in Arms 1 and 2 will continue until a maximum of 35 cycles. For pts in Arm 3, treatment will continue for the duration that is consistent with local guidelines/practice for this pt population. No crossover between arms will be permitted. For all pts, treatment is discontinued at disease progression or if other protocol-defined discontinuation criteria are met. In total, approximately 150 pts (50 pts/arm) are planned for enrollment globally. Clinical trial information: NCT06632951. Research Sponsor: AbbVie, Inc.; n/a

TPS4619 **Poster Session**

A phase 2/3 study of bicycle toxin conjugate zelenectide pevedotin (BT8009) targeting nectin-4 in patients with locally advanced or metastatic urothelial cancer (la/mUC; Duravelo-2). First Author: Yohann Loriot, Gustave Roussy Institute, University Paris-Saclay, Villejuif, France

Background: Zelenectide pevedotin (zele; BT8009) is a Bicycle Toxin Conjugate (BTC), comprising a highly selective bicyclic peptide targeting Nectin-4 linked to the cytotoxin monomethyl auristatin E (MMAE) via a cleavable linker. Nectin-4 is an adhesion molecule commonly expressed in many tumor types, including la/mUC, and is a validated therapeutic target (Hoffman-Censits 2021). Zele has a low molecular weight and short plasma half-life, with potential to rapidly penetrate solid tumors and reduce toxicity by minimizing exposure to normal tissue (Rigby 2022). Results from the ongoing phase 1/2 clinical trial of zele (NCT04561362) indicate preliminary antitumor activity and a tolerable safety profile in patients (pts) with advanced malignancies including UC (Baldini 2023). This global, open label, phase 2/3 multicenter adaptive study aims to evaluate the safety and efficacy of zele as monotherapy, or combined with pembrolizumab (pembro), vs chemotherapy in pts with la/mUC (NCT06225596/BT8009-230; Duravelo-2). **Methods:** The trial will enroll n$\leq$956 adult pts in 2 cohorts. Cohort 1 will include n$\leq$641 previously untreated pts eligible for platinum-based chemotherapy. Cohort 2 will include n$\leq$315 pts with $\geq$1 prior systemic therapy, excluding enfortumab vedotin or other MMAE-based therapy. Pts must have la/mUC of the renal pelvis, ureter, bladder, or urethra, ECOG performance status $\leq$2 (Cohort 1) or $\leq$1 (Cohort 2), and adequate organ function. Cohort 1 will be randomized 1:1:1 to receive: 1) zele 5 mg/m^2 on days [D]1, 8, and 15 + pembro 200 mg on D1; 2) zele 6 mg/m^2 on D1 and 8 + pembro 200 mg on D1; or 3) chemotherapy (gemcitabine + cisplatin / carboplatin, followed by avelumab maintenance in appropriate patients). Cohort 2 will be randomized 1:1 to receive: 1) zele 5 mg/m^2 on D1, 8, and 15 or 2) zele 6 mg/m^2 on D1 and 8. Cycle lengths will be 21D (28D for avelumab). After 30 pts in each dose arm have 9 weeks follow up, an interim analysis will determine the optimal dose of zele + pembro (Cohort 1) or zele monotherapy (Cohort 2) to be used for the rest of the study. An additional Cohort 2 arm, optimal dose of zele + pembro, will open after completion of the interim analysis. Treatment discontinuation criteria include planned completion of therapy, progressive disease, and intolerable toxicity. Primary endpoints are progression-free survival (PFS; Cohort 1) and objective response rate (ORR; Cohort 2) assessed by blinded independent central review. Secondary endpoints are ORR (Cohort 1), PFS (Cohort 2), overall survival, duration of response, disease control rate, safety/tolerability, and health-related quality of life (Cohorts 1 and 2). Pharmacokinetics, incidence/titers of antidrug antibodies, and tumor/peripheral biomarkers are exploratory endpoints. Efficacy endpoints will be assessed per RECIST v1.1. This study is actively recruiting. Clinical trial information: NCT06225596. Research Sponsor: BicycleTx Ltd.

TPS4620 **Poster Session**

A randomized phase 2 study of the efficacy and safety of stereotactic body radiation therapy (SBRT) in patients with metastatic urothelial carcinoma and oligoprogression on maintenance therapy with avelumab (VOLGA 2). First Author: Ilya Tsimafeyeu, Bureau for Cancer Research - BUCARE, New York, NY

Background: For metastatic urothelial cancer (mUC) with multiple metastases, the standard treatment involves platinum-based chemotherapy followed by maintenance avelumab. Despite this, disease progression occurs in approximately half of patients at a median of 5.5 months, often requiring a switch to second-line therapy. The concept of oligoprogressive mUC and its optimal management remain poorly defined compared to other tumor types. The VOLGA 2 study aims to assess the preliminary efficacy and safety of SBRT in patients with mUC and oligoprogression during maintenance therapy with avelumab. **Methods:** VOLGA 2 is a randomized, prospective, multicenter phase 2 trial. Patients with histologically confirmed mUC and measurable lesions according to RECIST 1.1, undergoing avelumab maintenance therapy with extracranial oligoprogression, are randomized to receive SBRT targeting oligoprogressive lesions or to second-line therapy of the physician's choice. Oligoprogression is defined as disease progression due to the appearance of up to five new metastases or a significant increase in up to five existing lesions, with other disease sites remaining stable under ongoing systemic or local therapy. For patients in the SBRT arm, repeat SBRT to previously non-irradiated lesions is allowed and recommended if the interval between progressions exceeds four months. Patients with brain metastases and cord compression are excluded from the study. The primary endpoint is 2-year overall survival (OS) rate. Secondary endpoints include median OS and progression-free survival, overall and irradiated lesion response rates, and safety. The study will enroll 58 patients (H0 = 45%, Ha = 80%, alpha = 0.05, power = 0.8). Clinical trial information: KCRB10122024. Research Sponsor: Bureau for Cancer Research - BUCARE.

TPS4621 **Poster Session**

A phase II trial to evaluate clinical efficacy, pharmacodynamics and exploratory analysis of pemetrexed in relation to MLL4 and UTX alteration status in patients with relapsed/refractory metastatic urothelial carcinoma and other solid tumors. First Author: Carolyn Moloney, Development of Therapeutics, Robert H. Lurie Comprehensive Cancer Center, Northwestern University Feinberg School of Medicine, Chicago, IL

Background: MLL4 (encoded by KMT2D) and UTX (encoded by KDM6A) are protein components of the epigenetic chromatin modifier complex COMPASS. MLL4 alterations are found in ~10% of all cancers including ~29% of bladder cancer (BLCA). UTX alterations are found in up to ~5% of all cancers including ~29% of BLCA. These alterations have not been previously therapeutically targeted as a precision oncology strategy in humans despite their frequency. We recently published the results of a CRISPR/Cas9 knockout screen in cells lacking MLL4/UTX-COMPASS function, which revealed synthetic lethality upon loss of genes that encode enzymes involved in de novo nucleotide synthesis (dnNS) [Zhao et al. J Clin Invest. 2023; Zhao et al. PNAS. 2023]. We also reported that MLL4 truncation mutations confer an inhibitor-targetable dependence on dnNS in colorectal cancer (CRC) and BLCA. We demonstrated sensitivity to lometrexol, which targets the enzyme GART (glycinamide ribonucleotide formyltransferase), in animal models of CRC and BLCA with MLL4 truncation. Our preclinical results clearly indicated the potential for dnNS inhibition as a targeted therapy for patients stratified by MLL4 or UTX status. Pemetrexed was identified as a more clinically relevant purine synthesis inhibitor for further development due to its well-established safety profile and prior use in BLCA. **Methods:** We have initiated an investigator-initiated, open-label phase II basket clinical trial at Northwestern University (NCT06630416). Patients with advanced, treatment-refractory tumors with MLL4 (KMT2D) or UTX (KDM6A) mutations (as identified by next generation sequencing) are enrolled in 2 cohorts: a) BLCA and b) other solid tumors. Other key inclusion criteria include ECOG performance status 0-2 and adequate organ function. Prior pemetrexed use is a key exclusion criterion. Patients are treated with pemetrexed 500mg/m2 IV Q 3 weeks. We intend to enroll up to 64 patients to allow for 58 evaluable patients (29 in each cohort) to achieve the null hypothesis. We will use a Simon 2-stage design, with 10 patients enrolled in each cohort in the first stage. The null hypothesis is that the true response rate is 0.1, and the alternative hypothesis is that the true response rate is 0.3. If there are 5 or more responses among these 29 patients, we reject the null hypothesis and claim that the treatment is promising. The design controls the type I error rate at 0.05 and yields a power of 0.8. This clinical trial has accrued 1 patient as of January 28th, 2025. Correlative studies will be carried out alongside the study to assess for mechanisms of resistance to pemetrexed. Molecular analysis of ctDNA will be performed on plasma for both arms and for plasma and urine for cohort A (bladder cohort) at pre-determined time points during treatment. Clinical trial information: NCT06630416. Research Sponsor: Robert Lurie Cancer Center, Northwestern Memorial Hospital, Chicago, IL, 60611.

TPS4622 **Poster Session**

Adjuvant sacituzumab govitecan (SG) plus nivolumab (N) in patients (pts) with muscle-invasive urothelial carcinoma (UC) at high-risk for recurrence. First Author: Nataliya Mar, University of California Irvine, Irvine, CA

Background: Pts with muscle-invasive UC of the bladder or upper genitourinary tract who undergo radical cystectomy or nephroureterectomy are at high risk for cancer recurrence if residual pathologic advanced disease is identified at the time of surgery. Emerging data demonstrates that pts with minimal residual disease following curative-intent surgery, as detected by circulating tumor DNA (ctDNA), may be at a particularly high risk of UC recurrence. Adjuvant N has been approved post curative-intent surgery, with or without prior neoadjuvant chemotherapy (NAC), in pts with muscle-invasive UC at high risk of recurrence based on results of the CheckMate 274 study, which demonstrated a disease free survival (DFS) at 6 months of 74.9% with N versus 60.3% with placebo. SG is an antibody-drug conjugate with activity in UC. Evaluating intensification of adjuvant therapy in order to reduce the chance of metastasis development is of great interest. **Methods:** This is an IRB-approved, prospective, multi-center, single-arm phase 2 study of combination therapy with SG plus N. To be eligible, pts must have documented muscle-invasive UC, with variant and mixed histology allowed, except small cell. Pts must have undergone curative-intent surgery within 180 days prior to study therapy initiation and be radiographically free of metastasis. Pts who received prior NAC must have T2-T4 or node positive disease on surgical pathology, while those without NAC must have pathologic T3-T4 or node positive disease. Pts must also be ineligible or refuse platinum-based adjuvant chemotherapy. Additional selected eligibility criteria include creatinine clearance of at least 30 ml/min and adequate bone marrow function. If eligible for the study, pts will receive SG 7.5 mg/kg on day 1 and 8 combined with Nivolumab 360 mg on day 1 given every 21 days for 4 cycles, followed by single-agent Nivolumab 480 mg on day 1 given every 28 days for an additional 11 cycles. Use of growth factor support is allowed, as per institutional practice. Primary study endpoint is investigator-assessed DFS at 6 months. Secondary study endpoints include DFS, distant metastasis-free survival (MFS), overall survival (OS), incidence of grade 3 or higher adverse events, rate of ctDNA clearance in baseline ctDNA positive patients as well as exploratory biomarker analysis. The sample size calculation was based on a one-sided one sample test for exponential hazard rate when the probability of DFS at 6-months in the experimental group is 85% and in the historical control group is 75% in order to detect a hazard ratio of 0.565 with a power of 80% at a 0.05 significance level. Projected study accrual time is 24 months and per pt follow-up time is 36 months. Out of 23 anticipated pts, 3 have been enrolled to date since study activation in 11/2024. Clinical trial information: NCT06682728. Research Sponsor: None.

TPS4623 **Poster Session**

Neoadjuvant stereotactic radiotherapy and enfortumab vedotin: A phase I/II study for localized, cisplatin ineligible, muscle invasive bladder cancer (STAR-EV). First Author: Tian Zhang, Department of Internal Medicine, Division of Hematology and Oncology, UT Southwestern, Dallas, TX

Background: Patients with muscle invasive bladder cancer (MIBC) may not be candidates for cisplatin-based chemotherapy based on their comorbidities and clinical status. Based on EV-103 cohort H, patients with localized, cisplatin ineligible MIBC respond well to enfortumab vedotin (EV), with 36% pathologic complete responses (pCRs). Radiation (XRT) is also an effective therapy for MIBC, with recent retrospective data showing safety when combining XRT-EV. Therefore, we designed a trial with EV and XRT to improve pCR rates. **Methods:** STAR-EV is a single center, phase 1/2 trial open at UT Southwestern Medical Center. Patients will receive EV 1.25mg/m2 IV days 1/8 every 3 weeks for 3 cycles, with either sequential or concurrent stereotactic body XRT (SBRT) in 5 fractions. The safety lead-in phase starts with SBRT given at cycle 3 day 21 and then escalated forward to start at cycle 2 day 15 (level 1) or cycle 1 day 15 (level 2). All patients undergo radical cystectomy (RC). Dose limiting toxicities during the safety portion include non-hematologic adverse events grade 3 or higher, not completing 3 cycles of EV, delaying SBRT over 2 weeks, or delaying RC over 8 weeks. Rate of pCR is the primary endpoint for efficacy, with a goal of 60% pCR. In a Simon's two-stage design, if more than 3 pCRs are seen in the first 8 patients, 11 additional patients will be enrolled (total n = 19). The null hypothesis will be rejected if more than 10 pCRs are found. Main inclusion criteria include urothelial cancer of the bladder, cT2-4aN0M0, $>$ 50% urothelial histology, and cisplatin ineligible; main exclusion criteria include any small cell/neuroendocrine histology, prior systemic therapy for bladder cancer, prior pelvic XRT, baseline grade 2 or higher neuropathy, prior allergic reaction attributed to EV, or uncontrolled intercurrent illness. Secondary endpoints include safety of combining EV and SBRT, rate of pathologic down-staging; and exploratory objectives include quality of life, disease free survival after RC, and delay of RC $>$ 8 weeks from end of EV/SBRT. Serum and urinary biomarkers will be explored. The study is open and enrolling. Clinical trial information: NCT06394570. Research Sponsor: Astellas.

TPS4624 **Poster Session**

PUNCH03: A phase II study of disitamab vedotin combined with tislelizumab and bacillus Calmette-Guerin (BCG) in Her2-positive high-risk non-muscle-invasive bladder cancer (HR NMIBC). First Author: Zongren Wang, Department of Urology, The First Affiliated Hospital, Sun Yat-sen University, Guangzhou, China

Background: Disitamab vedotin (RC48) was a novel antibody drug conjugate that targets the Her2 protein. The KEYNOTE-057 study has supported the benefits of PD-1 inhibitor in HR NMIBC patients (pts). Our study was established to evaluate the efficacy and safety of RC48 combined with tislelizumab and BCG as a bladder-preserving treatment for Her2-positive HR NMIBC pts. **Methods:** This open-label phase II study enrolled BCG-naïve HR NMIBC pts with multiple papillary tumors (high-grade Ta or T1 tumors), and all pts were Her2-positive (IHC 2+ or 3+). Firstly, the papillary tumors should be removed all visible lesions by transurethral resection of bladder tumor (TURBT). Secondly, pts were administered RC48 (2.0 mg/kg, ivgtt), every 2 weeks for 1 cycle, and were administered tislelizumab (200 mg, ivgtt), every 3 weeks for 1 cycle. Then, pts received second TURBT, and pts were administered 3 cycles of RC48 (2.0 mg/kg, Q2W, ivgtt) and tislelizumab (200mg, Q3W, ivgtt). Finally, pts received 18 instillations of BCG plus at least 1 year of tislelizumab (200 mg, Q3W, ivgtt). Specifically, pts were started on an induction course of BCG with 6 instillations every week, followed by maintenance with 3 instillations every 2 weeks and 9 instillations every 4 weeks. The primary end point was recurrence-free survival (RFS) rate at 12 months. Secondary end points were bladder-preservation rate, OS and safety. Our study estimated a RFS rate at 12 months was no less than 85% and the study would enroll 38 pts. Clinical trial information: ChiCTR2400093839. Research Sponsor: None.

TPS4625 **Poster Session**

Updates to CORE-008: A phase 2 multi-arm, multi-cohort study to evaluate intravesical cretostimogene grenadenorepvec in patients with high-risk non-muscle invasive bladder cancer. First Author: Gary D. Steinberg, Department of Urology, Rush University, Chicago, IL

Background: Treatment for High-Risk Non-Muscle Invasive Bladder Cancer (HR NMIBC) includes Transurethral Resection of Bladder Tumor (TURBT) followed by intravesical Bacillus Calmette–Guérin (BCG). Despite high initial response rates, over 50% of patients will recur and 20-40% are at risk for progression. Treatment of HR NMIBC is challenged by the ongoing BCG shortage, thus there exists a need for clinically effective, well-tolerated, and readily available treatment options. Cretostimogene grenadenorepvec is an oncolytic immunotherapy with a dual mechanism of action. It selectively replicates in and lyses bladder cancer cells with Retinoblastoma (Rb)-E2F pathway alterations. The subsequent release of virus- and tumor-specific antigens initiate antitumor immune activation which is further amplified by the GM-CSF transgene. Cretostimogene received Fast Track and Breakthrough Therapy Designations by the US FDA for HR BCG-Unresponsive NMIBC with CIS indication. Given the strength of these data, the CORE-008 clinical trial (NCT06567743) was developed as a Phase 2, multi-arm, multi-cohort trial to further evaluate the efficacy and safety of cretostimogene in patients with HR NMIBC. **Methods:** Eligibility criteria: pathologic confirmation of HR NMIBC, both CIS containing and papillary only, as defined by the American Urologic Association guideline. Cohort A (BCG-naive) includes patients who have not received prior BCG. Cohort B (BCG-exposed) consists of patients who have received prior BCG and recurred at the initial clinical evaluation or at a delayed timepoint. Cohort CX, recently added, will evaluate safety and High-Grade Event-Free Survival (HG-EFS) of cretostimogene in combination with intravesical gemcitabine, either concurrent (Arm 1) or sequential (Arm 2) in BCG-exposed and BCG-unresponsive patients. The combination is believed to leverage complementary mechanisms and potential immune modulating synergy to enhance outcomes. Intravesical cretostimogene will be instilled with n-dodecyl-β-D-maltoside (DDM), an excipient that enhances adenoviral delivery, for six weekly doses during the induction phase, followed by three weekly maintenance cycles quarterly through month 12, then every six months through month 36. Re-induction is permitted. The primary endpoint for CIS is Complete Response (CR) at any time and HG-EFS for papillary-only disease. Secondary endpoints will include Duration of Response, all-cause Event-Free Survival, Bladder Cancer Specific Survival, Cystectomy-Free Survival, safety, and tolerability. Exploratory outcome measures include Health-Related Quality of Life, Overall Survival, and biomarker assessments. All cohorts are open for enrollment. Cohort B has received collaborative support from the Society of Urologic Oncology-Clinical Trials Consortium (SUO-CTC). Clinical trial information: NCT06567743. Research Sponsor: CG Oncology.

TPS4626 **Poster Session**

Sasanlimab as bladder-sparing maintenance treatment after neoadjuvant chemotherapy in patients with muscle invasive bladder cancer (MIBC): The phase 2, SASAN-SPARING trial. First Author: Elena Sevillano, HM CIOCC MADRID (Centro Integral Oncológico Clara Campal), Laboratorio de Innovación en Oncología, Instituto de Investigación Sanitaria HM Hospitales, Madrid, Spain

Background: Radical cystectomy (RC), traditionally considered the gold standard for MIBC, carries significant morbidity, negatively impacting patients' quality of life. Recent studies have demonstrated that neoadjuvant cisplatin-based chemotherapy combined with immunotherapy can induce a complete or major pathological response in a subset of patients, allowing consideration of less invasive therapeutic alternatives. High comorbidity rates in MIBC often preclude radical cystectomy. Sasanlimab, a PD-1 inhibitor, may enhance the efficacy of neoadjuvant chemotherapy, potentially enabling bladder preservation in responding patients and improving outcomes. **Methods:** The SASAN-SPARING trial is a single-arm, non-randomized, non-blinded, phase 2 trial that evaluates the efficacy and safety of sasanlimab as a maintenance treatment in patients with localized MIBC that undergo a bladder sparing strategy with neoadjuvant cisplatin-based chemotherapy. A total of 70 patients will be accrued in 10 hospitals of Spain. Patients are $\geq$ 18 years, ECOG 0-1 and treatment-naïve for MIBC candidates to receive neoadjuvant cisplatin/gemcitabine followed by RC. All patients receive 4 cycles of neoadjuvant chemotherapy with cisplatin (70 mg/m2) on day 1 every 3 weeks and gemcitabine (1000 mg/m2) on days 1 and 8 of a 3-week cycle. After neoadjuvant chemotherapy, patients are restaged and those achieving a clinical response (absence of disease by cytology, imaging, and cT0/Ta/T1/Tis) are allowed to proceed without RC and receive maintenance with sasanlimab 300 mg subcutaneous every 4 weeks for up to 12 cycles. Tumor assessments including MRI, cystoscopy and cytology are scheduled every 12 weeks. The primary endpoint is the bladder-intact overall survival (biOS) rate at 12 months after the first dose of sasanlimab. Assuming a 12-month biOS of 81% (H0) and an increase with sasanlimab up to 93% (H1), the study requires 70 patients included of which 47 are treated with sasanlimab (one arm survival test; α = 0.05 β= 0.8). The study includes an ambitious biomarker substudy to evaluate the use of ctDNA in blood and urine samples for tumor assessment and molecular dynamics under therapeutic pressure. In addition, gut microbiome and tumor samples will be used for this end. Study of biomarkers will provide a useful tool to corroborate achievement of a clinical complete response, contributing to personalized treatments. The study is approved and started with recruitment of patients in December 2024. Clinical trial information: NCT06623162. Research Sponsor: Fundación de Investigación HM Hospitales supported by a grant (#87884561) from Pfizer.

TPS4627 **Poster Session**

Intravesical sacituzumab tirumotecan in participants with intermediate-risk non–muscle-invasive bladder cancer: The phase 1/2 TroFuse-027 study. First Author: Joshua J. Meeks, Northwestern University Feinberg School of Medicine, Chicago, IL

Background: Standard treatment for patients with intermediate-risk (IR) non–muscle-invasive bladder cancer (NMIBC) is transurethral resection of bladder tumor (TURBT) with or without adjuvant intravesical chemotherapy or bacillus Calmette-Guérin. However, 30% to 50% of patients experience disease recurrence, which leads to repeated endoscopic resections and intravesical therapies that contribute to patient morbidity and decreased urinary quality of life. Therefore, novel therapies with favorable efficacy and safety profiles are needed. Trophoblast cell-surface antigen 2 (TROP2) is a transmembrane glycoprotein expressed broadly in several tumors, including all stages of bladder cancer, making it a viable therapeutic target. Sacituzumab tirumotecan (sac-TMT; MK-2870) is an antibody-drug conjugate consisting of a humanized anti-TROP2 monoclonal antibody, a linker, and a cytotoxic belotecan-derivative topoisomerase I inhibitor. In *in vivo* mouse models, intravesical sac-TMT demonstrated antitumor activity, tolerability, and minimal systemic exposure. TroFuse-027 (NCT06637423) is a nonrandomized, open-label, phase 1/2 study designed to evaluate the safety and efficacy of intravesical sac-TMT as ablative therapy in participants with IR NMIBC. **Methods:** Eligible participants are adults with prior history of pathologically confirmed low-grade Ta diagnosed with recurrence by visual inspection on cystoscopy who have not yet undergone TURBT and have urine cytology negative for high-grade urothelial carcinoma. In the phase 1 dose-escalation part, approximately 32 participants will be sequentially enrolled into 4 escalating sac-TMT dose groups using the Bayesian optimal interval design with a target dose-limiting toxicity rate of 30%; 3 to 14 participants are planned for each dose group. Sac-TMT will be administered by intravesical instillation weekly for 6 weeks unless there is unacceptable toxicity or withdrawal of consent. Disease assessments (per local urine cytology, cystoscopy, and biopsy as indicated for visible tumors) will occur at week 12 in all participants, then every 12 weeks for the first year and every 24 weeks thereafter for up to 2 years unless progression to high-grade NMIBC or muscle-invasive bladder cancer occurs. Participants with low-grade Ta that persists at week 12 or recurs anytime after that will undergo TURBT and remain in efficacy follow-up. The primary objectives are to evaluate safety and tolerability and to establish the recommended phase 2 dose. Secondary objectives are pharmacokinetics and complete response rate (the proportion of participants with the absence of visible tumors at the 12-week assessment after initiating treatment) and duration of complete response per local assessment. Future studies (phase 2) will be initiated on completion of dose escalation and based on the totality of data. Clinical trial information: NCT06637423. Research Sponsor: Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA.

TPS4628 **Poster Session**

SOGUG-NEOWIN: A phase 2, open-label, multicenter, multinational interventional trial evaluating the efficacy and safety of erdafitinib (ERDA) monotherapy and the combination of ERDA and cetrelimab (CET) as neoadjuvant treatment in cisplatin-ineligible patients with muscle-invasive bladder cancer (MIBC) harboring FGFR gene alterations. First Author: Guillermo de Velasco, Hospital 12 de Octubre, Madrid, Spain

Background: The standard treatment for nonmetastatic MIBC is neoadjuvant cisplatin-based chemotherapy followed by radical cystectomy (RC). However, many patients are ineligible for cisplatin-based therapy. Immune checkpoint inhibitors (ICIs) have transformed the treatment of metastatic urothelial cancer (mUC), particularly for cisplatin-ineligible patients. Emerging evidence suggests that ICIs may also have potential as neoadjuvant therapy in resectable urothelial cancer, with preliminary data showing antitumor activity. Erdafitinib (ERDA), an FGFR inhibitor, has demonstrated efficacy in advanced urothelial cancer with FGFR2/3 mutations or fusions. In the phase 2 NORSE trial, ERDA combined with CET showed clinically meaningful activity in newly diagnosed FGFR-altered mUC. This study evaluates whether ERDA $\pm$ CET improves the pathological complete response (pCR) rate in FGFR-positive MIBC patients eligible for RC but ineligible for or declining cisplatin-based neoadjuvant therapy. **Methods:** SOGUG-NEOWIN is a prospective, non-comparative, open-label, multicenter trial assessing 9 or 12 weeks of neoadjuvant ERDA (cohort 1) or ERDA + CET (cohort 2) in patients with MIBC (cT2–T4a N0/1 M0) and FGFR alterations. Eligibility criteria include ECOG PS 0–1; predominant urothelial carcinoma histology; cisplatin ineligibility (GFR $<$ 60 mL/min, $\geq$grade 2 hearing loss, or $\geq$grade 2 neuropathy) or refusal; fitness for RC; no prior FGFR-targeted or anti-PD-(L)1 therapy, systemic therapy, or surgery (except TURBT or biopsies); prior BCG therapy allowed if completed $\geq$6 weeks before study treatment; and no current retinopathy. A total of 45 patients per cohort will be centrally allocated. Co-primary endpoints are pCR rate and pathological downstaging response ($<$ ypT2). Secondary endpoints include event-free survival, overall survival, response rate, safety, tolerability, and delay to surgery. Exploratory endpoints include biomarkers of response and resistance (baseline tissues, blood, urine), quality of life (FACT-BI, EQ-5D-5L), and PET-MRI tumor response in a subset of patients. This trial is approved in 4 countries (6 sites in Spain, 3 in Italy, 5 in the UK, 5 in France) and is the first to systematically evaluate ERDA $\pm$ CET in FGFR-positive MIBC. The first patient was pre-screened on January 31, 2024. As of January 21, 2025, 68 patients were pre-screened, 6 were FGFR2/3-positive, and 4 were enrolled. (EU CT Number 2024-512573-27-01). Clinical trial information: 2024-512573-27-01. Research Sponsor: Johnson & Johnson.

TPS4629 **Poster Session**

The uTRACT registry: A single-arm, multicenter, prospective, and retrospective registry study to evaluate the real-world use of UGN-101 in participants with upper tract urothelial carcinoma (UTUC) in the United States. First Author: Adam Feldman, Massachusetts General Hospital, Boston, MA

Background: Upper tract urothelial carcinoma (UTUC) constitutes 5–10% of primary urothelial carcinomas, affecting two in 100,000 people in the US annually. Peak incidence occurs in patients 70–90 years of age.[1-3] Low-Grade (LG) UTUC represents 40% of the total disease burden.[3] Endoscopically-guided ablation is often used to treat LG-UTUC, however recurrence is common, and the long-term surveillance risks potential complications in this elderly patient population. UGN-101 is a reverse thermal hydrogel formulation of mitomycin approved for chemoablative treatment of LG-UTUC, administered as a liquid in a chilled state, which converts to a gel depot at body temperature, resulting in a dwell time of 4–6 hours. In the phase 3 OLYMPUS trial, 42 of the 71 LG-UTUC patients treated with UGN-101 achieved complete response (CR) at 3 months.[4] Among the 41 patients followed after CR, median follow-up was 28.1 months (95% CI, 13.1-57.5), and median duration of response (DoR) was 47.8 months (95% CI, 13.0-not estimable).[5] **Methods:** The uTRACT registry (NCT05874921) is evaluating real-world data from patients administered UGN-101, post-FDA approval(15 Apr 2020). Approximately 400 patients >18 years old with UTUC who received ≥1 dose of UGN-101 will be enrolled at ~20 sites. Retrospective data will be collected from patients that received UGN-101 after approval as well as prospective data from newly eligible patients. UGN-101 is administered as 6 once weekly pyelocalyceal instillations retrograde via ureteral catheter or antegrade via a nephrostomy tube. Instillation volume is based on volumetric measurements, not to exceed 15 mL (60 mg of mitomycin). For participants with a CR 3 months after the first dose, once monthly maintenance instillations may be administered (up to 11 additional doses). Participant history and disease status are collected at baseline (prior to UGN-101 dosing), and dosing information, surveillance endoscopy and imaging results will be captured over a period of 3 years post baseline, at approximately 3, 6, 12, 24, and 36 months after the first instillation. Assessment of response will be based on endoscopic surveillance, imaging, cytology, and/or for-cause biopsy. Data analysis will be performed on the overall cohort (~400 participants) and the LG-UTUC cohort (expected to be ~340 participants). Outcomes collected include no evidence of disease at 3-months, DoR, recurrence free survival, time to recurrence/progression and adverse events. The uTRACT registry started enrollment in 2023 with 228 patients recruited to date. 1. Siegel RL, et al. CA Cancer J Clin. 2022;72:7-33. 2. Rouprêt M, et al. Eur Urol. 2023;84:49-64. 3. Raman J, Shore ND. Rev Urol. 2020;22:1-8. 4. Kleinmann N, et al. Lancet Oncol. 2020;21:776-785. 5. Pierorazio PM, et al. J Urol. 2024: 101097ju0000000000004331. Clinical trial information: NCT05874921. Research Sponsor: UroGen Pharma.

TPS4630 **Poster Session**

ABLE-22: Safety and efficacy evaluation of nadofaragene firadenovec alone or in combination with chemotherapy or immunotherapy—A randomized, open-label, phase 2 study. First Author: Siamak Daneshmand, Keck School of Medicine of USC, Los Angeles, CA

Background: Bacillus Calmette-Guérin (BCG) is the standard first-line therapy for patients with high-risk non–muscle-invasive bladder cancer (NMIBC) with carcinoma in situ (CIS) ± papillary tumors; however, patients whose disease is unresponsive to BCG therapy are unlikely to benefit from further courses of BCG. Bladder-preserving treatment options for patients with BCG-unresponsive NMIBC with CIS ± Ta/T1 include intravesical gene therapy (nadofaragene firadenovec-vncg), intravesical chemotherapy (gemcitabine and docetaxel), and immunotherapy (intravenous pembrolizumab and intravesical nogapendekin alfa inbakicept-pmln). In a pivotal phase 3 study, 53.4% of participants (55/103) with BCG-unresponsive NMIBC with CIS ± Ta/T1 achieved a complete response (CR) within 3 months of a single instillation of nadofaragene firadenovec, and of them, 45.5% (25/55) maintained a CR at 12 months. Nadofaragene firadenovec in combination with chemotherapy or immunotherapy may further improve clinical efficacy. ABLE-22 (NCT06545955) is an interventional study evaluating the safety and efficacy of nadofaragene firadenovec alone or in combination with chemotherapy (gemcitabine and docetaxel) or immunotherapy (pembrolizumab) in participants with high-risk BCG-unresponsive NMIBC. Participants not responding at month 3 will be offered reinduction. **Methods:** ABLE-22 will include approximately 40 to 75 sites across the United States and Canada; sites in Asia, Australia, and Europe may be included. Participants (anticipated N = 150) will be randomly assigned 1:1:1 to receive nadofaragene firadenovec (n = 50), nadofaragene firadenovec plus gemcitabine and docetaxel (n = 50), or nadofaragene firadenovec plus pembrolizumab (n = 50). Adults aged ≥18 years with documented NMIBC with CIS ± Ta/T1 that is unresponsive to ≥2 courses of BCG therapy within the last 12 months are eligible to enroll. The primary endpoint is CR (defined as absence of low- and high-grade NMIBC) at months 3 or 6, as participants with persistent NMIBC (any CIS, low-grade Ta, and > 3 cm or multifocal high-grade Ta) will be offered reinduction once, at month 3. Secondary endpoints include durability of CR, incidence of muscle-invasive progression, cystectomy-free survival, pathologic staging, overall survival, and safety. Durability of CR will be followed up to month 36 (assessed quarterly for the first 24 months); all other secondary endpoints will be assessed up to and including month 36. Exploratory endpoints include changes in expression of potential biomarkers in blood and urine. Results from this investigational, randomized, multicenter, open-label study evaluating the safety and efficacy of nadofaragene firadenovec alone or in combination with chemotherapy or immunotherapy are expected July 2028. Clinical trial information: NCT06545955. Research Sponsor: Ferring Pharmaceuticals, Inc.

TPS4631 **Poster Session**

LEGEND: A phase 1/2 study of detalimogene voraplasmid (EG-70), an intravesical monotherapy for patients with high-risk non–muscle-invasive bladder cancer (NMIBC). First Author: Jen-Jane Liu, Oregon Health & Science University, Portland, OR

Background: High-risk NMIBC is generally treated with adjuvant intravesical Bacille Calmette-Guérin (BCG). However, ~50% of patients experience recurrence and/or progression afterwards and are considered unresponsive. Detalimogene voraplasmid (EG-70) is an investigational, non-viral, non-integrating, intravesically administered gene therapy designed to elicit local stimulation of anti-tumor immune responses in the bladder and drive durable efficacy in NMIBC, while mitigating the risk of systemic toxicities from immune stimulation. The Phase 1 (dose-escalation) portion of the first-in-human Phase 1/2, open-label, multicenter study (LEGEND; NCT04752722) of detalimogene voraplasmid is complete. The Phase 2 dose was identified, treatment was generally well tolerated, with an overall complete response (CR) rate of 73% [Kalota S, et al. AUA 2024]. Herein, we describe the ongoing Phase 2 portion of the study, which opened to enrollment in May 2023, which recently added a new cohort of BCG-unresponsive HG Ta/T1 papillary only (no carcinoma *in situ* [CIS]) disease. **Methods:** Eligibility criteria: age ≥18 years; ECOG PS 0−2; NMIBC, with/without resected coexisting papillary tumors, ineligible for, or elected not to undergo, cystectomy; satisfactory bladder function. Patients receive detalimogene voraplasmid 0.8 mg/mL in 50 mL (intravesical administration, Weeks 1, 2, 5 & 6, 12-week cycle) for 4 cycles, and patients with CR at the end of the 4th cycle will enter maintenance treatment to receive 2 instillations per cycle (at Weeks 1 and 2) for up to another 8 cycles: BCG-unresponsive with CIS (Cohort 1); BCG-naïve with CIS (Cohort 2A) or BCG-exposed with CIS (Cohort 2B); BCG-unresponsive NMIBC with high-grade papillary disease without CIS (Cohort 3). Phase 2 primary endpoints: efficacy (CR rate at Week 48); safety. Secondary endpoints: progression-free survival; CR rate at Weeks 12, 24, 36, and 48; duration of response. The study is being conducted in accordance with the ethical principles of the Declaration of Helsinki and is consistent with ICH/GCP. All patients provide written informed consent. The Phase 2 portion of the study is enrolling and will recruit approximately 300 patients across all cohorts, from sites in the USA, Canada, Europe, and the Asia-Pacific region. Clinical trial information: NCT04752722. Research Sponsor: enGene Inc.

TPS4632 **Poster Session**

ABLE-32: A randomized, controlled, phase 3b clinical trial of nadofaragene firadenovec-vncg versus observation in patients with intermediate-risk non–muscle-invasive bladder cancer. First Author: Neal D. Shore, Carolina Urologic Research Center, Myrtle Beach, SC

Background: There is currently no Food and Drug Administration (FDA)-approved treatment for intermediate-risk non–muscle-invasive bladder cancer (IR NMIBC), defined as recurrence of low-grade (LG) Ta within 1 year, solitary LG Ta > 3 cm, multifocal LG Ta, high-grade (HG) Ta (≤3 cm), and/or LG T1. Nadofaragene firadenovec-vncg is the first FDA-approved intravesical nonreplicating gene therapy for treating high-risk BCG-unresponsive NMIBC with carcinoma in situ (CIS) ± papillary tumors. In a non-randomized, multicenter, open-label, repeat-dose, phase 3 study, 53.4% of participants (55/103) with CIS ± HG Ta/T1 achieved complete response 3 months after the first instillation. Nadofaragene firadenovec was well tolerated, with no grade 4/5 study drug-related AEs. Because maintenance treatment with nadofaragene firadenovec following tumor resection may improve clinical outcomes in patients with IR NMIBC, the ABLE-32 open-label randomized study is being conducted to evaluate the efficacy of nadofaragene firadenovec administered every 3 months versus observation in participants with IR NMIBC. **Methods:** This phase 3 study includes approximately 100 global sites with 454 anticipated participants. Adults aged ≥18 years, diagnosed with new or recurrent IR NMIBC, and having undergone transurethral resection of bladder tumor within 60 days prior to randomization are eligible. Participants will be randomly assigned 1:1 to receive nadofaragene firadenovec or continue observation. The nadofaragene firadenovec group will receive quarterly doses unless disease recurs or progresses. The observation group will be followed quarterly and may receive nadofaragene firadenovec if IR NMIBC recurs within 24 months. All participants will be evaluated for recurrence and progression using cytology, cystoscopy, and for-cause biopsy for up to 5 years. The primary endpoint is recurrence-free survival (RFS), from randomization to first documented recurrence, progression, or death. Secondary endpoints include RFS at 12 and 24 months and safety. Exploratory endpoints include effect on potential biomarkers and health-related quality of life. Final results are expected in 2031. Clinical trial information: NCT06510374. Research Sponsor: Ferring Pharmaceuticals.

5000 Oral Abstract Session

Phase 3, randomized, placebo-controlled clinical trial of CAN-2409+prodrug in combination with standard of care external beam radiation (EBRT) for newly diagnosed localized prostate cancer. First Author: Theodore L. DeWeese, Johns Hopkins University School of Medicine, Baltimore, MD

Background: Standard of care (SoC) for intermediate to high-risk localized prostate cancer (PrCa) includes surgery or external beam radiation (EBRT) +/- androgen deprivation therapy (ADT). Nearly 30% of men undergoing EBRT will experience recurrence requiring ADT and salvage therapies that negatively impact quality of life. CAN-2409 is a replication-defective adenovirus encoding the HSV-tk gene that, when combined with valacyclovir (prodrug), results in immunogenic cell death. This results in immunization against tumor antigens and long-term tumor control. **Methods:** We conducted a phase 3, multicenter, double-blinded, randomized, placebo (PBO)-controlled clinical trial in PrCa patients (pts) planning to receive EBRT+/- short course ADT (<6 mos); NCT01436968. 745 pts were randomized 2:1 (496 in CAN-2409+prodrug and 249 in PBO+prodrug) and stratified by NCCN risk group and ADT use. Three intraprostatic injections of CAN-2409 (5x10 ^{11}v/2mL) or PBO were administered, each followed by 14 days of prodrug. Follow-up included a prostate biopsy 2 years after EBRT. Primary endpoint was disease-free survival (DFS), defined as time from randomization to PrCa recurrence (local/regional failure or distant metastasis) or death in the intent-to-treat population. Median follow up time was 50.3 mos. The study was conducted under a special protocol assessment (SPA) granted by the FDA. **Results:** Treatment with CAN-2409 reduced the risk of PrCa recurrence or death by 30% (median DFS not reached vs 86.1 mos, p=0.0155, HR 0.7, 95% CI 0.52 to 0.94). PrCa-specific DFS (exclusion of non PrCa- related deaths) demonstrated an even greater effect with a 38% decreased risk in the CAN-2409 arm vs. PBO (p=0.0046; HR 0.62, 95% CI 0.44 to 0.87). Statistically significant secondary endpoints included increased percentage of patients achieving prostate-specific antigen nadir (67.1% vs 58.6%, p=0.0164) and an increase in pathological complete responses in the 2-year biopsies in the CAN-2409 arm vs. PBO (80.4% vs. 63.6%, p=0.0015). Most common treatment-related adverse events included chills (33.4% vs. 8.6%), flu-like symptoms (30.5% vs. 13.8%), and fever (25.1% vs. 3.9%), mostly Gr 1-2 and self-limited. Serious adverse events (SAEs, 5.8% vs. 7.3%) and treatment-related SAEs (1.7% vs. 2.2%) were uncommon across treatment groups. **Conclusions:** In this randomized, double-blind, Phase 3 trial, CAN-2409 significantly reduced the risk of PrCa recurrence or death when added to SoC EBRT+/- ADT. The addition of CAN-2409 was not associated with significant added toxicity. These data represent the first potentially new therapy for patients with intermediate and high risk PrCa in over 20 years. Clinical trial information: NCT01436968. Research Sponsor: Candel Therapeutics, Inc.; National Cancer Institute.

5001 Oral Abstract Session

Multimodal artificial intelligence (MMAI) model to identify benefit from 2nd-generation androgen receptor pathway inhibitors (ARPI) in high-risk non-metastatic prostate cancer patients from STAMPEDE. First Author: Charles Thomas Andrew Parker, University College London Cancer Institute, London, United Kingdom

Background: The STAMPEDE trials showed that adding abiraterone acetate + prednisolone (AAP) ± enzalutamide (ENZ) to standard of care androgen deprivation therapy (SOC) improves metastasis-free survival (MFS) in high-risk non-metastatic (M0) prostate cancer (PCa) patients (pts). However, variable responses & adverse events underscore the need for prognostic & predictive biomarkers. We evaluated performance of a validated MMAI algorithm (ArteraAI Prostate Test v1.2) to identify pts who benefit most from the addition of AAP ± ENZ (ARPI). **Methods:** High-risk M0 STAMPEDE pts treated with SOC+ARPI (N=555) or SOC (N=781) with sufficient quality H&E biopsy images & clinical data (T stage, age, PSA) were included. MMAI score association with PCa specific mortality (PCSM, primary outcome measure) & distant metastasis (DM) was analyzed using Fine-Gray regression & cumulative incidence curves, with other cause mortality treated as competing risks. MFS was assessed using Cox regression & Kaplan-Meier curves. An optimal cut-point was identified via grid search to maximize ARPI benefit separation across biomarker positive (pos, MMAI in top quartile) & negative (neg) subgroups. Hazard ratios [95% CI] & p values are reported. **Results:** PCSM median follow-up was 6.0 years (N=1336). Continuous MMAI scores were statistically significantly associated with poorer PCSM (1.65 [1.43-1.90], p<0.001), MFS (1.42 [1.29-1.56], p<0.001) & DM (1.54 [1.36-1.74], p<0.001). Using clinically-established prognostic cut-offs, 89% of pts were MMAI high-risk. The optimal ARPI MMAI cut-point identified 334 biomarker-pos pts who had significantly higher PCSM than biomarker-neg pts. A statistically significant biomarker-treatment interaction for PCSM (p-int=0.04) revealed that biomarker-pos pts treated with ARPI had improved PCSM (0.42 [0.24-0.74], p=0.003), while biomarker-neg pts did not derive a treatment benefit (0.85 [0.56-1.29], p=0.45). Estimated 5-year PCSM was 9% for biomarker-pos pts receiving ARPI vs. 17% with SOC, compared to 4% & 7% for biomarker-neg pts, respectively, with similar results observed in M0N0 pts (Table 1). **Conclusions:** For the first time, we demonstrate that a validated MMAI algorithm can identify high-risk non-metastatic PCa pts most likely to benefit from the addition of ARPI. Notably we identify a positive biomarker-treatment interaction in the highest MMAI score quartile, which in cases of clinical equipoise could inform clinical decision-making. We highlight MMAI's potential to optimize treatment decisions & spare biomarker-neg pts from unnecessary therapy & toxicities. Clinical trial information: NCT00268476. Research Sponsor: Prostate Cancer Foundation; Artera, Inc.; John Black Charitable Foundation; UK Medical Research Council; Prostate Cancer UK; Cancer Research UK; Sanofi Aventis; Janssen; Astellas; Novartis.

Estimated 5-yr absolute risk reduction from ARPI vs SOC-treated patients by biomarker groups in M0 (M0N0) pts.

	Biomarker-neg	Biomarker-pos
PCSM	3% (1%)	8% (9%)
MFS	2% (-1%)	17% (16%)
DM	5% (3%)	12% (15%)

5002 Oral Abstract Session

Prognostic significance of PSA>0.2 after 6-12 months treatment for metastatic hormone-sensitive prostate cancer (mHSPC) intensified by androgen-receptor pathway inhibitors (ARPI): A multinational real-world analysis of the IRONMAN registry. First Author: Michael Ong, The Ottawa Hospital Cancer Centre, Ottawa, ON, Canada

Background: Phase III post-hoc analyses show poor prognosis of PSA >0.2 in mHSPC treated by androgen deprivation therapy (ADT) and ARPI, but it remains unclear 1) when PSA cutoffs should be interpreted for prognostic significance, and 2) how PSA cutoffs may differ in real-world multinational data. IRONMAN (International Registry for Men with Advanced Prostate Cancer) prospectively enrolled mHSPC patients from 16 countries and is a unique large data set to investigate these questions. **Methods:** Patients with mHSPC who received ADT, ARPI +/- docetaxel with PSA data enrolled in the IRONMAN registry were included. 3 PSA strata (>0.2, 0.02 to 0.2, and <0.02ng/ml) were defined at 6- and 12-months (primary analysis) after treatment start. Multivariable Cox proportional hazard regression models were constructed for overall survival (OS) and progression-free survival (PFS, as defined by any of biochemical, radiographic or clinically progression) with adjustment for disease characteristics. A 12-month landmark population was constructed to determine conditional OS and PFS in each PSA stratum. **Results:** 1288 patients received ADT and ARPI within 90 days of IRONMAN enrolment and met inclusion. Key characteristics were median age 70 years, 69.5% de-novo metastatic, 59% Gleason 8-10, 73% Caucasian, 8.2% Black, 1.5% Asian, 7.3% lung metastases, 3.4% liver metastases, and 53.2% enrolment from centers outside US/Canada. Intensification agents were: abiraterone acetate (576, 44.7%), apalutamide (283, 22.0%), darolutamide (135, 10.5%), or enzalutamide (294, 22.8%), and 122 (8.7%) received docetaxel in addition to ADT-ARPI. PSA at 6, 12 month landmarks respectively were: <0.02 (10%, 21%); 0.02-0.2 (41%, 45%); >0.2 (49%, 34%), with 70% of patients with 6-month PSA >0.2 retained at 12-months. Outcome data in the 12-month landmark cohort are detailed in Table 1, with 3-year OS for the PSA >0.2 stratum significantly worse than the PSA<0.02 stratum (45.3 vs 92.7%, p<0.001), representing a 7-fold mortality risk in the Cox model adjusted hazard ratio (aHR) and 8-fold risk of progression. **Conclusions:** IRONMAN provides large real-world data validating the poor prognosis of mHSPC with PSA>0.2 after 6-12 months ADT-ARPI treatment and these patients could be targeted for intensification in future trials. Conversely, PSA<0.02 at 6-12 months defines the best prognosis and may be of interest for de-intensification strategies. Research Sponsor: Movember Foundation; Amgen, Astellas, AstraZeneca, Bayer, Janssen, Merck, Novartis and Sanofi.

OS and PFS outcomes by 12-month PSA strata.

12-mo PSA (ng/ml)	n	3-yr OS [95%CI]	3-yr PFS [95% CI]	OS Cox model mortality risk [95% CI]
>0.2	264	45.3% [36.7-55.9]	36.7% [28.6-47.1]	aHR 7.34 [3.66-14.71]
0.02-0.2	585	80.0% [74.5-85.9]	72.9% [66.9-79.1]	aHR 2.16 [1.06-4.41]
<0.02	439	92.7% [87.9-97.8]	93.0% [88.6-97.5]	reference

5003 Oral Abstract Session

Transcriptome classification of PTEN inactivation to predict survival benefit from docetaxel at start of androgen deprivation therapy (ADT) for metastatic prostate cancer (PC): An ancillary study of the STAMPEDE trials. First Author: Emily Grist, University College London Cancer Institute, London, United Kingdom

Background: Docetaxel (Doce) is effective for metastatic (M1) PC but its effect is varied. Combining Doce and hormone therapy can improve overall survival (OS) but is not appropriate for all. We previously reported the mRNA Decipher test predicts benefit from Doce. We then used transcriptome-wide data to interrogate differential associations with outcome for biologically-relevant pathways. **Methods:** PTEN inactivation using a previously described signature (Liu et al JCI, 2021; active score <= 0.3, inactive: score > 0.3) and Decipher score (high > 0.8, lower <= 0.8) was determined from transcriptome-wide expression data generated in a clinically-accredited lab on prostate tumor from M1 patients (pts) randomized 1:1 to ADT vs ADT + Doce +/- zoledronic acid (ZA) or ADT vs ADT + Abi (abiraterone acetate + prednisone) in the STAMPEDE protocol (Oct 2005-Jan 2014). Cox survival models were fitted with an interaction between treatment allocation and PTEN activity, adjusted for age, WHO PS, pre-ADT PSA, Gleason score, T-stage, N stage (N0, N1), metastatic volume (CHAARTED definition, high [HV] or low [LV]). Hypotheses were tested using partial likelihood ratios. Primary endpoint was OS. **Results:** We generated transcriptome-wide profiles on 832 M1 pts with no notable differences from the full M1 trial cohort (N=2224). 657 (79%) were reported to have died. 50% of tumors were classified as PTEN inactive (N=419). PTEN mRNA score distribution was similar across HV and LV disease (p=0.310). PTEN inactivity associated with shorter OS in pts allocated ADT+Abi (N=182; HR=1.56, 95%CI: 1.06-2.31) but not in pts allocated ADT+Doce+/-ZA (N=279; HR=0.93, 95%CI: 0.70-1.24). We found strong evidence (p=0.002) of an interaction between PTEN inactivation and Doce sensitivity: PTEN inactive pts benefited from Doce (HR=0.57, 95% CI 0.42-0.76) unlike PTEN active pts (HR=1.05, 95% CI 0.77-1.43). This was consistent in LV (N=244; PTEN inactive HR=0.53, 95% CI 0.33-0.86; PTEN active HR=0.82, 95% CI 0.48-1.40) and HV (N=295; PTEN inactive, HR=0.59, 95% CI 0.39-0.88; PTEN active HR=1.23, 95% CI: 0.83-1.81). In pts randomized to Abi, treatment effect was uniform (PTEN inactive HR=0.52, 95% CI 0.36-0.73; PTEN active HR=0.55, 95% CI 0.39-0.77; p=0.784). We estimated adding Doce for tumors classified as PTEN inactive and high Decipher reduced the hazards of death by 45% (HR 0.55, 99% CI 0.34-0.89). **Conclusions:** Prostate tumors classified as high Decipher and PTEN inactive have a 45% reduction in hazard of death when Doce is added to ADT. This biomarker should be tested in pts considered for triplet therapy of ADT + Abi + Doce. Research Sponsor: Prostate Cancer UK; National Institute for Health Research UK; Veracyte; Medical Research Council; Prostate Cancer Foundation; John Black Charitable Foundation; Cancer Research UK; Prostate Cancer Research; U.S. National Institutes of Health; Department of Defence; Orchid; The Benioff Initiative.

5004 **Oral Abstract Session**

Health-related quality of life (HRQoL) outcomes with darolutamide in the phase 3 ARANOTE trial. First Author: Alicia K. Morgans, Dana-Farber Cancer Institute, Boston, MA

Background: Effective and well tolerated treatments to maintain HRQoL are essential for patients with metastatic hormone-sensitive prostate cancer (mHSPC). Darolutamide (DARO) + androgen deprivation therapy (ADT) significantly reduced the risk of radiological progression or death (primary endpoint) by 46% (hazard ratio [HR] 0.54; 95% confidence interval [CI] 0.41–0.71; $P<0.0001$) vs placebo (PBO) + ADT in ARANOTE (NCT04736199). The incidence of adverse events (AEs) was low and similar to PBO, with fewer study drug discontinuations due to AEs in the DARO vs PBO group (6.1% vs 9.0%). We report HRQoL and pain outcomes in ARANOTE. **Methods:** Patients were randomized 2:1 to DARO 600 mg twice daily or PBO, with ADT. HRQoL was measured using the Functional Assessment of Cancer Therapy–Prostate (FACT-P). Deterioration in FACT-P total score by $\geq$10 points was a prespecified exploratory endpoint; deteriorations in FACT-P subscales by $\geq$3 points were analyzed *post hoc*. Pain was assessed using the Brief Pain Inventory–Short Form (BPI-SF), including the pain severity and pain interference subscales. Pain progression (secondary endpoint) was defined as an increase of $\geq$2 points in BPI-SF worst pain score (WPS) from nadir observed at 2 consecutive evaluations $\geq$4 weeks apart or initiation of opioid use for $\geq$7 consecutive days. Association of HRQoL and pain progression with prostate-specific antigen (PSA) response was assessed *post hoc*. HRs and 95% CIs were calculated using a Cox regression model, stratified by visceral disease (present vs absent) and prior local therapy (yes vs no) for FACT-P total score and pain progression, unstratified for FACT-P and BPI-SF subscales and association with PSA. **Results:** DARO extended time to deterioration in FACT-P total score (overall well-being) by 5.1 months vs PBO: median 16.6 vs 11.5 months; HR 0.76, 95% CI 0.61–0.93. The treatment benefit of DARO in FACT-P total score was strongly driven by longer time to deterioration in the subscales of social/family well-being (HR 0.79, 95% CI 0.64–0.98), functional well-being (0.78, 0.63–0.96), and urinary symptoms (0.78, 0.61–0.99). Additionally, DARO extended time to pain progression vs PBO: HR 0.72, 95% CI 0.54–0.96. In patients treated with DARO, achievement of PSA response $<$0.2 ng/mL at any time was associated with longer time to deterioration in FACT-P total score and longer time to pain progression vs detectable PSA response ($\geq$0.2 ng/mL) at any time. **Conclusions:** To our knowledge, DARO is the first and only androgen receptor inhibitor to demonstrate clinically meaningful delays in deterioration of important patient-relevant HRQoL outcomes vs PBO in men with mHSPC. Patients treated with DARO had improvements in overall well-being (FACT-P total score), social/family well-being, functional well-being, urinary symptoms, and pain. Combined with the efficacy and safety profile, these findings suggest that DARO also confers a positive impact on HRQoL. Clinical trial information: NCT04736199. Research Sponsor: Bayer and Orion Pharma.

5005 **Oral Abstract Session**

ARCHES: 5-year follow-up overall survival (OS) analysis of enzalutamide (ENZA) plus androgen-deprivation therapy (ADT) in patients (pts) with metastatic hormone-sensitive prostate cancer (mHSPC). First Author: Andrew J. Armstrong, Duke Cancer Institute Center for Prostate and Urologic Cancers, Duke University School of Medicine, Durham, NC

Background: In 2021, final prespecified OS (key secondary endpoint; defined as time from randomization to death from any cause) analysis of the global phase 3, randomized, double-blind, placebo (PBO)-controlled ARCHES trial (NCT02677896) demonstrated that ENZA + ADT significantly reduced risk of death by 34% versus PBO + ADT in pts with mHSPC (medians not reached [NR]; hazard ratio [HR] 0.66; 95% confidence interval [CI]: 0.53–0.81; $p<0.0001$; median follow-up, 44.6 months). To assess long-term efficacy of ENZA + ADT, we report an updated OS analysis as of July 31, 2024 (median follow-up, 61.4 months). **Methods:** In ARCHES, 1150 enrolled pts with mHSPC were randomized 1:1 to ENZA (160 mg once daily) + ADT or PBO + ADT. After primary analysis of radiographic progression-free survival (primary endpoint), ARCHES was unblinded to allow eligible patients who were randomized to PBO + ADT to cross over to ENZA + ADT in an open-label extension. Using extended follow-up data with median follow-up $>$5 years (cut-off date: July 31, 2024), Kaplan–Meier method was used to summarize the OS endpoint by treatment, with two-sided 95% CIs calculated by the Brookmeyer–Crowley method. HRs relative to PBO + ADT were determined using Cox regression model stratified for prior docetaxel use and disease volume. **Results:** ENZA + ADT (n=574; median [range] age = 70.0 [46–92] years) and PBO + ADT (n=576; median [range] age = 70.0 [42–92] years) cohorts had similar baseline characteristics. 184 (31.9%) PBO + ADT pts crossed over to open-label ENZA + ADT (median [range] age = 69.0 [51–89] years). After a median follow-up of 61.4 months, ENZA + ADT extended survival compared with PBO + ADT (medians NR; HR 0.70; 95% CI: 0.58–0.85; p=0.0003), with consistently improved survival across clinically relevant subgroups analyzed (Table), including a 36-month improvement in median OS in high-volume patients. **Conclusions:** Long-term follow-up of ARCHES demonstrated results consistent with previous OS analyses, with marked benefit in all study subgroups, including high- and low-volume patients, despite a substantial cross-over cohort. These findings further support ENZA + ADT as a standard-of-care for pts with mHSPC. Clinical trial information: NCT02677896. Research Sponsor: Astellas Pharma Inc.; Pfizer Inc.

Subgroup	ENZA + ADT N (events)	ENZA + ADT (median months)	PBO + ADT N (events)	PBO + ADT (median months)	HR (95% CI)
All	574 (191)	NR	576 (223)	NR	0.70 (0.58–0.85)
Age <65 years	148 (46)	86.4	152 (55)	NR	0.63 (0.42–0.93)
Age ≥65 years	426 (145)	NR	424 (168)	NR	0.73 (0.58–0.91)
Low-volume disease	220 (50)	NR	203 (57)	NR	0.71 (0.49–1.05)
High-volume disease	354 (141)	83.1	373 (166)	47.6	0.70 (0.56–0.88)
No prior docetaxel	471 (157)	NR	474 (179)	NR	0.71 (0.57–0.88)
Prior docetaxel	103 (34)	83.1	102 (44)	59.5	0.67 (0.43–1.05)
Synchronous (de novo): ≤90 days	438 (161)	86.4	439 (186)	58.9	0.71 (0.57–0.88)
Metachronous (relapsed): >90 days	132 (29)	NR	136 (37)	NR	0.66 (0.41–1.08)

LBA5006 **Oral Abstract Session**

Phase 3 AMPLITUDE trial: Niraparib (NIRA) and abiraterone acetate plus prednisone (AAP) for metastatic castration-sensitive prostate cancer (mCSPC) patients (pts) with alterations in homologous recombination repair (HRR) genes. First Author: Gerhardt Attard, Cancer Institute, University College London, London, United Kingdom

The full, final text of this abstract will be available at meetings.asco.org on the day of presentation and in the online supplement to the June 10, 2025, issue of the *Journal of Clinical Oncology*.

5007 **Oral Abstract Session**

A multicenter, randomized, phase 2, investigator-initiated ETCTN trial of olaparib + radium-223 vs. radium-223 in men with castration-resistant prostate cancer (CRPC) with bone metastases (BM) (COMRADE): Initial efficacy and biomarker analysis. First Author: Rana R. McKay, University of California San Diego, San Diego, CA

Background: Radium-223 is an α-emitting radioisotope which has improved overall survival (OS) in men with CRPC with BM. PARP inhibitors demonstrate synergy with radiation. Our phase 1 trial established olaparib 200 mg twice daily + radium-223 (55 kBq/kg IV q4weeks x 6) as the recommended phase 2 dose. Here, we report the phase 2 results (NCT03317392). **Methods:** Patients were randomized 1:1 to olaparib + radium-223 (Arm A) vs. radium-223 (Arm B), stratified by prior docetaxel and BM extent ($\leq$20/$>$20). Crossover was permitted in Arm B. Eligibility included any line of prior therapy, $\geq$2 BM by CT/MRI or bone scan, and at least 1 BM without prior radiation. Visceral metastases or lymphadenopathy $>$ 4 cm were excluded. Bone protecting agents (BPA) were required unless contraindicated. Homologous recombination repair gene (HRR) mutation status was determined using FoundationOne Monitor with algorithmic clonal hematopoiesis determination from baseline plasma (reported here) and Oncopanel assay from baseline biopsy or archival tissue. The primary endpoint was radiographic progression-free survival (rPFS). With 120 patients, the study was designed to have 88% power to detect an improvement in rPFS from 6.0 to 10.5 months (1-sided α=0.10). **Results:** 120 patients enrolled across 9 centers (Arm A=61, B=59). 96% received prior ARPI, 53% prior docetaxel, 32% with nodal disease, 46% had $>$ 20 BM, and 90% with concurrent BPA. Of the 103 evaluable patients, 18.5% in Arm A and 26.5% in Arm B had an HRR gene alteration by ctDNA, with 7.4% and 10.2% with *BRCA1/2* mutations, respectively. Olaparib + radium-223 had a significant improvement in rPFS vs. radium-223 (median 8.6 vs. 4.0 months, HR 0.51, 80% CI 0.37-0.70, 2-sided p=0.005). Secondary endpoints are in Table 1. The addition of olaparib improved rPFS regardless of HRR status (HRR+: HR 0.52, 80% CI 0.26-1.04; HRR-: HR 0.54, 80% CI 0.38-0.77). 56% of patients in Arm A and 35% of patients in Arm B had grade $\geq$3 treatment-related adverse events, the most common on Arm A/Arm B being: anemia (22.0%/18.0%), lymphocyte decrease (30.5%/9.1%), platelet decrease (6.8%/3.6%), and neutrophil decrease (5.1%/7.3%). **Conclusions:** In this phase 2, multicenter trial, olaparib + radium-223 demonstrated superior rPFS to radium-223, in both HRR+ and HRR- groups, with manageable side effect profile in CRPC patients with BM. Tissue and serial ctDNA analyses are underway and will be presented. Clinical trial information: NCT03317392. Research Sponsor: National Cancer Institute.

	Arm A median (months)/%	Arm B median (months)/%
rPFS	8.6	4.0
rPFS (HRR+)	5.5	3.8
rPFS (HRR-)	8.8	4.5
PSA response (confirmed)	13.1%	13.6%
Alkaline phosphatase response (confirmed)	49.2%	50.8%
Time to PSA progression	3.6	3.3
Time to Alkaline phosphatase progression	7.9	7.4
Time to next treatment	12.0	7.7
1-year symptomatic skeletal event	11.0%	22.1%
12-month OS	74%	71%

5008 Oral Abstract Session

C3NIRA: Randomized phase II study of carboplatin-cabazitaxel-cetrelimab (anti-PD-1) induction followed by niraparib +/- cetrelimab maintenance in men with aggressive variant prostate cancers (AVPC). First Author: Ana Aparicio, The University of Texas MD Anderson Cancer Center, Houston, TX

Background: AVPC have limited therapeutic options and a dismal prognosis. Although early data indicate that adding carboplatin (Carb) to cabazitaxel (Cab) benefits men with AVPC, responses are short-lived. In a previous study (NCT03263650) a subset of AVPC patients had long-term responses to CabCarb induction followed by PARP inhibitor maintenance. Tumor tissue analyses revealed upregulation of inflammatory and immune pathways in post-CabCarb treated tumors from prolonged responders. We therefore hypothesized that adding anti-PD-1 (cetrelimab, Cet) would increase the efficacy of CabCarb induction plus niraparib (Nira) maintenance in AVPC patients, and that correlates would expose tumor cell intrinsic and microenvironment pathways implicated in therapy response and resistance. **Methods:** In a single-institution study, men with CRPC meeting $\geq$ 1 of 9 AVPC criteria (listed in https://clinicaltrials.gov/study/NCT04592237) and ECOG performance status 0-2 received 6 cycles of Cab 20-25mg/m^2 and Carbo (AUC 3-4). Cet (360mg) was added to Cycles 2-6 of CabCarb. Men completing 6 cycles without progressive disease (PD) were randomized 1:1 to Nira 300mg BID $\pm$ Cet. The primary endpoint was progression free survival (PFS) in randomized patients. Subgroup comparisons between patients with PD in the first 6 cycles (Early PD) vs. patients who achieved randomization (Randomized) were made with chi-square and Kruskal-Wallis tests. Paired tumor biopsies were obtained after 1 cycle of CabCarb and 2 cycles of CabCarbCet. **Results:** 120 patients started CabCarb. Their median age was 68 years (30-83). Most were White/non-Hispanic (78%) and had not received prior docetaxel (58%). Of the 120, 20 (16.7%) went off study for reasons other than PD and 40 (33.3%) had Early PD and were not randomized. The Early PD group did not differ from the Randomized group in terms of age, race ethnicity, prior docetaxel, or baseline PSA. Post randomization median follow up was 20.5 months; median PFS was 3.4 months (95% confidence interval: 2.0, 4.4) with Nira (n=30) and 5.6 (3.7, 16.8) months with Nira+Cet (n=30, p=0.01); median overall survival was 10.2 (6.4, 19.6) with Nira and 24.3 (9.5, not reached) months with Nira+Cet (p=0.01). Single-cell RNA sequencing of paired biopsies revealed increased progenitor-like exhausted CD8+ T cells and decreased FoxP3+ Treg cells in Randomized patients (n=5) while Early PD patients (n=5) showed the opposite following the addition of Cet to CabCarb. **Conclusions:** A subset of men with AVPC derive meaningful benefit from the addition of anti-PD-1 to PARP inhibitor maintenance following platinum-taxane-anti-PD-1 induction. Ongoing correlates aim to identify biomarkers to select patients for this treatment strategy and reveal candidate mechanisms of resistance to guide future therapeutic combinations. Clinical trial information: NCT04592237. Research Sponsor: U.S. Department of Defense; W81XWH-20-1-0257; Janssen Scientific Affairs, LLC.

5009 Clinical Science Symposium

Lutetium-177-PSMA-617 in oligo-metastatic hormone sensitive prostate cancer (BULLSEYE trial). First Author: Bastiaan M. Privé, Radboudumc, Nijmegen, Netherlands

Background: [^{177}Lu]Lu-PSMA-617 (Pluvicto) is a novel treatment for patients with metastatic castration resistant prostate cancer. In a phase 1 dosimetry study, we previously showed that [^{177}Lu]Lu-PSMA-617 could be offered to patients with PSMA-expressing, recurrent, oligometastatic hormone-sensitive prostate cancer (oHSPC) with encouraging outcomes (Privé et al, CCR 2021). We here report the results of the following randomized phase 2 trial. **Methods:** This was an investigator initiated, international, multicenter, open-label, randomized phase 2 trial (NCT04443062). Fifty-eight oHSPC patients ineligible for salvage treatments, were randomized in a 1:1 fashion to [^{177}Lu]Lu-PSMA-617 vs. the standard of care (SoC) of deferred androgen deprivation therapy (ADT). Eligibility consisted of fast-progressing oHSPC (prostate specific antigen [PSA] doubling time $<$6 months) following radical prostatectomy or radiotherapy, with a maximum of 5 metastases on PSMA-PET/CT. Patients received 2 (+2 optional) cycles of 7.4 GBq [^{177}Lu]Lu-PSMA-617. The primary outcome was progression-free survival (i.e. time without ADT). Progressive disease (PD) was defined as a 100% increase in PSA since randomization, radiographic or clinical progression or earlier necessitation of subsequent therapy (e.g. ADT). Secondary outcomes were PSA response, adverse events and quality of life. **Results:** Between April 20, 2020 and July 29 2024, 58 of 78 screened men were eligible. Data cut-off was set on December 24th 2024. Median age was 72 years (range 51-82) with a median baseline PSA of 3.6 (1.2-29). Two patients received 2 cycles whereas 27 patients underwent 4 cycles of [^{177}Lu]Lu-PSMA-617. At a median follow-up time of 7 months (range 1-31), 93% (27/29) and 38% (11/29) of the SoC and arm, respectively, reached the definition for PD. The median progression free survival was 5 months (95% CI 4-6 months) for the SoC group whereas the median progression free survival was not reached for the [^{177}Lu]Lu-PSMA-617 group (HR, 0.07 [95% CI, 0.02 to 0.19]; P $<$.001). The median percentage PSA change was +125% vs. -91% in the SoC vs. [^{177}Lu]Lu-PSMA-617 arm, respectively. Twenty-one percent (6/29) of [^{177}Lu]Lu-PSMA-617 arm patients had a complete remission. The most common treatment-related adverse events were grade (G) 1 dry mouth (59%), G 1 fatigue (55%), G 1 nausea (48%), G 1 bone marrow toxicity (24-30%) which generally normalized during follow-up. G $\geq$2 adverse events were seldom observed ($<$15%) and not clinically relevant. **Conclusions:** [^{177}Lu]Lu-PSMA-617 showed promising efficacy as monotherapy in oligometastatic hormone sensitive prostate cancer patients to defer from androgen deprivation therapy, with minimal and mostly transient side effects. Following surgery and external beam radiotherapy, could become a third metastases-directed therapeutic option for oligometastatic prostate cancer patients to prolong ADT-free interval. Clinical trial information: NCT04443062. Research Sponsor: Novartis; Dutch Prostate Cancer Foundation.

5010 Clinical Science Symposium

First-in-human results of terbium-161[^{161}Tb]Tb-PSMA-I&T radioligand treatment in patients with metastatic castration-resistant prostate cancer (VIOLET): A single-centre, single-arm, phase I/II study. First Author: James Patrick Buteau, Molecular Imaging and Therapeutic Nuclear Medicine, Cancer Imaging; Prostate Cancer Theranostics and Imaging Centre of Excellence, Peter MacCallum Cancer Centre; and Sir Peter MacCallum Department of Oncology, University of Melbourne, Melbourne, VIC, Australia

Background: Terbium-161 (^{161}Tb) is a novel radionuclide emitting beta-radiation comparable to lutetium-177 (^{177}Lu), with additional higher-energy, ultra-short path-length Auger electrons which may better target micrometastases. ^{161}Tb has superior in-vitro and in-vivo efficacy in comparison with ^{177}Lu. We aim to evaluate the safety and effectiveness of [^{161}Tb]Tb-PSMA-I&T in patients with metastatic castration-resistant prostate cancer (mCRPC). **Methods:** Eligible patients in this investigator-initiated, single-centre, single-arm, phase I/II trial had progressive mCRPC previously treated with taxane chemotherapy (unless medically unsuitable) and an androgen receptor pathway inhibitor, PSMA-positive disease on PSMA PET/CT (SUVmax $\geq$20), no sites of discordance on FDG PET/CT, adequate bone marrow, hepatic and renal function, and ECOG performance status $\leq$2. The dose-escalation followed a 3+3 design to establish safety of three prespecified administered radioactivities of [^{161}Tb]Tb-PSMA-I&T (4.4, 5.5, and 7.4 GBq). Up to six cycles of [^{161}Tb]Tb-PSMA-I&T were administered intravenously every six weeks, with each subsequent radioactivity per cycle reduced by 0.4 GBq. The co-primary objectives were to establish the maximum tolerated dose (MTD) and safety profile (CTCAE v5.0) of [^{161}Tb]Tb-PSMA-I&T. Key secondary objectives for this interim analysis were PSA $\geq$50% and $\geq$90% response rates (PSA50-RR and PSA90-RR), PSA and radiographic progression-free survival (PSA-PFS and rPFS). **Results:** Between October 14, 2022 and February 15, 2024, 30 eligible patients were enrolled. Median (IQR) age 69.0 years (66.0-74.8), median baseline PSA 26.9 ng/mL (10.1-70.0), PSMA SUVmean 8.2 (7.4-10.8) and 20 patients (67%) had received prior docetaxel. There were no dose-limiting toxicities. The MTD and recommended phase 2 dose was 7.4 GBq. There were no treatment-related deaths and few grade 3 or higher treatment-related adverse events, which included pain flare and lymphopenia only. The remaining AEs are summarised in the table. PSA50-RR and PSA90-RR occurred in 21 (70% [95%CI 51-85]) and 12 (40% [95%CI 23-59]). Median PSA-PFS and rPFS were 9.0 months (95%CI 5.7-15.1) and 11.1 months (95%CI 6.6-11.7) with median follow-up of 11.2 and 11.0 months, respectively. **Conclusions:** [^{161}Tb]Tb-PSMA-I&T displayed highly encouraging efficacy with few Grade 3 or 4 adverse events. An additional cohort to assess a higher administered radioactivity is planned. Clinical trial information: NCT05521412. Research Sponsor: Prostate Cancer Foundation; Peter MacCallum Cancer Foundation; National Health and Medical Research Council; Isotopia Molecular Imaging.

Main treatment-related adverse events.

Adverse event	Grade 1	Grade 2	Grade 3	Grade 4	Total
Lymphocyte count decreased	8	10	1	0	19 (63%)
Pain	3	0	1	0	4 (13%)
Anemia	16	4	0	0	20 (67%)
Neutrophil count decreased	3	3	0	0	6 (20%)
Fatigue	12	1	0	0	13 (43%)
Dry mouth	21	0	0	0	21 (70%)
Nausea	7	0	0	0	7 (23%)
Platelet count decreased	6	0	0	0	6 (20%)
Any adverse event	13	14	2	0	29 (97%)

5011 Clinical Science Symposium

Predictive and prognostic value of baseline PSMA-PET total tumor volume and SUV mean within ENZA-p, a randomized phase II trial of enzalutamide versus enzalutamide plus [^{177}Lu] Lu-PSMA-617 (ANZUP1901). First Author: Louise Emmett, Department of Theranostics and Nuclear Medicine, St Vincent's Hospital; Faculty of Medicine, UNSW, Sydney, Australia

Background: [^{68}Ga]Ga-PSMA-11 PET (PSMA-PET) standardized uptake value (SUV)mean and total tumor volume (PSMA-TTV) have been respectively identified as predictive and prognostic of response to [^{177}Lu]Lu-PSMA-617 (LuPSMA) monotherapy. The addition of LuPSMA to enzalutamide (enza + LuPSMA) improved overall survival (OS) compared to enza-alone in mCRPC in the ENZA-p trial. This pre-specified sub-study of ENZA-p evaluated baseline PSMA-PET quantitative parameters as predictive and prognostic biomarkers for enza+ LuPSMA and enza-alone. **Methods:** ENZA-p is an open-label, randomized, phase 2 trial. Participants (pts) with mCRPC not previously treated with chemotherapy or AR antagonist (abiraterone permitted) and [^{68}Ga]Ga-PSMA-avid disease were randomized (1:1) to either enza-alone or enza + LuPSMA using adaptive-dosed [^{177}]Lu LuPSMA-617 7.5 GBq for (2 or 4 doses). All pts had a baseline [^{68}Ga]Ga-PSMA-11 PET/CT to assess eligibility (SUVmax $>$14 at a single site and SUVmax $>$10 at all larger tumor sites). PSMA-PET were quantified with semi-automated software to derive PSMA-TTV and SUVmean. The pre-specified tertiary study objective was to evaluate associations between quantitative parameters on the baseline PSMA-PET and both PSA progression-free survival (PSA-PFS) and OS. Prespecified cut-points were based on SUVmean highest quartile (Q4 vs Q1-3) and PSMA-TTV median at baseline. We used the Kaplan-Meier method and Cox regression models. **Results:** This sub-study included the 160 of 162 randomized pts who received study treatment. Median follow-up was 34 months with 96 OS events. Baseline PSMA-PET SUVmean Q4 was 9.8 and median PSMA-TTV was 234 mL. Median OS for PSMA-TTV above or below the median for enza-alone were 20 vs 39 months respectively (p$<$0.001). The corresponding median OS for enza + LuPSMA were 28 vs 35 months (p=0.18). The test for interaction between PSMA-TTV and treatment arm for OS was p=0.008. Median OS for SUVmean Q4 vs Q1-3 for enza alone were 29 vs 25 months (p=0.59). For enza + LuPSMA median OS for SUVmean Q4 vs Q1-3 were 32 vs 34 months (p=0.56). The test for interaction between SUVmean (Q4 vs Q1-3) and treatment for OS was p=0.88. Results for PSA-PFS are also tabulated below. **Conclusions:** Baseline PSMA-TTV was prognostic of shorter OS with enza-alone, but not with the addition of LuPSMA-617. In contrast to LuPSMA-617 monotherapy, PSMA SUVmean was neither predictive nor prognostic of improved OS, nor of PSA-PFS when LuPSMA-617 was given together with enza as first line treatment for mCRPC. Clinical trial information: NCT04419402. Research Sponsor: Prostate Cancer Research Alliance (PCRA): An Australian Government and Movember joint alliance and Australian and New Zealand Urogenital and Prostate Cancer Trials Group (ANZUP); GenesisCare, Roy Morgan Research; St Vincent's Clinic Foundation; Cancer Australia; Astellas and Endocyte - a Novartis Company Pharmaceutical/Biotech Company.

Treatment Arm	SUVmean Q4	SUVmean Q1-3	P	Interaction	PSMATTV >234mls	PSMATTV <234mls	p	Interaction
Enza-alone OS	29mo	25mo	0.59		20mo	39mo	0.001	
Enza+LuPSMA OS	32mo	34mo	0.56	**0.88**	28mo	35mo	0.18	**0.008**
Enza-alone PSA-PFS	7.8mo	5mo	0.55		3mo	11mo	0.001	
				0.17				**0.017**
Enza+LuPSMA PSA-PFS	15mo	13mo	0.22		11mo	15mo	0.11	

LBA5012 **Rapid Oral Abstract Session**

An open label randomized non-inferiority trial comparing adjuvant platinum plus paclitaxel to platinum plus 5-FU after curative resection in high-risk penile carcinoma. First Author: Aditya Dhanawat, Tata Memorial Centre, Mumbai, India

The full, final text of this abstract will be available at meetings.asco.org on the day of presentation and in the online supplement to the June 10, 2025, issue of the *Journal of Clinical Oncology*.

5013 **Rapid Oral Abstract Session**

Docetaxel with androgen deprivation therapy (ADT) and radiotherapy (RT) for high-risk localized prostate cancer (HRLPC): An ICECaP individual patient-data (IPD) meta-analysis of randomized controlled trials (RCTs). First Author: Praful Ravi, Dana-Farber Cancer Institute, Boston, MA

Background: There is no established role for the use of docetaxel with ADT and RT for HRLPC, with mixed results seen in prior RCTs. Prior work from ICECaP (Ravi et al, Eur Urol 2024) has shown that patients (pts) with very high-risk disease (i.e. 2 or 3 risk factors [RFs]: Gleason ≥8, PSA >20, ≥cT3 and/or cN1) have the poorest outcomes with RT+ADT for HRLPC, with 5-year metastasis-free survival (MFS) of ≤80%. We aimed to perform an IPD meta-analysis of the role of docetaxel with ADT+RT for HRLPC and specifically evaluate whether patients with very high-risk disease benefit from the addition of docetaxel. **Methods:** IPD from RCTs involving pts with HRLPC treated with RT+ADT +/- docetaxel collated by ICECaP were analyzed. "High-risk" disease was defined as presence of 1 RF and "very high-risk" disease as 2-3 RFs and/or cN1 disease. The primary outcomes of interest were MFS and overall survival (OS). Hazard ratios (HR) for MFS and OS were estimated using Cox regression, stratified by year of randomization and adjusted for age at randomization and ECOG performance status. 5-year MFS and OS rates were estimated using the Kaplan-Meier method. Subgroup analyses were performed according to the severity of disease (high- and very high-risk), and p-values for interaction were tested using the likelihood ratio test. **Results:** 1690 pts treated on 4 RCTs (GETUG-12, DFCI 05-043, STAMPEDE, RTOG-0521) between 2002-2015 were eligible. Median age was 65, median PSA was 23 (IQR 10-48); 154 (9%) pts had cN1 disease and 1444 (85%) received long-term ADT with RT. Median follow-up was 10 years (range: <1-15). Overall, the addition of docetaxel to RT+ADT was not associated with a significant benefit in MFS (HR=0.89 [0.76-1.05], p=0.160) or OS (HR=0.88 [0.74-1.05], p=0.167). Though there was some evidence for favoring docetaxel in pts with very high-risk disease (n=1054; MFS HR=0.86 [0.71-1.05]; OS HR=0.85 [0.68-1.07]) compared to high-risk disease (n=636; MFS HR=0.97 [0.74-1.27]; OS HR=0.95 [0.71-1.28]), there was no evidence of a significant difference in treatment effect by risk group (p-interaction >0.1). 5- and 10-yr MFS and OS in pts with high- and very high-risk disease, stratified by receipt of docetaxel, are shown in the Table. **Conclusions:** Some HRLPC pts with very high-risk disease may benefit from the addition of docetaxel to RT+ADT. Biomarker evaluation within this group may identify those who are candidates for treatment intensification with docetaxel with RT+ADT (+/- androgen receptor pathway inhibitors) in HRLPC. Research Sponsor: PCF.

	High risk		Very high-risk	
% (95% CI)	RT+ADT	RT+ADT+docetaxel	RT+ADT	RT+ADT+docetaxel
5yr MFS	87 (82-90)	90 (86-93)	74 (71-78)	80 (76-83)
5yr OS	90 (86-93)	93 (90-96)	84 (80-86)	89 (86-92)
10yr MFS	67 (61-72)	71 (65-76)	51 (46-55)	55 (49-60)
10yr OS	74 (69-79)	77 (72-82)	62 (57-67)	67 (62-72)

5014 **Rapid Oral Abstract Session**

Intensified hormonal blockade with SBRT in PSMA-PET detected oligometastatic prostate adenocarcinoma: Results from the phase II Metacure trial cohorts B2 and the B2 expansion. First Author: Eric Huttenlocher Bent, Memorial Sloan-Kettering Cancer Center, New York, NY

Background: Metastasis directed therapy (MDT) with stereotactic body radiotherapy (SBRT) is a standard of care in patients with oligometastatic hormone-sensitive prostate cancer (HSPC) and can delay the use of ADT. Combining SBRT with a defined period of systemic therapy may lead to durable control of oligometastatic disease and is often used in this setting, however the optimal intensity and duration of hormonal blockade with SBRT remains unclear. **Methods:** Metacure is a multi-center, multi-arm randomized phase 2 trial that tests novel systemic therapies in the context of a multimodality approach, including SBRT to oligometastatic sites. The B2 and B2 expansion cohorts of Metacure tested SBRT +/- salvage RT to prostate bed/nodes with time-limited ADT+ARPI hormonal blockade in patients (pts) with PSMA-PET detected metachronous oligometastatic HSPC. Eligible pts had biochemical recurrence or persistence (PSA >0.2) after prostatectomy with metastases treatable within max 3 RT plans. Cohort B2 randomized pts to metastasis-directed SBRT with either 10 months of ADT + apalutamide + abiraterone acetate plus prednisone (ADT+APA+AAP) or ADT + apalutamide (ADT+APA). In the B2 expansion cohort pts received 6 months of ADT+APA with SBRT. The primary endpoint was proportion of pts with undetectable PSA (PSA<0.1) at 12 months from treatment start in pts with recovered testosterone (T). Secondary objectives included PSA<0.1 at 24 months, time to PSA progression (PSA 0.2), time to T recovery, rPFS, and PFS (PSA, radiographic, or clinical progression or death). **Results:** 36 pts were treated in the combined B2 (10 pts) and B2 expansion (26 pts) cohorts. Median follow-up was 35 months for cohort B2 and 19 months for the B2 expansion. T recovery (>150ng/dl) at 12 months from treatment start occurred in 3/5 (60%) ADT+APA+AAP and 2/5 (40%) ADT+APA pts on cohort B2 and 14/26 pts (54%) on the B2 expansion (ADT+APA). Of those, 2/2 (100%) B2 ADT+APA+AAP pts, 3/3 (100%) B2 ADT+APA and 11/14 (79%) B2 expansion pts had PSA <0.1. This met the pre-specified threshold for activity for the B2 expansion of 4 pts. Median time to PSA progression and PFS was 26 months for the B2 ADT+APA+AAP arm and not reached for the B2 ADT+APA arm or B2 expansion cohort. Median rPFS was not reached in any group. At 12 months, all patients on B2 and B2 expansion were progression free. At 18 months, PFS for B2 was 100% (ADT+APA) and 60% (ADT+APA+AAP) and was 85% for the B2 expansion. At 24 months, PFS was 60% for ADT+APA and 60% for ADT+APA+AAP pts on cohort B2. Median T recovery was 3.0 and 5.5 months for the B2 and B2 expansion cohorts. Grade 3 TRAEs were seen in 0/10 B2 and 1/26 B2 expansion subjects (lymphopenia). **Conclusions:** SBRT with short course intensified hormonal blockade was well tolerated and led to durable disease control in pts with PSMA PET-detected metachronous oligometastatic prostate cancer. Clinical trial information: NCT03436654. Research Sponsor: Janssen.

5015 **Rapid Oral Abstract Session**

DB-1311/BNT324 (a novel B7H3 ADC) in patients with heavily pretreated castrate-resistant prostate cancer (CRPC). First Author: Andrew Ohyama Parsonson, Macquarie University, Sydney, Australia

Background: There is a high unmet need for effective therapy for patients (pts) with heavily pretreated CRPC. B7H3 ADCs have reported early clinical activity in CRPC, including DB-1311/BNT324, an investigational B7H3 ADC that received FDA Fast-Track Designation for previously treated CRPC. **Methods:** This phase 1/2 study (NCT05914116) enrolled pts with advanced/metastatic solid tumors, including previously treated CRPC (post docetaxel/hormonal therapy). Dose optimization cohorts randomized pts to receive 6 mg/kg or 9 mg/kg Q3W DB-1311/BNT324 until progression or unacceptable toxicity. The primary endpoints were objective response rate (ORR, based on investigator assessment per RECIST 1.1 and PCWG3 criteria) and safety. Secondary endpoints included disease control rate (DCR), duration of response (DOR) and radiographic progression-free survival (rPFS). **Results:** As of 3 Jan 2025, of 393 pts treated with DB-1311/BNT324, there were 65 pts with CRPC. Median age was 71 years (range 45–84), 49%/34%/14% were White/Asian/Black, 32%/37%/31% from Australia/USA/East Asia, 71% had ECOG PS 1, 29% had bone only disease. Median number of prior lines was 3 (range 1–14) and 28% had ≥5 prior lines. Most pts received prior docetaxel (93.8%) and hormonal therapy (96.9%); other therapies included PARP inhibitors (PARPi, 15.4%), Lutetium-177 (Lu-177, 15.4%), immunotherapy (IO, 13.8%). Among 43 response-evaluable pts (measurable disease at baseline per RECIST 1.1), best overall response was PR in 12 pts and SD in 29 pts for an unconfirmed ORR of 27.9% (95% CI 15.3, 43.7; 12/43, 8 confirmed) and DCR of 95.3% (95% CI 84.2, 99.4). Median DOR was not reached (95% CI 4.2, ne). After a median follow-up of 5.7 months (m) (range 0.6–16.0), median rPFS (N=57) was 8.3 m (95% CI 6.7, ne) with a 6-m rate of 86.6% (95% CI 67.8, 94.8). Outcomes were similar by dose (6 mg/kg [ORR 26.3%, DCR 100%, 6-m rPFS rate 88.7%], 9 mg/kg [ORR 29.2%, DCR 91.7%, 6-m rPFS rate 80.0%]), by line of treatment (≤3L [ORR 33.3%, DCR 77.8%], ≥4L [ORR 26.7%, DCR 100%]), and by type of prior treatment (ORR/DCR: Lu-177 [25.0%/100%], IO [33.3%/100%], albeit lower for PARPi [16.7%/100%]). The CRPC safety profile (N=65) is supported by the safety in the larger overall population (N=393). Treatment-related adverse events (TRAEs) occurred in 56 (86.2%) and 343 (87.3%) pts and were Grade ≥3 (G≥3) in 26 (40.0%) and 156 (39.7%) pts, respectively. TRAEs led to dose reduction in 8 (12.3%) and 39 (9.9%) pts, to discontinuation in 4 (6.2%) and 23 (5.9%) pts, and to death in 0 and 2 (0.5%) pts, respectively. Nausea and hematological events, primarily G1–2, were the most common TRAEs. Hematological TRAEs occurred more frequently with 9 mg/kg vs 6 mg/kg, both in the CRPC and overall populations. **Conclusions:** DB-1311/BNT324 showed encouraging efficacy and a manageable safety profile in heavily pretreated CRPC and is currently being evaluated in post Lu-177 CRPC and in taxane-naïve CRPC. Clinical trial information: NCT05914116. Research Sponsor: Sponsored by Duality Biologics and conducted in collaboration with BioNTech SE.

5016 Rapid Oral Abstract Session

^{177}Lu-PSMA-617 with ipilimumab (ipi) and nivolumab (nivo) in metastatic castration-resistant prostate cancer (mCRPC): An investigator-initiated phase 2 trial (EVOLUTION; ANZUP2001). First Author: Shahneen Sandhu, Peter MacCallum Cancer Center and the University of Melbourne, Melbourne, Australia

Background: LuPSMA improves progression-free survival (PFS) and overall survival (OS) in patients with mCRPC. Immune checkpoint inhibitors (ICI) have limited single-agent activity in mCRPC. Radiation may enhance ICI activity by inducing immunogenic tumor cell death and altering the tumor microenvironment. We evaluated the activity and safety of ipi plus nivo plus LuPSMA in mCRPC. **Methods:** Eligibility: prior androgen receptor pathway inhibitor therapy, PSMA-positive disease, normal organ function, no contraindications to ICIs, <= 1 line of chemotherapy. Randomized (1:2) to LuPSMA alone (7.4 GBq every 6 weeks, up to 6 doses) or LuPSMA plus induction ipi (3 mg/kg every 6 weeks for 4 doses) and nivo (1 mg/kg every 3 weeks for 8 doses) followed by maintenance nivo (480 mg every 4 weeks for 18 doses) (LuPSMA+ICI). Primary endpoint: PSA PFS at 12 months (PSA-PFS 12m). Secondary endpoints: PSA response rate (PSA-RR), adverse events (AEs), radiographic-PFS (rPFS), PSA-PFS, and OS. **Results:** 93 of 100 planned participants (pts) were randomized from July 2022 to July 2023. Recruitment was stopped early due to 4 cases of treatment-related myocarditis in pts assigned LuPSMA+ICI. Of 93 randomized, 30 pts received LuPSMA, 57 pts received LuPSMA+ICI. 6 pts who did not receive assigned LuPSMA+ICI (1 ineligible; 5 ceased ICI at the direction of the central study team) were excluded from the efficacy intention to treat analysis. However, 5 were included in the safety analysis. Median age was 70 years [range: 45-83]; 80% had prior docetaxel. The median follow-up was 18 months (IQR: 16-22). PSA-PFS 12m was higher in pts assigned LuPSMA+ICI than LuPSMA-alone (33% vs. 17%, see table). Grade 3-4 AEs were reported in more pts assigned LuPSMA+ICI than LuPSMA-alone (75% vs 29%). Among those assigned LuPSMA+ICI, Grade 3-4 AEs in ≤5% were: colitis (19%), anemia (11%), hypophysitis (14%), lung infection (9%), fatigue (7%), thrombocytopenia (7%), hepatitis (7%), pneumonitis (7%), thromboembolic event (5%) and rash (5%). Myocarditis was reported in 4 pts (7%) assigned LuPSMA+ICI. There were 2 deaths during LuPSMA+ICI treatment: myocarditis (treatment related) and sepsis (not treatment related). **Conclusions:** LuPSMA+ICI was associated with improved PSA-PFS 12m in mCRPC. The spectrum of AEs were keeping with established toxicities however significantly higher with LuPSMA+ICI, and frequency of ICI-related myocarditis lead to early trial cessation. Clinical trial information: NCT05150236. Research Sponsor: Bristol Myers Squibb; Novartis; Cancer Australia; Prostate Cancer Foundation of Australia (PCFA); Australasian Radiopharmaceutical Trials Network (ARTnet); MIM Software Inc.; ANSTO.

	LuPSMA+ICI (N=57)	LuPSMA alone (N=30)
Median (IQR) LuPSMA cycles	5 (4-6)	6 (4-6)
Median (IQR) cycles of ipi	2 (1-3)	
Median (IQR) cycles of nivo	3 (2-5)	
PSA-PFS 12m, %	33	17
PSA-PFS, median, months	7.6 (95% CI: 6.5, 11)	7.1 (95% CI: 4.9, 10)
HR (95% CI)	0.70 (0.43, 1.13)	
PSA 50% (95% CI)	75% (62, 85)	67% (47, 82)
PSA 90% (95% CI)	46% (33, 59)	43% (26, 62)
Pts with grade 3-4 AEs	43/57* (75%)	10/35* (29%)

*Safety population.

5017 Rapid Oral Abstract Session

Phase 1 study results of JNJ-78278343 (pasritamig) in metastatic castration-resistant prostate cancer (mCRPC). First Author: Capucine Baldini, Drug Development Department (DITEP), Institut Gustave Roussy, Villejuif, France

Background: Human kallikrein 2 (encoded by the *KLK2* gene and hereafter referred to as KLK2) is a novel target expressed on PC cells with limited normal tissue expression. Pasritamig is a first-in-class T-cell-redirecting bispecific antibody that simultaneously binds KLK2 on PC cells and CD3 receptor complexes on T cells. We report dose escalation and expansion results from a first-in-human study (NCT04898634) evaluating pasritamig in pts with mCRPC. **Methods:** Pasritamig target doses (TDs) were escalated from 0.5-2000 mg SC and 150-900 mg IV QW-Q6W, with various step-up (SU) dosing schedules. Pre-medication with dexamethasone (16 mg) was required in SU and 1st TD. The primary objective was to determine the safety and RP2D. Secondary objectives included preliminary assessment of antitumor activity. **Results:** As of October 7, 2024, 174 pts (median [range] age 69 [36-89] years) had received ≥1 pasritamig dose (Table). Pts had a median of 4 prior therapies (range 1-13; 99.4% ARPI, 78.2% taxane chemotherapy, 17.2% lutetium Lu 177 vipivotide tetraxetan). There were no pasritamig-related deaths. One pt experienced a DLT of transient Gr 3 ALT/AST elevation after 50 mg SU2 SC administration. While most pts reported ≥1 TRAE (82.2% overall; 68.1% IV; 92.2% SC), these were mostly low grade, with only 9.2% of pts (6.9% IV; 10.8% SC) experiencing a Gr ≥3 TRAE. In the RP2D safety population (n=45; 3.5 mg [Day 1], 18 mg [Day 8], 300 mg Q3W or Q6W IV), the most common TRAEs were infusion-related reactions (22.2%; Gr 1/2), fatigue (15.6%; Gr 1/2), and CRS (8.9%; all Gr 1, no tocilizumab was administered), no TRAEs led to treatment discontinuation, no ICANS was observed, and 2 serious TRAEs (Gr 1 CRS) were reported. In the RP2D efficacy population (n=33; 3.5 mg [Day 1], 18 mg [Day 8], 300 mg Q6W IV), PSA50 was 42.4% (14/33) and median rPFS was 6.77 (95% CI 2.89, NE) months with 39.4% of pts ongoing (13/33). ORR in the 85 pts with measurable disease was 16.1% (n=5/31) in pts with lymph node +/- bone and 3.7% (n=2/54) in pts with visceral disease, with a median DOR of 11.27 (95% CI 3.58, NE) months. **Conclusions:** Pasritamig was very well tolerated (<10% of pts experienced CRS [all Gr1] at the RP2D) with promising antitumor activity, demonstrating proof of concept for KLK2 as a target amenable to T-cell redirection. These results address an unmet need for a targeted T-cell based therapy that is safe to administer in an outpatient setting with clinically meaningful benefit in mCRPC. Phase 3 trials are planned. Clinical trial information: NCT04898634. Research Sponsor: Johnson & Johnson.

	Total N=174	SC n=102	IV n=72	RP2D n=45[a]
TRAEs leading to treatment discontinuation, n (%)	1 (0.6)	1 (1.0)	0	0
Gr ≥3 TRAEs, n (%)	16 (9.2)	11 (10.8)	5 (6.9)	2 (4.4)
CRS, n (%)	43 (24.7)	31 (30.4)	12 (16.7)	4 (8.9)
Gr 1	37 (21.3)	28 (27.5)	9 (12.5)	4 (8.9)
Gr 2	6 (3.4)	3 (2.9)	3 (4.2)	0
Radiographic PFS, months, median (95% CI)	4.40 (3.35, 6.47)	4.07 (2.79, 4.93)	5.88 (3.15, NE)	6.77 (2.89, NE)[b]

[a]RP2D safety pop.=TD 300 mg Q3W/Q6W.
[b]RP2D efficacy pop.=TD 300 mg Q6W (n=33).

5018 Rapid Oral Abstract Session

CA209-8TY trial, a randomized phase 2 trial of nivolumab and ipilimumab with or without stereotactic body radiation therapy in metastatic castration-resistant prostate cancer. First Author: Rikke Løvendahl Eefsen, Department of Oncology, Experimental Cancer Therapy Unit, Herlev, Copenhagen, Denmark

Background: Metastatic castration-resistant prostate cancer (mCRPC) is among the leading causes of cancer related mortality in men worldwide. Treatment options include chemotherapy and androgen receptor pathway inhibitors (ARPIs). Prostate cancer is considered an immunosuppressive tumor. As of today, immune checkpoint inhibitors (ICIs) have not demonstrated effect in patients with mCRPC. The use of stereotactic body radiation therapy (SBRT) may increase the expression of tumor associated antigens and enhance potential immune responses following systemic therapy. **Methods:** Patients with mCRPC, who had previously progressed on at least one taxane regimen and one ARPI, were screened for the trial. Eligible Patients were randomized to receive either ipilimumab 1mg/kg and nivolumab 3mg/kg every 4 weeks for the first 12 weeks followed by nivolumab monotherapy 480mg every 4 weeks for up to 52 weeks (arm B), or the same ICI with SBRT of a metastasis, 24Gy in 3 fractions (arm A). The co-primary endpoints were prostate specific antigen (PSA) response rate, defined as a ≥50% decline in PSA compared to baseline, confirmed after ≥4 weeks, and objective response rate (ORR) according to modified Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 and Prostate Cancer Working Group (PCWG) 3. Secondary endpoints included overall survival (OS), radiologic progression free survival (rPFS), and toxicity. **Results:** Between November 2019 and January 2024, 91 patients were randomized in the CheckPRO trial (NCT 05655715). A total of 81 patients received at least one treatment cycle and were eligible for evaluation. The confirmed PSA response rate was 21.6% in arm A and 20.5% in arm B. ORR was 16.7% (95% CI [4.7-37.4] %) and 22.2% (95% CI 10.1-39.2) in arm A and B, respectively. Median OS was 10.2 months (95% CI [7.1-14.1] %) in arm A and 9.2 months (95% CI [7.1-14.1] %) in arm B. rPFS was 2.1 months and 1.9 months in arm A and B, respectively. Serious adverse events related to ICIs occurred in 29.7% of patients in arm A and 31.8% in arm B. **Conclusions:** Objective responses were demonstrated in patients with mCRPC treated with combination ICI, however PFS was short and treatment-related toxicity significant. While the addition of SBRT was safe, it did not improve treatment outcomes in this study. Further analyses are ongoing to identify patients with mCRPC, who are most likely to respond to ICI. Clinical trial information: NCT05655715. Research Sponsor: Bristol Myers Squibb.

5019 Rapid Oral Abstract Session

Exploratory analyses of homologous recombination repair alterations (HRRm) by gene subgroup and potential associations with efficacy in the HRR-deficient population from TALAPRO-2. First Author: Stefanie Zschaebitz, National Center for Tumor Diseases (NCT), Heidelberg, Germany

Background: In TALAPRO-2, talazoparib (TALA) + enzalutamide (ENZA) significantly improved radiographic progression-free survival (rPFS) and overall survival (OS) vs ENZA + placebo (PBO) in patients (pts) with mCRPC harboring HRRm assessed prospectively. Here we report exploratory biomarker analyses which assessed HRR by gene subgroup and potential associations with efficacy in pts enrolled in the HRR-deficient cohort from TALAPRO-2. **Methods:** Pts were randomized 1:1 to TALA 0.5 mg (N=200) or PBO (N=199) + ENZA 160 mg QD. HRRm testing used a 12-gene HRR panel (HRR12; clinical trial assays based on FoundationOne CDx and FoundationOne Liquid CDx). HRRm status categorization by gene incorporated all available tumor and prescreening/screening ctDNA records using an algorithm similar to that previously used by others (Fallah et al, JCO 2024 PMID: 38484203). For non-*BRCA* gene analyses, pts with co-occurring *BRCA1/2* alterations were excluded. For *BRCA1*, pts with co-occurring *BRCA2* alterations were excluded. The efficacy endpoints assessed were overall response rate (ORR), rPFS, and OS. Data cutoff Sept 3, 2024. **Results:** For all HRRm pts, TALA + ENZA was superior to ENZA + PBO across all efficacy endpoints: ORR, 69.4% vs 39.1% (odds ratio [OR], 0.28 [95% CI, 0.13–0.61]); rPFS, median 30.7 vs 12.3 months (mo) (hazard ratio [HR]=0.47 [0.36–0.62]); OS, median 45.1 vs 30.8 mo (HR=0.60 [0.46–0.78]). TALA + ENZA vs ENZA + PBO demonstrated benefit for *BRCA2m* across endpoints: ORR, 86.4% vs 31.0% (OR, 0.07 [95% CI, 0.01–0.35]); rPFS, median not reached (NR) vs 10.9 mo (HR=0.25 [0.15–0.42]); OS, median NR vs 28.5 mo (HR=0.47 [0.29–0.76]). Similar rPFS and OS benefit was seen for *BRCA1m* and *PALB2m* (allowing for small n in the groups); for ORR, evaluable n of 8 across arms for each gene was too low to meaningfully assess ORR differences. Benefit for TALA + ENZA was also evident for *CDK12m*: ORR, 63.6% vs 22.2% (OR, 0.16 [95% CI, 0.01–1.61]); rPFS, 19.3 vs 13.8 mo (HR=0.36 [0.19–0.70]); OS, 36.4 vs 22.8 mo (HR=0.41 [0.23–0.74]). *ATMm* also showed benefit for TALA + ENZA: ORR, 75.0% vs 33.3% (OR, 0.17 [95% CI, 0.02–1.32]); rPFS, 30.4 vs 18.3 mo (HR=0.66 [0.37–1.18]); OS, 45.1 vs 39.5 mo (HR=0.70 [0.38–1.29]). *CHEK2m* showed modest overall benefit for TALA + ENZA: ORR, 53.3% vs 42.9% (OR, 0.66 [95% CI, 0.07–5.59]); rPFS, 24.8 vs 18.3 mo (HR=0.65 [0.34–1.22]); OS, 34.2 vs 39.5 mo (HR=0.96 [0.51–1.81]). The remaining six HRR12 genes could not be meaningfully assessed for efficacy benefit by gene with TALA + ENZA vs ENZA + PBO due to low mutational prevalence. **Conclusions:** An efficacy benefit was evident for TALA + ENZA vs PBO + ENZA across multiple mutational subgroups assessed by gene, and was most pronounced for the *BRCA1-PALB2-BRCA2* axis and *CDK12*, with benefit also apparent for *ATM*. Analyses of additional efficacy endpoints are planned and will be presented. Clinical trial information: NCT03395197. Research Sponsor: Pfizer.

5020 Rapid Oral Abstract Session

Clonal hematopoiesis (CH) in participants with metastatic castration-resistant prostate cancer (mCRPC) receiving ^{177}Lu-PSMA-617 or cabazitaxel: An exploratory post-hoc analysis of a randomized phase II trial (TheraP; ANZUP 1603). First Author: Aslı Doğa Munzur, Vancouver Prostate Centre, Vancouver, BC, Canada

Background: The prostate-specific membrane antigen (PSMA)-targeted radioligand [^{177}Lu]Lu-PSMA-617 (^{177}Lu-PSMA-617) is an effective new standard-of-care for mCRPC. Since radiation may cause CH, an age-related preleukemic condition, we hypothesized that ^{177}Lu-PSMA-617 drives an increase in CH compared to other mCRPC treatments. Here, we explored CH in the TheraP trial randomizing participants (pts) with docetaxel-refractory mCRPC to cabazitaxel or ^{177}Lu-PSMA-617 (NCT03392428). **Methods:** We performed targeted DNA sequencing with a CH gene panel on blood samples from trial baseline (n = 176) and disease progression (n = 103; 56 post-^{177}Lu-PSMA-617, 47 post-cabazitaxel). Baseline CH mutations were detected in both cell-free DNA (cfDNA) and leukocyte DNA with variant allele frequency (VAF) ≥0.25%. Progression leukocyte DNA was unavailable at analysis, so progression CH mutations were identified via cfDNA only. We used Fisher's exact test to compare proportions, and the Mann-Whitney U test for changes in VAF. **Results:** Data was evaluable in 174/176 pts with baseline samples, and 103/103 with progression samples. Median time between baseline and progression blood draws was 28 and 27 weeks for ^{177}Lu-PSMA-617 and cabazitaxel arms, respectively. CH was detected in 77% (135/174) of pts at baseline (median age: 72). 71 (41%) pts had baseline CH mutations with VAF≥2%. The most commonly mutated genes at baseline were *DNMT3A* (n = 67 pts, 38%), *TET2* (n = 44, 25%), *PPM1D* (n = 26, 15%) and *ASXL1* (n = 19, 11%), with no difference in gene mutation frequency between arms. At progression, new mutations of presumed CH origin were detected in 83% and 46% of ^{177}Lu-PSMA-617 and cabazitaxel pts, respectively (47 vs 22 pts, p=0.0001). The most frequently mutated gene at ^{177}Lu-PSMA-617 progression was the DNA damage repair gene *PPM1D*; and new *PPM1D* CH mutations were 8 times more common after ^{177}Lu-PSMA-617 than cabazitaxel (p = 0.00032). Progression mutations in *ATM* or *CHEK2* were also 5 times more commonly observed after ^{177}Lu-PSMA-617 (p = 0.01). Among CH variants concordantly detected at baseline and progression on ^{177}Lu-PSMA-617, the median VAF change for mutations in DNA damage repair genes was higher than in canonical CH genes *DNMT3A*, *TET2* and *ASXL1* (1.53% *vs.* 0.15%, p = 0.01). **Conclusions:** ^{177}Lu-PSMA-617 was associated with a greater number of new CH mutations, especially in DNA damage repair genes, compared to cabazitaxel. Whilst the clinical relevance of this finding in a population of patients with heavily-treated mCRPC is unclear, CH emergence and expansion may have implications as radioligand therapy is used as an earlier line of therapy. Clinical trial information: NCT03392428. Research Sponsor: Prostate Cancer Foundation of Australia (PCFA); Australian Nuclear Science and Technology Organisation (ANSTO); Endocyte Inc. (A Novartis company); It's a Bloke Thing; Movember; The Australian and New Zealand Urogenital and Prostate Cancer Trials Group (ANZUP); Terry Fox New Frontiers Program Project Grant; Canadian Cancer Society Challenge Grant; The Australian and New Zealand Urogenital and Prostate Cancer Trials Group (ANZUP); The Distinguished Gentleman's Ride; CAN4CANCER; Prostate Cancer Foundation Challenge Award.

5021 Poster Session

Association of hormone therapy usage with adverse cardiovascular events in prostate cancer patients of the All of Us Research Program cohort. First Author: Yuanchu J Yang, Vanderbilt University School of Medicine, Nashville, TN

Background: Hormone therapies (HT) such as GnRH agonists, GnRH antagonists, and/or anti-androgens have led to improved overall survival for prostate cancer patients. However, the usage of these drugs may also increase cardiovascular (CV) risk. **Methods:** This study examined participants in the All of Us Research Program who were diagnosed with prostate cancer, had no prior history of adverse cardiovascular events (ACE), and were either treated or not treated with HT. We defined ACE as myocardial infarctions, strokes, or heart failure. Covariates used in our analysis were age, dyslipidemia, type 2 diabetes, hypertension, chronic kidney disease, peripheral vascular disease, statin usage, and smoking history. Time-to-ACE was defined using longitudinal electronic health record data. Participants who did not develop ACE were right censored at the date of their last medical visit. We evaluated whether HT use affected the risk of ACE using a Cox proportional hazards model with adjustment for established CV risk factors as covariates. **Results:** The final cohort included 5156 *All of Us* participants. Of these participants, 851 received HT treatment, 624 received only non-HT treatment (other medical, radiation, or surgical treatment for their prostate cancer), and 3681 received no known treatment. In our overall survival analysis, HT was associated with increased risk of ACE (HR, 1.22; 95% CI, 1.01-1.48; P = 0.03). In participants with pre-treatment dyslipidemia (Table), HT usage was associated with increased risk of ACE (HR, 1.52; 95% CI, 1.19-1.95; P <0.001). In participants without pre-treatment dyslipidemia, no association was found between HT usage and ACE (HR, 0.96; 95% CI, 0.71-1.30; P = 0.81). **Conclusions:** In a study cohort with no prior history of ACE, HT was associated with increased risk of ACE in participants with pre-treatment dyslipidemia. These results suggest that risk stratification by dyslipidemia status may help improve CV outcomes when selecting treatment regimens for prostate cancer patients. Research Sponsor: NHGRI.

Cox model for adverse cardiovascular time-to-event stratified by pre-treatment dyslipidemia.

	Pre-treatment Dyslipidemia (n=2377)		No Pre-treatment Dyslipidemia (n=2779)	
	Hazard Ratio (95% CI)	P-Value	Hazard Ratio (95% CI)	P-Value
Hormone Therapy	1.52 (1.19-1.95)	<0.001	0.96 (0.71-1.30)	0.81
Type 2 Diabetes	1.34 (1.07-1.70)	0.01	1.18 (0.79-1.76)	0.41
Hypertension	1.68 (1.31-2.15)	<0.001	1.43 (1.15-1.78)	0.001
Chronic Kidney Disease	1.96 (1.46-2.62)	<0.001	1.45 (0.85-2.47)	0.18
Peripheral Vascular Disease	1.47 (1.02-2.01)	0.04	1.10 (0.54-2.26)	0.79
Age	1.05 (1.03-1.06)	<0.001	1.04 (1.03-1.05)	<0.001
Statin Usage	0.72 (0.59-0.89)	0.002	0.90 (0.65-1.23)	0.50
Smoking History	1.18 (0.96-1.45)	0.11	1.20 (1.00-1.44)	0.05

5022 Poster Session

Comprehensive genomic profiling of Black and non-Hispanic White (NHW) men with prostate cancer (PCa). First Author: Sharon H. Choi, University of California, San Diego, San Diego, CA

Background: Racial disparities are evident in PCa, with Black men experiencing a higher incidence and worse survival compared to NHW patients (pts). The molecular alterations that distinguish these groups remain incompletely characterized. Herein, we investigate the clinical-genomic features that potentially contribute to the differences in outcomes between Black and NHW pts with PCa. **Methods:** Comprehensive next-generation sequencing of DNA (592-gene panel/whole exome) and RNA (whole transcriptome) was performed at Caris Life Sciences on PCa tissue samples (n = 5,412), collected from 2015 to 2023. Transcriptomic signatures – Androgen Receptor (AR), Neuroendocrine PCa (NEPC) scores – were calculated. Real-world overall survival (OS) data was obtained from insurance claims and was analyzed using Kaplan-Meier estimation. **Results:** Overall, 1,078 pts with PCa identified as Black, while 4,334 were NHW. Black pts were younger at biopsy collection than NHW pts (median age 66 vs 71 years, P < 0.001). The proportion of metastatic samples was higher in Black pts compared to NHW pts (43% vs 38%, P < 0.01). The prevalence of castrated PCa specimens was similar between Black and NHW pts (26.0% vs 25.4%, P = 0.72). Among non-castrated PCa tumors, tumors from NHW pts had more frequent alterations in *TP53*, *PTEN*, *PIK3CA*, and *CHEK2*, while tumors from Black pts had more *SPOP* and *CTNNB1* mutations. In the castrate setting, *TP53* and *PTEN* alterations were more frequent in tissue samples from NHW pts, while *CDK12* and *SPOP* mutations were more frequent in tumors from Black pts. *TMPRSS2* fusions were more prevalent in the NHW cohort across both castrated and non-castrated tumors. Tumors from Black pts had higher *FOLH1/PSMA* and *STEAP1* expression, elevated AR scores, but lower *CD276/B7H3* expression and NEPC scores. In the overall cohort, Black pts demonstrated a shorter median OS from diagnosis compared to NHW pts (86 vs 94 mos, P = 0.03). Black pts had a significantly longer time on treatment with enzalutamide in both the non-castrate (HR 0.82, P= 0.04) and castrate subgroups (HR 0.77, P= 0.03). Among pts with homologous recombination repair (HRR) deficiency-harboring tumors, PARP inhibitors provided a numerically longer survival benefit in Black pts than in NHW pts (21 vs 13 mos, P = 0.09). **Conclusions:** This multi-institutional study reveals distinct molecular profiles between Black and NHW pts with PCa. Despite having molecular features associated with better prognosis, Black men demonstrated worse survival outcomes, pointing to multifaceted determinants of disease outcomes. Notably, Black pts had improved outcomes on enzalutamide and showed potential benefit from PARP inhibitors in the presence of HRR mutations. These findings highlight genomic differences in diverse PCa populations and suggest therapeutic opportunities to address outcome disparities. Research Sponsor: None.

5023 Poster Session

Prognostic impact of brain metastases on survival rates in patients with metastatic testicular cancer: A comprehensive registry-based analysis. First Author: Rohan Garje, Miami Cancer Institute, Baptist Health South Florida, Miami, FL

Background: Testicular cancer (TC) is a rare malignancy that accounts for less than 1% of all cancers. Advances in the treatment paradigm have improved survival rates. However, oncologic outcomes may vary based on the extent and location of metastasis. Brain metastases (BM) are rare but may lead to worse survival outcomes. We aimed to conduct the largest retrospective study of patients with metastatic TC (mTC) to evaluate the prognostic impact of brain metastasis on survival rates in patients with IGCCC intermediate or poor risk mTC. **Methods:** We utilized the National Cancer Database (2010-2021) to identify patients with mTC(T1-4, any N0-2, M1). Patients with isolated lung metastases were excluded, as lung involvement alone was considered a surrogate marker for patients with good risk disease. We utilized Kaplan Meier analysis and cox proportional hazard modelling to study the impact of BM on survival outcomes in patients with mTC. **Results:** A total of 4,076 patients with mTC met our study criteria, of which 11.14% (454) had BM. Among these, 36.11% (1,472) had seminoma, 27.16% (1,107) had non-seminomatous histology, and 36.73% (1,497) had mixed germ cell tumors. The 2- and 5-year survival rates for patients without BM were 82.63% (95% CI: 81.26–83.91) and 78.26% (95% CI: 76.72–79.71), respectively. For patients with BM, the 2- and 5-year survival rates were 51.01% (95% CI: 45.99–55.79) and 42.78% (95% CI: 37.72–47.72), respectively. In our adjusted analysis, patients with BM had 2.35-fold increased risk of death (HR: 2.35, 95% CI: 1.96–2.82, p<0.001), compared to those without BM. Additionally, compared to seminoma, non-seminomatous histology had a 1.72-fold increased hazard of death (HR: 1.72, 95% CI: 1.42–2.09, p<0.001), while mixed germ cell tumors had a 1.34-fold increased hazard of death (HR: 1.34, 95% CI: 1.10–1.62, p = 0.003). **Conclusions:** In this large-scale retrospective cohort study, patients with BM had 135% increased risk of death in patients with mTC compared to patients without BM. Additionally, non-seminomatous and mixed germ cell histology were associated with significantly worse outcomes compared to seminoma. These findings highlight the importance of aggressive, tailored treatment strategies to address the higher mortality risk posed by BM in patients with intermediate and poor risk metastatic testicular cancer. Research Sponsor: None.

Cox proportional hazard model in patients with mTC.

Variable	HR (95% CI)	P-value
Histology: Seminoma	Ref	
Non seminoma	1.72 (1.42–2.09)	< 0.001
Mixed germ cell	1.34 (1.10–1.62)	0.003
Brain Metastasis: No	Ref	
YES	2.35 (1.96–2.82)	< 0.001
Bone Metastasis No	Ref	
YES	1.43 (1.20–1.71)	< 0.001
Liver Metastasis: No	Ref	
YES	1.65 (1.40–1.96)	< 0.001

5024 Poster Session

Use of GIP and GLP-1 receptor agonists in prostate cancer patients. First Author: Amy L. Shaver, Department of Medical Oncology, Thomas Jefferson University, Philadelphia, PA

Background: The use of glucagon-like peptide 1 receptor agonist (GLP-1 RA) and dual glucose-dependent insulinotropic polypeptide (GIP) and GLP-1 RA (GIP/GLP-1 RA) classes has increased over the past several years. The GLP1 receptor is expressed in metastatic prostate tissue, and GLP-1 RA and GIP/GLP-1 RA medications may have an impact on prostate cancer (PCa) outcomes. However, a use analysis among patients with prostate cancer in a large, diverse, current, real-world database has not been published. **Methods:** This national, retrospective study analyzed adult patients in the Epic Cosmos database with an active diagnosis of PCa who initiated a GLP-1 RA or GIP/GLP-1 RA medication from January 1, 2015, to December 31, 2024. The primary endpoint was percent use and change in use over time. Secondary endpoints included factors associated with use. Data were reviewed from Epic Cosmos, a Health Insurance Portability and Accountability Act-defined limited data set using deidentified electronic health record (EHR) data from more than 293 million patients served by 1,633 hospitals and more than 37,900 clinics. **Results:** This study includes 1,533,762 patients with a median age of 75. 30.3% (464,477) of the patients had a concurrent diagnosis of T2DM. The percentage of PCa patients utilizing a GLP-1 RA or GIP/GLP-1 RA increased from 0.43% in 2015 to 6.1% in 2024. Odds of receiving a GLP-1 RA or GIP/GLP-1 RA in PCa patients with a T2DM diagnosis were higher among those with a low social vulnerability index (SVI) percentile (<25) compared to patients with an SVI 75 or above (OR 1.20, 95% CI 1.16, 1.24) and among obese compared to non-obese (OR 1.88, 95% CI 1.85, 1.90). Odds were lower in PCa patients with T2DM 65 years and above compared to those under 65 (OR 0.41, 95% CI 0.40, 0.42). Odds of an opioid medication were higher in T2DM PCa patients receiving a GLP-1 RA or GIP/GLP-1 RA compared to those who weren't (OR 1.14, 95% CI 1.12, 1.16). While most PCa patients who received a GLP-1 RA or GIP/GLP-1 RA had T2DM, the percentage with neither T2DM nor obesity has increased (Table 1). **Conclusions:** This study showed that GLP-1 RA and GIP/GLP-1 RA use is on the rise. Use is associated with age and social vulnerability and may impact opioid receipt. Ongoing and future investigations examine the impact of GLP-1 RA and GIP/GLP-1 RA use on PCa progression. Research Sponsor: U.S. National Institutes of Health; 5P30CA056-036; U.S. National Institutes of Health; 1L30CA284329-01.

PCa patients receiving GLP-1 RA or GIP/GLP-1 RA by year.

Year	PCa	T2DM*	BMI ≥30*	No T2DM+BMI<30*
2016	2,085	1,905 (91.37)	1,497 (71.80)	31 (1.49)
2017	3,436	3,168 (92.20)	2,448 (71.25)	50 (1.46)
2018	5,594	5,183 (92.65)	3,946 (70.54)	77 (1.38)
2019	8,594	7,975 (92.80)	5,861 (68.20)	109 (1.27)
2020	11,881	11,086 (93.31)	7,494 (63.08)	129 (1.09)
2021	18,460	17,033 (92.27)	11,820 (64.03)	298 (1.61)
2022	28,850	25,986 (90.07)	18,232 (63.20)	581 (2.01)
2023	47,596	40,638 (85.38)	31,230 (65.61)	1,393 (2.93)
2024	69,808	56,649 (81.15)	46,241 (66.24)	3,033 (4.34)

*Data displayed as absolute number and as percentage of PCa population for each characteristic.

5025 Poster Session

Barbados' first next-generation sequencing of a prostate cancer sample. First Author: Joanne Nicholls, Columbia University, New York, NY

Background: According to the WHO (2022), Prostate cancer is the most frequent of all cancers in Barbados. In 2022, it accounted for over 45% of the reported cancer cases on the island, second being colorectal cancer at an alarming, contrasted prevalence rate of 13.5%. Today, cancer is fought at the cellular level across the globe. Reportedly nearly 40% of prostate cancer may be attributed to inherited genetic susceptibility, yet only hand full of clinically relevant genes have been associated with risk and/or adverse outcomes after diagnosis with this type of cancer (NCI, 2025). NGS is not widely available in Barbados. The primary aim of this research was to evaluate the feasibility of providing Next Generation Sequencing capability to the patients and practitioners on the island and to discover more about the genomics of the prostate cancer present on the island at molecular, ethnic, and geographic levels. **Methods:** A genomic sequencing protocol was conducted to determine the feasibility of delivering Next Generation Sequencing to patients receiving oncological care on the island. A Barbadian multi-disciplinary team inclusive of a pathology group, prostate cancer surgical center and healthcare system partnered with their South American medical equipment distributor and a global genomics and human health innovation company to conduct the pilot study. Forty prostate cancer archive tissue samples were identified from a local tissue bank. The samples were donated to future use research by previously treated surgical cases. Patients provided written consent to future use research. Of the forty samples, 25 were batched and shipped to a genomics laboratory for DNA extraction. DNA was then shipped to Illumina Laboratories in Baltimore where the NGS sequencing was performed. The OncoReveal Multi-Cancer with CNV & RNA Fusion Panel on the Illumina MiniSeq system was utilized. **Results:** OncoReveal Multi-Cancer with CNV & RNA Fusion Panel had the capability to detect 60 variants and CNVs detected from DNA. Of the 25 cases sequenced, new actionable data were found on 52% (13 of 25) with 33.3% (3 of 12) of tests detecting a ATM. The remaining data found following variants APC, CDKN2A, JAK3 V722I, PIK3CA, TP53, PTEN, SMO, CDKN2A, TP53, ERBB2 and PTEN. All of which were 7.6% (1of 13) in therapeutics actionability. **Conclusions:** Next Generation Sequencing in Barbadian men is not performed as part of routine diagnostic care due to a lack of access to this companion diagnostic resource. Providing NGS to local patients was proven to be feasible utilizing a central laboratory transport and testing model. OncoReveal Panel performed on a random sample revealed new actionable data were found on 52% (13 of 25) with 33.3% (3 of 12) of tests detecting a ATM. This suggests approximately 50% of this male population may find clinical utility in the use of NGS as a companion diagnostic and more research is needed in the region to better understand the high prevalence of the ATM variant. Research Sponsor: None.

5026 Poster Session

BEP in intermediate- and poor-risk advanced non-seminomatous germ cell tumor (NSGCT): Standing the test of time. First Author: Aditya Dhanawat, Advanced Centre for Treatment, Research and Education in Cancer (ACTREC), Tata Memorial Centre, Mumbai, India

Background: Bleomycin, etoposide, and cisplatin (BEP) has been the cornerstone of treatment for advanced NSGCT for decades. With the advent of newer regimens such as VIP (Etoposide, ifosfamide and cisplatin) and improved outcomes over the years, it is imperative to assess whether BEP has truly stood the test of time, especially for those in the intermediate and poor risk. **Methods:** This was a retrospective analysis of a prospectively collected dataset of NSGCT patients treated at a comprehensive cancer care centre in India. Adolescent and adult males with intermediate or poor-risk as per IGCCCG were included. The progression-free survival (PFS) and overall survival (OS) were calculated from date of diagnosis to date of progression and death respectively. Log-rank method was used to compare outcomes between BEP and VIP. **Results:** A total of 351 patients were analysed. The median age was 28 years (IQR: 23-34 years) (Table 1). Primary high-inguinal orchidectomy (HIO) was done in 208 (59.3%) and after completion of chemotherapy in 63 (17.9%) patients. There were 209 (59.5%) patients with poor-risk. Forty-seven (13.4%) received less than 4 cycles of chemotherapy. Retroperitoneal lymph node dissection (RPLND) was done in 195 (55.6%) patients. Overall, 45 (12.8%) patients had toxicities requiring hospitalization. Viable residual disease was seen in 33 (9.4%) patients. The median follow-up of the cohort was 58.9 + 3.6 months (95% CI: 51.9 – 65.9 months). Patients who received BEP had better 7-year PFS (68.4% vs 47.5%, p< 0.001) and 7-year OS (77.9% vs 55.2%, p<0.001) as compared to VIP albeit higher lung toxicities and deaths due to chemotherapy. The cohort which received VIP had higher percentage of smokers, mediastinal primary, visceral metastases and S3 tumor markers. **Conclusions:** BEP has stood the test of time and remains the standard of care. However, for patients who are smokers, or have aggressive disease, VIP is a good alternative. Research Sponsor: None.

Patient, disease and treatment characteristics.

Characteristics	BEP (n = 226)	VIP (n = 125)	p-value
Age group (years)			**0.217**
< 35	181 (80.1%)	93 (74.4%)	
> 35	45 (19.9%)	32 (25.6%)	
ECOG PS			**0.004**
0-1	216 (95.6%)	110 (88%)	
2-3	10 (4.4%)	15 (12%)	
Smokers	19 (8.4%)	20 (16%)	**0.034**
Primary site			**< 0.001**
Testis	206 (91.2%)	95 (76%)	
Retro-peritoneum	12 (5.3%)	3 (2.4%)	
Mediastinum	8 (3.5%)	27 (21.6%)	
Tumor markers (S)			**0.061**
Sx	6 (2.7%)	1 (0.8%)	
S0	3 (1.3%)	0	
S1	11 (4.9%)	8 (6.5%)	
S2	124 (54.9%)	53 (43.1%)	
S3	82 (36.3%)	61 (49.6%)	
Sites of metastases			
None	53 (23.4%)	5 (4%)	**< 0.001**
Non-regional lymph nodes	92 (40.7%)	62 (49.6%)	**0.108**
Pulmonary	115 (50.9%)	86 (68.8%)	**0.001**
Non-pulmonary visceral	43 (19.0%)	28 (22.4%)	**0.074**
Less than 4 cycles chemotherapy	31 (13.7%)	16 (12.8%)	**0.809**
Toxicities			
Grade 3-4 febrile neutropenia	54 (23.9%)	42 (33.6%)	**0.214**
Grade 3-4 hematological toxicities	93 (41.1%)	77 (61.6%)	**0.003**
Lung toxicities	29 (12.8%)	2 (1.6%)	**< 0.001**
Toxicities requiring hospitalization	29 (12.8%)	16 (12.8%)	**0.806**
Deaths	5 (2.2%)	1 (0.8%)	**0.328**
Viable residual disease after chemotherapy	17 (7.52%)	16 (12.8%)	**0.041**

5027 Poster Session

Epidemiology, treatment patterns, and survival outcomes of spermatocytic seminoma: A National Cancer Database analysis. First Author: Nikhil A Furtado, Creighton University School of Medicine, Omaha, NE

Background: Spermatocytic seminoma (SS) is a rare germ cell tumor, representing 2-5% of seminomas. Unlike classical seminomas, SS primarily affects older men (median age: 55 years) and exhibits low metastatic potential, though rare sarcomatoid transformations can lead to aggressive behavior. Treatment typically involves orchiectomy, with adjuvant therapies reserved for advanced cases. Despite its distinct clinical behavior, SS remains understudied, with limited data on its epidemiology, demographic patterns, and socioeconomic influences. Leveraging the National Cancer Database (NCDB) could provide critical insights into its epidemiology and management. **Methods:** A retrospective cohort study using the 2004–2020 NCDB identified patients with histologically confirmed SS (ICD-O-3 code 9063). Demographic, socioeconomic, and clinical variables were analyzed descriptively, with incidence trends evaluated via regression analysis. **Results:** A total of 541 patients with histologically confirmed SS were identified in the NCDB from 2004–2020. The incidence rate remained stable (R^2 = 0.012). All patients were male, with a mean age of 58.9 years (SD = 16.6). The cohort was predominantly White (91.5%) and non-Hispanic (89.6%), with 49.2% privately insured and 38.6% covered by Medicare. Most patients (55.1%) resided in metropolitan areas, and treatment was primarily delivered at comprehensive community cancer programs (43.5%) and academic/research programs (26.1%). Most patients (67.8%) were diagnosed at Stage I, with 82.4% having a Charlson-Deyo comorbidity score of 0. Surgery was performed in 98.9% of cases, with 95.2% achieving no residual tumor. Radiation therapy (18.3%) and chemotherapy (5.9%) were rarely used. The 30-day mortality rate was 0.6%, and the 90-day mortality rate was 1.0%. Survival rates were 98.0% (2-year), 96.0% (5-year), and 91.5% (10-year). **Conclusions:** This represents the first NCDB in-depth demographic analysis of spermatocytic seminoma (SS), addressing a significant gap in the literature on this rare malignancy. The study shows that SS predominantly affects males, with a strong predilection for non-Hispanic White individuals, consistent with prior case reports and small-scale studies. Additionally, this analysis provides novel insights into the socioeconomic profile of SS patients, revealing a tendency toward higher income brackets, residence in urban metropolitan areas, and treatment at community-based cancer programs rather than academic institutions. Future research should explore how demographic and socioeconomic factors influence diagnostic pathways, treatment decisions, and survival outcomes in this patient population. Research Sponsor: None.

5028 **Poster Session**

Racial and socioeconomic disparities in testicular cancer survival outcomes: A SEER database analysis. First Author: Charmi Bhanushali, Saint Vincent Hospital, Worcester, MA

Background: Testicular cancer, the most common malignancy in men aged 15 to 45 years, has a high cure rate exceeding 95% with early diagnosis and proper treatment. However, these favorable outcomes are not equitably distributed across all racial and socioeconomic groups. This study aims to analyze these disparities in testicular cancer survival outcomes from 2014 to 2021. **Methods:** The Surveillance, Epidemiology, and End Results (SEER) database was queried to identify patients diagnosed with testicular cancer (ICD-O-3 site codes C620-C629) from 2014 to 2021. Variables including stage, treatment, ethnicity, income level, and geographic location (urban/rural) were extracted. Patients with missing data were excluded from the analysis. Statistical methods included chi-square tests, Kaplan-Meier survival curves, and Cox proportional hazards models. Analyses were conducted using R (v4.4.1). **Results:** A total of 20,508 patients were included in the study. The population was predominantly White (87%), followed by Asian/Pacific Islanders (5%) and African Americans (3%). The majority of patients were aged 20–39 years (60%), with T1 disease (42.89%) and no nodal involvement (N0-53.93%). Seminomas accounted for 52.7% of cases, followed by mixed germ cell tumors (25.88%) and embryonal carcinoma (7.73%). Primary treatments included surgery (95%) and chemotherapy (38%). Advanced disease stages (T3–T4, M1, Stage II–III) and extensive nodal involvement were significantly associated with poor survival outcomes ($p<0.001$). Multivariate stratified analyses revealed higher overall mortality (OM) among African Americans (HR = 1.75, $p < 0.001$) and Asian/Pacific Islanders (HR = 1.25, p = 0.003) compared to White patients. The Hispanic population exhibited an 8.8% higher hazard compared to non-Hispanics (HR = 1.088, p = 0.02). Patients with annual incomes below $40,000 had significantly elevated OM (HR = 2.41, $p < 0.001$), whereas those with incomes of $120,000 or more demonstrated better survival outcomes (HR = 0.77, p = 0.019) compared to the reference group ($40,000- $120,000). Multivariate analyses of cancer-specific mortality (CSM) revealed similar findings, with African American patients (HR = 1.69, $p < 0.001$) and individuals in lower-income brackets (HR = 2.12, $p < 0.001$) experiencing worse outcomes. **Conclusions:** This study highlights racial and socioeconomic disparities in testicular cancer survival outcomes, with African American patients and individuals in lower-income brackets experiencing significantly worse overall and cancer-specific mortality. It underscores the need for future research to investigate structural inequities and insurance-related barriers contributing to these disparities and develop actionable strategies to achieve equity in cancer outcomes. Research Sponsor: None.

5029 **Poster Session**

Therapeutic decisions and outcome of patients with stage I testicular germ cell tumor: Single-centre experience. First Author: Isabella Cavaglià, Università degli studi di Torino, Torino, Italy, Italy

Background: Testis cancer (TC) is the most common solid neoplasm affecting men aged 15 to 40, with most of diagnosis occurring at stage I. Despite excellent prognosis, optimal post-surgical management remains controversial, comprising adjuvant therapy (AT) or active surveillance (AS). **Methods:** Our study aimed to compare relapse-free survival (RFS) in patients (pts) with stage I TC undergoing AT [chemotherapy (CT) or radiotherapy (RT)], versus AS, between 2000 and 2023. Evolution of AT choices for seminomas was evaluated over different time periods (before 2014, 2014-2018, after 2018). Clinical histories of stage I TC treated at our institution were retrospectively collected. Traditional histopathological prognostic factors for relapse were assessed, and seminomas were reclassified according to the new EAU risk group classification. Overall survival (OS) was a secondary endpoint. Pts with inadequate follow-up, insufficient information, or histologies other than seminoma and nonseminoma were excluded. **Results:** Out of 240 cases, 184 (129 seminomas, 54 non-seminomas, 1 burned-out tumor) were eligible. AT was administered to 58.1% of seminomas and 57.4% of nonseminomas. In seminomas, AT was represented by CT in 40.3% and RT in 17.8% of cases. RT administration significantly decreased over time, representing 66.7% of AT before 2014, 9.1% between 2014 and 2018, and 0% after 2018. With a median follow-up of 56.9 months, 5-yr RFS rate was 94.6% and 84.7% for pts undergoing AT and AS, respectively (p=0.005). Particularly, 5-yr RFS rate was 92.5% vs 86.7% in seminomas (p=0.07), and 100% vs 79.9% in nonseminomas (p=0.015). Proportion of seminomas undergoing AT was 20.7% among those with $T<4$ cm and no rete testis invasion, 56.4% among those with 1 risk factor, and 82.2% among pts with 2 risk factors. AT was received by 3.2% and 96.8% of nonseminomas without and with lymphovascular invasion, respectively. In the new EAU classification, 31.4%, 48.8% and 19.8% of seminomas were classified into the very low, low, and high risk categories (8 cases not evaluable). Compared to the traditional classification, a lower proportion of pts resulted in the poorest risk category (19.8% vs 34.9%). AT receipt significantly increased with risk: very low 27.0%, low 67.8%, high 83.3% ($p<0.001$). 5-yr OS rate was 98.1% (99.1% in seminoma and 95.1% in nonseminoma). **Conclusions:** AT was associated with higher RFS rates across both histological types. AS and AT are both associated to excellent survival. A temporal trend in reduction of RT was observed. Further evaluations are needed to individualize treatment decisions. Histopathological risk factors and the new EAU risk classification provide valuable prognostic information, aiding in treatment stratification. Additionally, the EAU risk group classification emerges as a potential tool to better stratify seminoma pts and support the implementation of AS in lower risk categories. Research Sponsor: None.

5030 **Poster Session**

Risk factors and causes of early death among patients with germ cell testis tumors (GCTs): An international collaborative study supported by the Global Society of Rare Genitourinary Tumors. First Author: Michal Mego, Department of Oncology, Faculty of Medicine, Comenius University and National Cancer Institute, Bratislava, Slovakia

Background: GCTs are the most common solid tumor in young men aged 20 to 40 years and are curable in most cases. However, a small proportion of patients with very advanced or aggressive disease, die early after starting chemotherapy. These patients are often not included in clinical trials and therefore accurate data on their risk factors and causes of death are critically lacking. **Methods:** This retrospective cohort study included patients with GCTs who died within 3 months from the completion of first-line systemic chemotherapy. Anonymized patients were included in an international database from tertiary cancer centers. Inclusion criteria were age $\geq$18 years, diagnosis between 2000-2024, death within 3 months from the last cycle of first-line chemotherapy, and treatment with systemic anticancer therapy and/or intention to treat. The database included data on patient and tumor characteristics, treatment and outcomes. **Results:** We identified 94 patients who experienced early death. Majority had IGCCCG poor prognosis and 16 (17%) had extragonadal GCTs. The proportion of these patients ranged from 0.4% to 2.1% of all patients treated with first line chemotherapy. Median time from starting of platinum based-therapy to death was 32 days (range: 2-301 days). Initial chemotherapy dose was reduced in 44.3% of patients. The most common causes of death were acute respiratory failure (ARF) due to acute respiratory distress syndrome (35.1%), disease progression (18.1%), febrile neutropenia (FN) with septic shock (13.8%), fatal extrapulmonary hemorrhage (13.8%), venous thromboembolism and myocardial infarction, each with an incidence of 2.1%. Approximately 11.7% of patients died from other causes and in 3.2% of cases the cause of death remains unknown. Factors associated with ARF development were older age (median age 43 years), lung involvement >50%, resting dyspnea and hemoptysis, but not choriocarcinoma histology, and less likely received bleomycin and/or initial dose reduction. Death within 30 days from starting chemotherapy (n=47, 50.0%) was associated with liver metastases, lung involvement >50%, beta-HCG > 50,000 mIU/mL, ECOG performance status 2-3, higher neutrophil/lymphocyte ratio and intensive or ventilated care (all $p<0.05$). Beyond ARF, fatal extrapulmonary hemorrhage (19.6%) and FN with septic shock (17.4%) were the most common cause of death within 30 days of starting therapy, while disease progression (29%) was more common in patients who died later. **Conclusions:** The proportion of patients with early death is low, but this group presents significant clinical challenges. Among advanced GCTs, high beta-HCG levels, liver metastases, massive lung involvement, poor ECOG and/or need of intensive care are associated with a higher risk of early death and need targeted intervention to improve their therapeutic outcomes. Research Sponsor: None.

5031 **Poster Session**

TROP-2 expression in germ cell tumors (GCT). First Author: Noah Richardson, Indiana University Melvin and Bren Simon Comprehensive Cancer Center, Indianapolis, IN

Background: Trophoblast cell surface antigen 2 (TROP-2) is a tumor associated antigen overexpressed in several malignancies including breast and urothelial cancer. The TROP-2 antibody-drug conjugate (ADC) Sacituzumab govitecan is approved for treatment of metastatic breast cancer. The expression of TROP-2 in GCT is unknown. We present immunohistochemistry results of TROP-2 expression in GCT. **Methods:** Patients who underwent resection for GCT at Indiana University were included. Sixty formalin-fixed paraffin-embedded (FFPE) GCT samples were available. FFPE slides were selected from differing GCT histology and surgical sites including primary tumor, retroperitoneal lymph node, and distant metastases. Immunohistochemical (IHC) staining for TROP-2 (clone 1, mouse monoclonal, Enzo Life Sciences) was conducted and scored by intensity on a 0-3 scale by an experienced pathologist. **Results:** Samples from 60 individual specimens were available for IHC analysis. TROP2 expression was detected in 29 (48%) of these samples. Intensity expression differed from pure seminoma, mixed non-seminoma (NSGCT), teratoma, yolk sac tumor, and choriocarcinoma samples. Both primary and metastatic samples had TROP-2 expression of varying degrees. **Conclusions:** TROP-2 expression varies across histology in GCT. Seminoma appears to have the lowest expression of TROP-2. Higher TROP-2 expression was noted in choriocarcinoma and yolk sac tumor samples indicating potential as a target in these histologic subtypes in future clinical trials. Research Sponsor: John Cleland Fellowship.

Detectable TROP-2 by histology.

Sample histology (N)	Total detectable TROP-2 expression (%)	3+	2+	1+
Seminoma (20)	3 (15)		2	1
NSGCT (19)	12 (63)	9 (6*)	2*	1*
Teratoma (9)**	6 (66)	3*	3*	
Yolk sac (9)	5 (56)	2	3	
Choriocarcinoma (3)	3 (100)	1	1	1

*In epithelial elements of teratoma.

**Three negative samples with only small fragments of teratoma and false negative may be present.

5032 **Poster Session**

Clinical utility of a tumor-naïve circulating tumor DNA (ctDNA) test to predict outcomes in patients with advanced testicular germ cell tumors. First Author: Vitor Fiorin de Vasconcellos, Instituto do Câncer do Estado de São Paulo, São Paulo, Brazil

Background: Serum tumor markers (STM) used in the management of Testicular Germ Cell Tumors (TGCT) lack sufficient specificity and are not altered in up to 60% of patients (pts). We evaluated the clinical utility of a tumor-naïve ctDNA test to predict outcomes in pts with advanced TGCT. We also analyzed the correlation between ctDNA detection and STM levels. **Methods:** Blood samples were collected from 31 pts before and after first-line treatment (chemotherapy, primary radiotherapy or retroperitoneal lymphadenectomy). ctDNA detection was performed using a ddPCR assay to identify copy number gains in chromosome 12p, present in 90% of TGCTs. Progression-free survival (PFS) and overall survival (OS) were estimated using the Kaplan-Meier curves and the log-rank test. The correlation between ctDNA status and STM alterations was analyzed using Pearson's correlation test. **Results:** The median age of participants was 31 years, 81% were non-seminoma, 48% stage III, 45% IGCCCG intermediate-poor risk, 39% Sx-S0 stage, 83% received first-line chemotherapy, and the median follow-up time was 53 months. The ddPCR assay showed 88% sensitivity and 100% specificity for ctDNA detection. ctDNA detection before first-line treatment significantly correlated with altered LDH levels (r=0.78, $p<0.001$) but did not correlate with altered AFP (r=0.33, p=0.16) or bHCG levels (r=-0.03, p=0.88). Detection of ctDNA before first-line treatment was significantly associated with a shorter 2-year PFS rate (ctDNA positive 64% vs. ctDNA negative 100%, p=0.022) and 2-year OS rate (ctDNA positive 64% vs. ctDNA negative 100%, p=0.014). None of the patients who tested negative for ctDNA detection experienced disease progression or died. Elevated STM levels before first-line therapy were not significantly associated with PFS (p=0.07) or OS (p=0.053). Detection of ctDNA after first-line therapy did not significantly correlate with PFS (p=0.27) and OS (p=0.29), and was not predictive of viable tumor or teratoma in the surgical specimen. **Conclusions:** This is the first study to use a tumor-naïve ctDNA test to assess outcomes in pts with TGCT. ctDNA detection before first-line therapy may serve as a valuable prognostic biomarker, complementing STM for pts with advanced TGCT. Further prospective studies are needed to validate our findings. Research Sponsor: Hospital Sírio-Libanês.

5033 **Poster Session**

Initiation of high dose chemotherapy at rising tumor markers compared with radiographic progression in patients with relapsed germ-cell tumors (GCT). First Author: Rebecca Hassoun, Indiana University Melvin and Bren Simon Comprehensive Cancer Center, Indianapolis, IN

Background: Patients with GCT who relapse after first-line therapy can be cured with salvage high-dose chemotherapy (HDCT). We evaluate the outcomes of patients who received HDCT based on tumor maker rise only compared to radiographic progression only or both. **Methods:** The Indiana University Testicular Cancer database was queried for pts with GCT who were treated with salvage HDCT between 2004-2024. 2-yr progression free survival (PFS) and overall survival (OS) were analyzed among subgroups of patients who had tumor markers rise only (group 1) at start of HDCT compared to those who had radiological progression only or both (group 2). The Kaplan-Meier method was used to analyze PFS and OS. Comparisons between groups were done using the log-rank test. **Results:** 316 pts with GCT treated with salvage HDCT between March 2004 and May 2024 and had detailed information regarding progression leading to HDCT were included. Median age was 32.05 (16-70). Histology was non-seminoma in 237 (75.0%) pts and seminoma in 79 (25.0%) pts. Primary site was testis in 273 (86.4%) pts, retroperitoneum in 20 (6.3%) and mediastinum in 23 (7.3%). 156 (49.4%) pts had IGCCCG good risk disease at diagnosis, 28 (8.9%) had intermediate risk disease, and 132 (41.8%) had poor risk disease. 101 (32.0%) patients were platinum refractory at start of HDCT. HDCT was 2nd line therapy in 264 (83.5%) pts, 3rd line in 49 (15.5%), 4th line in 2 (0.6%) and 5th line in 1 (0.3%). At initiation of HDCT, 98 (31.0%) pts had tumor marker (AFP and/or hCG) rise only, 69 (21.8%) had radiographic progression only, and 149 (47.2%) had both. Median follow-up from start of HDCT was 3.67 years (0.03-19.5). For the overall population, 2-yr PFS was 62.4 with 95% CI (56.7-67.5) and 2-yr OS was 71.9 with 95% CI (66.3-76.8). 60 (59.4%) of patients in group 1 had platinum refractory disease compared to 41 (40.6%) in group 2. 2-yr PFS for group 1 was 44.8% (34.6-54.4%) vs 70.3% (63.6-76%) for group 2 ($P<0.001$). 2-yr OS was 58.8% (47.5-68.6%) for group 1 vs 77.4% (70.9-82.7%) for group 2 (P=0.001). **Conclusions:** Patients with relapsed GCT with rising tumor markers only at time of initiation of salvage HDCT had inferior 2-yr PFS and OS likely due to higher rates of platinum refractory disease in this population. Research Sponsor: None.

5034 **Poster Session**

Treatment of poor-risk non seminomatous germ-cell tumors (NSGCT) adapted by tumor marker decline: A 7-year multicenter real-world experience. First Author: Sara Faouzi, Gustave Roussy, Villejuif, France

Background: Since 2014, adaptation of chemotherapy based on tumor marker decline after the cycle of BEP (Bleomycin, Etoposide, Cisplatin) is a standard for patients with IGCCCG poor-risk NSGCT based on data from the GETUG-13 phase 3 trial (Fizazi et al, Lancet Oncol 2014; J Clin Oncol 2024). The aim of this multicenter study was to evaluate the GETUG-13 algorithm when used in routine practice. **Methods:** We collected data from all poor-risk NSGCT patients treated consecutively in 13 expert centers from 2013 to 2019. After one cycle of BEP, tumor marker levels were assessed at day 18-21. Pts with a favorable decline continued with BEP for 3 additional cycles (Fav group), whereas those with an unfavorable decline received up to 4 cycles of dose-dense chemotherapy (Unfav group). Data was analysed descriptively, and the Kaplan-Meier method was used to estimate progression-free (PFS) and overall survival (OS). **Results:** Data from 146 patients were collected (46 with PS $\geq$ 2, 35 with mediastinal NSGCT): 111 (76%) had an Unfav decline and 35 (24%) had a Fav decline. More pts with hCG $>$ 50 000 UI/L and AFP $>$ 10 000 were in the Unfav group (44.9% vs 17.6%, p=0.0045, and 26.9% vs 8.8%, p=0.0282). Surgery of residual masses was performed in 85.7% and 74.3% in the Fav and Unfav groups, and the procedure was complete in 83.3% and 59%, respectively. With a median follow-up of 5.8 years (95% CI,63.2-77.2), 5-year PFS rates were 68.6% (95% CI, 50.5-81.2) and 61.1% (95% CI, 51.2-69.6) in the Fav and Unfav groups, respectively. Five-year OS rates were 73.8% (95% CI, 55.6-85.4) and 64.6% (95% CI, 54.6; 73.0), respectively. In the short term, neuropathy, anemia and thrombopenia were more frequent in the Unfav group. Treatment-related deaths were reported in 2 (5.7%) and 5 (4.5%) (including 2 post-surgery deaths) pts in the Fav and Unfav groups, respectively. Peripheral neuropathy evolved favorably, with 4 (5.9%), 2 (3.8%) and no pts in the Unfav group reporting grade 3 toxicity at 6 months, 1 year and at last follow-up, respectively. Long-term side effects were infrequent with only one pt with grade 3 cardiovascular toxicity in the Unfav group. Late grade 2 toxicities included cardiovascular toxicity (1.4%), hypoacousia (1.4%), peripheral neuropathy (4.2%), chronic renal failure (CRF) (9.9%) in the Unfav group, and grade 2 CRF (8.3%) in the Fav group. In both groups, almost 80% pts had returned to work. Among pts with progression or relapse, salvage high-dose chemotherapy with stem-cell transplant was used in 4/11 (36.4%) and 13/33 (43.3%) in the Fav and Unfav groups, respectively. **Conclusions:** The GETUG-13 algorithm can be safely used in routine practice by expert centers, with a high cure rate similar to that reported in the original phase 3 trial and rare long-term toxicity. This data confirms that this algorithm is standard for poor-risk NSGCT. Research Sponsor: None.

5035 **Poster Session**

Predicting teratoma histology in postchemotherapy residual lesions of non-seminoma testicular cancer (NSTC) patients using integrated CT radiomics and circulating MicroRNAs modelling. First Author: Guliz Ozgun, British Columbia Cancer Agency, Vancouver, BC, Canada

Background: Chemotherapy is the primary treatment for metastatic NSTC, but patients often have residual masses afterward. Accurate non-invasive models are needed to predict the histology of these masses, guiding treatment and reserving surgery for those with teratoma. This study aims to enhance predictive accuracy by integrating CT-driven radiomics features with miRNAs 371 and 375 (miR371-375) to distinguish between teratoma and non-teratoma histologies in post-chemotherapy residual masses. **Methods:** We retrospectively reviewed 52 patients with teratoma (n=56), fibrosis/necrosis (n=34), vGCT (n=11), and seminoma (n=10) lesions, divided into training (N=78) and test (N=33) cohorts with equal class distribution. Lesions included lymph nodes (n=68 retroperitoneum, n=11 mediastinum, n=4 pelvic, n=4 neck), lung (n=21), and brain (n=3) with a median size of 1.6 cm (Q1-Q3 interval=1.2-2.73 cm). Using 3D Slicer version 5.6.1, metastatic masses $>$1 cm (short axis) were segmented and radiomics features were extracted from venous phase CT images. Plasma miR371 and miR375 levels were measured by RT-PCR before resection. Four machine learning models evaluated the predictive value of radiomics alone (R-only) and combined with miR371/miR375 levels for teratoma histology, and the best performer, Cat Boosting (CB) method, is reported. **Results:** The analysis of datasets revealed a consistent pattern of superior performance in training sets compared to test sets across all metrics. The CB model R+371+375 dataset demonstrated the most robust overall performance, with the highest AUC values (0.96 [95% CI 0.88-1.0] for training, 0.83 [95% CI 0.68-0.98] for test) and a well-balanced sensitivity (0.71) and specificity (0.76) in the test set for predicting teratoma histology. R+375 followed closely with an AUC of 0.82 (95% CI 0.66-0.97). **Conclusions:** Combining miR 371 and 375 with CT-driven radiomics features improves the accuracy of classifying teratoma histology in metastatic NSTCs. This method can help characterize teratoma in residual metastatic disease, aiding treatment decisions and minimizing under or over-treatment risks. Further refinement, including the integration of clinical features, will be reported. Research Sponsor: None.

5036 **Poster Session**

Survival outcomes of patients with mNSGCTs with and without teratoma in the primary tumor: An international retrospective study. First Author: Manuel Pedregal, Hospital Universitario Fundación Jimenez Diaz, Madrid, Madrid, Spain

Background: Recent studies have reported conflicting findings on the outcomes of patients with metastatic nonseminomatous germ cell tumors (mNSGCT) and the presence of teratoma in the primary tumor. To further investigate this association, we conducted an analysis using data from a distinct multicenter hospital databases. **Methods:** Clinical-pathological data of mNSGCT patients whose primary tumors were available for histologic review and who underwent cisplatin based chemotherapy between 1992-2014 were retrospectively collected from the IRB approved Dana Farber Cancer Institute (DFCI), Vall D'Hebron University Hospital (VHIO), University Hospital Virgen Del Rocio (HUVR) and Instituto Nacional Cancerologia (INC), GCT databases. We stratified NSGCT patients by the presence or absence of teratoma in the primary tumor(T+ vs T-) Demographic, clinical and pathological characteristics were analyzed using X2 test for categorical variables and T test for continuous variables. Kaplan-Meier methods estimated survival. **Results:** A total of 662 patients were included with a median follow-up of 8 years. 305 (46.1%) patients had teratoma in the primary tumor. Median ages were 28,7 (+- 8,61) and 31,0 years (+- 9,19) in T+ in T- groups respectively. The T+ group was more likely to have a testicular primary (94,4% vs 86,3%, p=0.003). There were no major differences in IGCCCG risk between the two groups, T+ vs T-, good: 155 (50,8%) versus 190 (53.2%); intermediate: 75 (24,6%) versus 60 (16,8%); poor: 66 (21,6%) versus 87 (24,4%), p=0.041. First line chemotherapy consisted of bleomycin, etoposide and cisplatin (BEP) in 233 (76,4%) and 286 (80,1%) of each group. The T+ group had more post- chemotherapy retroperitoneal lymph node dissections and other local resections n=211, 69,2% (95% CI: 59% - 74%) compared to the T- group n=160, 44,8% (95% CI: 37%-50%). There was no significant diference in 10-year survival between T+ and T- patients 79% (95%CI: 77% - 89%) vs. 82% (95% CI: 80% - 91%), p= 0,976 (log-rank). **Conclusions:** The presence of teratoma in the primary tumor was not an adverse prognostic factor in a series of 662 patients with mNSGCT with a median follow-up of 8 years treated in the modern era with predominantly BEP. Longer follow-up beyond 10 years is needed to see if there is an increased incidence of teratoma related deaths in patients with T+. Research Sponsor: None.

5037 **Poster Session**

Bilateral germ cell tumor of the testis (TGCT): Implications for a stem cell versus genetic origin of cancers. First Author: Jamaal Christopher Jackson, Department of Urology, The University of Texas MD Anderson Cancer Center, Houston, TX

Background: Bilateral TGCT provides a unique opportunity to elucidate a stem cell versus genetic origin of cancer. Comparison of the epigenetics and genetics of disparate tumors in either synchronous or metachronous bilateral TGCT from the same patients is feasible and may be informative. **Methods:** We examined the clinical characteristics and natural history of 38 patients with bilateral TGCT. We performed reduced representation bisulfite sequencing (RRBS) of FFPE DNA and whole exon sequencing (WES) of 9 of those patients whose tumor samples were available for the study. **Results:** From the database at MDACC, we identified 38 patients with bilateral TGCT, who underwent their first orchiectomy between January 1984 and April 2022 and the second between August 1997 and April 2022. Median follow-up was 134.2 months (IQR 69.5–222.1 months). Seven patients had synchronous, while 31 had metachronous bilateral TGCT. There were 13 bilateral seminomas, 14 bilateral nonseminomas, and 11 bilateral seminoma and nonseminoma. For those patients with metachronous bilateral TGCT, the median time between the two TGCT was 47.7 months (IQR 19.6–108.9). Out of approximately 20,000 genes investigated, 189 ($<$1%) had a detectable mutation in the 9 paired cases (n=18). A total of 8 genes were mutated in more than 1 sample, including KIT (n=4, 22%) and KRAS (n=6, 33%). Among the 4 bilateral TGCT showing a similar methylation profile in the RRBS analysis, the pattern of single nucleotide variants and type of specific genetic mutations were dissimilar between the right and left TGCT from the same patients in the WES study. Among the 5 bilateral TGCT that did not cluster in the RRBS study, there was differential methylation of the JUP and MAGE-A4 genes between the right and left TGCT from the same patients. **Conclusions:** The clinical course of our patients with synchronous and metachronous bilateral TGCT and the results of our RRBS and WES reaffirmed that a preponderance of TGCT was curable and suggested that epigenomic findings may supplement, if not complement, genomic data to elucidate a stem-cell versus genetic origin and nature of GCT and cancers in general. Research Sponsor: None.

5038 **Poster Session**

Spatial transcriptional dynamics of CD74$^+$ B cells in tertiary lymphoid structures and effects on immune evolution in penile squamous cell carcinoma. First Author: Zaishang Li, Shenzhen People's Hospital, Shenzhen, China

Background: Antitumor immunity has become a critical focus in improving Penile squamous cell carcinoma (PSCC) patient outcomes. Among various immune features, tertiary lymphoid structures (TLS) have emerged as crucial players in tumor immunity. Nevertheless, the specific role of B cells within TLS and their interaction with naive T cells in PSCC remain largely unclear. Therefore, this study aims to elucidate the role of CD74$^+$ B cells in TLS and their impact on immune regulation in PSCC. **Methods:** Spatial transcriptomics produced 519,608 cellular profiles from tumor samples of 18 patients. Additionally, scRNA-seq on tissues from 21 patients yielded 150,540 cells. Bulk RNA-seq was performed on tissues from 55 patients. TLS were identified and visualized using the DBSCAN algorithm, which clusters B cells, T cells, and DCs. Survival analyses were conducted to examine the association between TLS density and patient outcomes. Moreover, immune activity and cell infiltration were assessed via AUCell and CIBERSORT, while pseudotime analysis was used to explore dynamic gene expression changes during cell development. Additionally, pathway enrichment analysis identified key signaling pathways, and intercellular signaling was analyzed through cell communication models. **Results:** TLS, accurately identified using the DBSCAN algorithm, were significantly associated with improved prognosis in PSCC patients (Internal cohort, n = 152, $P < 0.01$; External cohort, n=63, $P < 0.05$). The spatial distribution, a high density of B cells was observed within the TLS regions. Notably, CD74$^+$ B cells were enriched within TLS, particularly during early developmental stages. Mapped the spatially in situ developmental trajectory of CD74$^+$ B cells and uncovered the dynamic changes in gene expression throughout their maturation process, we observed that CD74$^+$ B cells within the TLS of PSCC patients predominantly exhibited features of early developmental stages. In line with this, scRNA-seq data further validated these observations. These cells, through their HLA molecules, interacted with CD4/CD8 ligands on naive T cells, thereby activating critical transcription factors such as NFKB1, NFKB2, NFATC1, NFATC2, FOS, and RUNX1. This interaction ultimately amplified immune responses within the tumor microenvironment. Furthermore, patients with higher CD74$^+$ B cell expression exhibited better responses to immunotherapy (pCR : $P < 0.01$and CR: $P < 0.01$) and underscoring the therapeutic relevance of these cells. **Conclusions:** By activating naive T cells through antigen presentation, CD74$^+$ B cells within TLS significantly enhance local immune responses in PSCC. Thus, CD74$^+$ B cells not only serve as a promising biomarker but also represent a potential therapeutic target, providing novel insights into the immunological mechanisms underlying PSCC progression and response to immunotherapy. Research Sponsor: Shenzhen Science and Technology Innovation Commission Outstanding Youth Basic Research Project; Shenzhen People's Hospital Clinical Scientist Cultivation Project.

5039 **Poster Session**

Long-term outcomes of dynamic sentinel lymph node biopsy in clinically node-negative penile cancer. First Author: Vivaan Dutt, Cancer Institute (WIA), Adyar, Chennai, India

Background: Dynamic sentinel lymph node biopsy (DSLNB) has emerged as a viable alternative in management of clinically node-negative (cN0) penile cancers owing to the high morbidity associated with radical inguinal lymphadenectomy. However, data on efficacy of DSLNB in penile cancer is limited. This study analyses the long-term outcomes of DSLNB in patients with cN0 penile cancer. **Methods:** A retrospective analysis of patients who underwent DSLNB with dual technique (blue dye + radiocolloid) for cN0 penile cancer was done. Data was collected between 2010 to 2018 from a prospectively maintained database with a median follow up of 70.36 months (range - 4 to 150 months). Patients under all risk groups of the European Association of Urology (EAU) Risk Stratification were included. **Results:** The study included 168 consecutive patients who underwent DSLNB (307 groins). Glans penis was the commonest site of disease (92.9%). Partial penectomy was the most common type of surgery for the primary (72.1%). Median number of sentinel nodes identified was three. Based on the EUA risk stratification, 57.2% of the cases were in the high-risk group. Identification rate with dual technique DSLNB in our study was 98.5%. Clavien-Dindo score of 2 or more was seen in 3.57% of patients. A nodal recurrence was seen in 8 groins (8 patients) with a mean time to recurrence of 430 days (69 to 1355 days). This corresponds to a DSLNB false negative rate of 2.6% with median inguinal node recurrence-free survival of 74.4 months. **Conclusions:** In our institution, DSLNB was done with a false negative rate of 2.6% and an acceptable morbidity. The low rate of inguinal nodal recurrence shows the utility of SLNB in staging cN0 groins. By using DSLNB we have avoiding a potentially morbid inguinal dissection in 81.4% of patients with clinically node negative disease. Research Sponsor: None.

5040 **Poster Session**

Dedicated resources for veteran clinical trial participation: The Prostate Cancer Analysis for Therapy Choice (PATCH) program. First Author: Julie N. Graff, VA Portland Health Care System and Knight Cancer Institute, Oregon Health & Science University, Portland, OR

Background: The Veterans Affairs (VA) hospital system is the most extensive integrated healthcare system in the United States. It serves 9.1 million Veterans and has over 170 healthcare centers and 1,193 outpatient sites. Traditionally, clinical trial access has been limited at the VA. The Prostate Cancer Foundation (PCF) and the VA worked together to create the Precision Oncology Program for Cancer of Prostate (POPCaP) within the VA Healthcare System. By 2021, they had funded 21 Centers of Excellence. The program not only strived to bring cutting-edge clinical trials to Veterans but also sought to develop careers for VA investigators and encourage clinical trial participation by a more diverse group of men. **Methods:** PCF and VA-funded sites paid for genomic testing and established clinical trial infrastructure. PATCH developed centralized clinical trial resources- biostatistics, scientific advisory committees, and young investigator development meetings. PATCH also created a budget working group and hired a research nurse to help open complicated investigator-sponsored studies. POPCaP/PATCH provided two monthly meetings for investigators to discuss their research and for industry partners to review trials and drugs in the pipeline. Here, we report on the change in Veteran participation in clinical trials and the demographics of this population from December 2022 to October 2024. **Results:** Since the development of POPCaP/PATCH, Veteran participation in clinical research has rapidly increased from 100 to 400 men enrolled in clinical trials. The number of clinical trials increased from eight clinical trials to 21. Using an existing database containing genomic results, it enrolled patients in trials requiring specific genomic mutations (e.g., MSI-H, BRCA2). We efficiently screened patients for clinical trials, and more than half of those screened enrolled in trials (60%). Patients of different races and ethnicities participated- white 52.6%, black 36.1%, Hispanic/Latino 4.9%, Asian 2.2%, Native American 1.7%, unknown 2.5%. VA stations opened all phases of clinical trials. Through collaboration with other specialties, interventions included targeted oral therapies, immunotherapies, chemotherapies, radiation, and radiopharmaceuticals. **Conclusions:** The VA has dramatically increased clinical trial opportunities and participation over the past two years. We used VA databases of genomic results to enroll patients in studies with restrained eligibility requirements, such as the presence of microsatellite instability (3%). Sixty percent of patients screened for studies ultimately enrolled in those studies. The diversity of VA trials relative to other US prostate cancer trials makes the results of VA studies more generalizable to the US population. Research Sponsor: Prostate Cancer Foundation; Veterans' Affairs.

5041 **Poster Session**

Cardiovascular (CV) event risk in patients (pts) with metastatic castration-resistant prostate cancer (mCRPC) treated with enzalutamide (ENZA) or abiraterone acetate (AA) in the United States (US). First Author: Alan Haruo Bryce, City of Hope, Phoenix, AZ

Background: Prior studies suggest that chemotherapy-naïve pts with mCRPC treated with AA have a higher CV event-related hospitalization risk than those treated with ENZA. To further explore this association, this real-world, comparative causal inference study used a large US dataset to assess CV event risk in chemotherapy-naïve pts with mCRPC who initiated treatment (Tx) with ENZA or AA and provide outcome data based on history of (h/o) CV disease (CVD). **Methods:** Using US Medicare fee-for-service claims (Jan 2010–Dec 2022), we identified chemotherapy-naïve pts aged ≥65 years with mCRPC who initiated ENZA or AA between Sep 2014 and May 2017. The primary endpoint was a 4-point major adverse CV event (MACE-4; composite of acute myocardial infarction [AMI], stroke, unstable angina/revascularization [UA/R], and heart failure). Atrial fibrillation (AFib), venous thromboembolism (VTE), and all-cause death were also analyzed. Groups were propensity score matched (PSM) to adjust for differences in pt characteristics, assessed using standardized mean difference (SMD). Cause-specific Cox proportional hazards models were used to comparethe risk of CV outcomes between intention-to-treat cohorts, with death as a competing event. Subgroup analyses were conducted based on h/o CVD. Sensitivity analysis was performed with a MACE-5 endpoint, defined as MACE-4 or CV-related death. **Results:** Of 6319 pts in the total study population (ENZA: 2934; AA: 3385), 2913 PSM pts were included from each group. The ENZA and AA cohorts had similar baseline characteristics even before PSM (SMD<0.1), with a mean (standard deviation) age of 78.8 (7.3) years; 76% of pts had prior CVD. Compared with pts on ENZA, pts on AA had a significantly higher risk of experiencing MACE-4—particularly UA/R—as well as a higher risk of AFib and VTE (Table). Similar results were found in the subgroup of pts with a h/o CVD and the sensitivity analyses. Additionally, pts on AA had a higher risk of all-cause death than pts on ENZA, regardless of CVD history (h/o CVD hazard ratio [HR]: 1.14, 95% confidence interval [CI]: 1.07–1.21, *P*=0.0001; no h/o CVD HR: 1.12, 95% CI: 1.01–1.26, *P*=0.036). **Conclusions:** This matched analysis of US Medicare beneficiaries showed an increased risk for MACE-4, AFib, and VTE in pts with mCRPC treated with AA compared to ENZA, in the overall pt population and pts with a h/o CVD. The risk of all-cause death was higher with AA in all pts. These findings provide insights into Tx decision-making for pts with mCRPC, especially those at high risk of CV events. Research Sponsor: Astellas Pharma Inc.; Pfizer Inc.

Outcomes	HR* (95% CI)	*P*-value
MACE-4	1.12 (1.02–1.24)	**0.028**
AMI	1.01 (0.76–1.32)	0.987
Stroke	0.92 (0.70–1.20)	0.505
UA/R	1.13 (1.01–1.26)	**0.041**
Heart failure	1.19 (0.90–1.58)	0.237
AFib	1.73 (1.31–2.29)	**0.0001**
VTE	1.37 (1.02–1.85)	**0.037**
All-cause death	1.13 (1.07–1.19)	**0.0001**

*ENZA = reference group.

5042 **Poster Session**

A phase Ia/Ib study of talazoparib in combination with tazemetostat in metastatic castration-resistant prostate cancer (mCRPC). First Author: Atish Dipankar Choudhury, Department of Medical Oncology, Dana-Farber Cancer Institute, Boston, MA

Background: Enhancer of zeste homolog 2 (EZH2) is frequently overexpressed in metastatic castration-resistant prostate cancer (mCRPC), and is linked to lineage plasticity and therapy resistance. In pre-clinical studies, EZH2 directly regulates DNA damage repair (DDR) gene expression, and inhibition of EZH2 sensitizes prostate cancer cells to genotoxic stress as induced by poly-ADP ribose polymerase (PARP) inhibition. Here we report results of a Phase 1a/1b study of the combination of the PARP inhibitor talazoparib (tala) with the EZH2 inhibitor tazemetostat (taz) in mCRPC. **Methods:** Eligible patients (pts) had progressive disease after at least one secondary hormonal therapy and taxane-based chemotherapy (or felt not to be more appropriate for taxane), disease evaluable for response (PSA ≥ 2 ng/ml or measurable disease by RECIST 1.1) and a metastatic lesion amenable to biopsy adequate for next generation sequencing. The starting dose level (DL 0) in Phase 1a was tala 0.75 mg QD + taz 600 mg BID with dose escalation/de-escalation of both agents by up to 2 dose levels based on a 3+3 design to define the recommended phase 2 dose (RP2D). In Phase 1b, an additional 20 pts were treated at the RP2D to assess preliminary safety and efficacy. **Results:** 12 pts were treated in Phase 1a, of whom 2 of 11 DLT-evaluable pts experienced DLT (both Grade 4 thrombocytopenia): 0 of 3 at DL 0, 1 of 6 at DL +1 (tala 0.75 mg QD + taz 800 mg BID), and 1 of 2 at DL +2 (tala 1 mg QD + taz 800 mg BID). The other pt treated at DL +2 experienced Grade 3 anemia requiring transfusion just outside the DLT period, so DL +1 was selected as the RP2D. 27 pts were treated at the RP2D: 7 in Phase 1a (1 of whom was replaced due to progression prior to completion of the DLT period) and 20 pts in Phase 1b. Median PSA at enrollment was 21.8 ng/ml (range 0-3287), and median number of prior treatments was 4 (range 1-10). Grade ≥3 treatment-related AEs were reported in 59% of pts (16/27), including thrombocytopenia (8/27, 29.6%), anemia (8/27, 29.6%), fatigue (4/27, 14.8%), neutropenia (3/27, 11.1%), lymphopenia (1/27, 3.7%), and hyperglycemia (1/27, 3.7%). 14 of 27 pts (51.8%) required dose reduction. Confirmed PSA50 response was seen in 3 of 23 PSA-evaluable pts (13.0%), and PSA30 in 4 of 23 (17.4%). 1 of 12 pts with measurable disease (8.3%) experienced unconfirmed radiographic response, and 6 of 27 pts (22.2%) remained on study treatment for > 270 days. **Conclusions:** In a heavily pretreated biomarker-unselected population, the RP2D of talazoparib 0.75 mg daily and tazemetostat 800 mg BID was associated with expected myelosuppression but otherwise acceptable safety profile, with clinical benefit seen in a minority of patients. Companion blood and tissue-based correlative studies to characterize pharmacodynamic biomarkers of combined PARP+EZH2 inhibition and biomarkers of response and resistance are ongoing. Clinical trial information: NCT04846478. Research Sponsor: Pfizer; Prostate Cancer Foundation; Ipsen (drug only); National Cancer Institute; P50CA272390.

5043 **Poster Session**

Does cytoplasmic AR-V7 circulating tumor cell (CTC) detection add utility in predicting AR pathway inhibitor benefit in men with mCRPC? A retrospective analysis of the PROPHECY study. First Author: Santosh Gupta, Epic Sciences, San Diego, CA

Background: Androgen receptor splice variant-7 (AR-V7) is a constitutively active truncated protein that emerges during hormone therapy resistance in prostate cancer. We have shown that circulating tumor cell (CTC) AR-V7 nuclear localization is strongly associated with worse responses, PFS, and overall survival with AR pathway inhibitors (ARPIs) such as abiraterone or enzalutamide in the metastatic castration-resistant prostate cancer (mCRPC) setting. The measurement of cytoplasmic AR-V7, however, has unclear predictive value and we thus sought to determine whether an AR-V7-agnostic CTC scoring criterion would identify more patients with ARPI resistance as compared to nuclear AR-V7 in the PROPHECY study (NCT02269982). **Methods:** Blood samples were available from 110 of 118pre-ARPI mCRPC patients and evaluated for both nuclear and cytoplasmic CTC only AR-V7 detection utilizing Epic's CTC platform and associated with confirmed PSA50 response, overall survival (OS), and progression-free survival (PFS). We also assessed the correlation between AR overexpression and AR-V7 detection. The proportional hazards model was utilized to explore the prognostic significance of nuclear, cytoplasmic AR-V7 in predicting OS and PFS adjusting for Halabi clinical risk score and CellSearch CTCs≥5. **Results:** At baseline, 11/107 (10%) mCRPC samples had AR-V7 nuclear expression, 15/107 (14%) had cytoplasmic only AR-V7 detection, and thus 26/107 (24%) cases were CTC AR-V7 positive. All of the nuclear AR-V7 positive cases had AR overexpression, while only 67% of cytoplasmic AR-V7 positive cases exhibited AR overexpression. We observed a confirmed PSA50 in 0%, 13%, and 29.6% of nuclear V7+, cytoplasmic V7+, and V7- patients. See the table for PFS and OS outcomes. **Conclusions:** Cytoplasmic AR-V7 detection in CTCs is more prevalent than nuclear only scoring. Cytoplasmic AR-V7 positive cases appear to have worse PFS, PSA50, and OS as compared to AR-v7 negative cases. However, men with cytoplasmic only CTC AR-V7 detection were more likely to have post-ARPI short term PSA declines and improved overall survival, despite a similar poor PFS as compared to nuclear AR-V7 positive patients with mCRPC. Knowledge of both CTC nuclear and cytoplasmic AR-V7 status could be helpful for improved risk stratification of patients with mCRPC prior to ARPI therapy. Clinical trial information: NCT02269982. Research Sponsor: None.

N=107 baseline	Median (95% CI), months	Univariate HR (95%CI)	Multivariate HR (95%CI)
OS based on AR-V7 status			
Nuclear AR-V7	8.4 (7.0, NR)	3.6 (1.9, 7.0)	3.7 (1.7, 8.4)
Cytoplasmic AR-V7 only	14.7 (10.8, 27.3)	2.0 (1.1, 3.6)	1.2 (0.6, 2.5)
AR-V7 negative	21.8 (18.9, 29.2)	Reference	Reference
PFS based on AR-V7 status			
Nuclear AR-V7	3.7 (2.3, NR)	2.6 (1.4, 5.1)	2.9 (1.3, 6.2)
Cytoplasmic AR-V7 only	3.8 (2.7, 8.5)	2.2 (1.2, 3.9)	1.7 (0.8, 3.4)
AR-V7 negative	7.4 (5.5, 9.0)	Reference	Reference

5044 Poster Session

Effect of HLA class I expression on the tumor immune microenvironment and prognosis in prostate cancer. First Author: Pornlada Likasitwatanakul, University of Minnesota, Minneapolis, MN

Background: Human leukocyte antigen (HLA) class I comprises a family of peptide-binding proteins that regulate T-cell interactions. Here, we examined HLA class I mRNA expression and gene zygosity in prostate cancers (PCs), exploring associations with clinical outcomes, molecular features, and tumor microenvironment. **Methods:** We analyzed 10,790 PC samples, of which 8,040 (75%) contained HLA transcription data, and 2,792 (26%) contained HLA genotypes in the Caris Life Sciences database. Samples were stratified into HLA-high (>75th percentile) and -low (<25th percentile) groups. Genomic and transcriptomic alterations were compared at an adjusted significance level of 0.05. Immune cell fractions were inferred by quanTIseq. Overall survival was obtained from insurance claims data and computed using Cox proportional hazards. **Results:** Among 66 cancer types, PC ranked 2nd, 11th, and 19th lowest with respect to HLA-A, HLA-B, and HLA-C expression. In PC, genes related to AR signaling, immunoglobulins, and cell-surface antigens (CTLA4, PD-L1, TROP2, B7-H3, and PSMA) were significantly increased in HLA-high tumors. HLA-high status was associated with increased interferon-gamma scores and more cytotoxic and regulatory T cells, B cells, and NK cells. HLA-high tumors also exhibited a 2-fold depletion in CDK12 and AR/FOXA1 mutations but were enriched in tumor suppressor gene (RB1, PTEN) alterations. HLA-A high tumors exhibited increases in MSI-H/dMMR status (4.8% vs. 3.3% and 5.1% vs 3.1%, p=0.04 and 0.01), while dMMR was also increased in HLA-B high tumors (5.1% vs. 3.4%, p=0.03). HLA class I expression was generally lower in metastatic biopsies (Bx) compared to primary prostate Bx. Upon examining the zygosity of HLA alleles, metastatic Bx exhibited a higher proportion of homozygous HLA-B (7.2% vs. 5.1%, p=0.03) compared to prostate Bx. Last, worse overall survival was seen in prostate Bx that were high in HLA-A or HLA-B (HR = 1.36, 1.21, p<0.0001, 0.008) or metastatic Bx that were HLA-A high (HR = 1.18, p = 0.019). **Conclusions:** HLA class I expression is lower in PCs compared to other cancers, but elevated HLA class I levels correlate with immune cell activity, somatic alterations, and clinical outcomes. Unexpectedly, HLA-A and HLA-B high tumors portended shorter survival, perhaps due to significant enrichment of PTEN/RB1 alterations. Altogether, HLA status, immunogenicity, and tumor suppressor alterations should be considered in tandem when considering patient prognosis. Research Sponsor: University of Minnesota.

5045 Poster Session

Updated prostate cancer risk groups by PSMA-PET PROMISE (PPP2): Results from an international multi-centre registry study. First Author: Wolfgang Peter Fendler, Department of Nuclear Medicine, University of Duisburg-Essen, and German Cancer Consortium (DKTK), University Hospital Essen, Essen, Germany

Background: We previously established prognostic two-tier risk nomograms based on PSMA-PET and Prostate Cancer Molecular Imaging Standardized Evaluation (PROMISE) criteria in a large single-centre cohort. Here, we validate three-tier risk stratification by PSMA-PET PROMISE (PPP2) in a large international multi-centre registry study for prostate cancer survival. **Methods:** We included prostate cancer patients who underwent PSMA-PET at 20 hospitals in EU, USA or Australia between 2013 and 2022. PSMA-PET was standardized by PROMISE version 2 (V2). Total lesion count, total tumour volume, PSMA expression score, and overall survival follow-up were obtained. Investigator sites were split 2:1 into development and validation cohorts, considering site characteristics. In the development cohort we assessed PPP predictors and created version 2 for visual and quantitative PPP nomograms (PPP2) based on Cox regression models with least absolute shrinkage and selection operator penalty for overall survival. Performance of both nomograms was measured in the validation cohort using Harrell´s C-index and calibration plots. Head-to-head comparison to the National Comprehensive Cancer Network (NCCN) risk score was examined by ROC-curves. **Results:** We analyzed 6128 male patients (4044 development and 2084 validation cohorts) across all disease stages with 1915 (31·2%) reported deaths and median follow-up of 4·8 years (IQR 3·4-6·4). Predictors in the visual PPP2 nomogram were presence of distant metastases (extrapelvic nodal metastases [M1a], bone metastases [M1b; oligometastatic, disseminated or diffuse marrow involvement], and visceral metastases [M1c]), PSMA expression score, and total lesion count. Predictors in the reassessed quantitative PPP2 nomogram were distant metastases (M1a, M1b, and M1c), total tumour volume, and PSMA expression score. C-indices (95% CI) in the validation cohort were 0·80 (0·78-0·82) for the visual and 0·80 (0·79-0·82) for the quantitative nomogram, respectively. In the validation cohort for three-tier stratification (high, intermediate, low risk), accuracy of both PPP2 nomograms was superior when compared to the NCCN risk score (n=1034, AUC 0·84 vs. 0·76; p<0·0001, respectively). Performance of both PPP2 nomograms was independent from radiopharmaceutical (68Ga vs. 18F) or PROMISE version (V1 vs. V2; n=2084, visual: both AUC 0·79, respectively, p=0·11; quantitative: both AUC 0·79, respectively, p=0·56). **Conclusions:** PSMA-PET PROMISE nomograms were improved in an international multi-centre study to accurately stratify high vs. intermediate vs. low risk for overall survival across all stages of prostate cancer. PPP2 yields superior accuracy compared to the NCCN risk score. Follow-up continues in the PROMISE Registry (NCT06320223, promise-pet.org). Research Sponsor: Prostate Cancer Foundation; Innovative Health Initiative Joint Undertaking; AstraZeneca.

5046 Poster Session

Safety and pharmacokinetics of mevrometostat (M) in combination with enzalutamide (E) in patients with metastatic castration-resistant prostate cancer (mCRPC). First Author: Nobuaki Matsubara, National Cancer Center Hospital East, Chiba, Japan

Background: M is a potent and selective small molecule inhibitor of enhancer of zeste homolog 2 (EZH2). In the randomized dose-expansion part of a phase 1 study, M (1250 mg BID on an empty stomach) + E (160 mg QD) improved outcomes versus E alone, with a manageable safety profile in patients (pts) with mCRPC (NCT03460977). We report safety and pharmacokinetics for M at 875 mg with food + E from this study. **Methods:** This was an open-label, phase 1 dose escalation and dose expansion study. Pts with mCRPC who received prior treatment with abiraterone or E, with evidence of progression per modified Prostate Cancer Working Group 3 criteria were included. Pts received M (875 mg BID with food) + E (160 mg QD) + androgen deprivation therapy. Safety and pharmacokinetics of the food effect cohort were primary and secondary endpoints, respectively. **Results:** As of Nov 15, 2024, 29 pts received M at 875mg with food + E. Median (interquartile range [IQR]) duration of treatment was 5.5 (4.1–7.4) months. Overall, 28 (96.6%) pts experienced a treatment-emergent adverse event (TEAE; Table). The most common TEAEs of any grade related to M were diarrhea (41.4%), thrombocytopenia (41.4%), and dysgeusia (37.9%). Serious TEAEs related to M were reported in 3 (10.3%) pts (anemia, ECG QT prolonged, and hemorrhagic enterocolitis), all were grade 3. There were no grade 4 TEAEs. TEAEs led to withdrawal from M in 4 (13.8%) pts. One patient had a fatal event of osteonecrosis of the jaw (present at baseline) that was not considered related to M. Plasma exposures of M + E after multiple doses were comparable between M 1250 mg on an empty stomach (n=51) and M 875 mg with food (n=12) (geometric mean [coefficient of variation]: AUC_{tau}, h*ng/mL: 1250 mg, 8690 [54]; 875 mg, 8984 [48]; C_{max}, ng/mL:1250 mg, 2371 [54]; 875 mg, 1868 [85]). **Conclusions:** In pts with mCRPC treated with M + E, M 875 mg with food had an improved safety profile compared with M 1250 mg on an empty stomach. M 875 mg with food has similar plasma exposures to M 1250 mg on an empty stomach. M 875 mg with food + E was selected as the recommended dose for pivotal phase 3 studies. Clinical trial information: NCT03460977. Research Sponsor: This study is sponsored by Pfizer Inc. Enzalutamide for the study was provided by Astellas Pharma Inc. Editorial support was provided by Megan Christian, MBiolSci, and Rosie Henderson, MSc, of Onyx (a division of Prime, London, UK), funded by Pfizer Inc.

	M (875 mg with food) + E (n=29)		M (1250 mg on an empty stomach) + E (n=41)†	
n (%)	Any grade	Grade ≥3	Any grade	Grade ≥3
Any TEAE	28 (96.6)	10 (34.5)	40 (97.6)	22 (53.7)
TEAE related to M	28 (96.6)	7 (24.1)	39 (95.1)	20 (48.8)
Serious AE	8 (27.6)	6 (20.7)	14 (34.1)	13 (31.7)
Most common TEAEs that occurred in ≥30% of pts‡				
Diarrhea	13 (44.8)	0	32 (78.0)	7 (17.1)
Thrombocytopenia	13 (44.8)	2 (6.9)	12 (29.3)	1 (2.4)
Dysgeusia	12 (41.4)	0	24 (58.5)	0
Decreased appetite	10 (34.5)	0	24 (58.5)	0
Nausea	9 (31.0)	0	17 (41.5)	0

†Data presented at ASCO-GU 2025. Data cut-off Sept 2, 2024. Median (IQR) duration of treatment: 7.6 (3.7–12.8) months.
‡For pts treated with M (875 mg with food) + E.

5047 Poster Session

Final overall survival (OS) with talazoparib (TALA) + enzalutamide (ENZA) as an initial treatment in unselected patients (pts) with metastatic castration-resistant prostate cancer (mCRPC) in the China cohort of the phase 3 TALAPRO-2 trial. First Author: Xiaojie Bian, Fudan University Cancer Hospital, Xuhui, Shanghai, China

Background: In the China cohort of the TALAPRO-2 study, unselected pts with mCRPC who received TALA + ENZA had improved radiographic progression-free survival per BICR (rPFS; HR=0.30; 95% CI, 0.17–0.56; $P<0.0001$; data cutoff: Nov 15, 2023), consistent with the global population (HR=0.63; 95% CI, 0.51–0.78; $P<0.0001$; data cutoff: Aug 16, 2022). In final prespecified analyses, TALA + ENZA significantly improved OS vs PBO + ENZA in the global population. Here we report final OS, a descriptive update of rPFS, and an extended follow-up of secondary outcomes in the China cohort. **Methods:** The China cohort includes pts from the unselected cohort 1 of TALAPRO-2 and China extension (unselected homologous recombination repair [HRR] gene status). Pts had asymptomatic/mildly symptomatic mCRPC, received ongoing androgen deprivation therapy, and were prospectively tested for HRR alterations in tumor tissue. Pts were randomized 1:1 to TALA 0.5 mg/day (moderate renal impairment 0.35 mg/day) or placebo (PBO); all pts received ENZA 160 mg/day. Primary endpoint was rPFS by BICR. OS was a key secondary endpoint. Other secondary endpoints included BICR-assessed objective response rate (ORR), time to prostate-specific antigen (PSA) progression, safety, and pt-reported outcomes. All reported P values are 2-sided. **Results:** Overall, 125 pts were randomized (TALA + ENZA, 63; PBO + ENZA, 62). At data cutoff (Sep 3, 2024; median follow-up, 33.2 mo in both arms) 35 pts (56%) in the TALA + ENZA arm and 41 pts (66%) in the PBO + ENZA arm had died. Clinically meaningful benefit in OS with TALA + ENZA vs PBO + ENZA was observed: HR=0.591 (95% CI, 0.369–0.944; $P=0.0262$); median OS (95% CI), 36.9 mo (21.7–42.4) vs 24.1 mo (16.8–30.5), respectively. Updated rPFS by BICR continued to favor TALA + ENZA vs PBO + ENZA (HR=0.312; 95% CI, 0.173–0.561; $P<0.0001$, median rPFS, 33.3 vs 10.5 mo, respectively). TALA + ENZA was favored vs PBO + ENZA in ORR by BICR (50% vs 32%, respectively; $P=0.2845$) and time to PSA progression (HR=0.540; 95% CI, 0.298–0.976; $P=0.0411$). Consistent with global and China cohort primary results, the most common grade ≥3 treatment-emergent adverse events (TEAEs) with TALA + ENZA were anemia (57%) and neutropenia (32%). TEAEs were generally manageable; 14 pts (22%) discontinued TALA due to TEAEs. No clinically meaningful between-arm differences were observed in global health status/quality of life (QoL) measured by EORTC QLQ-C30, except for role functioning, which favored TALA + ENZA. **Conclusions:** At extended follow-up, initial treatment with TALA + ENZA resulted in clinically meaningful improvement in OS, rPFS by BICR, and secondary efficacy endpoints vs PBO + ENZA in unselected pts with mCRPC in the TALAPRO-2 China cohort. No new safety signals were identified; QoL was maintained. Clinical trial information: NCT03395197. Research Sponsor: Pfizer.

5048 **Poster Session**

Long-term safety of radium-223 (Ra-223) in metastatic castration-resistant prostate cancer (mCRPC): 7-year follow-up from the largest global prospective study. First Author: Alton Oliver Sartor, Mayo Clinic, Rochester, MN

Background: Ra-223, an alpha-emitting radionuclide, is the first agent of its kind approved for the treatment of mCRPC. Although a pivotal phase 3 study evaluated its short-term safety, there is a need to investigate its long-term safety. The REASSURE study prospectively examined the long-term safety of Ra-223, including secondary primary malignancies (SPMs), in a large patient (pt) population enrolled across Europe, the United States, Israel, and Latin America. **Methods:** We report final analyses (data cut-off Oct 24, 2024) of REASSURE (NCT02141438), a global, noninterventional study (enrolment 2014–2017). Primary outcomes were the incidence of SPMs, short- (30 days) and long-term (7 years) safety events, and bone marrow suppression (BMS) management in pts who had ≥1 Ra-223 dose. Secondary outcomes included overall survival (OS). **Results:** Analyses included 1472 pts; median follow-up was 17 months (range 0.3–95.4). Median age was 73 years and 80% of pts had an ECOG PS of 0/1. In evaluable pts, median alkaline phosphatase, prostate-specific antigen, and lactate dehydrogenase levels were 133 U/L, 59 ng/mL, and 266 U/L, respectively. Overall, 81% of pts had bone-only metastases at baseline; 19% of pts had metastases in the bone plus other sites (mostly lymph nodes). Prior treatments included abiraterone (48% of pts), enzalutamide (39%), docetaxel (39%), and cabazitaxel (9%). Pts received a median of 6 Ra-223 doses; 67% received ≥5 doses. SPMs occurred in 2% of pts (25 SPMs in 24 pts). Of these pts, 16 (67%) and 1 (4%) had received prior or concomitant radiotherapy, respectively. Overall, 3% of pts had drug-related serious adverse events >30 days after completing Ra-223. Fractures were reported in 10% of pts and were less common in pts with (7% of 605) than without (12% of 867) concomitant BHA use. During Ra-223 and up to 30 days after the last dose, there was no notable difference in the incidence of abnormal platelet counts between pts with (3%) or without (2%) prior chemotherapy; similar findings were seen for abnormal neutrophil counts (5% and 5%, respectively). BMS treatments, assessed from the start of Ra-223, were more common in pts who had received prior taxanes (38%) than in those who had not (26%). The most common life-prolonging therapies received after Ra-223 were docetaxel (18%), enzalutamide (15%), abiraterone (11%), and cabazitaxel (11%). Median OS was 15.6 months (95% CI, 14.6, 16.4); pt subgroups that survived the longest will be characterized and presented. **Conclusions:** This real-world safety analysis of pts with mCRPC is the longest follow-up of a radiopharmaceutical reported to date and supports the well-established favorable safety profile of Ra-223. The incidence of SPMs was low. The rate of fracture was low, especially in the presence of BHAs. Prior taxane chemotherapy use had no impact on hematological toxicity. Clinical trial information: NCT02141438. Research Sponsor: Bayer.

5049 **Poster Session**

Uptake of targeted therapy in a large cohort of patients with advanced prostate cancer and germline pathogenic variants. First Author: Hiba M. Khan, University of Washington/Fred Hutch Cancer Center, Seattle, WA

Background: Men with advanced prostate cancer (PrCa) and pathogenic germline variants (PGV) in homologous recombination repair (HRR) or mismatch repair (MMR) genes are eligible for targeted therapies, namely poly (ADP-ribose) polymerase inhibitors (PARPi), platinum chemotherapy, or immune checkpoint inhibitors (ICI). The influence of these PGV on uptake of targeted therapies is understudied and necessary to identify and intervene upon possible disparities. We describe PrCa targeted treatment patterns in men with advanced PrCa. **Methods:** Germline genetic testing (GGT) (Labcorp) and insurance claims data (Komodo Healthcare MapTM) were assembled for advanced PrCa (defined by ICD10/CPT codes) patients diagnosed from 2015-2024 with ≥ 1 year of claims pre-diagnosis. Treatment uptake by GGT result were compared with *X*2 tests (negative/variant of uncertain significance (VUS), vs HRR/MMR PGV) and multivariable logistic regression (negative/VUS vs *BRCA1/BRCA2*, other HRR/MMR PGV) (Table). **Results:** 11,545 men with advanced PrCa underwent GGT: 66% White, 50% commercial insurance, 27% PrCa family history, mean age at diagnosis: 65. 924 (8%) and 145 (1%) of men had ≥1 PGV in a HRR or MMR gene, respectively. 1,246 (11%) men received platinum chemotherapy, 332 (3%) received PARPi and 521 (5%) received ICI. Men with HRR PGV were more likely than men with VUS/negative results to receive platinum chemo (14% vs. 11%, p=0.001) and PARPi (16% HRR, 25% *BRCA1/2* vs. 2%, p<0.001 for both) and men with MMR PGV were more likely to receive ICI (19% vs. 4%, p<0.001). Black men had lower odds of platinum chemo and ICI than White men, but higher odds of PARPi . Among men with HRR PGV, Black men and those with *BRCA1/2* PGV were more likely to receive PARPi (Table). **Conclusions:** Less than 1 in 4 men with advanced PrCa and HRR/MMR PGV received appropriate targeted therapies. PARPi uptake among eligible patients was twice as high among Black men compared to White men, perhaps reflecting clinician perception of more aggressive disease; rates of platinum chemo and ICI were not similarly higher. These findings raise questions about appropriate receipt of targeted agents and future studies should qualitatively assess clinician prescribing patterns, including sequencing of therapies as approvals for first line PARPi expand. Research Sponsor: None.

Multivariable analysis of factors associated (p<0.05) with targeted therapy uptake.

	Platinum chemo OR (CI)	ICI OR (CI)	PARPi OR (CI)	PARPi (HRR PGV only) OR (CI)
History of non-prostate cancer	12 (10-14)	12 (9-16)	1.4 (1-2)	NS
Positive GGT result		**(ref: negative/VUS)**		**(ref: other HRR)**
BRCA1/BRCA2	NS	NA	18 (14-24)	4 (3-6)
Other HRR	NS	NA	5 (3-7)	NA
MMR	NA	3 (2-5)	NA	NA
Black race/ethnicity (ref: White)	0.7 (0.6-0.9)	0.4 (0.3-0.7)	1.9 (1-3)	2 (1-4)

OR, odds ratio; CI, 95% confidence interval; NA, not applicable; NS, not significant.
NS factors not shown: insurance, age at diagnosis, age2, family history of PrCa, geographic region.

5050 **Poster Session**

Molecular and clinical characterization of KLK2 mRNA expression in prostate cancer (PC). First Author: Rana R. McKay, Moores Cancer Center, University of California San Diego, La Jolla, CA

Background: KLK2 is an androgen-regulated gene that plays a critical role in PC biology. Given the development of KLK-2 targeted therapies, we sought to characterize the molecular and clinical features associated with KLK2 mRNA expression in PC. **Methods:** NextGen sequencing of DNA (592-gene/whole exome) and RNA (whole transcriptome) was performed on PC specimens (n=6,978) at Caris Life Sciences. KLK2-High/Low expression was defined as >75th /<25th quartile RNA transcripts per million (TPM). Castrate resistant PC (CRPC) and hormone sensitive PC (HSPC) were defined based on androgen deprivation therapy (ADT) duration prior to tissue collection: HSPC < 3 and CRPC ≥ 3 months from ADT start. Overall survival (OS) was defined as the time of collection or first androgen receptor pathway inhibitor (ARPI) to death/last follow-up. **Results:** Specimens were derived from primary prostate (n=4,464, 64.0%), lymph nodes (n=828, 11.9%) or other metastatic sites (n=1,686, 24.2%). Higher KLK2 was observed in tumors from Black vs. White patients (8.88 vs. 8.75 log_2[TPM+1], p<0.001). KLK2 was enriched in adenocarcinoma vs. mixed vs. NEPC (8.79 vs. 7.58 vs. 0.33 log_2[TPM+1], p<0.001). Relative to primary tumors (8.93 log_2[TPM+1]), KLK2 varied by metastatic site, with lowest expression in GI (7.46 Log_2[TPM+1], p<0.001), liver (7.88 log_2[TPM+1], p<0.001), and CNS (8.25 log_2[TPM+1], p<0.001). In primary tumors, high KLK2 associated positively with *SPOP* and negatively with *PI3K/PTEN*, *TP53*, and *RB1* alterations. Across primary, lymph node, and distant metastatic tumors, high KLK2 associated positively with AR signaling and negatively with NEPC signaling (all p<0.001). KLK2 strongly correlated with KLK3 (PSA) expression (R=0.87). KLK2 expression was higher in HSPC (n=1504) vs. CRPC (n=4519) tumors (1.78 Log_2[TPM+1], p<0.001). Among HSPC, KLK2-high tumors had decreased *TP53*, *RB1*, *AKT1*, *BRCA1* and increased *SPOP*, *CTNNB1*, *PTEN*, *BRCA2* mutations. CRPC tumors with high KLK2 had decreased *RB1*, *TP53*, *PIK3CA* and increased *RAD54L* and *ATM* mutations compared to low tumors. High KLK2 was associated with improved OS from collection time (median 69.7 vs. 35.9 months, p<0.001) and first ARPI initiation (median 48.9 vs. 39.5 months, p<0.001). KLK2-high HSPC and CRPC tumors had improved OS compared to low tumors (median 82.0 HSPC KLK2-high vs. 54.3 HSPC KLK2-low vs. 23.7 CRPC KLK2-high vs. 16.3 CRPC KLK2-low months, q<0.01). The combination of KLK2-high/AR-high was associated with increased OS compared to KLK2-high/AR-low, KLK2-low/AR-high, and KLK2-low/AR-low tumors (median 70.8 vs. 48.8 vs. 43.5 vs. 20.8 months, respectively, p<0.001). **Conclusions:** This large-scale clinic-genomic analysis reveals distinct patterns of KLK2 expression in PC. The correlation between high KLK2 expression, favorable genomic features, and improved OS supports its potential utility as a prognostic biomarker and may inform selection for KLK2-directed therapy. Research Sponsor: None.

5051 **Poster Session**

Promising early results of MHB088C (B7-H3 ADC) in patients (pts) with metastatic castration-resistant prostate cancer (mCRPC) from a phase 1/2 multicenter study. First Author: Lin Shen, Beijing Cancer Hospital, Beijing, China

Background: MHB088C is a novel B7-H3-targeted antibody-drug conjugate (ADC) incorporating the potent SuperTopoi payload, which is 5 to 10 times more potent than Dxd. Early data from an ongoing phase 1/2 study have shown that MHB088C is generally well tolerated, with early signs of clinical activity (ASCO 2024, abstract #3012). Here, we present preliminary findings from the subset of pts with mCRPC. **Methods:** This study consisted of 2 parts: dose-escalation (part 1) and expansion (part 2). Part 1 evaluated the safety and tolerability of MHB088C at doses ranging from 0.8 to 4.0 mg/kg, administered intravenously every 2 (Q2W) or 3 weeks (Q3W). Part 2 explored multiple doses to assess safety and prospective efficacy of MHB088C in selected tumor types, including mCRPC. **Results:** As of January 3, 2024, 36 pts with mCRPC were enrolled and received at least one dose of MHB088C (1.6~2.4 mg/kg, n=35; 3.0 mg/kg, n=1). The median age was 69 years (range: 51-83) and all pts had an ECOG performance status ≤1. These pts were heavily pretreated, with 100% having received novel androgen axis drugs (NAAD) and 80% having received docetaxel. The objective response rate (ORR) was 14.3%, and the disease control rate (DCR) was 95.2% in pts with measurable disease (n=21). At data cutoff, 19 pts (52.8%) remained on the treatment. Six-month radiographic progression-free survival (rPFS) was 87%. Preliminary data also indicate improvements in prostate-specific antigen (PSA) levels. Safety data were consistent with previous reports. The most common grade≥3 treatment-related adverse events were neutropenia (24.2%), platelet count decreased (11.1%) and anemia (15.2%). **Conclusions:** MHB088C demonstrated a manageable safety profile and promising antitumor activity in heavily pretreated pts with mCRPC. The preliminary safety and efficacy data are encouraging and warrant further investigation. Clinical trial information: CTR20231298. Research Sponsor: None.

5052 **Poster Session**

Evaluating the prognostic utility of cell-free (cf)DNA tumor fraction (TF) in metastatic castration-resistant prostate cancer (mCRPC). First Author: Daniel Boiarsky, Yale New Haven Hospital, New Haven, CT

Background: Accurate prognostication is essential for guiding treatment decisions. cfDNA TF provides a non-invasive quantitative assessment of tumor burden without the need for tissue biopsies, which are notoriously challenging to obtain in mCRPC patients. This study evaluates the utility of cfDNA TF as a prognostic biomarker in mCRPC. **Methods:** Patients treated for mCRPC at the Dana-Farber Cancer Institute with available plasma were identified. Plasma samples underwent (epi)genomic profiling using the Guardant360 platform. TF was estimated by normalizing cancer-specific differentially methylated regions with appropriately matched control regions within each sample. The association of TF with clinical prognostic biomarkers and overall survival (OS) from the time of plasma collection was assessed. Survival analysis was performed using cox proportional hazards methodology, continuous variables were compared using Mann-Whitney test, and linear correlations were calculated using Pearson correlation coefficient. Decision tree (DT) models were developed to evaluate the benefit of incorporating clinical prognostic biomarkers with TF in predicting OS at 12 months. A 70/30 split was used to separate the training and testing cohorts and hyper-parameters were optimized for the F1 score (harmonic mean of precision and recall). **Results:** A total of 103 patients with mCRPC were identified (median age at plasma collection: 72; median prior lines of therapy: 3; median mTF: 3.7%). 36%, 34%, and 30% of patients had TF $<$1%, 1-10%, and $>$=10% respectively. Compared to patients with TF $<$1% (median OS: 28 months), OS was significantly shorter among patients with TF 1-10% (median: 16 months; HR=2.6, p=.00032) and $>$=10% (median: 10 months; HR=7.8, p=6.0x10-12). TF was significantly correlated with max variant allele frequency (mVAF) (rho=0.79 ,p=2.1x10-23), a traditional genomic-based cfDNA measure of tumor burden; however, on multivariable analysis, only TF (HR=5.8,p=2.8x10-9), and not mVAF (HR=0.97,p=0.95), was independently associated with worse OS. Elevated TF was associated with known poor-risk disease features, including visceral metastases, higher ECOG scores, and elevated serum markers (alkaline phosphatase, PSA, LDH). Multivariable analysis identified TF $>$ median as the strongest negatively prognostic marker for OS (HR=3.5,p=.00029). TF alone demonstrated comparable predictive accuracy for 12-month OS (F1: 0.72) to a model including all clinical prognostic markers plus TF (F1: 0.72). Decision tree models identified an optimal TF cutoff of 5.6%, with 88% (53/60) of patients with TF $<$5.6% alive at 12 months, compared to 36% (11/42) for those with TF $\geq$5.6%. **Conclusions:** Our findings suggest that methylated tumor fraction is a robust independent non-invasive prognostic biomarker in mCRPC, outperforming traditional clinical markers and genomic metrics. Future studies should explore the integration of TF into standard prognostic workflows and its potential to guide therapeutic decisions. Research Sponsor: None.

5053 **Poster Session**

Real world outcomes for patients with metastatic castration resistant prostate cancer (mCRPC) and *AR* T878A alterations treated with enzalutamide. First Author: Matthew Siskin, Perlmutter Cancer Center, NYU Langone Health, New York, NY

Background: Androgen receptor (AR) antagonists such as enzalutamide (enza) are standard therapy for mCRPC. *AR* alterations such as amplification (amp) and ligand binding domain (LBD) point mutations (PMs) can cause resistance to hormonal therapies such as enza. The most prevalent *AR* PMs are T878A and L702H. Preclinical evidence suggests that *AR* T878A retains sensitivity to enza compared to *AR* L702H which confers resistance by increasing activation by glucocorticoids. Clinical data evaluating the efficacy of enza in patients with these AR PMs is limited. Here, we analyzed real world data from patients with *AR* T878A compared to *AR* L702H, *AR* amp, or no detected *AR* mutations (*AR* no alt), as identified by circulating tumor DNA (ctDNA), to assess enza efficacy in patients with *AR* T878A versus *AR* L702H. **Methods:** We used GuardantINFORM, a real-world database that combines genomic data from deidentified patients tested via ctDNA with clinical data taken from commercial-payer health claims. Adult mCRPC patients treated with enza who had baseline ctDNA testing and at least 2 claims post ctDNA testing were included. Patients with $\geq$2 *AR* PMs were excluded. Matched cohorts were used to assess real-world overall survival (rwOS), time to treatment discontinuation (rwTTD), and time to next treatment (rwTTNT). Propensity score matching was conducted using age and NCI comorbidity index, race, ethnicity, testing location, and enzalutamide line-of-therapy, and was evaluated using Wilcoxon tests. **Results:** 1,316 mCRPC patients met inclusion criteria. 59 had *AR* T878A, 56 had *AR* L702H, 231 had *AR* amp, and 970 had *AR* no alt. T878A was compared to L702H, amp, and no alt. Patients with T878A demonstrated significantly improved rwTTD (median 8.0 vs 3.5 mo, *P*=0.001) and rwTTNT (median 15.8 vs 4.3 mo, *P*=0.003), but not significantly different rwOS (19.1 vs 13.6 mo, *P*=0.066) relative to L702H. Patients with T878A demonstrated significantly improved rwTTD (7.7 vs 4.8 mo, *P*=0.022), but not statistically improved rwTTNT (10.4 vs 6.4 mo, *P*=0.059) or rwOS (20.2 vs 14.9 mo, *P*=0.14) relative to *AR* amp. Patients with T878A demonstrated significantly shorter rwOS (median 19.2 vs 43.6 mo, *P*=0.03), but no difference in rwTTD (7.7 vs 7.8 mo, *P*=0.88) or rwTTNT (10.4 vs 14.4 mo, *P*=0.423) relative to *AR* no alt. **Conclusions:** To our knowledge, this is the largest study assessing outcomes of mCRPC patients with *AR* PMs subsequently treated with enza. Using real-world evidence, we show that *AR* T878A patients have longer time on therapy with enza relative to patients with *AR* L702H. rwOS following enza was numerically longer for T878A versus L702H. These findings suggests that *AR* T878A is relatively more sensitive to enza compared to other resistance mutations. Future work in larger prospective cohorts comparing hormonal treatments in *AR*-altered patients will help confirm the clinical significance of different *AR* alterations. Research Sponsor: None.

5054 **Poster Session**

'One button push' fully automated PSMA PET quantification: Correlation with progression free and overall survival in patients undergoing [^{177}Lu] Lu PSMA therapy for metastatic castrate resistant prostate cancer. First Author: Louise Emmett, St Vincent's Hospital Sydney, Sydney, NSW, Australia

Background: [^{177}Lu]Lu-PSMA is an effective treatment in metastatic castrate-resistant prostate cancer (mCRPC). Whole body standardized uptake value (SUV)mean and total tumor volume (PSMA-TTV) are valuable screening biomarkers for ^{177}Lu-PSMA therapy but require labour intensive semi-quantitative software. This study aims to compare PSMA SUVmean, and PSMA-TTV from fully automated and semi-automated methods of PSMA-PET quantification for predictive and prognostic capability. **Methods:** Datasets of participants (pts) from ethics approved trials with mCRPC post androgen receptor signaling inhibition and post taxane (or unfit for taxane), treated with [^{177}Lu]Lu-PSMA with a prior screening ^{68}Ga-PSMA-11 PET/CT, and outcome data including PSA progression-free (PSA-PFS) and overall survival (OS) were included. Screening ^{68}Ga-PSMA-11 PET/CT of participants were quantified using MIM LesionID Pro to derive SUVmean and PSMA-TTV with a fully automated quantification process (Method A) and semi-automated quantification adjusted manually for error (Method B). Both methods utilised software that segmented all lesions above SUVmax 3 and a CT-based deep learning method to identify normal organs for automatic physiological uptake removal. SUVmean and PSMA-TTV were evaluated in quartiles. Associations between SUVmean and PSMA-TTV above and below the 75th percentile (Q4 vs Q1-3) were examined with Kaplan Meier estimates and log-rank tests. **Results:** Data from 139 pts were analysed, median age 72 years (IQR: 67–77) and median PSA 94 ng/ml (IQR: 34–325). The median time to PSA-PFS (120 events) 5.5 months (95%CI: 4–6.0) and OS (82 events) 13.5 months (95%CI:11– 18). With method A (fully automated), SUVmean Q4 was 9.7 and PSMA -TTV Q4 was 1156ml. The corresponding results with method B (manually adjusted) were SUVmean Q4 9.9 and PSMA-TTV Q4 1203ml. With-method A, median PSA-PFS for SUVmean Q1-3 was 4.5 (95%CI:3–6) vs 7 months (mo) (95% CI:5–11) for SUVmean Q4 (p=0.003). Median OS for SUVmean Q1-3 was 12.0 (95%CI:10–6) vs 20 mo (95%CI:12.0–NE) for SUVmean Q4 (p=0.011). For PSMA-TTV Q4 vs Q1-3, median OS was 8.5 (95%CI:7 –12.0) vs 18 mo (95%CI: 13–20) (p$<$0.001). With method B, median PSA-PFS for SUVmean Q1-3 was 4.5 (95%CI:3– 6) vs 7.5 mo (95%CI:5–11) for SUVmean Q4 (p=0.002). Median OS for SUVmean Q1-3 was 13 (95%CI:10–17) vs 20 mo (95%CI:11 – NE) for SUVmean Q4 (p=0.03). For PSMA-TTV Q4 vs Q1-3, median OS was 8.5 (95%CI:7–12) vs 18 mo (95%CI:13 – 20) (p$<$0.001). **Conclusions:** PSMA SUVmean and PSMA-TTV with a fully automated quantification method predicted both PSA-PFS and OS in patients undergoing [^{177}Lu]Lu-PSMA therapy. Fully automated vs manually adjusted predictive capability was not different. This is an important step in moving PSMA-PET quantitative biomarkers from research tool to routine clinical care. Research Sponsor: None.

5055 **Poster Session**

First-in-human study of ^{177}Lu-JH020002 in patients with metastatic castration-resistant prostate cancer. First Author: Fangning Wan, Department of Urology, Fudan University Shanghai Cancer Center, Shanghai, China

Background: ^{177}Lu-JH020002 is a novel radioligand therapy that delivers beta-particle radiation to PSMA-expressing tumor cells and the surrounding microenvironment, demonstrating high affinity and antitumor activity in preclinical studies. JH020002-01C is an ongoing, multicenter, open-label phase I/II study investigating the safety, tolerability, pharmacokinetics, dosimetry and preliminary antitumor activity of ^{177}Lu-JH020002 in patients (pts) with metastatic castration-resistant prostate cancer (mCRPC). Here, we reported the preliminary safety and efficacy results of phase I. **Methods:** Eligible pts for phase I had mCRPC, were refractory to or had progressed following at least one androgen receptor pathway inhibitor (ARPI) and chemotherapy, and had at least one PSMA-positive tumoral lesion (PET imaging). Pts received an intravenous dose of ^{177}Lu-JH020002 at the beginning of each 6-week cycle, up to a maximum of 6 cycles. Dose escalation and determination of the maximum tolerated dose (MTD) in phase I were based on an accelerated titration and 3+3 dose-escalation design, including 5 dose cohorts. The primary objective of phase I is to evaluate the safety and tolerability of ^{177}Lu-JH020002 and determine the recommended phase 2 dose. Secondary objectives are dosimetry, pharmacokinetics, efficacy and safety. Tumor response is assessed per PCWG3 criteria. **Results:** As of Jan 22, 2025, 12 pts received ^{177}Lu-JH020002 with a median cumulative dose of 18.06 GBq. 91.7% pts with bone, 33.3% nodal, 8.3% peritoneal metastases. 100% with $\geq$1 prior ARPI therapy, 50% $\geq$ 1 prior chemo regimen, 16.7% ^{223}Ra, 33.3% PARPi. No DLT was reported and MTD was not reached. The most common treatment related adverse events (TRAEs) were Grade1-2. No grade 4/5 AEs were reported. TRAEs of note were hematologic TRAEs, including lymphocyte count decreased (91.7%), platelet count decreased (50.0%), anaemia (66.7%) and white blood cell count decreased (16.7%). With follow-up ongoing, across cohorts 2-5, 63.6% with $\geq$ 50% PSA decline; 27.3% with $\geq$ 90% PSA decline. Seven pts were evaluated per PCWG3. None of them had progressive disease, and all of them remain under treatment follow-up. Among all pts, 1 was with measurable disease and had a partial response. **Conclusions:** ^{177}Lu-JH020002 exhibited excellent antitumor activity in heavily pre-treated pts with mCRPC. Toxicity was well tolerated and generally manageable. Further clinical trials are under planning. Clinical trial information: NCT06139575. Research Sponsor: Bivision Pharmaceuticals, Inc.

Exposure and clinical activity (cohorts 2~5, at doses ≥ 3.70 GBq).

Parameter, median (range) or n (%)	3.70 GBq	5.90 GBq	7.40 GBq	8.88 GBq	Total
No. of patients	2	3	3	3	11
Cumulative dose (GBq)	11.20 (4.2-18.2)	24.58 (5.4-35.2)	22.8 (22.1-29.1)	17.29 (17.28-17.9)	18.21 (4.2-35.2)
PSA decline ≥ 50% PSA decline	2 (100) 1 (50)	2 (66.7) 2 (66.7)	3 (100) 2 (66.7)	2 (66.7) 2 (66.7)	9 (81.8) 7 (63.6)

5056 **Poster Session**

Substudy C of the Canadian cancer trials group (CCTG) IND.234: PC_BETS (Prostate Cancer Biomarker Enrichment and Treatment Selection)—A phase II study of darolutamide (DARO) selected by androgen-receptor (AR) circulating tumor DNA (ctDNA) in patients (PTS) with metastatic castration-resistant prostate cancer (mCRPC) after prior AR pathway inhibitors (ARPIs).

First Author: Michael Ong, The Ottawa Hospital Cancer Centre, Ottawa, ON, Canada

Background: DARO is a unique AR antagonist, with preclinical studies suggesting activity in mCRPC models resistant to abiraterone or enzalutamide due to *AR* amplification (amp) or ligand binding domain mutations. In this substudy (SS) of the (PC-BETS) master protocol, we explored DARO in ARPI-resistant mCRPC stratified by ctDNA *AR* status. **Methods:** Pts had mCRPC, ECOG PS 0–1, evaluable disease, biochemical or radiographic progression, prior ARPI, and no cytotoxic chemotherapy in mCRPC. Genomic screening tested plasma cell-free DNA and matched leukocyte DNA via targeted sequencing with a prostate cancer panel including the *AR* exons, introns, and flank. Only patients with evidence of ctDNA ≥1% were eligible. Pts were assigned to SS by molecular tumor board if biomarker (BM)+; otherwise, BM- pts were randomized to BM- SS. SS-C tested DARO 600mg od in three cohorts—AR amp (C1), AR mutation (C2), or BM- (C3) in a 2-stage design. Primary endpoint was clinical benefit rate (CBR), defined by PSA50 response, RECIST CR/PR, or SD ≥12 weeks. **Results:** PC-BETS Arm C opened in Jan 2018 and closed Feb 2024; 72 pts were enrolled: 27, 26, and 19 in C1, C2, and C3, respectively. Median age was 74 y (53–88), 100% ECOG PS 0-1. Sixteen pts (22%) had docetaxel for hormone-sensitive disease and none for mCRPC. Prior ARPI were abiraterone (31/72, 43%), enzalutamide (37/72, 51%), or apalutamide (4/72, 6%). Pts had bone (67/72, 93%), lung (9/72, 13%), and/or liver (5/72, 7%) metastases. Baseline PSA was 2–20 in 13/72 (18%), 20–100 in 32/72 (44%) or >100 in 27/72 (38%). CBR was more frequent in AR amp or mutated cohorts than BM– (Table 1). DARO median exposure was 4 months (range 1–29). Common related AEs were fatigue (38%), diarrhea (18%), nausea (15%), and anorexia (11%). Median ctDNA fraction of CBR vs no CBR was: C1: 5 vs 16%, p=0.059; C2: 5 vs 19%, p=0.042; C3: 13 vs 13%, p=0.944. C1 CBR was higher with SPOP mutations (3/5, 60%) and all CBR pts had >10 AR copies. C2 CBR was seen with L702H (3/7, 43%) and T878A (4/7, 57%) but not F877L, W724C/L, or V716M. By data cutoff, all had discontinued therapy (radiographic ± biochemical 61%, biochemical only 22%, symptomatic 7%). DARO was well tolerated, with only 6% discontinuing for AEs. **Conclusions:** DARO demonstrates modest activity for unselected mCRPC following ARPIs. ctDNA analysis enriched for pts more likely to benefit from DARO including SPOP alterations, AR amp, and AR mutations L702H and T878A. Clinical trial information: NCT03385655. Research Sponsor: Bayer.

	C1: AR-amp	C2: AR-mutated	C3: BM negative
CBR	5/27 (19%)	7/26 (27%)	2/19 (11%)
PSA response	3/27 (11%)	4/26 (15%)	1/19 (5%)
TTP-PSA (mo)	2.8 (1.8–3.7)	2.8 (1.9–4.0)	1.9 (1.8–2.8)
OS (mo)	12.9 (6.6–19.9)	16.4 (12.9–29.0)	15.5 (12.2–NR)

5057 **Poster Session**

Substudy F of the Canadian Cancer Trials Group (CCTG) IND.234: PC_BETS (Prostate Cancer Biomarker Enrichment and Treatment Selection)—A biomarker-selected phase II study of durvalumab and tremelilumab (DT) in patients (pts) with previously treated metastatic castration-resistant prostate cancer (mCRPC) resistant to AR pathway inhibitors (ARPI).

First Author: Sebastien J. Hotte, Juravinski Cancer Institute, McMaster University, Hamilton, ON, Canada

Background: mCRPC with high neoantigen burden due to DNA mismatch repair deficiency (MMRd) and somatic hypermutation, or *CDK12* mutations, may respond best to immune checkpoint inhibition (ICI). CCTG IND.232 suggested that combination ICI with DT has efficacy in a subset of mCRPC but should be biomarker-directed. In this sub-study (SS) of the PC-BETS master protocol, we explored DT in ARPI-resistant mCRPC stratified by circulating tumor DNA (ctDNA) analysis. **Methods:** Pts had ECOG PS 0–1, evaluable disease, biochemical or radiographic progression, prior ARPI ± cytotoxic chemotherapy (max 1 in castrate resistant setting). Genomic screening tested plasma ctDNA and matched leukocyte DNA via deep targeted sequencing with a prostate cancer-specific panel including coding regions and introns of selected mismatch repair genes and estimating tumor mutational burden. Only pts with evidence of ctDNA ≥1% were eligible. Pts with a positive biomarker (BM+) on ctDNA were assigned to a specific SS by a molecular tumor board (MTB); BM- pts were randomized between SS. SS- F tested DT in 2 cohorts of pts: cohort 1: BM+ pts had either somatic hypermutation (HM) ± concomitant MMR gene alterations, or *CDK12* mutations, cohort 2: BM- pts without these alterations, in a 2-stage design. Primary endpoint was clinical benefit rate (CBR), defined by PSA50 response, RECIST CR/PR, or SD ≥12 weeks. Pts received T 225mg IV once on cycle 1, day 1 and D 1500mg IV day 1 every 4 weeks. **Results:** From January 2020 to February 2024, 25 pts were enrolled: 15 and 10 to cohort 1 and 2, respectively. Median age was 69y (63-84). Five pts had liver mets, 15 pts had had prior cytotoxics. 9 pts in cohort 1 had HM and the remainder had *CDK12* mutations only. Median N cycles given was 4 (1-45). 12 pts had a delayed or interruption of DT dosing. The most common related AEs were fatigue (36%), rash (36%), and diarrhea (32%). CBR was seen in 53% of BM+ pts: all also had PSA response and significantly higher median ctDNA% (34% vs 5%; 5-69%); no patient selected as BM+ due to *CDK12* mutations had CBR, while 8 of 9 pts selected based on HM had CBR. **Conclusions:** Liquid biopsy biomarker-informed treatment with DT demonstrated very promising efficacy in mCRPC pts with HM and merits further evaluation. *CDK12* mutations were not predictive of CBR. Toxicities experienced were characteristic of ICI. Clinical trial information: NCT03385655. Research Sponsor: AstraZeneca.

	BM +	BM -
CBR	8 (53%)	0
Median ctDNA%	25%	12.5%
TTP-PSA* (mo; 95% CI)	6.7 (1-NR)	1.9 (1.1-NR)
mOS (mo; 95% CI)**	15.2 (11.8-NR)	7.5 (2.1-NR)

*PSA time to progression; **median overall survival.

5058 **Poster Session**

Substudy G of the Canadian cancer trials group (CCTG) IND.234: PC_BETS (V)—A circulating tumor DNA (ctDNA)–directed phase II study of carboplatin in patients (Pts) with previously treated metastatic castration-resistant prostate cancer (mCRPC).

First Author: April A. N. Rose, McGill University, Montreal, QC, Canada

Background: PC-BETS registered pts with mCRPC for ctDNA-based genomic screening. A molecular tumor board (MTB) assigned pts to sub-studies (SS) based on prespecified biomarker (BM) criteria: BM-positive (BM+), or by randomization if BM-negative (BM-). IND.234G investigated carboplatin in 2 cohorts (C): C1 included BM+ pts with deleterious DNA damage response (DDR) gene alterations and C2 included BM- pts. **Methods:** Key inclusion criteria were: mCRPC, ECOG 0-1, evaluable disease, biochemical and/or radiological disease progression, received prior next-generation AR pathway inhibitor; prior chemotherapy allowed (max I regimen for mCRPC). The primary endpoint was clinical benefit rate (CBR: PSA50 response, RECIST CR/PR, or SD ≥12 weeks). Secondary endpoints included time to PSA progression (TTP-PSA), and overall survival (OS). Plasma ctDNA and matched leukocyte DNA underwent deep targeted sequencing with a prostate cancer specific panel that included ATM, BRCA1/2, and 22 other DDR genes. Patients with ctDNA <1% were not eligible unless they carried a germline DDR gene alteration. Pts received IV carboplatin (AUC5) on day 1 of 21-day cycles. **Results:** From 09/2020 to 02/2024, 36 pts were enrolled: 19 and 17 in C1 and 2, respectively. All pts were evaluable for safety while 1 pt was not evaluable for CBR (biochemical only disease). Median age was 69y (55-83) and 66y (54-77); 67%/82% had prior chemotherapy; 21%/6% had prior PARPi, and 6%/0% had liver metastases in C 1/2, respectively. In C1, qualifying gene alterations were: ATM (n=8 pts), BRCA2 (8), BRCA1 (1) and ATR (1). Median number of cycles was 4 (1-31). The most common adverse events (AEs) were anemia (97%), thrombocytopenia (89%), lymphopenia (69%), nausea (58%), neutropenia (42%), diarrhea (22%), vomiting (22%), and constipation (33%). Grade ≥3 non-hematologic AEs occurred in 28% of patients; 1 pt died from an unrelated myocardial infarction. 22 pts had dose delays and 15 pts had dose reductions for hematologic AEs. A summary of results is shown in Table 1. For C1, CBR was observed in 5/8 pts with BRCA2 alterations (4 pts had PSA response), 2/8 pts with ATM alterations (0 PSA responses), and 0/2 pts with ATR/BRCA1 alterations. CBR (with PSA response) was observed in 1 pt enrolled to C2 who did not have DDR gene alterations. **Conclusions:** Carboplatin was associated with meaningful clinical benefit in mCRPC pts with DDR alterations detected in ctDNA, but not in pts without DDR alterations. Carboplatin warrants further evaluation in mCRPC pts with DDR gene alterations. Clinical trial information: NCT03385655. Research Sponsor: Canadian Cancer Society.

	Cohort 1 (BM +) N=18	Cohort 2 (BM -) N=17
Median ctDNA% at baseline	16.5%	20%
Clinical Benefit (n, %)	7 (39%)	1 (6%)
TTP-PSA (mo; 95% CI)	2.0 (1.4-9.9)	1.7 (0.8-2.6)
mOS (mo; 95% CI)	21 (9.3-NR)	9.6 (6.5-NR)

5059 **Poster Session**

Phase 1b/2 KEYNOTE-365 cohort I: Pembrolizumab (pembro) plus carboplatin and etoposide chemotherapy (chemo) or chemo alone for metastatic neuroendocrine prostate cancer (NEPC).

First Author: Gunhild Von Amsberg, University Medical Center Hamburg-Eppendorf, Hamburg, Germany

Background: Patients with NEPC are often treated with platinum-based chemotherapy but novel therapies with favorable efficacy and safety profiles are needed. Cohort I of the phase 1b/2 KEYNOTE-365 study (NCT02861573) was designed to evaluate the safety and efficacy of adding pembro to chemo in participants (pts) with NEPC. Preliminary data are presented. **Methods:** Adultpts with pathologically (morphology and immunohistochemistry) confirmed treatment-emergent (t-NE) or de novo metastatic NEPC (small cell, large cell, or mixed morphology per central review), disease progression ≤6 mo before screening, and ECOG PS of 0 or 1, with or without prior androgen deprivation therapy, are included. Enrollment is ongoing. Prior treatment (Tx) with ≤2 chemo regimens for metastatic castration-resistant prostate cancer and ≤2 next-generation hormonal agents are allowed. Prior Tx with platinum-containing regimens is not permitted. Pts are randomly assigned 1:1 to receive 4-6 cycles of carboplatin AUC 5 IV on day 1 Q3W + etoposide 100 mg/m^2 IV on days 1-3 Q3W with or without pembro 200 mg IV Q3W for ≤35 cycles. Primary end points are safety, ORR per RECIST v1.1 by blinded independent central review (BICR), and confirmed prostate-specific antigen (PSA) response rate (≥50% decrease from baseline [BL] measured twice ≥3 wk apart). Secondary end points include rPFS per PCWG3-modified RECIST v1.1 by BICR and OS. No formal hypothesis testing was performed. **Results:** As of August 26, 2024, 40 pts have been randomized; 19 pts received ≥1 dose of pembro + chemo and 18 pts ≥1 dose of chemo. Of treated pts, 29 (78%) had t-NE. Median follow-up was 11.7 mo (range, 0.5-28.7); 7 and 2 pts remain on Tx with pembro + chemo or chemo, respectively. For pts with RECIST-measurable disease, confirmed ORR was 33% (6/18; 95% CI, 13-59; 6 partial responses [PRs]) with pembro + chemo versus 6% (1/16; 0-30; 1 PR) with chemo. For pts with a BL PSA measurement, confirmed PSA response rate was 37% (7/19; 95% CI, 16-62) versus 18% (3/17; 4-43). In all treated pts, median rPFS was 5.1 mo (95% CI, 3.9-8.1) with pembro + chemo versus 4.0 mo (2.0-4.3) with chemo; 6-mo rPFS rate was 49% versus 21%. Median OS was 11.4 mo (95% CI, 5.1-not reached) versus 7.8 mo (3.6-8.5); 6-mo OS rate was 80% versus 65%. Grade 3 or 4 Tx-related AEs (TRAEs) occurred in 58% of pts with pembro + chemo versus 78% with chemo, most commonly anemia (32% vs 39%); no grade 5 TRAEs occurred. Immune-mediated AEs and infusion reactions occurred in 32% of pts with pembro + chemo versus 11% with chemo, most commonly hyperthyroidism (16% vs 6%) and infusion reactions (16% vs 6%). **Conclusions:** Based on these preliminary data in pts with NEPC, the addition of pembro to chemo is associated with promising efficacy outcomes compared with chemo alone and does not result in new or unexpected safety signals. Updated data from cohort I will be presented at the meeting. Clinical trial information: NCT02861573. Research Sponsor: Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA.

5060 **Poster Session**

Impact of germline vs somatic BRCA mutation status on the efficacy of rucaparib vs physician's choice in the TRITON3 study of patients with metastatic castration-resistant prostate cancer. First Author: Simon Chowdhury, Guy's and St. Thomas' NHS Foundation Trust, London, United Kingdom

Background: Rucaparib significantly improved radiographic progression-free survival (rPFS) in men with BRCA-mutated chemotherapy-naïve metastatic castration-resistant prostate cancer (mCRPC) vs a control arm of physician's choice of therapy (docetaxel or androgen-receptor pathway inhibitor [ARPI] therapy: abiraterone acetate or enzalutamide) in the randomized, multicenter, open-label, phase 3 TRITON3 (NCT02975934) study. Herein, we conducted an analysis to determine the impact of germline vs somatic mutation status on the efficacy of rucaparib. **Methods:** Patients were randomized 2:1 to receive rucaparib 600 mg BID or physician's choice of docetaxel or ARPI following progression while on 1 prior second-generation ARPI in any setting. The primary endpoint was rPFS. Color Health did genetic testing. Treatment-emergent adverse events (TEAEs) were reported for the BRCA subgroup. **Results:** In the rucaparib arm, 201/270 patients had BRCA mutations, and in the physician's choice arm, 101/135 patients had BRCA mutations. Of patients with BRCA mutations: in the rucaparib arm, 80/201 (40%) were germline and 116/201 (58%) were somatic with 5/201 (2%) BRCA mutation status unknown, while in the physician's choice arm, 39/101 (39%) were germline and 48/101 (48%) were somatic with 14/101 (14%) BRCA mutation status unknown. rPFS was significantly improved with rucaparib treatment vs physician's choice in both the germline and somatic mutation groups (germline: HR, 0.52 [95% CI, 0.32–0.84]; somatic: HR, 0.38 [95% CI, 0.25–0.59]). Incidence rates of TEAEs were similar overall between patients with germline and somatic BRCA mutations in both arms. **Conclusions:** Rucaparib improves progression-free survival for patients with mCRPC with either germline or somatic BRCA mutations with a manageable safety profile. These data support the use of rucaparib as a beneficial treatment option for patients with BRCA-mutated mCRPC with germline or somatic mutations. Clinical trial information: NCT02975934. Research Sponsor: pharma& GmbH.

5061 **Poster Session**

Prognostic relevance of Aurora kinase A (*AURKA*) expression in prostate cancer (PCa). First Author: Maroun Bou Zerdan, Winship Cancer Institute, Emory School of Medicine, Atlanta, GA

Background: Amplification and overexpression of the *AURKA* gene characterize aggressive variants of prostate cancer, such as castration-resistant (CR) PCa and neuroendocrine PCa (NEPC), representing both a marker of progression and a promising therapeutic target. **Methods:** 7755 PCa specimens were sequenced for DNA and RNA at Caris Life Sciences and stratified into top (Q4) and bottom quartiles (Q1) based on *AURKA* expression. Castration status was defined as castrate (CS) if a specimen was androgen deprivation therapy (ADT)-naïve or collected within 90 days from the initiation of 1st generation ADTs. Additionally, specimens that received 2nd generation ADTs prior to collection were excluded from the CS cohort. All other ADT treated specimens (excluding the CS cohort) were considered CR. AR and NEPC scores were calculated as previously reported (Beltran, Nat Med 2016) and categorized into highest (H) and lowest (L) quartiles. Real-world survival was obtained from insurance claims data, and Kaplan–Meier estimates were calculated from specimen collection to last clinical contact for overall survival (OS) and from initiation to termination of specific ADTs to estimate time on treatment (TOT). Hazard ratios (HR) and p-values were calculated using the Cox model and log-rank test, with multiple testing corrections applied ($q<0.05$). **Results:** Compared to Q1, Q4 was associated with a higher median age (69 vs 67 years) and a higher proportion of non-Hispanic/Latinos (75 vs 70%), NEPC-H (42 vs 15%), metastatic (60 vs 22%), CR (46 vs 20%, all $q<0.05$) disease. *Q4* was also associated with poor prognosis independent of race and ethnic backgrounds. Despite the significant enrichment of aggressive disease, *Q4* was associated with poor prognosis independent of metastatic, NEPC-L or castration status. Further within NEPC-H specimens, *Q4* was prognostic only among those that were also AR-L (Table 1). Relative to Q1, Q4 samples were enriched for mutations in *TP53* (48 vs 23%), *RB1* (10 vs 1%) and *PTEN* (11 vs 7%, all $q<0.05$). Interestingly, *Q4* was associated with a longer Leuprolide-TOT (HR: 0.9(0.8-0.97), $p<0.01$) and a shorter Enzalutamide-TOT (HR: 1.2 (1-1.4), $p<0.05$). **Conclusions:** Analysis of a large dataset revealed that high *AURKA* expression correlates with poor prognosis across clinical and demographic subpopulations. *AURKA* inhibitors might enhance outcomes of metastatic PCa treated with AR pathway inhibitors by intensifying AR inhibition, increasing DNA-damage-related cell death, and/or preventing escape mechanisms like NEPC. Further studies are needed to identify contexts where *AURKA* inhibitors can improve metastatic PCa outcomes. Research Sponsor: None.

HR comparing OS in Q4 vs Q1 (all p<0.0001).

Conditions	HR (95% CI)
White	2.6 (2.3-2.9)
Black/AA	1.9 (1.5-2.5)
non-Hispanic/Latino	2.6 (2.3-2.9)
Hispanic/Latino	2.3 (1.7-3.2)
Primary	1.7 (1.5-2)
Metastatic	2 (1.7-2.4)
NEPC-L	2.3 (1.7-3.1)
NEPC-H/AR-L	2.1 (1.6-2.8)
CS	1.9 (1.6-2.2)
CR	2.4 (2-3)

5062 **Poster Session**

PSA and alkaline phosphatase changes in the EORTC-1333 PEACE-3 study evaluating the addition of six cycles of radium 223 in metastatic castration-resistant prostate cancer (mCRPC) starting enzalutamide. First Author: Ananya Choudhury, The Christie NHS Foundation Trust, Translational Radiobiology and University of Manchester, Manchester, United Kingdom

Background: The EORTC/UNICANCER/CTI/CUOG/LACOG Peace 3 showed that adding Ra233 to enzalutamide significantly improves investigator-assessed progression-free survival (PFS) and overall survival (OS) in mCRPC with bone metastases. We examined the effect of the combination on the decline in prostate-specific antigen (PSA) and alkaline phosphatase (ALP). **Methods:** From 11/2015 to 03/2023, 446 men with mCRPC and bone metastasis were randomized 1:1 to enzalutamide alone (ENZ) or combined with 6 cycles of Ra223 (ENZ-RAD). The PSA/ALP response rate is estimated at 6/12 months based on the drop from baseline in all PSA/ALP evaluable patients. For PSA, any decline $\geq$ 50 or 90% from baseline is considered a PSA response. For ALP, any decline of $\geq$30% from baseline is regarded as a response. Each response needed to be confirmed by a second evaluation at least three weeks later. Time to response is from treatment start until the first date a response was observed. ALP normalization is a decline to $\leq$ 115 U/L in patients with baseline ALP >115 U/L. **Results:** PSA: The baseline median (Q1-Q3) for ENZ-RAD was 24.0 (7.8-68.8) ng/dl, and 21.4 (8.0-57.6) ng/ml for ENZ. The median time (95%CI) to a PSA response > 50% in months (mo.) was 2.79 (2.56-3.02) in the ENZ-RAD arm and 2.76 (2.63-2.79) in the ENZ arm (HR (95%CI) 1.00 (0.80-1.24)). PSA response rates $\geq$50% at 6 and 12 months were 77.1% (145/188) and 76.8% (109/142) in the ENZ-RAD arm, compared to 69.9% (127/182) and 66.2% (88/133) in the ENZ arm. The median time (95%CI) to a PSA response $\geq$ 90% in mo. was 1.87 (1.44-2.53) in the ENZ-RAD arm and 7.44 (3.67-NE) in the ENZ arm (HR (95%CI 1.48 (1.13-1.93)). PSA response rates $\geq$90% at 6 and 12 mo. were 50.5% (95/188) and 54.9% (78/142) in the ENZ-RAD arm, compared to 34.1% (62/182) and 37.6% (50/133) in the ENZ arm. ALP: The baseline median (Q1-Q3) ALP in the ENZ-RAD arm was 106 (78-183) UI/L, and in the ENZ arm, 124.5 (85-216). In the ENZ/RAD and ENZ arms, 45.6% (99/217) and 54.4% (122/224) of patients had ALP $\geq$ 115 UI/L at baseline. The ENZ-RAD arm had a median time (95%CI) to ALP response > 30% of 2.40 (1.97-2.79) mo., while the ENZ arm had a median of 3.71 (2.83-5.49) mo. (HR (95%CI) 1.42 (1.13-1.80)). ALP >30% response rates at 6 and 12 mo. were 56.5% (108/191) and 50.0% (71/142) in ENZ-RAD and 50.8% (93/183) and 47.4% (63/133) in ENZ. The median (95%CI) time to ALP normalization in the ENZ-RAD arm is 1.97 (1.87-2.50) mo. and 4.47 (2.99-14.06) mo. In the ENZ arm(HR 1.42 (1.13-1.80)). At 6 and 12 mo., the ENZ-RAD arm ALP normalization rates were 76.2 (64/84) and 77.4 (41/53), while 50.5% (47/93) and 61.3% (38/62) in the ENZ arm. **Conclusions:** The addition of six cycles of RA 223 to enzalutamide in the PEACE-3 trial improves PSA response time and rates ($\geq$90%), ALP reduction time ($\geq$30%), and ALP normalization time and rates at 6 and 12 months. Clinical trial information: NCT02194842. Research Sponsor: Bayer Healthcare, Astellas.

5063 **Poster Session**

A novel prognostic model to optimize the timing of docetaxel (Doc) following an androgen receptor pathway inhibitor (ARPi) in metastasic castration-resistant prostate cancer (mCRPC). First Author: Lola Rodríguez Nogueira, Oncology Department, Hospital Universitario 12 de Octubre,, Madrid, Madrid, Spain

Background: ARPi has become a standard of care for advanced prostate cancer due to its activity and safety profile. DoC is a therapeutic alternative as first-line in unselected mCRPC patients (pts) after a first ARPi. Best timing to initiate Doc following an ARPi remains uncertain, with most predictive models based on baseline characteristics and without variables related to the disease evolution. We have developed and validated a tool to predict progression-free survival (PFS) and overall survival (OS) with Doc to capture individual tumor behavior and guide the optimal timing of Doc. **Methods:** mCRPC pts from PROREPAIR-B (NCT03075735) treated with an ARPi followed by Doc were selected for a derivation cohort (n=111). Those pts from PROSTAC (NCT02362620), PROSABI (NCT02787837) and/or PROSENZA (NCT02922218) not included in PROREPAIR-B treated with an ARPi followed by Doc were included in the validation cohort (n=243). Baseline characteristics at ARPi initiation, type and time of response/progression to ARPi and prognostic variables at initiation of Doc were collected. All variables underwent univariate Cox regression for PFS and OS from Doc in the derivation set. Only significant variables underwent the least absolute shrinkage and selection operator (LASSO) method to select the most relevant. Individual risk scores for PFS and OS were generated using Cox to classify patients into low- and high-risk groups and to construct a nomogram. Finally, an external validation was conducted in our second independent cohort. Predictive accuracy was assessed using Harrell's C-index. **Results:** The Lasso method identified 6 variables associated to PFS and OS: age at diagnosis, time to (t)mCRPC, development of new nodal and/or new visceral metastasis during ARPi, elevated LDH and ECOG at Doc initiation (Table). After bootstrap correction for internal validation the PFS and OS model showed a C-index of 0.71 (CI95% 0.66–0.77) and 0.74 (0.68–0.80), respectively. The model was validated in our second cohort with c-index of 0.62 (0.6-0.7) and 0.64 (0.6-0.7) for PFS and OS, respectively. **Conclusions:** Our validated model provides a pragmatic and widely accessible tool for physicians to estimate the potential benefit of Doc after an ARPi according to pts age and time to mCRPC, particularly in settings where targeted therapies at the time of progression to ARPi are not available. Research Sponsor: None.

Variable	PFS risk coefficient (rc)	PFS (HR CI95%)	OS rc	OS (HR CI95%)
Age (<60, 60-70, >70)	.35	1.5 (1.1-1.9)	.33	1.6 (1.2-2.3)
tmCRPC (>98, 98-23, <23)	-.17	0.7 (0.5-0.9)	-.49	0.4 (0.2-0.7)
Visceral MTS (never, persistent, new)	.48	1.2 (0.9-1.6)	.54	1.9 (0.9-3.9)
Nodal MTS (never, persistent, new)	.58	1.4 (1.0-1.9)	.66	2.0 (1.0-4.2)
LDH (xULN)	.10	1.2 (1-1.2)	.8	1.9 (1.0-2.4)
ECOG at Doc	.63	2.1 (1.4-2.9)	.74	4.1 (2.1-8.2)
Total Score (Low vs high)		**1.9 (1.2-3.1)**		**2.13 (1.3- 3.5)**

5064 Poster Session

Additive clinical utility of tissue biomarkers of microsatellite instability (MSI) status and tumor mutational burden (TMB) to predict immune checkpoint inhibitor (ICI) effectiveness for real-world patients with metastatic castration-resistant prostate cancer (mCRPC). First Author: Nicolas Sayegh, Huntsman Cancer Institute, University of Utah Health Care, Salt Lake City, UT

Background: FoundationOneCDx (F1CDx) supports two FDA-approved biomarkers to guide treatment decisions for ICI for patients with mCRPC: MSI status and TMB. MSI-H and TMB-H (10+ mut/MB) have strongly overlapping prevalence. We sought to better characterize ICI outcome associations of TMB-H / non-MSI-H population and relative effectiveness of taxanes & ICI among patients who received these agents in sequence. **Methods:** Following a prespecified analysis plan, this study used the nationwide (US-based) de-identified Flatiron Health-Foundation Medicine mCRPC clinico-genomic database (FH-FMI CGDB), with data originating from ~280 US cancer clinics (~800 sites of care). Inclusion criteria included patients with mCRPC treated with single-agent anti-PD(L)1 therapy in the FH network between 1/1/2011 - 3/30/2024. This study used the MSI and TMB algorithms from the tissue based F1CDx. Time to next treatment (TTNT) and OS were assessed with Kaplan-Meier plots and in multivariable Cox models adjusted for ECOG performance score, socioeconomic status, prior treatment history, and baseline PSA. Among patients who received taxanes in a prior line of therapy, the effectiveness (TTNT1 vs. TTNT2) of taxane and ICI were compared. **Results:** Among 2995 prostate cancer tissue specimens in the database, 95 (3.1%) were MSI-H and 142 (4.7%) were TMB-H. 94 (3.1%) were MSI-H & TMB-H, 1 was MSI-H & TMB-L, and 48 (1.6%) were TMB-H & not MSI-H. Among these, 84 patients with mCRPC were treated with ICI and met inclusion criteria, including MSI-H & TMB-H (n = 30), non-MSI-H & TMB-H (n = 8), and non-MSI-H and TMB-L (n = 46). The respective median TTNT on ICI was 8.0 vs. 9.6 vs. 3 months. The respective median OS from initiation of ICI was 10.9 vs. not reached vs. 4.4 months. In multivariable models evaluating ICI only, compared to non-MSI-H & TMB-L, the MSI-H & TMB-H group had more favorable TTNT (HR: 0.20, 95%CI: 0.10 – 0.41, $p < 0.001$) and OS (HR: 0.33, 95%CI: 0.16 – 0.70, p = 0.004), and the non-MSI-H & TMB-H group also had more favorable TTNT (HR: 0.13, 95%CI: 0.04 – 0.45, p = 0.002) and OS (HR: 0.20, 95%CI: 0.05 – 0.75, p = 0.017). 50 of the 84 (60%) patients treated with ICI had prior mCRPC taxane treatment. Better TTNT2 on subsequent ICI vs. prior taxane was observed for MSI-H (HR: 0.49, 95%CI: 0.23 – 1.01, p = 0.051) and TMB-H (0.54, 95%CI: 0.30 – 0.98, p = 0.044), but the opposite was true for non-MSI-H and TMB-L subgroups, with significant treatment interactions for each (p = 0.0018, p = 0.00052). **Conclusions:** TMB-H (4.7%) is more prevalent than MSI-H (3.1%) by F1CDx in mCRPC. Non-MSI-H / TMB-H (1.6%) in the routine practice cohort have similar outcome associations on ICI to MSI-H. Both MSI-H and TMB-H by F1CDx are predictive of differential benefit for ICI vs. taxanes in later mCRPC treatment lines. Research Sponsor: None.

5065 Poster Session

Suboptimal suppression of serum androgen levels among men treated with apalutamide and abiraterone acetate plus prednisone compared with abiraterone acetate plus prednisone alone. First Author: Elahe A. Mostaghel, VA Puget Sound Health Care System, Seattle, WA

Background: Phase III studies of dual therapy with an androgen receptor (AR) antagonist, apalutamide (Apa) or enzalutamide (Enza) with abiraterone acetate (AA) plus (+) prednisone (P) in metastatic castration resistant prostate cancer (mCRPC) have not shown a survival benefit vs single agent therapy. Apa and Enza induce CYP3A4 activity, resulting in decreases in serum AA and P levels. The decrease in AA levels has not been considered clinically significant, but the potential impact of AR antagonist-mediated CYP3A4 induction on serum steroid levels, in context of clinical studies combining an AR antagonist with AA, has not been previously reported. **Methods:** We measured levels of AA, its metabolites and androgens using LC/MS-MS in available serum samples obtained at baseline and at 4 weeks of therapy in the PANTHER phase II study (n=86) of Apa (240 mg daily) and AA (1000mg daily) + P (10mg daily), and in the Abi Race phase II study (n=75) of AA (1000mg daily) + P (10mg daily) among men with mCRPC. Samples were batched and all sera assessed contemporaneously. Comparison of metabolite levels between studies used the Mann-Whitney test, and within study the Wilcoxon matched-pairs signed rank test. **Results:** At 4 weeks, median (med) levels of AA and its primary metabolites delta-4 and keto-Abi in PANTHER vs Abi Race were 13.1 vs 39.6 ng/ml, 0.49 vs 1.93 ng/ml, and 0.75 vs 8.98 ng/ml ($p=<0.0001$ for all), equating to 66%, 75%, and 92% lower levels with Apa and AA + P vs AA + P. Baseline steroid levels did not differ between the studies, but steroids downstream of CYP17A were suppressed markedly less effectively in the dual therapy PANTHER study: DHEAS was detectable in 80% vs 14% of samples (med 1.23 vs 0.49 ng/ml, $p=<0.0001$), DHEA in 90% vs 26% (med 0.44 vs 0.01 ng/ml, $p=<0.0001$), AED in 70% vs 11% (med 0.017 vs 0.010 ng/ml, $p=<0.0001$), and testosterone in 50% vs 17% (med 0.006 vs 0.005 ng/ml, p=0.0005). Despite the decrease in AA levels, steroids upstream of CYP17A in PANTHER were markedly elevated vs treatment with AA + P alone: pregnenolone (4.1 vs 0.79ng/ml, $p=<0.0001$), consistent with a suboptimal prednisone-mediated suppression of ACTH. **Conclusions:** Serum AA levels at week 4 are substantially lower, and androgen levels substantially higher, among men with mCRPC treated with Apa and AA + P vs AA + P. Our data suggest that Apa decreased P levels to the point that circulating ACTH remained sufficient to mediate ongoing basal adrenal androgen synthesis. Suboptimal suppression of steroids may explain why AA and AR antagonist combination studies have not been more effective. The clinical activity when both treatment strategies are at full efficacy remains to be fully tested, and will likely require use of dexamethasone or higher than standard dosing of prednisone. This may be particularly important for treatment of prostate cancers with greater dependence on AR signaling. Research Sponsor: Janssen Scientific Affairs, LLC.

5066 Poster Session

Canadian Cancer Trials Group (CCTG) IND.234/223: PC_BETS (Prostate Cancer Biomarker Enrichment and Treatment Selection)—A molecularly selected cooperative group platform study. First Author: Alexander William Wyatt, Vancouver Prostate Centre, Vancouver, BC, Canada

Background: PC-BETS registered patients (pts) with metastatic castration-resistant prostate cancer (mCRPC) for circulating tumour (ct)DNA-based genomic screening to biomarker select and stratify pts for enrolment in a multi-arm platform trial testing clinical activity of investigational therapies. **Methods:** Pts ($\geq$ 18 years old, ECOG PS 0-1, life expectancy $\geq$ 6 months) had mCRPC, disease progression (PD), no CNS involvement or serious illnesses and had received AR pathway inhibitor therapy +/- chemotherapy. Eligible pts were registered and screened using plasma ctDNA and enrolled to a substudy (SS) based on the presence (or absence) of a prespecified biomarker (BM), using a prespecified algorithm and a virtual web-based Molecular Tumour Board (MTB). ctDNA testing used an established targeted sequencing approach customised for mCRPC. Pts without BM positive genomic alteration(s) for an open SS were randomized to a BM negative SS cohort; pts who were never enrolled were followed for outcomes. Pts without detected ctDNA were not eligible for enrolment but could be rescreened after >8 weeks. Pts who discontinued a SS could be rescreened. Primary endpoint was clinical benefit rate (CBR; PSA50 response, RECIST CR/PR, or SD $\geq$12 weeks). Eight SS opened between 2017-2020. **Results:** From 2017-2024, 568 pts were screened from 11 centres across Canada. Pts: median age 71.5 (range 47.7-94.7), prior chemotherapy in 47.0%, and median ctDNA fraction was 7%. 216 pts were enrolled to 1 or more SS (3 pts enrolled to >1). See Table for summary of results. For all SS, toxicities were as expected. In SS-E, 1 pt had CBR and 1 pt received 25 cycles but did not meet CBR (both pts had AKT mutations). Clinical and genomic correlations will be presented. SS C, F and G are reported separately. **Conclusions:** Biomarker selected platform designs are an efficient way to screen potential new therapeutics, are well suited to multi-centre cooperative group settings and are strongly supported by patients advocates. CBRs were not reported for SS 223, B and D while modest clinical activity was seen for SS A (in the BM- cohort only) and E. Clinical trial information: NCT03385655. Research Sponsor: Pfizer; Canadian Cancer Society; AstraZeneca; F. Hoffmann-La Roche Ltd.; Treadwell Therapeutics; Bayer.

Total Screens / N pts				**606 / 565**				
ctDNA+ screen / pts				443 / 426				
N pts enrolled to SS				216				
SS	223	A	B	C	D	E	F	G
Drug/s	Palbociclib	Adavosertib	Savolitinib	Darolutamide	CFI-40095	Ipatasertib	Durvalumab / tremelimumab	Carboplatin
Target/pathway	CDK[1]	BRCA/ATM[2]	MET	AR	PTEN	PIK3CA/AKT	TMB high	BRCA/ATM[2]
Drug supplied by	Pfizer	AstraZeneca		Bayer[3]	Treadwell	Hoffman-La Roche[3]	AstraZeneca[3]	-
Enrolled to SS(BM+/-)	19 (9/10)	25 (11/14)	16 (6/10)	72 (53/19)	18 (9/9)	8 (BM+)	25 (15/10)	35 (18/17)
CBR (BM+)	0	0	0		0	1		
CBR (BM-)	0	3	0		0			

[1]CDK4/6/CCND1 amplification or CDK12 mutations; [2]or other HRR-related defects; [3]Plus partial funding to support SS.

5067 Poster Session

Phase 1 study of gotistobart (BNT316/ONC-392) in combination with lutetium Lu 177 vipivotide tetraxetan (Lu 177) in patients with metastatic castration-resistant prostate cancer (mCRPC). First Author: David R. Wise, Perlmutter Cancer Center, NYU Langone Health, New York, NY

Background: When used in combination with physician's choice of care, Lu 177 showed significant PFS and OS improvements in mCRPC. Combinations with novel agents are being explored to extend the therapeutic benefit. Preclinical models have demonstrated that radiotherapy selectively expands and functionally activates regulatory T cells (Tregs) in the tumor microenvironment (TME). Given the role of gotistobart (a unique pH-sensitive anti-CTLA-4 antibody that preserves CTLA-4 recycling and avoids lysosomal degradation) in selective depletion of Tregs in the TME, this study will initially test the safety and toxicity of gotistobart plus Lu 177 in mCRPC. **Methods:** PRESERVE-006 (NCT05682443) is an open-label, randomized, active control, multi-center, phase 1/2 study of gotistobart in combination with Lu 177 in patients with mCRPC who have progressed after androgen receptor pathway inhibition. Patients were randomized to receive gotistobart at 3 mg/kg, Q4W, 6 mg/kg Q6W, or 10 mg/kg Q6W for up to 13 doses plus Lu 177 7.4 GBq (200 mCi) Q6W for up to 6 doses, or to the control arm to receive Lu 177 7.4 GBq (200 mCi), Q6W for up to 6 doses. Here we report results from the dose escalation phase (Phase 1) that aims to assess safety and select two dose regimens for the Phase 2 dose optimization study. **Results:** As of December 20, 2024, 24 patients received at least 1 drug dose with a median 6.21 (range 1.2–11.3) months on study. Median age was 70.5 (range 52–86) years, and 62.5%, 25.0% and 4.2% were White, Black, and Asian, respectively. Median follow-up was 10.9, 2.6 and 5.4 months for the 3 mg/kg Q4W (N = 6), 6 mg/kg Q6W (N = 5) and 10 mg/kg Q6W (N = 6) combination regimens, respectively, and 6.5 months for Arm B Lu 177 (N = 7). No deaths, dose-limiting toxicity, or Gr 4–5 treatment-related AEs (TRAEs) were observed at any gotistobart dose. TRAEs related to gotistobart or Lu 177 were Gr 1–2 at 3 mg/kg Q4W and 6 mg/kg Q6W; one patient (16.7%) in the 3 mg/kg regimen had Gr 2 colitis leading to treatment discontinuation. At 10 mg/kg Q6W, two patients (33%) had Gr 3 colitis (both of whom discontinued treatment) and one patient (16.7%) had Gr 3 fatigue. Infusion-related reactions (Gr 1–2) were seen in 6 mg/kg (40.0%) and 10 mg/kg (66.7%) regimens. In the efficacy-evaluable population, confirmed PSA50 (a key secondary endpoint for Phase 2) was observed in 4 of 6 patients and 3 of 6 patients in 3 and 10 mg/kg regimens, respectively versus 1 of 6 patients in the Lu 177 control group. **Conclusions:** With known limitations in sample size during dose escalation,gotistobart in combination with Lu 177 demonstrated a manageable safety profile and promising preliminary PSA50 rates in patients with mCRPC during the dose escalation phase. Overall findings support combination regimens with gotistobart doses less than 10 mg/kg in the ongoing Phase 2 randomized dose optimization study. Clinical trial information: NCT05682443. Research Sponsor: OncoC4 Inc; BioNTech SE.

5068 **Poster Session**

Survival and hospitalizations with lutetium (Lu)-177 vipivotide tetraxetan in veterans with underlying genomic alterations. First Author: Sumrah Khan, Saint Louis University School of Medicine, St. Louis, MO

Background: Lutetium-Lu 177 vipivotide tetraxetan (^{177}Lu-PSMA-617) is a radioligand therapy used to treat metastatic castration resistant prostate cancer (mCRPC) with limited real-world survival data outside of large academic centers. Emerging data suggests outcomes are associated with somatic tumor genomic profiles, such as status of tumor suppressor gene (TSG) alterations, including TP53, PTEN, or RB1. We utilized a nationwide retrospective cohort within the Veterans Health Affairs (VHA) to evaluate overall survival of patients treated with ^{177}Lu-PSMA-617 and considered tumor suppressor gene alteration status, which could serve as a biomarker for personalized treatment. **Methods:** Veterans with mCRPC treated in the VHA who received at least one dose of ^{177}Lu-PSMA-617 through November 2024 were included. The National Precision Oncology Program (NPOP) was used to identify patients who underwent tumor sequencing and had TSG alterations. Age, Charlson comorbidity index (CCI), and number of hospitalizations were collected. The Kaplan-Meier method was used to estimate overall survival (OS), logistic regression for risk of hospitalization, and Cox proportional hazards models to estimate mortality. **Results:** A total of 228 Veterans who had received at least one dose of ^{177}Lu-PSMA-617 were identified. Mean age was 76.5 years (SD 7.6) with median CCI of 2 (IQR 1-4). Median OS was 11.4 months (95% CI 8.6-14.2) in the entire cohort and 29.8% of Veterans (68/228) were hospitalized in the year after first dose. Age was not associated with mortality or hospitalization, however CCI was associated with mortality (HR 1.12, 95% CI 1.01-1.24) and any hospitalization (OR 1.21, 95% CI 1.05-1.41). There were no differences in OS based on receipt of NPOP testing (HR 0.97, 95% CI 0.62-1.5). In 108 patients with NPOP testing, 44% (48/108) were found to have at least one TSG alteration. Median OS was shorter in patients with TSG alterations (5.8 vs. 18.0 months, p=0.001, HR 2.8, 95% CI 1.5-5.3) compared to patients without TSG alterations. When accounting for age and CCI, risk of death was increased in Veterans with TSG alterations (aHR 3.0, 95% CI 1.6-5.9). **Conclusions:** In US Veterans treated with ^{177}Lu-PSMA-617, median OS was 11.4 months, shorter than observed in other cohorts, although the mean age was higher. Comorbidities were prognostic for mortality and hospitalization while age was not. Veterans who had TSG alterations had significantly shorter OS in unadjusted and adjusted analyses, suggesting that patients with TSG alterations are less likely to benefit from ^{177}Lu-PSMA-617 and could consider different treatment modalities. Prospective studies are needed to identify additional clinical outcomes over time. Research Sponsor: Prostate Cancer Young Investigator Award to MWS; The Rate Elements Skewing Outcomes Linked to Veteran Equity in PCa (RESOLVE PCa) Consortium: Multilevel Modeling to Predict Prostate Cancer Incidence and Aggressiveness to Dr. Garraway and Dr. Maxwell; Department of Defense W81XWH-22-1-0602.

5069 **Poster Session**

A phase I and randomized phase II trial of radium-223 dichloride, peposertib, and avelumab in advanced metastatic castrate-resistant prostate cancer (mCRPC): Phase I results. First Author: Hiram Alberto Gay, Washington University School of Medicine, Department of Radiation Oncology, St. Louis, MO

Background: Ra-223 improves the overall survival in patients with mCRPC to the bone. We assessed the safety of standard-of-care Ra-223 in combination with peposertib, a DNA-dependent protein kinase inhibitor, with or without avelumab, an anti-PD-L1 antibody. **Methods:** Patients with mCRPC and two or more skeletal metastases identified by bone scintigraphy with or without lymph node metastases up to 3 cm in size, but no visceral metastases, were eligible. Progression after progression after at least one androgen receptor pathway inhibitor or taxane was required. Phase 1 consisted of a two-step sequential safety lead-in using a 3+3 design. Step 1 combined 6 standard cycles of Ra-223 (55 kBq/kg), with increasing doses of peposertib: 50, 100, and 200 mg PO bid on days 3-26 of each cycle. Step 2 combined Ra-223 with the maximum tolerated dose of peposertib and added standard avelumab 800 mg IV every 14 days, starting at cycle 2 of Ra-223. **Results:** A total of 9 patients participated in Step 1, where the maximum tolerated peposertib dose of 200 mg PO bid with Ra-223 was deemed tolerable. A total of 6 patients participated in Step 2 and the combination of Ra-223, peposertib at 200 mg PO bid, and standard avelumab was deemed tolerable. Of the 15 patients in Phase 1, none experienced grade 4 or higher treatment-related toxicities, while 7 experienced grade 3 toxicities, including neutropenia (1), anemia (1), cardiac chest pain (1), fall (1), maculopapular rash (2), and lymphopenia (2). The median (Q1, Q3) PSA velocity from the beginning to the end of treatment was lower for Step 2 versus Step 1: 2.1 (-0.1, 4.6) versus 23.5 (18.6, 77.1) ng/mL/month (p = 0.0067). OS and PFS were calculated with the limitation that the Phase 1 was non-randomized. Median OS was not reached for Step 2, as only 1 of 6 patients had died, versus 15.2 months for Step 1, where 8 out of 9 patients had died (p = 0.0537). The patient who died in Step 2 discontinued therapy prematurely after 3 cycles due to progression and survived 15.2 months (the 5 alive completed all 6 cycles). The median radiographic PFS was 7 months for Step 2 versus 12.7 months for Step 1 (p = 0.8910). **Conclusions:** The combination of Ra-223 and peposertib, with or without avelumab was well tolerated. The triplet combination showed the most promising results at this early evaluation. We continue to accrue in the randomized Phase II portion of the trial. Clinical trial information: NCT04071236. Research Sponsor: National Cancer Institute; EMD Serono; CrossRef Funder ID: 10.13039/100004755; Bayer.

5070 **Poster Session**

PSMA-targeted actinium-225 therapy in metastatic castration-resistant prostate cancer (mCRPC): Baseline and follow-up PSMA PET parameters associated with outcomes. First Author: Valentina Marulanda Corzo, Molecular Imaging & Therapeutics, Department of Radiology, Weill Cornell Medicine, New York, NY

Background: Prostate-specific membrane antigen (PSMA) is a validated therapeutic target in mCRPC. 225Ac-J591, an alpha-emitting radionuclide linked to an anti-PSMA antibody, has been studied in several early phase clinical trials. We evaluated baseline and follow-up (12 weeks post 225Ac-J591) PSMA PET metrics (SUVmax, SUVmean, and total tumor volume [TTV]) and their association with biochemical response (PSA50), overall survival (OS), and adverse events. **Methods:** Patients enrolled in phase I dose-escalation trials of 225Ac-J591, either as a single agent (NCT03276572, NCT04506567; n = 87) or in combination (with 177Lu-PSMA-I&T, NCT04886986, n = 18; or pembrolizumab and androgen receptor (AR) inhibitors, NCT04946370 n = 12), were included. 68Ga-PSMA-11 PET metrics were quantified using MIM Encore software. Outcomes assessed included PSA50, OS, and adverse events. Statistical analyses utilized univariate and multivariate logistic regression for PSA50, Cox regression for OS and Kruskal-Wallis and Wilcoxon rank sum tests for adverse events. **Results:** 117 patients were included with a median age of 71 yr and median baseline PSA of 58 ng/mL (range 0.67–9614). Prior therapies included chemotherapy (62%), >1 AR pathway inhibitor (53%), immunotherapy (42%), 177Lu-PSMA (28%), and radium-223 (17%). Metastatic sites included bone (88%), lymph nodes (63%), and visceral organs (29%). High CALGB (Halabi) risk in 56% of patients. Median baseline SUVmax, SUVmean, and TTV on PSMA-PET were 50 (31-85), 8.3 (5.7-11.8), and 308 (105-1066), respectively. Baseline SUVmean (OR 1.13, 95% CI 1.04–1.24, p = 0.006) and SUVmax (OR 1.01, 95% CI 1.00–1.02, p = 0.018) were associated with higher odds of PSA50, though only SUVmean remained significant on multivariable analysis (OR 1.11, p = 0.023). Baseline SUVmean and TTV were associated with OS (HR 0.95, p = 0.025; HR 1.000, p < 0.001), TTV remaining significant on multivariable analysis (HR 1.00, p = 0.007), along with prior chemotherapy (HR 1.45, p < 0.001) and CALGB high risk group (HR 1.84, p = 0.014). In multivariable analysis controlling for injected radioactivity, prior chemotherapy, and CALGB risk, TTV reduction was associated with PSA50 (OR 1.31, 95% CI 1.1–1.7, p = 0.015), but changes in SUVmean or SUVmax were not. Higher baseline TTV was more likely to have higher grade myelosuppression (anemia Gr 3/4 673 vs Gr 1/2 203, Gr0 284, p = 0.041), but less nausea and xerostomia. **Conclusions:** Higher baseline PSMA PET metrics, including SUVmean, SUVmax, and TTV are associated with PSA50 response and survival in patients receiving antibody-delivered alpha emitter 225Ac. Higher TTV, yielding more radionuclide delivery to tumor (most commonly bone) is associated with higher grade myelosuppression. However, the tumor antigen sink effect may decrease exposure to other PSMA+ organs leading to less xerostomia and nausea. Clinical trial information: NCT03276572, NCT04506567, NCT04886986, NCT04946370. Research Sponsor: Weill Cornell Medicine; Prostate Cancer Foundation; U.S. Department of Defense; POINT Biopharma; Merck; U.S. National Institutes of Health.

5071 **Poster Session**

Preliminary phase 2 results of PT-112 monotherapy in late-line metastatic castration-resistant prostate cancer (mCRPC). First Author: Alan Haruo Bryce, City of Hope, Phoenix, AZ

Background: Late-line mCRPC has shown poor outcomes as a result of disease heterogeneity, metastases in bone and viscera including liver, and limited immunotherapeutic options. PT-112 is a novel therapy that inhibits ribosome biogenesis, induces robust immunogenic cell death, concentrates in bone and soft tissue, and previously exhibited clinical activity in patients (pts) with mCRPC. We report the results of a Phase 2 study of monotherapy PT-112 in the late-line mCRPC population. **Methods:** mCRPC pts with ≥3 prior standard of care treatments, including ≥1 androgen receptor pathway inhibitor (ARPI) and 1-2 taxanes with radiographic progression at entry were randomized to one of three dosing arms: Arm 1 (360 mg/m² Q2W), Arm 2 (250 mg/m² Q2W), and Arm 3 (360 mg/m² Q2W in cycle 1, then 250 mg/m² D15 of subsequent 28-day cycles). The primary endpoint was to determine the optimal dosing regimen based on safety and efficacy per FDA Project Optimus. **Results:** Pts on the study (N=111) had a median of 4 prior lines of therapy, 69% with ≥2 ARPis, 59% with 2 taxanes, and 24% with PSMA-Lu-177. At entry, pts had liver metastases (19%), bone-only metastases (28%), and evidence of bone progression (74%). The most common treatment-related adverse events (TRAEs) were fatigue (53%), nausea (42%), and anemia (41%); no G5 TRAEs. Discontinuation due to AEs was 12%. Due to superior balance of efficacy and tolerance at interim analysis, Arms 2 and 3 proceeded to full enrollment, while Arm 1 was discontinued. Safety and efficacy metrics are summarized in Table 1. In the more mature Arm 2, OS in pts without prior cabazitaxel (22 pts) was 16.4m and without cabazitaxel or PSMA-Lu-177 (17 pts) was 20.5m. 4% of pts had confirmed PCWG3 bone progression on study. A signal of immune response was observed via TCR sequencing with a statistically significant 20% increase in the percentage of TCR+ blood cells. **Conclusions:** PT-112 treatment resulted in a manageable and reasonably low rate of G3-4 TRAEs and was active in pts with very late-line mCRPC. The better balance of safety and efficacy in Arms 2 and 3 is indicative of an optimized RP3D. Biomarker responses (ALP, CTC and T cell) may reflect broad activity of PT-112. ctDNA analyses are ongoing. OS duration in these heavily pretreated patients, with low rates of bone progression and symptomatic skeletal events (SSEs) on study, are encouraging and supportive of a Phase 3 study of PT-112 vs standard of care. Clinical trial information: NCT02266745. Research Sponsor: Promontory Therapeutics Inc.

Study metrics.

Metric	Arm 1 (n=19)	Arm 2 (n=46)	Arm 3 (n=46)	All Pts (N=111)
G3-4 TRAEs (% of pts)	47	27	43	37
Adherence of dose regimen for first 2 cycles (% of pts)	42	59	67	59
Disease control rate (SD, PR, or CR) at 4 months (% of pts)	27	28	18	23
Median OS (m)	9.0	9.7	10.0	9.7
Median rPFS (m)	3.6	2.5	3.4	3.4
PSA50 (% of pts)	5	17	12	13
CTC0 (n, % of pts)	3/15 (20%)	5/22 (23%)	8/15 (53%)	16/52 (31%)
≥10% ALP decline (% of pts)	74	41	56	52
SSEs in first 4 months (% of pts)	16	4	2	5

5072 **Poster Session**

Molecular characterization of STEAP1 and -2 in advanced prostate cancer. First Author: Kevin Kayvan Zarrabi, Department of Medical Oncology, Sidney Kimmel Cancer Center, Thomas Jefferson University Hospital, Philadelphia, PA

Background: *STEAP*1 and 2 (six-transmembrane epithelial antigen of prostate) are metalloreductase proteins involved in a variety of biologic processes. *STEAP1/2* are tumor-associated cell surface antigens highly expressed in prostate cancer (PC), although their role in cancer is poorly understood. *STEAP1/2* have emerged as successful targets for adoptive T-cell therapy trials for PC. We employed a multi-omics approach to investigate the molecular features associated with *STEAP1* and *STEAP2* expression in PC. **Methods:** NextGen Sequencing of DNA (592 genes or whole exome) and RNA (whole transcriptome) was performed for PC tumors (n = 7089) submitted to Caris Life Sciences (Phoenix, AZ). PC samples were stratified by *STEAP1/2* mRNA levels into top (high) and bottom quartile (low). Immune cell infiltration in the tumor microenvironment (TME) was inferred by quanTIseq. Transcriptomic signatures of androgen receptor signaling (AR), neuroendocrine classification (NEPC), and interferon gamma signaling (IFN) were calculated. Mann-Whitney U and X2/Fisher-Exact tests were applied where appropriate, with P-values adjusted for multiple comparisons (q< .05). **Results:** Of 7,089 samples, 63.2% were from the prostate; 11.7% from lymph node metastases (LNM); 7.3% from bone; and 17.8% from visceral/soft tissue metastases (V/STM). *STEAP*-1 and -2 were significantly correlated to each other (R= 0.90, p<.001), with significantly higher expression of *STEAP1* observed in primary prostate and LNMs, compared with reduced expression in V/STM (*STEAP1* TPM: 105.2 vs 140.6 vs 91.9 p<.001). Mutations in *AR* (3.8% v 1.9%), *KDM6A* (4.2% v 2.2%), *SPOP* (10.9% v 8.4%) and *ARV*7 (23.0% v 10.5%) were enriched in *STEAP1* high PC (each q<.01). Mutations in *KDM6A* (3.8% v 2.5%) and *ARV*7 (17.6% v 14.3%) were enriched in *STEAP2* high PC (each q<.05). *STEAP1/2* expression negatively correlated with TMB count (R =-0.03, p<.05) and IFN score (R = -0.26, p<.001). Concordantly, fewer proinflammatory immune cell fractions (M1 Macrophages, NK cells, CD4+/CD8+ T cells, myeloid dendritic cells) were observed within the TME of *STEAP1/2* high PC (p<.0001). However, *STEAP1/2* expression correlated positively with the AR signature (R = 0.39, p<.001) and androgen response pathways, while correlating negatively with the NEPC signature (R = -0.15, p<.001). **Conclusions:** PC tumors expressing high *STEAP1/2* display distinct genomic and transcriptomic profiles compared to *STEAP1/2*-low PC, and *STEAP 1/2* expression varies across sites of metastases. Immune biomarkers and immune cell infiltration data suggest that STEAP1/2 may be associated with a cold TME. The recent success of STEAP1-targeting T-cell redirecting therapies mechanisms by which adoptive T-cell strategies may overcome immunosuppressive factors within the TME. Ongoing development of T-cell immunotherapeutics targeting STEAP1 may account for the differential expression profiles in guiding patient selection and combination strategies. Research Sponsor: None.

5073 **Poster Session**

Characterization and impact of B7-H3 (*CD276*) expression across disease states and racial groups in prostate cancer. First Author: Justin Hwang, University of Minnesota, Masonic Cancer Center, Minneapolis, MN

Background: B7-H3 (*CD276*) is an immunomodulatory protein overexpressed in prostate cancer (PC), representing a promising therapeutic target. However, expression of B7-H3 across PC disease states (hormone sensitive [HSPC], castration resistant [CRPC], neuroendocrine [NEPC]) and across races is poorly understood. We analyzed PC samples from a large clinico-genomic database to comprehensively characterize B7-H3 expression and elucidate its therapeutic potential in PC patients. **Methods:** We analyzed 7,682 PC samples with paired DNA/RNA profiling from Caris Life Sciences. Using *CD276* mRNA expression measured by transcripts per million (TPM), samples were stratified into B7-H3-high (>75% centile) or low (<25% centile) groups. Annotations of HSPCs and CRPCs were based on time of biopsy collection relative to first use of androgen deprivation therapies. NEPC was defined histologically (Epstein, AJSP 2014). Transcriptomic alterations were compared using Mann-Whitney U tests. Overall survival (OS) was obtained from insurance claims data and assessed by Kaplan-Meier and Cox proportional hazards analyses. **Results:** B7-H3 was expressed at similar levels across specimen sites (prostate, lymph node, bone, liver, lung). HSPCs and CRPCs had similar levels of B7-H3 expression, but was reduced in NEPCs (TPM = 5.07, 4.96, 4.48; q<0.0001). While B7-H3-high was associated with worse OS in HSPCs (HR 1.32, 95CI 1.14-1.53, p=0.0002), it was associated with better OS in CRPC (HR 0.82, 95CI 0.69-0.97, p=0.018). B7-H3 expression was comparable in white, African American (AA), and Asian patients. However, Asian patients with high B7-H3 had worse outcomes (HR 4.08, 95CI 2.10-7.93, p<0.0001) while AA patients had improved outcomes (HR 0.74, 95CI 0.57-0.97, p=0.027). In co-expression analyses, B7-H3 was positively correlated with AR transcriptional co-factors (*HOXB13*, *FOXA1*) (R=0.59, 0.47; q<0.0001) but had weaker correlations with lineage plastic factors (*EZH2*, *SOX2*, *ASCL1*) (R=0.26, 0.11, -0.02). Further, B7-H3-high correlated with high AR-score and low-NEPC. Given emergent bi-specific therapeutics in PC, we examined co-expression of B7-H3 with other cell surface targets. TROP2 (*TACSTD2*) and NECTIN-4 (*PVRL4*) exhibited the greatest correlation with B7-H3 (R=0.42, 0.40; q<0.0001); whereas PD-L1 (*CD274*), *CTLA4*, *DLL3*, and *CEACAM5* had weaker correlations (R=0.18, 0.08, 0.14, 0.09). **Conclusions:** High B7-H3 expression worsens prognosis in HSPC but improved prognosis in CRPC. Outcomes differed by race, with B7-H3-high Asian patients exhibiting worse OS while AA patients had better OS. The positive correlation between B7-H3 and AR co-factors suggests that B7-H3 is AR-regulated, at least in CRPC. Lastly, bi-specific approaches may be valuable against B7-H3-high tumors, with co-targeting of TROP2 and/or NECTIN-4. Research Sponsor: National Cancer Institute/U.S. National Institutes of Health; R37 1R37CA288972-01.

5074 **Poster Session**

Plasma epigenomic profiling to reveal molecular correlates of response and resistance to 177Lu-PSMA-617 in metastatic castration-resistant prostate cancer (mCRPC). First Author: Jacob E. Berchuck, Winship Cancer Institute of Emory University, Atlanta, GA

Background: The PSMA-directed radioligand therapy, 177Lu-PSMA-617, is the most recent FDA approved therapy in mCRPC. Despite prolonging progression-free survival (PFS) and overall survival (OS) at a population level, response to therapy is heterogeneous and resistance remains poorly understood. Benchmarking molecular correlates of clinical outcomes following 177Lu-PSMA-617 could provide critical insights into predicting response and resistance to therapy. We applied a multimodal epigenomic liquid biopsy platform to plasma samples from mCRPC patients treated with 177Lu-PSMA-617 to characterize molecular features associated with treatment response. **Methods:** Baseline plasma samples were collected from patients with mCRPC at the time of PSMA PET imaging and initiation of 177Lu-PSMA-617 therapy. Epigenomic profiling of genome-wide signals from promoters, enhancers, and DNA methylation was performed on 1 mL of plasma (N=85, ctDNA ≥ 0.5%). Plasma epigenomic signals were analyzed to evaluate pathway activity, their association with treatment response using Cox proportional hazards model and neuroendocrine transformation. Response to 177Lu-PSMA-617 was determined by investigator-assessed clinical-radiographic (CR)-PFS. **Results:** We observed a significant association between predicted PSMA PET SUV_{mean} from plasma epigenomic signals (using a previously derived model) and response to 177Lu-PSMA-617 (hazard ratio [HR] = 0.27, P<0.05). Further, unbiased analysis of plasma epigenomic signal across the genome identified *FOLH1* (the gene encoding PSMA) as being significantly associated with CR-PFS (P<0.05). Low circulating tumor fraction was also independently associated with favorable CR-PFS (HR = 0.42, P<0.05). Pathway analysis identified activation of estrogen signalling and cellular plasticity to be associated with shorter CR-PFS, and immune signalling gene signatures to be associated with longer CR-PFS (all FDR<0.1). A subset of patients (n=4) exhibited increased plasma epigenomic signal at neuroendocrine genes, such as *CHGA*, *DLL3* and *SEZ6*. While too small to draw statistical conclusions, elevated neuroendocrine gene activity in plasma was associated with numerically shorter OS. **Conclusions:** Epigenomic profiling of plasma cfDNA enabled minimally-invasive characterization of molecular correlates of response and resistance, identifying genes and pathways associated with favorable and poor outcomes to 177Lu-PSMA-617 in mCRPC. By providing real-time insights into tumor biology and therapeutic efficacy, this platform supports precision medicine approaches for optimizing outcomes in PSMA-targeted therapies. Research Sponsor: None.

5075 **Poster Session**

Exploring PSMA heterogeneity and alternative targets expression in PSMA-negative prostate cancer. First Author: Yelin Mulati, Department of Urology, Peking University First Hospital, Beijing, China

Background: This study aimed to systematically characterize the heterogeneity of PSMA expression in hormone-sensitive prostate cancer (HSPC) and metastatic castration-resistant prostate cancer (mCRPC), and to explore the expression profiles of alternative well-established tumor-associated antigens (TAAs) in PSMA-negative cases. **Methods:** Formalin-fixed paraffin-embedded (FFPE) real-world clinical samples were retrospectively collected from prostate biopsies and bone metastasis surgeries at Peking University First Hospital from 2013 to 2023. Standard immunohistochemistry (IHC) was performed to evaluate PSMA expression, quantified using membranous H-score (MHscore) and cytoplasmic H-score (CHscore).Intra-patient PSMA expression heterogeneity was assessed by Shannon diversity index (SDI) . The normalized membrane ratio (NMR) was defined as: MHscore / (MHscore + CHscore). PSMA-negative PCa was defined as PSMA MHscore ≤ 20. PSMA-negative samples were further assessed the expression of alternative TAAs: HER2, NECTIN4, TROP2, TF, B7H3 and STEAP1. **Results:** A total of 127 HSPC and 76 mCRPC cases were identified, including 27 pairs of matched samples. High PSMA expression heterogeneity (SDI >1) was observed in 86 (67.7%) HSPC and 23 (30.1%) mPCa, while moderate heterogeneity (0.5<SDI<1) was found in 20 (15.7%) HSPC and 25 (32.9%) mPCa. PSMA-negative cases were identified in 15.0% of HSPC and 36.8% of mCRPC. PSMA MHscore in HSPC was significantly higher than in mPCa (p < 0.001). The expression profiles of alternative TAAs in PSMA-negative cases are shown in Table 1. Additionally, the NMR of PSMA in HSPC was significantly higher than in mPCa (p < 0.001). STEAP1 and B7H3 exhibited consistently high NMR in PSMA-negative cases. No significant correlations were observed between PSMA alteration and novel anti-androgen therapy, chemotherapy, or radiation history in matched samples. **Conclusions:** PSMA expression exhibit notable inter- and intra-patient heterogeneity in both HSPC and mCRPC. B7H3 and TROP2 may have relatively more advantageous expression levels in PSMA-negative HSPC, while B7H3 and STEAP1 may potentially show better complementarity in PSMA-negative mCRPC. Research Sponsor: National High Level Hospital Clinical Research Funding (Interdepartmental Clinical Research Project of Peking University First Hospital), Beijing, China.

The expression profiles of alternative TAAs in PSMA-negative prostate cancer.

TAA	PSMA-negative HSPC (n=19) MHscore median(Q1-Q3)	PSMA-negative mCRPC (n=28) MHscore median(Q1-Q3)	p value					
			HER2	TROP2	NECTIN4	TF	B7H3	STEAP1
HER2	3.2(2.8-3.6)	29.3(11.6-70.3)	-	NS	#	###	NS	##
TROP2	84.8(51.2-137.1)	9.9(3.5-56.1)	***	-	NS	#	##	###
NECTIN4	7.1(6.2-12.9)	3.7(2.8-26.8)	***	***	-	NS	##	###
TF	12.5(9.0-72.0)	3.2(2.6-11.0)	***	NS	*	-	###	###
B7H3	110.0(98.9-133.0)	63.5(40.4-96.0)	***	NS	***	***	-	NS
STEAP1	25.7(9.4-103.1)	66.6(23.4-104.0)	***	NS	*	NS	**	-

*for HSPC #for mCRPC. */# p<0.05, **/## p<0.01,***/### p<0.001; NS: not significant.

5076 **Poster Session**

Comparative effectiveness of cabazitaxel (C) vs. lutetium Lu-177 vipivotide tetraxetan (Lu) in patients (pts) with metastatic castration-resistant prostate cancer (mCRPC). First Author: Zeynep Irem Ozay, Huntsman Cancer Institute at the University of Utah, Salt Lake City, UT

Background: C and Lu are both life-prolonging therapies for pts with mCRPC after progression on androgen receptor pathway inhibitor (ARPI) and docetaxel (D). Herein, our objective was to assess the comparative effectiveness of C vs. Lu in pts with mCRPC with prior progression on D and ARPI in real-world pts in the USA. **Methods:** A de-identified nationwide Flatiron Health electronic health record (EHR)-derived database was used to extract pt-level data. Eligibility: pts with mCRPC who progressed on D and ARPI and received for the first-time single-agent C or Lu. Pts who received alternative Lu or C in a later line of therapy (LOT) were excluded. Endpoints: real-world time to next therapy (rwTTNT) and real-world overall survival (rwOS). These were summarized via Kaplan-Meier survival estimates with a 95% confidence interval (CI) and compared in the context of propensity score (PS) matching weighted analysis using the Cox proportional hazard model. PS model included the following covariates: age, race-ethnicity, socioeconomic status, treatment year, Gleason score, ECOG performance status, log2PSA, alkaline phosphatase, hemoglobin, creatinine, LOT, insurance, and practice type. All the covariates achieved balance after PS matching weighting. **Results:** Among 24,105 pts with metastatic prostate cancer in the dataset, 1,445 met the eligibility criteria and were included (1,227 treated with C, 218 treated with Lu). In C cohort: median age was 73 (IQR 67 – 78), 66.9% had Gleason score $\geq$ 8, and median LOT was 4 (IQR 3-4). In Lu cohort: median age was 75 (IQR 67.25 – 80), 68.1% had Gleason score $\geq$ 8, and median LOT was 4 (IQR 3-5). In PS matching weighting analysis, there was evidence that pts receiving Lu had a significantly improved rwTTNT (median 8.3 months [mo], 95% CI 6.3 – 9.8) compared to those receiving C (median 4.7 mo, 95% CI 4.2 – 5.4) (HR 0.49, 95% CI 0.37 – 0.63, $p < 0.001$), which persisted after adjusting for covariates (HR 0.43, 95% CI 0.32 – 0.57, $p < 0.001$). Additionally, there was evidence that rwOS was longer in pts receiving Lu (median 10.3, 95% CI 8.9 – 12.8) compared to those receiving C (median 8.8 mo, 95% CI 6.6 – 10.8) (HR 0.69, 95% CI 0.51 – 0.92, p = 0.01). This improvement in rwOS with Lu compared to C persisted after adjusting for covariates (HR 0.61, 95% CI 0.44 – 0.84, $p < 0.001$). **Conclusions:** This is the largest real-world data to date assessing the comparative effectiveness of Lu vs. C, and it showed significantly longer rwTTNT and rwOS with Lu compared to C in pts with mCRPC pretreated with ARPI and D. Limitations: retrospective nature, selection bias, missingness, lack of randomization, etc. and residual confounding in real-world datasets. Upon external validation, these findings could guide treatment selection in the clinic and design of clinical trials. Research Sponsor: None.

5077 **Poster Session**

Real-world prevalence of homologous recombination repair alterations (HRRa) and poly (ADP-ribose) polymerase inhibitor (PARPi) use/outcomes in patients (pts) with metastatic prostate cancer (mPC) by race and ethnicity. First Author: Qian Qin, Department of Internal Medicine, Division of Hematology and Oncology, UT Southwestern, Dallas, TX

Background: Racial/ethnic (R/E) disparities in prostate cancer incidence and outcomes have long been noted. Increasing evidence points to underlying genetics/biology as potential drivers, which could influence response to targeted tx such as PARPi. Here, we used real-world evidence (RWE) to assess R/E variations in the prevalence of HRRa and outcomes of PARPi therapies in pts with mPC. **Methods:** This retrospective, RWE study used GuardantINFORM, a deidentified clinical genomic database combining claims and genomic data reported from the liquid biopsies, Guardant360 (G360) CDx (HRRa: *BRCA1/2, ATM, CDK12, MLH1*) and LDT (HRRa: *BRCA1/2, ATM, CDK12, CHECK2, FANCA, MLH1, PALB2, RAD51D*). Pts with mPC, age >18, and tested between July 2014 - Sep 2024 were included and grouped into non-Hispanic Black (NHB), non-Hispanic White (NHW), Asian/Other, and Hispanic (any race) cohorts. HRRa and frequency of PARPi treatment (tx) were assessed with two-sided Fisher's exact tests. Outcomes were assessed for PARPi tx overall, as monotherapy, or in combination with androgen receptor pathway inhibitor (ARPI) using pairwise comparisons and log-rank tests. **Results:** 30,913 pts with G360 liquid testing were identified. The rates of HRRa on the LDT panel were significantly higher for NHW (22.8%) when compared to NHB (18.1%, $p<0.0001$) and Hispanic (19.6%, p=0.017) cohorts. This was similarly seen on the CDx panel for NHW (16.7%) vs. NHB cohorts (15.0%, p=0.018). Similar *BRCA1/2* detection rates (range 5.2-5.8%) and frequencies of PARPi use were observed among R/E groups. No significant differences were observed in real world overall survival (rwOS), time to tx discontinuation, or time to next tx among R/E groups. While not significant, there was a numerical rwOS improvement for NHB when compared to NHW pts treated with PARPi/ARPI combinations (CDx panel, median NR vs. 20.5m, p=0.09), with no NHB pts known to be deceased at the end of follow up (median 10.5 months). **Conclusions:** Using a RWE dataset, we demonstrate distinct rates of HRRa between R/E groups identified using ctDNA analysis. Similar PARPi use among R/E groups suggest tx equity for pts receiving genomic sequencing. The numerically improved rwOS for NHB pts on combination PARPi/ARPI tx is hypothesis generating. This may support other studies demonstrating distinct outcomes in Black vs. White pts treated with ARPI, with potential added benefit in a combination paradigm. Research Sponsor: None.

Cohort	G360, n	LTD: HRRa, %	LTD: PARPi use in HRRa pts, %	CDx: HRRa, %	CDx: PARPi use in HRRa pts, %	LTD+CDx: BRCA1/2+, %	LTD+CDx: PARPi use in BRCA 1/2+ pts, %
All mPC	30,913	21.5	28.0	16.2	29.1	5.6	37.5
NHB	3,216	18.1	30.5	15.0	33.1	5.8	41.9
NHW	19,482	22.8	28.1	16.7	28.8	5.6	38.6
Asian/Other	1,150	20.3	28.9	15.7	28.0	5.7	36.1
Hispanic (any race)	2,152	19.6	30.0	15.3	32.1	5.2	37.5

LBA5078 **Poster Session**

Lower-dose versus standard-dose abiraterone in patients with metastatic castration resistant prostate cancer: A multicentric randomized phase III non-inferiority trial. First Author: Minit Jalan Shah, Tata Memorial Centre, Mumbai, India

The full, final text of this abstract will be available at meetings.asco.org on the day of presentation and in the online supplement to the June 10, 2025, issue of the *Journal of Clinical Oncology*.

5079 **Poster Session**

Assessment of PSMA PET/CT derived predictive markers for ^{177}Lu-PSMA-617 treatment outcomes: Results from the U.S. Expanded-Access program. First Author: Koichiro Kimura, Ahmanson Translational Theranostics Division, Department of Molecular and Medical Pharmacology, David Geffen School of Medicine at UCLA, Los Angeles, CA

Background: ^{177}Lu-PSMA-617 (Lu-PSMA) contributes to prolong progression-free survival (PFS) and overall survival (OS) in metastatic castration-resistant prostate cancer (mCRPC) patients who progressed after chemotherapy. Pretherapeutic prostate-specific membrane antigen (PSMA) PET/CT information can be used to predict Lu-PSMA therapy response patterns and outcomes, with various quantitative and visual methods proposed. We aimed to test various proposed PSMA PET/CT-derived outcome predictors in the U.S. expanded-access program (EAP) cohort. **Methods:** Patients enrolled in the EAP (NCT04825652) for Lu-PSMA at 3 institutions with available pretherapeutic PSMA PET/CT and outcomes were included in this analysis. Quantitative analysis was performed for all tumor lesions on PSMA PET/CT with semi-automatically contouring. Total tumor volume (TV), total tumor SUVmean, total tumor SUVmax, total lesion uptake (TLU = TV * SUVmean), total lesion quotient (TLQ = TV / SUVmean), and quantitative PSMA PET tumor–to–salivary gland ratio (qPSG: high, $\geq$ 1.5; intermediate, 0.5–1.5; low, $\leq$ 0.5) were calculated for each patient. For visual analysis, visual PSG (vPSG: high, most of the lesions showed higher uptake than the parotid glands; intermediate, neither low nor high; low, most of the lesions showed lower uptake than the parotid glands) and heterogeneity and intensity of tumors (HIT: 1, SUVmax $<$ 15; 2, 15–79 with heterogeneous intensity; 3, 15–79 with homogeneous intensity; 4, $\geq$ 80) scores were used for assessment. Outcomes included a prostate-specific antigen (PSA) PFS, and OS. We evaluated the predictive performance of each model using Cox proportional hazards regression analysis and assessed their performance with the concordance index (c-index). **Results:** In total, 88 patients who received Lu-PSMA within the EAP between May 2021 and March 2022 were eligible and included in this analysis. For the PSA PFS, the total tumor SUVmean achieved the highest c-index of 0.678 (HR 0.91 [95% CI, 0.85–0.97], p = 0.004), followed by the total tumor SUVmax with a c-index of 0.640 (HR 0.99 [95% CI, 0.99–1.00], p = 0.034). For OS, the TLQ achieved the highest c-index of 0.658 (HR 1.01 [95% CI, 1.00–1.01], $p < 0.001$), followed by the total tumor SUVmean with a c-index of 0.634 (HR 0.89 [95% CI, 0.83–0.96], p = 0.004). The HIT score showed the third highest c-index of 0.632; however, when using score 1 as the reference, the HR did not exhibit a sequential trend across ordinal categories as anticipated. **Conclusions:** Quantitative analysis outperformed visual analysis in predicting the outcome of mCRPC with Lu-PSMA therapy in the EAP cohort. Total tumor SUVmean was identified as the most robust predictor for PSA PFS, while TLQ showed promise as a predictor for OS. Incorporating these predictors into clinical decision-making for pre-Lu-PSMA therapy could aid in patient selection and treatment planning. Clinical trial information: NCT04825652. Research Sponsor: None.

5080 **Poster Session**

Molecular correlates of response in patients with metastatic castration-resistant prostate cancer treated with olaparib with or without cediranib (NCI9984). First Author: Alok Tewari, Dana-Farber Cancer Institute, Boston, MA

Background: The phase 2 NCI 9984 study (NCT02893917) randomized patients with progressive metastatic castration resistant prostate cancer (mCRPC) 1:1 to the PARP inhibitor (PARPi) olaparib (O) +/- the vascular endothelial growth factor receptor inhibitor (VEGFRi) cediranib (C+O). (C+O) improved radiographic progression free survival (rPFS) compared to (O). Though further development of this combination was precluded in part by toxicity, we hypothesized that defining molecular correlates of response in this study could suggest alternative combination strategies, including alternative VEGFRi, to improve the therapeutic efficacy of PARPi in prostate cancer. **Methods:** Tumor biopsies were reviewed by a pathologist to ensure adequate tumor content. Whole exome DNA sequencing (WES) was performed on pre-treatment biopsies and germline DNA from blood, and RNA sequencing (RNA-seq) was performed on both pre- and on-treatment biopsies. Sequencing data was analyzed using standard computational pipelines to determine tumor-specific DNA variants and gene expression. Mutational signatures were inferred using SigMA, and clonal architecture was inferred using PhylogicNDT. Transcriptome changes were inferred using gene set enrichment analysis and DESeq2. Molecular features were associated with rPFS using descriptive statistics. **Results:** 23 pre-treatment biopsies– 11 (O) and 12 (C+O) – yielded WES data that passed quality control (QC). 62 RNA-seq samples passed QC – 28 (O) and 34 (C+O) – with 30 pair pre-post samples. After stratifying patients with WES data by response above or below the median rPFS for each treatment arm, no genomic alteration was significantly associated with response. We detected evidence of COSMIC mutational signature 3 (Sig3), indicative of HRR deficiency, in 9 pre-treatment samples – 4 (O) and 5 (C+O), only 2 of which contained a *BRCA2* alteration. The presence of Sig3 was not associated with improved rPFS in either treatment arm. RNA-seq demonstrated decreased in HRR and double strand DNA break repair gene sets as well as an increase in interferon signaling with (C+O) treatment. **Conclusions:** Molecular profiling of pre- and on-treatment tumor biopsies confirms prior preclinical observations that the addition of cediranib suppresses the expression of genes associated with HRR, which may explain the improved rPFS of (C+O) treatment relative to (O). No DNA alterations were significantly associated with therapeutic response in this more limited genomic cohort, but we confirm findings from other studies that mCRPC tumors possess mutational signatures of HRR deficiency in the absence of *BRCA2* alterations, which has implications for PARPi deployment in mCRPC. Additionally, our work broadly demonstrates the both the feasibility and sample attrition rate of correlative studies on clinical trials. Research Sponsor: National Cancer Institute.

5081 **Poster Session**

Clinical implications of HER3 overexpression in a diverse patient cohort with prostate cancer. First Author: Hannah Maluvac, University of Illinois, Chicago, IL

Background: Prostate cancer (PCa) contributes to almost 15% of US cancer cases annually with significant racial disparities, where black men are more likely to develop and die from prostate cancer than any other cohort. Previously, we reported that *HER3/ERBB3* overexpression (OE) was enriched in the tumors of Black/ African American patients and was correlated with a unique androgen receptor signature as well as worse clinical outcomes. Here, we evaluate an expanded and more mature patient cohort to understand the effect of HER3 OE on clinical outcomes. In vitro experiments further support the targeting of HER3 in prostate cancer disease. **Methods:** Chart review was performed on a diverse cohort of PCa patients from the University of Illinois Health (n=106). Tempus laboratories performed whole transcriptome RNA sequencing, and HER3/*ERBB3* OE status was determined by Tempus as compared to a reference database. Patients were grouped into HER3 OE and wild-type groups, and clinical outcomes were analyzed between groups using students' t-test and Kaplan Meier plots with the Gehan-Breslow-Wilcoxon test. LNCaP cells were virally transduced with HER3 overexpression and non-targeting control vectors and validated via Western blot. Cell growth was quantified via nuclear fluorescence object count using Incucyte instruments and software. Drug treatment efficacy was validated via Western blot. **Results:** The final cohort (n= 71 Black/AA, 19 white, and 5 other) demonstrated 42% of patients presenting with HER3 OE. A majority of patients presented with de novo metastases (55% of HER3 OE, 45% of HER3 WT). Of patients who initially presented with localized disease, time to metastasis was significantly faster in the HER3 OE group (p=0.04). HER3 OE was also associated with faster time to the development of castration resistance (p=0.02). In preclinical PCa models, HER3 OE cells grew significantly faster than control($p \leq 0.01$), and were less sensitive to enzalutamide($p \leq 0.01$). Additionally, we found that by inhibiting HER3 signaling (patritumab, erlotinib, trastuzumab, capivasertib) PCa cells become more sensitized to enzalutamide($p \leq 0.01$), suggesting a role for dual AR and HER3 targeting in PCa treatment. **Conclusions:** Our clinical and translational data supports the role of HER3 overexpression as a novel and targetable prognostic marker in diverse patients with PCa. Future studies should further evaluate HER3 inhibition in combination with AR targeted therapies to improve therapy sensitivity and reduce development of resistant disease. Research Sponsor: None.

5082 **Poster Session**

Ceramides and response to dual secondary hormonal therapy in metastatic castration-resistant prostate cancer (mCRPC) among Black men. First Author: Jennifer A. Freedman, Duke Cancer Institute Center for Prostate & Urologic Cancers, Durham, NC

Background: Multiple reports suggest that Black patients with mCRPC have different responses to radiation, immunotherapy, chemotherapy, and secondary hormonal therapy compared with White patients with mCRPC. In our prospective trial of combination therapy with apalutamide (Apa) and abiraterone acetate (AA) plus prednisone (P) among Black and White men with mCRPC (PANTHER, ClinicalTrials.gov identifier NCT03098836), we previously reported the 24-month radiographic progression-free survival (rPFS) for Black and White men were 61% (95% CI 49, 78) and 38% (95% CI 27, 54), while the 36-month overall survival (OS) rates were 68% (95% CI 55, 83) and 50% (95% CI 37, 66), respectively. Our previously reported exploratory genome-wide analysis identified genetic ancestry-related single nucleotide polymorphisms in genes that were known to play a role in ceramide metabolism that associated with time to prostate specific antigen (PSA) progression on AA + P therapy in mCRPC. Ceramides are associated with cancer biology and therapeutic outcomes, with ceramide Cer(d18:1/20:0), in particular, having been reported as a biomarker for colon cancer. Ceramide Synthase 4 (CerS4), which produces Cer(d18:1/20:0), has been reported to be associated with worse prognosis in colorectal cancer. We therefore hypothesized that expression of distinct ceramide species may be associated with rPFS or OS among Black and White patients with mCRPC treated with combination Apa and AA + P in the PANTHER study. **Methods:** Serum from 37 White and 28 Black patients enrolled in the PANTHER study who had fasted for 8-12 hours was collected and evaluable at baseline. Metabolomic profiling was done using the Biocrates MxP Quant 500 Kit. Median levels for each of 26 ceramides were calculated using the study population and used as a cut point. Cox proportional hazard models were used to calculate the hazard ratio for rPFS and OS associated with above or below median ceramide expression. Models were stratified by race. **Results:** In the PANTHER study, among Black patients, expression of Cer(d18:1/20:0) was associated with rPFS (HR 4.02; 95% CI 1.06, 15.2; p value = 0.041), but there was no significant association found among White patients. Expression of Cer(d18:1/20:0) was also associated with improved OS among Black patients (HR 4.82; 95% CI 1.51, 15.4; p = 0.008), but there was no significant association found among White patients. No significant associations were found with any other ceramides. **Conclusions:** Our study showed that Cer(d18:1/20:0) associated with prolonged rPFS and OS among Black patients with mCRPC treated with the combination of Apa and AA + P therapy. Pending validation, this distinct ceramide species has potential to serve as a predictive indicator of response to combination Apa and AA + P therapy among Black mCRPC patients. Drug and funding for Abi Race and PANTHER provided by Janssen Scientific Affairs, LLC. Research Sponsor: Janssen Scientific Affairs, LLC; Department of Defense Prostate Cancer Research Program; W81XWH1910458.

5083 **Poster Session**

Integrated CTC- and EV-based detection of PSMA protein and efficacy of ^{177}Lu-PSMA-617 radioligand therapy. First Author: Ali Arafa, University of Minnesota, Minneapolis, MN

Background: Blood-based predictive biomarkers of sensitivity to ^{177}Lu-PSMA-617 are lacking, and may facilitate clinical decisions. Here, we studied whether integrated PSMA protein detection in circulating tumor cells (CTCs) and extracellular vesicles (EVs) is associated with outcomes in patients receiving ^{177}Lu-PSMA therapy. **Methods:** We enrolled 100 metastatic castrate-resistant prostate cancer (mCRPC) pts who were candidates for ^{177}Lu-PSMA into a prospective biomarker trial. Blood samples were collected for CTC and EV analysis at baseline, at the time of response, and at progression. Baseline characteristics included serum PSA, alkaline phosphatase (ALP), hemoglobin, albumin, and radiographic tumor burden. PSMA+ CTCs were enumerated using an AI-empowered holographic imaging platform combined with in-flow protein marker analysis (Astrin Biosciences, St. Paul, MN); PSMA protein was quantified in plasma EVs using shotgun proteomics via mass spectrometry (Arafa et al., *Cancers* 2024; 16: 4261). We assessed the impact of PSMA+ CTCs and EV-derived PSMA protein on PSA_{50} responses, PFS, and OS. Multivariable Cox regressions were used to adjust for baseline PSA, ALP, and hemoglobin. Exploratory analyses of other EV-derived proteins were also conducted. **Results:** Of 100 enrolled pts, 47% had Gleason sum 9-10, 62% had >10 bone mets, 12% had visceral mets, 72% had received ≥3 prior systemic therapies, and median PSA was 57 (range 1.5–5,000) ng/mL. High PSMA+ CTC counts (> median) were associated with shorter overall survival (OS) (HR 2.71, 95%CI 1.18–6.21, p=0.02). PSA_{50} response rates were similar for those with high and low PSMA+ CTC counts (39% vs 42%, p=0.8). Shotgun proteomics from plasma EV samples identified >11 000 unique proteins, of which 12% represented the cell surfaceome. EV-PSMA protein correlated with baseline PSA, ALP, and tumor burden (all $p<0.05$). High EV-PSMA protein (> median) was associated with worse OS (1.81, 95%CI 0.97–3.35, p=0.06). PSA_{50} response rates were similar for those with high and low EV-PSMA protein (48% vs 42%, p=0.5). After multivariate adjustment, nonsignificant trends for shorter OS persisted for pts with high PSMA+ CTCs (HR 1.71, 95%CI 0.72–4.05) and high EV-PSMA levels (HR 1.49, 95%CI 0.78–2.84). Worse OS was also observed in pts with high EV levels of B7-H3 (HR 2.85, 95%CI 1.58–5.14, p=0.002), Trop-2 (HR 2.23, 95%CI 1.22–4.05, p=0.008), and STEAP1 (HR 1.69, 95%CI 0.93–3.06, p=0.08) proteins. **Conclusions:** In mCRPC pts receiving ^{177}Lu-PSMA, high PSMA+ CTC counts and high EV-derived PSMA levels portended poor survival. PSMA protein may be a novel blood-based biomarker of ^{177}Lu-PSMA sensitivity, facilitating treatment decisions, with relevance for other PSMA-targeting strategies. The robust detection and prognostic impact of additional cell-surface proteins (*e.g.* B7-H3, Trop-2, STEAP1) may fuel the development of alternative novel therapeutics. Research Sponsor: The American Cancer Society; Novartis; University of Minnesota Translational Working Group.

5084 **Poster Session**

Transcriptional profiling to identify a program of enzalutamide extreme non-response in lethal prostate cancer. First Author: Anbarasu Kumaraswamy, Rogel Cancer Center, University of Michigan, Ann Arbor, MI

Background: The androgen receptor pathway inhibitor (ARPI) enzalutamide is one of the principal treatments for metastatic hormone-naïve and castration-resistant prostate cancer (CRPC). Most patients respond to enzalutamide. However, tumors from a subset of patients exhibit extreme non-response and are primary refractory to treatment. We sought to understand the gene expression program of enzalutamide extreme non-response (ENR) and identify alternate therapeutic approaches for tumors driven by this program. **Methods:** We analyzed gene expression by RNA-sequencing in pre-treatment metastatic biopsies from men with CRPC treated on a prospective enzalutamide clinical trial (NCT02099864). We focused on those with ENR (progression within 3 months) vs. long-term response (progression after 24 months) and identified a gene program linked to enzalutamide ENR. We validated the utility of this program in additional patient cohorts using a multivariable analysis and in preclinical models. **Results:** Unsupervised clustering correctly classified ENR patients whose tumors harbored proliferative, epithelial-to-mesenchymal transition, and stemness genes sets. Using a supervised approach, we developed a gene signature to measure the ENR program. High expression of this program in CRPC patient validation cohorts was independently associated with poor tumor control with AR targeting in multivariable analysis. Conversely, high expression of the program was independently associated with benefit with docetaxel chemotherapy, suggesting the ENR program is predictive and not merely prognostic. In support of our findings, high expression of the ENR program was strongly linked to docetaxel sensitivity in a large panel of CRPC models. Finally, we identified putative regulators of the ENR program—several of which can be targeted pharmacologically with agents that are FDA-approved or in clinical trials. **Conclusions:** The enza ENR program we identified is independently predictive of ENR to AR targeting. However, patients whose tumors harbor this program may be good candidates for docetaxel chemotherapy or clinical trials testing agents that block putative regulators of this program. Research Sponsor: Stand Up to Cancer-Prostate Cancer Foundation (PCF) Prostate Dream Team; SU2C-AACR-DT0409; National Cancer Institute; R01CA251245, R01CA282005, R01GM147365, T90 DE030859, P50 CA186786; National Comprehensive Cancer Network (NCCN)/Astellas Pharma Global Development, Inc./Pfizer, Inc.; National Comprehensive Cancer Network (NCCN)/Astellas Pharma Global Development, Inc./Pfizer, Inc. Award; U.S. Department of Defense; W81XWH-21-1-0539,W81XWH-22-1-0833, HT94252410252.

5085 **Poster Session**

Integrated analysis of tissue genomic sequencing and high purity circulating tumor cell RNA sequencing for prostate cancer lineage states as a prognostic factor for survival and resistance to 177Lu-PSMA-617 in patients with metastatic castrate resistant prostate cancer. First Author: Marina Nasrin Sharifi, University of Wisconsin, Madison, WI

Background: Genomic mutations, including *RB1*, *PTEN*, and HRR genes, associate with poor prognosis and treatment resistance in metastatic prostate cancer (mPC). mPC lineage states such as neuroendocrine prostate cancer (NEPC) also drive resistance and poor survival. Identifying the timing and association of genomic mutations with lineage states has been limited by the challenges of obtaining serial tumor biopsies. We report an integrated analysis of clinical next-generation sequencing (NGS) data, ctDNA, and mPC lineage state phenotypes with a novel high purity circulating tumor cell (CTC) RNA sequencing method. **Methods:** We collected 273 CTC samples from 117 patients with mPC in a prospective biomarker trial. 69 patients had clinical NGS from a recent tissue biopsy and 60 patients treated with $PSMA^{LU}$. CTCs were purified via immunomagnetic capture on a microfluidic platform and analyzed via RNA-seq. We compared CTC lineage states, somatic mutation status and median overall survival (mOS). **Results:** Gene expression analysis of high CTC purity samples identified four CTC phenotypes: luminal A-like (LumA), luminal B-like (LumB), low proliferation (LP), and neuroendocrine (NE). Compared to patients with low CTC burden/purity (mOS NR), patients with LumA and LP phenotypes had similar survival ((LumA: mOS 13mo, p=ns, LP: mOS: 11.8mo, p=ns), while patients with LumB and NE phenotypes had shorter survival (LumB: mOS 6mo, HR 9.1[3.8-21.8], $p<0.0001$, NE: mOS 3.7mo, HR 11.8[2.4-57.2]), p=0.0019). mOS for patients with high-risk genomic mutations (*RB1*, *PTEN*, *TP53*) and a LumA or LP lineage state was 12.7mo versus 4mo for patients with high-risk mutations and a LumB or NE lineage state (HR 3.59 [1.51-8.51], p=0.004). mOS was not reached for patients without high-risk mutations and a LumA or LP lineage state vs 8mo for patients without high-risk mutations but a LumB or NE lineage state (HR 19.7 [1.99-1.95], $p<0.0001$). Among patients treated with 177Lu-PSMA-617 in a prospective substudy (n=37), no patients had pretreatment CTC NE phenotype, but pre-treatment CTC LumB phenotype was associated with decreased rPFS (3.5mo vs 11.7mo, HR 4.8 [95% CI 1.4-16.1], $p<0.005$) and OS (7.6mo vs NR, HR 9.3 [95% CI 2.3-37.8], $p<0.0005$) compared to pre-treatment LumA/LP/Low CTC burden phenotypes. **Conclusions:** Lineage states detected by high purity CTC RNAseq are prognostic for poor OS and decreased benefit from 177Lu-PSMA-617. The presence of high-risk genetic mutations including *RB1* is prognostic for poor OS and combined evaluation of high-risk genetic mutation status with lineage state phenotype identifies patients with the worst clinical outcomes that would benefit from treatment intensification and early disease monitoring for these more aggressive subtypes of mCRPC. Research Sponsor: None.

5086 **Poster Session**

Association between epigenomic biomarkers and baseline clinical characteristics in patients with mCRPC treated with rucaparib in TRITON2. First Author: Brooke Overstreet, Guardant Health, Palo Alto, CA

Background: TRITON2 is a phase 2 study evaluating rucaparib in 277 patients with metastatic castration resistant prostate cancer (mCRPC). PSA has been used to predict radiographic progression free survival (rPFS), overall survival (OS) and monitor response, however, new approaches are needed to improve performance. Recently, it has been demonstrated that hypermethylated tumor DNA in the peripheral blood can be used to detect and monitor response and as a prognostic marker. Here, we evaluate the association between baseline methylation-based tumor fraction (TF) and clinical outcomes in patients with mCRPC. **Methods:** Pre-treatment plasma samples from patients participating in TRITON2 were sequenced using Guardant Infinity, a next-generation sequencing platform that evaluates genomics and epigenomics with ~15Mb of coverage for methylation-profiling and quantification. TF is calculated from thousands of cancer-type specific differentially hypermethylated regions. Patient outcomes were evaluated using the median-split baseline values for TF and PSA vs rPFS and OS by Cox proportional hazard model. **Results:** Two hundred thirty of 277 patients were eligible for baseline analysis and were successfully sequenced. Methylation-based TF was detected in 229/230 patients (99.6%). TF ranged from 0.02% to 99%, with a median of 25.1%. Baseline methylation-based TF was associated with Gleason score (p=0.012) but was only very weakly correlated with PSA levels (R^2=0.09). Patients with baseline TF $\leq$ median demonstrated superior rPFS and OS vs those $>$ median (HR=0.54, p=0.013; HR=0.42, p= 3.72e-07), respectively. In contrast, baseline PSA was only associated with superior OS (HR=0.52, p=1.31e-04), but not rPFS (HR=0.71, p=0.186). **Conclusions:** In patients from TRITON2, methylation-based TF appeared superior to PSA for tracking disease activity, both in terms of rPFS and OS. This suggests that methylation-based TF is a candidate disease monitoring tool that should be further investigated as a potential replacement for both radiological and PSA-based disease monitoring. Clinical trial information: NCT02952534. Research Sponsor: None.

5087 **Poster Session**

Genomic landscape and clinical characteristics of patients (pts) with neuroendocrine prostate cancer (NEPC) with or without aggressive variant prostate cancer characterized by molecular signature (AVPC-MS). First Author: Hedyeh Ebrahimi, City of Hope Comprehensive Cancer Center, Duarte, CA

Background: NEPC is a rare, aggressive subtype that can arise *de novo* or after treatment with androgen receptor inhibitors. Recent NEPC clinical trials have also included pts who have AVPC-MS (Aggarwal *et al*, ASCO 2024). However, the prevalence and clinical characteristics of NEPC with or without AVPC-MS need further investigation. **Methods:** The de-identified Tempus Lens dataset was used to retrieve records of pts diagnosed with NEPC. Pts were classified as having AVPC-MS if they had $\geq$2 alterations in *TP53*, *RB1*, and/or *PTEN*. Demographic and clinical characteristics were summarized using descriptive statistics and compared between individuals with and without AVPC-MS using chi-square and Fisher's exact tests. The prevalence of genomic alterations between pts with and without AVPC-MS was compared using a two-proportions Z-test with False Discovery Rate (FDR) correction to account for multiple comparisons. **Results:** A total of 308 pts diagnosed with NEPC were identified and included in this analysis. Among them, 124 (40.3%) had *RB1*, 141 (45.8%) had *TP53*, and 64 (20.8%) had *PTEN* alterations. A total of 109 (35.4%) pts met the criteria for AVPC-MS whereas 81 (26.2%) pts harbored only a single alteration in either *TP53*, *RB1*, or *PTEN* and thus did not meet the criteria. The proportion of individuals aged $>$60 years was similar between those with and without AVPC-MS (56.0% vs. 58.8%, p=0.70). Additionally, 48.6% of pts with AVPC-MS were white, compared to 60.8% of those without AVPC-MS (p=0.03). Mortality rates did not significantly differ between the groups (66.1% in AVPC-MS vs. 61.8% in non-AVPC-MS, p=0.40). Individuals with AVPC-MS had significantly higher alterations of *TMPRSS2* (38.5% vs. 18.1%) and *PIK3CA* (8.3% vs. 2.5%) compared to those without AVPC-MS (FDR-adjusted $p < 0.05$). However, no significant difference was observed for alterations in *FOXA1* and *BRCA2* in the AVPC-MS group compared to non-AVPC-MS (10.1% vs. 10.1% and 8.3% vs. 11.1%, respectively). Among pts with available data, high tumor mutational burden (TMB) was observed in 7.8% (8 of 103) of pts with AVPC-MS compared to 2.1% (2 of 97) of those without AVPC-MS (p=0.10). Similarly, microsatellite instability-high (MSI-high) was detected in 6.6% (7 of 106) of pts with AVPC-MS and 1.9% (2 of 106) of those without AVPC-MS (p=0.17). **Conclusions:** Approximately one in three patients with NEPC also meet the criteria for AVPC-MS. Our findings suggest that the biological drivers for NEPC are mutually exclusive from AVPC-MS in most patients, and highlight the importance of utilizing pathologic confirmation of NEPC rather than relying on genomic surrogates. Further research is warranted to explore the clinical implications of these genomic differences and to develop personalized treatment approaches for pts with AVPC-MS. Research Sponsor: None.

5088 **Poster Session**

Triplet versus doublet therapy in older patients with metastatic hormone-sensitive prostate cancer: A network meta-analysis. First Author: Susu Zhou, Mount Sinai West/Morningside, New York, NY

Background: Multiple treatment options are now available for metastatic hormone-sensitive prostate cancer (mHSPC) with the expanded approval of androgen receptor axis-targeted (ARAT) agents. Comparing the therapeutic benefits of these treatments in older patients would contribute to selecting the optimal treatment for this population. **Methods:** We performed a systematic search of PubMed, Embase, Web of Science and Cochrane library for randomized controlled trials (RCTs) evaluating the efficacy of androgen deprivation therapy (ADT) in combination with ARAT agents and/or docetaxel in older patients (aged ≥70 or ≥75 years) with mHSPC. A network meta-analysis (NMA) was conducted to compare and rank the efficacy of the available treatment options. The first NMA compared four treatment classes, grouping ARATs as a single class: ARAT + ADT + docetaxel, ARAT + ADT, ADT + docetaxel, and ADT alone. The second NMA analyzed seven treatment options, treating different ARAT agents as independent regimens: two triplets (abiraterone or darolutamide) + ADT + docetaxel, three doublets (abiraterone, enzalutamide, or apalutamide) + ADT, ADT + docetaxel, and ADT alone. A random effects model was used to estimate hazard ratio (HR) for overall survival (OS) for each treatment. **Results:** 10 RCTs comprising 3,496 patients were analyzed. In the first NMA (grouping ARAT agents as a single class), triplet therapy was associated with a significant 30% lower risk of death compared to ADT + docetaxel (HR 0.70, 95% CI 0.50-0.96), and a non-significant 31% lower risk of death compared to ARAT + ADT (HR 0.69, 95% CI 0.43-1.11). In the second NMA (treating different ARAT agents as independent treatments), darolutamide + ADT + docetaxel was associated with a significant improvement in OS with HRs of 0.47 (95% CI: 0.28-0.78) and 0.61 (95% CI: 0.40-0.94) compared to ADT alone and doublet (ADT + docetaxel), respectively. However, the triplet of abiraterone + ADT + docetaxel was associated with a non-significant OS benefit, with HRs of 0.61 (95% CI 0.36-1.04) and 0.80 (95% CI 0.51-1.25) compared to ADT alone and ADT + docetaxel, respectively. The triplet therapies with darolutamide and abiraterone ranked first and second, with P score of 0.92 and 0.69, respectively, followed by apalutamide + ADT (0.62), enzalutamide + ADT (0.59), ADT + docetaxel (0.42), abiraterone + ADT (0.21) and ADT alone (0.05). Further, our data suggest a clear additional benefit from adding docetaxel as a component of doublet and triplet therapies, as shown by the superiority of ADT + docetaxel over ADT alone (P score 0.42 vs 0.05) and abiraterone + ADT + docetaxel over abiraterone + ADT (P score 0.69 vs 0.21). **Conclusions:** Triplet therapy of darolutamide + ADT + docetaxel should be prioritized over other treatment options for fit older patients with mHSPC. Further research utilizing real-world effectiveness data is essential to validate this recommendation. Research Sponsor: None.

5089 **Poster Session**

Prognostic validation of six androgen production, uptake, and conversion genes (APUC-6) in the CHAARTED prostate cancer trial. First Author: Xiaolei Shi, University of Maryland School of Medicine, Baltimore, MD

Background: Metastatic prostate cancer (mPC), whether synchronous or metachronous, remains incurable. Persistent androgen receptor (AR) activation promotes tumor progression and metastasis and impacts patient survival. A group of six genes (*HSD3B1, HSD3B2, CYP3A43, CYP11A1, CYP11B1, CYP17A1*) involved in androgen production, uptake, and conversion (APUC-6) has been identified, exhibiting cohesive behavior that may define a subset of mPC with distinct clinical outcomes. Our study investigates the association of APUC-6 genes with clinical outcomes in metastatic hormone-sensitive prostate cancer (mHSPC) and their potential to predict differential therapeutic responses. **Methods:** We analyzed APUC-6 and *AR* expression in microarray data from the phase 3 ECOG-ACRIN E3805 CHAARTED trial (n=160). Synchronous high-volume disease patients (n=113 or 70%) composed the majority of profiled cases. Patients were stratified into four subgroups based on APUC-6 and *AR* gene expression: APUC-6 high/*AR* low (n=34), APUC-6 high/*AR* high (n=6), APUC-6 low/*AR* low (n=86) and APUC-6 low/*AR* high (n=34). Key clinical outcomes included progression-free survival (PFS), time-to-castration resistance (ttCR) and overall survival (OS), with subgroup analyses based on the timing of metastasis. **Results:** Standard clinicopathologic factors were balanced between subgroups except lower proportion of patients with Gleason score ≥8 in APUC-6 high/*AR* low subgroup (68.8% versus 81.0%-100% other subgroups).APUC-6 expression was significantly negatively correlated with *AR* expression (R= -0.26, p=0.001). Patients with APUC-6 high/*AR* low expression represented a distinct subgroup that showed significantly improved PFS (median PFS 47.3 months, $p<0.0001$), ttCR (median ttCR 17.3 months, p=0.0011) and OS (median OS 58.1 months, $p<0.0001$) compared to other subgroups, including APUC-6 low/*AR* high (PFS: median PFS 17.7 months, hazard ratio (HR) 0.43, CI 0.22-0.82, p=0.0092; ttCR: median ttCR 12.0 months, HR=0.56, CI 0.32-1, p=0.049; OS: median OS 29.4 months, HR 0.31, CI 0.16-0.61, p=0.00032). Similar survival benefits of APUC-6 high/*AR* low subgroup were observed within patients with synchronous high-volume disease (median PFS 23.1 months, p=0.0022; median ttCR 14.9 months, p=0.021; median OS 57.6 months, p=0.00038). **Conclusions:** In the CHAARTED mHSPC cohort, APUC-6 expression was inversely correlated with *AR* expression. The APUC-6 high/*AR* low subgroup exhibited favorable PFS, ttCR and OS outcomes and maintained the survival benefits in synchronous high-volume disease. These findings suggest that high APUC-6 expression with low *AR* expression may define a favorable-risk mHSPC subgroup with distinct therapeutic implications. Research Sponsor: National Cancer Institute/U.S. National Institutes of Health; U54CA273956; The Movember Foundation; The Distinguished Gentlemen's Ride; The Prostate Cancer Foundation; The Department of Defense; W81XWH-21-1-0296; From an anonymous donor.

5090 **Poster Session**

8-year outcomes of enzalutamide (ENZA) versus a non-steroidal anti-androgen (NSAA) for metastatic, hormone-sensitive prostate cancer (ENZAMET; ANZUP 1304). First Author: Alison Yan Zhang, NHMRC Clinical Trials Centre, University of Sydney, Sydney, NSW, Australia

Background: We previously reported that ENZA improved overall survival (OS) after median follow-up times of 34 and 68 months, in comparison with a NSAA, when added to testosterone suppression, with or without concurrent early docetaxel, for mHSPC. We now report outcomes after median follow-up of 98 months. **Methods:** Participants (pts) with mHSPC were randomly assigned (1:1) from 31MAR2014-24MAR2017 to treatment with ENZA 160 mg or NSAA, in addition to testosterone suppression. Concurrent early docetaxel was used in 45%. OS was the primary endpoint and analysed with the Kaplan-Meier method, log-rank test for p-values, and Cox regression for hazard ratios (HR). Secondary outcomes included deaths due to prostate cancer (PC) versus (vs) other causes. The numbers of pts experiencing specified adverse events (AE) of grade 3-5 are expressed per 100 person-years of study treatment exposure to account for differing treatment durations. **Results:** After a median follow-up of 98 months, data cut-off 30JUN2024, death was reported in 285/563 (51%) pts assigned ENZA vs 337/562 (60%) assigned NSAA. OS was longer among those assigned ENZA than NSAA (medians 95 vs 70 months; OS at 96 months 50% vs 40%; HR 0.73, 95% CI 0.63 to 0.86; p=0.0001). Clinical PFS also continued to favour ENZA over NSAA (HR 0.49; 95% CI 0.42 to 0.57; p<0.0001). PC accounted for 468 of all 622 deaths, and were less frequent among those assigned ENZA than NSAA (207 vs 261). Deaths due to other causes accounted for a total of 154 deaths, and were similarly frequent among those assigned ENZA vs NSAA (78 vs 76). Mean duration of study treatment was longer for ENZA than NSAA (58 vs 36 months). 185/562 (33%) remain on ENZA with 88% on full dose. G3-5 AE of interest were reported in the following numbers of pts per 100 years of study treatment with ENZA vs NSAA: cardiac disorder 2.2 vs 2.2, nervous system disorder 2.3 vs 2.0, fall 0.70 vs 0.24. Causes of death according to PSA at 7 months are tabulated below. Among those with PSA at 7 months ≤0.2, deaths were due to PC in 29%, and other causes in 13%. Among those with PSA at 7 months >0.2, deaths were due to PC in 60%, and other causes in 13%. **Conclusions:** Treatment with enzalutamide continues to confer substantial OS benefits at 8 years. These findings highlight long-term safety, toxicities, non-PC causes of death, and survival outcomes of those with and without PSA ≤0.2 at 7 months. ClinicalTrials.gov Identifier NCT02446405. Clinical trial information: NCT02446405. Research Sponsor: Astellas; Cancer Council Australia; The Australian and New Zealand Urogenital and Prostate Cancer Trials Group (ANZUP).

Landmark analysis by PSA at 7 months	ENZA (N=555)	NSAA (N=549)	ALL (N=1104)
Deaths due to prostate cancer, PSA ≤0.2	100/375 (27%)	87/270 (32%)	187/645 (29%)
Deaths due to other causes, PSA ≤0.2	54/375 (14%)	33/270 (12%)	87/645 (13%)
Deaths due to prostate cancer, PSA >0.2	104/180 (58%)	170/279 (61%)	274/459 (60%)
Deaths due to other causes, PSA >0.2	22/180 (12%)	39/279 (14%)	61/459 (13%)

5091 **Poster Session**

Prognostic value of PSMA PET against CHAARTED criteria in an ENZAMET sub-cohort. First Author: Zahra Sabahi, St Vincent's Hospital Sydney and Garvan Institute of Medical Research, Sydney, Australia

Background: CHAARTED criteria using CT and bone scan are widely recognized as prognostic in metastatic, hormone-sensitive prostate cancer (mHSPC) and can guide decisions about treatment, including intensification. However, clinicians are increasingly using PSMA PET/CT (PSMA-PET) instead of conventional imaging. Currently, PSMA-PET criteria for identifying poor prognostic mHSPC has limited evidence. The aim of this study is to identify features on PSMA PET/CT that correlate to progression free survival (PFS) and overall survival (OS) in the context of CHAARTED criteria in an ENZAMET sub-cohort. **Methods:** ENZAMET (ANZUP 1304, NCT02446405) is an international, open-label, randomized, phase 3 trial. Eligible participants had mHSPC evident on CT and/or bone scan. Participants (pts) were randomly assigned (1:1) to receive testosterone suppression plus enzalutamide or a non-steroidal antiandrogen (NSAA). Pts who underwent PSMA-PET prior to study enrolment were identified for this substudy. Imaging (PSMA-PET, CT, bone scan) were de-identified, and centrally evaluated by three imaging experts blinded to clinical outcomes for number, site, and intensity of metastatic deposits. Additional correlative findings on bone scan and PSMA-PET/CT were determined. A semi-automated quantitative imaging analysis was undertaken to derive PSMA-total tumor volume (PSMA-TTV). The analysis evaluated the association between PSMA-TTV (analysed continuously and as quartiles Q1-3 vs Q4), site (lymph node, bone, viscera) with PFS, OS, and CHAARTED criteria. Kaplan-Meier survival estimates, log-rank tests, and Cox regression after adjusting for treatment arm were used for analysis. **Results:** 100 pts (51 enzalutamide, 49 control NSAA) had a PSMA-PET/CT prior to enrolment. In this sub-cohort, median age was 69 years, 36 were synchronous, 74 patients were low volume on CHAARTED criteria. On PSMA-PET 19 pts had bone only disease, 37 had lymph node (LN) only, 33 bone and LN and 9 visceral involvement. In 54 pts with bone involvement on PSMA-PET, 53 had concordant findings on bone scan. Median PSMA TTV in the study cohort was 28 mL (61 mL vs 22 mL in CHAARTED high vs low volume) with the highest PSMA TTV quartile (Q4) >71mL. 5-year PFS for PSMA TTV Q4 vs Q1-3 was 36% vs 61% (p=0.011), with HR per doubling of TTV = 1.19 (95%CI: 1.03 – 1.38). In the pts with CHAARTED criteria low volume mHSPC, 5-year PFS for PSMA TTV Q4 vs Q1-3 was 21% vs 57% (p<0.001). 5-year OS for PSMA TTV Q4 vs Q1-3 was 60% vs 74% (p=0.18) with HR per doubling of TTV = 1.10 (95%CI: 0.91 – 1.32). **Conclusions:** PSMA-TTV is associated with PFS in mHSPC in this ENZAMET sub-cohort with the highest volume quartile (>71mls) showing significantly shorter PFS, including within the CHAARTED criteria low volume cohort. Further validation of PSMA-TTV as a prognostic biomarker with potential to identify patients for intensification is warranted in larger mHSPC cohorts. Clinical trial information: NCT02446405. Research Sponsor: Astellas; Cancer Council Australia; The Australian and New Zealand Urogenital and Prostate Cancer Trials Group (ANZUP).

5092 Poster Session

How low do you need to go? Association between various prostate-specific antigen (PSA) response measures and clinical outcomes in metastatic castration-sensitive prostate cancer (mCSPC) in the Veteran Health Administration (VHA) data. First Author: Stephen J. Freedland, Cedars-Sinai Medical Center, Los Angeles, CA; Durham VA Medical Center, Durham, NC

Background: Clinical trials show that combined treatment (tx) with androgen deprivation therapy (ADT) and androgen receptor pathway inhibitors (ARPIs) improves PSA response and overall survival (OS) in patients (pts) with mCSPC. Our real-world study assessed the impact of PSA response on OS and progression in pts receiving ADT ± other tx. **Methods:** VHA data (2017–2024) were analyzed for adults with mCSPC who initiated index tx, ie, ADT ± other tx (ARPI, nonsteroidal antiandrogen [NSAA], docetaxel), and had PSA values at baseline (365 days prior to ADT initiation [index date]) and during index tx. PSA response was examined as: 1) ≥90% decline from baseline PSA; 2) PSA <0.2 ng/mL during index tx. Progression was defined as PSA progression (≥25% rise and ≥2 ng/mL increase from nadir PSA during PSA follow-up [index date to 8/31/2024]), initiation of a new tx, hormone resistance or death. Landmark analyses with Cox proportional hazards regressions assessed the association of PSA response (by 9 months [mo] post index date) with OS and time to progression after 9 mo post index date. **Results:** Overall, 4890 pts started first line mCSPC tx: ADT alone, 47%; ADT + ARPI, 40%; ADT + NSAA, 7%; ADT + docetaxel (± ARPI ± NSAA), 6%. Median follow-up was 24.7 mo, with a median PSA follow-up of 14.6 mo. During PSA follow-up, 44% of pts reached PSA <0.2 ng/mL and 74% had ≥90% PSA decline from baseline. PSA decline of ≥90% was related to a 22% reduced risk of death but was unrelated to progression (Table). In contrast, PSA <0.2 ng/mL was associated with greater reduction in the risk of death (54%) and progression (55%). **Conclusions:** In a real-world mCSPC setting, pts who achieved PSA <0.2 ng/mL within 9 mo of initiating ADT ± other tx had lower risk of death and progression than pts who did not. Reaching ≥90% PSA decline was modestly associated with improved OS but not progression, suggesting a PSA nadir of <0.2 ng/mL is needed for optimal outcomes. Disclosure: A genAI tool (01/09/25; Pfizer; GPT-4o) developed the 1st draft; authors assume content responsibility. Research Sponsor: The study was sponsored by Pfizer Inc. and Astellas Pharma Inc., the co-developers of enzalutamide. Medical writing support was provided by Roham Sadeghimakki and Rosie Henderson of Onyx (a division of Prime, London, UK), funded by the sponsors.

	≥90% PSA decline		PSA <0.2 ng/mL	
	Achieved	Not achieved†	Achieved	Not achieved†
OS‡§				
Pts at risk, n	2609	683	1512	1780
Events, n (%)	672 (26)	224 (33)	236 (16)	660 (37)
Median (95% CI), mo	NR (53, NE)	50 (39, NE)	NR (NE, NE)	37 (33, 42)
HR (95% CI); *P* value	0.78 (0.66, 0.91); <0.001	–	0.46 (0.40, 0.54); <0.001	–
Time to progression§‖				
Pts at risk, n	2395	569	1444	1520
Events, n (%)	1060 (44)	271 (48)	440 (31)	891 (59)
Median (95% CI), mo	27 (24, 29)	26 (20, 32)	51 (44, 57)	15 (13, 16)
HR (95% CI); *P* value	0.93 (0.81, 1.06); 0.28	–	0.45 (0.40, 0.50); <0.001	–

†Comparator group.
‡Time from post-index day 270 to death.
§Adjusted for age, race, region, index year, log of time from metastasis to index date, site of metastasis and comorbidities.
‖Time from post-index day 270 to first evidence of disease progression.

5093 Poster Session

Association of circulating immune and metabolic markers with clinical outcomes in the ENZAMET trial (ANZUP 1304). First Author: Lisa Horvath, Chris O'Brien Lifehouse, University of Sydney, Sydney, NSW, Australia

Background: ENZAMET showed that enzalutamide (ENZ) significantly improves overall survival (OS) of metastatic hormone-sensitive prostate cancer (mHSPC) compared to conventional non-steroidal anti-androgen (NSAA). However, intrinsic and acquired resistance to ENZ are ongoing problems. In the CHAARTED mHSPC cohort, elevated circulating IL8 and IGFBP1, and a low IGF1:IGFBP1 ratio, were associated with shorter OS and shorter time to castration-resistance. The aim of this study was to confirm the prognostic association of IL8, IGFBP1, and IGF1:IGFBP1 in mHSPC, and also explore the relationship of a set of immune markers with ENZ treatment by post-hoc analysis of ENZAMET. **Methods:** Baseline plasma levels of IL8, IGF1, IGFBP1, C-reactive protein (CRP), and 14 other cytokines were profiled in 852 participants of ENZAMET (ENZ n=420; NSAA n=432) using Milliplex antibody assays (Merck). The association of these markers with OS and clinical progression-free survival (cPFS) was assessed by Cox regression. **Results:** In the whole study cohort, we confirmed that high IGFBP1 and IL8, and low IGF1:IGFBP1 were significantly associated with shorter OS and shorter cPFS (p≤0.029). High CRP, CXCL16, IL6, MIC1 and YKL40, and low IL28A were also associated with shorter OS (p≤0.015). These markers were independently associated with OS in multivariable analysis with treatment arm, volume of disease, concurrent docetaxel, and presence of visceral metastases (p≤0.047, Table). None of these markers were predictive of ENZ response. In subgroup analyses by treatment arm, IGFBP1 and IGF1:IGFBP1 were prognostic in the ENZ arm (OS p≤0.042, cPFS p≤0.02) but not in NSAA (OS p=0.08, cPFS p≥0.2). IL8 was prognostic in the NSAA arm (OS p=0.02, cPFS p=0.006) but not in ENZ (OS p=0.5, cPFS p=0.5). MIC1 was the only marker that was prognostic in both treatment arms (OS & cPFS p≤0.002). **Conclusions:** These data validate IL8, IGFBP1, and IGF1:IGFBP1 as prognostic biomarkers in mHSPC. Furthermore, pro-inflammatory and macrophage-associated cytokines are associated with poorer clinical outcomes. Clinical trial information: NCT02446405. Research Sponsor: Astellas; Cancer Council Australia; The Australian and New Zealand Urogenital and Prostate Cancer Trials Group (ANZUP).

Hazard ratio (HR) for OS from univariable analyses and multivariable analyses with clinical variables.

Variable (log2)	HR (95% CI) from univariable analysis	P-value	HR (95% CI) from multivariable analysis with clinical variables	P-value
IL8	1.10 (1.01-1.19)	0.029	1.09 (1.00-1.18)	0.047
IGFBP1	1.12 (1.04-1.21)	0.004	1.10 (1.02-1.18)	0.018
IGF1/IGFBP1	0.94 (0.90-0.98)	0.008	0.94 (0.90-0.98)	0.004
CXCL16	1.43 (1.10-1.84)	0.007	1.31 (1.04-1.65)	0.020
CRP	1.10 (1.05-1.16)	<0.001	1.08 (1.03-1.14)	0.002
IL6	1.13 (1.07-1.20)	<0.001	1.10 (1.04-1.17)	0.001
MIC1	1.39 (1.23-1.58)	<0.001	1.23 (1.08-1.40)	0.002
YKL40	1.19 (1.08-1.32)	<0.001	1.17 (1.06-1.29)	0.001
IL28A	0.93 (0.88-0.99)	0.015	0.91 (0.86-0.97)	0.002

5094 Poster Session

Impact of somatic/germline homologous recombination repair (HRR) alterations on metastatic hormone-sensitive prostate cancer (mHSPC) outcomes by disease volume. First Author: David Olmos, Hospital Universitario 12 de Octubre. Instituto de Investigación Sanitaria Hospital 12 de Octubre, Madrid, Spain

Background: The impact of HRR mutations in castration-resistant prostate cancer has previously been reported, but their role in mHSPC patients (pts) contemporaneously treated has not been established. Here we report the prevalence of somatic/germline HRR mutations, and their effect on the outcomes in mHSPC pts stratified by CHAARTED disease volume and BRCA/HRR alterations. **Methods:** Eligible mHPSC pts diagnosed between Jan. 2018 and Dec. 2023 underwent paired somatic/germline DNA sequencing. Cases with alterations in ≥1 HRR gene were hierarchically classified as BRCA, non-BRCA, HRR non-BRCA, or non-HRR. Radiographic progression free survival (rPFS), time to castration resistance (TTCR), and overall survival (OS) were reported for all subgroups; associations between mutations and outcomes were assessed using inverse probability of treatment weighting (IPTW) models, which were controlled for treatment modality and other baseline characteristics. **Results:** Of 556 pts, 69 (12.4%) harbored alterations in *BRCA1* and/or *BRCA2* genes (BRCA) and 90 (16%) had alterations in HRR non-BRCA genes. mHSPC was synchronous in 451 pts (81.1%) and was classified by conventional imaging as high-volume (HV) in 306 (55%) and low-volume (LV) in 250 (45%) pts as per CHAARTED criteria. Most pts (44.8%) were treated with androgen deprivation therapy (ADT)+androgen-receptor-pathway inhibitor (ARPi), 30.4% received docetaxel (Doc)+ADT, and 11.3% were treated with ADT+ARPi+Doc. Only 13.5% received ADT alone. Baseline pt characteristics and treatments administered were similar across all subgroups after adjustment. BRCA pts had significantly shorter rPFS, TTCR, and OS compared with non-BRCA in all groups (Table) using IPTW models. Similar significant differences were observed when BRCA pts were compared with HRR non-BRCA pts, but no clinically relevant differences were observed between HRR non-BRCA and non-HRR pts. **Conclusions:** Presence of BRCA mutations significantly worsened survival outcomes in HV and LV mHSPC treated with doublet or triplet therapy or ADT alone. Research Sponsor: Janssen; Fundación CRIS; 19-26; Instituto de Salud Carlos III; PI22/01593, PI19/01380.

Outcomes	ALL BRCA (n=69) vs non-BRCA (n=487)	HV BRCA (n=42) vs non-BRCA (n=264)	LV BRCA (n=27) vs non-BRCA (n=223)
rPFS			
Median (95% CI)[a]	14.6 (12.4–16.8) vs 30.6 (27.8–36.6)	13.0 (11.2–16.4) vs 21.5 (19.0–28.6)	16.0 (12.5–28.8) vs 43.0 (35.0–54.7)
HR (95% CI)	2.4 (1.8–3.3)**	2.1 (1.4–3.0)*	3.7 (2.3–5.8)**
TTCR			
Median (95% CI)[a]	11.5 (10.1–14.6) vs 22.9 (20.4–26.9)	10.9 (9.6–12.4) vs 17.0 (14.5–20.2)	13.8 (9.8–18) vs 35.9 (26.9–43.0)
HR (95% CI)	2.2 (1.7–3.0)**	1.9 (1.3–2.7)*	3.6 (2.3–5.5)**
OS			
Median (95% CI)[a]	26.4 (24.0–34.6) vs 55.2 (50.2–62.5)	25.0 (17.8–33.1) vs 41.4 (33.4–52.8)	34.6 (24.0–50.0) vs 71.6 (62.5–78.5)
HR (95% CI)	2.7 (2.0–3.6)**	2.5 (1.7–3.5)**	3.4 (1.8–6.5)*

*p<0.05; **p<0.0001.
[a]Observed, in months.
CI, confidence interval; HR, hazard ratio.

5095 Poster Session

^{177}Lu-PSMA-617 consolidation therapy post docetaxel in patients with de-novo high-volume metastatic hormone-sensitive prostate cancer: A randomized, phase 2 trial. First Author: Ashwani Sood, Department of Nuclear Medicine, PGIMER, Chandigarh, India

Background: De-novo high-volume metastatic hormone-sensitive prostate cancer (mHSPC) presents a therapeutic challenge with a dismal five-year survival rate. Till recently, androgen deprivation therapy (ADT) with docetaxel had been the standard-of-care for such patients. Nevertheless, a substantial proportion of patients continue to harbour residual disease after completion of docetaxel. ^{177}Lu-PSMA-617 has shown positive survival outcomes in the metastatic castrate-resistant setting. Here, we intended to evaluate the role of upfront ^{177}Lu-PSMA-617 as consolidation therapy for residual disease following docetaxel in de-novo high-volume mHSPC patients. **Methods:** This was an investigator-initiated randomized, parallel-group, open-label, phase 2 trial. Patients with de-novo high-volume mHSPC who were initiated on ADT plus docetaxel (75 mg/m^2/cycle x 6) and had residual non-progressive disease after completion of six cycles of docetaxel (defined as serum PSA >0.2 ng/mL with PSMA-positive disease on ^{68}Ga-PSMA-11 PET/CT) were randomized in 1:1 ratio to the experimental arm (^{177}Lu-PSMA-617, 7.4 GBq/cycle x 2, 6 weeks apart with continued ADT) or control arm (continued ADT only). The primary end-point was the proportion of patients achieving a serum PSA of ≤0.2 ng/mL at 6 months from randomization. Major secondary end-points included radiographic progression-free survival (rPFS), PSA-PFS, and treatment-emergent adverse events (TEAEs). A total sample size of 78 patients was estimated to be recruited assuming a 30% improvement in the primary end-point in the experimental arm with two-sided alpha of 5% and power of 80%. **Results:** The trial was terminated early due to poor accrual COVID-19 pandemic and following the change in standard of care from doublet to triplet therapy incorporating an androgen-receptor pathway inhibitor along with ADT plus docetaxel. Thirty high-volume mHSPC patients (15 in each arm) were recruited between January 2021 and May 2024. The primary end-point was achieved in 9/15 (60%) patients in the experimental arm versus 2/15 (13.3%) patients in the control arm (risk ratio: 4.5, 95% CI: 1.2-17.4, p=0.008). The median rPFS was 18 months in the experimental arm versus 9 months in the control arm, while the median PSA-PFS were 15 months and 9 months, respectively. No major grade 3/4 TEAEs were seen in the experimental arm. **Conclusions:** In de-novo high-volume mHSPC patients treated with docetaxel and having residual disease, ^{177}Lu-PSMA-617 consolidation therapy demonstrated remarkable efficacy in terms of biochemical response. Larger phase 3 trials are needed to definitively establish its survival benefits. Clinical trial information: CTRI/2021/01/030267. Research Sponsor: None.

5096 **Poster Session**

Real-world patient (pt) characteristics, treatment patterns, and overall survival (OS) in metastatic hormone-sensitive prostate cancer (mHSPC): Insights by *PTEN* status. First Author: Dana Rathkopf, Memorial Sloan Kettering Cancer Center, New York, NY

Background: The loss of function of the tumor suppressor gene *PTEN* is associated with an increased risk of recurrence and poor clinical outcomes in advanced prostate cancer (PC). Current understanding of *PTEN* prevalence and pt characteristics, treatment patterns, and survival outcomes by *PTEN* status in mHSPC is limited. **Methods:** This cohort study used retrospective longitudinal data from the US-based deidentified Flatiron Health-Foundation Medicine mPC clinicogenomic database. Male pts diagnosed (dx) with mHSPC between January 1, 2018, and March 31, 2024, who underwent comprehensive genomic profiling of a solid tumor specimen were included. Pts with *PTEN* alterations were classified as *PTEN*-homs del (homozygous deletion, defined as a copy number variant [CNV]=0) or *PTEN*-mut (CNV=1, pathological short variant alterations or rearrangements). Pts without *PTEN* alterations identified were classified as *PTEN*-nonaltered. Pt characteristics and treatment patterns were descriptively analyzed. Kaplan-Meier survival probabilities for real-world overall survival (rwOS; unadjusted) were estimated by *PTEN* status (*PTEN*-homs del, *PTEN*-mut, and *PTEN*-nonaltered). **Results:** Of 1630 included pts, 39.8% had tumors with *PTEN* alterations (*PTEN*-homs del, 23.2%; *PTEN*-mut, 16.6%). Overall, pts were predominantly non-Hispanic White with a mean (SD) age of 69 (9.1) years at mHSPC dx. At initial dx, 66.7% presented with a Gleason score of 8 to 10, and 68.1% had de novo metastatic disease. Median (IQR) prostate-specific antigen level (ng/mL) at metastatic diagnosis was lower in *PTEN*-homs del (47 [9-193]) and *PTEN*-mut (42 [11-157]) mHSPC relative to *PTEN*-nonaltered (68 [15-337]) mHSPC. *BRCA* mutations were less frequent in *PTEN*-homs del (6.1%) tumors relative to *PTEN*-mut (9.6%) and *PTEN*-nonaltered (10.3%) tumors. All other pt characteristics were generally similar across *PTEN* groups. The most common first-line treatments across all *PTEN* groups were ADT alone and ARPI ± ADT. Median (95% CI) rwOS (months) was 29.0 (24.1-33.6) in *PTEN*-homs del, 32.7 (27.8-37.9) in *PTEN*-mut, and 42.3 (38.7-46.0) in *PTEN*-nonaltered mHSPC groups. Pts with *PTEN* alterations tended to have lower landmark survival probabilities than pts without *PTEN* alterations (Table). **Conclusions:** Among pts with mHSPC, worse survival was observed in pts with tumors harboring *PTEN* alterations relative to pts without *PTEN* tumor alterations, despite similar pt characteristics and treatment patterns across *PTEN* groups. Research Sponsor: AstraZeneca.

rwOS probability, % (95% CI)	*PTEN*-homs del (n=378)	*PTEN*-mut (n=271)	*PTEN*-nonaltered (n=981)
12 month	81.6 (76.0-87.6)	83.9 (77.9-90.4)	90.7 (88.2-93.4)
24 month	56.8 (50.6-63.7)	64.4 (57.5-72.0)	73.8 (70.3-77.4)

5097 **Poster Session**

Outcomes of initial vs delayed docetaxel therapy in veterans with metastatic hormone sensitive prostate cancer and high volume of disease. First Author: Jasnoor Malhotra, Saint Louis University School of Medicine, St. Louis, MO

Background: Docetaxel (DOC) continues to demonstrate efficacy in metastatic hormone sensitive prostate cancer (mHSPC), particularly in combination with androgen deprivation therapy (ADT) ± androgen receptor pathway inhibitors (ARPI). However, a paucity of data exists evaluating treatment sequencing with DOC for patients with high volume disease. We assessed overall survival (OS) of patients with mHSPC treated with either DOC followed by ARPIs or ARPIs followed by DOC. **Methods:** A nationwide retrospective study of 696 US Veterans with de novo (synchronous) mHSPC who received both DOC and an ARPI in combination with ADT in the Veterans Health Administration between 2015-2023. Of these, 581 (83.5%) had high-volume disease. Patients either received DOC (1) within 4 months of and (2) greater than 4 months after ADT. The early DOC group received an ARPI after the initial 4 months while the late DOC group received an ARPI within 4 months of ADT. Age, baseline PSA, Charlson comorbidity index (CCI) and BMI values were acquired for each patient. Survival analysis was performed using the Kaplan-Meier method. **Results:** Of the 581 Veterans with high-volume disease, 400 received DOC early (68.8%) and 181 received DOC later (31.2%). Patients who received DOC early had a significantly longer OS than those who received it later (median 36.3 vs 29.3 months, $p<0.001$, HR 0.65, 95% CI 0.53-0.80). Findings were similar when adjusted for age, baseline PSA, and CCI (aHR 0.69, 95% CI 0.56-0.85). Additionally, patients who received DOC early had a significantly longer rwPFS than those who received it later (median 17.0 vs 12.5 months, $p<0.001$, HR 0.63, 95% CI 0.52-0.76). Findings were similar when adjusted for age, baseline PSA, and CCI (aHR 0.64, 95% CI 0.53-0.78). Evaluation of baseline characteristics between DOC vs ARPI combination therapy showed that the early DOC group was younger (mean 66.4 vs 69.6 years, $p<0.001$). However, no other statistically significant differences were found between the two groups when comparing baseline PSA, BMI, and CCI. **Conclusions:** Initial DOC in Veterans with de novo high volume mHSPC was associated with longer survival. While all patients were candidates for chemotherapy, the Veterans who were treated early with DOC were younger. These finding support early docetaxel in patients with aggressive disease that are likely to develop castration-resistance and require subsequent therapies. Research Sponsor: None.

Patient characteristics.

	Docetaxel Early (n=400)	Docetaxel Late (n=181)	p-value
Age (mean)	66.4	69.6	< 0.001
Baseline PSA (median)	174	217	0.23
Creatinine Value (median)	1.00	1.02	0.1
BMI (mean)	28.7	28.0	0.06
Charlson Comorbidity Index (mean)	1.66	1.90	0.36

5098 **Poster Session**

Prospective monitoring of prostate specific membrane antigen–positive biochemically recurrent prostate cancer (PSMA+ BCR): Preliminary data from 6-month PSMA follow-up. First Author: Ravi Amrit Madan, Genitourinary Malignancies Branch, Center for Cancer Research, National Cancer Institute, National Institutes of Health, Bethesda, MD

Background: PSMA imaging can identify recurrent prostate cancer after definitive surgery/radiation prior to detection on computed tomography (CT) or bone scan. Radiation to PSMA+ findings is common but lacks clear data demonstrating long term benefit. PSMA+ biochemically recurrent prostate cancer (PSMA+ BCR) is often defined and treated as metastatic castration sensitive prostate cancer (mCSPC), yet PSMA imaging alone as an eligibility criteria was never studied in the mCSPC trials. PSA+ BCR requires better understanding to define at-risk patients (pts). **Methods:** NCT05588128 enrolls pts after definitive and possibly salvage therapies. Pts are required to be 1 year removed from definitive therapy with a PSA>0.5 ng/ml, testosterone>100 ng/dL, and negative CT/bone scans. Lymph nodes (LNs) up to 1.5 cm and prior therapies are permitted. At enrollment pts have a baseline PSMA, which is repeated every 6 months (mos) if positive. If negative PSMA is done annually. CT and bone scan are also repeated annually. Pts are allowed to have radiation therapy or systemic therapies for ≤6 mos and remain on-study. Up to 350 pts will be enrolled and followed for up to 5 years. **Results:** Over 120 pts have enrolled since 3/2023 and 86 pts are evaluable after the 6-month PSMA scan/follow-up. The pts have a median age of 71 years, PSA=3.05, PSA doubling time=11.1 mos (29% less than 6 mos). In an overlapping descriptive analysis 10 pts were PSMA- and 17 pts had only local disease. For PSMA+ LNs, 17 pts had 1 LN, 9 pts had 2-3 LNs+, 5 pts had 4 LNs+, and 18 pts had 5+ LNs. 7 pts had bone findings, but negative bone scan. 4 pts had PSMA+ serosal nodules. 4 pts had radiation to solitary LNs. 1 pt elected androgen deprivation and 1 pt had salvage radiation. 4 pts enrolled on a clinical study at the NCI without androgen deprivation. At 6 mos PSMA scan only 1 pt had metastatic disease (bone scan findings). No pts had LNs beyond eligibility size criteria. No pts had new visceral findings. **Conclusions:** These preliminary data from an ongoing study suggest PSMA+ BCR is an indolent disease process and pts are at limited risk for clinically relevant progression within 6 mos. This study continues to accrue at the NCI and will seek to better define high risk PSMA+ BCR. These preliminary data may better inform the risk/benefits of aggressive treatment of PSMA+ BCR and clinical studies in PSMA+ BCR. Clinical trial information: NCT05588128. Research Sponsor: NCI Intramural Porgram.

5099 **Poster Session**

Evaluation of de novo oligometastatic, oligorecurrent, and oligoprogressive prostate cancer patients managed with radiation therapy: A multi-institution, real-world dataset. First Author: Sophia C. Kamran, Massachusetts General Hospital, Harvard Medical School, Boston, MA

Background: Oligometastatic prostate cancer (omPCa) is historically defined as ≤5 metastases, with non-standard treatment approaches and unknown prevalence in the molecular diagnostic imaging (MDI) era. Clinical trials in advanced PCa based on conventional imaging modalities (CIM) complicate extrapolation of findings to omPCa detected by MDI. We evaluated outcomes of omPCa patients (pts) treated with radiotherapy (RT) in a multi-institutional cohort. **Methods:** Pts presenting with de novo (synchronous), oligorecurrent (OR, metachronous), or oligoprogressive (OP, progressive) omPCa (<5 non-visceral lesions), detected by CIM and/or MDI and treated with RT across 7 institutions were identified. RT was metastasis-directed (MDT) only (or in the case of de novo pts, prostate-only or prostate + MDT) using conventional, hypofractionated or stereotactic body RT (SBRT) regimens. Clinical outcomes, including disease (dz) progression (any biochemical recurrence or distant metastasis, DM) and survival were assessed. Progression-free survival (PFS), DMFS, and overall survival (OS) were determined using the Kaplan-Meier method; univariable analyses were performed with Cox proportional hazard regression. **Results:** 625 omPCa pts (193 de novo, 342 OR, 90 OP) received RT between 2014-2024. Most pts (415/625, 66%) were diagnosed using MDI. 25% presented with pelvic lymph nodes (LNs) only, 7% non-regional LNs only, 56% bone-only dz, and 12% with a combination. Most pts (551/625) received systemic therapy with RT: 51% androgen deprivation therapy (ADT) alone, 43% ADT + androgen receptor signaling inhibitor (ARSI, n=239), and 6% ADT + ARSI + docetaxel. Median FU post-omPCa diagnosis was 26 months (range, 1-225) for 613 pts with details available. 153 pts developed new DM (outside of documented OM). Five-year OS post-diagnosis was 87% (95%CI 81,91). 5-year PFS post-RT was 34% (95%CI 24,44), with median PFS of 43 months. Concurrent ARSI use improved PFS (HR 0.67, 95%CI 0.50,0.91, p=0.01) on Cox proportional hazard regression. Use of any systemic therapy improved DMFS (HR 0.46, 95%CI 0.29,0.72, p<0.001). Both OR and OP dz were associated with worse DMFS (HR 2.2, 95%CI 1.4,3.5; HR 6.3, 95% CI 3.7,10.6, respectively, p<0.001 for both) and OP dz was associated with poor OS (HR 5.8, 95%CI 2.7,12.7). There was no impact by RT approach on outcomes. **Conclusions:** In this multi-institutional omPCa cohort reflecting real-world practice patterns of detection and treatment, the addition of ARSI to RT improved PFS, and use of any systemic therapy with RT improved DMFS. De novo omPCa had more favorable clinical outcomes compared to OP/OR presentations. Research Sponsor: None.

Characteristic	Age	Gleason score		Number of lesions	
	Median (range)	Score	n (%)	#	n (%)
	70 (44-92)	6	43 (7%)	1	351 (56%)
		7	206 (33%)	2-3	229 (37%)
		8	163 (26%)	4-5	45 (7%)
		9	166 (27%)		
		10	20 (3%)		
		n/a	27 (4%)		

5100 Poster Session

Assessment of the impact of delays to radiotherapy on prostate cancer mortality in localized prostate cancer. First Author: Yang Xu, Arthur J.E. Child Comprehensive Cancer Centre, Calgary, AB, Canada

Background: Resource constraints and patient preferences may lead to delays in the treatment of localized prostate cancer, but the implications of such delays remain unclear. We aimed to investigate the impact of time from diagnosis to treatment initiation (TTI, including neoadjuvant ADT) on prostate cancer-specific mortality (PCSM) in patients receiving radiotherapy for localized prostate cancer. **Methods:** Patients diagnosed with localized prostate cancer from 2004 to 2020 who received radiotherapy as part of their first course of treatment were identified from the SEER 17 database. Those who initially underwent active surveillance or surgery, as well as those whose TTI exceeded 24 months, were excluded. The remaining patients were divided into cohorts with prespecified TTI intervals of 0-3 months, 4-6 months, and >6 months. Covariates were age, race, county median income, county remoteness, diagnosis year, T stage, PSA, Gleason grade, and treatment modality (external beam radiotherapy, brachytherapy, or a combination). Missing covariates were imputed 50 times using multiple imputations with chained equations, after which propensity score weighting using Bayesian additive regression trees was performed for each imputed dataset. Pooled marginal Cox models, in accordance with Rubin's rules, were used to compare the PCSM of the three TTI cohorts. Additionally, a prespecified subgroup analysis based on NCCN risk classification was completed. **Results:** A total of 230,278 patients with a median follow-up of 7.8 years were eligible for analysis, of whom 168,432 (73.1%) had a TTI of 0-3 months, 46,738 (20.3%) had a TTI of 4-6 months, and 15,108 (6.6%) had a TTI of >6 months. After propensity score weighting, the maximal standardized mean difference across all covariates and imputations was less than 0.03. Weighted 10-year PCSMs were 5.9%, 5.6%, and 7.1% for patients with TTIs of 0-3 months, 4-6 months, and >6 months, respectively. The PCSM of patients with a TTI of 4-6 months did not differ from that of patients with a TTI of 0-3 months (HR 0.95, 95% CI 0.89-1.01; P=0.09). However, patients with a TTI of >6 months had a higher risk of PCSM than those with TTIs of 0-3 months (HR 1.22, 95% CI 1.09-1.36; P<0.001) or 4-6 months (HR 1.28, 95% CI 1.13-1.45; P<0.001). There was no significant interaction between TTI and NCCN risk group (P=0.49). **Conclusions:** A TTI exceeding 6 months was associated with an increased risk of prostate cancer mortality. These findings support the timely initiation of treatment for patients undergoing radiotherapy for localized prostate cancer. Research Sponsor: None.

PCSM by NCCN risk subgroup.

Subgroup	4-6 months vs. 0-3 months HR (95% CI)	>6 months vs. 0-3 months HR (95% CI)	>6 months vs. 4-6 months HR (95% CI)
Overall	0.95 (0.89-1.01)	1.22 (1.09-1.36)	1.28 (1.13-1.45)
Low risk	1.02 (0.89-1.17)	1.05 (0.86-1.29)	1.04 (0.83-1.30)
Intermediate risk	0.94 (0.86-1.03)	1.19 (1.02-1.38)	1.27 (1.07-1.50)
High risk	0.94 (0.85-1.03)	1.28 (1.06-1.54)	1.37 (1.11-1.68)

5101 Poster Session

Five-year outcomes of SABR in intermediate- and high-risk prostate cancer without ADT. First Author: Nidal Salim, European Medical Center, Moscow, Russian Federation

Background: Stereotactic ablative body radiotherapy (SABR) is emerging as a prominent treatment option for localized prostate cancer (PCa). Most existing studies have primarily focused on low- and intermediate-risk PCa patients, who typically have favorable prognoses regardless of treatment. Additionally, the necessity of adding androgen deprivation therapy (ADT) remains a subject of ongoing debate, given its associated side effects and limited impact on overall survival (OS). In this study, we present the long-term outcomes of patients predominantly with intermediate- and high-risk PCa who were treated with SABR without ADT. **Methods:** This was a single-center prospective study of 87 patients with localized PCa who underwent SABR without subsequent ADT. SABR was delivered in an ultra-hypofractionation regimen (36.0 – 42.7 Gy) using Varian TrueBeam/EDGE linear accelerators between July 2015 and June 2024. The primary endpoint was biochemical recurrence-free survival (bRFS), with secondary endpoints including toxicity and overall survival (OS). **Results:** A total of 87 patients, with a median age of 68.8 years (range: 50–86 years), were included. The median follow-up period was 31 months (range: 3–105 months). The distribution of patients by risk group was as follows: low-risk (21.8%), intermediate-risk (55.1%), and high-risk (17.9%). The 1-, 3-, and 5-year bRFS rates were 97.6%, 92.2%, and 90.0%, respectively. Importantly, no patient died as a result of PCa progression during the observation period. No clinically significant toxicity was reported. **Conclusions:** The findings of this study suggest that SABR as a standalone treatment modality is a safe and effective approach for localized PCa, providing durable biochemical control without significant toxicity. However, further investigations involving larger patient cohorts and longer follow-up periods are needed to confirm these results and enhance their reliability. Research Sponsor: None.

5102 Poster Session

COBRA: Assessment of the efficacy of ^{64}Cu-SAR-bisPSMA using histopathology and standard of care imaging as reference standard in patients with biochemical recurrence of prostate cancer following definitive therapy. First Author: Luke Nordquist, XCancer/Urology Cancer Center, Omaha, NE

Background: Accurate staging of recurrent prostate cancer (PC) is essential to inform the best treatment strategy. ^{64}Cu-SAR-bisPSMA may offer several advantages over the currently approved PSMA positron emission tomography (PET) agents due to its bivalent structure (SAR-bisPSMA) and longer half-life of ^{64}Cu (12.7h vs. <2h for ^{18}F and ^{68}Ga), as previously reported (2-3x higher tumor uptake and detection of additional PC lesions vs. approved PSMA PET agents). **Methods:** This was a Phase 1/2 study assessing the safety/efficacy of ^{64}Cu-SAR-bisPSMA (200 MBq) in PC patients with biochemical recurrence (BCR) and negative/equivocal standard of care (SOC) imaging (NCT05249127). PET/computed tomography (CT) imaging was performed on Day 0 and Day 1 (1-4h and 24±6h post-dose, respectively) and interpreted by 3 blinded central readers. PET/CT results were assessed against a composite Reference Standard (histopathology, SOC imaging [interpreted by 2 readers], prostate specific antigen response post-focal therapy). Efficacy endpoints included detection rate (DR; % participants with a positive scan out of all scanned participants) and correct detection rate (CDR; % participants with a true positive scan out of all scanned participants with at least one evaluable Reference Standard). **Results:** Fifty-two participants were enrolled (50 had ^{64}Cu-SAR-bisPSMA PET results); 39 and 30 had follow-up SOC imaging by Day 90 and by Day 180, respectively, and 9 had histopathology. ^{64}Cu-SAR-bisPSMA DR range across readers on Day 0 was 44–58% (95% confidence interval [CI]: 30–71.8), increasing on Day 1 to 58–80% (95% CI: 43.2–90). DR on follow-up SOC imaging by Day 90 ranged from 15-31% and 7-10% by Day 180. CDR as assessed against the composite Reference Standard on Day 0 was 19.0–26.2% (95% CI: 8.6; 42.0), increasing to 26.2–33.3% (95% CI: 13.9; 49.5) on Day 1. CDR was considerably higher when using histopathology as the Reference Standard (44.4–55.6% and 55.6–77.8% for Day 0 and Day 1, respectively), than SOC imaging (10.3–20.5% and 23.1%–25.6% for Day 0 and Day 1, respectively). **Conclusions:** ^{64}Cu-SAR-bisPSMA is effective in detecting PC in BCR of PC, with lesions identified in up to 80% of participants with negative/equivocal baseline SOC imaging. CDR was considerably higher when using the gold standard of histopathology to verify ^{64}Cu-SAR-bisPSMA PET lesions vs SOC imaging, which highlights the limitations of using less sensitive methods to verify the ^{64}Cu-SAR-bisPSMA PET findings. These results have important clinical implications, as the identification of lesions in BCR patients can inform different treatment pathways. Clinical trial information: NCT05249127. Research Sponsor: Clarity Pharmaceuticals.

5103 Poster Session

Secondary outcomes by prior definitive treatment (tx) in patients (pts) with high-risk biochemically recurrent prostate cancer (hrBCR) treated with enzalutamide (enza) monotherapy (mono): EMBARK post hoc analysis. First Author: Stephen J. Freedland, Department of Urology, Samuel Oschin Comprehensive Cancer Institute, Cedars-Sinai Medical Center, Los Angeles, CA

Background: The phase 3 EMBARK trial demonstrated clinically meaningful improvement in metastasis-free survival and secondary efficacy endpoints with enza mono vs leuprolide alone. Herein, we descriptively report secondary endpoints for enza mono vs leuprolide alone across prior definitive tx subgroups. **Methods:** Eligible pts had hrBCR, with a prostate-specific antigen (PSA) doubling time of ≤9 months. Pts were randomized 1:1:1 to enza + leuprolide, leuprolide alone, or enza mono. Secondary endpoints included time to PSA progression, first use of new antineoplastic tx, distant metastasis, resumption of any hormonal therapy after tx suspension, and symptomatic progression. Post hoc subgroup analyses descriptively compared secondary endpoints for enza mono vs leuprolide alone in pts with radical prostatectomy (RP) only, radiotherapy (RT) only, or RP + RT. **Results:** In both tx groups (enza mono and leuprolide alone), nearly half of pts had prior RP + RT (Table). Enza mono vs leuprolide alone numerically reduced the risk of PSA progression, first use of new antineoplastic tx, distant metastasis, and symptomatic progression in all prior definitive tx subgroups (Table). Time to resumption of any hormonal therapy favored leuprolide alone vs enza mono across all prior definitive tx subgroups. **Conclusions:** Tx with enza mono showed improvements in all secondary endpoints except time to resumption of any hormonal therapy vs leuprolide alone, regardless of prior definitive tx. The small sample sizes of the nonrandomized prior tx subgroups and low event numbers should be considered when interpreting the results. Interaction analyses of secondary endpoints across prior definitive tx subgroups will be reported in the presentation. Disclosure: A genAI tool (10/01/24; Pfizer; GPT-4o) developed the 1st draft; authors assume content responsibility. Clinical trial information: NCT02319837. Research Sponsor: The study was sponsored by Pfizer Inc. and Astellas Pharma Inc., the co-developers of enzalutamide. Medical writing support was provided by Roham Sadeghimakki and Rosie Henderson of Onyx (a division of Prime, London, UK), funded by the sponsors.

	Mono (n=355)						Leuprolide alone (n=358)†		
	RP only (n=99)		RT only (n=90)		RP + RT (n=166)		RP only (n=75)	RT only (n=104)	RP + RT (n=179)
Secondary endpoints Time to:	Event, n	HR (95% CI)	Event, n	HR (95% CI)	Event, n	HR (95% CI)	Event, n	Event, n	Event, n
PSA progression	12	0.62 (0.28, 1.34)	18	0.53 (0.30, 0.95)	7	0.14 (0.06, 0.33)	17	37	39
First use of new antineoplastic tx	23	0.68 (0.38, 1.22)	33	0.76 (0.48, 1.20)	28	0.37 (0.23, 0.58)	25	48	67
Distant metastasis	10	0.81 (0.32, 2.08)	14	0.65 (0.31, 1.34)	16	0.45 (0.24, 0.85)	9	20	30
Resumption of any hormonal therapy	77	1.68 (1.14, 2.46)	60	2.23 (1.46, 3.39)	142	1.58 (1.22, 2.03)	54	47	116
Symptomatic progression	28	0.61 (0.36, 1.03)	38	0.79 (0.52, 1.22)	51	0.56 (0.39, 0.80)	32	52	85

†Leuprolide alone was the comparator.
CI, confidence interval; HR, hazard ratio.

5104 Poster Session

Neoadjuvant niraparib in men with DNA repair gene deficient clinically localized prostate cancer: Clinical and molecular results from a phase 2 investigator-initiated trial. First Author: Marc Dall'Era, Department of Urology, University of California, Davis, Sacramento, CA

Background: Many men with clinically localized prostate cancer experience disease progression and recurrence despite curative local therapy. Neoadjuvant treatments may reduce recurrence risk and the need for salvage therapy. Primary prostate cancer is genomically diverse and PARP inhibitors (PARPi) represent a novel class of targeted cancer therapy with known activity in advanced prostate cancers, particularly in the setting of DNA damage repair (DDR) gene alterations. **Methods:** Men with National Comprehensive Cancer Network unfavorable intermediate to high-risk prostate cancer were screened for somatic or germline DDR gene alterations. Consenting men were enrolled into a single arm phase II pilot study (NCT04030559) of neoadjuvant niraparib 200mg per day for 90 days prior to planned radical prostatectomy (RP). The primary endpoint was complete or partial pathologic response [minimal residual disease (MRD) defined as $<$0.5 cc of residual tumor]. Secondary endpoints were toxicity and biochemical progression free survival (bPFS). Raw tissue and ctDNA sequencing data was obtained by the clinical NGS vendor and analyzed. **Results:** Eleven (of planned 30) men were enrolled with a median age of 68 years and median PSA at diagnosis of 10.7 ng/mL. Germline-mutations were noted in *BRCA2* (n=3 patients with loss-of-function, 2 with additional loss-of heterozygosity detected), *MSH6* (n=1), *CHEK2* (n=1); somatic mutations were noted in *ATM* (n=3), *SPOP* (n=4), *PPP2R1A* (n=1), *ZFHX3* (n=1), and *ZMYM3* (n=2). No complete or partial pathologic responses were observed. PSA responses were variable on niraparib. There was one grade 3+ adverse event (thrombocytopenia) requiring a dose reduction. After a median follow up of 27 months, bPFS is 56% for the overall cohort. One patient with bi-allelic loss of *BRCA2* (germline and somatic) and a coincident *ATM* mutation had the most dramatic change in PSA (-76%) with notable radiographic regression on MRI. We detected a decline in ctDNA for the somatic mutations seen in the pre-niraparib prostate biopsy NGS (*ATM* and PIK3R1) within 7 weeks of niraparib treatment. A new reversion mutation in *BRCA2* was detected in the serum of this patient by 12 weeks which disappeared after stopping niraparib. This BRCA2 reversion mutation was also detected in the prostatectomy tissue. **Conclusions:** In this small study, neoadjuvant niraparib did not result in substantial pathologic response after RP in a group of men with prostate cancer and heterogeneous mutations in genes involved in DDR. Variable responses even in the face of bi-allelic BRCA2 loss suggest that additional biomarkers including ctDNA analysis to identify patients who may benefit are needed. Early reversion mutations may contribute to PARPi resistance in hormone sensitive prostate cancer. Clinical trial information: NCT04030559. Research Sponsor: Janssen.

5105 Poster Session

A randomised clinical trial to improve healthy lifestyle adherence in prostate cancer patients undergoing radiotherapy (Microstyle study). First Author: Sara Gandini, Department of Experimental Oncology, European Institute of Oncology IRCCS, Milan, Italy

Background: The standard non-surgical approach for localized Prostate Cancer (PCa) is radiotherapy (RT) but PCa patients may experience worsening of bowel disorders affecting quality of life and attributable to RT. The main aim of the study was to examine whether personalized dietary and physical activity counselling, provided at the start of RT, improves adherence to a healthy lifestyle, according to the standardised WCRF/AICR score[1] that assists clinicians in providing evidence-based recommendations to reduce risk of morbidity and improve quality of life in cancer patients. **Methods:** We designed a randomized controlled cross-over trial with two arms – MicroStyle[2]: an intervention (IG) and a control (CG) group, which were enrolled at the start of RT and followed for six months (T6) and 12 months (T12) respectively. Clinical data, questionnaires and circulating biomarkers were collected at two Italian Cancer Centres (Milan and Naples) on different time points. Linear regression models and logistic models were applied to estimate differences by arms in the WCRF/AICR score and its association with toxicity and circulating biomarkers. **Results:** Of the 308 patients enrolled, 299 completed the baseline evaluation, and 286 completed the six-month follow-up. The intervention showed at T6 a greater WCRF adherence compared to the CG: change from baseline 0.2 95%CI: 0.03, 0.36, p =0.02 IG vs CG) adjusting for baseline. The proportion of adherent subjects significantly increase at T6 with IG (26% vs 19%, P=0.04) and at T12 (28% vs 13%, P=0.01) more than CG. A high WCRF score at T6 was found to be associated with a significantly reduced rectal toxicity (P=0.03). IG at T12 was associated with lower Testosterone (P=0.04) and lower Estradiol (P=0.02) adjusting for hormonal therapy and baseline values. Patients with WCRF improvement were associated with lower IL6 and higher adiponectin Improvement of WCRF adherence is significantly associated with improvement in quality of life (P=0.04, IPSS) and prostate symptom (p=0.05, IPSS), sexual function (P=0.01, IIEF) and in particular erectile dysfunction (P=0.03, IIEF) and functional assessment of cancer therapy (P=0.01, FACT-P), adjusting for baseline values. **Conclusions:** This innovative trial showed that that a personalized dietary and physical activity counselling during RT significantly improves adherence to a healthy lifestyle, influencing rectal toxicity and circulating biomarkers. Future analyses will explore the toxicity associated with RT, changes in microbiome and its potential interactions with lifestyle factors. Funding: This study is funded by Italian Ministry of Health, Ricerca Finalizzata 2019 (RF-2019-12368771). ClincalTrial.gov registration number: NCT05155618. 1) https://epi.grants.cancer.gov/wcrf-aicr-score/details.html. 2) Gnagnarella, BMC Cancer (2022) doi s12885-022-09521-4. Clinical trial information: NCT05155618. Research Sponsor: Italian Ministry of Health, Ricerca Finalizzata 2019.

5106 Poster Session

External validation of a pathology-based multimodal artificial intelligence biomarker for predicting prostate cancer outcomes after prostatectomy. First Author: Chien-Kuang Cornelia Ding, University of California, San Francisco, San Francisco, CA

Background: Radical prostatectomy (RP) improves survival and delays metastasis in localized prostate cancer (PCa) patients (pts), yet 20-40% of men experience biochemical recurrence (BCR) within 10 years, with one-third of these progressing to metastatic disease. Predictive tools for risk stratification and treatment-decision making in this population remain limited. We previously developed and validated an RP digital pathology-based multimodal AI (MMAI) model using RP H&E images and select clinical variables to predict post-surgical outcomes in BCR pts (RP MMAI v1.1). We present the first external validation of this model in both BCR and non-BCR post-RP pts. **Methods:** Surgical pts with localized disease, clinical data, and long-term follow-up we re identified at UCSF (n=738). MMAI scores were generated from RP H&E images and clinical data (age, Gleason grade group (GG), pT-stage, surgical margins (SM), post-RP PSA). Fine & Gray regression with other-cause mortality as a competing risk was performed to determine the ability of MMAI score to predict any metastasis (primary analysis), bone metastasis (BM), and disease progression (DP: 2 consecutive PSA $\geq$0.2 ng/ml or salvage treatment) after RP. Hazard ratios, 95% confidence intervals, and p-values (for primary analysis) are reported. **Results:** MMAI scores were returned for 640 (87%) cases with images and clinical data. Median (IQR) post-RP follow-up was 11.5 (7.7-24.8) years. Post-RP Cancer of the Prostate Risk Assessment (CAPRA-S, range 0-12) scores were 56% low (0-2), 31% intermediate (3-5) and 13% high ($\geq$6) risk. Characteristics at RP were 71% GG1/2, 64% pT2, and 79% negative SM. The majority of pts had undetectable PSA$<$0.05 after RP (87%). Cumulative incidence of DP and metastasis were 27% and 7% at 10 years, respectively. After adjusting for CAPRA-S, MMAI was independently associated with any metastasis (HR 1.76, [95% CI 1.23-2.53], p$<$0.001) and BM (HR 2.72, [95% CI 1.71-4.32]) in post-RP pts, as well as with DP in 561 pts with undetectable PSA after RP (HR 1.51, [95% CI 1.27-1.80]). Using a cutoff previously defined in BCR pts, 10-yr risk of any metastasis or BM after RP was higher in RP MMAI high risk (18% and 16%) vs. low risk pts (3% and 1%). In a subgroup of 211 salvage-eligible pts (detectable PSA and/or salvage treatment), MMAI remained independently associated with any metastasis (HR 1.71, [1.18-2.47]) and BM (HR 2.71, [1.74-4.23]) after CAPRA-S adjustment. **Conclusions:** This study validates the RP MMAI model, originally developed in BCR pts, as an independent prognostic tool in both BCR and general post-RP settings, even when controlling for a validated clinical risk model. These findings support its potential to guide personalized management strategies for post-RP pts, while offering advantages in accessibility, efficiency, and cost compared to existing platforms. Research Sponsor: None.

5107 Poster Session

Utility of the PROSTest, a novel blood-based molecular assay, versus PSA for prostate cancer stratification and detection of higher grade disease. First Author: Pawel Rajwa, Division of Surgery and Interventional Sciences, University College London, London, United Kingdom

Background: Prostate cancer (PCa) is the most common solid organ cancer in men and the fifth leading cause of cancer-related deaths globally. PSA has utility for identifying men at risk but has low specificity and is associated with significant biopsy-related morbidities through over-investigation and over-diagnosis of disease. The PROSTest is a novel 27-gene mRNA expression machine learning-based liquid biopsy assay that was developed to help detect PCa. We evaluated the utility of this assay to predict prostate cancers in symptomatic men undergoing biopsy or surgery for PSA $>$2ng/mL. **Methods:** One hundred and twenty-three men were evaluated, 105 (85%) met eligibility criteria (age $>$55 years, PSA $>$2ng/ml, symptomatic) and underwent image-guided biopsy or surgery. Samples for PSA and PROSTest were collected prior to biopsy. PROSTest was measured following RNA isolation and cDNA production from RNA stabilized blood samples. The PCR results were fed into a machine learning algorithm that reports a score on a scale 0-100, and with the use of cutoff 50, the score is transformed into a binary readout; positive or negative. In addition to the 2x2 table below, the diagnostic value of the PROSTest was demonstrated by ROC curve. Separately, we examined whether scores could be used to differentiate Gleason Grade 1 vs Gleason Grade 2-5 patients. **Results:** The median age of the cohort was 68 years (55-86 years). Baseline PSA median was 8.2ng/mL (IQR: 7.2-92ng/mL). Sixty-five (62%) had a PCa diagnosis (27 GG1; 38 GG2-5) as confirmed by biopsy or after surgery. Baseline PROSTest results were $>$50 in 65 (62%). The distribution of PROSTest versus outcomes is included in Table 1. PROSTest sensitivity was 97% and specificity of 96% for detecting PCa. The AUROC for PROSTest was 0.39 higher than PSA (PROSTest: 0.99 vs. PSA: 0.61, p$<$0.0001). GG2-5 exhibited significantly higher (p$<$0.0001) PROSTest scores (92$\pm$3.8) than GG1 and BPH (41$\pm$41). PROSTest scores $>$93 were 79.1% accurate and 92.5% specific for detecting higher risk disease. **Conclusions:** In this head-to-head comparison, baseline PROSTest was a more sensitive and more specific biomarker than PSA in the diagnosis of all Gleason's grades and may have value for differentiating GG1 from GG2-5. This requires validation in a larger, prospectively collected cohort. Research Sponsor: None.

2x2 table identifying PROSTest score relationship with PCa detection (tissue diagnosis).

	Biopsy/Surgery	
	Prostate cancer detected (n=65)	No Prostate cancer (including 5 prostatitis, 35 BPH) (n=40)
PROSTest +ve (score ≥50)	63 (96.9%)	2 (5.0%)
PROSTest -ve (score <50)	2 (3.1%)	38 (95%)

5108 Poster Session

A large language model (LLM)-based multi-agent framework for risk stratification and treatment recommendations in localized prostate cancer (locPCa). First Author: Umair Ayub, Mayo Clinic Arizona, Phoenix, AZ

Background: We previously proposed a hybrid framework combining LLMs and rule based algorithm (RBA) for automating risk stratification in locPCa. Herein, we aim to validate the risk stratification agent (RSA) in a prospective cohort, develop & evaluate the treatment recommendation agent (TRA) based on NCCN guidelines, and develop an interactive interface to facilitate clinicians for accurate risk stratification and treatment recommendations at the point of care. **Methods:** This study included pts with locPCa (2004-2024) presenting at Mayo Clinic with at least 1 positive prostate biopsy and MRI report available. For RSA prospective validation, GPT4 extracted key phenotypic variables (PSA, T stage, prostate volume, number of cores, Gleason patterns, grade group) from unstructured MRI and biopsy reports using a zeroshot prompt. An RBA then classified pts into NCCN risk groups. The agent performance was compared with the treating clinician's documentation and evaluated against gold-standard labels manually annotated by two independent clinicians. For development of TRA, two experiments were performed using GPT4 with and without retrieval-augmented generation (RAG) to generate treatment plans. Generated treatment plans were evaluated using NCCN guideline-informed treatment decision tree based algorithm (DTA). Evaluation metrics, weighted – accuracy (acc) and F1, were computed. A clinician facing interface (lisr.org/risk) was developed to provide accurate risk stratification and treatment plans. **Results:** A total of 858 pts were included (500 for prospective validation, 358 for treatment recommendations). Prospective validation for RSA demonstrated a higher F1 score of 0.89 compared to the treating clinician (F1: 0.58). Treatment recommendation experiments showed that GPT4 with RAG achieved higher acc (64% full – all correct treatment options and 36% partial – at least 1 correct treatment option) compared to GPT4 alone (35% and 65%, respectively). Sensitivity analysis using DTA-informed GPT4 note generation achieved 94% full acc and 6% partial acc. GPT4 alone generated hallucinated treatment options in 71% of cases, while GPT4 with RAG reduced this to 32%. **Conclusions:** The multi-agent framework based on LLM and RBA achieves high accuracy in risk stratification and treatment recommendation for locPCa. A multi-agent framework with an interactive interface holds high promise to enable efficient, accurate decision-making, and improve locPCa management at the point of care Research Sponsor: None.

Performance evaluation.

	RSA (acc; F1) %		TRA (full acc; partial acc) %		
	Clinician	RSA*	GPT4	RAG+GPT4	DTA+GPT4
Overall	**60; 58**	**89; 89**	**29; 71**	**64; 36**	**94; 6**
V. High	94; 33	96; 96	55; 45	69; 31	93; 7
High	46; 52	92; 89	-	-	-
Int. Unf	80; 61	91; 90	5; 95	38; 62	93; 7
Int. Fav	57; 64	84; 87	0; 100	98; 2	100; 0
Low	57; 65	87; 80	100; 0	95; 5	90; 10
V. Low	8; 13	50; 67^	-	-	-

*Statistical significance ($p<0.01$) except for ^V. Low.

5109 Poster Session

Insight into the global mortality trends due to prostate cancer among the under-55 population: An analysis of the Global Burden of Disease-2021. First Author: Amar Lal, Penn State Health Milton, St. Hershey Medical Center, The Pennsylvania State University, Hershey, PA

Background: Prostate cancer (PC) is the most prevalent non-skin cancer among males, and it is increasingly diagnosed in those under 55. This younger demographic often faces more aggressive disease progression and a higher risk of metastasis, driven by genetic predispositions, family history, and racial factors. **Methods:** Data were systematically collected from the GBD-2021 covering key metrics such as incidence, prevalence, death rates, Disability-Adjusted Life Years (DALY), Years of Life Lost (YLL), and Years Lived with Disability (YLD) across the age group of 20-54 years. Global estimated and stratified data based on 204 regions were further analyzed to assess average annual percentage changes (AAPC) and 95% confidence interval (CI) from 1990 to 2021. **Results:** There were 2,06,612 deaths due to prostate cancer among those aged 20-54 from 1990-2021. Between 1990 and 2021, the global PC incidence in individuals aged 20-54 increased from 0.82 to 1.55 per 100,000, with an AAPC of 2.03 (CI: 1.65-2.41, $p<0.0001$). The highest incidence was recorded in Lithuania, Bermuda, and Australia, while Vietnam, Bhutan, and Algeria reported the lowest. Notable AAPC increases were observed in Cabo Verde (7.26, CI: 6.80-7.72, $p<0.0001$), followed by the Republic of Korea and Vietnam. Conversely, Somalia experienced a significant decline (-1.73, CI: -2.04 to -1.43, $p<0.0001$). During the same period, the global prevalence of PC rose from 7.18 to 13.94 per 100,000, with an AAPC of 2.13 (CI: 1.75-2.54, $p<0.0001$). Prevalence trends across countries were similar to incidence trends. Between 1990 and 2021, the global mortality rate for prostate cancer in individuals aged 20-54 rose slightly from 0.37 to 0.41 per 100,000, with an AAPC of 0.20 (CI: 0.07-0.32, p=0.003). Significant increases were observed in Cabo Verde (AAPC 4.24, CI: 3.89-4.58, $p<0.0001$) and the Northern Mariana Islands. Conversely, Sweden and Luxembourg showed declines, with AAPCs of -2.55 (CI: -3.11 to -1.98) and -2.28 (CI: -2.49 to -2.06), respectively. The highest increases across DALY, YLD, and YLL were observed in Cabo Verde, Zambia, and the Republic of Korea, while Somalia, Sweden, and Luxembourg observed significant declines. **Conclusions:** There has been a rise in mortality rates among young prostate cancer patients aged 20-54, along with increasing morbidity indicators such as YLD, DALY, and YLL. African countries have consistently noted significant rises in both incidence and mortality rates, while a decline was noted in European countries. This could be attributed to the lack of screening protocols and the inadequacy of treatment. The global incidence and prevalence of prostate cancer in this age group have nearly doubled over the past 30 years. Future research should focus on regional disparities and develop strategies to reduce the impact of this disease on younger populations. Research Sponsor: None.

TPS5110 Poster Session

Study protocol: Phase 2 trial of re-treatment with 177Lu-PSMA-617 molecular radiotherapy for metastatic castration resistant prostate cancer (RE-LuPSMA trial). First Author: John Nikitas, University of California, Department of Radiation Oncology, Los Angeles, CA

Background: The phase III VISION trial demonstrated that ^{177}Lu-PSMA-617 radioligand therapy (RLT) improved overall survival (OS) in patients with metastatic castration-resistant prostate cancer (mCRPC) who previously received taxane-based chemotherapy and at least one androgen receptor pathway inhibitor (ARPI). As a result, ^{177}Lu-PSMA-617 therapy has been approved in this patient population by the U.S. Food and Drug Administration for up to six cycles (7.4 GBq per cycle) every 6 weeks. Unfortunately, this treatment is not curative and patients relapse even after initially favorable responses. When this occurs, patients have limited treatment options given they have had prior chemotherapy and ARPI regimens. Re-administration of ^{177}Lu-PSMA-617 in patients who previously benefited from therapy and had limited toxicity seems to be a promising option. Small retrospective studies have reported favorable outcomes. Further prospective data with larger sample sizes are needed to confirm these findings. **Methods:** RE-LuPSMA is an investigator-initiated, single-arm, single-center, open-label, phase 2 clinical trial (NCT06288113). This study plans to enroll 40 patients with progressive mCRPC who previously completed 4-6 cycles of ^{177}Lu-PSMA-617 therapy with a favorable response. Favorable response is defined as a prostate-specific antigen (PSA) decline $\geq$50% during the first regimen. Progression following the first regimen is defined using imaging or PSA (two consecutive PSA increases $\geq$3 weeks apart). Patients who received another line of prostate cancer therapy within two months of completing the first regimen of ^{177}Lu-PSMA-617 are excluded. Patients must meet PSMA PET/CT VISION criteria. PSMA PET/CT must have been completed within 8 weeks of the planned first cycle of re-challenge therapy. Upon enrollment, participants will receive up to 6 additional cycles of ^{177}Lu-PSMA-617 (7.4GBq every 6 weeks). Patients will follow-up every 6 months until 2 years from the end of re-challenge therapy. The primary endpoint is 12-month OS measured from the start of re-challenge therapy. The study will have 80% power to detect a difference between the null hypothesis of 50% and the study hypothesis of 71%. Secondary endpoints include adverse event rates, PSA response rates (proportion of patients with a PSA decrease of $\geq$50%), biochemical progression-free survival (time until PSA level increases 25% and 2 ng/mL above the nadir), radiographic progression-free survival, and health-related quality of life changes (measured using Functional Assessment of Cancer Therapy - Radionuclide Therapy [FACT-RNT] and Brief Pain Inventory [Short Form]). Enrollment has started with a planned study duration of 4 years of which subject accrual occurs in the first 12 months. Clinical trial information: NCT06288113. Research Sponsor: UCLA Ahmanson Translational Theranostics Division; Novartis.

TPS5111 Poster Session

Phase 1, open-label, first-in-human study of ABBV-969, a dual variable antibody-drug conjugate, in patients with metastatic castration-resistant prostate cancer. First Author: Anthony W. Tolcher, NEXT Oncology San Antonio, San Antonio, TX

Background: Metastatic castration-resistant prostate cancer (mCRPC) is an incurable disease with high unmet need. Six-transmembrane epithelial antigen of prostate 1 (STEAP1) is highly enriched in $>$ 85% of prostate cancer (PC),[1] and prostate-specific membrane antigen (PSMA) expression is $>$ 100-fold higher in patients (pts) with mCRPC.[2] These are well-established and actionable targets in mCRPC. ABBV-969, a dual variable domain IgG1 drug conjugate, targets STEAP1 and PSMA and includes a topoisomerase-1 inhibitor (Top1i) payload. Based on preclinical data, ABBV-969 is expected to have greater efficacy and wider activity than targeting either antigen alone. We describe a first-in-human study of ABBV-969 in pts with mCRPC. **Methods:** This phase 1 open-label study (NCT06318273) of ABBV-969 monotherapy evaluates safety, pharmacokinetics (PK), pharmacodynamics (PD), and efficacy. Eligible pts, $\geq$ 18 years of age, have mCRPC treated with and progressed on $\geq$ 1 prior novel hormonal agent for mPC/CRPC and $\geq$ 1 taxane for PC (or have refused, are intolerant to, or unable to access taxanes). Pts must have a life expectancy $>$ 6 months, serum testosterone levels $\leq$ 50 ng/dL, $\geq$ 1 metastatic lesion at baseline, and serum prostate-specific antigen (PSA) levels $\geq$ 1.0 ng/mL. Part 1 (dose escalation) of the study will enroll up to ~80 pts and is guided by the Bayesian optimal interval design primarily based on the dose-limiting toxicity rate. Part 2 (dose expansion) will randomize up to 60 pts in 2 (1:1) or 3 (1:1:1) dose levels (determined in part 1). Part 1 will enroll pts in US, Israel, Japan, and Australia with Canada, France, and Spain added in part 2. Optimal (recommended phase 2) dose will be determined by the totality of PK, PD, safety, and efficacy data. Pts will receive intravenous ABBV-969 until disease progression, intolerable toxicity, or other study discontinuation criteria are met. The study objectives and endpoints are shown in the Table. 1. Xu M, et al. Cancers 2022;14:4034. 2. Sweat SD, et al. Urology 1998;52:637–40. Clinical trial information: NCT06318273. Research Sponsor: AbbVie Inc.

Objectives and endpoints.

Objective	Endpoint
Primary	
Safety and tolerability	Adverse events and dose-limiting toxicities Clinical laboratory parameters, vital signs, ECG
Secondary	
Preliminary efficacy	**Primary** $\geq$ 50% prostate-specific antigen (PSA) decrease from baseline **Secondary** Confirmed complete response(CR)/partial response (PR) per RECIST v1.1 PSA response duration Duration of response for pts with CR or PR Overall survival Progression-free survival
Pharmacokinetic (PK) characterization	PK parameters including C_{max}, T_{max}, $t_{1/2}$, and area under the curve using noncompartmental methods Determination of antidrug antibodies
Dose optimization	Recommended phase 2 dose determined using all available information

Previously presented at ESMO 2024, FPN: 1660TiP, Raanan Berger et al - reused with permission.

TPS5112 **Poster Session**

VALOR study: A phase II trial of vorinostat to augment response to 177Lutetium-PSMA-617 in the treatment of patients with PSMA-low metastatic castration resistant prostate cancer. First Author: Ruben Raychaudhuri, University of Washington and Fred Hutchinson Cancer Center, Seattle, WA

Background: ^{177}Lu-PSMA-617 (LuPSMA), a prostate specific membrane antigen (PSMA) targeting radioligand therapy, is approved for men with mCRPC. However, responses are only observed in ~50% of patients, with pre-clinical and clinical data indicating that those with high, homogenous PSMA expression experience the greatest benefit. Therefore, therapeutic strategies to increase PSMA expression may improve outcomes to LuPSMA and potentially other PSMA targeting therapeutics. Our group recently showed that epigenetic repression of the *FOLH1* (PSMA gene) promoter was associated with decreased PSMA expression and that treatment with a histone deacetylase inhibitor (HDACi) consistently resulted in increased PSMA protein expression both in vitro and in vivo. Based on these results, we are conducting a proof-of-concept clinical trial testing whether the HDACi vorinostat can increase PSMA expression in patients and prime them for improved response to subsequent therapy with LuPSMA. **Methods:** This single-arm, single-center, open label pilot trial seeks to enroll 15 patients with PSMA-low mCRPC who are otherwise eligible for LuPSMA. PSMA-low is defined as baseline total tumor PSMA SUVmean $<$10, a threshold that has been correlated with inferior outcomes with LuPSMA compared to those with higher SUVmean (PSMA-high). patients receive a 28-day treatment cycle of vorinostat (400mg PO daily) followed by repeat ^{68}Ga-PSMA-11 PET. Patients will then proceed to receive subsequent treatment with LuPSMA per investigator's discretion. The primary endpoint is to determine the conversion rate of PSMA-low to PSMA-high expression as determined by ^{68}Ga-PSMA-11 PET. The target enrollment provides 86% power to detect a conversion rate of 33% with vorinostat- a rate believed to be clinically meaningful and would justify a future randomized trial- relative to an assumed null conversion rate of 5% based on a 1-sample test of binomial proportions with 2-sided α=5. Key secondary endpoints include clinical efficacy of LuPSMA (e.g., radiographic and PSA response rates, PFS, OS) following vorinostat and safety and tolerability of the proposed sequential therapy. Patients enrolled on the trial undergo serial blood collection and metastatic tissue (if safe and feasible) at baseline, post-vorinostat treatment, and following progression on LuPSMA. Blood samples will be processed for analysis of circulating tumor cells (CTC) and (ct) DNA. Detailed analyses of these biospecimens will include orthogonal assessments of PSMA expression (including IHC, CTC staining), RNA sequencing, and methylation profiling. These molecular studies will be correlated with the pre/post vorinostat PSMA PET images and clinical outcomes with LuPSMA. Clinical trial information: NCT06145633. Research Sponsor: Novartis.

TPS5113 **Poster Session**

Mevrometostat in combination with enzalutamide in patients with metastatic castration-resistant prostate cancer (mCRPC) previously treated with abiraterone acetate: The phase 3, randomized MEVPRO-1 study. First Author: Neeraj Agarwal, Huntsman Cancer Institute (NCI-CCC), University of Utah, Salt Lake City, UT

Background: Resistance to androgen receptor (AR) pathway inhibitors (ARPI; e.g., abiraterone, enzalutamide) in mCRPC may be driven by preservation of AR signaling through various mechanisms. Enhancer of zeste homolog 2 (EZH2) is implicated in the pathogenesis of prostate cancer and ARPI resistance. Combining ARPI with therapies that modulate alternative signaling pathways, including epigenetic modifiers such as EZH2, could be a promising treatment approach to overcome resistance. Mevrometostat is a potent and selective small molecule EZH2 inhibitor. The optimal treatment sequence for patients with mCRPC who progress after first-line treatment with ARPI is not defined; a second ARPI or docetaxel are options used in real-world settings. Results from the dose-escalation period of a phase 1 study (NCT03460977) showed promising activity for mevrometostat combined with enzalutamide, with a manageable adverse-event profile in abiraterone-exposed patients with mCRPC (Schweizer MT, et al. *J Clin Oncol*. 2024;42(16_suppl):5061). Diarrhea, dysgeusia, and anemia were the most common adverse events considered to be related to mevrometostat. The current trial aims to evaluate radiographic progression-free survival (rPFS), overall survival (OS), and safety of mevrometostat plus enzalutamide compared with standard of care in patients with mCRPC previously treated with abiraterone. **Methods:** MEVPRO-1 (NCT06551324) is a global, open-label, phase 3 trial in patients with mCRPC aged $\geq$18 years with progression on $\geq$12 weeks of abiraterone, castration testosterone levels $\leq$50 ng/dL, ECOG performance status 0–2, and life expectancy $\geq$6 months. Approximately 600 patients will be randomized 1:1 to receive mevrometostat (875mg twice daily with food) with enzalutamide (160 mg once daily [QD]), or physician's choice of enzalutamide (160 mg QD) or docetaxel (75 mg/m^2 intravenously every 21 days). Randomization will be stratified by previous docetaxel in the metastatic castration-sensitive setting, physician's choice of comparator (enzalutamide/docetaxel) prior to randomization, and presence of hepatic metastases. The primary endpoint is blinded independent central review-assessed rPFS per RECIST 1.1 (soft tissue) and PCWG3 (bone) assessed by blinded central radiology review. Key secondary endpoint is OS. Secondary endpoints include antitumor activity by objective response rate and duration of response, safety, pharmacokinetics, ctDNA, and patient-reported outcomes. Time to event endpoints will be compared between treatment arms using a stratified log-test. HRs and 95% CIs will be estimated using a stratified Cox proportional hazard model, and Kaplan–Meier analysis will summarize time-to-event endpoints. Clinical trial information: NCT06551324. Research Sponsor: This study is sponsored by Pfizer Inc. Enzalutamide for the study is provided by Astellas Pharma Inc. Medical writing support was provided by Michelle Mancher, Allison TerBush, and Rosie Henderson of Onyx (a division of Prime), funded by Pfizer Inc.

TPS5114 **Poster Session**

Precision diagnostics in prostate cancer treatment (PREDICT): A phase 2 multi-arm biomarker based study (Alliance A032102). First Author: Rana R. McKay, Moores Cancer Center, University of California San Diego, La Jolla, CA

Background: Advances in genomic sequencing have allowed for a deeper understanding of the molecular complexity of metastatic castration-resistant prostate cancer (mCRPC) with several actionable alterations now identified, fueling new biomarker-based treatment strategies. For this reason, it is recommended that all patients with mCRPC undergo germline and somatic tumor profiling. In addition to DNA aberrations, gene expression changes can capture actionable targets and activated pathways. The phase 2 PREDICT trial is using both DNA and RNA aberrations to select patients with mCRPC for rationally designed biomarker-based therapeutic strategies. **Methods:** This is a multi-center, multi-arm, biomarker-driven phase 2 umbrella study with a primary objective of objective response rate for patients with mCRPC and measurable disease. Secondary objectives include radiographic progression-free survival, PSA response, time to first symptomatic skeletal event, overall survival, safety, and correlative studies. Eligible patients must have progressive mCRPC of any histology, received a prior androgen receptor pathway inhibitor (ARPI), and received or refused taxane chemotherapy. Patients with measurable and non-measurable disease are eligible. Patients must have standard of care next generation DNA sequencing via any CLIA-certified tissue or circulating tumor DNA assay for initial trial enrollment. For arm allocation based on RNA alterations, testing will be via the CLIA-certified Caris MI Tumor Seek assay, which includes whole exome and whole transcriptome sequencing, derived from tissue obtained within 12 months of enrollment. A real-time molecular tumor board will convene to review genomic reports and confirm arm allocation on a rolling basis as biomarker results become available. Patients with Rb loss (DNA), Rb functional loss signature (RNA), NEPC signature (RNA) will be allocated to treatment with the EZH1/2 inhibitor valemetostat. Patients with at least 2 of 3 tumor suppressor gene DNA alterations (TP53, RB1, PTEN), FANC alteration (DNA), or SLFN11 overexpression (RNA) will be allocated to cabazitaxel plus carboplatin. Patients without any study-defined alterations will be allocated to physician choice treatment with either cabazitaxel, ARPI, or ^{177}Lu-PSMA-617. The study is designed to accommodate future biomarker arms. A maximum of 64 patients with measurable disease and 94 patients with non-measurable disease for a total of 158 patients will be accrued to each treatment arm. A Simon two-stage minimax design per arm was used to determine whether the response rate for measurable disease patients was greater than 0.20. This design has a type 1 error equal to 0.05 and has power equal to 0.90 if the probability of response is 0.37. Clinical trial information: NCT06632977. Research Sponsor: https://acknowledgments.alliancefound.org; Daiichi Sankyo; U10CA180882.

TPS5115 **Poster Session**

An oral prostate cancer RIPTAC therapeutic in phase 1 for metastatic castrate resistant prostate cancer (mCRPC). First Author: Katherine J Kayser-Bricker, Halda Therapeutics, New Haven, CT

Background: New therapies are urgently needed to treat prostate cancer, especially for patients progressing on existing drugs that inhibit the activity of the Androgen Receptor (AR) (e.g. Androgen Receptor Pathway Inhibitors (ARPIs)). Metastatic Castration-Resistant Prostate Cancer (mCRPC) is a more aggressive stage of the disease, characterized by increased AR expression and signaling. To address this unmet medical need, we have developed a Regulated Induced Proximity Targeting Chimera (RIPTAC™) Therapeutic HLD-0915. HLD-0915 is a heterobifunctional small molecule that leverages full length AR (FL-AR) expression in tumor cells to form a trimeric complex with an Essential Protein (EP) needed for cell survival. This results in EP loss of function in prostate cancer cells and a selective antitumor effect. HLD-0915 activity requires only the presence of FL-AR and retains activity regardless of whether there are AR or non-AR aberrations that may otherwise serve as drivers of disease. Preclinically, HLD-0915 treatment results in tumor shrinkage and PSA declines following oral dosing in murine models of castration-resistant and ARPI-resistant forms of the disease, while delivering a favorable therapeutic index. The Phase 1 trial in mCRPC will investigate safety and early signs of efficacy in the intended patient population. **Methods:** This first-in-human, multicenter, open label Phase 1/2 study evaluates the safety, tolerability, and clinical activity of HLD-0915 in patients with mCRPC. Phase 1 consists of monotherapy dose levels employing a Bayesian Optimal Interval (BOIN) design with each dose level starting with a minimum of 3 patients per cohort with the primary objectives of defining the maximal tolerated dose and/or recommended dose for expansion and characterizing safety and tolerability of HLD-0915. This study also aims to characterize the PK profile and assess clinical activity by PSA declines and objective response rate per RECIST and will explore ctDNA, tumor cell genetics, and PD biomarkers. Patients with progressive mCRPC who may or may not have received prior novel antiandrogen therapy, a taxane, or PSMA targeted radioligand will be enrolled. Cohort 1 enrollment begins in January 2025. The Phase 2 portion of the study will confirm the RP2D and clinical activity in up to 3 cohorts which will be decided in the future based on emerging data. Clinical trial information: NCT06800313. Research Sponsor: None.

TPS5116 **Poster Session**

Mevrometostat in combination with enzalutamide for androgen receptor pathway inhibitor (ARPI)-naïve patients with metastatic castration-resistant prostate cancer (mCRPC): The phase 3, randomized MEVPRO-2 study. First Author: Neal D. Shore, Carolina Urologic Research Center, Myrtle Beach, SC

Background: Mevrometostat is a potent, selective inhibitor of the histone methyltransferase enhancer of zeste 2 (EZH2), which is canonically involved in epigenetic repression of target genes. In prostate cancer, EZH2 overexpression is associated with poor prognosis, contributing to disease progression through transcriptional repression of tumor suppressor genes and androgen receptor (AR) activation, co-regulation of AR-mediated transcriptional programs, and cell cycle deregulation through methylation of non-histone targets. Given the associations between EZH2 and the AR, the addition of an EZH2 inhibitor to ARPI is hypothesized to extend the duration of clinical response and delay antiandrogen resistance compared with ARPI alone. In a nonrandomized, phase 1 dose-escalation study, objective responses to mevrometostat with enzalutamide were observed in patients with CRPC and prior abiraterone or enzalutamide treatment (NCT03460977; Schweizer MT, et al. *J Clin Oncol*. 2024;42(16_suppl):5061). The most common adverse events considered to be related to mevrometostat were diarrhea, dysgeusia, and anemia. Despite guideline recommendations for treatment intensification with ARPIs or chemotherapy for metastatic castration-sensitive prostate cancer (mCSPC), many patients do not receive ARPIs at the mCSPC stage. MEVPRO-2 (NCT06629779) will evaluate mevrometostat plus enzalutamide compared with enzalutamide alone in ARPI-naïve patients with mCRPC. **Methods:** MEVPRO-2 is a global, double-blind, randomized, phase 3 trial. Key inclusion criteria are males, ≥18 years, with progressive mCRPC, castrate testosterone of ≤50 ng/dL, Eastern Cooperative Oncology Group performance status of 0 or 1, and life expectancy of ≥12 months. Patients with systemic treatments for mCRPC (except androgen deprivation therapy and first-generation antiandrogens) are excluded. Approximately 900 patients will be randomized 1:1 to receive mevrometostat (875 mg, twice daily) with enzalutamide (160 mg, once daily) or placebo with enzalutamide. The primary endpoint is blinded independent central review-assessed radiographic progression-free survival per Response Evaluation Criteria in Solid Tumours 1.1 (soft tissue) or Prostate Cancer Working Group 3 criteria (bone). Key secondary endpoints are overall survival and time to pain progression (Brief Pain Inventory – Short Form question 3 or opioid use). Hazard ratios and 95% confidence intervals will be estimated using a Cox proportional hazard model, stratified by prior docetaxel and presence of hepatic metastases. *P*-values will be provided using a stratified log-rank test. Safety and tolerability will also be assessed. Clinical trial information: NCT06629779. Research Sponsor: This study is sponsored by Pfizer Inc. Enzalutamide for the study will be provided by Astellas Pharma Inc. Medical writing support was provided by Michelle Mancher, Allison TerBush, and Rosie Henderson of Onyx (a division of Prime), funded by Pfizer Inc.

TPS5117 **Poster Session**

A first-in-human, phase 1 dose escalation and expansion study evaluating the safety, tolerability, and anti-tumor activity of [225Ac]Ac-FL-020, an anti-PSMA radioconjugate, in patients with metastatic castration-resistant prostate cancer (mCRPC). First Author: Andrei Iagaru, Division of Nuclear Medicine and Molecular Imaging, Stanford University, Stanford, CA

Background: Prostate-specific membrane antigen (PSMA) targeted radioligand therapy is an emerging treatment modality for metastatic castration-resistant prostate cancer (mCRPC). Alpha emitting [^{225}Ac]Ac-FL-020 represents a new generation of PSMA-targeted radioconjugates (RDC) with potential improvements in pharmacokinetics and pharmacodynamics, aiming to enhance tumor uptake while minimizing healthy tissue exposure, including the salivary glands. This novel compound was discovered using our proprietary Clear-X technology platform. This Phase 1 study evaluates the safety, tolerability, and anti-tumor activity of [^{225}Ac]Ac-FL-020 in patients with mCRPC. **Methods:** This first-in-human, open-label, multicenter Phase 1 study consists of two parts: dose escalation (Part 1) and cohort expansion (Part 2). In Part 1, the study aims to establish the safety profile and maximum tolerated dose/recommended Phase 2 dose (MTD/RP2D) of [^{225}Ac]Ac-FL-020, guided by a Bayesian logistic regression model (BLRM) with overdose control. Eligible patients must show PSMA-positive lesions on a PSMA PET/CT scan, have histologically confirmed mCRPC with documented progression, and have received prior treatments including androgen receptor signaling inhibitors or CYP17 inhibitors, along with at least 1 previous taxane regimen. Exclusion criteria include patients with extensive PSMA-negative disease. The dose escalation follows cohorts starting with 1-3 patients, expanding to 3-6 patients, with provisional dose levels from 1 to 5 MBq. Part 2, the cohort expansion, will commence once the RP2D is established, enrolling an additional 18 patients to further evaluate safety and gather preliminary efficacy data. The primary objective is to establish the safety profile and determine the MTD/RP2D of [^{225}Ac]Ac-FL-020 in mCRPC patients. Secondary objectives include assessing pharmacokinetics, dosimetry, and anti-tumor activity, with the overarching goal of exploring the potential of this novel actinium RDC for improving outcomes in patients with mCRPC. The study is enrolling in Australia and US, with European sites planned to open later in 2025. Clinical trial information: NCT06492122. Research Sponsor: Full-Life Technologies GmbH.

TPS5118 **Poster Session**

Trial in progress (XALute): Phase 3 study of xaluritamig vs investigator's choice of cabazitaxel or second androgen receptor directed therapy (ARDT) in post-taxane metastatic castration-resistant prostate cancer (mCRPC). First Author: William Kevin Kelly, Thomas Jefferson University Hospital, Philadelphia, PA

Background: The median overall survival of patients with mCRPC remains under 2 years even with newer therapies. Xaluritamig, an XmAb 2+1 T-cell engager that targets the six-transmembrane epithelial antigen of prostate 1 (STEAP1), facilitates lysis of STEAP1-expressing cancer cells, such as those in advanced prostate cancer. In a first-in-human study, xaluritamig demonstrated encouraging efficacy and a manageable safety profile for patients with mCRPC refractory to standard of care therapies (Kelly WK, et al. Cancer Discov. 2024;14(1):76-89). **Methods:** XALute is a randomized, multicenter, open-label, phase 3 study to evaluate the efficacy and safety of xaluritamig vs cabazitaxel or second ARDT in men with mCRPC previously treated with taxane chemotherapy. Enrollment in the control arm treatments will be split evenly between cabazitaxel and second ARDT. Stratification factors include LDH ≤ or > 260 IU/L, liver metastases (Y/N), prior prostate-specific membrane antigen radioligand therapy (PSMA-RLT) (Y/N) and the intention to treat with cabazitaxel or ARDT switch. Approximately 675 patients will be enrolled. Participants will be randomly assigned in a 2:1 ratio to xaluritamig monotherapy or standard care. Participants will receive treatment until radiographic disease progression per Prostate Cancer Clinical Trials Working Group 3 (PCWG3), unacceptable toxicity, initiation of other anticancer therapy, withdrawal of consent, death, or end of study as determined by the sponsor. The primary efficacy endpoint is overall survival. The key secondary efficacy endpoint is radiographic progression-free survival per PCWG3 by blinded independent central review. Key inclusion criteria are pathological/cytological confirmation of prostate adenocarcinoma; mCRPC with at least one metastatic lesion; evidence of progressive disease; prior treatment with at least one ARDT; one taxane therapy in the mCRPC setting, and ongoing androgen deprivation with serum testosterone levels (<50 ng/dL or <1.7 nmol/L). Prior treatment with PSMA-RLT, poly ADP-ribosylation inhibitors, and immune checkpoint inhibitors are permitted. Exclusion criteria include prior STEAP1-targeted therapy, any anticancer therapy within 4 weeks prior to first dose of study treatment (not including androgen deprivation therapy), prior PSMA-RLT within 2 months of first dose of study treatment unless less than 2 cycles received, and prior radionuclide therapy (radium-223) within 2 months of first dose of study treatment To mitigate risk of cytokine release syndrome, xaluritamig will be administered with step dosing. Cabazitaxel or second ARDT will be administered according to regional prescribing information. Funded by Amgen Inc. Clinical trial information: NCT06691984. Research Sponsor: Amgen Inc.

TPS5119 **Poster Session**

A phase 3 trial of the androgen receptor ligand-directed degrader, BMS-986365, versus investigator's choice in patients with metastatic castration-resistant prostate cancer (CA071-1000 - rechARge). First Author: Kim N. Chi, Department of Medical Oncology, BC Cancer Agency, Vancouver, BC, Canada

Background: Prostate cancer relies on the androgen receptor (AR) pathway as a key oncogenic driver. BMS-986365 is a heterobifunctional, orally bioavailable ligand-directed degrader targeting the AR via a first-in-class dual mechanism of AR degradation and antagonism. Results from the first-in-human phase 1 study showed that BMS-986365 was well tolerated with a manageable safety profile and demonstrated antitumor activity in heavily pretreated patients with metastatic castration resistant prostate cancer (mCRPC) regardless of AR gene alterations (Rathkopf et al. *Ann Oncol* 2025;36:76–88). Here, we present the study design of rechARge (NCT06764485), a phase 3, 2-part, randomized, open-label trial evaluating the efficacy and safety of BMS-986365 versus investigator's choice of AR pathway inhibitor (ARPI) or docetaxel, in patients with mCRPC who have failed treatment with 1 prior ARPI. **Methods:** Approximately 960 patients will be randomized in this phase 3, 2-part study. In Part 1 (dose selection), patients will be randomized 1:1:1 to receive either BMS-986365 400 or 300 mg BID Q28D, or investigator's choice comprising ARPI (enzalutamide [160 mg QD] or abiraterone [1000 mg QD + prednisone] Q28D); or docetaxel 75 mg/m^2 + prednisone Q21D up to a maximum of 10 cycles. In Part 2, patients will be randomized 1:1 to receive either BMS-986365 (dose determined from Part 1) or investigator's choice treatment (same as Part 1). Randomization is stratified by prior type of ARPI and investigator's choice (2nd ARPI vs docetaxel). Patients will be treated until radiographic progressive disease by blinded independent central review (BICR) or unacceptable toxicity; all patients must continue androgen deprivation therapy as part of the standard of care. Key inclusion criteria include no more than 1 previous ARPI, confirmed progressive mCRPC defined by having ≥1 of the following: prostate-specific antigen (PSA) progression or radiographic disease progression in soft tissue based on RECIST 1.1 criteria or bone defined as the appearance of ≥2 new lesions on a bone scan; ECOG PS of 0–1, asymptomatic or mildly symptomatic from prostate cancer (Brief Pain Inventory-Short Form, worst pain in last 24 hr <4), no liver metastases, and no prior chemotherapy in the mCRPC setting (docetaxel permitted for mCSPC if >12 months since completion). The primary endpoint is radiographic progression-free survival by BICR using RECIST 1.1 (soft tissue) and PCWG3 (bone) criteria. The key secondary endpoint is overall survival. Other secondary endpoints include safety, overall response rate, confirmed PSA response rate (PSA30 and PSA50), and patient reported outcomes. The study is recruiting at 230 sites in 24 countries/territories across North America, Europe, Latin America, and East Asia. Clinical trial information: NCT06764485. Research Sponsor: Bristol Myers Squibb.

TPS5120 **Poster Session**

The impact of DNA repair genetic alterations identified by circulating tumor DNA on sensitivity to radium-223 in bone metastatic, castration-resistant prostate cancer. First Author: Steven M. Blinka, Fred Hutchinson Cancer Center, Seattle, WA

Background: Selection, timing, and sequencing of therapy for men with bone metastatic castration-resistant prostate cancer (mCRPC) for optimal clinical outcomes is not well-defined. Accordingly, identification of predictive biomarkers for response and outcomes to a given therapy is critical to guide clinical decision-making. Prior research from our group and others has demonstrated that a high proportion (up to 25%) of mCRPC patients harbor aberrations in DNA damage repair (DDR) genes. These findings are clinically meaningful given the efficacy of PARP inhibitors in treating a subset of mCRPC patients with DDR defects. Radium-223 acts by delivering high-energy alpha particles selectively to bone metastases leading to double-stranded DNA breaks. Retrospective studies have shown patients with DDR alterations who are treated with radium-223 have overall survival benefit, improved alkaline phosphatase (ALP) response, and more commonly complete radium-223 treatment. Therefore, we hypothesize that mCRPC with alterations in DDR genes should be particularly vulnerable to treatment with radium-223 and should be evaluated for resultant outcomes prospectively. **Methods:** This Phase 2, multi-center, prospective single-arm biomarker trial aims to enroll 60 patients. Eligible patients must have mCRPC, radiographic evidence of bone disease, symptoms, and PSA $\geq$10 to ensure successful ctDNA analysis. All patients will receive radium-223 (55 kBq/kg) for up to 6 doses. Patients who have received prior platinum containing chemotherapy will be excluded. ctDNA will be obtained for OncoPlexCT to determine if a patient has a DDR gene alteration (results will not affect treatment plan). Leukocyte analysis will be performed to confirm whether specific alterations are germline vs somatic. The primary objective is to determine the response rate of bone mCRPC with DDR deficiency to treatment with radium-223. Response will be defined as having PSA and/or ALP decline of $\geq$30% from baseline. The null hypothesis is that the true response rate is 0.40, and the alternate hypothesis is the true response rate is 0.80 (TOPARP, NCT01682772). It is estimated that 25% of the patient population will have DDR alterations and outcomes will be compared with those who are DDR proficient. Using 90% power and an alpha of 0.05, we will accrue 60 patients to ensure the goal of 12 patients with DDR alterations is met. Secondary objectives include determining whether patients who received a prior PARP inhibitor have no decrement in response, overall survival, number of cycles of radium-223 received, and effect of germline vs somatic alterations on response. This trial is currently open to enrollment at Fred Hutch, University of Wisconsin, and Johns Hopkins, and 22/60 patients have already been enrolled. Clinical trial information: NCT04489719. Research Sponsor: Fred Hutch Cancer Center is the primary sponsor of this study. Bayer provided some financial support for this research.

TPS5121 **Poster Session**

A randomized phase 2 trial of flexible and extended dosing of ^{177}Lu-PSMA-617 molecular radioligand therapy in mCRPC (FLEX-MRT): Trial in progress update. First Author: Adrien Holzgreve, Ahmanson Translational Theranostics Division, University of California, Los Angeles, Los Angeles, CA

Background: The U.S. Food and Drug Administration (FDA) approved ^{177}Lu-PSMA-617 radiopharmaceutical therapy (RPT) for patients with metastatic castration-resistant prostate cancer (mCRPC) with a fixed dosing schedule: Six cycles of 7.4 GBq administered in six-week intervals. However, a patient-tailored more flexible and extended dosing schedule of ^{177}Lu-PSMA RPT may increase treatment efficacy. In this randomized trial in men with mCRPC, we aim to determine the efficacy of a response-based flexible dosing schedule of ^{177}Lu-PSMA-617 RPT administered up to 12 treatment cycles compared to the current standard of care. **Methods:** This is an investigator-initiated prospective phase 2, open-label, randomized, controlled, parallel group, single-center trial. The aim is to assess the 2-year survival rate in mCRPC patients treated with a flexible dosing schedule of ^{177}Lu-PSMA RPT up to 12 cycles in comparison to the fixed dosing schedule of 6 cycles. Patients with progressive mCRPC post-ARSI, post taxane-based chemotherapy are eligible by PSMA positron emission tomography (PET) VISION trial criteria. Exclusion criteria include prior RPT and less than 6 weeks since the last myelosuppressive therapy. We hypothesized 2-year survival rates of 55% in the investigational group and 30% in the control group. A two-sided log rank test with an overall sample size of 90 subjects (45 treatment group, 45 control group) achieves 80.3% power at a 0.05 significance level to detect a hazard ratio of 0.050. Patients will be randomized in a 1:1 ratio: The investigational arm is treated with up to 12 cycles including potential "treatment holidays" depending on the treatment response (n=45); the control arm receives 6 cycles administered in six-week intervals (n=45). Imaging response to RPT is assessed using ^{177}Lu-PSMA-617 SPECT/CT after each cycle and PSMA PET/CT during treatment holidays (every 12 weeks), respectively. In the investigational arm, RPT will be re-started after a treatment holiday if the patient experiences a $\geq$25% PSA progression and an imaging progression according to the Response Evaluation Criteria in PSMA PET/CT (RECIP). Primary endpoint is the 2-year survival rate calculated from the date of the first cycle of RPT. Secondary endpoints include safety by Common Terminology Criteria for Adverse Events (CTCAE) and dosimetry, and determination of overall and progression-free survival (evidence of progression as defined by either radiographic, PSA, or clinical progression, or death from any cause). The FLEX-MRT trial has been approved by the FDA (IND #168362), and the UCLA IRB (#23-000931). The trial is registered on ClinicalTrials.gov (NCT06216249). The FLEX-MRT trial is currently recruiting. Start of enrollment was in August 2024. As of January 27th, 2025, 19 patients have been enrolled. Clinical trial information: NCT06216249. Research Sponsor: Prostate Cancer Foundation; Deutsche Forschungsgemeinschaft (DFG, German Research Foundation); 545058105; Novartis.

TPS5122 **Poster Session**

A randomized phase III trial investigating platinum and taxane chemotherapy in metastatic castration resistant prostate cancer (mCRPC) patients with alterations in DNA damage response (DDR) genes (OPTION-DDR) CCTG-PR-25 NCT06439225. First Author: Michael Paul Kolinsky, Cross Cancer Institute, University of Alberta, Edmonton, AB, Canada

Background: For patients (pts) with mCRPC there are numerous treatment options including single agent docetaxel after treatment with androgen receptor pathway inhibitors (ARPI). Despite the availability of varied treatments, overall survival (OS) for pts with mCRPC after ARPI remains poor (12-19 months). Improvements in outcomes are desperately needed. 25% of pts have alterations in DDR genes and are potentially sensitive to treatment with platinum agents. Carboplatin has been previously evaluated in smaller trials in pts with mCRPC and shows promise in patients with DDR gene alterations. PR-25 leverages standard of care testing for DDR genes to evaluate in a rigorous manner whether addition of carboplatin to docetaxel improves overall survival (OS) in pts with DDR gene alterations and mCRPC. **Methods:** PR25 is a phase III randomised controlled trial led by the Canadian Cancer Trials Group comparing docetaxel to docetaxel and carboplatin in pts with DDR alterations. Pts have to receive prior ARPI for mCRPC, and demonstrate radiographic or PSA progression prior to enrollment. Qualifying DDR gene alterations include: BRCA1, BRCA2, ATM, ATR, BRIP1, BARD1, CDK12, CHEK1, CHEK2, ERCC2, FANCA, FANCC, FANCD2, FANCL, PALB2, RAD51B, RAD51C, RAD51D, RAD54L. The primary endpoint is OS. Secondary endpoints include: radiographic progression free survival (PCWG3 and RECIST 1.1), PSA response, time to next systemic therapy, patient reported quality of life and economic evaluation. Statistical design: The target accrual is 236 patients over 3.25 yrs with 2 year follow-up to detect a HR of 0.65 in OS, using a 5% (2 sided) level test with power of 80%. Conduct to date: Study activation – October 2024. First patient enrolled - December 2024. Accrual to date: 2 Supported by CIHR grant #189966, NCTN grant #CA180863 and CCS grant #707213. Clinical trial information: NCT06439225. Research Sponsor: Canadian Institutes of Health Research; 189966; NCI's National Clinical Trials Network; CA180863; Canadian Cancer Society; 707213.

TPS5123 **Poster Session**

A randomized, open-label, phase 2b study of the BET bromodomain inhibitor (BETi) ZEN-3694 plus enzalutamide vs. enzalutamide in patients with metastatic castration resistant prostate cancer (mCRPC). First Author: Rahul Raj Aggarwal, University of California, San Francisco, San Francisco, CA

Background: Androgen receptor signaling inhibitors (ARSI), such as enzalutamide (Enza), and abiraterone (Abi), are standard therapies for metastatic hormone-sensitive and metastatic castration-resistant prostate cancer (mHSPC, mCRPC). Patients who respond to the initial ARSI are frequently prescribed a 2nd ARSI upon progression. A suboptimal response to first line ARSI, including the ~ 20% treated with an ARSI for mHSPC who progress within 12 months of treatment initiation, may enrich for cancers harboring AR-independent mechanisms of resistance including treatment-emergent neuroendocrine prostate cancer (t-NEPC). BETi have been shown pre-clinically to block the neuroendocrine prostate cancer lineage plasticity program through modulating E2F1, a transcription factor involved in stemness and cell differentiation. Prior results from a mCRPC Ph. 1b/2a trial of ZEN-3694+ Enza support this notion, as lower AR transcriptional activity in baseline tumor biopsies was associated with longer radiographic progression-free survival (rPFS). Additionally, mCRPC patients who were primary refractory to 1st line abiraterone had prolonged rPFS with ZEN-3694 + Enza, suggesting that the patients with primary resistance may benefit from the combination. To test this hypothesis, a Ph. 2b randomized trial was initiated, enriching for mCRPC with suboptimal response to 1st line ARSI. **Methods:** This is a multi-national (USA and China), open-label, randomized, two cohort, Ph. 2b study of ZEN-3694 + Enza vs. Enza in mCRPC patients who have progressed on Abi (NCT04986423). Cohort A (N = 150): Patients with poor response to Abi defined either as progression in $<$ 12 months or failure to achieve PSA nadir of 0.2 ng/mL while taking Abi in HSPC setting, or progression in $<$ 6 months and/or failure to achieve a PSA50 response while taking Abi in the CRPC setting. Cohort B (N = 50): Patients who responded to Abi, defined as $>$ 12 months duration without progression while on Abi in the HSPC setting and achieving a nadir PSA $<$ 0.2 ng/mL, or $>$ 6 months duration without progression while on Abi in the CRPC setting and confirmed PSA50 response. The primary endpoint is radiographic progression-free survival (rPFS) by blinded independent central review (BICR) in Cohort A evaluated by PCWG3. Key secondary endpoints include rPFS by BICR for Cohorts A + B, PFS by investigator assessment, overall survival, PSA50 response rate, objective response rate by RECIST 1.1, efficacy endpoints for only USA patients, and patient-reported health status and quality of life, evaluated in Cohorts A, and Cohorts A + B together. The trial, conducted in collaboration with Newsoara has dosed approximately 150 of 200 patients to date. Astellas is providing enzalutamide for this study. Clinical trial information: NCT04986423. Research Sponsor: Newsoara Biopharma Co., Ltd; Zenith Epigenetics; Astellas Pharma Inc.

TPS5125 **Poster Session**

SECuRE: A dose escalation/expansion study to assess the anti-tumor efficacy of ^{67}Cu-SAR-bisPSMA in patients with metastatic castrate resistant prostate cancer. First Author: Geoffrey Bates Johnson, Department of Nuclear Medicine, Mayo Clinic in Rochester, Rochester, MN

Background: Prostate cancer (PC) is common and despite recent advances in treatment options, patients with metastatic disease still have poor outcomes. The double PSMA binding moiety of SAR-bisPSMA in ^{64}Cu-SAR-bisPSMA (imaging) and ^{67}Cu-SAR-bisPSMA (therapy) may offer advantages compared to currently used single-target PSMA agents. Clinical evidence demonstrated 2-3 times higher uptake of ^{64}Cu-SAR-bisPSMA compared to the single-target PSMA agent, ^{68}Ga-PSMA-11. Pre-clinical efficacy data of ^{67}Cu-SAR-bisPSMA in mice showed statistically significant tumor growth inhibition and increased survival in a PC xenograft study. These results led to the development of the SECuRE trial, which aims to assess the safety and anti-tumor efficacy of ^{67}Cu-SAR-bisPSMA in patients with metastatic castrate resistant PC (mCRPC). **Methods:** SECuRE is a Phase I/IIa multi-center, open-label, non-randomized, dose-escalation and cohort expansion study of ^{64}Cu-SAR-bisPSMA and ^{67}Cu-SAR-bisPSMA in patients with mCRPC. The target population is patients who have progressed despite having at least one androgen receptor pathway inhibitor and demonstrate positivity on ^{64}Cu-SAR-bisPSMA PET. The study comprises 3 phases: Dosimetry (N=6), Dose Escalation (N~24) and Cohort Expansion (N=24). The ^{67}Cu-SAR-bisPSMA dose levels investigated in the Dose Escalation Phase are: 4 GBq (cohort 1, single dose), 8 GBq (cohort 2, single dose), 12 GBq (cohort 3, single dose) and 24 GBq across two doses (cohort 4, two doses at the maximum tolerated dose or maximum feasible dose [MTD/MFD] established in cohorts 1-3; two additional doses may be offered in case of radiological non-progression). In the Cohort Expansion phase, participants will receive 2 doses of ^{67}Cu-SAR-bisPSMA at the recommended dose determined in the Dose Escalation Phase (those with radiological non-progression may be offered up to 2 additional doses). A recent protocol amendment increased the number of participants from 14 to 24 in the Cohort Expansion phase, in which 8 will receive combination therapy of ^{67}Cu-SAR-bisPSMA with enzalutamide. The primary and key secondary objectives include assessment of ^{64}Cu- and ^{67}Cu-SAR-bisPSMA's safety and dosimetry and determining the anti-tumor efficacy of ^{67}Cu-SAR-bisPSMA. Response to ^{67}Cu-SAR-bisPSMA will be assessed biochemically ($\geq$50% decline in prostate-specific antigen) and radiographically (by RECIST V1.1 and PCWG3). Clinical trial information: NCT04868604. Research Sponsor: Clarity Pharmaceuticals.

TPS5126 **Poster Session**

A phase 3 study of 177Lu-rosptamab plus standard of care vs. standard of care alone in patients with metastatic castration-resistant prostate cancer (ProstACT Global). First Author: Scott T. Tagawa, Weill Cornell Medical College of Cornell University, New York, NY

Background: The treatment of advanced prostate cancer (PC) is challenging, with undesirable side effects that impact patient quality of life. Radioimmunotherapy (RIT) can localize therapy to specific tumor cells in multiple organs to reduce or eliminate damage to normal tissue. The cell surface glycoprotein prostate-specific membrane antigen (PSMA) is an ideal therapeutic target as it is highly expressed by malignant prostate cells. There is a strong rationale for further investigation of the ^{177}Lu-labeled, chelator-conjugated antibody, ^{177}Lu-rosopatamab, as a potential first-line RIT candidate for the treatment of PC. **Methods:** This multinational, multicenter, prospective, randomized, open label phase 3 study will have 2 parts: a dosimetry and safety lead-in (n=30) and a randomized treatment expansion (n=490). In Part 1, patients will be divided into 3 groups (n=10 each) to receive 2 single intravenous (IV) injections of 76 millicuries (mCi) each, 14 days apart, of ^{177}Lu-rosopatamab with best standard of care (SoC) combinations with abiraterone, enzalutamide, or docetaxel to fully characterize biodistribution and safety profiles of ^{177}Lu-DOTA-rosopatamab + SoC. SoC received will be determined prior to treatment with ^{177}Lu-rosopatamab. In Part 2, patients will be enrolled in a 2:1 ratio to receive either the best SoC or 2 single IV injections of 76 mCi each of ^{177}Lu-rosopatamab, given 14 days apart, plus best SoC. SoC will be determined prior to randomization. Eligible patients must have PSMA-expressing metastatic castration-resistant PC (mCRPC) that have progressed despite prior therapy with either enzalutamide or abiraterone plus prednisone, and 1 line of prior taxane therapy or have refused or are ineligible for taxanes. Patients must have adequate organ function including at least 150x10^9/L platelets, hemoglobin 10 g/dL, and have PSMA-positive disease on ^{68}Ga-PSMA-11 PET/CT imaging as confirmed by a central reader. Key exclusion criteria include small cell histology, increased risk of hemorrhage or bleeding, known brain or hepatic metastases, or history of stroke, seizure, or treatment with radioisotopes within 6 months prior to randomization. The primary endpoint is radiographic progression-free survival (rPFS). Key secondary endpoint is OS. Additional secondary endpoints include 5-year overall survival, tumor objective response rate, time to symptomatic skeletal event, and health-related quality of life. An alpha control and 95% confidence intervals will be used; patients will be substratified between TLX591 + 2nd ARPI or TLX591 + docetaxel. This study is currently enrolling. Clinical trial information: NCT06520345. Research Sponsor: Telix Pharmaceuticals.

TPS5127 **Poster Session**

PSMA-delay castration (DC): An open-label, multicenter, randomized phase 3 study of [^{177}Lu]Lu-PSMA-617 versus observation in patients with metachronous PSMA-positive oligometastatic prostate cancer (OMPC). First Author: Alton Oliver Sartor, Mayo Clinic, Rochester, MN

Background: Androgen deprivation therapy (ADT) $\pm$ androgen receptor pathway inhibitor therapy is a primary treatment for metastatic hormone-sensitive prostate cancer, but is non-curative and has significant toxicities when used long-term. In patients with OMPC for whom delaying ADT is appropriate, metastasis-directed therapy such as stereotactic body radiation therapy (SBRT) has been shown to provide local disease control. However, many patients do not experience a complete prostate-specific antigen (PSA) response and develop poly-metastatic disease. [^{177}Lu]Lu-PSMA-617 (^{177}Lu-PSMA-617) is a prostate-specific membrane antigen (PSMA)-targeted radioligand therapy with demonstrated efficacy and a manageable safety profile in patients with PSMA-positive metastatic castration-resistant prostate cancer in the VISION and PSMAfore trials. PSMA-DC (NCT05939414) is an ongoing, international, randomized phase 3 trial to evaluate the efficacy of ^{177}Lu-PSMA-617 versus observation after SBRT in delaying castration and disease progression in patients with PSMA-positive OMPC. **Methods:** Eligible patients have histologically confirmed prostate cancer, biochemical recurrence post-definitive treatment, OMPC with $\leq$ 5 PSMA-positive metastatic lesions including $\geq$ 1 distant metastasis on PSMA PET/CT scans (all must be amenable to SBRT), PSA doubling time $<$ 10 months and non-castration testosterone levels ($>$ 100 ng/dL). Exclusion criteria include distant metastasis by conventional imaging (CI; CT/MRI and bone scans) at screening, prior ADT (except adjuvant ADT completed $>$ 12 months before randomization), or other systemic therapy for metastatic prostate cancer. Patients (N = ~450) will be randomized 2:1 to ^{177}Lu-PSMA-617 or observation and will receive SBRT to all metastatic lesions within 14 days, completed within 3 weeks. Patients will then receive either intravenous ^{177}Lu-PSMA-617 (7.4 GBq/6 weeks; 4 cycles), starting 7–21 days after SBRT, or undergo observation only. Additional SBRT for new lesions is allowed. ADT is allowed after a metastasis-free survival (MFS) event by CI confirmed by blinded independent review committee (BIRC). Safety follow-up will occur 42 days after the last ^{177}Lu-PSMA-617 dose and at the week 24 visit for the observational arm. Long-term follow-up for the ^{177}Lu-PSMA-617 arm will include safety assessments every ~32 weeks. The primary endpoint is MFS by CI as assessed by BIRC using RECIST v1.1, or death. To provide 90% power to detect a hazard ratio of 0.6, 187 MFS events are required. The key secondary endpoint is time to next hormonal therapy. Additional secondary endpoints include time to PSA progression, radiographic progression-free survival, symptomatic progression, patient-reported health-related quality of life, overall survival and safety. Shore et al. PSMA-delay castration (DC): an open-label, multicenter, randomized phase 3 study of [^{177}Lu]Lu-PSMA-617 versus observation in patients with metachronous PSMA-positive oligometastatic prostate cancer (OMPC). J Urol 2025;213 (5S2_suppl):e28. https://www.auajournals.org/doi/10.1097/01.JU.0001110444.53548.eb. Reused with permission; ©American Urological Association, 2025. This abstract previously presented at 2025 AUA Annual Meeting. Clinical trial information: NCT05939414. Research Sponsor: Novartis.

TPS5128 **Poster Session**

METANOVA: A phase II trial of metastasis-directed radiotherapy for de novo oligometastatic prostate cancer treated with long-term androgen deprivation therapy in the STAMPEDE trial. First Author: Angela Y Jia, University Hospitals Seidman Cancer Center, Case Western Reserve University, Cleveland, OH

Background: Men with de novo oligometastatic hormone-sensitive prostate cancer (omHSPC) represent a unique subgroup where metastasis-directed radiotherapy (MDRT) may improve outcomes when added to systemic therapy. Retrospective data suggest potential survival benefits of MDT in oligometastatic prostate cancer (PCa), but prospective randomized evidence in the de novo setting is lacking. The METANOVA trial aims to determine whether MDRT, combined with standard systemic therapy (SST) and prostate-directed local therapy, improves outcomes for these patients. **Methods:** METANOVA is a phase II, randomized, open-label trial enrolling 200 men with histologically confirmed de novo omHSPC (NCT06150417). Oligometastatic disease defined as 1–5 metastatic sites by traditional imaging (MRI, CT, or ^{99m}Tc bone scan) or 1–10 sites by PSMA PET/CT. Patients are allowed up to 30 days of androgen deprivation therapy (ADT) prior to enrollment. Patients are randomized 1:1 to standard of care (SOC) or SOC + MDRT to all metastatic sites. SOC includes 12 months of SST (ADT, with addition of an androgen receptor signaling inhibitor; triplet therapy is not allowed) and definitive treatment of the primary. Planned local therapy may be prostate-directed radiation therapy with definitive dose (moderate hypofractionation and ultra-hypofractionation allowed) or radical prostatectomy (maximum 50 patients to receive surgery), determined prior to randomization. MDRT will be delivered using stereotactic body radiation therapy (SBRT) to all metastatic lesions on conventional imaging or PSMA PET/CT. Patients are stratified to the use of PSMA PET/CT to stage, number of bone metastasis (0 vs 1-3 vs 4-10), local treatment (RT vs RP), and plan to MDRT all sites of PSMA disease (yes vs no). The primary endpoint is failure-free survival (FFS), defined as the time from randomization to biochemical failure, local or distant progression, skeletal-related event, any salvage intervention after 12 months planned SOC therapy, or death from prostate cancer. Secondary endpoints include overall survival, radiographic progression-free survival, quality of life (EPIC-26 domains), and toxicity. Correlative studies will explore imaging and molecular features from the primary, metastasis, and circulating disease to develop a predictive biomarker of which patients would derive the greatest benefit from MDRT. This study is designed to demonstrate a 34% relative reduction in the hazard of FFS from the addition of MDRT to SOC, providing 80% power at a one-sided alpha level of 0.05. The trial activated in July 2024, aims to complete accrual within 3 years. Data from this trial is pre-planned to be pooled with the STAMPEDE2 (NCT06320067) trial in the United Kingdom, which is assessing overall survival benefit of MDRT in men with de novo omHSPC. Funding: NIH U01CA257638. Clinical trial information: NCT06150417. Research Sponsor: NIH-NCI.

TPS5129 **Poster Session**

TRIPLE-SWITCH (SWOG/CCTG-PR26): A randomized phase III clinical trial for the addition of docetaxel to androgen receptor pathway inhibitors in patients with metastatic castration sensitive prostate cancer (mCSPC) and suboptimal PSA response (NCT06592924). First Author: Michael Ong, The Ottawa Hospital Cancer Centre, Ottawa, ON, Canada

Background: Management of patients (pts) with mCSPC remains a challenge due to its incurable nature and heterogeneous response to androgen deprivation therapy (ADT) and androgen receptor pathway inhibitors (ARPI). Recent analyses of phase III ADT + ARPI trials show that mCSPC with suboptimal PSA response (≥0.2ng/ml at 6-12 months) have poor prognosis, short time to castration-resistance (CRPC) and 30-36 month median overall survival (OS). While docetaxel could also be utilized in mCSPC, there is equipoise about its use in ARPI-treated pts because of 1) an absence of randomized data for docetaxel in this setting, 2) toxicity of docetaxel with impact on quality of life for pts, and 3) selection of docetaxel treatment by disease volume rather than disease biology. CCTG-PR26 (TRIPLE-SWITCH) is a joint CCTG-SWOG trial run through the NCI National Clinical Trials Network. This study investigates whether adding docetaxel prior to development of CRPC, regardless of disease volume, will improve OS in ARPI-treated mCSPC pts that show evidence of suboptimal response. **Methods:** This international, open-label, randomized phase III trial compares standard ADT + ARPI against the addition of docetaxel to ADT + ARPI in mCSPC pts with suboptimal PSA response, defined as PSA ≥0.2 ng/mL after 6-12 months of ADT and ≥4 months of ARPI. Stratification will be based on PSA levels, ARPI type, presence of liver metastasis, disease recurrence status, and time since ADT initiation. Arm 1 will continue standard ADT + ARPI (abiraterone acetate with prednisone, apalutamide, enzalutamide or darolutamide). Arm 2 will receive docetaxel 75mg/m^2 IV every 3 weeks for up to 6 cycles in addition to continuing standard ADT + ARPI. Sample size is 830 pts in order to detect a targeted 33% improvement in overall survival (hazard ratio 0.75) using a 1-sided 0.025 level test with 85% power. Key eligibility criteria are: ≥18 years, histologically confirmed prostate adenocarcinoma, metastatic disease present and confirmed by conventional imaging (CT and/or bone scan), PSA ≥5.0 ng/mL prior to ADT, receipt of ADT for 6-12 months and ARPI for ≥4 months, PSA ≥0.2 ng/mL within 14 days of enrolment, adequate organ and marrow function, ECOG performance status 0-2, eligible for docetaxel chemotherapy, no evidence of disease progression or biochemical progression on ADT prior to enrolment. Primary endpoint is overall survival. Secondary endpoints include PSA response, PSA kinetics, and clinical progression free-survival. Correlative studies will explore the prognostic and predictive value of circulating tumor DNA (ctDNA) and the association between molecular signatures in primary prostate cancer tissue and clinical outcomes. Enrolment has been initiated in January 2025 and is ongoing. Clinical trial information: NCT06592924. Research Sponsor: Canadian Institutes of Health Research; 195838; NCI National Clinical Trials Network (NCTN); CA180863; Canadian Cancer Society; 707213.

TPS5130 **Poster Session**

A phase II study of niraparib (N), abiraterone acetate (AA) plus prednisone (P) for Hispanic/Latino (HL) and non-Hispanic Black (NHB) patients with metastatic hormone sensitive prostate cancer (mHSPC) and deleterious homologous recombination repair alterations (HRRa; HARMONY). First Author: Qian Qin, Department of Internal Medicine, Division of Hematology and Oncology, UT Southwestern, Dallas, TX

Background: Patients with prostate cancer and deleterious HRRa have poorer prognosis but derive benefit from poly (ADP-ribose) polymerase (PARP) inhibition. However, prevalence of HRRa and response to PARP inhibition are less well defined in racial/ethnic minorities. We designed the HARMONY trial to evaluate the efficacy of N/AA/P in HL and NHB patients with mHSPC and deleterious HRRa. **Methods:** This multicenter, open label, phase II study is open through the Hoosier Cancer Research Network in the United States. The trial enrolls patients who self-identify as HL or NHB and have mHSPC with HRRa including *BRCA 1/2, BRIP1, CHEK2, FANCA, PALB2, RAD51B,* and/or *RAD54L.* Eligible patients will have hormone sensitive, treatment naïve or minimally treated prostate cancer (i.e., bicalutamide ≤ 45 days, androgen deprivation therapy [ADT] ± AA plus P ≤ 45 days allowed). Prostate cancer variants, other therapy in mHSPC setting, or symptomatic brain metastases are exclusionary. Enrolled patients will receive 24 weeks (w) of ADT plus N/AA dual action tablet (DAT) plus P, followed by an adaptive approach based on prostate specific antigen (PSA) response. Subjects in Arm A (PSA > 4.0 ng/mL at 24 w) can continue ADT/N/AA/P for max 2 years or stop N and escalate therapy to ADT/AA/P plus 6 cycles of docetaxel followed by standard of care (SOC) therapy. Subjects in Arm B (PSA ≤ 4.0 ng/mL at 24 w) will continue ADT/N/AA/P for a total of 12 months. At 12 months in Arm B, subjects with PSA ≥ 0.2 ng/mL will continue ADT/N/AA/P for max 2 years, and subjects achieving PSA < 0.2 ng/mL have the option to continue ADT/N/AA/P for max 2 years or discontinue all therapy with the option to start SOC treatment at disease progression. PSA decline to < 0.2 ng/mL at 24w (primary endpoint) will be evaluated for each racial/ethnicity group against a historic rate of 50%. Thirty patients per racial/ethnic cohort will give 80% power at 0.1 significance to determine noninferiority with a no-inferiority margin of 0.185. Estimating 5% drop out, 64 patients will be enrolled (n=32 HL and n=32 NHB). Key secondary/exploratory endpoints include PSA reduction ≥ 90%, overall response rate, PSA/radiographic progression free survival, overall survival, time to subsequent anti-cancer therapy, quality of life and safety. Key genomic correlatives will be evaluated. ClinicalTrials.gov: NCT06392841. Study support of drug and funding: Janssen Scientific Affairs LLC. Clinical trial information: NCT06392841. Research Sponsor: Janssen Scientific Affairs LLC.

TPS5131 **Poster Session**

Darolutamide plus androgen deprivation therapy (ADT) in patients with high-risk biochemical recurrence (BCR) of prostate cancer: A phase 3, randomized, double-blind, placebo-controlled study (ARASTEP). First Author: Alicia K. Morgans, Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA

Background: Patients with prostate cancer treated with radiotherapy (RT) or radical prostatectomy (RP) as primary therapy may develop BCR – a prostate-specific antigen (PSA) increase with no evidence of metastases on conventional imaging (e.g. magnetic resonance imaging/computed tomography). Prostate-specific membrane antigen positron emission tomography/computed tomography (PSMA PET/CT) is more sensitive than conventional imaging and may detect lesions in patients with BCR that conventional imaging cannot. BCR is an indicator of disease progression and warrants effective treatment to delay further progression, particularly if lesions are detected by PSMA PET/CT. The androgen receptor inhibitor darolutamide is structurally different by design to deliver robust clinical efficacy with a differentiated tolerability profile. In the phase 3 ARAMIS trial, darolutamide significantly improved metastasis-free survival (MFS) and overall survival (OS) in patients with nonmetastatic castration-resistant prostate cancer (nmCRPC). ARASTEP is a phase 3 trial (NCT05794906) evaluating whether darolutamide plus ADT improves radiological progression-free survival (rPFS) by PSMA PET/CT vs placebo plus ADT in patients with high-risk BCR and PSMA PET/CT-positive lesions following primary therapy. **Methods:** Key eligibility criteria included: prior primary RT or RP ± adjuvant RT (ART) or salvage RT (SRT), with high-risk BCR (PSA doubling time [PSADT] <12 months and PSA ≥0.2 ng/mL after primary RP [± ART/SRT] or PSA ≥2 ng/mL above nadir after primary RT only), ≥1 PSMA PET/CT-positive prostate cancer lesion with no visible lesions on conventional imaging, and serum testosterone ≥150 ng/dL. ARASTEP is planned for 750 patients from 23 countries to be randomized 1:1 to oral darolutamide 600 mg twice daily or placebo, both with ADT, for 24 months or until disease progression, unacceptable toxicity, or withdrawal of consent. During the 24-month treatment period, patients will be monitored for safety every 12 weeks, and every 24 weeks for PSMA PET/CT and conventional imaging events. After 24 months, patients with PSA values ≥0.2 ng/mL will continue study treatment as part of active follow-up until PSMA PET/CT progression is confirmed by blinded independent central review (BICR), followed by long-term follow-up for conventional imaging progression. Patient stratification factors are PSADT (<6 vs ≥6–<12 months), intent to treat baseline PSMA PET/CT lesions with image-guided RT/surgery (Yes vs No), and distant ± locoregional vs locoregional-only lesions. The primary endpoint is rPFS by PSMA PET/CT assessed by BICR. Secondary endpoints include MFS on conventional imaging by BICR, time to CRPC, OS, quality of life, and safety. As of January 2025, 458 patients have been randomized from 220 sites. Clinical trial information: NCT05794906. Research Sponsor: Bayer.

TPS5132 **Poster Session**

Androgen suppression combined with elective nodal irradiation and dose escalated prostate treatment: A non-inferiority, phase III randomized controlled trial of stereotactic body radiation therapy versus brachytherapy boost in patients with unfavourable risk localized prostate cancer (ASCENDE-SBRT; CCTG PR24; NCT06235697). First Author: Andrew Loblaw, Sunnybrook Health Sciences Centre, Toronto, ON, Canada

Background: External beam radiotherapy (EBRT), brachytherapy boost and androgen deprivation therapy (ADT) is the evidence-based standard of care for unfavourable (unfavourable intermediate, high and very high) risk non-metastatic prostate cancer. Preliminary data demonstrate that treatment with 5 fractions of stereotactic body radiotherapy (SBRT) delivered to the pelvis and prostate with ADT is efficacious and tolerable in this patient population (Murthy Int J Rad Onc Biol Phys 2025) Other potential advantages associated with this treatment strategy include fewer treatment visits, lower cost, avoidance of a general anesthetic and decreased resource utilization. Rigorous evaluation of this treatment strategy within a clinical trial is required to inform adoption in practice. **Methods:** PR24 is a Canadian Cancer Trials Group led, intergroup, randomized phase III, non-inferiority study comparing pelvic EBRT + brachytherapy boost to SBRT (5 fractions delivering 40Gy to prostate and 25Gy to pelvis) in brachytherapy eligible, unfavourable risk, non-metastatic prostate cancer patients. All patients will receive risk-adapted duration of ADT. The primary objective is to determine if SBRT is non-inferior to conventional EBRT with brachytherapy boost in terms of disease progression free survival (PFS). Secondary objectives include a comparison between arms of: safety and tolerability; efficacy including PSA response rate at 4 years, metastasis-free survival, prostate cancer cause-specific survival, overall survival; patient-reported and economic outcomes. Biobanking for future correlative studies is included in study design. Statistical design:The target accrual is 710 patients over 3.6 years with 5-year follow-up up to rule out a target HR 1.65 (6.5% inferiority difference at 5-years) in PFS, using type 1 error rate 5% (one sided) and 80% power with 5% lost to follow-up. Conduct to Date: Study activation - March 2024. First patient enrolled - April 2024. Accrual to date: 45. Supported by CIHR grant #183644, NCTN grant #CA180863 and CCS grant #707213. Clinical trial information: NCT06235697. Research Sponsor: CIHR; 183644; NCTN; CA180863; CCS; 707213.

LBA5500 **Oral Abstract Session**

TRUST: Trial of radical upfront surgical therapy in advanced ovarian cancer (ENGOT ov33/AGO-OVAR OP7). First Author: Sven Mahner, Department of Obstetrics and Gynecology, University Hospital, Ludwig-Maximilians-Universität München, Munich, Germany

The full, final text of this abstract will be available at meetings.asco.org on the day of presentation and in the online supplement to the June 10, 2025, issue of the *Journal of Clinical Oncology*.

LBA5501 **Oral Abstract Session**

Sentinel lymph node biopsy versus pelvic lymphadenectomy in cervical cancer: The PHENIX trial. First Author: Hua Tu, Sun Yat-sen University Cancer Center, Guangzhou, China

The full, final text of this abstract will be available at meetings.asco.org on the day of presentation and in the online supplement to the June 10, 2025, issue of the *Journal of Clinical Oncology*.

5502 **Oral Abstract Session**

Ultrasensitive detection and tracking of circulating tumor DNA (ctDNA) and association with relapse and survival in locally advanced cervical cancer (LACC): Phase 3 CALLA trial analyses. First Author: Jyoti Mayadev, University of California San Diego Medical Center, La Jolla, CA

Background: In LACC, there is an unmet need for prognostic biomarkers as about 1/3 of patients (pts) relapse after chemoradiotherapy (CRT). The global randomized CALLA trial (NCT03830866) of durvalumab (D) in combination with CRT followed by D (D+CRT arm) vs CRT (CRT arm) did not significantly improve progression-free survival (PFS) in a biomarker unselected intent-to-treat (ITT) population. We analyzed the association of ultrasensitive ctDNA detection with relapse and survival in the largest ctDNA data set in LACC to date. **Methods:** Adult women with Stage IB2-IIB node positive (N+) or IIIA-IVA any N LACC (ITT) were randomized 1:1 to D+CRT or CRT alone. NeXT Personal (Personalis, Fremont, CA), an ultrasensitive tumor-informed MRD assay with up to 1,800 patient-specific variants from WGS, was used for ctDNA analysis from Cycle 1 Day 1 (C1D1; baseline [BL]), C3D1, and 6 mo post treatment initiation. Correlations were analyzed between ctDNA detection and outcomes (PFS, overall survival [OS]). **Results:** Of 770 pts randomized, the biomarker-evaluable population (BEP) comprised 185, 186, and 130 pts at BL, C3D1, and 6 mo, respectively. BL pt characteristics, PD-L1, PFS, and OS between BEP and ITT populations were generally similar. ctDNA was detected in 99% of pts at BL and decreased after treatment, reaching 23% in the D+CRT and 36% in the CRT arm at 6 mo. The lower detection rate in the D+CRT arm was associated with the PD-L1 tumor area positivity (TAP) $\geq$20% subpopulation. At BL, pts with low ($<$BL median [5268.2 ppm]) ctDNA levels had a reduced risk of progression vs pts with high ($\geq$median) ctDNA levels (PFS hazard ratio [HR] D+CRT 0.58 [95% CI, 0.27-1.24]; CRT 0.66 [0.34-1.28]). Pts with detectable ctDNA at C3D1 or 6 mo had a higher risk of progression independent of treatment arm (Table). No differences in risk of progression between the D+CRT vs CRT arms were observed based on ctDNA detection. Correlations between ctDNA and OS will be presented. **Conclusions:** This pre-planned analysis of a large, global LACC population from CALLA demonstrates the high sensitivity of a personalized ctDNA assay. High ctDNA levels at BL were associated with higher risk of progression or death. Lower ctDNA detection rates after treatment with D+CRT and CRT correlated with improved survival and highlight increased tumor control by D, especially in the PD-L1 TAP $\geq$20% subpopulation. This analysis supports the potential utility of ultrasensitive ctDNA analysis to guide treatment decisions in LACC. Clinical trial information: NCT03830866. Research Sponsor: AstraZeneca.

	D+CRT		CRT	
	Not detected	Detected	Not detected	Detected
C3D1	n=60	n=33	n=56	n=37
Median PFS (95% CI), mo	NC (37.52-NC)	14.03 (7.49-NC)	NC (NC-NC)	10.68 (7.39-19.61)
HR (95% CI)	0.25 (0.12-0.53)		0.16 (0.08-0.34)	
6 mo	n=49	n=15	n=42	n=24
Median PFS (95% CI), mo	NC (NC-NC)	10.35 (7.49-NC)	NC (NC-NC)	12.98 (10.38-NC)
HR (95% CI)	0.04 (0.01-0.16)		0.05 (0.02-0.16)	

NC, not computed.

5503 **Oral Abstract Session**

Patient-reported outcomes (PROs) in locally advanced cervical cancer (LACC): Insights from the OUTBACK trial. First Author: Rebecca Mercieca-Bebber, NHMRC Clinical Trials Centre, The University of Sydney, Camperdown, Australia

Background: OUTBACK (ACTRN12610000732088), an open-label, international, randomized phase 3 trial of 919 participants (pts) with LACC, showed that adding adjuvant chemotherapy (ACT) after chemoradiotherapy (CRT) increased adverse events without improving overall survival compared to CRT alone. PRO objectives of OUTBACK were to determine the: 1) prevalence of patient-reported moderate-severe symptom issues at years 1-3 post-randomisation 2) duration of common issues; 3) long-term psychosexual health. **Methods:** Pts completed the EORTC core questionnaire QLQ-C30; cervical cancer module QLQ-CX24 (questions 50-54 only for sexually active pts); EORTC Item Library questions on abdominal, urinary, bowel and chemotherapy side-effects; & FACT-GOG-NTX4 neurotoxicity over 36 months. A moderate-severe long-term symptom issue was defined as a score in the worst 2 response categories (EORTC items), a total score $\leq$8/16 on FACT-GOG-NTX4 at years 1, 2 or 3 for Objectives 1-2, or equivalent subscale score for Objective 3. The availability of PROs for analysis was not related to 11 pre-specified demographic/clinical variables so no imputation for missing data was performed. **Results:** PRO completion rates were 94% at baseline, 64% at year 1 & 37% by year 3. Table 1 shows the 10 top-ranked issues at year 1 & their persistence or resolution by years 2-3. These may be underestimates, due to lower PRO completion rates at years 2-3. Issues and frequencies were similar across treatment arms by year 1. Moderate-severe peripheral neuropathy affected 24% post CRT+ACT & 18% post CRT (year 1); 19% post CRT+ACT & 12% post CRT (year 3). At baseline, 77% reported no sexual activity in the past 4 weeks. Overall, 92% of pts reported low sexual activity at years 1, 2 or 3; 68% reported low enjoyment, 40% moderate-severe vaginal tightness, 37% vaginal dryness during sex and 32% were moderately-severely worried sex would be painful. **Conclusions:** Long-term symptom issues & sexual health concerns are common & persistent following CRT +/-ACT for LACC and need dedicated survivorship care. Clinical trial information: 12610000732088. Research Sponsor: National Health and Medical Research Council; National Cancer Institute; SHCC MU NCORP Grant.

Frequency and duration of top-ranked moderate-severe symptoms.

Item	CRT + ACT n (%)	CRT alone n (%)	All participants n (%)		
	Issue rated moderate-severe at Year 1	Issue rated moderate-severe at Year 1	Issue rated moderate-severe at Year 1	Issue from Year 1 resolved by Year 2 or 3	Issue from Year 1 persistent at Year 2 or 3
Worried future health	76 (50)	59 (38)	135 (44)	14 (10)	49 (36)
Hot flushes/ sweats	68 (39)	64 (35)	132 (37)	24 (18)	49 (37)
Frequent urination	67 (38)	59 (32)	126 (35)	24 (19)	45 (36)
Sexual activity (not) enjoyable	59 (63)	66 (65)	125 (64)	11 (9)	43 (34)
Trouble sleeping	62 (35)	55 (30)	117 (32)	19 (16)	37 (32)
Tired	53 (30)	51 (28)	104 (29)	22 (21)	33 (32)
Changed bowel habit	56 (32)	46 (25)	102 (28)	22 (22)	41 (40)
Financial difficulties	51 (27)	50 (28)	101 (28)	17 (17)	32 (32)
Pain	54 (29)	42 (24)	96 (27)	21 (22)	23 (24)
Dissatisfied with body	48 (26)	47 (27)	95 (26)	21 (22)	27 (28)

LBA5504 **Oral Abstract Session**

Pembrolizumab with chemoradiotherapy in patients with high-risk locally advanced cervical cancer: Final analysis results of the phase 3, randomized, double-blind ENGOT-cx11/GOG-3047/KEYNOTE-A18 study. First Author: Linda R. Duska, University of Virginia School of Medicine, Charlottesville, VA

The full, final text of this abstract will be available at meetings.asco.org on the day of presentation and in the online supplement to the June 10, 2025, issue of the *Journal of Clinical Oncology*.

LBA5506 **Oral Abstract Session**

FIRST/ENGOT-OV44: A phase 3 clinical trial of dostarlimab (dost) and niraparib (nira) in first-line (1L) advanced ovarian cancer (aOC). First Author: Anne-Claire Hardy-Bessard, Centre Armoricain d'Oncologie, CARIO-HPCA, and GINECO, Plérin, France

The full, final text of this abstract will be available at meetings.asco.org on the day of presentation and in the online supplement to the June 10, 2025, issue of the *Journal of Clinical Oncology*.

LBA5507 **Oral Abstract Session**

ROSELLA: A phase 3 study of relacorilant in combination with nab-paclitaxel versus nab-paclitaxel monotherapy in patients with platinum-resistant ovarian cancer (GOG-3073, ENGOT-ov72). First Author: Alexander Olawaiye, University of Pittsburgh School of Medicine and Magee-Women's Hospital, Gynecologic Oncology Group, Pittsburgh, PA

The full, final text of this abstract will be available at meetings.asco.org on the day of presentation and in the online supplement to the June 10, 2025, issue of the *Journal of Clinical Oncology*.

5508 **Oral Abstract Session**

Benmelstobart plus carboplatin/paclitaxel with or without anlotinib, followed by maintenance benmelstobart with or without anlotinib, as first-line treatment for advanced or recurrent endometrial cancer: A randomized, open-label, phase II trial. First Author: Xiaojun Chen, Shanghai Tenth People's Hospital, Shanghai, China

Background: Immunotherapy combined with chemotherapy has demonstrated efficacy in treating endometrial cancer (EC), with greater benefit in mismatch repair (MMR)–deficient (dMMR) tumors compared to MMR-proficient (pMMR) disease. Adding an anti-angiogenic inhibitor could potentially enhance treatment outcomes, particularly in patients with pMMR tumors. Benmelstobart (BMSB, TQB2450) is a humanized monoclonal antibody against PD-L1 and Anlotinib (ALTN) is an anti-angiogenic oral multi-target tyrosine kinase inhibitor. Here, we report the results of a randomized, open-label, phase 2 trial comparing BMSB plus carboplatin/paclitaxel ± ALTN followed by maintenance BMSB ± ALTN as first-line treatment for advanced or recurrent EC patients. **Methods:** Eligible patients with primary advanced stage III/IV or recurrent EC, who had not received first-line systemic anticancer therapy, were randomized in a 1:1 ratio to receive either BMSB 1200mg, Carboplatin (CBP, AUC=5 mg/ml.min) and Paclitaxel (PTX, 175mg/m^2) every 3 weeks for 6-8 cycles plus ALTN 8mg orally once daily (2-week on/1-week off), followed by maintenance BMSB 1200mg every 3 weeks and ALTN 10mg once daily (2-week on/1-week off) (BMSB + ALTN arm); or BMSB 1200mg, CBP (AUC=5 mg/ml.min) and PTX 175mg/m^2 every 3 weeks for 6-8 cycles followed by maintenance BMSB 1200mg every 3 weeks (BMSB arm). Stratification factors included MMR status (dMMR or pMMR). The primary endpoint was objective response rate (ORR) as assessed by investigator according to RECIST 1.1. **Results:** As of November 1, 2024, a total of 71 patients were enrolled: 38 in the BMSB + ALTN arm, and 33 in the BMSB arm. The median duration of follow-up was 16.2 mo vs. 14.2 mo in the two arms respectively. The ORR was 86.1% (95% CI: 70.5-95.3) in the BMSB + ALTN arm and 80.6% (95% CI: 62.5-92.5) in the BMSB arm. A significant PFS benefit was observed in the BMSB + ALTN arm (HR 0.38 [95% CI 0.18-0.81]; median not reached (NR) vs. 8.41 mo) compared to the BMSB arm. The median overall survival (OS) was not reached in either arm (HR=0.29 [95% CI: 0.07-1.16]). PFS benefit was also observed in subgroups with pMMR tumors (HR 0.35 [95% CI 0.15-0.79]). The incidence of Grade ≥3 TEAEs was similar between the two arms (81.58% vs 75.76%). The most frequent Grade ≥3 TEAEs(≥20%) were decreased white blood cell count (52.63% vs 60.61%), thrombocytopenia (28.9% vs 27.2%) and anemia (26.3% vs 27.7%). **Conclusions:** Benmelstobart combined with carboplatin/paclitaxel and anlotinib, followed by maintenance benmelstobart and anlotinib, demonstrated clinically meaningful ORR and PFS benefits in patients with previously untreated advanced or recurrent EC. The regimen was particularly helpful in improving outcomes for patients with pMMR tumors, potentially providing a new treatment option. Clinical trial information: NCT05481645. Research Sponsor: None.

5509 Rapid Oral Abstract Session

Cadonilimab plus platinum-based chemotherapy ± bevacizumab for persistent, recurrent, or metastatic cervical cancer: Subgroup analyses of COMPASSION-16. First Author: Yang Sun, Clinical Oncology School of Fujian Medical University, Fujian Cancer Hospital, Fuzhou, China

Background: The phase 3 COMPASSION-16 trial demonstrated statistically significant progression-free survival (PFS) and overall survival (OS) benefits with cadonilimab plus chemotherapy ± bevacizumab in patients with persistent, recurrent, or metastatic cervical cancer (R/M CC). This analysis assessed efficacy in several key clinical subgroups. **Methods:** R/M CC pts who had no prior systemic treatment were randomized 1:1 to receive cadonilimab (10 mg/kg) or placebo Q3W plus platinum-based chemotherapy ± bevacizumab (15 mg/kg). The dual primary endpoints were PFS per RECIST v1.1 assessed by blind independent central review and OS in the ITT population. Treatment effects on PFS and OS were evaluated in subgroups including age (<65 or ≥65 years), bevacizumab use (yes or no), prior concurrent chemoradiotherapy (CCRT; yes or no), metastatic disease at baseline (yes or no), PD-L1 CPS (<1, ≥1, or ≥10), and platinum use (cisplatin or carboplatin). Hazard ratios (HRs) and 95% CIs were estimated from an unstratified Cox model. **Results:** 445 patients were randomized (222 to the cadonilimab group and 223 to the placebo group). At the Apr 30, 2024 data cutoff, the median follow-up was 26 months. The addition of cadonilimab prolonged PFS and OS in all investigated subgroups (Table). **Conclusions:** Subgroup analyses of COMPASSION-16 showed that the addition of cadonilimab to chemotherapy ± bevacizumab improved PFS and OS across subgroups defined by age, bevacizumab use, prior CCRT, metastatic disease, PD-L1 CPS, and platinum use, consistent with results for the overall population. Cadonilimab plus standard treatment is a potential treatment option for patients with R/M CC. Clinical trial information: NCT04982237. Research Sponsor: Akeso Biopharma.

Subgroup (N)	Median PFS (mo) Cadonilimab	Median PFS (mo) Placebo	PFS, HR (95% CI)	Median OS (mo) Cadonilimab	Median OS (mo) Placebo	OS, HR (95% CI)
<65 yrs (369)	13.5	9.5	0.68 (0.52, 0.88)	NR	25.3	0.69 (0.50, 0.95)
≥65 yrs (74)	12.0	7.4	0.39 (0.22, 0.68)	26.6	15.5	0.49 (0.27, 0.91)
With bevacizumab (265)	15.1	11.5	0.78 (0.57, 1.06)	NR	NR	0.84 (0.56, 1.26)
Without bevacizumab (180)	11.7	6.7	0.44 (0.31, 0.63)	28.8	15.1	0.50 (0.33, 0.75)
CCRT, yes (215)	16.1	7.9	0.55 (0.39, 0.78)	NR	22.8	0.54 (0.35, 0.82)
CCRT, no (230)	12.0	8.5	0.67 (0.49, 0.93)	27.0	24.5	0.76 (0.52, 1.12)
Metastatic, yes (323)	12.0	8.3	0.70 (0.54, 0.92)	28.8	25.3	0.73 (0.52, 1.02)
Metastatic, no (122)	NR	8.0	0.42 (0.25, 0.70)	NR	17.6	0.48 (0.27, 0.86)
PD-L1 CPS<1 (116)	12.0	8.2	0.65 (0.42, 1.03)	NR	25.3	0.77 (0.44, 1.34)
PD-L1 CPS≥1 (312)	14.7	8.3	0.62 (0.47, 0.83)	NR	22.7	0.69 (0.49, 0.97)
PD-L1 CPS≥10 (180)	17.1	8.1	0.54 (0.37, 0.79)	NR	29.0	0.68 (0.42, 1.08)
Cisplatin (192)	14.7	8.1	0.49 (0.34, 0.72)	NR	23.9	0.43 (0.27, 0.70)
Carboplatin (253)	12.0	8.2	0.72 (0.53, 0.97)	27.8	22.8	0.82 (0.57, 1.18)

5510 Rapid Oral Abstract Session

Nimotuzumab combined with chemotherapy in the first-line treatment for patients with stage IVB, recurrent or persistent cervical squamous cell carcinoma: A multi-center, randomized, double-blind, and controlled study. First Author: Jusheng An, Department of Gynecologic Oncology, National Cancer Center /National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, Beijing, China

Background: Stage IVb, recurrent or persistent cervical cancer patients have limited treatment options and poor survival prognosis. Additionally, 70-90% of cervical cancers have overexpression of EGFR (epidermal growth factor receptor), a promising therapeutic target. Nimotuzumab (nimo), an EGFR antibody, 95% humanization degree, had applied in the treatment of various advanced solid tumors. So, we conducted the study to investigate its efficacy and safety. **Methods:** This trial is a prospective study with a total of 118 patients enrolled. There were 55 patients (pts) in the experimental group (nimo+chemotherapy) and 63 pts in the control group (chemotherapy alone). Primary efficacy endpoint is overall survival (OS). Secondary endpoints included progression-free survival (PFS), objective response rate (ORR), quality of life (QoL) and exploratory endpoints including the relationship between EGFR expression level and clinical efficacy and prognosis. The study of NCT approval number is 06781073. **Results:** The median age of the study population was 51.3 (range, 24.7-69.5) years. The average number of organs involved in the lesion was 2. The disease stage at initial diagnosis (2018 FIGO stage) was Ia-IVb. According to the disease status at the time of enrollment, IVB/recurrence/persistence accounted for 14.4%, 92.4%, and 9.3%, respectively. The results showed that the median OS was 15.7 (95% CI, 11.8-26.9) months in the nimo arm and 12.4 (95% CI, 7.9-21.0) months in the control arm. For recurrence pts, median OS was 21.7 (95% CI, 21.1-32.9) months vs. 12.4 (95% CI, 8.0-21.4) months for both groups. Median PFS was 7.4 (95% CI, 4.9-8.9) months in the nimo arm and 5.6 (95% CI, 4.1-6.1) months in the control arm. For recurrence pts, median PFS was 7.9 (95% CI, 5.6-12.0) months vs. 5.2 (95% CI, 3.7-8.0) months for both groups. In terms of safety, SAEs occur as follows. There were 8 pts (14.5%) in the nimo and 13 pts (23.6%) in the control group, respectively. For AEs above grade 3, there were 43 pts in the nimo and 45 pts in the control group. Adverse events related to the study drug, there were 6 cases in the nimo group with neutropenia. Among all AEs, the highest frequency was in the nimo group with 20 cases of leukopenia, 16 cases of nausea, 23 cases of anemia, and 11 cases of alopecia. In the control group, there were 17 cases of leukopenia, 21 cases of nausea, 23 cases of vomiting and 20 cases of alopecia. There was no significant difference between the two groups for adverse events. **Conclusions:** Adding nimotuzumab to chemotherapy in the first-line treatment for stage IVB, recurrent or persistent cervical squamous cell carcinoma could have an improvement trend on progression-free and overall survival with well tolerated toxicity, and should be considered as a new first-line therapy option. Research Sponsor: None.

5511 Rapid Oral Abstract Session

Primary results of a phase 2 study of cisplatin-sensitized radiation therapy and pembrolizumab for unresectable vulvar cancer. First Author: Oladapo O. Yeku, Massachusetts General Hospital, Harvard Medical School, Boston, MA

Background: Locally advanced vulvar cancer is a rare but lethal disease more common in underserved populations. In contrast to other gynecologic cancers, the incidence and mortality of this disease has increased over the past decade. Treatment for locoregional disease involves surgery and chemoradiation, while systemic chemotherapy and immunotherapy are reserved for patients with distant metastases. Cisplatin and radiation (cis-RT) have been reported to have anti-tumor immunomodulatory properties in addition to their cytotoxic effects. We hypothesized that immune checkpoint inhibitors could synergize with chemotherapy and improve outcomes for this disease. **Methods:** In this single-arm phase II trial (NCT04430699), patients with primary unresectable, incompletely resected, recurrent, or metastatic squamous cell carcinoma of the vulva undergoing RT were eligible. Patients who had received prior chemotherapy were also eligible. Patients received cisplatin 40 mg/m2 weekly concurrently with intensity modulated (IM) RT, and pembrolizumab 200 mg was administered every three weeks for a total of 12 cycles. The primary endpoint was overall response rate (ORR), and the secondary objective was six-month recurrence free survival (RFS). PD-L1 expression and T-cell receptor beta clonality were assessed among other translational endpoints. An ORR ≥ 60% was considered worthy of further study. **Results:** The study closed to accrual on 10/11/2024 after 24 patients had enrolled. Twenty-two patients (92%) had primary unresectable disease and two (8%) had recurrent disease. All patients were treated with definitive intent RT, with a median dose to the primary of 68.4 Gy (range, 26.2, 70.2) and 45 Gy to pelvic, inguinal, vulva CTV (range, 21.6, 50.4). One patient stopped RT early due to disease progression. At the data cutoff on 01/22/2025, the ORR (CR+PR) was 75%. The 6-month RFS rate was 70% (95% CI: 48 – 85%). The median PFS has not been reached. Any grade adverse events (AE) occurred in all patients. Grade (G) 3 or 4 AEs occurred in 19 (78.6%) patients, most of which were related to cisplatin. The most common treatment-emergent adverse events were nausea (88%), diarrhea (71%), fatigue (67%) and anemia (50%). There were 6 serious AEs, only 2 of which were related the treatment (both AKI). Most immune related toxicities were G1/2, except for G3 diarrhea (4%). Immune mediated colitis led to discontinuation in 1 patient (4%). PD-L1 (CPS ≥ 1) was positive in all patients. There was an increase in mean TCR clonality after 2 cycles. **Conclusions:** The study met its primary endpoint. Concurrent treatment with chemoradiation and pembrolizumab improved ORR and 6-month RFS in vulvar cancer. The addition of pembrolizumab did not lead to any unexpected AEs. Chemoradiation with pembrolizumab could be considered in patients with primary unresectable or incompletely resected vulvar cancer. Clinical trial information: NCT04430699. Research Sponsor: Merck Sharp & Dohme Corp.

5512 Rapid Oral Abstract Session

Durvalumab plus carboplatin/paclitaxel followed by durvalumab with or without olaparib as first-line treatment for endometrial cancer: Longitudinal changes in circulating tumor DNA. First Author: Shannon Neville Westin, Department of Gynecologic Oncology and Reproductive Medicine, The University of Texas MD Anderson Cancer Center, and GOG-F, Houston, TX

Background: DUO-E (NCT04269200) showed statistically significant and clinically meaningful progression-free survival (PFS) with carboplatin/paclitaxel (CP) plus durvalumab (D) followed by D (CP+D) ± maintenance olaparib (O) vs CP in endometrial cancer (intent-to-treat [ITT] population; primary endpoints). The greatest benefit for CP+D was in mismatch repair deficient (dMMR) patients (pts); addition of O (CP+D+O) further enhanced PFS in MMR proficient (pMMR) pts (prespecified exploratory analyses). We present exploratory longitudinal circulating tumor (ct)DNA analyses. **Methods:** Pts were randomized 1:1:1 to CP (CP alone), CP+D, or CP+D+O arms. ctDNA was analyzed in plasma at baseline (BL; Cycle 1 Day 1 [C1D1]), during the chemotherapy phase (C3D1), prior to maintenance initiation (C7D1), and during the maintenance phase (C9D1) using the methylation-based Guardant Infinity assay (Guardant Health, Palo Alto, CA). **Results:** Of 718 pts randomized, the biomarker-evaluable population (BEP) comprised 347, 349, 350, and 349 pts at BL, C3D1, C7D1, and C9D1, respectively. Pt characteristics were similar to the ITT population but fewer pts had Eastern Cooperative Oncology Group status 1. ctDNA was detectable in 80% (278/347) of C1D1 samples, and presence of BL ctDNA was associated with shorter PFS across treatment arms. In both dMMR and pMMR pts, CP+D treatment during the chemotherapy phase led to numerically greater reductions in detectable ctDNA vs CP at C3D1; continued treatment with D led to lower ctDNA detection at C9D1 (Table) due to a lower proportion of pts switching from no detectable ctDNA to detectable (re-emergence) ctDNA between C7D1 and C9D1. The addition of maintenance O to CP+D had limited effect on ctDNA levels in dMMR pts; however, in pMMR pts, the ctDNA detection rate was lower at C9D1 vs CP or CP+D due to increased ctDNA clearance from C7D1 to C9D1 (CP+D+O vs CP+D: 48% vs 17%). **Conclusions:** In this post hoc exploratory analysis, BL ctDNA was associated with shorter PFS. The addition of D was associated with rapid reductions in ctDNA detection during chemotherapy and less re-emergence of ctDNA during maintenance. The addition of maintenance O was associated with further reduction of detectable ctDNA and increased ctDNA clearance in pMMR pts, reflecting an additional activity of the combination. Clinical trial information: NCT04269200. Research Sponsor: AstraZeneca.

ctDNA detection rates (% [n/N]).

Population	Treatment arm	C1D1	C3D1	C7D1	C9D1
BEP	CP	80 (94/118)	44 (51/117)	35 (41/117)	50 (58/117)
	CP+D	86 (96/112)	26 (29/112)	27 (30/112)	33 (37/112)
	CP+D+O	75 (88/117)	31 (37/120)	21 (26/121)	25 (30/120)
dMMR	CP	79 (11/14)	57 (8/14)	21 (3/14)	43 (6/14)
	CP+D	91 (21/23)	23 (5/22)	32 (7/22)	22 (5/23)
	CP+D+O	85 (22/26)	41 (11/27)	18 (5/28)	22 (6/27)
pMMR	CP	80 (83/104)	42 (43/103)	37 (38/103)	50 (52/103)
	CP+D	84 (75/89)	27 (24/90)	26 (23/90)	36 (32/89)
	CP+D+O	73 (66/91)	28 (26/93)	23 (21/93)	26 (24/93)

5513 Rapid Oral Abstract Session

Phase 2 study of letrozole, abemaciclib, and metformin in estrogen receptor (ER)−positive recurrent endometrial cancer (EC). First Author: Panagiotis A. Konstantinopoulos, Dana-Farber Cancer Institute, Boston, MA

Background: Preclinical studies have demonstrated synergism with simultaneous inhibition of the estrogen receptor (ER), CDK4/6 and PI3K pathways. Metformin suppresses PI3K signaling directly via activation of the AMP-activated protein kinase (AMPK) and indirectly via downregulating the insulin/IGF-1 signaling pathway. We conducted a phase 2 study of letrozole/abemaciclib/metformin in ER positive EC. **Methods:** Patients (pts) with recurrent ER positive (≥1% immunoreactive tumor nuclei) endometrioid EC, measurable disease, any number of prior therapies and any prior hormonal therapy but no prior CDK4/6 inhibitor received abemaciclib 150 mg PO bid, metformin 500mg PO qd and letrozole 2.5 mg PO qd until progression or unacceptable toxicity. Primary endpoints were objective response (OR) rate (ORR) and progression-free survival (PFS) rate at 6 months (PFS6). A safety lead-in was included, and target accrual was 25 pts; if there were ≥6 ORs or ≥9 pts without disease progression or death at 6 months, letrozole/abemaciclib/metformin would be considered worthy of further investigation. Correlative studies included pharmacokinetic (PK) analyses of metformin alone and in combination with letrozole/abemaciclib, molecular profiling using Oncopanel targeted NGS, and progesterone receptor (PrgR) expression by IHC. **Results:** As of 10/4/2024, all 25 pts received protocol therapy. Median follow up was 17 months, median number of prior lines was 2 and 18 (72%) pts had previously received hormonal therapy. Eight pts exhibited OR: 3 complete responses (CRs) and 5 partial responses (PRs),ORR 32% (95% CI 14.9% to 53.5%). Sixteen (64%) pts had stable disease (SD) and 1(4%) pt progressive disease (PD) as best response. Kaplan Meier estimate of PFS6 was 69.7% and median PFS was beyond 19.3 months. Most common G3+ treatment-related toxicities were G3 neutropenia (24%) and G3 fatigue (16%). No pts discontinued therapy because of toxicity. PK analyses demonstrated that metformin plasma concentrations were ~3-fold higher when combined with letrozole/abemaciclib compared to metformin monotherapy. Molecular profiling showed no objective responses in *TP53* mutated ECs and no objective responses in pts with NSMP ECs with *RB1* or *CCNE1* alterations; median PFS was only 3.8 months in these tumors. All objective responses were observed in pts with NSMP ECs without *RB1* and *CCNE1* alterations; these pts exhibited an ORR of 50% and PFS6 of 87.5%. There were no MMRD and no *POLE*-mutated tumors. Responses were observed regardless of PrgR expression. **Conclusions:** Addition of metformin (at plasma concentrations sufficient to inhibit the PI3K pathway) to letrozole/abemaciclib is feasible and safe, and appears to induce deeper responses (including complete responses) and more prolonged PFS than letrozole/abemaciclib alone. NSMP tumors without *RB1* and *CCNE1* alterations derive the most benefit from this regimen. Clinical trial information: NCT03675893. Research Sponsor: None.

5514 Rapid Oral Abstract Session

Safety and preliminary efficacy from a phase 1 study of INCB123667, a selective CDK2 inhibitor, in patients with advanced platinum-resistant and refractory ovarian cancer (OC). First Author: Silvia Damian, Department of Medical Oncology and Hematology, Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy

Background: Inhibition of cyclin-dependent kinase 2 (CDK2), the binding partner of cyclin E1 (CCNE1), is a potential therapeutic approach for cancers with increased CCNE1 activity. In an ongoing phase 1 study, the potent and selective CDK2 inhibitor, INCB123667, has shown acceptable safety and preliminary efficacy in patients (pts) with advanced solid tumors (NCT05238922). Here, we present safety and preliminary efficacy data for enrolled pts with OC. **Methods:** Eligible pts had ECOG PS ≤1 and measurable disease (RECIST V1.1). Part 1A (dose escalation) enrolled pts with advanced/metastatic solid tumors with no maximum prior lines of treatment; *CCNE1* amp (locally tested) was not mandatory. INCB123667 dosing started at 50 mg and escalated up to 150 mg daily. In part 1B (dose expansion), selected RDEs from part 1A were expanded in 6 tumor cohorts, including platinum-refractory/resistant (r/r) OC with ≤4 prior lines of systemic treatment; pts must have had locally tested *CCNE1* amp or centrally confirmed CCNE1 overexpression. Blood samples were collected for ctDNA analysis. **Results:** As of Dec 19, 2024, 90 pts with advanced/metastatic platinum-r/r OC received INCB123667: 45 in part 1A (50 mg qd, n=1; 50 mg bid, n=4; 75 mg qd, n=12; 75 mg bid, n=4; 125 mg qd, n=18; 150 mg qd continuous or intermittent, n=6) and 45 in part 1B (RDEs: 50 mg bid, n=16; 100 mg qd, n=14; 125 mg qd, n=15). Sixty one pts (67.8%) had prior PARPi. Median number of prior systemic therapies was 4 (1-12). Median duration of treatment was 4.9 months (0.1-13.6), with 17 pts (18.9%) still on treatment. Overall, 88 pts (97.8%) had treatment-emergent adverse events (TEAEs), predominantly nausea (n=51 [56.7%]), anemia (n=34 [37.8%]), and vomiting (n=33 [36.7%]). Of 38 pts (42.2%) with grade ≥3 TEAEs, most common were intestinal obstruction (n=8 [8.9%]), anemia (n=6 [6.7%]), neutropenia (n=5 [5.6%]), and thrombocytopenia (n=5 [5.6%]). Treatment was discontinued due to TEAEs in 3 pts (3.3%). Overall response rate (ORR) among all pts in parts 1A and 1B was 21.1% (19/90; complete response, n=4; partial response, n=15) and 43 (51.2%) achieved stable disease, with an ORR of 33.3% (10/30) at selected RDEs of 100 mg daily (ie, 50 mg bid and 100 mg qd) in part 1B. All but 1 responder had CCNE1 overexpression (18/19); responses were observed in pts with *CCNE1*-amp (6/19) and in pts without *CCNE1*-amp but with CCNE1 overexpression (13/19). Consistent decreases in ctDNA were observed on treatment compared with baseline. **Conclusions:** In this phase 1 study of pts with heavily pretreated advanced/metastatic platinum-r/r OC, single agent INCB123667 at various doses showed an acceptable safety profile including expected cytopenia and nausea. The encouraging antitumor activity in this difficult-to-treat population support the advancement of INCB123667 into pivotal studies in pts with platinum-resistant OC. Clinical trial information: NCT05238922. Research Sponsor: Incyte Corporation.

5515 Rapid Oral Abstract Session

A phase II trial of pembrolizumab and lenvatinib in recurrent or persistent clear cell ovarian carcinoma (NCT05296512). First Author: Elizabeth Katherine Lee, Dana-Farber Cancer Institute, Boston, MA

Background: Clear cell ovarian carcinoma (CCOC) is a chemoresistant subtype of ovarian cancer. Immune checkpoint inhibitors have been reported to have clinical activity in CCOC. Additionally, CCOC harbors molecular alterations suggesting a role for anti-angiogenic agents. We therefore conducted a single-arm two-stage phase 2 trial to investigate the clinical activity of the combination of the PD-1 inhibitor pembrolizumab with the anti-angiogenic tyrosine kinase inhibitor lenvatinib in patients (pts) with CCOC. **Methods:** Pts with CCOC and measurable disease received pembrolizumab 200 mg IV every 3 weeks and lenvatinib 20 mg daily. Pts could have received an unlimited number of prior therapies; prior bevacizumab and immune checkpoint inhibitors were allowed, but prior lenvatinib was exclusionary. Malignant bowel involvement was not allowed. Co-primary endpoints were objective response rate (H_0 5%; H_a 25%) and rate of PFS at 6 months (mo) per RECIST v1.1 (H_0 10%; H_a 30%), restricting the probabilities of type I and type II errors to 10% and 10%, respectively. Two pts with objective responses or 3 pts progression-free and alive at 6 mos were needed to proceed from stage 1 (n=18) to stage 2 (n=13); 5 pts with objective responses or 6 pts progression-free and alive at 6 mos were needed to declare the combination worthy of further study. **Results:** Data cut-off occurred 22-Oct-2024. Of 30 enrolled pts, 83.3% were white; the mean age among all pts was 54.1 years. 30% of pts (9/30) experienced a confirmed response (2 CR, 7 PR); an additional 3 pts (10%) experienced unconfirmed PRs and 4 pts (13.3%) had SD ≥6 mo. As of data cut-off, 3 pts (10%) had not yet reached their first radiographic assessments, and 17 pts were still receiving study therapy. With a median of 9.72 mo of follow up, 16 pts were alive and progression-free at 6 months. The estimated 6-month PFS was 75.96% (95% CI 53.82-88.51%). Median PFS was 10.9 mo. The estimated 12-month PFS was 48.86% (95% CI 23.67-70.04%). The most common any-grade TRAEs were hypertension (71%), hypothyroidism (66%), and fatigue (60%). There were no unanticipated TRAEs. **Conclusions:** The combination of pembrolizumab/lenvatinib demonstrates encouraging evidence of clinical activity in CCOC, with 9 pts experiencing a confirmed response and 16 pts alive and progression-free at 6 months. As both co-primary endpoints of the study were met, enrollment closed with 30 pts. Updated data for all pts will be reported. There were no new safety signals. Clinical trial information: NCT05296512. Research Sponsor: Merck.

5516 Rapid Oral Abstract Session

A phase I/II study of the safety and efficacy of intraperitoneal IMNN-001 in combination with neoadjuvant chemotherapy (NACT) of paclitaxel and carboplatin in patients newly diagnosed with advanced epithelial ovarian cancer (EOC): Updated survival analysis from OVATION-2 trial. First Author: Premal H. Thaker, Division of Gynecologic Oncology, Department of Obstetrics and Gynecology, Washington University School of Medicine, St. Louis, MO

Background: OVATION-2 (NCT03393884) is a randomized, controlled phase I/II study evaluating IMNN-001 in newly diagnosed advanced epithelial ovarian cancer (EOC) patients. The study's purpose was to assess safety and efficacy of IMNN-001, an interleukin-12 (IL-12) gene therapy in combination with standard of care (SoC) chemotherapy. **Methods:** Patients were randomized 1:1 to NACT alone or NACT +IMNN-001. Carboplatin/paclitaxel IV was administered every 21 days for 3 cycles before and after interval debulking surgery (IDS) in the control arm, and concurrently with intraperitoneal IMNN-001 given weekly for 8 weeks prior to and for 9 weeks after IDS in the experimental arm. PFS was the primary endpoint with secondaries of OS, chemotherapy response score (CRS), surgical response score (SRS) and overall response rate (ORR). Hazard ratios are reported for PFS and OS as the study was not powered for statistical significance. Additional statistical methods quantified Totality of Evidence (ToE, Wang et al 2023, Claggett 2022) by considering PFS and OS outcomes simultaneously. Data lock was June 2024, with OS updated with data through November 2024. **Results:** 112 patients were enrolled with a median follow-up 31 months. Stage IV disease (31.0% vs 22.2%) and ECOG PS≥1 (48.3% vs 35.2%) were more common in the experimental arm. PARPi maintenance was less frequent in the experimental arm (32.8% vs 44.4%) despite balanced HRD status. IMNN-001 was well-tolerated with common adverse events (AEs) primarily including abdominal pain, nausea, and vomiting. There was no report of cytokine release syndrome or elevated risk of immune-related adverse events. Median PFS was 14.9 vs 11.9 months (HR:0.79, 95% CI: 0.51-1.23), and median OS was 46.0 vs 33.0 months (HR:0.69, 95% CI: 0.4-1.19) favoring the experimental arm. Rates of CRS with CRS3 outcome (complete or near complete response) and SRS R0 Section outcome were higher in the experimental arm; ORR was similar. In investigator choice PARPi subgroups, median PFS was 33.8 vs 22.1 months favoring the experimental arm (HR:0.79, 95% CI: 0.51-1.23), median OS was not reached in the experimental arm vs 37.1 months in the control arm (HR:0.38, 95% CI: 0.13-1.06). By simultaneously considering individual patients' progression and death times (ToE), the experimental arm shows 6.5 months improvement (less time lost) compared to the control arm with one-sided p = 0.375. **Conclusions:** IMNN-001 demonstrated trends towards material improvement in overall survival and acceptable safety in advanced EOC, especially in HRD+ patients. These results are supportive of further development in the upcoming pivotal phase 3 study. Clinical trial information: NCT03393884. Research Sponsor: None.

5517 Rapid Oral Abstract Session

Safety and efficacy of BAT8006, a folate receptor α (FRα) antibody drug conjugate, in patients with platinum-resistant ovarian cancer: Update on the dose optimization/expansion cohort of BAT-8006-001-CR trial. First Author: Songling Zhang, Department of Gynecologic Oncology, Gynecology and Obstetrics Center, The First Hospital of Jilin University, Changchun, Jilin Province, China

Background: This report presents an update results of the BAT-8006-001-CR trial, which evaluated the safety and clinical activity of BAT8006, an antibody drug conjugate (ADC) consisting of a humanized anti-folate receptor alpha (FRα) monoclonal antibody linked to the topoisomerase I inhibitor exatecan, in patients with platinum-resistant ovarian cancer (PROC). **Methods:** Patients with platinum-resistant epithelial ovarian, fallopian tube, or primary peritoneal cancer received BAT8006 monotherapy every 3 weeks. The adverse events, incidence of dose interruptions or reductions, tumor response, progression-free survival (PFS) and overall survival (OS) were determined. **Results:** As of January 1st, 2025, 131 PROC patients were enrolled across various cohorts: 1.8 mg/kg (n=2), 2.1 mg/kg (n=16), 2.4mg/kg(n=15), 84 mg/m^2 (n=50) or 93mg/m^2(n=48) cohorts during the dose escalation and dose optimization/expansion study. The most common treatment-emergent adverse events (TEAEs) were anemia (82%), leukopenia (80%), neutropenia (77%), vomiting (67%), nausea (60%) and thrombocytopenia (55%). The most frequent grade ≥3 treatment related adverse events (TRAEs) were neutropenia (42%), leukopenia (33%), anemia (30%) and thrombocytopenia (26%). Notably, no cases of interstitial lung disease (ILD), ocular toxicities, or treatment-related deaths were reported. In the 84 and 93 mg/m^2 dose cohorts, selected for further exploration in the dose optimization/expansion study, the incidences of grade ≥3 neutropenia, anemia and thrombocytopenia were 35% vs 45% ,20% vs 32% and 18% vs 32%, respectively. Among 108 efficacy-evaluable patients with PROC (regardless the FRα expression and prior lines of treatments), the objective response rate (ORR) was 32.4% (35/108) and disease control rate (DCR) was 75.9% (82/108). The median PFS was 6.9 months (95% CI: 4.3-7.9), while the median OS was not reached (NR). In cohort 1 (n = 77), PROC patients with ≤3 lines of prior systemic anti-tumor therapies and FRα expression ≥1% were randomly assigned to received BAT8006 at 84 mg/m^2 (n=40) or 93mg/m^2 (n=37) every 3 weeks. Among 64 efficacy-evaluable patients in this cohort, the ORRs were 30.6% (11/36) and 32.1% (9/28) for the 84 mg/m^2 and 93mg/m^2 doses, respectively, while the DCRs were 75.0% (27/36) and 78.6% (22/28). The median PFS were 7.5 months (95% CI: 4.0-NR) and 5.5 months (95% CI: 2.9-NR), respectively. The median OS were NR. **Conclusions:** The safety profile is consistent with previous results, with no reports of ILD or ocular toxicity. The preliminary efficacy of BAT8006 appears promising in PROC patients with FRα expression ≥1%. On the basis of these findings, the target population, dose and schedule have been identified for a phase III trial of BAT8006 monotherapy in PROC patients. Clinical trial information: NCT05378737. Research Sponsor: Bio-Thera Solutions.

5518 Poster Session

A phase II study of tumor microenvironment profiling at single cell level in patients with locally advanced cervical cancer (LACC) treated with immunotherapy combined with concurrent chemoradiotherapy (CICRT). First Author: Yuhan Sheng, Union Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China

Background: Concurrent chemoradiotherapy (CCRT) followed by intrauterine brachytherapy is the standard treatment for LACC, while the therapeutic efficacy can be limited by an immunosuppressive tumor microenvironment (TME). PD-1 inhibition has displayed efficacy and a clinically manageable safety profile in patients with cervical cancer. Single-cell RNA sequencing (scRNA-seq) of paired pre-treatment and on treatment samples offers a dynamic and detailed examination of the transcriptomic changes in the TME under different treatment conditions. Here, we present the results of patients with LACC treated with either CCRT or CICRT, along with the paired analysis of various cellular components in the TME from pre-treatment and on-treatment samples through scRNA-seq. **Methods:** Patients with untreated, high-risk stage III–IVA and stage IVB cervical cancer (limited to groin lymph nodes metastasis) according to FIGO 2018, with measurable disease per RECIST 1.1 and ECOG performance status ≤1, were included and randomly assigned (1:1) to receive either tislelizumab combined with chemoradiotherapy, followed by tislelizumab (200mg, Q3W for 6 cycles), or chemoradiotherapy alone (cisplatin 40 mg/m^2, Q1W for 3-5 cycles; pelvic external beam radiation therapy 50.4 Gy in 28 fractions; brachytherapy 28 Gy in 4 fractions). Single-cell transcriptomic profiles were obtained from paired biopsies at two time points: pre-treatment and on-treatment. **Results:** A total of 18 patients were included, with 12 single-cell analysis samples collected (6 CCRT and 6 CICRT). At the end of pelvic radiotherapy, the CICRT group exhibited a trend toward a greater reduction in tumor volume compared to the CCRT group (7.4% vs. 3.0%; p = 0.08), albeit not reaching statistical significance. Cancer cells in CICRT group exhibited with an increased expression of MHCII genes and chemotaxis-related genes on treatment. CICRT reduced the proportion of immunosuppressive regulatory CD4+ T cells and exhausted CD8+ T cells compared to CCRT. In myeloid cells, TNF-α signaling via NF-κB and inflammatory response pathways were enriched following CICRT, and tumor-associated macrophages were reprogrammed to a relatively pro-tumorigenic phenotype. The cancer-associated fibroblast (CAF) subset CAF_FTH1, characterized by a pro-inflammatory gene signature, was increased during CICRT. Moreover, CICRT induced higher expression of MHC-II-related molecules and chemotaxis-associated genes in CAFs compared to CCRT. **Conclusions:** The CICRT treatment group demonstrated a trend toward improved local control during the early phase of treatment compared to the CCRT group. Single-cell profiling revealed the differences in the potential to reshape the TME between CCRT and CICRT, with CICRT showing a greater ability to reduce immune suppression. Clinical trial information: ChiCTR2200067166. Research Sponsor: None.

5519 Poster Session

Impact of pre-treatment counseling on uptake of hormone replacement therapy in patients undergoing chemoradiation for cervical cancer. First Author: Keizra Mecklai, NYU Langone, New York, NY

Background: Chemoradiation therapy (CRT) for cervical cancer can lead to premature ovarian insufficiency (POI) in premenopausal women, accelerating the onset of menopause and its related symptoms, and adversely affecting sexual health. This study aimed to assess the impact of pre-CRT counseling on the initiation of hormone replacement therapy (HRT) in patients with cervical cancer, and to describe common practice patterns in the management CRT-related side effects. **Methods:** This retrospective cohort study included patients treated for cervical cancer at four New York City hospitals (one public and three private) from 2010 to 2024. Patients were included if they underwent CRT as first-line treatment and were premenopausal before treatment initiation. Data were extracted from medical records including demographics, pretreatment counseling, CRT side effects, and HRT use. Descriptive statistics and chi-square were used for analysis, with $p<0.05$ as significant. **Results:** Of the 2,009 patients identified with a history of cervical cancer at our institutions, 81 premenopausal patients who underwent CRT were included, with a median age of 41.9 years at diagnosis. Prior to CRT, 69.1% of patients (n=56/81) were counseled on potential vaginal toxicity (e.g., stenosis/shortening), 63% (n=51/81) on the risk of POI, and 11.3% (n=9/81) on CRT's impacts on sexual health. Following treatment, 46.9% of patients (n=38/81) experienced menopausal symptoms, including vasomotor symptoms (84.2%, 32/38), vaginal dryness (36.8%, 14/38), and mood alternations (18.4%, 7/38). Among symptomatic patients, 55.3% (n=21/38) were prescribed HRT. Common regimens included vaginal estrogen (33.3%, 7/21) and combined estrogen/progestin pills (28.6%, n=6/21) followed by systemic estrogen patches (19%, n=4/21) and systemic estrogen pills (19%, n=4/21). Factors statistically significantly associated with HRT use after CRT included pre-treatment counseling on vaginal toxicity (X^2=13.77, p=0.008) and POI (X^2=13, p=0.011), as well as vaginal dilator use after CRT (X^2=31.68, $p<0.01$). Compared to patients at the public hospital, private hospital patients were more likely to be prescribed HRT (18.5% vs 40%, p=0.046). No significant differences were noted in HRT initiation rates by language (p=0.201), insurance type (p=0.234), or race (p=0.617). **Conclusions:** In this study we demonstrate that pre-CRT counseling on risks of vaginal toxicity and POI leads to a significant increase in HRT uptake after treatment. Further, we highlight a notable gap in counseling, as only two-thirds of premenopausal patients at our institutions undergoing CRT were counseled on side effects. To enhance patient care, vigilant screening on vaginal toxicity and vasomotor symptoms should be performed with each surveillance visit to ensure rapid treatment initiation and reduce morbidity from CRT. Research Sponsor: None.

5520 Poster Session

Toripalimab with chemoradiotherapy followed by toripalimab maintenance therapy for newly diagnosed, high-risk, locally advanced cervical cancer (TorCH-CC): A single-arm phase II study. First Author: Shuangzheng Jia, Cancer Hospital Chinese Academy of Medical Sciences, Beijing, China

Background: Despite concurrent chemoradiation (CRT) being the standard treatment, patients with high-risk locally advanced cervical cancer (FIGO 2018 III-IVA, HR-LACC) experience suboptimal survival outcomes. This phase II clinical trial aimed to evaluate the efficacy and safety of toripalimab, an innovative and cost-effective PD-1 inhibitor, combined with CRT and followed by toripalimab maintenance, in patients with HR-LACC. **Methods:** Patients with untreated HR-LACC were enrolled. All patients were treated with cisplatin-based CRT combined with toripalimab, and followed by toripalimab maintenance therapy. Toripalimab is administered at a fixed dose of 240mg every 3 weeks intravenously, with the concurrent CRT and immunotherapy phase not exceeding 8 weeks. The primary endpoint was 2-year PFS rate, with secondary endpoints including overall response rate (ORR), duration of response (DoR), treatment-related adverse events (TRAEs), immune-related adverse events (irAEs), 2-year OS, and quality of life. **Results:** From October 2023 to December 2024, 43 patients were enrolled, with a median age of 52 years (range: 28–72). Most patients (79%) were at stage IIIC, while others were stage IIIB (16.3%) or IVB (with inguinal or supraclavicular lymph node metastasis, 4.7%). PD-L1 expression was CPS <10 in 32.6% and CPS ≥10 in 67.4%. All received VMAT radiotherapy and image-guided high-dose-rate intracavitary/interstitial brachytherapy, with 74.4% receiving 5-6 cycles of concurrent chemotherapy and 90.7% receiving 3 cycles of concurrent toripalimab. The median CRT duration was 52.7 days (range: 43–62), and the median D90 HR-CTV was 93.9 Gy (EQD2, range: 84–114). With a median follow-up of 8 months (range: 3–15 months), the ORR was 97.1% at 3 months post-treatment, with 32 complete and 2 partial responses, and 1 stable disease. The best ORR after CRT was 100%, with 41 complete and 2 partial responses. Grade 3 or 4 hematologic TRAEs occurred in 27.9% of patients, and non-hematologic in 2.3%, with no discontinuations or deaths. Grade 3 or 4 hematologic irAEs occurred in 7% of patients. **Conclusions:** Toripalimab combined with cisplatin-based CRT followed by toripalimab maintenance was well-tolerable and demonstrated promising antitumor efficacy in patients with HR-LACC. Trial registration: The study was registered at ClinicalTrials.gov, NCT06416696. Clinical trial information: NCT06416696. Research Sponsor: None.

5521 **Poster Session**

Nimotuzumab with chemoradiotherapy for newly diagnosed, high-risk, locally advanced squamous cervical cancer (CC11): A prospective single-arm phase II study. First Author: Shuangzheng Jia, Cancer Hospital Chinese Academy of Medical Sciences, Beijing, China

Background: Cervical cancer ranks as the fourth most common cancer, with 32% of cases being locally advanced (stage IIB-IVA, LACC). The standard treatment is concurrent chemoradiotherapy (CCRT) with platinum drugs, but many patients only achieve partial or short-term remission. Nimotuzumab has shown promise in treating LACC, but few studies focus on high-risk cases (FIGO 2018 III-IVA). This study aims to evaluate the efficacy and safety of combining nimotuzumab with CCRT for high-risk LACC. (NCT06771596). **Methods:** Patients aged 18-75 with confirmed cervical squamous cell carcinoma, an ECOG status of 0-2, and at least one measurable lesion were eligible. All patients received nimotuzumab 400 mg weekly for 4-6 weeks combined with CCRT. CCRT included external beam radiotherapy (45 Gy/1.8Gy/25 fractions) using volumetric modulated arc therapy (VMAT), concurrent with weekly cisplatin (40mg/m^2 for 4-6 weeks), followed by image-guided high-dose-rate brachytherapy, aiming for a cumulative dose $\geq$87 Gy (EQD2). The primary endpoint was 1-, 2-year progression free survival (PFS) per RECIST 1.1. The secondary endpoints were 1-, 2-year overall survival (OS), objective response rate (ORR), disease control rate (DCR) rate per RECIST v1.1, and safety per CTCAE v5.0. **Results:** In total, 40 patients were enrolled. The baseline characteristics are shown in the table. 36 (90%) patients had CR, 3 (7.5%) patients had PR, ORR was 97.5% (95% CI: 86.84%-99.94%), and DCR was 97.5% (95% CI: 86.84%-99.94%). The median follow-up time was 21.32 months (95% CI: 20.01~24.34) months, with mPFS and mOS not yet reached. The 1-, 2-year PFS rates were 79.11% (95% CI: 62.53%-88.97%) and 76.29% (95% CI: 59.33%-86.91%), respectively, and 1-, 2-year OS rate were 100% (95% CI: 100%~100%) and 85.27% (95% CI: 64.8%~94.32%). The most common AEs were leukopenia (42.5%), myelosuppression (40%), and anemia (37.5%), all of which were graded 1-2. **Conclusions:** Nimotuzumab combined with chemoradiotherapy in the treatment of high-risk squamous LACC demonstrated prolonged PFS and favorable safety profile. Clinical trial information: NCT06771596. Research Sponsor: None.

Baseline characteristics.

Characteristic	All patients (n=40)
Age (mean ± SD, years)	53.9±11.69
FIGO stage	
IIIA-IIIB	6(15.0%)
IIIC1R-IIIC2R	33(82.5%)
IVA	1(2.5%)
Tumor differentiation	
Low differentiation	8(20.0%)
Medium differentiation	1(2.5%)
Highly differentiation	31(77.5%)

5522 **Poster Session**

Enlonstobart in patients with PD-L1 positive recurrent/metastatic cervical cancer: Updated survival results of the phase II study. First Author: Jing Zuo, National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China

Background: Enlonstobart is a PD-1 inhibitor that has demonstrated durable anti-tumor activity and acceptable safety in patients with PD-L1 positive recurrent/metastatic cervical cancer in a multicenter, single-arm, open-label, phase II study. At primary cutoff date (May 27, 2023), the overall survival (OS) was not reached. Here, we report results from a pre-planned further follow-up (August 20, 2024). **Methods:** Eligible patients were $\geq$18 years old with PD-L1-positive (combined positive score $\geq$ 1) cervical cancer who had progression during or after or intolerance to the first-line platinum-based therapy. A total of 107 patients received enlonstobart 240 mg every two weeks for up to 24 months or until disease progression, intolerable toxicities, or other study discontinuation criteria were met. At the updated cutoff date, analyses of progression-free survival (PFS) and OS in the full analysis set (FAS), which consisted of all patients who had received at least one dose of enlonstobart treatment, and the per protocol set (PPS), which consisted of all patients in the FAS who had at least one available postbaseline tumor assessment were conducted. **Results:** At the cutoff date of August 20 2024, the median follow-up time was 15.84 months (range 0.4 ~ 35.6 months). In FAS, the median PFS was 3.06 (95 % CI 2.23–6.90) months. The median OS was 19.38 (95 % CI 14.95–25.40) months and the estimated OS rate was 68.14 % (95 %CI 58.20–76.19) at 12 months, 50.78 % (95 % CI 40.46–60.20) at 18 months, and 42.84 % (95 % CI 32.76–52.53) at 24 months. In PPS, the median PFS was 3.81 (95 % CI 2.63–7.49) months. The median OS was 21.26 (95 % CI 15.44–27.66) months and the estimated OS rate was 71.53 % (95 %CI 61.48–79.40) at 12 months, 53.32 % (95 % CI 42.64–62.87) at 18 months, and 44.98 % (95 % CI 34.50–54.89) at 24 months. **Conclusions:** Enlonstobart monotherapy showed a promising survival in patients with PD-L1 positive recurrent/metastatic cervical cancer, whose disease experienced progression after first-line platinum-based therapy. Clinical trial information: NCT04886700. Research Sponsor: CSPC Zhongqi Pharmaceutical Technology Co., Ltd.

5523 **Poster Session**

miRNA(s) expression as predictive biomarkers in recurrent/metastatic cervical cancer: The NRG Oncology/GOG-0240 NIH Cancer Moonshot. First Author: Alyssa Bujnak, University of California, Irvine, Orange, CA

Background: Chemotherapy + pembrolizumab +/- bevacizumab (BEV) is the standard treatment for recurrent/metastatic (R/M) cervical cancer (CC). GOG-0240 was a predecessor registration trial demonstrating survival benefit with incorporation of BEV with chemotherapy in R/M CC. In the wake of KEYNOTE A18, prior exposure to immunotherapy (I-O) via incorporation of pembrolizumab with ChemoRT for frontline therapy (FIGO stage III-IVA) may limit I-O use in 1st-line R/M CC. The need for new agents and predictive biomarkers to guide BEV use is implicit. Aberrant expression of miRNAs in CC can drive oncogenic pathways and/or suppress tumor suppressor genes, highlighting their potential as therapeutic targets. Here we present miRNA differential expression from the NIH Cancer Moonshot, which aims to identify biomarkers and predictors of survival outcomes in R/M CC through evaluation of miRNA differential expression among patients treated with Chemotherapy +/- BEV. **Methods:** miRNA-sequencing of R/M CC tumors from GOG-0240 was performed. miRNA expression was profiled and correlated with overall survival across all cohorts and differentials among tumors treated with ChemoRx+BEV or ChemoRx-alone were compared. **Results:** In the ChemoRx-alone group, lower expression of miR443 was associated with improved survival. miR-4443 may play a role in modulating tumor progression and metastasis through its impact on cell migration/invasion mechanisms. In the ChemoRx+BEV group, lower miR-196b-3p was associated with better overall survival. MiR-196b-3p has been implicated in the progression of various cancers, acting as an oncogene by regulating gene expression pathways that promote cell proliferation, inhibit apoptosis, and enhance metastatic potential. In the overall study population, higher expression of miR-10a and miR-1307 was associated with better survival. miR-1307 is thought to down-regulate ING5, which in turn may regulate the PIK3A pathway. In contrast, higher expression of several miRNAs, notably miR-584, mi-223, miR-144 was associated with worse survival. Multiple miRNAs that interact with ARID1A, VEGFA, and PIK3A were implicated. Higher expression of miR-223-5p was associated with worse outcomes. miR-223-5p is hypothesized to inhibit ARID1A expression and has been suggested to affect inflammatory response. Similarly, miR-144-5p and miR-144-3p are thought to affect both ARID1A and VEGFA. expression. Higher miR-144-3p expression was associated with lower survival, which may imply that more suppression of ARID1A expression by miR-144-3p results in a worse outcome. Finally, miR-193-5p negatively effects survival and is suggested to affect PIK3CA. **Conclusions:** Low expression of miR443 (ChemoRx-alone group) and miR196b-3p (ChemoRx+BEV group) track with survival in R/M CC and may serve as biomarkers to guide bevacizumab use in this orphan disease. Research Sponsor: National Cancer Institute/U.S. National Institutes of Health; 75N91019D00024.

5524 **Poster Session**

An NCDB study examining disparities in the administration of immunotherapy among advanced cervical cancer patients. First Author: Alicia Youssef, Massachusetts General Hospital, Boston, MA

Background: The addition of immunotherapy (IO) to standard therapy has demonstrated substantial survival benefits in the upfront treatment of advanced cervical cancer. Our primary objective was to investigate the role of race on the administration of IO among patients with stage IV cervical cancer, following the publication of KEYNOTE-826 in 2021. Secondarily, we aimed to describe additional factors that may be associated with disproportionate administration. **Methods:** This was a retrospective cohort study utilizing the National Cancer Database (NCDB). We included all patients diagnosed in 2022 with stage IV adenocarcinoma, adenosquamous carcinoma, and squamous cell carcinoma of the cervix. Proportions were used to estimate the administration of IO. Multivariable models adjusted for age, insurance, education, Charlson-Deyo comorbidity scores, geography, distance to treatment center, as well as treatment facility type, location, and volume. **Results:** There were 937 cases identified, of which 368 (39.3%) received IO and 569 (60.7%) did not. A higher proportion of patients received IO at age $<$ 65 compared to $>$ 65 (74.5% vs 25.5%). Patients with Medicaid received IO at similar rates compared to privately-insured patients, at 33.4% verses 34.5%, respectively. When controlling for all other variables, higher education was associated with a greater likelihood of receiving IO (RR 1.46, CI 1.10 – 1.95, p=0.01). Patients with comorbidity scores $>$ 2 were less likely to receive IO than those with lower scores (RR 0.71, CI 0.52 – 0.98, p=0.038). Proportions of patients receiving IO in urban verses rural communities was also similar, at 33.3% and 39.4%, respectively. There were no significant differences in administration of IO associated with treatment center type (RR 1.05, CI 0.89 – 1.23, p=0.55) or volume (RR 0.95, CI 0.79 – 1.13, p=0.55). Mean distances to treatment centers were similar between patients who did and did not receive IO (29.31 vs 30.0 miles). Hispanic patients received IO at higher rates than non-Hispanic White, non-Hispanic Black, and Asian patients at a rate of 47.2% compared to 37.6%, 38.5%, and 38.1%, respectively. Even after adjusting for demographic and tumor factors, the increased receipt of IO among Hispanic patients could not be explained. **Conclusions:** Not only were there no racial disparities observed in the administration of IO among racial groups, but there were no disparities recognized among traditionally marginalized groups. Interestingly, the overall administration IO was lower than expected. The population included in KEYNOTE-826 had a PD-L1 combined positivity score of $>$1 among approximately 88% of participants. This difference in overall IO administration may be explained by PD-L1 positivity, however our study was limited by the lack of this data. Further investigation is warranted to understand trends in IO administration. Research Sponsor: None.

5525 **Poster Session**

Clinicopathological and prognostic characteristics of gastric-type endocervical adenocarcinoma: A single-center retrospective study. First Author: Yang Liu, Obstetrics & Gynecology Hospital of Fudan University, Shanghai, China

Background: Gastric-type endocervical adenocarcinoma (G-EAC) is a rare and highly aggressive subtype of cervical cancer. Limited screening methods often lead to late-stage diagnosis, contributing to its poor prognosis. This study reviews cases of G-EAC managed at a tertiary gynecological oncology center over the past six years, focusing on prognostic characteristics and responses to adjuvant therapies. **Methods:** We reviewed demographic, pathological, clinical, and prognostic data from patients diagnosed with cervical adenocarcinoma and treated surgically at Obstetrics and Gynecology Hospital Fudan University from January 1, 2018, to December 31, 2023. G-EAC patients were assigned to the study group, while those with usual endocervical adenocarcinoma (UEA) served as the control. The groups were matched 1:1 using propensity score matching to compare prognosis. Primary endpoints were 3-year progression-free survival (PFS) and overall survival (OS). Kaplan-Meier and Cox regression analyses were used to assess survival, and univariate and multivariate analyses were conducted to identify risk factors for G-EAC. **Results:** A total of 960 patients were included in this study, comprising 195 cases of G-EAC and 765 cases of UEA. After matching, the G-EAC group exhibited significantly lower 3-year OS and PFS compared to the UEA group (OS: 74.9% vs. 84.6%, PFS: 66.1% vs. 79.8%, χ^2 = 4.59/6.04, p = 0.032/0.014). Parametrial involvement (OS/PFS: HR = 3.19/2.54, p = 0.003/0.009) and pelvic lymph node metastasis (OS/PFS: HR = 2.64/2.26, p = 0.012/0.013) as independent risk factors for death and recurrence in G-EAC patients. G-EAC patients treated with combined radiotherapy and chemotherapy had significantly better 3-year OS and PFS than those receiving either modality alone (OS: 74.3% vs. 54.5%, PFS: 65.2% vs. 43.6%, χ^2 = 4.86/4.23, p = 0.028/0.039). Cox regression analysis showed that G-EAC patients receiving radiotherapy or chemotherapy alone had significantly higher risks of death and recurrence compared to UEA patients (OS/PFS HR: 5.88/8.37, p = 0.037/0.009). Similarly, G-EAC patients treated with combined radiotherapy and chemotherapy exhibited slightly higher risks of death and recurrence than UEA patients (OS HR: 2.61 vs. 1.63, PFS HR: 3.91 vs. 2.66). **Conclusions:** G-EAC is a rare pathological subtype of cervical cancer with an exceptionally poor prognosis, significantly worse than that of UEA. Parametrial involvement and pelvic lymph node metastasis are independent risk factors for recurrence and death in G-EAC patients. Postoperative combined radiotherapy and chemotherapy reduce the risks of recurrence and death compared to single-modality treatments. However, G-EAC remains less responsive to adjuvant chemoradiotherapy than UEA. Further research to develop more effective therapeutic strategies for this rare and aggressive subtype. Research Sponsor: Shanghai Shenkang Hospital Development Center's Promotion of Clinical Skills and Clinical Innovationin Municipal Hospitals Three-Year Action Plan (2020—2023) Major Clinical Research Project; SHDC2020CR1048B; the shanghai Hospital Development Center Foundation of Clinical Technology Promotion and Management Optimization Project of Shanghai municipal hospitals in 2024; SHDC12024105; the General Program of National Natural Science Foundation of China; 82271654; the Public Welfare Project "JiShiQiYi" of Beijing Health Alliance Charitable Foundation; KM-JSQY-002; the "ZaiDing-Le" Foundation from Beijing Kanghua Foundation for the Development of Traditional Chinese and Western Medicine; KH-2020- LJJ-008.

5526 **Poster Session**

Adjuvant, neoadjuvant and surgical treatment for locally advanced cervical cancer: A network meta-analysis. First Author: Rafael Lara Nohmi, University of São Paulo, São Paulo, Brazil

Background: Concurrent chemoradiotherapy (CCRT) is the standard treatment for locally advanced cervical cancer (LACC). Alternative strategies, including induction chemotherapy followed by CCRT (IC + CRRT) and CCRT with immune checkpoint inhibitors (CCRT + ICI), have shown promising yet conflicting results. This study used a network meta-analysis (NMA) to compare the efficacy of these treatments. **Methods:** A systematic review identified RCTs published until November 25, 2024, comparing treatments for FIGO stage IB2-IVA LACC, including neoadjuvant chemotherapy, adjuvant chemotherapy (ACT), radiotherapy (RT), CCRT+ICI, surgery, or combinations. Progression-free survival (PFS) and overall survival (OS) were evaluated. Hazard ratios (HRs) were extracted or reconstructed from Kaplan–Meier curves using IPDfromKM. Bayesian NMA was conducted with random-effects models using the gemtc package. Three chains were run for 600,000 iterations, discarding the first 60,000 as burn-in. Results included 95% credible intervals (CrIs) for HRs. Treatment rankings were derived using the surface under the cumulative ranking curve (SUCRA), and probabilities of treatment superiority (SP) were calculated. **Results:** A total of 46 trials (49 reports) involving 13,895 patients were included in the analysis, with 89% having squamous cell histology. CCRT and RT were the most frequently used comparator treatments. Data from 39 trials (11,727 patients) were analyzed for OS, comparing 10 treatment regimens. CCRT significantly improved OS compared to RT (HR 0.76; 95% credible interval [CrI] 0.63–0.94) and showed a trend toward superiority over surgery (HR 0.71; 95% CrI 0.49–1.02; SP = 96.9%). However, no significant differences were observed between CCRT and either CCRT + ICI (SP = 6.2%) or IC + CCRT (SP = 28.3%). CCRT + ACT further improved OS compared to RT (HR 0.60) and surgery (HR 0.56). CCRT + ICI also demonstrated superiority over RT and surgery. Based on SUCRA scores, CCRT + ICI ranked highest for OS. For PFS, data from 37 trials (12,025 patients) were analyzed. CCRT demonstrated superiority over RT (HR 0.77; 95% CrI 0.65–0.92). No significant differences were observed between CCRT and other regimens, including CCRT + ICI (SP = 5.4%), IC + CCRT (SP = 34.1%), and CCRT + ACT (SP = 29.2%). Both CCRT + ACT and CCRT + ICI were superior to RT alone (HR 0.71 and HR 0.59, respectively). Additionally, CCRT + ICI was more effective than IC + RT. In a subgroup analysis of trials limited to squamous cell carcinoma, CCRT was superior to CCRT + ACT (HR 0.4; 95% CrI 0.2–0.85). Based on SUCRA scores, CCRT + ICI ranked highest for PFS. **Conclusions:** CCRT demonstrates consistent superiority in OS and PFS over RT and surgery, with comparable efficacy to regimens such as CCRT + ACT, IC + CCRT, and CCRT + ICI. These findings reaffirm CCRT's position as the cornerstone treatment for LACC, while supporting the potential of novel strategies in select populations. Research Sponsor: None.

5527 **Poster Session**

A phase II study of anlotinib plus penpulimab as first-line treatment for persistent, recurrent, or metastatic cervical cancer: Results from ALTER-GO-020 trial. First Author: Dengfeng Wang, Sichuan Clinical Research Center for Cancer, Sichuan Cancer Hospital and Institute, Sichuan Cancer Center, Affiliated Cancer Hospital of University of Electronic Science and Technology of China, Chengdu, China

Background: In patients with recurrent, or metastatic cervical cancer, atezolizumab combined with bevacizumab and chemotherapy has significantly enhanced progression-free survival (PFS) and overall survival (OS) regardless of PD-L1 status. ALTER-GO-020 trial was designed to evaluate the efficacy and tolerability of anlotinib (a multitarget anti-angiogenic TKI) and penpulimab (anti-PD-1 antibody) as a chemotherapy-free regimen for patients (pts) with recurrent or metastatic gynecological cancer. This report presents the latest efficacy and safety data from the completed cervical cancer cohort. **Methods:** ALTER-GO-020 is a single arm, open-label, multi-cohort, multi-center phase II clinical study. In cervical cancer cohort, 26 pts were planned to be enrolled. Eligible pts were histologically confirmed persistent, recurrent, or metastatic cervical cancer (including adenocarcinoma, adenosquamous carcinoma, or squamous-cell carcinoma), not amenable to curative treatment, and had no prior systemic treatment for metastatic, persistent, or recurrent disease. Pts were treated with anlotinib (12mg, po qd, d1-14, q3w) plus penpulimab (200mg, IV, d1, q3w) until disease progression or unacceptable toxicity. The primary endpoint was objective response rate (ORR) and the secondary endpoints included PFS, duration of response (DOR), disease control rate (DCR), OS and safety. **Results:** 26 pts were enrolled. The median age was 52 years (range, 31-70), 65% of pts were squamous-cell carcinoma, 88% received previous chemoradiotherapy with or without surgery, and 71% had previously received neoadjuvant/adjuvant platinum-containing chemotherapy. As of date cutoff (Dec, 2024), the median follow-up time was 11.7 months (range, 1.3-30.0 months). In the efficacy analysis (n=26), the preliminary ORR was 50% (95% CI: 32.1%-67.9%), DCR was 92.3% (95% CI: 75.9%-98.6%). The mPFS was 11.0 months (95% CI: 5.8m-16.2m months). The mOS was not reached. Treatment-related adverse events (TRAEs) of any grade occurred in all 26 pts, in which 12 (46.2%) were grade $\geq$3. The most common grade $\geq$3 TRAEs were hypertension (19.2%), hand foot syndrome (11.5%), fatigue (3.8%), and diarrhea (3.8%). TRAEs led to dose reduction and interruption were 15.4%, and 38.5% of pts, respectively. No TRAEs leading to death. **Conclusions:** Anlotinib combined with penpulimab as a chemotherapy-free regimen showed a significant improvement in ORR, a trend towards longer PFS, and favorable safety in the treatment of pts with recurrent or metastatic cervical cancer. Clinical trial information: NCT05028504. Research Sponsor: None.

5528 **Poster Session**

Preliminary results of ZG005, a bispecific antibody targeting PD-1 and TIGIT, as monotherapy in patients with advanced cervical cancer. First Author: Hanmei Lou, Zhejiang Cancer Hospital, Hangzhou, China

Background: ZG005, a PD-1 and TIGIT dual-specific antibody, is a promising immunotherapy for tumors. By blocking both pathways, it can synergistically activate T cells and enhance the anti-tumor activity of NK cells. Preliminary results of this first-in-human (FIH) study were presented at ASCO 2023 and ASCO 2024. Here, we report the efficacy and safety results in patients with advanced cervical cancers. **Methods:** Following the dose-escalation phase, patients with specified tumor types were enrolled into dose-expansion stage. Within each tumor type cohort, subjects were randomized 1:1 to receive ZG005 10 mg/kg Q3W or 20 mg/kg Q3W by intravenous infusion. Efficacy was assessed by both the investigator and the independent radiology committee (IRC) according to RECIST v1.1. **Results:** As of December 05, 2024, a total of 55 patients with advanced cervical cancer had been randomized to receive at least one dose of ZG005 10 or 20 mg/kg. The median age was 52.0 years. Of these patients, 98.2% had failed to at least one prior line of therapy, and 24.7% had previously received immune checkpoint inhibitor (ICI) treatments. 87.3% patients were squamous cell carcinoma, 9.1% adenocarcinoma and 3.6% adenosquamous carcinoma. Among the total 22 patients on the 20 mg/kg group who hadn't treated any prior ICI treatments before, 3 achieved a complete response (CR) and 6 partial responses (PR) per the IRC's assessments. The confirmed objective response rate (ORR) was 40.9%, and the disease control rate (DCR) was 68.2%. The median progression free survival (mPFS) has not yet been reached. Among the 55 patients for the safety analyses, 46 (83.6%) reported treatment related adverse events (TRAEs), with 5 (9.1%) grade 3-4, including one patient each with hypocalcemia, myositis, rash, hypertension and anemia. Serious adverse events (SAEs) occurred in 8 subjects (14.5%), with one myositis case (1.8%) was the only SAE related to ZG005 and also the sole TRAE that led to treatment discontinuation. No death was attributed to ZG005. Grade 3-4 Immune-related adverse events (irAEs) were observed in 4 patients (7.3%), including myositis, rash, hypertension and anemia. No new safety signals were observed compared with other ICIs. **Conclusions:** ZG005 has demonstrated a tolerable safety profile and promising anti-tumor activity at the 20 mg/kg dose as monotherapy in patients with advanced cervical cancer. Clinical trial information: NCT06233293. Research Sponsor: None.

5529 **Poster Session**

Preliminary results of ZG005, a bispecific antibody targeting PD-1 and TIGIT, in combination with chemotherapy with or without bevacizumab as first-line treatment for advanced cervical cancer. First Author: Hanmei Lou, Zhejiang Cancer Hospital, Hangzhou, China

Background: ZG005, a PD-1 and TIGIT dual-specific antibody, is a promising immunotherapy for tumors. By blocking both pathways, it can synergistically activate T cells and enhance the anti-tumor activity of NK cells. This report presents the results for the combination of ZG005 and the chemotherapy with or without bevacizumab as a first-line systematic treatment in patients (pts) with advanced cervical cancer. **Methods:** ZG005-003 was a multicenter, open-label, phase I/II clinical trial. In the Part 1, the escalating doses were 10 mg/kg and 20 mg/kg. In the Part 2, pts were randomized at 1:1 ratio to receive ZG005 at 10 mg/kg or 20 mg/kg in combination with the standard chemotherapy (paclitaxel [175 mg/m^2] plus carboplatin [AUC 5] or cisplatin [50 mg/m^2]), with or without bevacizumab (15 mg/kg) every 3 weeks for six cycles, followed by the maintenance therapy of ZG005 with or without bevacizumab for up to 2 years. Safety and efficacy (per RECIST v1.1) were assessed. **Results:** As of December 19, 2024, the Part 1 had completed and the Part 2 was ongoing, a total of 41 pts had been enrolled for the both Parts, with 12 pts in Part 1 and 29 pts in Part 2. The median age was 54 years, and 87.8% of pts were squamous carcinoma. 53.7% of pts received bevacizumab during the trial. No dose-limiting toxicity (DLT) were observed during the Part 1. Among all the 41 pts, 31 (75.6%) experienced treatment-related adverse events (TRAEs) which attribute to ZG005. Most TRAEs were grade 1-2, while 12 pts (29.3%) reported grade 3 or higher TRAEs. There was no treatment discontinuation or death due to TRAEs. Only one serious adverse event (SAE) of bilateral lung pneumonia in the 10 mg/kg group was assessed related to ZG005 by the investigator. No ZG005-related SAE was reported in the 20 mg/kg group. Of the 28 pts evaluable for efficacy, 13 on 10 mg/kg and 15 on 20 mg/kg, the unconfirmed overall response rates (ORR) was 69.2% for the 10 mg/kg group, and 80.0% for the 20 mg/kg group. **Conclusions:** ZG005 in combination with the chemotherapy, with or without bevacizumab, demonstrated favorable safety and tolerability profiles at both 10 mg/kg and 20 mg/kg dosages. Additionally, this regimen exhibited a significant antitumor activity in first-line cervical cancer pts, with the 20 mg/kg dose group showing a notably better efficacy in comparison with the 10 mg/kg dose group. Clinical trial information: NCT06241235. Research Sponsor: None.

5530 **Poster Session**

Induction cadonilimab combined with chemotherapy followed by chemoradiotherapy for locally advanced cervical cancer: A multicenter, single-arm, phase II trial. First Author: Lin Ding, Sun Yat-sen University Sun Yat-sen Memorial Hospital, Guangzhou, China

Background: Short-course weekly induction chemotherapy followed by chemoradiotherapy (CCRT) improves survival for locally advanced cervical cancer (LACC) in the CxII and INTERLACE trial. However, only 70% patients achieved objective response (CR or PR) whereas 20% grade 3-4 adverse events were reported during induction chemotherapy in the CxII study. Cadonilimab is a bi-specific antibody targeting both PD-1 and CTLA-4. The COMPASSION-16 trial has recently demonstrated the encouraging effectiveness and safety of cadonilimab combined with chemotherapy in recurrent/metastatic cervical cancer. This study was aimed to assess the combination of induction cadonilimab and chemotherapy before CCRT. **Methods:** In this multicenter, single-arm, phase 2 study, we used a Simon two-stage design. Previous studies of induction chemotherapy showed a ORR of 68.8%-80% in LACC. Null hypothesis of ORR 80% was adopted in this study. Estimating a ORR of 95% would be achieved following induction therapy, a total of 29 patients (including 9 in the first stage) were required with type I and type II errors set at 0.05 and 0.2, respectively. Eligible patients were women aged 18 years or older, newly diagnosed disease with stage IB3-IVA (International Federation of Gynecology and Obstetrics [FIGO] 2018), with histologically confirmed cervical carcinoma, and had an ECOG performance status of 0 or 1. Patients received 2 cycles of induction therapy consisting of cadonilimab at a dose of 10mg/kg plus nab-paclitaxel at a dose of 260 mg/m² and cisplatin at a dose of 75mg/m² followed by CCRT. The primary endpoint was objective response rate (ORR) at 2 weeks after the completion of induction therapy and secondary endpoints included progression-free survival (PFS) and overall survival (OS). **Results:** Between January and October 2024, 29 patients were enrolled, with a median age of 58 years (range 32–70). All patients were ECOG performance status of 1. Of these, 26 had squamous cell carcinoma, and 3 had adenocarcinoma. FIGO stages included stage II (9 [31.0%]), III (18 [62.1%]), and IVA (2 [6.9%]). As of January 19, 2025, 26 patients completed CCRT. Median PFS and OS were not reached. At 2 weeks post-induction therapy, ORR was 93.1% (27 PR, 2 SD). Thirteen patients underwent evaluation at 3 months post-CCRT, all achieving CR (100%). Grade 3–4 treatment-related adverse events occurred in 10.3% of patients (3/29), including leukopenia (n=2) and primary adrenal insufficiency (n=1) during induction therapy. **Conclusions:** Cadonilimab combined with chemotherapy as induction therapy shows promising anti-tumor activity and manageable safety profile in LACC patients. These findings suggest the potential of induction chemoimmunotherapy followed by CCRT and warrants further follow-up. Clinical trial information: NCT06511726. Research Sponsor: None.

5531 **Poster Session**

A real-world analysis of the effectiveness of pembrolizumab by type of associated treatment in patients with metastatic cervical cancer: Added value of bevacizumab. First Author: Alberto Farolfi, IRCCS Istituto Romagnolo per lo Studio dei Tumori (IRST) "Dino Amadori", Meldola, Italy

Background: Pembrolizumab (pembro) showed a statistical significant survival benefit in persistent, recurrent, or metastatic cervical cancer (CC) when added to chemotherapy. In this real-world study we aimed to evaluate if the effectiveness of pembro may vary according to the type of platinum used or by the incorporation of bevacizumab (bev). **Methods:** The analysis was conducted with the TriNetX Global Collaborative Network. In our study, we defined different cohort of patients by type of platinum (cisplatin or carboplatin) and bev use (yes or no). First, we compared 597 CC patients treated cisplatin with 1.080 CC patients treated with carboplatin, in addition to paclitaxel and pembro. After this analyses, we evaluated the addition of bev (701 patients) to a platinum-based regimen compared to a cohort of patients treated without bev (562 patients). A propensity score matching (PSM) was used to balance the cohorts by age, race, previous radiotherapy, body mass index and treatment (bev for first analyses and cisplatin for the second). Subsequently, a COX analyses, adjusted for the same factors, was used in unmatched cohorts to validate our results. Hazard ratio (HR) was used to compare the overall survival (OS) and the development of fistulae, bowel perforation or pulmonary embolism (PE) in the matched cohorts. **Results:** PSM generated 583 pairs of CC patients treated with cisplatin (mean age of 50.6, +/-12.6 standard deviation, SD) or carboplatin (mean age of 50.2, +/-12.7 SD). Median OS was not statistical different between the groups (HR 0.92, 95% CI 0.75-1.28), confirmed also by the Cox model (HR 0.95, 95% CI 0.79-1.15). Among the 386 matched pairs of CC patients treated with (mean age of 53.8, +/-13.1 SD) or without bev (mean age of 53.8, +/-13.4 SD), median OS was 35.7 months versus 20.1 months (HR 0.64, 95% CI 0.49–0.84, p = 0.001), without differences in the rate of fistulae (HR 0.77, 95% CI 0.50-1.18), but an increased risk in bowel perforation (HR 3.08, 95% CI 1.01-9.38, p = 0.037) and a lower risk of PE (HR 0.57, 95% CI 0.35-0.93, p = 0.022). In multivariate analyses, bev significantly reduced the risk of death (HR 0.75, 95% CI 0.61-0.94, p = 0.01). **Conclusions:** The survival rates associated with immunotherapy treatment in our real-world study are consistent with those reported in previous studies. Specifically, we showed that the effectiveness of pembro is not influenced by the type of platinum used. However, the addition of bev may extend OS in patients with CC, without increasing the risk of fistulae or PE. Research Sponsor: None.

5532 **Poster Session**

A non-invasive metabolomic biomarker for detecting cervical intraepithelial neoplasia and cervical cancer. First Author: Jihoon Kang, Oncocross., Ltd., Seoul, South Korea

Background: Cervical intraepithelial neoplasia (CIN) is a precancerous lesion that can progress to cervical cancer, a leading malignancy affecting women worldwide. Although current screening strategies and diligent follow-up are essential for identifying high-grade CIN, there remains a critical need for minimally invasive tests to aid in both early detection and disease monitoring. This study evaluated the utility of a blood-based metabolomic liquid biopsy for differentiating CIN from cervical cancer and investigated the role of 2,3,6-Trichlorobenzaldehyde as a novel biomarker. **Methods:** From September 2023 to December 2024, 177 participants (cervical cancer, n=18; CIN, n=49; healthy controls, n=110) were enrolled at Soonchunhyang University Hospital in Cheonan, South Korea. All participants were adults ($\geq$18 years) with no cancer history in the previous five years and were not receiving anticancer therapy at the time of serum collection. Serum samples underwent untargeted metabolomic profiling via headspace gas chromatography–mass spectrometry (GC–MS). Relative metabolite abundances were compared among the groups, and pairwise t-tests ($p < 0.05$) assessed statistical significance. **Results:** Six metabolites demonstrated strong detection and classification performance, with 2,3,6-Trichlorobenzaldehyde emerging as the most prominent biomarker. This metabolite effectively differentiated among cervical cancer, CIN, and healthy controls (ANOVA, $p < 0.0001$). Specifically, 2,3,6-Trichlorobenzaldehyde yielded a sensitivity of 94.5% and a specificity of 95% for detecting cervical cancer, and a sensitivity of 95.9% and a specificity of 95% for identifying CIN. It also significantly distinguished Stage I cervical cancer from CIN grades 1, 2, and 3, as well as from adenocarcinoma in situ (AIS) (t-test, $p < 0.0001$). Five additional metabolites—p-Xylene, 3,6,9,12-Tetraoxahexadecan-1-ol, Ethylbenzene, Indole, and Cyclohexanone—were significantly elevated in both the cervical cancer and CIN groups compared to healthy controls (t-test, $p < 0.0001$), although they did not differ substantially between the cancer and CIN groups (t-test, $p > 0.05$). **Conclusions:** These findings highlight 2,3,6-Trichlorobenzaldehyde as a promising candidate for a blood-based metabolomic panel aimed at distinguishing cervical cancer from CIN and healthy controls. A minimally invasive assay incorporating this biomarker may improve cervical disease screening, refine risk stratification, and support continuous disease surveillance. Further prospective validation in larger cohorts is warranted to establish its clinical applicability. Research Sponsor: None.

5533 **Poster Session**

GT101 autologous TIL therapy in patients with recurrent and metastatic cervical cancer: A phase 1 study. First Author: Haifeng Qin, The Fifth Medical Centre of Chinese PLA General Hospital, Beijing, China

Background: GT101 is Grit's tumor-infiltrating lymphocyte (TIL) product. Adoptive cell therapy using autologous TILs has shown efficacy and long-term responses in patients with certain advanced solid tumors that have progressed after conventional therapies. We present data from 11 patients with recurrent or metastatic cervical cancer enrolled in a Phase 1, open-label, single-arm, multicenter trial (NCT05430373) of GT101. The study aims to investigate the safety profile, efficacy trends, and duration of response. **Methods:** Eleven patients with recurrent or metastatic cervical cancer were enrolled in the study, receiving a lymphodepletion regimen followed by GT101 infusion and IL-2 administration. The study's primary endpoints were treatment-emergent adverse events (TEAEs), including serious adverse events (SAEs) and adverse events (AEs), assessed using the CTCAE version 5.0 grading scale. Secondary endpoints included objective response rate (ORR), disease control rate (DCR), progression-free survival (PFS), duration of response (DoR), and overall survival (OS) based on RECIST version 1.1. **Results:** As of August 1, 2024, 11 patients received treatment, with a median age of 48 years and two prior therapy lines. Following FC lymphodepleting chemotherapy, patients received GT101 infusion at doses of $\geq 5\times10^9$ viable cells, with a median dose of 4.1×10^{10} viable cells, followed by high-dose IL-2 (600,000 IU/kg, up to 6 doses). Most adverse events (AEs) were Grade 1 or 2. Grade $\geq$3 AEs, primarily related to lymphodepleting chemotherapy and IL-2, included decreased lymphocyte, white blood cell, and neutrophil counts, anemia, pyrexia, and decreased platelet count. Most Grade $\geq$3 AEs resolved or downgraded to Grade $\leq$2 within 14 days. Among 11 cervical cancer patients, the objective ORR was 45.5% (5/11), with disease control in 10/11 patients (90.9%). Four patients (36.4%) had confirmed PR, one (9.1%) achieved CR, and five (45.5%) had SD; one patient had unconfirmed PD. The median PFS was 4.83 months, and median OS has not yet been reached. A patient with CR maintained this response for 14.5 months, diagnosed with stage IIIC2 cervical squamous cell carcinoma, and underwent surgical resection of metastatic lymph nodes. The SOD at baseline was 71.57 mm, reduced to 29.12 mm after 28 days. At week 12 post-GT101 treatment, imaging showed complete response of the lesion, achieving CR. **Conclusions:** In the GT101 Phase 1 study, no treatment-related SAEs or DLTs were observed. GT101, infused after FC lymphodepleting chemotherapy and high-dose IL-2, exhibited a manageable safety profile. It demonstrated clinically meaningful activity and durable responses in patients with recurrent and metastatic cervical cancer. These promising results indicate favorable long-term survival outcomes, durable responses, and no long-term safety concerns related to GT101. Clinical trial information: NCT05430373. Research Sponsor: None.

5534 **Poster Session**

Management of loop electrosurgical excision procedure with positive margins. First Author: Christopher M Mayer, University of Alabama at Birmingham, Birmingham, AL

Background: Loop Electrosurgical Excision Procedure (LEEP) is a primary management for preinvasive cervical disease. While often successful, around 10% will have disease extend to the margin of the LEEP specimen, leaving the possibility of pathology extended beyond the excised region. The American Society for Colposcopy and Cervical Pathology (ASCCP) provides management options for LEEP with positive margins, which include hysterectomy, repeat LEEP, or follow-up in 6 months with either: HPV-based testing or colposcopy with endocervical curettage. Limited data exists in the comparison of management options. **Methods:** This retrospective study included patients with cervical preinvasive disease referred to a single academic institution between 1/2022 to 12/2024 who underwent LEEP found to have a positive margin. Demographics and pathology results were obtained from medical records. The primary outcome was follow-up colposcopy pathology in patients who had a positive margin from LEEP. Statistical analysis was performed using GraphPad. **Results:** 67 patients underwent follow-up colposcopy after a LEEP with a positive margin. At time of LEEP, the median age was 34.5 years with 36% Hispanic, 34% African American, 22% White, and 2% Asian. With HPV status prior to LEEP, 72% were non-genotyped high risk (HR), 6% HPV16+, 6% HPV18+, and 3% were other HR+. Positive margins were either CIN 2 (N=12) or CIN 3 (N=55) and either endocervical (N=40), peripheral (N=15), both endocervical and peripheral (N=7), or unspecified (N=5). Pathology at follow-up colposcopy was primarily negative/low-grade disease (83.6%) with a minority being high-grade disease (16.4%). CIN 2 or CIN3 at the margin was not associated with high-grade disease on follow-up colposcopy (0% vs. 26.7%; p=0.108). The median age at time of LEEP did not significantly differ between CIN 2 or CIN3 positive margins (37.5 vs 34.9y; p=0.274) and was not associated with negative/low-grade or high-grade disease at follow-up colposcopy (38.4 vs 35.7y, p=0.251). Race was not associated with high-grade disease on follow-up colposcopy (p=0.239). There was no difference between high-grade lesion on colposcopy and location LEEP positive margin (p=0.998). HPV 16+ or 18+ was not associated with high-grade pathology at follow up colposcopy (p=0.289). **Conclusions:** In our diverse population, the prevalence of high-grade disease on follow-up colposcopy is low regardless of having CIN 2 or CIN 3 at any margin at time of LEEP. Numerically, CIN 2 margins were less likely to have positive high-grade colposcopy when compared to CIN 3 margin. Race nor age were associated with high-grade disease on follow-up colposcopy. While ASCCP offers follow-up repeat colposcopy in the setting of positive margins, prospective studies could be beneficial in determining if less-invasive options, such as HPV testing are sufficient for follow-up in this population. Research Sponsor: None.

5535 **Poster Session**

Global cervical cancer outcomes and national cancer system characteristics. First Author: Erin Jay Garbes Feliciano, Department of Medicine, NYC Health + Hospitals/Elmhurst, Icahn School of Medicine at Mount Sinai, Queens, NY

Background: Significant global health disparities persist in cervical cancer, with over 85% of cases and deaths occurring in low- and middle-income countries (LMICs). In many settings, access to screening, vaccination, and treatment is limited. Despite being largely preventable through HPV vaccination and early detection, many women around the world still face inadequate healthcare infrastructure, lack of awareness, cultural stigma, and gender barriers to seeking care. Therefore, we evaluated global health system metrics that may inform efforts to improve equity in access to cervical cancer care globally. **Methods:** Estimates of age-standardized mortality-to-incidence ratios (MIR) were derived from GLOBOCAN 2022 for female patients of all ages with cervical cancer. We collected health spending as a percent of gross domestic product, physicians/1000 population, nurses and midwives/1000 population, surgical workforce/1000 population, GDP per capita, Universal Health Coverage Service Coverage Index (UHC index), availability of pathology services, human development index (HDI), gender inequality index (a combined metric of health, empowerment, and economic agency), radiotherapy centers/1000 population, and out-of-pocket expenditure as percentage of current health expenditure. We evaluated the association between MIR and each metric using univariable linear regressions. Metrics with $p<0.0045$ (Bonferroni corrected) were included in multivariable models. Variation inflation factor (VIF) allowed exclusion of variables with significant multicollinearity. R2 defined goodness of fit. **Results:** On univariable analysis, all 11 metrics were significantly associated with MIR of cervical cancer (<0.001 for all). After including metrics that were significant on univariable analysis, HDI demonstrated significant collinearity (VIF=19). Therefore, after correcting for multicollinearity, the final multivariable model with 10 variables had R2 of 0.79. On multivariable analysis, the following variables were independently associated with lower (improved) MIR for cervical cancer: 1) nurses/midwives per 1000 population ($\beta=-0.0071$, p=0.029) and 2) UHC index ($\beta=-0.0023$, P=0.013). In addition, greater gender inequality was associated with greater (worse) MIR ($\beta=0.30$, P=0.002). **Conclusions:** This global analysis of health-system metrics suggests promoting progress towards UHC and strengthening the nursing/midwifery workforce may be independently associated with improved cervical cancer mortality-to-incidence ratio. Furthermore, greater gender inequality was associated with worse MIR. These findings may inform further efforts to improve global cervical cancer care and underscore the importance of gender equity in improving global cancer outcomes. Research Sponsor: None.

5536 **Poster Session**

Atezolizumab and stereotactic body radiation in metastatic, recurrent, or persistent cervical cancer: Results from a phase II multi-institutional study. First Author: Kamran A. Ahmed, H. Lee Moffitt Cancer Center and Research Institute, Tampa, FL

Background: Pembrolizumab is approved for PD-L1+ but not PD-L1 negative metastatic, recurrent, or persistent cervical cancer. Response rates to single agent anti-PD-1/PD-L1 therapy have been modest with no responses noted in PD-L1 negative tumors. **Methods:** The study is designed as a prospective, phase II multi-institutional trial of SBRT followed by atezolizumab (1200 mg intravenously q3 weeks). Key eligibility criteria included patients with metastatic, recurrent, or persistent cervical cancer with at least 2 distinct lesions. The primary objective was objective response rate measured at the unirradiated target lesion. Secondary endpoints included overall response, progression free survival (PFS), overall survival (OS), and adverse events. Clinical trial information: NCT03614949. **Results:** A total of 21 patients were enrolled. Median follow-up is 23.6 months. The majority of patients had adenocarcinoma (n=10; 48%) and were PD-L1 negative (n=15; 71%). The best overall response was a partial response in 5 (24%) and stable disease in 12 (57%) patients. The median duration of response was 8.6 months (95% CI: 4.5-13.6 months). An objective response at the unirradiated target lesion was observed in 8 patients (38%), meeting the study defined endpoint. Responses were noted in PD-L1 negative tumors. The median PFS was 4.7 months (95% CI: 3.9- 7.4) with a 6-month PFS of 48%. The median OS was 26 months (95% CI 7.6 – 54) with a 6-month OS of 76%. No differences were noted in OS or PFS by PD-L1 status. The most common grade $\geq$ 2 toxicities at least possibly attributed to study therapy included lymphopenia (n=6; 29%), nausea/vomiting (n=3; 14%), and hyponatremia (n=3; 14%). **Conclusions:** In this first trial of SBRT and atezolizumab in metastatic cervical cancer unselected for PD-L1, combination therapy was well tolerated. Responses were noted in PD-L1 negative tumors. Combination therapy may allow for improved response rates to immune checkpoint inhibition in metastatic cervical cancer particularly in PD-L1 negative tumors. Clinical trial information: NCT03614949. Research Sponsor: Genentech; ML40521.

5537 **Poster Session**

Real-world efficacy and safety of cadonilimab (PD-1/CTLA-4 bispecific antibody) in patients with advanced, recurrent, and metastatic cervical cancer. First Author: Dapeng Li, Shandong Cancer Hospital and Institute, Shandong First Medical University and Shandong Academy of Medical Sciences, Jinan, China

Background: Immune checkpoint inhibitors have become one of the important treatment modalities for advanced, recurrent and metastatic cervical cancer (A/R/M CC). Cadonilimab, a PD-1 and CTL-4 bispecific antibody, has showed considerable efficacy for treatment of A/R/M CC. This study aims to investigate the real-world efficacy and adverse event profile of cadonilimab in the treatment of A/R/M CC. **Methods:** We enrolled patients with histologically confirmed CC, who had received at least two cycles of cadonilimab for A/R/M disease and had imaging evaluation at Department of Gynecologic Oncology in Shandong Cancer Hospital and Institute in China, between July 2022 and March 2024. Efficacy including objective response rate (ORR), disease control rate (DCR), progression-free survival (PFS), overall survival (OS) and adverse events (AEs) were analyzed. **Results:** 96 patients treated with cadonilimab monotherapy or cadonilimab plus chemotherapy with/without radiotherapy were enrolled. The median follow-up duration was 12.5 months. The overall ORR was 69.8%, the DCR was 89.6%. (Table 1). The median PFS was 12 months (95%CI 8.4-15.6), and the median OS was not reached. The ORR of first and second line's treatment was 77.7% and 56.6%, respectively. DCR was 91.7% and 80.0%, respectively. Among the 18 patients treated with third-line and above, four (22.2%) patients achieved CR, ORR was 72.2%, and DCR was 88.8%. Among all patients, PD-L1 positive patients had a higher ORR (74.4%, P=0.049). Comparing with non-SCC, patients with SCC had better ORR (78.6% vs.38.0%, P=0.001). It's also worth noting that, among 19 patients who had progressed on first or second line's therapy of PD-1 monospecific antibody, cadonilimab mono or combination therapy achieved an overall ORR of 63.1% (1 CR, 11 PR) and a DCR of 94.7%, and a median PFS of 15.2 months (95% CI 5.7-24.7). Among them, 16 patients with SCC had a 100% DCR and a median PFS of 15.2 months (95%CI 5.1-25.3). The incidence of immune-related adverse events (irAEs) was 33.3%, mainly including 21 hypothyroidism (21.9%), seven hyperthyroidism (7.3%), etc. Two (2.1%) had ≥ grade 3 irAEs (one pneumonia and one myocardial injury). No death was caused by irAEs. **Conclusions:** Cadonilimab showed encouraging efficacy and manageable safety in the treatment of A/R/M CC in real world, even in patients with PD-L1 negative. And it also present promising disease control in patients who have progressed on previous PD-1 monospecific antibody. Research Sponsor: None.

The best overall response, PFS and OS in first-, second-, ≥ third-line and total patients.

Best overall response, PFS and OS	First-line (n=48)	Second-line (n=30)	≥Third-line (n=18)	Total
CR (%)	16.6	16.6	22.2	17.7
PR (%)	60.4	40.0	60.0	52.0
ORR (%)	77.7	56.6	72.2	69.8
DCR (%)	91.7	80.0	88.8	89.6
mPFS (months)	12.0	8.9	18.7	12.0
6-month PFS rate (%)	87.5	66.6	88.8	81.2
6-month OS rate (%)	100.0	100.0	100.0	100.0

5538 **Poster Session**

Integrative analysis of VB10.16 and atezolizumab in advanced HPV16-positive cervical cancer: Linking biomarker insights to clinical outcomes. First Author: Kristina Lindemann, Department of Gynecological Oncology, Oslo University Hospital & Institute of Clinical Medicine, Faculty of Medicine, University of Oslo, Oslo, Norway

Background: Therapeutic cancer vaccines combined with immune checkpoint inhibitors offer a promising strategy to enhance anti-tumor responses. We recently demonstrated the safety and clinical efficacy of VB10.16, a DNA-based therapeutic cancer vaccine encoding HPV16 E6/E7 oncoproteins fused to CCL3L1 for antigen-presenting cell targeting, in HPV16-positive persistent, recurrent or metastatic cervical cancer[1]. This analysis explores the association between HPV16-specific T cell responses, tumor microenvironment (TME) characteristics, and clinical outcomes in the phase 2a trial. **Methods:** In this multicenter, open-label trial, 52 patients with advanced HPV16-positive cervical cancer received VB10.16 (3 mg intramuscularly) combined with atezolizumab (1200 mg intravenously) for up to 48 weeks. Primary endpoints were safety and objective response rate per RECIST v1.1. Secondary endpoints included overall survival (OS) and HPV16-specific T cell responses via IFN-γ ELISpot (n=36). Predefined exploratory endpoints included systemic immunosuppression and TME inflammatory status in baseline tumors, assessed via myeloid cell counts (baseline to ~week 9, n=47), flow cytometry (T cell/myeloid-derived suppressor cells [MDSC] ratio, n=21), and gene expression analyses (n=29). **Results:** Patients with reduced on-treatment systemic immunosuppression demonstrated stronger HPV16-specific T cell responses than patients without (myeloid cell counts decreased in 17/47 patients; T cell/MDSC ratio increased in 12/21 patients). On-treatment reduction in systemic immunosuppression was associated with a higher clinical benefit rate (complete response [CR]/partial response [PR]/stable disease [SD] in 17/28 vs 4/19 patients by myeloid counts and 10/12 vs 2/9 by T cell/MDSC ratio), suggesting associations between T cell response, systemic immunosuppression and effect of immunotherapies. Among the 9 responders in the efficacy population (n=47; 3 CR; 6.4% and 6 PR; 12.8%), 5 patients had available gene expression data from baseline tumors. Patients with pro-inflammatory/proliferative TME signatures demonstrated higher CR/PR rates (4/14 vs. 1/15) and longer OS compared to patients with stromal/immunosuppressive signaling (mOS not reached vs 8.3 months). Clinical benefit was also observed in stromal/immunosuppressive TMEs (1/15 CR, 6/15 SD), highlighting VB10.16's potential to overcome local immunosuppression. **Conclusions:** VB10.16 combined with atezolizumab induces durable responses, mitigates local and systemic immunosuppression, and demonstrates synergy between biomarkers and clinical outcomes. High CR/PR rates with favorable immune and TME characteristics highlight the promise of this combination therapy, warranting further exploration. [1]Hillemanns P *et al*, 2025 doi:10.1136/jitc-2024-010827. Clinical trial information: NCT04405349. Research Sponsor: Nykode Therapeutics; Nykode Therapeutics was supported by the Norwegian SkatteFUNN R&D tax deduction government program; 322860; F. Hoffmann-La Roche Ltd provided atezolizumab.

5539 **Poster Session**

A meta-analysis of induction chemotherapy (ICT) followed by chemoradiotherapy for locally advanced cervical cancer: The role of ICT type and duration on efficacy outcomes. First Author: Matheus de Oliveira Andrade, Instituto do Câncer do Estado de São Paulo (ICESP), Faculdade de Medicina da Universidade de São Paulo (FMUSP), São Paulo, Brazil

Background: The treatment of locally advanced cervical cancer (LACC) is based on concomitant chemotherapy and radiotherapy (CCRT). While the recent incorporation of pembrolizumab for stage III-IVA disease has expanded treatment options, immunotherapy remains inaccessible in many regions with high cervical cancer prevalence. The addition of induction chemotherapy (ICT) prior to CCRT is controversial, as trials have yielded conflicting results. This study aims to evaluate the impact of the type and duration of the ICT for LACC. **Methods:** We systematically searched PubMed, Embase and Cochrane for studies with patients diagnosed with LACC receiving ICT followed by CCRT. Studies that included surgery, definitive radiotherapy (without concurrent chemotherapy), or immunotherapy were excluded. We compared ICT regimens between each other based on drug type and duration, and conducted a meta-analysis of trials comparing ICT followed by CRT versus CRT alone. Meta-analyses were carried out using random-effects model, with heterogeneity assessed via I^2 statistics and Cochran's Q test. Sensitivity analyses were performed using the leave-one-out approach, and meta-analyses of proportions with subgroup analyses. **Results:** Among 5,282 screened studies, 20 met the inclusion criteria, representing 1,543 patients treated with ICT. Meta-analysis of proportions revealed a 2-year overall survival (OS) of 84.1% for studies utilizing platinum–paclitaxel compared to 72.2% for platinum–gemcitabine (p-value for subgroup difference = 0.022). Studies with ICT duration of ≤6 weeks showed a 2-year OS of 84.8% compared to 71.7% for ICT duration >6 weeks (p = 0.003). Other subgroup comparisons (cisplatin versus carboplatin, cycle duration of ≤14 days versus >14 days, and cisplatin dose intensity <25 mg/m²/week versus ≥25 mg/m²/week) did not show statistically significant differences in 2-year OS. A meta-analysis of the five controlled studies exhibited high heterogeneity in OS and progression-free survival (PFS), driven by the CIRCE trial — the only study employing a platinum–gemcitabine ICT regimen lasting >6 weeks. Sensitivity analysis excluding this trial demonstrated a significant improvement in OS (HR 0.68; 95% CI 0.47–0.99; p = 0.049) and PFS (HR 0.46; 95% CI 0.31–0.69; p = 0.0002) with the addition of ICT to CCRT, compared to CCRT alone. **Conclusions:** In patients with LACC, the addition of ICT to CCRT significantly improves PFS and OS compared to CCRT alone, provided that the ICT involves a platinum doublet with paclitaxel and is administered within ≤6 weeks. Research Sponsor: None.

5540 **Poster Session**

A TORC1/2 inhibitor onatasertib combined with toripalimab in patients with advanced cervical cancers with prior anti-PD-(L)1 therapy. First Author: Li Zheng, Clinical Trial Center, West China Hospital, Chengdu, China

Background: Clinical findings on onatasertib (ATG-008), an oral TORC1/2 inhibitor, showed promising anti-tumor efficacy and manageable safety when used in combination with toripalimab, an anti-PD-1 monoclonal antibody, in treatment-naïve cervical cancer (CC) patients who had not received prior anti-PD-(L)1 therapy. Here, we present results from the anti-PD-(L)1 therapy treated CC cohort of the TORCH-2 study who had at least prior 1 line of anti-PD-(L)1 therapy with the combination of onatasertib and tori. **Methods:** The TORCH-2 study is a phase 1/2 open-label, dose escalation and expansion trial of onatasertib in combination with tori in patients (pts) with advanced solid tumours (NCT04337463). Eligibility criteria included at least one measurable lesion, ECOG 0-1 and adequate organ function. Pts with prior PI3K/AKT/mTOR inhibitor therapy were excluded. CC pts with at least prior 1 line of anti-PD-(L)1 therapy and 1 line of platinum chemotherapy regardless of PD-L1 expression, were enrolled and received onatasertib 15mg orally once a day (QD) in combination with tori 240 mg, once every 21 days (Q3W). Efficacy assessments were reported based on RECIST1.1 criteria and the endpoints included overall response rate (ORR), disease control rate (DCR), duration of response (DOR), progression free survival (PFS) and overall survival (OS). **Results:** As of Nov 25, 2024, 30 advanced CC pts who had at least prior 1 line of anti-PD-(L)1 therapy and 1 line of platinum chemotherapy were enrolled. Median age was 56.5 years. Baseline ECOG scores were 0 (26 pts) and 1 (4 pts). There were 14 and 16 pts who had received 1 and ≥2 prior lines of systemic therapy, respectively. Additionally, 16 pts had prior abraxane treatment and 11 pts had prior bevacizumab therapy. The median time since initial diagnosis was 37 months(m). The efficacy-evaluable population (27 CC pts) had an ORR of 22.2% (6/27, all confirmed). The DCR was 85.2%. The median time to response was 1.7 m (1.4, 4.2) and median DOR was 5.7 m (95% CI: 2.7, NE). Median PFS and median OS was 4.2 m (95% CI: 3.3, 5.8) and 21.4 m (95% CI: 15.5, NE), respectively. The ORRs of PD-L1 positive and PD-L1 negative populations were 30% (3/10) and 33.3% (2/6), respectively. Thirty pts (100%) had ≥ 1 TEAEs; 22 (73.3%) pts had grade ≥ 3 TRAEs. The most common all grade TRAEs included hyperglycaemia (56.7%), rash (43.3%) and white blood cell decreased (43.3 %). No TEAE led to death. **Conclusions:** Onatasertib in combination with tori is tolerable with encouraging response rate and disease stabilisation in advanced CC pts with prior anti-PD-(L)1 therapy, regardless of PD-L1 expression. The expansion cohorts are ongoing. Clinical trial information: NCT04337463. Research Sponsor: Antengene.

5541 Poster Session

Evolving global burden and trend of cervical cancer in G20 countries: Age, sex, regional disparities from 1990-2021. First Author: Jahnavi Chaudhari, HCA Oak Hill Hospital, Brooksville, FL

Background: Cervical Cancer (CC) is the 6th leading cause of death and 4th leading cause of disability amongst all cancer in G20 countries. The G20 nations, which represent about 85% of the global GDP, hold a pivotal role in shaping the world's economic and health landscapes. This economic dominance underscores the substantial impact that public health issues, like CC, can have not only on individual countries but on global stability and productivity. **Methods:** We estimated the incidence, prevalence, deaths, disability-adjusted life years (DALYs), and years lived with disability (YLDs) attributed to CC across the G20 countries from 1990 - 2021, disaggregated by age, sex, year, and location, using the standardized methodology of the Global Burden of Disease Study 2021. Non-fatal health outcomes were modeled using DISMOD MR 2.1, a machine learning tool, while fatal health outcomes were assessed using the Cause of Death Ensemble Model (CODEm). The results are reported as absolute counts and age-standardized rates per 100,000 population. **Results:** The total prevalence count of cervical cancer increased from 1.3 (95% uncertainty interval: 1.2–1.3) million in 1990 to 2.2 (2.0–2.5) million in 2021. Deaths rose from 140,740 (128,861–152,835) to 183,343 (166,174–200,956), while disability-adjusted life years (DALYs) increased from 4.8 (4.4–5.2) million to 5.9 (5.3–6.4) million during the same period. The highest annual percentage change (APC) in the age-standardized incidence rate (ASIR) was observed in Italy (1.59%), followed by South Africa (1.14%), China (0.43%), Argentina (0.3%), Bulgaria (0.2%), and Canada (0.1%). In contrast, the majority of countries, including the United States, experienced a decline in ASIR, with the United States showing a 1.5% reduction from 1990 to 2021. For age-standardized mortality rate (ASMR), South Africa (1.12%) and Italy (0.47%) demonstrated an increase in APC, while all other countries observed a decline. Age-wise analysis revealed that for the 20–54 age group, APC in incidence increased by 1.12%, while for the 55+ age group, it rose by 1.77%. In terms of mortality, the 20–54 age group recorded a 0.26% increase in APC, and the 55+ age group experienced a 1.25% increase. Regarding DALYs, APC for the 20–54 age group increased by 1.4%, while the 55+ age group saw a rise of 2.15% from 1990 to 2021. **Conclusions:** Death due to Cervical Cancer accounted for 2.35% of all cancer causalities in 2021. Study findings underscore the need for urgent public health interventions. Disparities in incidence and mortality trends reflect unequal access to healthcare, screening, and HPV vaccination. The higher APC in older age groups (55+ years) highlight the importance of targeted healthcare access, while modest increases among younger populations (20–54 years) emphasize sustaining vaccination and screening efforts. Research Sponsor: None.

5542 Poster Session

Ceralasertib (cerala) + olaparib (ola) in patients (pts) with homologous recombination repair (HRR)-deficient platinum-sensitive relapsed ovarian cancer (OC) after progression on prior PARP inhibitor (PARPi) treatment (tx). First Author: Rene Lynnette Roux, Department of Oncology, Churchill Hospital, Oxford University Hospitals NHS Foundation Trust, Oxford, United Kingdom

Background: Combining an ATR inhibitor (ATRi) and a PARPi may overcome acquired PARPi resistance based on preclinical and clinical data. We report a Phase 1 study (NCT02264678) of cerala (ATRi) + ola (PARPi) in pts with HRR-deficient OC who had progressed on prior PARPi tx. **Methods:** Pts had histologically confirmed high-grade serous/endometrioid epithelial ovarian, fallopian tube, or primary peritoneal cancer, with deleterious or suspected deleterious *BRCA* or HRR mutations (*BRCA*m; HRRm: *RAD51C/D*m, *PALB2*m) or HRR-deficiency (HRD+). Pts received oral cerala 80 mg (d 1–14 every 28 d) + ola 150 mg (throughout) twice daily without/with (Cohort [Co] 1/2) intervening platinum-based tx after initial response and subsequent progression on prior PARPi tx. Primary endpoints were safety/tolerability; ORR per RECIST v1.1 and PFS were secondary endpoints. Emergence of PARPi resistance mechanisms was analyzed in archival/pre-study tx tissue samples. **Results:** 32 pts were treated, 30 in Co1 (7 ongoing tx at data cutoff: Mar 5, 2024) and 2 in Co2 (cohort closed early). Median age was 63.0 yrs; 68.8% (22/32) had *BRCA*m/HRRm and 31.3% (10/32) HRD+/non-*BRCA*m by local assessment. All pts had adverse events (AEs); 40.6% had grade ≥3 AEs (most common were anemia and platelet count reduced, each 21.9%); 6.3% discontinued tx due to AEs. Table shows efficacy in Co1. 24 pts had post-PARPi biopsies evaluable for genomics analysis: 3 (12.5%) had *BRCA* reversions (rev; 13 pts were *BRCA*m); 3 (12.5%) had loss of function alterations in DNA damage response (DDR) rewiring genes. Of 16 pts with post-PARPi biopsies evaluable for RAD51 foci, 81.3% (13) had RAD51 high status suggesting HRR functional proficiency as a prevalent PARPi resistance mechanism; of these 13, 61.5% (8; 80% CI, 40.2–79.9) responded to cerala + ola, while no responses occurred in 3 RAD51 low pts (80% CI, 0.0–53.6). Responders included patients with *BRCA* rev or *TP53BP1*m, indicating cerala + ola activity in pts with *BRCA* rev and alterations in DDR rewiring genes. Other PARPi resistance mechanisms were rare. **Conclusions:** In this setting of high unmet need, cerala + ola had acceptable safety, a low discontinuation rate, and clinical activity in both *BRCA*m/HRRm and HRD+/non-*BRCA*m pts after progression on a prior PARPi. Exploratory analyses highlighted emerging PARPi resistance mechanisms; ongoing assessments of PARPi resistance to inform pt selection and novel combination strategies in post-PARPi settings will be presented. Clinical trial information: NCT02264678. Research Sponsor: AstraZeneca.

	*BRCA*m/HRRm n=20	HRD+/non-*BRCA*m n=10	Total N=30
ORR, % (80% CI)	45 (29.3–61.5)	30 (11.6–55.2)	40 (27.7–53.3)
Best response, n (%)			
Complete	2 (10)	1 (10)	3 (10)
Partial	7 (35)	2 (20)	9 (30)
Stable	8 (40)	4 (40)	12 (40)
PFS			
Events, n	10	8	18
Median, months (80% CI)	7.5 (5.3–not calculable)	4.5 (1.8–5.3)	5.5 (4.7–7.5)

5543 Poster Session

Hyperthermic intraperitoneal chemotherapy combined with cytoreductive surgery versus cytoreductive surgery alone for ovarian cancer: An updated meta-analysis. First Author: Osama Ijaz, Services Institute of Medical Sciences, Lahore, Pakistan

Background: Hyperthermic Intraperitoneal Chemotherapy (HIPEC) delivers high-dose chemotherapy directly to the abdominal cavity to treat cancers that have spread to the peritoneal lining. When combined with cytoreductive surgery (CRS), HIPEC has been shown to improve survival outcomes in patients with advanced and recurrent ovarian cancer. This updated meta-analysis compares the efficacy and adverse events of CRS with HIPEC to cytoreductive surgery alone. **Methods:** A comprehensive literature search was conducted across Medline, Embase, Google Scholar, Cochrane CENTRAL, Scopus, and ClinicalTrials.gov up to December 2024. Only observational studies and randomized controlled trials (RCTs) involving adult patients with advanced or recurrent ovarian cancer treated with HIPEC in combination with CRS were included. The primary outcomes assessed were overall survival and the incidence of grade 3 or higher adverse events. A meta-analysis using a fixed-effects model was performed to calculate the pooled odds ratio (OR) and pooled hazard ratio (HR), with 95% confidence intervals (CI), to estimate the overall treatment effect. **Results:** A total of twelve studies involving 1,893 participants were included, with 1,067 participants in the control group and 826 in the treatment group. Regarding overall survival, the pooled HR was 0.67 (95% CI: 0.57–0.78; $p<0.00001$; $I^2=42\%$). In subgroup analyses, the HR was 0.67 (95% CI: 0.54–0.83) for treatment-naïve patients and 0.66 (95% CI: 0.52–0.84) for patients undergoing secondary cytoreduction for recurrent ovarian cancer. The test for subgroup differences showed no significant heterogeneity ($I^2=0\%$). In terms of adverse events, the pooled OR was 1.01 (95% CI: 0.89–1.14; $p<0.00001$; $I^2=82\%$). **Conclusions:** This updated meta-analysis demonstrates that HIPEC combined with CRS significantly improves overall survival in patients with ovarian cancer. Subgroup analysis indicated that this treatment enhances survival in both treatment-naïve patients and those undergoing secondary cytoreduction for recurrent ovarian cancer, aligning with findings from previous meta-analysis. However, in contrast to earlier meta-analysis, this study shows that HIPEC plus CRS does not increase the risk of adverse events. Therefore, HIPEC combined with CRS is both an effective and safe treatment option for patients with advanced and recurrent ovarian cancer. Research Sponsor: None.

5544 Poster Session

Gynecologic oncology referral rates of adnexal masses suspicious for ovarian cancer in an academic health system: A cohort study. First Author: Anna Jo Bodurtha Smith, University of Pennsylvania, Philadelphia, PA

Background: Ovarian-Adnexal Reporting Data System (O-RADS) is an international lexicon and risk stratification tool. O-RADS 4 or 5 lesions are complex adnexal masses that a 10-90% risk of malignancy, and national guidelines recommend gynecologic oncology referral. Our objective was to examine patient, clinician, and imaging factors associated with referral to gynecologic oncology for complex adnexal masses. **Methods:** This retrospective cohort study was exempt from IRB review. We identified all patients with O-RADS 4 or 5 lesions on ultrasound (US) or MRI from July 1, 2020 to December 31, 2023. Our primary outcome was referral to gynecologic oncology. We gathered patient demographic data and ordering clinician characteristics from electronic health records. We performed descriptive statistics and multivariate logistic regression of patient demographics and ordering clinician characteristics associated with gynecologic oncology referral. **Results:** Our cohort included 373 patients with O-RADS 4 or 5 lesions and no prior gynecologic oncology care. The referral rate to gynecologic oncology was 68%, and referral within 30 days of abnormal imaging was 43%. Time from abnormal imaging to referral ranged from 0 to 407 days (mean 15.3, median 4 days). In multivariate analyses, the likelihood of referral to gynecologic oncology was higher among patients with repeat abnormal imaging compared to those with single instance of abnormal imaging (aOR 20.61, 95%CI 2.63-161.6), O-RADS 5 lesions compared to O-RADS 4 lesions (aOR 9.15, 95%CI 3.47-24.85) and detection on MRI compared to US (aOR 7.79, 95%CI 1.57-38.65). The likelihood of referral to gynecologic oncology was lower among non-white patients (aOR 0.24, 95%CI 0.08-0.76). There were no differences by Hispanic ethnicity, rurality, insurance, or language. Referral was higher among patients whose imaging was ordered by an internal medicine clinician (aOR 3.89, 95% CI 1.48-10.20) compared to ob/gyn. **Conclusions:** One-third of patients with complex adnexal masses were not referred to gynecologic oncology. Disparities in referral to gynecologic oncology for complex adnexal masses rates based on patient race and ordering clinician specialty highlight the need for system-based approaches including clinician education or automated referrals. Research Sponsor: Conquer Cancer, the ASCO Foundation.

Gynecologic oncology referral after O-RADS 4/5.

	Multivariate OR (95%CI)
Postmenopausal (≥55 years)	1.89 (0.95-3.74)
Race	
- White	Reference
- Black	0.57 (0.27-1.21)
- Asian	1.03 (0.30-3.58)
- Some other race	0.24 (0.08-0.76)
Ordering specialty	
- Obstetrics/Gynecology	Reference
- Emergency Medicine	0.93 (0.33-2.62)
- Internal Medicine	3.89 (1.48-10.20)
- Family Medicine	1.62 (0.66-3.98)
- Other specialty	0.87 (0.27-2.76)
Has PCP	1.66 (0.81-3.42)
O-RADS	
- 4	Reference
- 5	9.15 (3.27-24.85)
Imaging	
- MRI	7.79 (1.57-38.65)
- US	Reference
Repeat abnormal imaging	20.61 (2.63-161.79)

5545 **Poster Session**

Progression-free survival as a surrogate outcome for overall survival in ovarian cancer maintenance therapy randomized controlled trials. First Author: Rachel P. Mojdehbakhsh, University of Wisconsin Carbone Cancer Center, Madison, WI

Background: A traditional primary outcome in prospective trials is progression-free survival (PFS). PFS often functions as a surrogate outcome for overall survival (OS) to speed up the translation of research findings into practice. While PFS has been validated as a surrogate for OS in contemporary therapeutic trials for patients with advanced ovarian cancer, there is little evidence to support the validity of PFS as a surrogate for OS in contemporary trials of maintenance therapies. Our objective was to evaluate whether PFS is a reliable surrogate outcome for OS in patients with ovarian cancer receiving maintenance therapy after platinum-based chemotherapy. **Methods:** In May 2024, MEDLINE was queried for all phase 3 trials evaluating poly (ADP) ribose polymerase (PARP) inhibitors and bevacizumab in the maintenance setting for ovarian, fallopian tube and primary peritoneal cancers. Included trials studied PARP inhibitors, bevacizumab or both as an intervention compared to control. Enrollment numbers, median follow up, PFS, OS and hazard ratios were abstracted. Using a meta-analytic approach, correlation analysis was performed using weighted linear regression and Pearson's correlation coefficient. Trials included contained complete survival data. Criteria for PFS surrogacy required R^2 >0.8. **Results:** Sixty trials were identified, 11 of which met inclusion criteria. Six trials investigated PARP inhibitors in the maintenance setting, while 4 trials investigated bevacizumab. One trial investigated both a PARP inhibitor and bevacizumab. The pooled sample size from all trials was n=6,243. Median follow up time was 60.35 months. Across all trials, the relationship between OS and PFS HRs was approximately linear. Corresponding R^2 values were low (R^2=0.35, 95% CI 0-0.63). Pearson correlation when weighted by total study sample size, was of low strength (r=0.59, 95% CI -0.05-0.87). Four trials evaluating bevacizumab as a maintenance therapy demonstrated favorable PFS benefit with no statistically significant difference in OS, while only one PARP inhibitor trial demonstrated a statistically significant benefit in PFS and OS. Weighted Pearson correlation coefficient for bevacizumab trials demonstrated moderate correlation between PFS and OS HRs (r=0.81, 95% CI -0.75-0.99) while PARP inhibitor trials demonstrated a low strength of correlation (r=0.26, 95% CI -0.71-0.88). **Conclusions:** Phase 3 clinical trials assessing maintenance therapies for ovarian cancer demonstrate poor correlation between PFS and OS. This effect may be modulated by type of maintenance therapy and the inclusion of platinum-based chemotherapy in trial arms. PFS as a surrogate outcome in maintenance therapy ovarian cancer clinical trials must be supported by additional studies and caution should be taken prior to regulatory approval based on PFS data alone. Research Sponsor: None.

5546 **Poster Session**

Development and validation of a proteo-metabolic panel for detection of asymptomatic ovarian cancer with minimal serum sample requirements: A multi-center prospective study. First Author: Ruomeng Bi, Tongji University, Shanghai, China

Background: Early diagnosis is crucial for improving the prognosis of ovarian cancer (OC). However, most patients (pts) are diagnosed at advanced stages due to subtle symptoms and traditional biomarkers' limitations. We aimed to develop an serum panel using multi-omics data for cost-effective detection of asymptomatic OC (asym-OC). **Methods:** Participants were recruited from the Shanghai Ovarian Cancer and Family Care Project (NCT06118307) involving five centers. A total of 843 individuals were included: 135 asym-OC pts and 708 non-OC individuals (290 pts with benign lesions and 418 healthy controls). Fasting serum samples (1 μL each) were analyzed using MALDI-TOF MS to generate proteo-metabolic (pro-met) data. For each sample, the original MS have ~43,900 data points from 100-13,000 Da. Preoperative data from three centers (N=680) were used to develop Light Gradient Boosting Machine (LGBM) models to identify key signals differentiating OC from non-OC. An independent external validation set (N = 163) was assembled by the other two centers. To develop a biologically interpretable and generalizable panel, the model was further refined to minimize biomarkers while maintaining efficacy. Validation of the panel was conducted using postoperative pro-met data from 42 asym-OC pts, transcriptomic data from 89 with asym-OC and 39 with benign lesions, supported by bioinformatic analyses. **Results:** Ten biomarkers, which are involved in coagulation, complement system, carcinogenesis, epithelial-mesenchymal transition, and the Warburg effect, were selected in the panel. The panel achieved an AUC of 0.90 (95% CI: 0.82-0.98) in the external validation set. The enhanced model that integrating the panel, age, BMI and HE4 achieved an AUC of 0.94 (95% CI: 0.90-0.99). In subgroup analyses, the enhanced model outperformed CA125, HE4, and ROMA, with AUCs of 0.96 (early-stage OC vs. non-OC) and 0.96 (OC vs. endometriosis) (See Table). Moreover, postoperative levels of the biomarkers in the panel approached those of the non-OC ($p < 0.05$). Transcriptomic data of the tissues corresponded to the pathophysiological alterations associated with OC development or progression. **Conclusions:** This study introduces a novel, non-invasive, and cost-effective serum panel that demonstrates high sensitivity and specificity for detecting asym-OC, offering a promising tool for early diagnosis of the disease. Research Sponsor: National Natural Science Foundation of China; 82072866 (Y.W.), 82272888 (Y.W.), 82204047 (Z.L.); Shanghai Hospital Development Center Foundation; SHDC12022106 (Y.W.).

	Early-stage OC vs. Non-OC (N=58/708)	OC vs. Endometriosis (N=135/80)
Enhanced model: 10-biomarker Pro-Met panel + BMI +age + HE4	0.96 [0.94-0.99]	0.93 [0.90-0.97]
CA125	0.87 [0.82-0.93]	0.77 [0.71-0.83]
HE4 premenopausal	0.73 [0.63-0.83]	0.91 [0.80-0.94]
postmenopausal	0.67 [0.58-0.74]	0.88 [0.76-0.86]
ROMA premenopausal	0.75 [0.60-0.81]	0.91 [0.80-0.93]
postmenopausal	0.89 [0.67-0.84]	0.87 [0.53-1.00]

5547 **Poster Session**

Comparison of predictive models in women with advanced epithelial ovarian cancer triaged to primary debulking or neoadjuvant chemotherapy. First Author: Shalini Rajaram, All India Institute of Medical Sciences (AIIMS), Rishikesh, India

Background: Triaging women with advanced epithelial ovarian cancer (AEOC) into primary debulking surgery (PDS) or neoadjuvant chemotherapy (NACT) remains largely subjective. **Methods:** This prospective observational study recruited women over 18 years with stage III-IV AEOC. Decision for PDS or NACT was based on patient-specific factors and radiological parameters. The agreement between clinical decisions and predictive models—Aletti's surgical complexity score, MSKCC Team Ovary criteria, Mayo triage algorithm, and Integrated Predictive Model (IPM) was assessed using kappa statistics. **Results:** 72 women with AEOC were included, with 17 (23.6%) assigned to the PDS and 55 (76.4%) to NACT. Amongst NACT patients, interval debulking surgery (IDS) was feasible in 30 women (54.5%), while 25 (45.5%) did not undergo surgery due to reasons such as disease progression, death, poor performance status, stable disease, or loss to follow-up. No difference was observed between the NACT and PDS groups in demographic parameters. Performance scores differed significantly, with higher scores observed in the NACT group compared to the PDS group: median ECOG (2 [1–2] vs. 1 [1–1], $p < 0.001$), ASA score (2 [2–3] vs. 2 [2–2], p = 0.005), and frailty index (0.26 ± 0.11 vs. 0.15 ± 0.05, $p < 0.001$). Serum albumin levels were lower (3.0 ± 0.51 vs. 3.7 ± 0.30 g/dL, $p < 0.001$), and median CA125 levels were higher (1170 [341–2637] vs. 494 [219.7–1000] U/mL, $p < 0.001$) in the NACT group. Radiological parameters, including median peritoneal carcinomatosis index (PCI) scores (16 [10–23] vs. 5 [3–8], $p < 0.001$), volume of ascites, pleural effusion, and disease at challenging operative sites, were also higher in the NACT group ($p < 0.05$). Surgical outcomes, including surgical PCI scores (5[2-6] vs 6[3-11], =0.35), residual disease rates (complete/optimal debulking: 96.6% vs. 88.2%, p = 0.42), surgical complexity score (4.7 ± 1.45 vs. 4.4 ± 1.33, p = 0.82), blood transfusion rates (80% vs. 70.6%, p = 0.76), and grade 2-3 complications (60% vs. 58.8%, p = 0.58) were similar in both groups. Baseline predictive scores were significantly higher in the NACT group compared to the PDS group: Aletti's surgical complexity score (8.4 ± 2.80 vs. 5.2 ± 1.25, $p < 0.001$), MSKCC Team Ovary criteria (6.4 ± 3.31 vs. 1.9 ± 1.49, $p < 0.001$), Mayo triage algorithm (0.87 ± 0.39 vs. 0.24 ± 0.44, $p < 0.001$), and IPM final score (high-risk: 69.1% vs. 52.8%, $p < 0.001$). Clinical decisions showed moderate concordance with the Mayo triage algorithm (κ = 0.57) and IPM score (κ = 0.51) and fair concordance with Aletti's score (κ = 0.33) and MSKCC criteria (κ = 0.23). **Conclusions:** Triage decisions based on patient performance status, nutritional factors, and disease extent demonstrated moderate concordance with predictive models. Both PDS and IDS had excellent cytoreductive outcomes with similar perioperative performance aligning with results from literature. Research Sponsor: None.

5548 **Poster Session**

Concordance of circulating tumor DNA and tissue genomic profiling in ovarian cancer: Influencing factors and clinical significance. First Author: Hao Su, Department of Obstetrics and Gynecology, National Clinical Research Center for Obstetric & Gynecologic Diseases, Peking Union Medical College Hospital, Chinese Academy of Medical Sciences & Peking Union Medical College, Beijing, China

Background: Next-generation sequencing of plasma circulating tumor DNA (ctDNA) shows promise in ovarian cancer management as a minimally invasive alternative to tissue sequencing. However, concordance between genomic alterations detected in tissue and ctDNA remains incompletely characterized, with limited understanding of influencing factors and clinical implications. **Methods:** We analyzed 29 matched pretreatment tissue and plasma samples from treatment-naïve ovarian cancer patients using a customized 2365-gene panel. Overall and individual concordance rates were calculated as the ratio of total concordant mutations to total tissue mutations, with patients stratified into high concordance (≥50%) and poor concordance (<50%) groups. Clinicopathological and tumor molecular factors influencing concordance were analyzed. Relationship between concordance rates and clinical outcomes, including chemosensitivity (KELIM score) and progression-free survival (PFS), was assessed in advanced-stage patients. **Results:** The cohort predominantly comprised FIGO III-IV disease (89.7%) and high-grade serous histology (89.7%), with median follow-up of 306 (66-570) days. Overall tissue-plasma concordance rate was 42%, with shared variants exhibiting identical abundance patterns across sample types (r=0.25, p=0.0074) and encompassing 66.1% of tissue driver mutations. Tissue-specific mutations displayed lower variant allele frequencies than shared mutations (median 4.4% vs 28.7%). Single nucleotide variants showed higher plasma detection rate than structural variants (47.3% vs 25.4%). Individual concordance rates varied substantially (0-83.3%). High concordance group exhibited higher tumor Ki-67 index (median 85% vs 70%), tissue tumor mutation burden (TMB, median 5.1 vs 4.1 muts/Mb), and plasma ctDNA fraction (median 8.1% vs 0.9%). No significant differences were observed in largest tumor diameter, CA125 levels, tumor sample locations (from primary site or metastatic site), or BRCA mutation/homologous recombination status between groups. By multivariable analysis, higher TMB (OR 1.931, 95% CI 1.064-3.504) and plasma ctDNA fraction (OR 1.416, 95% CI 1.060-1.893) independently associated with high concordance rates. In advanced-stage patients, poor concordance group showed lower KELIM scores (median 0.7 vs 1.2; 15.4% vs 69.2% of patients with score ≥1), indicating reduced chemosensitivity. Concordance rates strongly correlated with KELIM scores (r=0.71, p<0.0001). Poor concordance group demonstrated shorter PFS (median 436 days vs not reached, p=0.037). **Conclusions:** Our study revealed moderate concordance between pretreatment tumor tissue and plasma ctDNA mutation profiles in ovarian cancer, influenced by technical and biological factors. Tissue-plasma concordance may serve as a novel chemosensitivity and prognostic indicator. Research Sponsor: Beijing Xisike Clinical Oncology Research Foundation.

5550 Poster Session

Validation of the performance of Ovarian Cancer Score for diagnosing ovarian cancer in a multicenter study. First Author: Haixia Wang, Department of Gynecologic Oncology, Chongqing University Cancer Hospital & Chongqing Cancer Institute & Chongqing Cancer Hospital, Chongqing, China

Background: Early detection is crucial for improving survival of patients with ovarian cancer (OC), yet current diagnostic tools lack adequate sensitivity and specificity, especially for early stage disease. The Ovarian Cancer Score (OCS) is a newly developed serum extracellular based diagnosis marker for detection of ovarian cancer. The study aimed to explore the performance of OCS in detecting OC. **Methods:** This multicenter study included 1183 adult females with adnexal masses from four hospitals in China (October 2019 - April 2023). Of these, 1,024 samples were prospectively collected, and 159 were from biobanks. All serum samples were collected before surgery. The concentrations of sEV carbohydrate antigen 125 (CA125), human epididymis protein 4 (HE4) and complement component 5a protein (C5a) were quantified using chemiluminescence immunoassay and then used for calculating OCS. Sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) were calculated. CA125, HE4, and ROMA index results were retrieved from the medical record system at each hospital. The differences was calculated using. **Results:** The OCS demonstrated high sensitivity (95.5%, 95% CI: 93.3%-97.7%) and specificity (90.2%, 95%CI: 88.2%-92.2%) in OC in the cohort (n = 1183), significantly outperforming CA125 (90.0%, 95%CI: 86.8%-93.3% and 69.1%, 95%CI: 65.9%-72.2%) and ROMA (89.2%, 95%CI: 83.2%-95.2% and 83.1%, 95%CI: 79.3%-86.8%, all $p<0.05$). OCS was superior to HE4 in sensitivity (75%, 95%CI: 70.1%-79.9%, $p<0.001$), but not specificity (94.8%, 95%CI: 93.2%-96.5%, $p<0.001$). Subgroup analysis revealed that in premenopausal women, OCS showed higher sensitivity (94.3%, 95%CI: 90.2%-98.4%) compared to HE4 (79.0%, 95%CI: 71.5%-86.4%, $p<0.001$) and ROMA (83.0%, 95%CI: 72.2%-93.7%, $p<0.05$). The specificity of OCS was higher than CA125 and ROMA, but lower than HE4 (all $p<0.05$). In postmenopausal women, OCS showed higher sensitivity (96.2%, 95%CI: 93.6%-98.8%) than CA125 (89.9%, 95%CI: 85.8%-94.0%, $p<0.05$) and HE4 (72.6%, 95%CI: 66.2%-79.0%, $p<0.001$), but there was no significant difference in sensitivity between OCS and CA125 or ROMA ($p>0.05$). In early-stage OC (FIGO I+II), OCS's sensitivity (91.4%, 95%CI: 86.8%-96.1%) was significant higher than CA125 (78.4%, 95%CI: 71.6%-85.3%, $p<0.01$), HE4 (63.5%, 95%CI: 55.1%-71.9%, $p<0.001$) and ROMA (77.8%, 95%CI: 65.6%-89.9%, $p<0.05$). Particularly in FIGO Stage I patients, OCS demonstrated significant higher sensitivity than CA125 (89.7%, 95%CI: 83.0%-96.5% vs.70.1%, 95%CI: 59.9%-80.4%, $p < 0.01$), HE4 (51.4%, 95%CI: 39.8%-62.9%, $p < 0.001$) and ROMA (74.2%, 95%CI: 58.8%-89.6%, $p < 0.05$). The specificity of OCS was higher than CA125 and ROMA (all $p<0.001$), but lower than HE4 across all stage subgroups. **Conclusions:** This multicenter study demonstrated that the OCS is a promising non-invasive diagnostic tool for the detection of OC. Clinical trial information: NCT06366997. Research Sponsor: Chongqing Science and Technology Bureau; Talent Program of Chongqing; Chongqing Municipal Education Commission; Chongqing Health Commission; Beijing Health Alliance Charitable Foundation.

5551 Poster Session

Impact of disease progression on health-related quality of life (HRQOL): Updated results from the PRIMA/ENGOT-OV26/GOG-3012 trial of niraparib first-line (1L) maintenance therapy in patients with newly diagnosed advanced ovarian cancer (aOC). First Author: Mark S. Shahin, Hanjani Institute for Gynecologic Oncology, Abington Hospital–Jefferson Health, Asplundh Cancer Pavilion, Sidney Kimmel Medical College of Thomas Jefferson University, Willow Grove, PA

Background: The phase 3 PRIMA trial (NCT02655016) demonstrated that niraparib 1L maintenance therapy significantly extended progression-free survival (PFS) compared with placebo in patients with newly diagnosed aOC that responded to 1L platinum-based chemotherapy. Using data from the Nov 2019 cutoff (median follow-up, ≈1.7 y), pooled results from both treatment arms found that disease progression negatively affected HRQOL. Here we report updated HRQOL results from the PRIMA final analysis. **Methods:** In PRIMA, patients were randomized 2:1 to niraparib or placebo 1L maintenance once daily. HRQOL was assessed as a prespecified secondary endpoint using patient-reported responses to multiple instruments, including the European Organisation for Research and Treatment of Cancer QOL Core Questionnaire (EORTC QLQ-C30) and the EORTC QLQ Ovarian Cancer Module (EORTC QLQ-OV28). Assessments were collected at baseline, at designated intervals while on study treatment; at the end of treatment (EOT); and at 4, 8, 12, and 24 weeks after the last dose of study treatment. Post hoc analysis results are reported herein (clinical cutoff: Apr 8, 2024; median follow-up, 6.2 y). **Results:** In the overall population (niraparib, n=487; placebo, n=246), EOT survey completion rates exceeded 80% across both instruments. In both treatment arms, disease progression significantly reduced overall HRQOL per the EORTC QLQ-C30, with marked decreases from the last on-treatment visit (LOTV) for global health status/QOL that never recovered to LOTV levels (Table). Disease progression was also associated with deterioration across all 5 functional scales of the EORTC QLQ-C30 and worsening symptoms of fatigue, nausea/vomiting, pain, dyspnea, appetite loss, diarrhea, and financial difficulties. On the EORTC QLQ-OV28, progression was associated with decreased scores for body image, sexuality, and attitude toward disease/treatment functional scales and worsening abdominal/gastrointestinal symptoms. **Conclusions:** Disease progression negatively impacted HRQOL across treatment arms in PRIMA. These results support PFS as a clinically relevant endpoint in patients with aOC, as delays in disease progression help preserve HRQOL. Clinical trial information: NCT02655016. Research Sponsor: GSK.

LS mean change from LOTV (95% CI)	Niraparib (n=487)	Placebo (n=246)
EORTC QLQ-C30 global health status/QOL		
EOT	−8.6 (−10.9, −6.4)	−7.4 (−10.1, −4.7)
Week 4 post EOT	−10.0 (−12.7, −7.3)	−10.7 (−14.0, −7.4)
Week 8 post EOT	−10.1 (−12.9, −7.2)	−12.2 (−16.0, −8.5)
Week 12 post EOT	−11.5 (−14.0, −9.1)	−9.5 (−12.6, −6.3)
Week 24 post EOT	−10.7 (−13.4, −8.1)	−9.6 (−13.1, −6.2)

EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer QOL Core Questionnaire; EOT, end of treatment; LOTV, last on-treatment visit; LS, least squares; QOL, quality of life.

5552 Poster Session

HER2 and HER3 expression in ovarian cancer: Evolution across chemotherapy exposure and implications for targeted therapies. First Author: Felix Blanc-Durand, Institut Gustave Roussy, Villejuif, NA, France

Background: HER2 and HER3 are critical members of the ERBB receptor family, playing pivotal roles in tumorigenesis across multiple cancers, including ovarian cancer (OC). While their potential as therapeutic targets is under investigation, the clinical significance of their expression in OC remain understudied. This study investigates the expression patterns of HER2 and HER3 in OC tissues and evaluates the impact of neoadjuvant chemotherapy (NACT) on their expression levels. **Methods:** Patients with advanced epithelial ovarian cancer were identified and included in this study. Tumor samples were collected at three timepoints: prior to NACT, during interval debulking surgery and at relapse. HER2 and HER3 expressions were assessed using immunohistochemistry and scored with the gastric Herceptest scoring system (1+, 2+ or 3+), where 3+ expression was considered positive. **Results:** A total of 163 patients were analyzed, of whom 73% had high-grade serous histology and 21% harbored *BRCA* mutations. Tumor samples were available for analysis at the following timepoints: 110 pre-NACT, 81 post-NACT, and 22 at relapse. HER2 expression was rare, with 2.3% of tumors exhibiting HER2 1+ expression and 3.1% exhibiting HER2 3+ before NACT. HER2 expression remained stable at interval debulking surgery and relapse. In contrast, HER3 expression was more common with 2.7% of samples exhibiting HER3 1+ expression, 1.8% with 2+ expression and 60.9% with 3+ expression. HER3 expression remained consistent across timepoints, with 65.4% at interval debulking and 63.6% at relapse. HER3-positive samples were significantly associated with high-grade serous histology (81.5% vs 65%, p = 0.005), while *BRCA* mutation rates did not differ significantly between both groups (16.2% vs 28%, p = 0.267). Progression-free survival (PFS) and overall survival (OS) were comparable between HER3-positive and negative groups. Median PFS was 11.1 months versus 11.2 months (p = 0.537) and median OS was 44.9 months versus 44.3 months (p = 0.734). **Conclusions:** This study confirms that HER2 overexpression is rare in OC and remains stable throughout the treatment timeline. Conversely, HER3 is frequently expressed, with over 60% of tumors exhibiting 3+ HER3 expression. HER3 expression is strongly associated with serous histology, is stable across NACT exposure, and does not appear to impact clinical outcomes. These findings highlight HER3's potential as a promising therapeutic target in the OC landscape. Research Sponsor: None.

5554 Poster Session

Final analysis of SCORES, a phase III randomized, double-blinded, placebo-controlled study of suvemcitug combined with chemotherapy for platinum-resistant ovarian cancer. First Author: Guangwen Yuan, National Cancer Center/ National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China

Background: At the SCORES interim analysis, suvemcitug (a recombinant humanized anti-VEGF rabbit monoclonal antibody) plus chemotherapy demonstrated a significant improvement of progression free survival (PFS) compared with single-agent chemotherapy (CT) in patients with platinum-resistant Ovarian Cancer (PROC). Here we present the preplanned final analysis of OS for the SCORES along with the updating analysis of safety, PFS, and other endpoints. **Methods:** This randomized, double-blind, placebo-controlled, phase 3 trial (SCORES) conducted at 55 centers in China enrolled women with histologically-confirmed epithelial ovarian, fallopian tube or primary peritoneal cancer. Patients were required to have platinum- resistant or refractory disease with at least one measurable lesion. Eligible patients were randomly assigned (2:1) to either Suvemcitug (1.5 mg/kg q2w) or placebo combined with investigators chose CT (weekly paclitaxel, topotecan or pegylated liposomal doxorubicin) until progression or unacceptable toxicity. The primary endpoint was progression-free survival (PFS) by blinded independent review committee (BIRC) according to the RECIST 1.1. And the key secondary endpoint is the overall survival (OS). **Results:** Between June 5, 2021 and October 11, 2024, 421 patients were enrolled. At the data cutoff for the final analysis (October 11, 2024), the median follow-up duration was 23.7 and 23.4 months for the suvemcitug arm and the placebo arm. A total of 279 OS events (66.3%) occurred, the median OS was 15.31 months versus 14.03 months (stratified hazard ratio, 0.768; 95% CI, 0.595-0.991; P = 0.0304). Suvemcitug plus chemotherapy led to a significant improvement of OS versus placebo plus chemotherapy, with a 23% reduction in the risk of death and a more than 10% improvement of the 24-month OS rate (33.0% vs 22.3%). The efficacy results are summarized below. The most common grade ≥ 3 TEAEs (treatment-emergent adverse events) in suvemcitug arm included neutrophil count decreased, white blood cell count decreased, and hypertension. No Suvemcitug-related grade 5 TEAE occurred. **Conclusions:** The addition of suvemcitug to chemotherapy significantly improved the outcomes of patients with PROC with manageable toxicities. To the best of our knowledge, this is the first phase III study demonstrated a significant OS benefit of anti-angiogenic agent in patients with PROC. Clinical trial information: NCT04908787. Research Sponsor: Shanghai Xianxiang Medical Technology Co., Ltd.

	Suvemcitug + CT (N = 281)	Placebo+CT (N = 140)
OS, month (95% CI)	15.31 (13.73,17.81)	14.03 (11.27,16.56)
Hazard Ratio (95% CI)	0.768 (0.595,0.991)	
P value (rerandomization log-rank)	0.0304	
24-month OS rate, % (95% CI)	33.0 (26.8-39.2)	22.3 (14.8-30.8)
Median PFS by BIRC, month (95% CI)	5.49 (4.93,6.64)	2.73 (1.94,3.75)
Median PFS by investigator, month (95% CI)	5.39 (4.80,5.59)	2.46 (1.94,3.65)
ORR by BIRC, %	26.0	12.1
DCR by BIRC, %	76.5	49.3

5555 Poster Session

Assessment of tumors, blood, and ascites to establish correlations with treatment benefit in platinum resistant or refractory ovarian cancer patients treated with igrelimogene litadenorepvec and pembrolizumab combination therapy. First Author: Victor Cervera, TILT Biotherapeutics Ltd., Helsinki, Finland

Background: Platinum-resistant/refractory ovarian cancer presents a significant therapeutic challenge and despite several attempts, immunotherapies have not delivered satisfactory results to be approved. Identifying biomarkers of response to novel therapies is crucial for personalizing treatments and improving patient outcomes, especially since certain patients do experience long term benefit after the treatment with pembrolizumab and igrelimogene litadenorepvec (TILT-123; an oncolytic adenovirus coding for TNF and IL-2). **Methods:** Tumor biopsies (n=62), ascites (n=8) and blood (n=234) were collected from 15 patients treated in the PROTA trial (Phase I, NCT05271318). These patients received pembrolizumab intravenously plus igrelimogene litadenorepvec intravenously, followed by local administration intratumorally or intraperitoneally. Sampling took place prior to therapy, during therapy and after it. Tumor proteome (IHC, mIF) and transcriptome was analyzed to assess immune changes and virus presence. Ascites and blood samples were assayed to measure cell counts, phenotypes, cytokine and protein counts, as well as for the presence of antiviral neutralizing antibodies (NAbs). Biological parameters were correlated with overall survival (OS), RECIST 1.1 evaluations and tumor size changes. For analysis of OS, logrank test was used. For group comparisons two-tailed Mann-Whitney U-test was used. Pearson or Spearman tests were used for correlations. **Results:** Patients experiencing a drop in circulating lymphocytes 8-24 hours after treatment were more likely to experience longer OS (p=0.044). Additionally, patients with a higher lymphocyte count at baseline experienced similar OS benefit (p=0.018) plus a positive correlation with disease control (p=0.023). Most patients (11/15) showed antiviral immunity at baseline but eventually all patients developed neutralizing activity, and the same was observed in ascites. The presence of NAbs at baseline as well as development of highest titers were positively correlated with longer OS (p=0.004) and disease control (p=0.003). **Conclusions:** Igrelimogene litadenorepvec and pembrolizumab are therapies designed to attract, activate and/or protect lymphocyte-mediated antitumor activity. These findings suggest that having a fit immune system able to mobilize effector immune cells as well as responding to immunostimulant agents increases therapeutic success. As a disease with few therapeutic options, ovarian cancer patients often receive multiple lines of chemotherapy that might decrease the efficacy of immediate immunotherapies. The potential use of these biomarkers will be studied in larger studies to validate their utility in guiding the use of immunotherapy in this challenging patient population. Clinical trial information: NCT05271318. Research Sponsor: None.

5556 Poster Session

Biomarker results from the KGOG3056/NIRVANA-R trial: Maintenance niraparib plus bevacizumab in patients with platinum-sensitive, recurrent ovarian cancer previously treated with a PARP inhibitor. First Author: Hyun-Woong Cho, Korea University Guro Hospital, Seoul, South Korea

Background: While poly(ADP-ribose) polymerase inhibitors (PARPi) have demonstrated clinical success in prolonging progression-free survival (PFS) in ovarian cancer, the efficacy of subsequent chemotherapy following progression from PARPi maintenance is markedly decreased. Modest PFS benefits with PARPi rechallenge following a response to platinum-based chemotherapy has been reported, but the efficacy of PARPi rechallenge with bevacizumab remains unknown. **Methods:** NIRVANA-R, a phase 2 study, evaluated niraparib rechallenge with bevacizumab in patients with platinum-sensitive recurrent ovarian cancer previously treated with PARPi. Eligibility required a response to the most recent platinum regimen. The primary endpoint was 6-month progression-free rate. Biomarker exploration included the analysis of BRCA status, homologous recombination deficiency (HRD) status, circulating tumor DNA (ctDNA), and circulating tumor cells (CTCs) using whole-exome sequencing, as well as CA-125 levels. **Results:** Between 2019 and 2023, 44 patients were enrolled; over 65% had received ≧3 lines of chemotherapy. The estimated 6-month progression-free rate was 68% [95% confidence interval (CI) 55–85%]. Key prognostic factors included treatment-free interval after penultimate platinum-based chemotherapy (TFI_P) ($TFI_P \geq 24$ months vs. $TFI_P < 24$ months; 82% vs. 56%), achieving a complete response (CR) [CR vs. partial response; 86% vs. 57%] or normal CA-125 levels (0–35 vs. >35 U/mL; 72% vs. 25%) in response to the most recent chemotherapy. Median PFS was 11·5 months [95% CI 7.9-not reached (NR)]. Ongoing biomarker analysis includes BRCA status, HRD status, ctDNA and CTCs, and these results will be updated in subsequent reports. No new safety signals were identified with niraparib rechallenge plus bevacizumab. **Conclusions:** Niraparib rechallenge with bevacizumab showed promising efficacy, particularly in patients with $TFI_P \geq 24$ months, CR, or normal CA-125 levels following previous chemotherapy, supporting further clinical research. Ongoing exploration of HRD, ctDNA, CTCs, and other biomarkers will provide further insights into treatment stratification and outcomes. Clinical trial information: NCT04734665. Research Sponsor: None.

Estimated 6-month progression-free rate according to prognostic factors.

Factors		N	6 month PFS rate (95% CI)	p-value
1. Response to most recent chemotherapy	CR	17	85% (69-100%)	0.148
	PR	27	57% (40-82%)	
2. platinum-free interval from penultimate chemotherapy	<24 months	24	56% (38-83%)	0.018
	≥24 months	20	82% (65-100%)	
3. BRCA status	BRCA wild-type	16	56% (35-90%)	0.806
	BRCA mutation	22	73% (55-96%)	
	unknown	6	80% (52-100%)	
4. Progression during/after previous PARPi therapy	Progression during previous PARPi	30	68% (52-89%)	0.846
	Progression after previous PARPi	14	68% (50-100%)	

5557 Poster Session

JSKN003, a biparatopic anti-HER2 antibody drug conjugate (ADC), in the treatment of platinum-resistant ovarian cancer (PROC): Updated findings from two clinical trials. First Author: Xiaohua Wu, Fudan University Shanghai Cancer Center, Shanghai, China

Background: JSKN003 is a biparatopic HER2-targeting ADC conjugated to a topoisomerase I inhibitor with an average DAR of 4, who has preliminarily exhibited promising efficacy and safety in the treatment of PROC (QX Rao, et al. 2024 ESMO). This update presents the latest findings in patients (pts) who were not primary platinum-refractory. **Methods:** A pooled analysis of pts with PROC was performed from the phase I JSKN003-101 trial conducted in Australia (NCT05494918) and phase I/II JSKN003-102 trial conducted in China (NCT05744427), which enrolled pts with advanced solid tumors to receive JSKN003 monotherapy. Tumor tissue samples were collected for central lab assessment of HER2-expression. **Results:** As of November 29, 2024, the median follow up time was 6.9 months. A total of 46 PROC pts received JSKN003 Q3W, with 2, 2, 40, 1 and 1 pts in 4.2, 5.2, 6.3, 7.3 and 8.4 mg/kg dose groups, respectively. Median age was 59.0 years, 65.2% had ≥ 3 prior lines of systemic therapy, 80.4% and 63.0% had previously received bevacizumab and PARP inhibitor, 39.1% were classified as HER2-expressing (IHC: 1+/2+/3+), with 21.7%, 10.9% and 6.5% in 1+, 2+ and 3+, respectively; 45.7% as HER2-no-expressing (IHC: 0), and 15.2% had no tissue samples for assessment. For 45 efficacy-evaluable pts, the overall response rate (ORR) was 64.4%, the median progression-free survival (PFS) was 7.1 months, and the 9-month overall survival (OS) rate was 84.9% (Table). JSKN003 demonstrated effectiveness across various HER2 expression subgroups. Notably, for pts with HER2-expression, the ORR reached 72.2%, with a median PFS of 9.4 months. Grade 3/4 treatment-related adverse events (TRAEs) occurred in only 6 (13.0%) pts. Serious TRAE occurred in only 4 (8.7%) pts. No TRAEs led to treatment discontinuation or death. The most common TRAE was Grade 1/2 Nausea (39.1%). Additionally, Grade 1/2 Interstitial lung disease (ILD) was observed in 4 (8.7%) pts, with no cases of Grade 3/4 reported. **Conclusions:** The maturer updated efficacy data reveal that JSKN003 provided substantial improvement in ORR, as well as benefit in PFS and OS in heavily treated PROC, irrespective of HER2 expression. The well tolerated toxicity with long-term observation was consistent with prior experience. A confirmatory trial (NCT06751485) is ongoing in all comers at any HER2 expression level to further support JSKN003 as a treatment option in this population. Clinical trial information: NCT05494918 and NCT05744427. Research Sponsor: Alphamab Oncology.

Efficacy summary.

	HER2 IHC			
	1+/2+/3+ (n = 18)	0 (n = 20)	Unknown (n = 7)	Total (n = 45)
ORR, % (95% CI)	72.2 (46.5, 90.3)	55.0 (31.5, 76.9)	71.4 (29.0, 96.3)	64.4 (48.8, 78.1)
CR, n (%)	2 (11.1)	0	0	2 (4.4)
PR, n (%)	11 (61.1)	11 (55.0)	5 (71.4)	27 (60.0)
Median PFS, month (95% CI)	9.4 (5.7, NE)	5.6 (4.1, NE)	9.6 (2.6, NE)	7.1 (5.6, 9.7)
9-mo OS Rate, % (95% CI)	83.0 (45.7, 95.6)	100.0 (100.0, 100.0)	85.7 (33.4, 97.9)	84.9 (56.6, 95.4)

5560 Poster Session

Analyzing the relationship between glutaminase expression and features of the immune tumor microenvironment in epithelial ovarian cancer using imaging mass cytometry. First Author: Neha Verma, Johns Hopkins University School of Medicine, Baltimore, MD

Background: Immunotherapy has thus far shown limited efficacy in epithelial ovarian cancer, likely driven in part by an immune suppressive tumor microenvironment (TME). Increased glutamine metabolism by cancer cells via upregulation of the drug-targetable enzyme glutaminase (GLS) may contribute to an immune suppressive TME. Inhibiting GLS may not only inhibit tumor growth but also enhance the anti-tumor immune response in patients with epithelial ovarian cancer. We investigated the relationship between GLS expression and features of the immune TME in epithelial ovarian cancer using imaging mass cytometry. **Methods:** Tissue microarrays constructed from 41 epithelial ovarian cancer (38 high-grade serous, 3 low-grade serous) surgical specimens were stained by immunohistochemistry for GLS, which was quantified using modified histologic score (H-score). Imaging mass cytometry was then performed on tissue microarrays using a panel of 43 channels, including markers for delineating tissue architecture and assessing lymphoid cells, myeloid cells, and stromal fibroblasts. Resulting multiplexed images were segmented into a single-cell dataset to quantitatively compare between specimens, according to GLS H-score, abundances of cell types and average shortest distances between cell types. **Results:** Median GLS H-score was 150. Compared to GLS-low (H-score 0-150) specimens, GLS-high specimens (H-score >150) demonstrated lower T cell abundance (9.18% vs. 16.84% of cells; p=0.010) and lower B cell abundance (1.09% vs. 6.66% of cells; p=0.022). Compared to GLS-low (H-score <130) and GLS-medium (H-score 130-150) specimens, GLS-high specimens (H-score >150) demonstrated the lowest T cell abundance (high: 9.18% < medium: 10.46% < low: 21.28% of cells; p=0.0015) with subtype analysis showing the lowest effector helper T cell abundance (high: 0.11% < medium: 0.25% < low: 3.39% of cells; p=0.040). On spatial analysis, based on average shortest distances between cell types, GLS-high specimens demonstrated longer distances between tumor cells and lymphoid/myeloid immune cells and shorter distances between tumor cells and stromal cells than GLS-low/medium specimens. **Conclusions:** In this cohort of patients with epithelial ovarian cancer, higher levels of GLS expression were associated with several features of an immune suppressive TME, including lower T cell abundance with lower effector helper T cell abundance on subtype analysis, lower B cell abundance, and decreased proximity between tumor cells and immune cells. Further clinical studies investigating the use of GLS inhibitors to modulate the immune TME in patients with epithelial ovarian cancer are warranted. Research Sponsor: ASCO Conquer Cancer, Norman & Ruth Rales Foundation; NIH/NCI Ovarian SPORE; P50CA228991.

5561 **Poster Session**

Re-VOLVE: Phase II clinical trial in women with ovarian cancer progressing post-PARP inhibitor with treatment adapted to real-time assessment of evolving genomic resistance. First Author: Pamela Soberanis Pina, Division of Medical Oncology and Hematology, Princess Margaret Cancer Centre, University Health Network, Toronto, ON, Canada

Background: As the use of PARPi increases in high-grade serous ovarian cancer (HGSOC) resistance mechanisms ultimately arise. Emerging therapeutic strategies to overcome PARPi resistance is a pressing concern. Re-VOLVE study is a phase II in HGSOC women post-PARPi with treatment adapted to real-time assessment of evolving genomic resistance to guide treatment decision (NCT05065021). **Methods:** It enrolled patients (pts) with HGSOC progressing post-PARPi to receive induction phase (IP) 2-3 cycles of niraparib 200-300mg/bevacizumab 7.5mg/kg followed by personalized phase based on initial RECIST response and real-time assessment of evolving genomic resistance from baseline biopsy (whole genome RNA sequencing/WGTS) and ctDNA (12 gene panel). If progression/stable disease after IP pts were assigned to cohort A (niraparib/bevacizumab/dostarlimab 500mg) if no resistance mechanisms and to B (weekly paclitaxel 80mg/m2/bevacizumab/dostarlimab) if any present and to cohort C (continue niraparib/bevacizumab) if partial response after IP. Primary endpoint was to assess response rate of combination therapies. **Results:** 50 pts were screened; 7 were screen fail and 43 were enrolled. Of the 43, 3 pts were taken off due to progression during IP, 1 withdrew from study, 3 are on IP and 36 continued to personalized phase. Of these 36, 78% were white, 20% Asian, 2% others; 69% *BRCA* wild-type (25/36); 61% platinum-resistant (PR; 22/36) and 39% platinum-sensitive (PS;14/36). Median age 62.5 years (33-87). Pts had median 2 prior therapy lines (1-5); 22% (8/36) prior bevacizumab. Median days from collection to ctDNA results were 59 days and to WGTS 54 days. Twenty-seven pts (75%) had biopsy and ctDNA to guide therapy. 36 pts were assigned to personalized phase: 78% cohort A, 14% to B (4 *CCNE1* amplification and 1 *CHEK2* mutation) and 8% to C (3 with response during IP). Of the 31/36 pts assessed for response during personalized phase (others too early) 10 achieved partial response (32.2%; 7 PR, 3 PS). Nineteen pts (61.3%; 11 PR, 8 PS) had stable disease. By cohort, 3 pts had partial response (12.5%; 3/24) cohort A, 4 partial response cohort B (100%; 4/4 all with resistance mechanisms) and 3 partial response (100%; 3/3) cohort C. Median PFS in the personalized phase was 7.8 months (m) for those in cohort A, 6.2m for B and 13.1m for C. Median PFS for PR pts was 6.9m (4.4-13.1) and for PS pts not reached. Grade (G) 3 AE related to therapy per cohort: A) 4 pts with anemia, 2 neutropenia, 1 thrombocytopenia, 1 nausea; B) 2 pts neutropenia; C) no G3. No G4 AE. No G3-G4 immune related AE. **Conclusions:** These findings highlight the potential clinical activity of a chemo-free approach and confirmed the feasibility of guiding personalized therapy in real-time in recurrent OC pts post-PARPi. This strategy was safe and provided clinical benefit to some pts. Further translational analysis is ongoing. Clinical trial information: NCT05065021. Research Sponsor: GSK; Apobiologix; Princess Margaret Cancer Foundation; OICR.

5562 **Poster Session**

Phase I study of sustained and local delivery of intraperitoneal IL-2 using encapsulated cells in patients with platinum-resistant high-grade serous carcinoma. First Author: Helen D. Clark, The University of Texas MD Anderson Cancer Center, Houston, TX

Background: Platinum-resistant high-grade serous carcinoma's (HGSC) propensity to metastasize throughout the peritoneal cavity has generated interest in the development of high-intensity locoregional treatment administered intraperitoneally. Prior efforts have been limited by administration difficulties and potential for local toxicity. We describe a phase I trial using AVB-001, a novel intraperitoneally administered, alginate-encapsulated, allogeneic cell line modified for constitutive expression of human interleukin-2 (hIL-2). Preclinically, this new platform allows self-limited anti-tumor immune-activation without the toxicities associated with systemic administration or prior intraperitoneal formulations. The primary objectives of this study were to investigate the feasibility, safety, and tolerability of treatment with AVB-001. Secondary objectives included evaluation of clinical efficacy and translational correlates. **Methods:** This was an open-label, multicenter, phase I dose escalation study. A single dose of AVB-001 was administered via laparoscopy at 1 of 4 dose levels ranging from 0.6 to 3.6 μg hIL-2/kg/day. Escalation to a higher dose was based upon Bayesian optimal interval 3+3 design. Toxicity was evaluated via NCI CTCAE v5.0 and response was assessed via RECIST v1.1. Translational analyses were performed to evaluate serum hIL-2 concentration and immunological changes in peripheral blood. **Results:** The trial enrolled 14 patients. Eleven patients had ovarian cancer, two had fallopian tube cancer, and one had peritoneal cancer. Median age was 68 (range 47-75). In terms of safety, 4 of 14 patients (28.6%) experienced a grade 3 treatment-related adverse event (TRAE). There were no grade 4 or 5 TRAEs. One patient exhibited an unconfirmed partial response lasting 29 days (ORR 1/14, 7.1%). Stable disease was observed in 7 patients with a median duration of clinical stability lasting 2.57 months (range 2.03-4.23). On translational analyses, dose-dependent immunologic changes were noted in the peripheral blood. CTLA-4 receptor expression was upregulated with increasing dose levels in both CD8+ and CD4+ T cells, however significant upregulation was not observed for either PD-1 or TIM-3. The study was terminated early due to funding limitations. **Conclusions:** The administration of AVB-001 is safe, feasible, and shows potential for meaningful clinical activity. A dose-dependent upregulation of the CTLA-4 checkpoint on CD8+ and CD4+ T cells was noted after administration, suggesting a rationale for combination therapies involving cytokines as "priming agents" to engage checkpoint inhibition. Finally, we demonstrate feasibility of this approach for delivery of hIL-2 and other future biologics via our ability to reproducibly manufacture multiple clinical batches of AVB-001 and deliver at point of patient care. Clinical trial information: NCT05538624. Research Sponsor: Avenge Bio, Inc; MD Anderson T32 Training Grant; T32CA101642; MD Anderson CCSG Core Grant; P30CA016672.

5563 **Poster Session**

Circulating tumor DNA (ctDNA) monitoring in participants (pts) with ovarian cancer treated with neoadjuvant pembrolizumab (pembro) + chemotherapy (chemo) ± anti–immunoglobulin-like transcript 4 (ILT4) monoclonal antibody MK-4830. First Author: Jung-Yun Lee, Yonsei Cancer Center and Severance Hospital, Yonsei University College of Medicine, Seoul, South Korea

Background: ctDNA is a promising biomarker for predicting disease progression, survival, and surgical outcomes in patients with solid tumors. In a phase 1 study (NCT03564691), ILT4 inhibitor MK-4830 + pembro had a manageable safety profile and showed antitumor activity in pts with solid tumors. We present results from a global, randomized phase 2 study (NCT05446870) evaluating quantitative change in ctDNA in pts with high-grade serous ovarian cancer (HGSOC) who received neoadjuvant pembro + chemo ± MK-4830. **Methods:** Eligible pts were female, aged ≥18 y, with previously untreated histologically confirmed FIGO stage 3 or 4 HGSOC and an ECOG performance status of 0 or 1, and were candidates for interval debulking surgery. Pts were randomly assigned 1:1 to receive neoadjuvant MK-4830 800 mg + pembro 200 mg + chemo (paclitaxel 175 mg/m^2 and carboplatin AUC 5-6) (arm 1) or pembro + chemo (arm 2) IV Q3W for 3 cycles. Pts underwent interval debulking surgery followed by 3 cycles of adjuvant therapy with the neoadjuvant regimen; adjuvant bevacizumab IV Q3W was permitted. ctDNA was assessed at each cycle using the Signatera assay (Natera, Inc.). A constrained longitudinal data analysis model was used to estimate the posterior probability that the coefficient for treatment assignment was <0, evaluating whether the reduction in ctDNA from cycle 1 (C1) was larger in arm 1. The primary end point was change in ctDNA from C1 at C3 in pts with detectable ctDNA; safety was a secondary end point. **Results:** At data cutoff (Dec 20, 2023), 160 pts were enrolled; 159 pts received treatment (arm 1, n = 79; arm 2, n = 80). Median study follow-up was 8.3 months (range, 1.9-16.4) in arm 1 and 8.3 months (range, 2.1-16.3) in arm 2. Median age was 61.5 y in both arms. 64 pts (80.0%) in arm 1 and 68 pts (85.0%) in arm 2 had available ctDNA data at C1; 51 pts (63.8%) and 63 pts (78.8%), respectively, had available ctDNA data at C3. Median ratio of ctDNA C3 to C1 was 0.02 (range, 0-1.53) in arm 1 and 0.01 (range, 0-0.60) in arm 2. The posterior probability that the coefficient for treatment assignment was <0 in the model was 38.8%, indicating a low posterior certainty of larger ctDNA reduction in arm 1. AEs occurred in 75 pts (94.9%) in arm 1 and all pts (100%) in arm 2. TRAEs occurred in 74 pts (93.7%) in arm 1 and in 79 pts (98.8%) in arm 2; grade 3-5 events occurred in 37 pts (46.8%) and 44 pts (55.0%), respectively. TRAEs led to death in 2 pts in arm 1; no treatment-related deaths occurred in arm 2. **Conclusions:** In pts with HGSOC, reductions in ctDNA were similar between neoadjuvant/adjuvant MK-4830 + pembro + chemo vs pembro + chemo. Real-time tumor-informed ctDNA testing may be feasibly incorporated into future clinical trials as a surrogate outcome to evaluate response. The safety profile of MK-4830 + pembro + chemo was comparable to pembro + chemo. Clinical trial information: NCT05446870. Research Sponsor: Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA.

5564 **Poster Session**

Preliminary analysis of disitamab vedotin combined therapy for HER2-expressing platinum-sensitive recurrent ovarian/peritoneal/fallopian tube cancer (Diversity study): A single-arm, multicenter phase II trial. First Author: Tong Shu, Key Laboratory of Carcinogenesis and Translational Research (Ministry of Education), Department of Gynecologic Oncology, Peking University Cancer Hospital & Institute, Beijing, China

Background: Platinum-sensitive recurrent epithelial ovarian/peritoneal/fallopian tube cancer (PSROC) patients often exhibit reduced responsiveness to chemotherapy following initial platinum-based regimens, necessitating the development of more effective treatment strategies. Disitamab vedotin (DV; RC48) is a novel humanized anti-HER2 antibody-drug conjugate (ADC) with greater specificity than conventional agents like paclitaxel. This study (NCT06420973) evaluates the efficacy and safety of DV-based combination therapy in patients with HER2-expressing PSROC. **Methods:** This single-arm, open-label, multicenter phase II study examines DV combination therapy in patients with HER2-expressing (IHC 1 to 3+) PSROC. Patients received DV (2.5 mg/kg) plus carboplatin (AUC 5), with or without bevacizumab (7.5–15 mg/kg), every 21 days for six cycles. Maintenance therapy included DV (up to eight cycles) with or without bevacizumab until disease progression. The primary endpoint is PFS. Secondary endpoints include ORR, DCR, OS and safety. An exploratory endpoint assesses quality of life using the EORTC QLQ-CIPN20 (excluding Item 20). **Results:** As of January 2025, 15 patients (median age 58 years, range 47-73) were enrolled, with 86.7% diagnosed with ovarian cancer and 93.3% having high-grade serous carcinoma. Genetic analysis identified 4 gBRCA1 mutations, 1 sBRCA2 mutation, 5 wild-type cases, and 5 with unknown status. HER2 expression was 73% for IHC 1+ and 27% for 2+. The median number of prior treatment lines was one, with a median follow-up of 3.2 months (range 1-6.8m). Efficacy was evaluated in 10 patients, while safety was assessed in all 15. The ORR was 70% (1 CR, 6 PR), with a DCR of 100%. The ORR for both BRCA mutations and wild-type was 66.7%. Among patients with HER2 IHC 1+, the ORR was 71.4%, while for 2+, it was 66.6%. Patients with PFI >12 months had a 75% ORR, compared to 50% for those PFI <12 months. Treatment-related adverse events (TRAEs) were reported in 80% of patients, with ≥ Grade 3 TRAEs at 26.7%, including neutropenia (n=1), thrombocytopenia (n=2), and diarrhea (n=1). No Grade 4 or 5 TRAEs were observed. The EORTC QLQ-CIPN20 score showed no significant impact on quality of life compared to baseline. As of January 23, 2024, one patient had disease progression. **Conclusions:** The preliminary findings indicate that DV combined therapy is effective and safe for the treatment of HER2-expressing PSROC, highlighting its potential as a valuable therapeutic option. Further research in this area is essential to validate these results. Clinical trial information: NCT06420973. Research Sponsor: Clinical Research Fund for Distinguished Young Scholars of Peking University Cancer Hospital; QNJJ2023003.

5565 **Poster Session**

IBI354, an anti-HER2 antibody-drug conjugate, in patients with locally advanced unresectable or metastatic ovarian cancers: Updated results from a phase I trial. First Author: Jin Shu, Chongqing University Cancer Hospital, Chongqing, China

Background: IBI354 is an antibody-drug conjugate consisting of trastuzumab (anti-HER2 antibody) conjugated to a topoisomerase I inhibitor. It has showed manageable safety and encouraging efficacy in patients (pts) with advanced gynecologic cancers (including ovarian cancers [OC], Shu et al, abstract No. 720MO at 2024 ESMO annual meeting). Here, we present the updated safety and efficacy in OC. **Methods:** Eligible OC pts with HER2 alteration (IHC 1+, 2+, 3+ and/or ISH+ and/or NGS confirmed mutation or amplification) who failed or were intolerant to standard treatment were enrolled from China and Australia. Pts received IBI354 at 2−12 mg/kg every three weeks (Q3W) or Q2W. Primary endpoint was safety. Secondary endpoints were objective response rate (ORR), disease control rate (DCR), duration of response (DoR), and progression-free survival (PFS) per RECIST v1.1. **Results:** As of November 12, 2024, 92 pts were enrolled (median age, 58.0 years; Asian, 95.7%; White, 4.3%; ECOG PS 1, 73.9%; IHC 1+, 65.2%; IHC 2+, 29.3%). The median follow-up time was 11.0 months (range: 8.0−19.0). Median treatment duration was 24.1 (range: 3.1−60.3) weeks with 21 (22.8%) pts still on treatment. Treatment-related adverse events (TRAEs) occurred in 79 (85.9%) pts with grade ≥ 3 TRAEs in 27 (29.3%) pts. The most common TRAEs were anemia (51.1%), white blood cell count decreased (45.7%), neutrophil count decreased (40.2%), and nausea (35.9%). Serious TRAEs occurred in 10 (10.9%) pts. Interstitial lung disease or pneumonitis was observed in 1 (1.1%) pt, which was grade 2 and not related to IBI354 considered by the investigator. TRAEs led to dose reduction in 2 (2.2%) pts. No TRAEs led to treatment discontinuation or death. For efficacy-evaluable pts (who had at least 1 post-baseline tumor assessment) dosed at 12 mg/kg Q3W (n = 40), confirmed ORR and DCR reached 55.0% (95% CI: 38.5−70.7) and 90.0% (95% CI: 76.3−97.2), respectively. In 22 pts with confirmed response in 12 mg/kg Q3W dose group, the median DoR was not reached with events occurred in 6 (27.3%) pts, and 9-month DoR rate of 58.1% (24.2−81.2). The median PFS was 7.1 months (95% CI: 5.2−not reached) with events occurred in 21 (51.2%) pts. The median overall survival (OS) was not reached with events occurred in 12 (29.3%) pts, and the 9 month OS rate was 70.7% (95% CI: 54.3−82.2). For the pts with HER2 IHC 1+ OC dosed at 12 mg/kg Q3W (accounting for 67.5% [27/40] of efficacy-evaluable pts at 12 mg/kg Q3W), ORR and DCR reached 55.6% (95% CI: 35.3−74.5) and 88.9% (70.8−97.6), respectively. **Conclusions:** IBI354 was well tolerated with a manageable safety profile and showed promising efficacy in pts with locally advanced unresectable or metastatic OC, especially in pts with HER2 lower expression. Clinical trial information: NCT05636215. Research Sponsor: None.

5566 **Poster Session**

Successful induction of tumor-directed immune responses in high grade serious ovarian carcinoma patients after primary treatment using a whole tumor cell vaccine. First Author: Annegé Vledder, University Medical Centre Groningen, Groningen, Netherlands

Background: Improving disease free and overall survival in advanced high grade serous ovarian carcinoma (HGSOC) after primary treatment remains challenging. This phase 1 trial (NCT04739527) evaluated safety and immunogenicity of a whole tumor cell vaccine, vididencel, to prime or boost immune responses in HGSOC after primary treatment. Vididencel expresses tumor associated antigens (TAA) frequently upregulated in HGSOC. **Methods:** Patients with advanced HGSOC who completed primary treatment received 6 intradermal injections with vididencel: 4 biweekly doses of 25 million cells (week 0, 2, 4 and 6) followed by 2 boosters of 10 million cells (week 14 and 18). Peripheral blood mononuclear cells were obtained at week 0, 4, 10, 14, 18 and 22. Disease status was evaluated at week 22 using clinical assessment and CA125 levels. Primary endpoint was safety and the induction of immune responses, measured by IFNγ ELISPOT, to at least one TAA (i.e. WT-1, PRAME, NY-ESO, or MAGE-A3/4). Secondary endpoints were disease status at week 22 and survival. **Results:** Primary analysis at week 22 has been completed for all 17 patients. In total,16 received all 6 planned injections and 1 patient discontinued treatment after 4 injections due to disease progression. Vididencel showed in 12 out of 17 patients a vaccine-induced response (VIR) to at least one of the tested antigens and 7 of these patients showed a sustained immune responses to the same antigen (sVIR). Table 1 shows the distribution of induced immune responses. Five patients were also given maintenance treatment with PARP inhibitors and all these patients showed a VIR. Vididencel was well-tolerated, with no trAEs above grade 2. The most common trAEs were mild to moderate local injection site reactions, characterized by redness, swelling and inflammation. Two unrelated serious AEs occurred, both linked to disease progression. At week 22, 4 weeks after last vididencel treatment, 10 patients (59%) had stable disease, and 7 had progressive disease, with all patients still alive. Patients with a VIR or sVIR had a higher rate of SD than patients without a vaccine-induced immune response (67% and 71% versus 40%, respectively). Long-term follow of patients continues of which a swimmers plot will be shown. **Conclusions:** Vididencel is well tolerated and effective in eliciting or boosting a broad T-cell response in HGSOC patients after primary treatment. Short-term evaluation of clinical response at week 22 suggests better responses in patients developing a VIR or sVIR compared to those patients not having a detectable immune response to the vaccine. Clinical trial information: NCT04739527. Research Sponsor: Mendus AB.

Immune response outcome (N=17)		Responses to individual TAAs			
		WT1	PRAME	NY-ESO	MAGEA3/A4
Immune responders (N=12)	VIR (n=12)	6 of 12	3 of 12	4 of 12	7 of 12
	sVIR (n=7)	4 of 7	2 of 7	1 of 7	2 of 7
Non-responders (N=5)	No VIR (n=5)				

(s)VIR; (sustained) vaccine induced response.

5567 **Poster Session**

Optimizing an NGS low-pass–based method to detect genomic instability as a PARP inhibitor predictive biomarker in high-grade serous ovarian cancer. First Author: Ignacio Romero, Instituto Valenciano de Oncología (IVO) and GEICO, Valencia, Spain

Background: In high-grade serous ovarian cancer (HGSOC) PARP inhibitors constitute a standard treatment in tumors harboring Genomic Instability (GI). This biomarker constitutes a valuable predictive tool for the use of PARP inhibitors. Available commercial solutions to determine the GI status, present some caveats that must be overcome. This study aims to set up an academic test in a cost-effective manner by applying open-source R libraries to establish GI status in Formalin-Fixed and Paraffin-embedded (FFPE) samples. **Methods:** The study was carried out in two stages, technical and analytical setup and clinical validation. Firstly, 16 FFPE samples, 8 tumoral tissue from gynecological malignancies, and 8 from healthy tissues were sequenced. This step aimed to establish favorable sequencing conditions followed by the tune-in of specific parameters for the analytical pipelines, QDNA, and Shallow-HRD (R v.4.3.11). Secondly, 44 FFPE samples from patients diagnosed with HGSOC and known GI score (GIS) were used for clinical validation. For this analysis, GIS determined by GIInger from Sophia Genetic was considered the gold standard. The series was constituted of 23 samples carrying genomic instability (GIS>=0) and 21 stable samples (GIS<0). Of note, intermediate libraries from targeted sequencing performed in clinical routine were used as input for sequencing. Individual libraries were then pooled and sequenced in a NextSeq 2000 (2x100 paired-end) (Illumina, San Diego, CA, USA) to achieve a 0.5x coverage. Recalibration of the method was performed using Maxstat algorithm implemented in R. All the analyses were performed in Python v3.8 or R v.4.3.11. **Results:** Best technical and analytical results were obtained for the QDNA pipeline without an X chromosome and bin size of 1 mb plus shallowHRD. By using this parameter, clinical validation comparing the GI results with GIS score obtained from the Sophia Genetics test was performed. In-house determination of GI resulted in 23 samples classified as unstable (score>=20) and 21 stable samples (score < 20). Re-calibration of the score using 20 as a new cut-off to dichotomize the variable, showed an optimum performance with a concordance of 86.4 % (p < 6.2 -6) with GIS classification. Thus, borderline samples called by shallowHRD pipeline (5/44) were re-classified as stable. Both continuous scores showed a correlation of 0.855 (p < 1.5 -13) and an Area Under the ROC curve of 0.906, presenting an excellent performance as a biomarker for genomic instability. **Conclusions:** We present a validated, routine-based and cost-effective test to determine GI in HGSOC, being easily transferrable to daily practice. Research Sponsor: Conselleria de Educación, Cultura, Universidades y Empleo. Generalitat Valenciana.; CIGE/2023/206

5568 **Poster Session**

Real-world analysis of folate receptor alpha (FRα; FOLR1) expression in pan-tumor samples from over 6000 patients in the US. First Author: Thomas C. Krivak, Division of Gynecologic Oncology, Allegheny Health Network Cancer Insitute, Pittsburgh, PA

Background: FRα is overexpressed in several cancers, including ovarian and endometrial. The FRα-targeted antibody-drug conjugate mirvetuximab soravtasine-gynx (MIRV) showed survival benefit vs chemotherapy in patients with platinum-resistant ovarian cancer (PROC) with high FRα expression (Moore K, et al. *N Engl J Med*. 2023;389(23):2162-2174). Greater understanding of FRα expression and distribution in real-world (RW) settings may help enable FRα testing implementation for biomarker-guided treatment strategies. Here, we present analyses of FRα expression in RW patient tumor samples referred for FRα testing by immunohistochemistry (IHC). **Methods:** Uniquepatient tumor samples across different malignancies (N=6695) were acquired from RW healthcare settings in the US over a 12-month period. FRα expression was assessed by IHC using the VENTANA FOLR1 (FOLR1-2.1) RxDx Assay. Trained pathologists scored samples with ≥75% tumor cells with ≥2+ membrane staining as FRα positive. The clinicopathological features of each case, FRα prevalence, and impact of sample age were evaluated. **Results:** From the entire dataset (N=6695), 41% of samples were FRα positive, 54% were negative, and 5% were not evaluable. Of 2000 samples with known primary tumor origin: 1632 (82%) were primary or metastatic sites of disease from patients with ovarian cancer (39% FRα positive); 266 (13%) originated from distinct non-ovarian tumor types, including primary peritoneal, Müllerian, pelvic, and gynecological sites of unspecified origin (combined 33.1% FRα positive); the remaining 102 (5%) had unconfirmed tumor origin. Of 1678 samples with known histological subtype, FRα positive expression was observed in samples from serous (43.5% [646/1486]), mixed (37% [14/38]), and endometrioid (10% [5/48]) histology, whereas FRα positive expression was absent across all clear cell (0/91) and mucinous subtypes (0/15). FRα positive expression was detectable in unique patient samples across all sample ages, which ranged from <1 to >5 years. **Conclusions:** RWanalysis of 6695 patient tumor samples referred for FRα testing demonstrated FRα prevalence of 41%. Ovarian cancers represented most cases evaluated, and the 39% FRα positive rate was consistent with the FRα positive prevalence observed in MIRV clinical trials (35%). This RW analysis demonstrates that FRα is measurable in samples ranging from <1 to >5 years, suggesting prior samples may be utilized for FRα testing if a recent sample is unattainable. This is consistent with previous analyses from MIRV clinical trials where most patients with PROC were selected for enrollment based on high FRα expression from archival tumor specimens. Collectively, this large RW data set helps to characterize the RW prevalence of the clinically actionable biomarker FRα and supports using FRα testing for personalized ovarian cancer treatment plans. Research Sponsor: AbbVie.

5569 **Poster Session**

Association of HIPEC response in ovarian cancer with PI3K/RAS/Notch gene signatures: A whole transcriptomic analysis of U.S. and French HIPEC treated ovarian cancer patients. First Author: Thanh Hue Dellinger, City of Hope, Duarte, CA

Background: Hyperthermic intraperitoneal chemotherapy (HIPEC) is associated with improved overall survival in Stage III epithelial ovarian cancer (EOC) patients. We set out to evaluate the gene signatures associated with HIPEC response in EOC patients. **Methods:** Ninety-one EOC patients who underwent HIPEC with pre-operative tumor samples at City of Hope (51) and CHU Lyon (40) were identified between 2014 and 2022. RNA isolation was performed from formalin-fixed paraffin-embedded samples, followed by Whole-transcriptome library construction. Following exclusion of non-high grade serous (HGS) samples, and quality control steps, twenty-four samples were excluded. Progression-free survival (PFS) was used to define HIPEC response. Cut-off PFS values were used to distinguish good vs poor responders in primary EOC patients (18 months, based on KGOG, CARCINO-HIPEC trials), and recurrent EOC patients (12 months, based on MSK, CHIPOR HIPEC trials). Differential Gene Expression Analysis comparing good and poor HIPEC responders identified significantly changed genes. Pathway analysis was conducted using gene set enrichment analysis (GSEA) against Hallmark. **Results:** A total of sixty HGS tumor samples with available survival data were analyzed. 63.3% were primary EOC, 36.7% recurrent EOC. Germline BRCA mutations affected 21.7% of patients. With a median follow up of 31.9 months, median PFS was 29.3 (95%CI: 15.3, 63.5) months in primary EOC patients and 26.0 (95%CI: 14.7, 37.1) months in recurrent patients. Median OS was not reached in either group. 60.0% had a recurrence. Thirty-eight patients were identified as good responders, with a median PFS of 37.1 mos. (95%CI: 26.4, NR); 18 patients were identified as poor responders, with median PFS of 11.4 months (95%CI: 7.5, 14.2). Differential gene expression analysis between good and poor responders revealed 29 significantly upregulated 35 downregulated genes in HIPEC responders. Top upregulated genes in HIPEC responders include MAPK signaling pathway genes (RIB2, ETV5, CAPN8, IGFR1), in addition to CCND1 and CEACAM1. In HIPEC responders, the top-ranking gene sets in the transcriptional signature included Notch, KRAS, and Wnt/beta-catenin signaling pathways. In poor HIPEC responders, the DNA damage repair associated pathways E2F targets and G2M checkpoint, were activated. Similar transcriptomic pathway signatures were observed in Non-recurrent versus Recurrent HIPEC patients: Non-recurrent tumors were enriched with Notch signaling, while Recurrent tumors were enriched with E2F target and G2M checkpoint pathways. **Conclusions:** Good HIPEC response is characterized by transcriptional signatures consistent with Type I EOC characteristics of PI3K/RAS/Notch signaling. Recurrence after HIPEC in HGS ovarian cancer is higher in patients with E2F/G2M transcriptional signatures. Research Sponsor: None.

5570 **Poster Session**

Immunotherapy with anti-PD-1 or PD-L1 in advanced ovarian cancer (OC): A meta-analysis of randomized trials. First Author: Riccardo Vida, Department of Medical Oncology, Centro di Riferimento Oncologico (CRO), IRCCS; Department of Medicine (DMED), University of Udine, Aviano, Italy

Background: Immunotherapy (IO) has shown promising results in several solid tumors, including gynaecological malignancies. While PARP inhibitors and bevacizumab had deeply improved outcomes in OC, prognosis remains poor, underscoring the need for innovative treatment strategies. Anti-PD-1 and PD-L1 monoclonal antibodies have been evaluated in randomized trials across both first-line and recurrent OC settings. This meta-analysis summarizes the available evidence to assess progression-free survival (PFS) benefits from IO-based strategies. **Methods:** Phase II and III randomized clinical trials (RCTs) evaluating IO-based strategies using PD1 or PDL1 inhibitors published between 2019 and 2024 were identified through PubMed, Embase, and the Cochrane Library, as well as conference proceedings. Eight trials with PFS as primary endpoint, conducted in first-line and recurrence settings, were included. Data on PFS by PD-L1 status were available in seven trials. Three trials included two experimental arms and were analysed separately. Hazard ratios (HRs), 95% confidence intervals (CIs), and PFS events were extracted for overall populations and subgroups. A random-effects model was employed for data analysis, with sensitivity analyses performed to explore outcome variability. **Results:** The meta-analysis included 8 trials comprising 6,205 patients. The addition of IO to chemotherapy or placebo showed no improvement in PFS (HR = 1.02, 95% CI 0.86-1.22). Subgroup analyses indicated no significant differences in PFS in first-line (HR = 0.99, 95% CI 0.78-1.26) or recurrence settings (HR= 1.07, 95% CI 0.80-1.44). In trials reporting PD-L1 status (47.5% PD-L1 positive population), IO-based therapies demonstrated a non-significant trend towards PFS improvement (HR = 0.94, 95% CI 0.77-1.13). Excluding IO-only arms yielded similar results (HR = 0.94, 95% CI 0.79-1.11). **Conclusions:** IO-based strategies did not provide a substantial PFS benefit in advanced OC, irrespective of disease setting or PD-L1 status. Identifying effective combination strategies and patient subgroups that may benefit from IO remains an open research question. Research Sponsor: None.

5571 **Poster Session**

Harnessing EHR for goals of care: The role of electronic alerts for care optimization in gynecologic cancer patients at risk of death in 6 months. First Author: Katherine Fitch, Duke University, Durham, NC

Background: This study employed the validated Surprise Question to evaluate the ability of an electronic health record (EHR) alert to predict 6-month mortality, prompt goals of care (GOC) documentation, and facilitate high-quality end of life (EOL) care for patients with gynecologic cancer. **Methods:** EHR coding identified patients in an outpatient academic gynecologic oncology practice seen more frequently than annually with scheduled imaging, CA125 values, or chemotherapy. Patients without a diagnosis of primary gynecologic cancer were excluded. An outpatient EHR alert posed the modified Surprise Question: "Would you be surprised if the patient passed away in the next 6 months?" Choices were "Yes" and "No" (both considered meaningful responses) and "Show me next time" (deferral response; excluded). "No" responders were instructed on-screen to document a GOC discussion and consider palliative care referral. We analyzed EHR alert data from August 1, 2021-December 31, 2022, and clinical events up to 22 months after this period. Continuous variables were compared using Wilcoxon rank-sum tests, categorical variables were compared with chi-square tests, and both Cox proportional hazards regression and log-binomial models were used to predict death/time to death. **Results:** Meaningful responses were elicited for 804 unique patients, of which 130 (16.2%) were "No" (not surprised). Among patients whose providers replied "No", 35.4% died within 6 months of that encounter, compared to 4.2% of "Yes" replies ($p<0.001$). Among patients with a documented GOC conversation, the median time from first "No" response to documented conversation was 0 days (IQR 0.0, 84), compared to 255 days (IQR 81, 501) for "Yes". Among patients who died, subjects in the "No" group were more likely to be enrolled in hospice at EOL than those in the "Yes" group (79.0% vs 63.5%, p=0.014). A "No" response to the Surprise Question had a higher RR for death at 6 and 12 months compared to age, race, or cancer type. **Conclusions:** For patients with gynecologic cancer, responses to a Surprise Question EHR alert effectively predict 6-month mortality and are associated with increases in both GOC discussions and hospice utilization. Research Sponsor: None.

Log-binomial predictors of death at 6 months (univariate model).

		Risk Ratio (RR)	95% CI of RR	p-value	% deaths
Age at 1st alert	<49	Reference		0.010	4%
	50-59	1.00	0.95-1.05		4%
	60-69	0.93	0.87-0.98		11%
	70+	0.93	0.88-0.98		11%
Race	Caucasian	Reference		0.063	8%
	Black/Other	0.95	0.91-1.00		12%
Cancer Type	Ovarian	Reference		0.16	8%
	Other	1.03	0.99-1.08		10%
Surprise Question Response	Yes	Reference		<.0001	4%
	No	1.48	1.31-1.69		35%

5572 **Poster Session**

Safety and effectiveness of fuzuloparib in patients with ovarian cancer: A nationwide, multicenter, prospective real-world study. First Author: Qinglei Gao, Department of Gynecological Oncology, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China

Background: Fuzuloparib, a poly (ADP-ribose) polymerase (PARP) inhibitor, is approved in China for the treatment of platinum-sensitive recurrent (PSR) ovarian cancer (OC) and for maintenance therapy in newly diagnosed advanced and PSR OC. This study aims to evaluate the safety and effectiveness of fuzuloparib in OC patients under real-world settings. **Methods:** This multicenter, prospective real-world study included patients from 27 centers across China between January 2022 and August 2024. Eligible patients were aged ≥18 years and suitable for fuzuloparib treatment (monotherapy or combination therapy). Patients also had histologically or cytologically confirmed epithelial OC, primary peritoneal or fallopian tube cancer. The outcomes observed in this study included the incidence of treatment-related adverse events (TRAEs), progression-free survival (PFS), and overall survival (OS). **Results:** A total of 260 patients who received fuzuloparib (171 on monotherapy, 66 on combination therapy, and 23 with unknown treatment type) were analyzed. Of these, 97 (37.3%) received first-line maintenance therapy, 112 (43.1%) received maintenance therapy for PSR disease, 23 (8.8%) received treatment for PSR disease, 20 (7.7%) received treatment for platinum-resistant recurrent disease, and 8 (3.1%) received other treatments. The median age was 57 years (interquartile range [IQR]: 51.0, 65.0). Among the patients, 215 (82.7%) had epithelial OC, 169 (65.0%) were diagnosed at stage III/IV. Of the 239 patients with available safety data, 149 (62.3%) reported at least one TRAE. The most common TRAEs were anemia (23.4%), thrombocytopenia (23.4%), leukopenia (18.8%), and lymphopenia (12.6%). Fifty-four patients (22.6%) reported grade 3 or higher TRAEs. The median follow-up time for the first-line maintenance therapy group was 11.4 months (IQR: 6.0, 17.4), with median PFS and OS not yet reached; the 1-year PFS rate was 90.7%, and the 1-year OS rate was 97.1%. In the PSR maintenance therapy group, the median follow-up time was 9.1 months (IQR: 4.2, 15.9), with median PFS of 17.3 months (95% confidence interval [CI]: 12.1-26.3) and median OS not yet reached; the 1-year PFS rate was 66.2%, and the 1-year OS rate was 92.0%. In the PSR treatment group, the median follow-up time was 12.7 months (IQR: 5.6, 19.9), with median PFS and OS not yet reached; the 1-year PFS rate was 77.8%, and the 1-year OS rate was 90.2%. In the platinum-resistant relapse treatment group, the median follow-up time was 8.9 months (IQR: 5.1, 13.2), with median PFS and OS not yet reached; the 1-year PFS rate was 59.1%, and the 1-year OS rate was 80.0%. **Conclusions:** This is the first large-scale real-world study assessing the safety and effectiveness of fuzuloparib. In the real-world setting, fuzuloparib shows favorable safety, with no new safety signals. The effectiveness outcomes align with trends observed in key clinical trials. Clinical trial information: NCT05206890. Research Sponsor: None.

5573 **Poster Session**

EON: Phase II trial of etigilimab (MPH313) in combination with nivolumab in patients with recurrent platinum-resistant clear cell ovarian cancer. First Author: Ji Son, The University of Texas MD Anderson Cancer Center, Houston, TX

Background: A predictor of response to anti-PD1 therapy is the extent of CD8+ infiltration within the pretreated tumor. TIGIT has shown to suppress anti-tumor immune responses via increased CD4+ Tregs and disruption of CD226 co-stimulation. We hypothesized inhibition of TIGIT may reverse the immune suppressive tumor microenvironment thereby potentiating the efficacy of PD-1 blockade in ovarian cancer. We sought to explore toxicity and efficacy of the combination of TIGIT inhibitor, etigilimab, and PD-L1 inhibitor, nivolumab. **Methods:** Eligible patients (pts) had platinum-resistant recurrent clear cell ovarian cancer with no prior immunotherapy and unlimited prior lines. Measurable disease and adequate end organ function were required. Pts received etigilimab 1000mg IV and nivolumab 240mg IV every 2 weeks. Bayesian optimal phase 2 design was used to conduct the trial. Dual primary end points were toxicity assessment by CTCAE v5.0 and objective response per modified RECIST v1.1. Clinical benefit (CBR) was defined as objective response or stable disease (SD) for >/= 4 months. Progression-free survival was defined as time from first treatment to documented disease progression. NCT05715216. **Results:** 23 pts received at least one cycle of treatment. Median age was 54 years (range 38-73); 65.2% of pts were Non-Hispanic white, 17.4% Hispanic, 8.7% Black and 8.7% Asian. Median lines of prior therapy was 2 (range 0-8). No patient received prior PARP inhibitor. Grade 3 or 4 adverse events were observed in 47.8% of pts, the most common of which was abnormal liver function tests. Other common adverse events of any grade included nausea/vomiting (34.8%), fatigue (30.4%), and anemia (30.4%). Of 20 pts evaluable for response, objective response rate was 15.0% (95% CI 3.2-37.9%) with 1 complete response (CR) and 2 partial responses (PR). CBR was 30.0% (95% CI 11.9%-54.3%). Median duration of response was 8.6 months, with ongoing responses in 2 pts at 20.0 and 8.6 months. Median duration of clinical benefit was 7.5 months. Single-cell RNA seq analysis of tumor tissues from 9 pts (CR/PR=2, SD=4, PD=3) revealed immunologic changes in the tumor microenvironment after treatment. Notably, an increased frequency of plasma B cells (p=0.02) was associated with clinical response. **Conclusions:** The combination of etigilimab and nivolumab was well tolerated. Promising clinical response and duration of benefit was observed in a heavily pretreated population of pts with clear cell ovarian cancer. Our data highlight a potential role of B cells in clinical response. Further analysis on the association of benefit by molecular features is ongoing. Clinical trial information: NCT05715216. Research Sponsor: Mereo BioPharma Group PLC; U.S. National Institutes of Health; Focus Fund; U.S. National Institutes of Health; U.S. National Institutes of Health.

5574 **Poster Session**

Potential of tumor-informed ctDNA as an early predictive indicator for relapse in advanced ovarian cancer. First Author: Christina Victoria Isabella Tauber, Department of Obstetrics and Gynecology and Comprehensive Cancer Center Munich, LMU University Hospital, LMU Munich, Bayern, Munich, Germany

Background: Prediction of relapse following firstline treatment in patients (pts) with high-grade serous ovarian cancer (HGSOC) remains a major challenge despite recent advances. Reliable markers for assessment of recurrence risk are urgently needed to tailor treatment strategies with circulating tumor DNA (ctDNA) emerging as a promising candidate. **Methods:** In this prospective feasibility study, pts with advanced HGSOC who underwent primary surgical and systemic treatment at two large-volume centers for gynecologic oncology were evaluated between July 2021 and September 2024. Whole genome sequencing was used to develop a personalized multiplex digital polymerase chain reaction fingerprint assay by identifying structural variants, single nucleotide variants and indels in FFPE tumor tissue. Longitudinal blood samples were collected perioperatively (preop, postop day 2 and 10), during firstline chemotherapy (cycle 1, 3 and 6 [c6]) and follow up. CA-125 levels were tested accordingly. For statistical analyses, chi squared, log rank tests and Kaplan-Meier method for PFS were applied as appropriate. **Results:** As of 21st January, 2025, a total of 31 pts have available samples from preop through c6 with completed ctDNA data. In this cohort, 11 recurrences (35%) have been diagnosed at a median clinical follow-up of 16.8 months [mo] (range 5.7-38.4 mo), median progression-free survival (PFS) was 11.8 mo (range 5.7-22.9 mo). At c6, levels of CA-125 were $<$35 kU/L in 25 (81%) and $\geq$35 kU/L in 6 (19%) of the 31 pts. Clearance of ctDNA was noted for 19 out of 31 pts (61%). 16 of these 19 pts (84%) had previous complete cytoreduction. While rates for recurrence did not align with CA-125 levels $<$35 kU/L (63.6%) and $\geq$35 kU/L (36.4%, *P*=0.075) at c6, a significantly lower recurrence rate was observed for patients with ctDNA clearance at c6 (4 of 19, 21.1%) compared to 7 of 12 patients with persistent ctDNA (58.3%, *P*=0.034). In 21 patients with complete cytoreduction, five pts still had detectable ctDNA levels at c6. Three of these five pts had recurrence (60%), compared to two of 16 pts with ctDNA clearance (12.5%, *P*=0.023). Detection of residual ctDNA at c6 was strongly associated with an increased risk for recurrence in the overall cohort compared to pts with ctDNA clearance (HR: 5.78, 95%CI: 1.93 – 31.99, *P*=0.004). This effect appears to be more pronounced in pts with macroscopic complete cytoreduction, but was not seen in pts with residual tumor. **Conclusions:** Findings of this interim analysis underline the potential of tumor-informed ctDNA as a powerful tool for recurrence risk assessment in pts undergoing primary treatment for HGSOC. In contrast to CA-125, ctDNA evaluation at the time of completed firstline chemotherapy might serve as an early predictive marker for relapse. This information could help to develop patient-specific treatment strategies, especially in the subgroup of pts with complete macroscopic cytoreduction. Research Sponsor: None.

5575 **Poster Session**

AI-powered quantification of tumor-infiltrating lymphocytes from H&E stained images in ovarian cancer and its association with PARP inhibitor therapy outcomes. First Author: Hiroshi Asano, Department of Obstetrics and Gynecology, Hokkaido University Graduate School of Medicine, Sappro, Japan

Background: Maintenance therapy with PARP inhibitors improves the prognosis of patients with advanced or recurrent ovarian cancer. However, a simple biomarker detectable at treatment initiation remains unclear. This study evaluated the relationship between prognosis and artificial intelligence (AI)-powered quantification of immune cells in tumor and stroma areas in hematoxylin and eosin (H&E) slides. **Methods:** We evaluated 28 ovarian cancer patients treated with PARP inhibitors in our institution from 2019 to 2021. We developed an AI model to detect the epithelium and lymphocytes, specifically T cells (CD3+) and B cells (CD20+), from H&E-stained slides. This model was trained using annotated datasets, which included 26,509 images of the epithelium and 12,273 images of lymphocytes. The tumor bed areas were precisely defined by pathologists. Subsequently, the AI model identified epithelial and lymphocyte regions within these predefined areas. Using a treatment duration of PARP inhibitor with 12 months or more as the criterion, we identified the most relevant immune cell type based on the AUCs of the ROC curve and determined cutoff values. Furthermore, tumor BRCA1/2 status was assessed by a custom-targeted NGS testing panel. A log-rank test with a p-value $<$ 0.05, considered statistically significant, examined the relationship between prognosis and tumor characteristics. **Results:** A total of 61 H&E slides were analyzed by AI: 28 slides before first-line chemotherapy, 25 after first-line chemotherapy, and 8 were the recurrent sample. The highest AUC was the lymphocyte-to-tumor area ratio (tumor-infiltrating lymphocyte score in tumor area, tTIL score) before the initial treatment, with an AUC of 0.73. The cutoff value of the tTIL score was set to 0.000534 based on the Youden index, dividing patients into tTIL-low (n=14) and tTIL-high (n=14) groups. The median follow-up period of the censored cases was 62.5 months vs. 77.3 months (p = 0.71). There were no significant differences in age, histological subtype, initial treatment method, proportion of R0 surgery, or that of tumor BRCA1/2 pathogenic mutations between groups. PARP inhibitors were used as maintenance therapy for recurrent settings in 71.4% of cases in both groups. The 5-year overall survival (5-y OS) rate of tTIL-high was significantly better than that of tTIL-low (84.4% vs. 30.8%, p = 0.0068). The median duration of OS after initiation of PARP inhibitors was significantly longer in the tTIL-high group (23.8 months vs. not reached, p = 0.046), and especially in tumor BRCA1/2-negative cases, tTIL-high had a significantly better 5-y OS rate of 90% vs. 12.5% (p = 0.0015). **Conclusions:** AI-powered tTIL score may predict the prognosis of ovarian cancer patients treated with PARP inhibitors. Future efforts will focus on increasing sample size and optimizing the tTIL score cutoff to improve accuracy. Research Sponsor: None.

5576 **Poster Session**

Genomic instability score (GIS) and benefit from olaparib (ola) and bevacizumab (bev) maintenance in high-grade ovarian cancer (HGOC): Phase III PAOLA-1 GINECO/ENGOT-ov25 trial exploratory analysis. First Author: Jose Sandoval, Oncology Department, Geneva University Hospitals and Department of Medicine, Division of Oncology, Faculty of Medicine, University of Geneva, Geneva, Switzerland

Background: The PAOLA-1 trial showed that adding ola to bev as maintenance therapy improved overall survival (OS) of HGOC patients with *BRCA1/2* mutations (BRCAm) or homologous recombination (HR) deficiency (HRD) defined by the MyChoice HRD Plus assay with a GIS threshold of 42. This post hoc analysis of PAOLA-1 explored if alternative thresholds could better identify patients who benefit most from ola. **Methods:** New cutoffs were determined through OS analyses using Cox proportional hazards models with an interaction term for GIS. Tumors were categorized into HRP (GIS$<$42), HRDlow (42–60 for *BRCA1/2* wild-type [BRCAwt], 42–67 for BRCAm), and HRDhigh ($>$60 for BRCAwt, $>$67 for BRCAm). Genomic analyses included promoter methylation, BRCA loss of heterozygosity (LOH) and HR repair gene mutations. **Results:** Among 623 patients, 194 (31%) were BRCAm and 429 (69%) BRCAwt. Main clinical prognostic features were well-balanced across BRCAwt/HRDhigh, BRCAwt/HRDlow and BRCAwt/HRP as well as among BRCAm/HRDhigh, BRCAm/HRDlow and BRCAm/HRP. Ola+bev improved progression-free survival (PFS) and OS in BRCAwt/HRDhigh and BRCAm/HRDhigh (Table). Ola+bev improved PFS but not OS in BRCAwt/HRDlow and BRCAm/HRDlow. HRP tumors showed no PFS or OS benefit regardless of BRCA status. *BRCA1*/*RAD51C* promoters were methylated in 75% of BRCAwt/HRDhigh, 47% of HRDlow, and 3% of HRP. HRDlow tumors had fewer HR repair gene mutations than HRDhigh. Among HRP/BRCAm, 37% lacked BRCA LOH, suggesting functional BRCA. **Conclusions:** Our post-hoc subgroup analyses suggest that refined GIS thresholds identify three distinct populations of HGOC patients with varying survival benefits from ola+bev maintenance. Optimized GIS cutoffs may further improve patient stratification in future PARP inhibitors trials. Research Sponsor: None.

	BRCA WT				BRCA Mut			
	HRP	HRD low	HRD high	p	HRP	HRD low	HRD high	p
N	277	72	80		19	124	51	
BRCA mutation								0.36
BRCA1	-	-	-		11 (57.9%)	82 (66.1%)	38 (74.5%)	
BRCA2	-	-	-		8 (42.1%)	42 (33.9%)	13 (25.5%)	
No BRCA LOH	-	-	-		7 (36.8%)	1 (0.8%)	2 (4.0%)	p$<$0.001
HR gene methylation (NA=134)				p$<$0.001				
No	187 (96.9%)	26 (53.1%)	13 (24.5%)		-	-	-	
BRCA1	1 (0.5%)	15 (30.6%)	34 (64.2%)		-	-	-	
RAD51C	5 (2.6%)	8 (16.3%)	6 (11.3%)		-	-	-	
mPFS (95%CI), months								
Ola + bev	16.6 (15.2-18.2)	28.9 (20.3-NR)	38.9 (22.1-NR)		21.2 (13.9-NR)	51.4 (38.9-NR)	75.2 (NR-NR)	
Placebo + bev	16.2 (13.9-18.8)	16.4 (12.9-27.7)	17.0 (12.9-23.4)		20.3 (14.7-NR)	19.4 (16.6-24.0)	15.5 (8.7-NR)	
HR (95%CI)	1.00 (0.76-1.32)	0.51 (0.29-0.91)	0.42 (0.24-0.72)		0.80 (0.28-2.26)	0.39 (0.24-0.62)	0.17 (0.07-0.41)	
mOS (95%CI), months								
Ola + bev	36.8 (30.7-40.9)	54.0 (48.3-NR)	NR (54.1-NR)		47.0 (24.2-NR)	NR (NR-NR)	75.2 (NR-NR)	
Placebo + bev	40.4 (33.0-53.3)	52.4 (45.8-NR)	41.2 (34.0-NR)		43.1 (29.0-NR)	NR (59.8-NR)	55.2 (29.8-NR)	
HR (95%CI)	1.19 (0.87-1.62)	1.07 (0.55-2.07)	0.49 (0.26-0.94)		0.88 (0.28-2.79)	0.61 (0.32-1.17)	0.15 (0.05-0.50)	

5577 **Poster Session**

Survival outcomes of advanced ovarian cancer treated with neoadjuvant chemotherapy versus primary cytoreductive surgery using a quality-assured decision-making approach. First Author: Ji Hyun Kim, Gynecologic Oncology, National Cancer Center Korea, Goyang-Si, Gyeonggi-Do, South Korea

Background: Neoadjuvant chemotherapy (NACT) is recommended for advanced ovarian cancer patients with a low likelihood of achieving complete cytoreduction through primary cytoreductive surgery (PCS) or those with high perioperative risk profiles. The decision between NACT and PCS requires careful evaluation of the feasibility of achieving optimal cytoreduction, emphasizing an individualized approach. This study evaluates whether quality-assured decision-making regarding PCS, based on institutional protocols, improves survival outcomes. **Methods:** This retrospective study included 1,256 patients diagnosed with FIGO stage IIIB-IVB ovarian, fallopian tube, or primary peritoneal carcinoma who underwent either primary or interval cytoreductive surgery at the National Cancer Center Korea between January 2016 and December 2023. The institutional criteria approach determined NACT eligibility based on patient performance status and/or computed tomography findings indicative of suboptimal cytoreduction. The primary objective was overall survival (OS), while the secondary objective was progression-free survival (PFS). **Results:** Of 1,256 patients, 666 (53.0%) received NACT followed by ICS, while 590 (47.0%) underwent PCS. Median PFS was significantly longer in the PCS group than in the NACT group (28.6 vs 17 months; HR: 0.63, 95% CI: 0.55–0.73, $p < 0.001$). Median OS was also longer in the PCS group compared to the NACT group (92.8 vs 62.1 months; HR: 0.61, 95% CI: 0.51–0.74, $p < 0.001$). Five-year PFS and OS rates were 33.8% and 65.1% in the PCS group vs. 18.3% and 51.3% in the NACT group, respectively. Complete resection of macroscopic disease was achieved in 70.7% of patients overall, with comparable rates between the two groups ($p = 0.1$). **Conclusions:** PCS demonstrates superior OS and PFS compared to ICS following NACT in advanced ovarian cancer patients, underscoring its critical role within an individualized decision-making approach. Research Sponsor: None.

Summary of key outcomes.

Outcome	PCS (n = 590)	NACT + ICS (n = 666)	p-value	Hazard Ratio (HR, 95% CI)
Median PFS (months)	28.6 (24.2–31.7)	17.0 (16.1–18.6)	< 0.001	0.63 (0.55–0.73)
Median OS (months)	92.8 (89.1–NR)	62.1 (53.8–67.9)	< 0.001	0.61 (0.51–0.74)
5-year PFS rate (%)	33.8%	18.3%	-	-
5-year OS rate (%)	65.1%	51.3%	-	-
Complete Resection (%)	70.7%	70.7%	0.1	-

5578 **Poster Session**

Impact of rucaparib on circadian rhythms and adverse events in ovarian cancer: Insights from the MAMOC trial. First Author: Deeksha Malhan, Institute for Systems Medicine and Faculty of Human Medicine, MSH Medical School Hamburg, Hamburg, Germany

Background: Ovarian cancer (OC) is a leading cause of gynaecologic cancer mortality, with most cases diagnosed at an advanced stage. Standard treatment involves cytoreductive surgery followed by chemotherapy. In high-grade OC, maintenance therapy, including PARP inhibitors (PARPi), plays a crucial role in delaying disease progression. PARP1, the primary target of these agents, interacts with the CLOCK-BMAL1 complex, which regulates circadian rhythms. This study investigates circadian disturbances in BRCA wild-type OC patients receiving rucaparib compared to placebo and evaluates their impact on patient-reported outcomes. **Methods:** This study is part of the Phase III, randomized, double-blind, placebo-controlled MAMOC trial (NCT04227522), which enrolled 42 patients with advanced high-grade OC after platinum-based chemotherapy and bevacizumab maintenance. Rucaparib was given to 28 patients, while 14 received placebo. Daily activity data and patient-reported outcomes, including quality of life (EORTC-QLQ-C30/OV28), Fatigue Symptom Inventory (FSI), and adverse event (AE/SAE) data, were collected for all patients. A subset of 15 patients (5 placebo, 10 rucaparib) underwent molecular circadian clock analysis using saliva samples collected pre-, during, and post-treatment to assess changes in the clock and cancer-related pathways via qPCR and NanoString technology. Mathematical modelling was used to determine 24-hour toxicity profiles. **Results:** Rucaparib treatment caused significant disruptions in circadian gene expression, notably a reduction in *BMAL1* expression, followed by an increase in *BMAL1* and *PER2* levels post-treatment. Dysregulation of *BMAL1* and *PER2* correlated with the frequency and severity of side effects, including fatigue. Circadian parameters such as amplitude, MESOR, and phase were predictive of patient-reported outcomes. In the rucaparib group, circadian parameters exhibited opposing associations with outcomes compared to placebo. Clock-associated genes, including *NFIL3* and *GSK3B*, showed altered expression patterns that normalized after treatment. Additionally, rucaparib induced phase shifts and amplitude changes in clock and cancer-related genes like *CRY2*, *RORC*, and *TP53*, which were associated with increased adverse effects, particularly fatigue and nausea. Mathematical modelling revealed variability in toxicity profiles based on individual circadian rhythms pointing to the relationship between clock disruption and side effect severity. **Conclusions:** Our findings highlight the role of circadian rhythm dysregulation in the toxicity of PARPi in OC. The study suggests that chronotherapy, aligning drug administration with patients circadian rhythms, may reduce side effects. Incorporating circadian biology into treatment strategies could thus contribute to optimize cancer therapies by enhancing efficacy while minimizing toxicity. Clinical trial information: NCT04227522. Research Sponsor: Clovis Oncology; MSH Medical School Hamburg; Charité/ BIH Digital Health Accelerator Program; Dr. Rolf Schwiete Stiftung.

5579 **Poster Session**

Efficacy of third-line and later (3L+) therapies post poly (ADP-ribose) polymerase inhibitor (PARPi) exposure in recurrent platinum-sensitive ovarian cancer (PSOC): A pooled clinical trial database analysis. First Author: Robert Louis Coleman, Texas Oncology, US Oncology Research, The Woodlands, TX

Background: Patients (pts) with PSOC often experience reduced efficacy and tolerability with each successive treatment (tx). While PARPi therapies have demonstrated clinical benefit in frontline and maintenance settings, most pts eventually experience progression of disease (PD) with limited tx options. Data establishing standard of care for PSOC was published prior to the PARPi era. This study evaluated the efficacy of tx in PSOC subsequent to PARPi exposure. **Methods:** Pooled pt-level data from <5 multinational clinical trials (CT) involving PARPi tx were sourced from the Medidata Clinical Cloud and included pts with PSOC diagnosis, ≥2 prior lines of platinum-based chemotherapy (PBC), most recent platinum-free interval (PFI) ≥6 months (mo), prior PARPi tx, initiation of tx subsequent to PARPi (defined as the index tx), and ECOG Performance Status (PS) ≤1 prior to the index tx. Index date was defined as the initiation of index tx. Outcomes included overall response rate (ORR), progression-free survival (PFS), and overall survival (OS). PFS was defined as the time from the index date to PD, death or start of new tx; pts with no PFS event were censored at the end of follow-up. PFS and OS were estimated using the Kaplan-Meier method and compared across subgroups with the log-rank test. Exploratory subgroup analyses of PFS and OS were conducted per factors identified in multivariable Cox models. **Results:** Among 130 pts (≥65 years, 36.9%; White, 87.7%; FIGO Stage III/IV, 89.2%; ECOG PS 0/1, 59.2%/40.8%; ≥3 prior lines of PBC, 23.8% [range, 2-5]; PFI ≥12 mo, 61.5%), the median duration of PARPi use was 13.24 mo (IQR, 9.22), and 96.9% experienced PD ≤106 days from PARPi discontinuation. Index tx included PBC (74.6%) and non-PBC (25.4%); 61.5% received combination tx. Median duration of index tx was 4.01 mo (95% CI, 3.71-4.93). ORR on index tx was 16.9% (95% CI, 10.9-24.5). Median PFS was 6.11 mo (95% CI, 5.06-7.39), with longer PFS in pts with PFI ≥12 mo vs 6 to <12 mo (7.39 mo [95% CI, 6.08-8.77] vs 4.44 mo [3.25-6.14]; *P*=0.002) and in pts with combination therapy vs monotherapy index tx (7.39 mo [95% CI, 6.21-8.61] vs 3.71 mo [95% CI, 3.12-5.75]; *P*=0.026). Median OS was 19.35 mo (95% CI, 17.77-22.08), with longer OS in pts with PFI ≥12 mo vs 6 to <12 mo (23.03 mo [95% CI, 19.29-33.81] vs 15.08 mo [95% CI, 11.89-19.68]; *P*<0.0001). PFS and OS were similar in PBC vs non-PBC as index tx. **Conclusions:** Median PFS with 3L+ tx for PSOC following PARPi exposure was 6.11 mo, establishing an efficacy benchmark for tx subsequent to PARPi exposure in this unique pt population and highlighting the need for more effective tx. Due to the lack of regular per-protocol imaging assessments after the start of non-trial tx, PFS values may be overestimated. However, pooled CT data with long-term follow-up provide valuable insights not available from other sources. Research Sponsor: AbbVie.

5581 **Poster Session**

A multi-omics approach using lipids and proteins for early detection in individuals with signs and symptoms of ovarian cancer. First Author: Rachel Culp-Hill, AOA Dx, Denver, CO

Background: Late-stage ovarian cancer (OC) is diagnosed in 80% of patients, leading to a five-year survival rate below 30% and ranking OC as the fifth leading cause of cancer-related deaths in women. Non-specific abdominal symptoms overlap with benign disorders, delaying diagnosis. Testing symptomatic individuals can detect low disease burden, enabling high complete cytoreduction rates. However, current diagnostic tools lack sensitivity and specificity for early-stage OC, underscoring the critical need for novel biomarkers and approaches. **Methods:** We conducted a multi-omics analysis of serum from two independent, clinically annotated cohorts. Specimens were analyzed using UHPLC-MS untargeted lipidomics and a protein biomarker panel. Cohort #1 (N=544) from the University of Colorado Gynecologic Tissue and Fluid Bank and commercial vendors included patients diagnosed with OC (N=219: 80 early-stage I/II, 139 late-stage III/IV), and non-cancerous controls (N=325) for biomarker discovery. Cohort #2 (N=423) from Manchester University NHS Foundation Trust and commercial vendors included prospectively enrolled individuals with signs and symptoms of OC. Samples included patients diagnosed with OC (N=109 total: 52 stage I/II, 57 stage III/IV), and non-cancerous controls (N=314). Cohorts were processed independently. **Results:** Over 1000 features were identified in both cohorts. There was a significant overlap in common features confirming importance in indication for use population. The top features confirmed in both cohorts enabled machine learning-based modeling. Biomarker classes were modeled separately (lipids only, proteins only) and in combination (lipids and proteins), employing 20-fold cross validation. Models containing multi-omic features consistently exhibit the highest AUC compared to individual biomarker classes. AUC for the top-performing model applied to both cohorts was 95% (CI 94-96) for all controls vs. all OC, and 92% (CI 89-95) for all controls vs. early-stage OC. When compared with normal individuals, the AUC vs all OC across stages and sub-types was 97% (CI 96-98). **Conclusions:** Our top-performing models contain >50 multi-omic features common across two independent cohorts, comprised of 967 unique individuals. Combining LC-MS-based lipidomic profiling of serum with proteins represents a promising new approach as a clinical diagnostic for detecting OC in this complex patient population. Early detection in women with signs and symptoms of OC and faster triage to specialty care may lead to improved patient outcomes. Research Sponsor: None.

5582 **Poster Session**

Early detection of ovarian cancer: An accurate high-throughput extracellular vesicle test. First Author: Carlos Salomon, Translational Extracellular Vesicles in Obstetrics and Gynae-Oncology Group, Centre for Clinical Diagnostics, UQ Centre for Clinical Research (UQCCR), Royal Brisbane and Women's Hospital, Faculty of Medicine, The University of Queensland, Brisbane, Australia

Background: The high mortality of Ovarian cancer (OC) has been attributed to late-stage diagnosis and the lack of an effective early detection strategy, particularly for asymptomatic women. In this study, we developed and validated a high-throughput OC detection test based on plasma extracellular vesicle (EV)-associated biomarkers. **Methods:** A case-control study was conducted to evaluate blood-borne EV-associated ovarian cancer biomarkers, including miRNAs, proteins, lncRNAs, miscRNAs, MtrRNAs, MttRNAs, rRNAs, scaRNAs, snRNAs, and tRNAs. Protein and RNA biomarkers were identified by mass spectrometry and RNA sequencing, respectively. Training (n=453) and independent test (n=471) sample sets were used to develop and validate a multivariate index assay (MIA). The MIA was further validated using a high-throughput, pathology laboratory compatible, EV isolation platform (EXO-NET) and two independent sample cohorts (n=97 and n=532). The classification accuracy, sensitivity and specificity of the MIA was compared to that of CA125 levels. **Results:** Discovery and Training phases - more than 100,000 EV-associated biomarkers were identified from 453 EV samples. The classification performance of these biomarkers was assessed using machine learning algorithms. EV-associated protein and miRNA biomarkers delivered the highest performing classifiers and, therefore, were used in subsequent MIA development and training. During the training phase, multivariate classification algorithms were validated using a 10-fold cross-validation method. The highest performing classifiers for EV-associated protein and miRNA, at specificity of 98%, achieved sensitivities of 90% and 82%, respectively. Validation phase: Locked classification algorithms (*i.e.* MIAs) were validated using two independent sample cohorts and reported classification accuracies of 92-98%, significantly outperforming CA-125 (CE = 62%, $p<0.001$). Automated high-throughput MIA – All stages OC: the best performing automated high-throughput MIA demonstrated an overall sensitivity of 92% (95% CI, 75–96%) and specificity of 93% (95% CI, 86–96%) for all stages of OC, Positive Predictive Value of 95% (CI, 93-96%) and Negative Predictive Value of 80% (CI, 76-89%) at 98% specificity (n=532). Stage I OC: Importantly, the MIA displayed a sensitivity of 90% (95% CI, 76–100%) and specificity of 96% (95% CI, 40%–99%) for stage I OC. While CA125 have an overall sensitivity for all stages of OC of 61% (95% CI, 53–69%), with a sensitivity of 44% for stage I (95% CI, 28–62%). **Conclusions:** In this study we report the development and validation of an accurate, automated high-throughput EV-based test for early detection of ovarian cancer. The test delivers significant improvements in sensitivity and specificity compared to CA-125, especially in detecting early-stage OC. Research Sponsor: Lion Medical Research Foundation; 2015001964; Ovarian Cancer Research Foundation; 2018001167; Medical Research Future Fund; MRF1199984 GA187319; National Health and Medical Research Council; 1195451; INOVIQ.

5583 **Poster Session**

Hyperthermic intraperitoneal chemotherapy (HIPEC) for primary advanced-stage or recurrent ovarian cancer: A systematic review and meta-analysis of randomized controlled trials. First Author: Gabriela Branquinho Guerra, Escola Superior de Ciências da Saúde, Brasília, DF, Brazil

Background: Ovarian cancer is the gynecologic malignancy with the highest mortality rate. Despite cytoreductive surgery (CRS) and adjuvant or neoadjuvant systemic therapy, the rate of peritoneal recurrence remains high. Hyperthermic intraperitoneal chemotherapy (HIPEC) has emerged as a potential treatment option, delivering high concentrations of heated chemotherapy directly to the tumor site, enhancing local cytotoxicity. **Methods:** We searched PubMed, Embase, and Cochrane for randomized clinical trials (RCTs) comparing CRS plus HIPEC versus CRS alone. Hazard ratios (HR), odds ratios (OR) and mean differences (MD) were pooled using Review Manager software version 5.4. Heterogeneity was assessed with I^2 statistics. The main outcomes were overall survival (OS), median OS, progression-free survival (PFS), median PFS, operative time in minutes, Grade 3 or higher adverse events, time from surgery to adjuvant chemotherapy and length of hospital stay (LOS) in days. Subgroup analysis was performed for primary and recurrent cancer outcomes. **Results:** A total of 1,259 patients from 8 RCTs were included, with 636 (50.52%) undergoing CRS with HIPEC. The median follow-up period ranged from 32 to 121.2 months. CRS plus HIPEC significantly improved OS (HR 0.76; 95% CI 0.62-0.93; p = 0.009; I^2 = 27%), with a significant benefit also observed in the subgroup analyses of primary ovarian cancer (HR 0.66; 95% CI 0.52-0.85; p = 0.001; I^2 = 0%). However, no significant difference was observed for recurrent ovarian cancer (HR 0.87; 95% CI 0.63-1.19; p = 0.38; I^2 = 39%). Median OS also significantly favored CRS plus HIPEC (MD 9.99; 95% CI 2.40-17.58; p = 0.01; I^2 = 0%). PFS was not significantly different between groups (HR 0.74; 95% CI 0.52-1.06; p = 0.10; I^2 = 76%). In subgroup analysis, PFS was significantly improved for primary ovarian cancer (HR 0.62; 95% CI 0.49-0.79; p = 0.0001; I^2 = 0%), but not for recurrent ovarian cancer (HR 0.80; 95% CI 0.41-1.56; p = 0.52; I^2 = 84%). Median PFS showed no statistical difference (MD 1.98; 95% CI -1.20-5.15; p = 0.22; I^2 = 29%). Time from surgery to adjuvant chemotherapy was not statistically different (MD -0.13; 95% CI -4.49-4.23; p = 0.95; I^2 = 0%). Operative time was significantly shorter in the control group (MD 127.75; 95% CI 89.61-165.89.; $p < 0.00001$; I^2 = 51%), as were LOS (MD 1.49; 95% CI 0.12-2.87; p = 0.03; I^2 = 0%) and Grade 3-5 adverse events (OR 1.50; 95% CI 1.05-2.16; p = 0.03; I^2 = 40%). **Conclusions:** In patients with ovarian cancer, HIPEC significantly improved OS, particularly in the subgroup of primary ovarian cancer. PFS was also significantly improved in this subgroup. However, these benefits were associated with higher rates of adverse events and longer LOS. Our analysis supports the use of HIPEC in the treatment of ovarian cancer, especially for patients with primary ovarian cancer. Research Sponsor: None.

5584 **Poster Session**

Hyperthermic intraperitoneal chemotherapy in recurrent ovarian cancer: An updated systematic review and meta-analysis. First Author: Yemesrach Mekonen, St. Barnabas Hospital, Bronx, NY

Background: Ovarian cancer is the leading cause of mortality among gynecological malignancies in women. Disease recurrence remains a formidable challenge in the management of primary ovarian cancer. This systematic review and meta-analysis evaluate the impact of hyperthermic intraperitoneal chemotherapy (HIPEC) on overall survival (OS) and progression-free survival(PFS) in patients with recurrent ovarian cancer. **Methods:** A comprehensive literature search was conducted in PubMed, Embase, and Cochrane databases to identify randomized controlled trials (RCTs) published up to November 2024, comparing the outcomes of HIPEC combined with cytoreductive surgery (CRS) versus CRS alone in patients with recurrent ovarian cancer. A total of 459 articles were screened in accordance with the PRISMA guidelines. The primary endpoints analyzed were OS, PFS, and postoperative complications. Hazard ratios (HR) and 95% confidence intervals (CI) were calculated using the inverse variance method for time-to-event outcomes, while the Mantel-Haenszel method was applied for binary outcomes to estimate relative risk (RR) and corresponding 95% CIs. Statistical heterogeneity was assessed using Cochrane's Q test and Higgins' I^2 statistic. Statistical significance was set at a p-value < 0.05. Data analysis was performed using R software version 4.4.2. **Results:** Following the screening process, four RCTs involving a total of 801 patients were included in the meta-analysis, and 398 patients (49.6%) received HIPEC. The pooled analysis demonstrated a non-significant improvement in OS for the HIPEC group (HR 0.8; 95% CI [0.55, 1.17]; p=0.159). Similarly, PFS did not significantly differ between the treatment and control groups (HR 1.04; 95% CI[0.46, 2.35];p=0.867). In terms of postoperative complications, patients who underwent HIPEC were at a significantly increased risk of developing anemia (RR 1.36; 95% CI[1.08, 1.72];p=0.028) and sepsis (RR 2.11; 95% CI[1.44, 3.08];p=0.014). However, no significant differences were observed between the treatment and control groups regarding other postoperative complications, including urinary tract infection (RR 0.95;95% CI[0.19, 4.69];p=0.895), bowel obstruction (RR 0.77; 95% CI [0.25, 2.37]; p=0.426), pleural effusion (RR 1.49;95% CI[0.16, 14.16];p=0.525), and thrombosis (RR 1.99;95% CI[0.98, 4.07];p=0.053). **Conclusions:** The findings suggest that while HIPEC may offer a potential, albeit statistically non-significant, survival benefit in patients with recurrent ovarian cancer, it is associated with an increased risk of anemia and sepsis. Research Sponsor: None.

5585 **Poster Session**

Impact of body mass index, diabetes, and tumor mutational burden in ovarian, fallopian tube, and primary peritoneal carcinoma with BRCA1/2 alteration on poly(ADP-ribose) polymerase inhibitors. First Author: Ryan Tan, Memorial Sloan Kettering Cancer Center, New York, NY

Background: Obesity and hyperinsulinemia are associated with increased fallopian tube (FT) epithelial DNA damage in women carrying germline BRCA1/2 mutations. Whether these states impact survival in patients with ovarian, FT, or primary peritoneal carcinoma (PPC) with BRCA1/2 mutations, particularly when treated with Poly (ADP-ribose) polymerase inhibitor (PARPi), remains unclear. Research on tumor mutational burden (TMB) in these malignancies and survival have yielded inconsistent results. **Methods:** Ovarian/FT/PPC patients with germline/somatic BRCA1/2 mutation who received ≥1 dose of PARPi therapy between 2015-2023 were included in this retrospective cohort. Clinical characteristics abstracted include age, ethnicity, histology, DM status, pre-treatment TMB (pTMB) on MSK-IMPACT, PARPi use. Progression-free survival (PFS) was estimated using Kaplan-Meier. Cox regression was used to evaluate associations with PFS. **Results:** 202 patients treated between March 2015 – Aug 2024 were included; median age was 60 (interquartile range 50.3-67.2), 117 (57.9%) were overweight/obese (body mass index [BMI] ≥ 25) and 21 (10%) had DM. 160 (79%) and 33 (16%) had ovarian and FT cancer respectively. 182 (90.1%) had high grade serous carcinoma. 80 (40%) had germline BRCA1, 48 (24%) had germline BRCA2, 50 (25%) had somatic BRCA1 and 28 (14%) had somatic BRCA2 mutations. 91 (58%) had pTMB ≤5 mutations/megabase [mut/Mb], 56 (36%) had pTMB >5 to <10 mut/Mb and 9 (6%) had pTMB ≥10 mut/Mb. Median pTMB was higher in overweight/obese than normal BMI (4.9 vs 4.3 mut/Mb, p=0.093). 118 (58%) received PARPi as first-line and 59 (29%) received PARPi as second-line maintenance. 190 (94%) received PARPi as monotherapy, 6 (3%) in combination with bevacizumab and 6 (3%) in combination with immunotherapy +/- bevacizumab on a clinical trial. 168 (83%) received olaparib, 24 (12%) received niraparib and 9 (4.5%) received rucaparib. In multivariable (MV) Cox regression analysis, somatic BRCA status (BRCA1 hazard ratio [HR]=2.22, 95% confidence interval [95% CI]: 0.55-8.98; BRCA2 HR=0.66, 95% CI: 0.12-3.77; p=0.022; reference was somatic BRCA wildtype) was independently associated with PFS, pTMB (>5 to <10 mut/Mb HR=0.62, 95% CI: 0.32-1.19; ≥10 mut/Mb HR=0.19 95% CI: 0.02-1.56; p=0.088) had borderline significance while BMI and DM status were not associated. A MV Cox model additionally including the interaction between BMI and DM illustrated worse PFS in overweight/obese DM patients with borderline significance (p=0.094). **Conclusions:** Higher pTMB trended toward longer PFS in ovarian/FT/PPC patients with BRCA1/2 mutations receiving maintenance PARPi and was more common in overweight/obese. Prospective trials should evaluate if TMB may predict for response to PARPi and whether obesity-mediated DNA damage alters treatment outcomes. Research Sponsor: None.

5586 **Poster Session**

Survival outcomes for ovarian cancer patients in the post–poly ADP-ribose polymerase inhibitor (PARPi) era in the US. First Author: Henry Becerra, Brookdale University Hospital and Medical Center, Brooklyn, NY

Background: PARPi introduction in clinical practice has led to major changes in the therapeutic landscape for ovarian cancer (OC)[1]. Olaparib is approved alone or in combination with bevacizumab for the first line maintenance therapy of BRCA-mutated or homologous repair deficient (HRD) OC. We hypothesize that the introduction of PARPi in routine clinical practice for maintenance therapy in OC has resulted in improvements in survival outcomes among OC patients (pts) treated in the real world. **Methods:** Pts with a diagnosis of stage III/IV epithelial OC age ≥18 years between 2000-2021 were obtained from the Surveillance, Epidemiology, and End Results (SEER) Database. A cutoff on 2017 was made based on the initial approval of PARPi for maintenance therapy. Statistical analyses were conducted with SPSS. Pts characteristics were reported in frequencies and compared with the Chi-squared test. The Kaplan-Meier method was used to estimate median OS. Cox Regression was used identify independent prognostic factors of survival. P-value ≤0.05 was considered statistically significant. **Results:** 59,913 pts were included with median age 63 years, 60.9% non-hispanic white, and 55.8% with serous histology. 44,873 pts were diagnosed in the pre-PARPi cohort and 15,040 in the post-PARPi cohort. 76.3% and 76.1% of pts received any chemotherapy and surgery, respectively. Similar distribution in analyzed variables was found when comparing among eras. The median OS for pre-PARPi pts was 37 months (95%CI: 36.4-37.6) and post-PARPi pts was 38 months (36.6-39.4), p=0.023. In multivariate analysis, pts diagnosed in the post-PARPi era had improved OS compared with pts in pre-PARPi era (HR=0.93, 95%CI:0.91-0.96, p<0.001). **Conclusions:** To the extent of our knowledge, this study is the first real world analysis of survival outcomes in OC pts after the introduction of PARPi at a population level in the US. The introduction of PARPi maintenance therapy has resulted in a modest improvement in OS in the overall OC population unselected for BRCA or HRD status. 1. Tew WP et al. J Clin Oncol. 2020 Oct 20;38(30):3468-93. Research Sponsor: None.

5587 **Poster Session**

Oregovomab in combination with non-platinum chemotherapy for the treatment of PARP inhibitor– and platinum-resistant ovarian cancer: A two-cohort, single-arm phase 2 study (OPERA/KGOG3065/APGOT-OV6). First Author: Junsik Park, Soonchunhyang University Bucheon Hospital, Bucheon, South Korea

Background: Oregovomab, an investigational murine monoclonal antibody against CA-125, has shown promising efficacy in a phase 2 study in patients with recurrent ovarian cancer. Herein, we report the primary results of OPERA/KGOG 3065/APGOT-OV6 on oregovomab in combination with non-platinum-based chemotherapy in patients with PARP inhibitor (PARPi)- and platinum-resistant epithelial ovarian cancer (EOC). **Methods:** This multicenter, investigator-initiated, two-cohort, single-arm phase 2 trial evaluated the efficacy and safety of oregovomab in combination with PLD or weekly paclitaxel in patients with PARPi- and platinum-resistant EOC. Patients who received one to three prior lines of chemotherapy will be assigned to Cohort 1 (oregovomab [C1,2,3,5,7 for five doses] + PLD q4w, n=28), whereas patients who received more than three prior lines of chemotherapy will be assigned to Cohort 2 (oregovomab [C1,2,3,5,7 for five doses] + weekly paclitaxel [D1,8,15 q4w], n=28). The primary endpoint of the study was objective response rate (ORR) based on RECIST version 1.1. The secondary endpoints are progression-free survival (PFS), overall survival (OS) and safety. For the exploratory endpoints, immunologic response was measured at pretreatment and at C2, 3, 5, 7, or EOT by assessing serum HAMA levels and performing flow cytometric analysis of PBMCs. This trial is registered with ClinicalTrials.gov (NCT05407584). **Results:** A total 56 patients (Cohort 1, n=28; Cohort 2, n=28) have been enrolled between July 12, 2022 and September 19, 2023. Median age was 59 years (range, 36–79). Fifty-two (92.9%) patients had high-grade serous adenocarcinoma. At the data cut-off, the median follow-up was 8.0 months for Cohort 1 and 6.5 months for Cohort 2. The ORR was 0.0% (95% CI: 0.0–12.3) in Cohort 1, and 28.6% (95% CI: 13.2–48.7) in Cohort 2. Eight patients (28.6%) in Cohort 2 achieved a partial response, while 12 (42.9%) patients in Cohort 1 and 3 (10.7%) patients in Cohort 2 had stable disease. Three patients withdrew from the study due to treatment-related adverse events (TRAEs). These included one case of neutropenia in Cohort 1 and cases of anemia and lymphedema in Cohort 2. No TRAEs leading to death were reported. The median PFS was 2.5 months (95% CI: 2.1–4.7) in Cohort 1, and 2.6 months (95% CI: 2.0–3.7) in Cohort 2. Serum HAMA levels significantly increased after C3 exclusively in Cohort 2, but no significant changes in peripheral T cells have been observed. **Conclusions:** Oregovomab plus weekly paclitaxel chemotherapy demonstrated encouraging activity and safety in heavily pre-treated PARPi- and platinum-resistant EOC. Clinical trial information: NCT05407584. Research Sponsor: Canariabio Inc.

5588 **Poster Session**

Platinum or non-platinum therapy in post-olaparib recurrent ovarian cancer: Analysis in matched cohorts. First Author: Alexey Rumyantsev, Federal State Budgetary Institution "N.N. Blokhin National Medical Research Center of Oncology" of the Ministry of Health of the Russian Federation (N.N. Blokhin NMRCO), Moscow, Russian Federation

Background: Due to potential cross-resistance mechanisms efficacy of platinum agents may be dramatically reduced in patients with ovarian cancer which progressed during maintenance therapy with PARP-inhibitors. We conducted this study to examine whether administration of platinum compounds has clinical value in post-olaparib setting of treatment for epithelial ovarian cancer treatment. **Methods:** This was a single center retrospective study in matched cohorts. We selected ovarian cancer patients from N.N. Blokhin NMRCO ovarian cancer who were treated in 2014-2024 years for any FIGO stage high-grade serous or endometrioid advanced epithelial ovarian cancer and progressed during olaparib maintenance therapy. Patients were treated with standard platinum-based or non-platinum chemotherapy for recurrent advanced epithelial ovarian cancer. Cardinality matching was considered to ensure adequate balancing of the study arms. The primary endpoint of the study was progression-free survival (PFS) in patients treated with platinum-based and non-platinum chemotherapy. Overall survival was a secondary endpoint. **Results:** Cardinality matching with 1:2 ratio resulted in 126 matched patients for further analysis. Groups were well balanced without any significant differences in baseline characteristics. Median age in both treatment arms was 50 years with no differences in patients' age, risk groups, prevalence of BRCA-mutations, duration of olaparib therapy and platinum-free interval. With a median follow up of 7.4 mo. median PFS was 6.0 in the non-platinum chemotherapy arm and 6.5 mo. in the platinum-based therapy arm (HR 1.17; 95% CI 0.77-1.77; p=0.46). Estimated 1-year PFS was 13.1% and 8.3%, respectively. Median OS was 21.3 mo. and 23.1 mo. in platinum-based chemotherapy arm and non-platinum arm (HR 0.98; 95% CI 0.55-1.76; p=0.96). Subgroup analyses revealed no heterogeneity in therapy efficacy. **Conclusions:** Our study suggest no additional benefit from platinum-based chemotherapy in post-olaparib ovarian cancer, further prospective trials are warranted to find optimal therapeutic approaches for these patients. Research Sponsor: N.N. Blokhin NMRCO.

5589 **Poster Session**

A prospective, single-arm, phase 2 trial exploring the use of pamiparib combined with surufatinib as neoadjuvant therapy for advanced, unresectable ovarian cancer (PASSION). First Author: Bairong Xia, The First Affiliated Hospital of USTC, Division of Life Sciences and Medicine, University of Science and Technology of China, Hefei, China

Background: Pamiparib is a selective PARP1/2 inhibitor, while surufatinib targets VEGFR1-3, FGFR1, and CSF-1R. We evaluated the efficacy and safety of combining pamiparib and surufatinib in neoadjuvant therapy (NAT) for advanced unresectable ovarian cancer (OC) in a broad, molecularly unselected population. **Methods:** This phase 2, single-arm study enrolled patients aged 18–70 with newly diagnosed OC in China. Participants received pamiparib (40 mg twice daily, 3 cycles) combined with surufatinib (250 mg twice daily, 2 cycles), followed by interval debulking surgery (IDS) and 4 cycles of platinum-based chemotherapy. Primary endpoint: complete resection (R0). Secondary endpoints: objective response rate (ORR), pathological complete response (pCR), progression-free survival (PFS), overall survival (OS), and safety. Tumor samples before and after treatment were analyzed by transcriptomics, proteomics, and single-cell transcriptomics. **Results:** Between Nov 2022 and Jan 2025, 32 patients were enrolled, 31 treated, and 1 withdrew. 26 patients completed NAT and underwent IDS, while 5 switched to other chemotherapy due to adverse events. Among resected patients (median age 56, 10 with stage IV), all showed objective responses. R0 was achieved in 24 (92.3%), R1 in 2 (7.7%). Median PFS and OS are not yet reached. Common grade 3/4 adverse events: leukopenia (32.2%), neutropenia (29%), and anemia (29%). No treatment-related deaths were recorded. Post-treatment, B and T cell proportions increased, associated with improved PFS and clinical outcomes. TLS formation was observed, and higher TLS density correlated with better prognosis and reduced tumor biomarkers. **Conclusion:** Pamiparib and surufatinib show promising efficacy and manageable toxicity in advanced OC, reshaping the tumor microenvironment and promoting immune infiltration. Clinical trial information: NCT05652283. Research Sponsor: None.

5590 **Poster Session**

A comparative study of the real-world safety and effectiveness of metronomic cyclophosphamide and bevacizumab with or without pembrolizumab for recurrent ovarian cancer. First Author: Alicia Youssef, Massachusetts General Hospital, Boston, MA

Background: Metronomic cyclophosphamide and bevacizumab (CB) alone or in combination with pembrolizumab (CBP) are active regimens in heavily pretreated patients with recurrent ovarian cancer. However, it is unknown to what extent the addition of pembrolizumab augments the effectiveness or increases the toxicity compared to CB alone. **Methods:** We conducted a multi-institutional retrospective cohort study utilizing electronic medical records of patients treated for recurrent ovarian cancer in oncology practices affiliated with four New England hospitals from 2012 through 2024. We included patients who received either CB or CBP and abstracted baseline characteristics, outcomes, and adverse events. The overall response rate (ORR) was defined as the proportion of patients with a complete or partial response. Net benefit (NB) was defined as the proportion of patients with a response or stable disease based on clinician assessment. Kaplan Meier curves were used to summarize progression-free survival (PFS) and overall survival (OS). Cox regression models were used to calculate and estimate the relative hazard of death (OS) and death or progression (PFS). Multivariable models adjusted for age, number of prior lines of therapy, time since diagnosis, platinum sensitivity, BRCA status, and Charlson comorbidity index. **Results:** We identified 163 patients, of whom 126 (77.3%) received CB and 37 (22.7%) received CBP. The median age at enrollment was 65.4 in the CB arm and 62.9 in the CBP arm (p=0.21). Most patients were non-Hispanic White (85.9%), with high grade (96.6%) serous (87.1%), platinum-resistant (76.7%) ovarian cancer. There were no statistically significant differences in BRCA status (21.4% vs. 18.9%, p=0.04), the median number of prior lines (3 vs. 3, p=0.25), or the proportion of platinum-resistant patients (77.8 % vs. 73.0%, p=0.41) between the CB and CBP arms. The ORR was 19.8 vs 21.6 % (p=0.81), and NB was observed in 44.8% in the CB arm and 41.2% in the CBP arm (p=0.71). The median PFS was 5.2 versus 4.8 months in the CB and CBP groups (HR 1.02; CI 0.67 - 1.55, p=0.37). Median OS was 17.3 vs 15.2 months, respectively (HR 1.51; CI 0.93 – 2.46, p=0.96). Adjustment for potential confounders produced similar results for PFS (adjusted HR=1.25, CI 0.77 – 2.02, p=0.37) and OS (adjusted HR=1.56, 95% CI 0.91 – 2.70 p=0.16). Seventeen (45.9%) patients in the CBP arm developed an immune reaction during treatment, but hospitalization rates were similar in both groups (25.4% vs 21.6%, p = 0.64). **Conclusions:** The addition of pembrolizumab to metronomic cyclophosphamide and bevacizumab was not associated with an improved response rate, PFS, or OS among patients with heavily pretreated recurrent ovarian cancer. Research Sponsor: None.

5591 **Poster Session**

Folate receptor alpha (FRα; FOLR1) expression and persistence in ovarian cancer in clinical trial samples and real-world patient cohort. First Author: Elizabeth M. Swisher, University of Washington, Seattle, WA

Background: The FRα-directed antibody-drug conjugate mirvetuximab soravtansine-gynx (MIRV) provides survival benefit vs investigator's choice chemotherapy for FRα-high, platinum-resistant ovarian cancer (PROC). Understanding targetable FRα expression is important to inform patient care and guide trial development. FRα protein expression patterns, consistency over time, association with mRNA expression, and prognostic value in patients (pts) with ovarian cancer was evaluated. **Methods:** FRα protein expression was retrospectively established by immunohistochemistry (IHC) using the VENTANA FOLR1 (FOLR1-2.1) RxDx Assay (FOLR1 CDx) in high-grade serous ovarian cancer tumors from pts in the VELIA trial (NCT02470585) and a real-world (RW) cohort. RW tumors were tested at Caris Life Sciences and linked to health record data from the ConcertAI RWD360 product. FRα-high positivity was defined by a cutoff of ≥75% of viable tumor cells with ≥2+ membrane staining (used for MIRV treatment eligibility with approved FOLR1 CDx). RNA was measured using whole transcriptome RNAseq. IHC and mRNA concordance was determined using Receiver Operating Curve (ROC) analysis. **Results:** In the RW cohort (N=611), 40.9% were FRα-high. FRα-high prevalence was 40.3% and 40.5% in tumors with and without *BRCA1* mutations, respectively (mutation prevalence, 12.4%). FRα-high prevalence was 47.4% and 39.8% in tumors with and without *BRCA2* mutations, respectively (mutation prevalence, 8.8%). Thirty-six pts had 2 biopsies longitudinally collected with IHC results. Consistency of FRα IHC status across biopsies was 86%. FRα mRNA expression associated with IHC status (ROC area under the curve [AUC]=0.88; 95% CI, 0.84-0.91), with sensitivity and specificity of 83% using a cutoff maximizing Youden's Index. To understand the prognostic nature of pts with tumors with FRα-high expression, samples from the VELIA trial were used. FRα IHC was conducted on a subset of tumors, and 56/186 (30%) were FRα-high. FRα mRNA could robustly predict IHC status (ROC AUC=0.82; 95% CI, 0.75-0.88) with sensitivity of 85% and specificity of 72%. An mRNA cutoff best associated with FRα-high IHC was applied to an extended VELIA cohort in newly diagnosed pts with mRNA data available (N=709), and FRα mRNA was identified as a negative prognostic factor for progression free survival (Hazard Ratio=1.27; 95% CI, 1.05-1.5). **Conclusions:** FRα-high expression at both the protein and mRNA level was common and concordant in VELIA trial samples and RW patient samples. The expression status was consistent in longitudinally collected samples in most pts, suggesting that IHC on the diagnostic tumor sample may effectively establish FRα protein expression status over time. High FRα mRNA expression was a negative prognostic factor in VELIA despite positive association with homologous recombination deficiency and *BRCA* mutations. Research Sponsor: None.

5592 **Poster Session**

Distinguishing tumor vs. clonal hematopoiesis (CH)–derived *TP53* and *BRCA1/2* alterations in ovarian cancer liquid biopsies with a predictive algorithm to inform clinical decision-making. First Author: Natalie Danziger, Foundation Medicine, Inc., Boston, MA

Background: CH results from mutations in hematopoietic stem cells and can occur in clinically relevant genes that are detected in liquid biopsy (LBx) of solid tumor patients. *TP53* and less frequently *BRCA1/2* can be detected in tumor and as CH potentially confounding interpretation of LBx results. Using an algorithmic method for CH prediction in a cohort of tubo-ovarian carcinoma (OC) LBx, we evaluated the prevalence of CH and non-CH alterations in *TP53* and *BRCA1/2* genes, CH frequency by circulating tumor DNA tumor fraction (ctDNA TF) and concordance in samples with paired tissue biopsies. **Methods:** Patients (pts) with a diagnosis of OC and LBx via FoundationOne Liquid CDx were included. ctDNA was quantified via TF. A machine learning model incorporating fragmentomics and other sequencing features was trained using LBx samples with equal-depth sequencing of plasma and white blood cells for short variant origin prediction (VOP) with output probabilities of origin (germline, tumor-somatic, or CH). Oncogenic short variants (i.e. mutations [mut]) with probability of being CH >0.5 were classified as CH and with probability <0.5 as tumor. Detection of CH and tumor *TP53*mut in paired tissue samples (FoundationOne CDx) was evaluated (n=355). **Results:** 1,405 pts met criteria for study inclusion. 498 (35%) had TF≥1%. Overall, *TP53*mut was detected in 74% (origin 30% tumor only, 23% CH only, and 21% both CH and tumor *TP53*mut), and 26% had no detected *TP53*mut Prevalence of VOP *TP53*mut groups varied by TF with TF<1% having more pts with no detected *TP53*mut (35% vs 9%) or only CH *TP53*mut (33% vs 4%) and fewer pts with only tumor *TP53*mut (18% vs 51%) or both CH and tumor *TP53*mut (13% vs 36%) than TF≥1%. The emerging drug target *TP53* Y220C was predicted to be CH in 42/68 (62%) LBx samples. Of the 333 individual *TP53*mut predicted to be CH on LBx, 310 (93%) were not detected in corresponding tissue. Of the 200 *TP53*mut predicted to be tumor on LBx, 176 (88%) were detected in paired tumor tissue. Overall, 9% of pts had at least one germline *BRCA1/2*mut, 4% had no germline *BRCA1/2*mut but had a tumor-somatic *BRCA1/2* alteration (51 with mut, 4 with truncating rearrangements or copy number loss), and 1% had only CH *BRCA1/2*. Of patients with non-germline *BRCA1/2*mut, 12/63 (19%) had only CH-derived *BRCA1/2*mut. **Conclusions:** >60% of OC LBx with *TP53*mut, including *TP53* Y220C, had evidence of CH contributing to cell free DNA. TF <1% was associated with higher rates of CH only *TP53*mut, but tumor-derived variants in *TP53* and other genes were still detected. The majority (93%) of TP53mut predicted to be CH were not detected in tissue biopsies of paired samples. While the majority of LBx with a *BRCA1/2*mut had germline or tumor-somatic muts, 6% of *BRCA1/2*mut LBx only harbored *BRCA1/2*mut predicted to be CH. Together, CH prediction and TF can be used to correctly contextualize LBx findings to support informed clinical decision making. Research Sponsor: Foundation Medicine Inc.

5593 **Poster Session**

Neoadjuvant pamiparib in patients with newly diagnosed advanced ovarian cancer: A single-arm, prospective phase II trial. First Author: Jing Liu, De-Department of Gynecologic Oncology, Clinical Oncology School of Fujian Medical University, Fujian Cancer Hospital, Fuzhou, China

Background: While PARP inhibitors have shown robust efficacy as maintenance therapy in newly diagnosed ovarian cancer, their potential benefit in the neoadjuvant setting remains unclear. The Chemotherapy Response Score (CRS) serves as an important prognostic indicator following neoadjuvant chemotherapy. This study aims to investigate the efficacy and safety of combining pamiparib with neoadjuvant chemotherapy and bevacizumab in patients with newly diagnosed advanced ovarian cancer. **Methods:** In this single-arm, prospective phase II trial, eligible patients have newly diagnosed FIGO stage III–IV ovarian, fallopian tube, or primary peritoneal cancer; histologically confirmed high-grade serous or endometrioid adenocarcinoma; are ineligible for optimal primary debulking; have an ECOG performance status of 0–2; are aged ≥18 years; and have measurable lesions per RECIST 1.1. The treatment regimen comprises paclitaxel (175 mg/m^2, Day 1) and carboplatin (AUC 5, Day 2) every three weeks for up to six cycles. Bevacizumab (15 mg/kg, Day 1) is given every three weeks and discontinued six weeks before surgery. Pamiparib (40 mg twice daily) is administered for up to six cycles. Patients who tolerate therapy and become surgical candidates undergo interval debulking surgery, followed by consolidation and maintenance therapy at the investigator's discretion. The primary endpoint is the proportion of patients with CRS 3, assessed via postoperative pathology. Secondary endpoints include the pathological complete response (pCR) rate, the R0 resection rate, progression-free survival (PFS), and safety. The trial is ongoing. **Results:** Between March 2023 and January 2025, 29 patients (median age 61 years, range 44–79) were enrolled. FIGO stages were III in 19 patients (65.5%), IVA in 1 (3.4%), and IVB in 9 (31.0%). Of these, 28 had high-grade serous adenocarcinoma and 1 had endometrioid adenocarcinoma. Two patients withdrew consent after receiving one cycle of neoadjuvant therapy. Of the remaining 27, 17 received four cycles, 7 received three cycles, and 3 received two cycles. Interval debulking surgery was performed in 24 patients—all achieved R0 resection—while 2 patients declined surgery and 1 had the treatment regimen changed due to elevated CA125. Among the 24 surgical cases, CRS 3 was observed in 8 (34.8%), CRS 2 in 15 (65.2%), and CRS 1 in 1 (4.3%). No patient achieved pCR. Common adverse events included leukopenia (96.6%), neutropenia (96.6%), anemia (96.6%), and thrombocytopenia (72.4%), with grade 3–4 incidences of 58.6%, 72.4%, 27.6%, and 24.1%, respectively. No treatment-related deaths were reported. **Conclusions:** The preliminary results suggest that the addition of pamiparib to neoadjuvant chemotherapy plus bevacizumab offers promising efficacy and acceptable safety in newly diagnosed advanced ovarian cancer. Further data will be provided as the study progresses. Clinical trial information: 2200059119. Research Sponsor: None.

5595 **Poster Session**

Characterization of copy number variations (CNV) patterns and pseudotime trajectories in high-grade serous ovarian cancer (HGSOC). First Author: Luca Mastrantoni, Medical Oncology, Comprehensive Cancer Center, Fondazione Policlinico Universitario Agostino Gemelli–IRCCS, Catholic University of the Sacred Heart, Rome, Italy, Italy

Background: HGSOC is characterized by genomic instability, resulting in frequent CNVs. This study aimed to characterize CNV patterns and derive pseudotime trajectories in HGSOC. **Methods:** Patients with a diagnosis of HGSOC enrolled in the CGP program (NCT06020625) at Fondazione Policlinico Universitario A. Gemelli between March 2022 and December 2023 were analyzed using the TruSight Oncology 500 (TSO500) platform, covering CNVs across 523 genes. CNVs were classified as high- or low-level based on log2 segmented CN profiles. An absolute log2 value of 0.3 was used to define the fraction of altered genes. High-variability genes were identified using a variance threshold. The Leiden algorithm was applied to identify clusters based on modularity, and connectivity structures were mapped using the partition-based graph abstraction (PAGA) method. Pseudotime trajectories were modeled using diffusion-like random walks, with the root cluster chosen based on the fraction of altered genes. Non-negative matrix factorization (NMF) was used to identify gene-level CNV patterns. The number of altered genes per region was normalized to the total number of genes per chromosome arm. Chi-squared test was used to compare categorical variables. **Results:** A total of 597 HGSOC patients, 91% of whom were FIGO stage III-IV, were included. *TP53* mutations were identified in 96% of patients. *MYC* (13%) and *CCNE1* (9%) were the most frequently high-level amplified genes. 104 highly variable genes were included in the trajectory analysis. The Leiden algorithm identified 7 patient clusters, with a significant trend observed across clusters in the fraction of altered genes ($p<0.001$, Kendall's test for trend). Clusters 2 and 3 showed the lowest fraction of altered genes and were the most connected in the PAGA analysis. Using cluster 3 as the root, trajectory analysis revealed divergent branching patterns, with a significant Spearman correlation between pseudotime and the fraction of altered genes ($\rho=0.20$, $p<0.001$). Clusters also showed different percentages of homologous recombination (HR)-proficient patients ($p<0.001$) and mutations in *BRCA1* (p=0.02) and *BRCA2* (p=0.006). NMF identified 4 gene clusters based on CNV patterns, with distinct amplification and deletion profiles. Each cluster showed a different ratio of low/high-level CNVs. In the cluster characterized by high-level amplifications, *CCNE1* and *MYC* low/high-level ratios were 1.1 and 2.0, respectively. While specific chromosomal regions were enriched in the cluster characterized by low-level CNVs ($p<0.001$), clusters with high-level CNVs lacked specific regional associations. **Conclusions:** This study suggests that distinct patterns of CNVs in HGSOC are linked with genomic and clinical features. This application of CGP for CNV profiling could offer a cost-effective strategy to stratify HGSOC patients and guide personalized treatments. Clinical trial information: NCT06020625. Research Sponsor: None.

5596 **Poster Session**

Analysis of serous carcinoma subgroup in FRUSICA-1: Fruquintinib plus sintilimab in treated advanced endometrial cancer (EMC) patients (pts) with pMMR status. First Author: Xiaohua Wu, Fudan University Shanghai Cancer Center, Shanghai, China

Background: Serous carcinoma represents approximately 10% of all EMC, has the highest recurrence rate and is responsible for a disproportionate 40% of mortality in EMC. Additionally, the overall 5-year survival rate is only 33% for stage III-IV serous carcinoma. Fruquintinib (F, a highly selective VEGFR inhibitor) plus sintilimab (S, an anti-PD-1 monoclonal antibody) was evaluated in an open-label, single-arm phase 2 pivotal study (FRUSICA-1, NCT03903705), and demonstrated encouraging efficacy and favorable safety profile in treated advanced EMC pts with pMMR (proficient mismatch repair) status (Wu X, et al; 2024 ASCO). Here, we report the ad hoc updated analysis results of the serous carcinoma subgroup (data cutoff: May 15, 2024). **Methods:** Eligible pts had histologically confirmed, previously treated advanced EMC with pMMR status confirmed by central lab. They received F (5 mg QD, 2 weeks on/1 week off, orally) plus S (200 mg, IV, Q3W) in 21-day cycles until disease progression or unacceptable toxicity. Ad hoc analyses were conducted to evaluate the primary endpoint (ORR) and secondary endpoints (DCR, DoR, TTR, PFS, OS, and safety) of F+S in pts with endometrial serous carcinoma. **Results:** As of data cutoff date (May 15, 2024), 98 EMC pts with pMMR status were enrolled and received the combination treatment (ITT population), among them, 27 pts had serous carcinoma. In these 27 pts, median age was 63.1 years, 22 (81.5%) pts were in stage IV disease, 7 (25.9%) pts had received prior bevacizumab therapy, and 5 (18.5%) pts had received prior pelvic radiotherapy. IRC-assessed ORR was 37.0% (95%CI: 19.4%, 57.6%), DCR was 88.9% (95%CI: 70.8%, 97.7%). Median DoR and TTR was 17.9 (95%CI: 3.3, not estimable [NE]) months, and 2.4 (95%CI: 1.2, 4.0) months, respectively. With the median PFS and OS follow-up of 8.3 and 21.7 months, the median PFS and OS was 8.8 (95%CI: 6.9, 19.2) months and 19.0 (95%CI: 11.4, NE) months, respectively. These efficacy findings were similar with those observed in ITT population. Grade $\geq$3 treatment related adverse events (TRAE) occurred in 63.0% pts, and the most common $\geq$Grade 3 TRAEs included palmar-plantar erythrodysesthesia syndrome (22.2%) and hypertension (11.1%). **Conclusions:** F+S was tolerable and showed clinically meaningful efficacy in endometrial serous carcinoma, characterized by durable responses that were comparable across the ITT population. Clinical trial information: NCT03903705. Research Sponsor: HUTCHMED Limited.; Innovent Biologics, Inc.

5597 **Poster Session**

A phase II trial of pembrolizumab plus olaparib for the treatment of patients with persistent/recurrent endometrial cancers. First Author: Maria M Rubinstein, Memorial Sloan Kettering Cancer Center, New York, NY

Background: Copy number-high (CNH) ECs are characterized by high levels of copy-number alterations and *TP53* mutations, and a subset may have a homologous recombination-deficiency (HRD) phenotype. The presence of an HRD-phenotype within CNH EC provides the rationale for using OLA in combination with PEM, as this exploits the mechanism of immune priming which creates further genomic instability and drives immune response. **Methods:** This is an investigator-initiated, single- arm, open-label, phase II trial evaluating the efficacy and safety of PEM + OLA in pts with persistent/recurrent *TP53*-mutant EC. Key eligibility criteria included age $\geq$18 years, measurable disease, £3 prior lines of therapy, all histologic types allowed with aberrant p53 IHC and/or mutant *TP53*. Carcinosarcomas were eligible if the epithelial component met the p53/*TP53* criteria. dMMR/MSI-H and *POLE* hotspot tumors were not eligible. All were PEM and OLA naïve and received OLA orally at 300mg every 12 hours and PEM 200mg every 3 weeks IV. Primary endpoint was objective response rate (ORR) by 24 weeks per RECIST 1.1. **Results:** At data cut off (December 12, 2024), 26 patients (pts) initiated therapy and 25 pts were evaluable for efficacy. Median age was 68 years (range:59-83). 13 pts (50%) had serous, 8 pts (31%) were mixed/high grade, and 4 pts (15%) had carcinosarcoma histology. 24 pts (92%) had 1 line of prior chemotherapy. 1 pt had a germline *BRCA2* and 1 pt had a somatic *BRCA1* mutation. 2 pts achieved complete response (CR), 6 pts achieved partial response (PR), resulting in an ORR of 32% (90% one-sided CI: 19.6-100%). Median duration of response was 10.5 months (80% CI:6.4-11.8). Median progression-free survival (PFS) was 4.8 months (80% CI: 3.6-5.9), and median overall survival (OS) was 21.2 months (80% CI: 9.4-NE). 50% (2/4) of carcinosarcoma pts achieved CR and PR, respectively. Most common $\geq$ grade 3 treatment related adverse events were anemia (12%), neutropenia (19%). 1 pt developed grade 3 pneumonitis, 2 pts developed grade 2 adrenal insufficiency. No new safety signals were identified. **Conclusions:** The combination of PEM + OLA has promising activity with durable responses observed in pts with persistent/recurrent *TP53*-mutant EC, including carcinosarcomas. Molecular subtype selection is critical in further investigation of this combination. Clinical trial information: NCT05156268. Research Sponsor: Merck; AstraZeneca.

5598 **Poster Session**

Molecular testing in primary advanced or recurrent endometrial cancer: A cost-effectiveness analysis. First Author: Yilin Chen, Curta Inc., Seattle, WA

Background: The Proactive Molecular Risk Classifier for Endometrial Cancer (ProMisE) algorithm is a classification scheme for endometrial cancer (EC) based on sequential testing for DNA mismatch repair deficiency (dMMR), *POLE* exonuclease domain mutations, and p53 mutations. The cost-effectiveness of ProMisE vs no molecular testing to inform initial systemic treatment choice in patients with stage III/IV primary advanced/recurrent EC (pA/rEC) was assessed from payer and societal perspectives. **Methods:** A hybrid model comprising a decision tree for molecular classification (ProMisE vs no testing) followed by partitioned survival models (PSM; progression-free disease, progressed disease, and death) was developed. Lifetime costs and outcomes following first-line systemic treatments were estimated using this model. Patients in the no-testing arm were assigned to receive carboplatin-paclitaxel (CP), dostarlimab + CP, pembrolizumab + CP, or hormonal therapy (everolimus/letrozole). Patients in the ProMisE arm were assigned to the same treatments or bevacizumab + CP, according to their molecular profile. Survival functions were derived from published trial results. EQ-5D-5L utility values were sourced from the RUBY trial (NCT03981796). Costs were sourced from US-focused databases and publicly available literature. The base case presented a US third-party payer perspective. A scenario analysis presented a modified societal perspective. Model outcomes were total costs, total life-years (LYs), total quality-adjusted LYs (QALYs), and the incremental cost-effectiveness ratio (ICER) of ProMisE vs no testing. An annual discount rate of 3% per year was applied to future costs and outcomes. Uncertainty was evaluated using one-way (OWSA) and probabilistic sensitivity analyses (PSA). **Results:** From a third-party payer perspective, total LYs and total QALYs were 5.36 and 4.08, respectively, with ProMisE vs 3.83 and 2.89 with no testing. Total costs were $233,989 with ProMisE vs $155,305 with no testing. Thus, incremental LYs and QALYs were 1.53 and 1.19 greater with ProMisE vs no testing; incremental costs over a lifetime were $78,684 greater with ProMisE. Assuming a cost-effectiveness threshold of $150,000 per QALY gained, ProMisE was cost-effective with an ICER of $66,321 per QALY gained compared with no testing. In the OWSA, ProMisE remained cost-effective over all parameter ranges ($\pm$10%). In the PSA, ProMisE was below the threshold of $150,000/QALY for 97.7% of iterations. From a societal perspective, lifetime costs were lower ($-$$22,973) and QALYs greater with ProMisE vs no testing. **Conclusions:** ProMisE testing is cost-effective vs no testing when using a $150,000/QALY-gained threshold. Given the heterogeneity of molecular subtypes in stage III/IV pA/rEC, molecular testing enables personalized treatment that is clinically meaningful and high value from payer and societal perspectives. Research Sponsor: GSK.

5599 Poster Session

E7386 study 102: Global dose-expansion cohort of E7386 + lenvatinib (LEN) in patients (pts) with advanced endometrial cancer (aEC) that progressed on platinum-based chemotherapy (chemo) and an anti-PD-(L)1 immunotherapy (IO). First Author: Jung-Yun Lee, Yonsei Cancer Center and Severance Hospital, Yonsei University College of Medicine, Seoul, South Korea

Background: There is a need for novel therapies for aEC that recurs after chemo and IO. LEN has antitumor activity in pts with aEC after platinum-based chemo [Vergote 2020] and is approved in combination with pembrolizumab for aEC following prior systemic therapy. E7386 is a novel oral anticancer agent that inhibits the interaction between β-catenin and CREB-binding protein. Study 102 evaluates E7386 + LEN in pts with solid tumors including aEC. A preliminary analysis of Study 102 (n=16) showed manageable safety and promising antitumor activity in aEC that progressed after platinum-based chemo and anti-PD-(L)1, including responses in pts with prior LEN. We report safety and antitumor activity for the complete dose expansion cohort (n=30) of pts with aEC. **Methods:** Pts with aEC that progressed after platinum-based chemo and IO received E7386 120 mg BID + LEN 14 mg QD (amended from 20 mg during enrollment). The primary endpoint was safety; secondary endpoints included ORR, duration of response (DOR), clinical benefit rate (CBR), and PFS by investigator per RECIST v1.1. **Results:** 30 pts were enrolled; 16 (53.3%) previously received LEN. By data cutoff (Oct 22, 2024), 9 (30.0%) pts had treatment ongoing. 29 (96.7%) Pts had treatment-related adverse events (TRAEs), most commonly vomiting (n=21, 70.0%). 12 (40.0%) Pts had grade 3 TRAEs, most commonly nausea/proteinuria/diarrhea/hypertension/anemia (n=2 each, 6.7%). No grade 4-5 AEs were observed. TRAEs led to study drug withdrawal of LEN and E7386 in 1 patient. Overall, 9 pts (3 with prior LEN) had a confirmed response (1 complete and 8 partial) for an ORR of 30.0%. In pts without prior LEN (n=14), the ORR was 42.9%. Additional data are in the Table. **Conclusions:** E7386 + LEN showed promising antitumor activity with a manageable safety profile in heavily pretreated pts with aEC following platinum-based chemo and IO. The dose-optimization phase of Study 102 for E7386 + LEN in pts with aEC is currently enrolling pts (NCT04008797). Clinical trial information: NCT04008797. Research Sponsor: None.

Age, median, yrs (range)	62.0 (36–76)
1 / 2 / 3 prior lines of therapy, n (%)	4 (13.3) / 16 (53.3) / 10 (33.3)
Endometrioid / serous / clear cell / other histology, n (%)	16 (53.3) / 3 (10.0) / 2 (6.7) / 9 (30.0)
Mismatch repair proficient / deficient / NA[a], n (%)[b]	16 (53.3) / 6 (20.0) / 8 (26.7)
***TP53* wild type/ mutation, n (%)[c]**	16 (53.3) / 14 (46.7)
Serious TRAEs, n (%)	7 (23.3)
ORR / CBR[d], % (95% CI)	30.0 (14.7–49.4) / 46.7 (28.3–65.7)
SD, n (%)	12 (40.0)
DOR, median, mos (95% CI)	8.0 (3.7–9.5)
PFS, median, mos (95% CI)	5.3 (3.0–8.9)

[a]Microsatellite instability-low (n=3); unknown (n=4); NA (n=1); [b]as reported by sites; [c]circulating tumor DNA analyses were conducted using plasma samples collected at baseline, and were annotated using OncoKB database to identify mutations in *TP53*; [d]complete response + partial response + stable disease ≥23 wks.
NA, not available.

5600 Poster Session

Time to quality of life (QoL) improvement or deterioration in patients (pts) with primary advanced or recurrent endometrial cancer (pA/R EC) treated with dostarlimab plus chemotherapy in the ENGOT-EN6-NSGO/GOG-3031/RUBY trial. First Author: Florian Heitz, Kliniken Essen-Mitte, Essen, and Center for Oncologic Surgery Charité Campus Virchow-Klinikum, Charité – Universitätsmedizin Berlin, Humboldt-Universität zu Berlin, and Berlin Institute of Health, Berlin, Germany

Background: In Part 1 of the phase 3 RUBY trial (NCT03981796) in pts with pA/rEC, dostarlimab + carboplatin-paclitaxel (DOST+CP) significantly improved progression-free survival and overall survival vs placebo (PBO)+CP. Patient-reported outcomes were a secondary endpoint. Here we present a post hoc analysis comparing timing of QoL improvement or deterioration by treatment. **Methods:** Pts were randomized 1:1 to receive DOST+CP or PBO+CP Q3W (6 cycles) followed by DOST or PBO monotherapy Q6W for ≤3 y. QoL was collected at each visit. Using data from the Sept 22, 2023 data cut (median follow-up 37.2 mo), analyses on time to first QoL improvement (TTI1) or deterioration (TTD1) were conducted for the EORTC QoL Questionnaire Core 30 (QLQ-C30) and Endometrial Cancer 24 (EN24) assessments using Cox regressions. Improvement or deterioration was classified ≥10-point change in the appropriate direction, per domain, from baseline. Results are reported for the primary study populations (overall and mismatch repair deficient/microsatellite instability-high [dMMR/MSI-H]). **Results:** A total of 494 pts were randomized, of which 118 were dMMR/MSI-H. For all QLQ-C30 and EN24 domains, TTI1 was similar between arms except pain in the overall population and role function in the dMMR/MSI-H population which reached nominal significance for earlier improvement in the DOST+CP arm (Table). The overall population had similar TTD1 in both arms, while time to deterioration was delayed in the DOST+CP arm for several domains (eg, global QoL, pain) in the dMMR/MSI-H population. **Conclusions:** With over 3 years of follow-up, DOST+CP was comparable to PBO+CP for TTI1 and TTD1 in the overall population of the RUBY trial and TTD1 was delayed in several QoL domains in the dMMR/MSI-H population. These results on patient experience of treatment further support the efficacy and safety data of dostarlimab for use in patients with pA/rEC. Clinical trial information: NCT03981796. Research Sponsor: GSK.

	Overall population			dMMR/MSI-H population		
	DOST+CP (N=245) n	PBO+CP (N=249) n	HR, *P* value	DOST+CP (N=53) n	PBO+CP (N=65) n	HR, *P* value
Time to first improvement						
Pain	154	131	1.37, *P*=0.008	32	37	1.20, *P*=0.442
Role function	111	97	1.28, *P*=0.076	32	26	1.67, *P*=0.048
Time to first deterioration						
Global QoL	194	222	0.85, *P*=0.109	33	57	0.61, *P*=0.027
Role function	203	219	0.97, *P*=0.796	36	57	0.58, *P*=0.015
Social function	200	219	0.97, *P*=0.763	33	57	0.60, *P*=0.020
Pain	202	218	0.86, *P*=0.119	37	55	0.63, *P*=0.031
Sexual interest	126	157	0.82, *P*=0.104	19	40	0.38, *P*=0.001
Sexual activity	114	143	0.81, *P*=0.102	15	34	0.42, *P*=0.005
Sexual enjoyment	105	140	0.77, *P*=0.044	13	31	0.56, *P*=0.092
Urological symptoms	173	201	0.83, *P*=0.073	30	52	0.50, *P*=0.003

n=number of patients with events.
CP, carboplatin-paclitaxel; dMMR, mismatch repair deficient; DOST, dostarlimab; MSI-H, microsatellite instability-high; PBO, placebo.

5601 Poster Session

Time to subsequent therapy in patients (pts) with primary advanced or recurrent endometrial cancer (pA/rEC) receiving dostarlimab plus carboplatin-paclitaxel (DOST+CP) compared with pts receiving placebo plus CP (PBO+CP) in the ENGOT-EN6-NSGO/GOG-3031/RUBY trial. First Author: Cara Amanda Mathews, Legorreta Cancer Center, Alpert Medical School of Brown University, Providence, RI

Background: In Part 1 of the phase 3 RUBY trial (NCT03981796), DOST+CP significantly improved progression-free survival (PFS) and overall survival (OS) in pts with pA/rEC, leading to approval for frontline treatment in the US and the EU. Time to first subsequent therapy (TFST) and second subsequent therapy (TSST) can provide further insights on the clinical benefit of a regimen as well as any clinical impact beyond first progression. **Methods:** Pts were randomized 1:1 to receive DOST+CP or PBO+CP Q3W (6 cycles) followed by DOST or PBO monotherapy Q6W for ≤3 years. Primary endpoints were PFS and OS in the overall population and PFS in the mismatch repair deficient/microsatellite instability-high (dMMR/MSI-H) population. Post hoc TFST and TSST analyses were performed at the second interim analysis (data cut, Sept 22, 2023) in the overall, dMMR/MSI-H, and mismatch repair proficient/microsatellite stable (MMRp/MSS) populations. TFST and TSST were defined as the time from randomization to the date of the first dose of first or second subsequent anticancer therapy after study drug, respectively, or death by any cause, whichever occurred first. **Results:** Of 494 pts randomized, 118 were dMMR/MSI-H and 376 were MMRp/MSS (Table). TFST and TSST were improved in all three populations. Median TFST was 5.1 and 2.5 mo longer in pts treated with DOST+CP vs PBO+CP in the overall and MMRp/MSS populations, respectively; median TFST was not reached (NR) in the DOST+CP arm of the dMMR/MSI-H population. Median TSST was extended by 11.4 and 8.1 mo in pts treated with DOST+CP vs PBO+CP in the overall and MMRp/MSS populations, respectively; median TSST was NR in the DOST+CP arm of the dMMR/MSI-H population. Hazard ratios favoring DOST+CP remained consistent between TFST and TSST in all populations evaluated. **Conclusions:** These results indicate prolonged TFST and sustained benefits through TSST with DOST+CP compared with PBO+CP across the overall, dMMR/MSI-H, and MMRp/MSS populations in the RUBY trial. Together with the statistically significant PFS and OS benefits, these findings support the frontline use of dostarlimab + CP as a standard of care in all pts with pA/rEC. Clinical trial information: NCT03981796. Research Sponsor: GSK.

	Overall		dMMR/MSI-H		MMRp/MSS	
	DOST+CP (n=245)	PBO+CP (n=249)	DOST+CP (n=53)	PBO+CP (n=65)	DOST+CP (n=192)	PBO+CP (n=184)
TFST, median (95% CI), mo	15.3 (12.3–20.1)	10.2 (9.1–10.9)	NR (19.8–NR)	10.5 (7.3–12.0)	12.7 (11.4–17.1)	10.2 (9.0–10.8)
HR (95% CI)	0.63 (0.51–0.78)		0.34 (0.20–0.57)		0.73 (0.58–0.92)	
TSST, median (95% CI), mo	31.3 (24.6–40.8)	19.9 (16.3–23.1)	NR (NR–NR)	24.0 (16.1–39.1)	26.8 (22.1–32.6)	18.7 (15.3–22.0)
HR (95% CI)	0.67 (0.53–0.85)		0.41 (0.23–0.74)		0.73 (0.57–0.94)	

NR, not reached; TFST, time to first subsequent treatment; TSST, time to second subsequent treatment.

5602 Poster Session

A phase II efficacy and safety study of HB0025 (a PD-L1/VEGF bispecific antibody) in combination with chemotherapy as first-line treatment for advanced or recurrent endometrial cancer. First Author: Judong Li, Sun Yat-sen University Cancer Center, Guangzhou, China

Background: HB0025, developed by Huaota, is a novel anti-PD-L1/VEGF bispecific antibody, with VEGFR1D2 linked at the N-terminal of anti- PD-L1 antibody. Carboplatin and paclitaxel (CP) alone or in combination with PD-(L)1 is a recommended regimen for first-line treatment of advanced endometrial carcinoma (EC) that the ORRs were 40%-68% regardless MMR status. This study assesses the efficacy and safety of HB0025 in combination with chemotherapy in EC patients. **Methods:** This open-label, multi-center phase II study of HB0025 with CP in primary advanced (stage III or IV) or first recurrent EC. Patients received 20mg/kg HB0025 every 3 weeks with CP for 4-6 cycles, followed by maintenance therapy with HB0025. The primary endpoint was objective response rate (ORR), assessed by RECIST v1.1. **Results:** As of Dec 25, 2024, 39 patients were enrolled. The median age was 59.0 years (range, 32.0-71.0). The median follow-up time was 3.3 months (range: 0.6-6.9). 31 patients had at least one post-baseline tumor assessment. The ORR and disease control rate (DCR) were 83.9% (26/31) and 100.0% (31/31), respectively. The ORR were 84.0% (21/25) in pMMR patients and 100.0% (4/4) in dMMR patients. Median duration of response (DOR) and progression-free survival (PFS) were not reached. Grade ≥3 treatment-related adverse events (TRAEs) occurred in 18 patients (46.2%), The most common grade ≥3 TRAEs (≥10%) included neutropenia (30.8%), leukopenia (15.4%), thrombocytopenia (10.3%). Any-grade immune-related adverse events (irAEs) only occurred in 2 patients (5.1%). Treatment-related serious adverse events (SAEs) were observed in 5.1% (2/39) of patients. No TRAE led to treatment discontinuation or death. Any-grade hemorrhage events occurred in 7 (17.9%) patients which were all grade 1 in severity. **Conclusions:** HB0025 in combination with chemotherapy demonstrated promising anti-tumor efficacy with good safety profile. Regardless MMR status, ORR with HB0025 plus CP improved significantly over histologically reported data. A multicentre, randomized, double-blind, controlled phase III trial will commence in 2025. Clinical trial information: NCT06758557. Research Sponsor: Shanghai Huaota Biopharmaceutical Co., Ltd.

5603 **Poster Session**

Interim safety and antitumor activity data from a phase 1 study of INCB123667, a selective CDK2 inhibitor, in patients with metastatic recurrent endometrial cancer. First Author: Domenica Lorusso, Fondazione Policlinico Universitario Agostino Gemelli IRCCS, Rome and Humanitas San Pio X, Milan, Italy

Background: Cyclin E1 (CCNE1) overexpression or *CCNE1* amplification is a predictive indicator of poor prognosis in some endometrial cancers. Inhibition of cyclin-dependent kinase 2 (CDK2), the binding partner of CCNE1, is a potential therapeutic approach for cancers with increased CCNE1 activity. In an ongoing phase 1 study, INCB123667, a potent and selective CDK2 inhibitor, has shown acceptable safety and preliminary efficacy in patients (pts) with advanced solid tumors (NCT05238922). Here, we present interim safety and efficacy data from enrolled pts with metastatic recurrent endometrial cancer. **Methods:** Eligible pts had ECOG PS ≤1 and measurable disease (RECIST V1.1). Part 1A (dose escalation) enrolled pts with advanced/metastatic solid tumors; CCNE1 amplification (locally tested) was not mandatory. INCB123667 dosing started at 50 mg and escalated to 150 mg daily. In Part 1B (dose expansion), selected RDEs from Part 1A were expanded in 6 tumor-specific cohorts, including an ongoing cohort of pts with metastatic recurrent endometrial cancer with ≤3 prior lines of systemic treatment; pts were required to have locally tested *CCNE1* amplification or centrally confirmed CCNE1 overexpression. Blood samples were collected for ctDNA analysis. **Results:** As of Dec 19, 2024, 17/30 pts with metastatic recurrent endometrial cancer have been enrolled and received INCB123667: 3 in Part 1A (50 mg bid, n=2; 150 mg qd, n=1) and 14 in Part 1B (RDEs: 50 mg bid, n=9; 125 mg qd, n=5). Histologies included carcinosarcoma (n=5), high grade serous (n=6), endometroid (n=4), clear cell (n=1), and mixed serous and clear cell (n=1). Median number of prior systemic therapies was 3 (1-5), including 11 pts pretreated with anti-PD-1 based therapy. Median duration of treatment was 2.3 months (0.3-19.4) and 4 pts (23.5%) are still on treatment. Overall, 16 pts (94.1%) had treatment-emergent adverse events (TEAEs), predominantly anemia (n=8 [47.1%]), nausea (n=6 [35.3%]); thrombocytopenia, abdominal pain, and asthenia (n=5 [29.4%] each). Seven pts (41.2%) had grade 3-4 TEAEs, including neutropenia and thrombocytopenia (n=2 each). No pts discontinued due to TEAEs. Four out of 17 pts had a partial response and 3 had stable disease. Three responders had prior immunotherapy. Cyclin E1 overexpression was present in 3/4 responders, and 2/4 had *CCNE1* amplification and overexpression. Decreases in ctDNA were observed on treatment compared with baseline. **Conclusions:** In this interim analysis, single-agent INCB123667 at various doses has shown an acceptable safety profile in pretreated pts with metastatic recurrent endometrial cancer, including expected cytopenia. The encouraging antitumor activity including post-PD-1 based therapy failure supports future development of INCB123667 in advanced/metastatic endometrial cancer. Clinical trial information: NCT05238922. Research Sponsor: Incyte Corporation.

5604 **Poster Session**

Clinicopathological features and survival outcomes in women with endometrial neuroendocrine tumors. First Author: Morgan Bou Zerdan, University of Texas MD Anderson Cancer Center, Houston, TX

Background: Endometrial neuroendocrine tumors (ENET) are rare, representing about 0.8% of endometrial cancers. Due to their aggressive nature, they are often diagnosed at an advanced stage with no standardized treatment guidelines. This study provides data on the clinicopathological features and survival outcomes of ENETs. **Methods:** This IRB-approved retrospective cohort study evaluated patients with ENETs seen at MD Anderson Cancer Center between 1994 and 2024. All patients with a histology-confirmed diagnosis of ENET were included. Descriptive statistics was used to summarize patients' clinicopathologic features. Event-free survival (EFS) was defined as the time from 1st treatment to recurrence, progression, or death. Overall survival (OS) was defined as the time from start of 1st treatment to death. Kaplan-Meier was used to estimate OS and EFS, and Cox regression was used to estimate hazard ratios for prognostic factors. **Results:** A total of 97 patients were included. Median age at diagnosis was 60 years (range: 30–85). Median BMI was 30.3 kg/m2 (range: 17.1 - 76.7). 87% were white. FIGO stage at diagnosis was 31% stage I/II, 62% stage III/IV, and 5% unknown. 84% underwent primary surgery and 16% had neoadjuvant chemotherapy. For those who underwent surgery, 59% had chemotherapy and 39% had radiotherapy. 39% of patients were NED after completion of primary treatment, 38% progressed and 23% recurred. Median follow-up was 1.4 years (range 6 days to 15.7 years). Median EFS was 0.8 years (95% CI: 0.6–1.3). On multivariate analysis, patients treated with carboplatin/paclitaxel (C/P) (HR= 0.43, 95% CI: 0.24–0.79, p =0.006), or cisplatin/etoposide (C/E) (HR = 0.35, 95% CI: 0.20–0.62, p = 0.001) had a decreased risk of recurrence compared to no adjuvant therapy. Among Stage I/II patients treated with C/E had a decreased risk of recurrence compared to patients treated with C/P (HR= 0.16 (95% CI: 0.03–0.80), p=0.025). Median OS was 1.6 years (95% CI: 1.2–3.0). Multivariate analysis showed stage III/IV disease had almost 3 times the risk of death (p=0.0008). Treatment with C+P (HR =0.40, 95% CI: 0.22–0.74, p=0.003) or C+E had a HR= 0.35 (95% CI: 0.20–0.63), p= 0.0005, compared to patients receiving other or no chemotherapy. **Conclusions:** This study highlights the aggressive nature of ENETs, often diagnosed at advanced stage. Adjuvant therapy with cisplatin/etoposide was associated with reduced the risk of death compared to other treatments. Despite chemotherapy, median EFS was short, highlighting the need for improved treatment strategies. Research Sponsor: None.

5606 **Poster Session**

Quality of life and lifestyle changes during and after therapy in women with endometrial cancer: A global study of 1,066 patients (NOGGO, ENGOT, GCIG, ENGAGe-IMPROVE/EXPRESSION XI). First Author: Lukas Chinczewski, North-Eastern German Society of Gynecological Oncology (NOGGO) & Department of Gynecology with Center for Oncological Surgery, Charité-Universitätsmedizin Berlin, Berlin, Germany

Background: Endometrial cancer (EC) affects many women worldwide, yet the impact of the disease and its treatment on symptoms, lifestyle and quality of life is still poorly understood. This study aims to explore differences in symptoms, lifestyle and perceptions between patients undergoing active treatment and those undergoing follow-up care in order to better understand their needs. **Methods:** Patients diagnosed with EC were invited to complete an 80-item survey, available in both paper and online formats. General patient characteristics such as comorbidities, tumor stage and therapy as well as symptoms during and after treatment were recorded. Participants were categorized into two cohorts: those undergoing active treatment (cohort A) and those in follow-up monitoring (cohort B). **Results:** A total of 1,660 patients with EC from 17 countries participated between December 2021 and December 2024. The median age of the participants was 66 years [range: 20–94]. Of these, 581 (35%) were in cohort A, and 1,079 (65%) were in cohort B. No differences in common comorbidities were observed between cohorts. Anticoagulant use was higher in cohort A (22.7%) compared to cohort B (17.0%), while vitamin intake was more common in cohort B (32.4% vs. 25.8%). Quality of life was lower in cohort A, with 68.5% currently experiencing side effects compared to 45.8% in cohort B. Symptoms such as fatigue (39.6% vs. 15.1%), pain (23.6% vs. 10.8%), constipation (16.7% vs. 8.3%), loss of appetite (14.6% vs. 1.6%), and weight loss (11.5% vs. 2.1%) were more prevalent in cohort A. Physical activity levels increased after diagnosis for 49.7% in cohort B compared to 34.1% in cohort A. Smoking habits remained largely unchanged, with 15.3% (cohort A) and 14.0% (cohort B) reporting current smoking, and only 4.9% of all patients quitting after diagnosis, despite 19.2% acknowledging potential benefits. Interest in nutritional counseling was higher in cohort A (26.2% vs. 21.7%). Patients in cohort A perceived EC as a greater health threat compared to their other comorbidities (69.2% vs. 43.6%). **Conclusions:** Patients tend to recover from the physical and psychological burden of active treatment, showing improvements in physical activity levels and a reduction in symptoms. However, structured programs in follow-up care are essential to achieve long-term lifestyle changes, including enhanced physical activity and dietary habits. The observed interest in nutritional counselling during treatment presents an opportunity to develop targeted interventions. Despite encouraging increase in physical activity during follow-up, additional efforts are needed to maintain and reinforce these positive changes over time. Clinical trial information: DRKS00025954. Research Sponsor: GSK Research & Development Limited.

5607 **Poster Session**

The landscape of chromosomal instability in uterine leiomyosarcoma. First Author: Sara Moufarrij, Memorial Sloan Kettering Cancer Center, New York, NY

Background: Uterine leiomyosarcoma (uLMS) has heterogeneous clinical presentations and outcomes. Although most uLMSs are associated with chromosomal instability, limited data exist on chromosomal instability patterns and their association with clinical outcomes. We sought to examine the chromosomal and genomic landscape of uLMSs and their association with survival outcomes. **Methods:** We identified 162 patients with uLMS who underwent matched tumor-normal next-generation sequencing at our institution between 2007 and 2024. Allele-specific copy number analysis was performed using the FACETS algorithm with genome-wide summary data as well as focal copy number data extracted and compared with clinical variables and survival outcomes. Appropriate statistical analyses were performed. **Results:** The median age at diagnosis was 55 years (range, 30-92). The uLMS in the cohort predominantly had conventional spindle cell morphology (n=122/162, 75%). At the time of diagnosis, 42% presented as FIGO stage I disease (68/162) followed by FIGO stage IV disease (60/162, 37%). ER expression data was available for 155 cases, with the majority of cases being ER positive (106/155, 68%). PR expression data was available for 145 cases, with most of the tumors expressing PR (87/145, 60%). The most common alterations in the cohort were *TP53* (117, 72%), *RB1* (78, 48%), *ATRX* (62, 38%), and *PTEN* (31, 19%). FACETS analysis showed that 15% of tumors (25/162) were hypoploid and 12% had whole-genome duplication (20/162). The median telomeric size was 50.1 Mb (interquartile range [IQR]: 40-59.3). The median number of telomeric allele imbalances was 6 (IQR: 3-9). The median fraction of genome with loss of heterozygosity was 0.28 (IQR: 0.14-10.5). Centromeric allele imbalance, whole-genome duplication, and fraction of copy number altered were associated with ER expression (adjusted P=0.025, 0.015, and 0.002, respectively). Multivariate survival analysis demonstrated that hypoploidy (hazard ratio: 3.3) and copy number alterations in *PIK3CD* (hazard ratio: 1.82) were associated with worse overall survival ($P<0.001$ for both). **Conclusions:** Although most uLMSs are caused by underlying chromosomal instability, the patterns in these tumors are variable, with some of the chromosomal instability configurations having prognostic implications. Further studies are needed to better understand the role of chromosomal instability in the stratification of the disease. Research Sponsor: None.

5608 Poster Session

Post-hoc analysis evaluating selinexor maintenance therapy in patients with *TP53*wt endometrial cancer: Progression-free survival by clinical factors in the ENGOT-EN5/GOG-3055/SIENDO study. First Author: Jalid Sehouli, Charité Universitätsmedizin Berlin, Berlin, Germany

Background: At primary analysis of the phase 3 study of selinexor (SEL) maintenance treatment in patients (pts) with advanced/recurrent endometrial cancer (EC), improvement in median progression-free survival (PFS) for the intent-to-treat population was not clinically meaningful. However, a promising efficacy signal was seen in a pre-specified exploratory analysis of *TP53*wt EC. We present further exploratory PFS analyses of long-term follow-up data in *TP53*wt EC. **Methods:** ENGOT-EN5/GOG-3055/SIENDO (NCT03555422) was a double-blind randomized (2:1) study evaluating SEL vs placebo as maintenance treatment in pts with advanced/recurrent EC following response to prior systemic therapy. Post-hoc exploratory subgroup analyses include response to prior systemic chemotherapy, disease at time of prior systemic therapy, Eastern Cooperative Oncology Group (ECOG) performance status, histopathological subtype at initial diagnosis, and duration of last systemic therapy. Additional subgroups will be reported at the time of presentation. **Results:** Of 263 pts in the study, 113 (43.0%) had *TP53*wt EC (SEL, n = 77; placebo, n = 36). At data cut-off (April 1, 2024), PFS subgroup analyses generally showed benefit for SEL compared with placebo in the *TP53*wt subgroup regardless of clinical factor (table). Adverse events (AEs) were generally manageable and reversible. The most common AEs (overall/Grade ≥3) with SEL were nausea (89.5%/13.2%), vomiting (60.5%/2.6%), and diarrhea (44.7%/3.9%). Dual anti-emetics were not mandated. No meaningful differences in AEs were observed across subgroups. 17.1% of pts discontinued SEL due to AEs; 1 death occurred in the placebo group. **Conclusions:** A strong PFS signal was observed in the *TP53*wt subgroup across a range of key clinical factors at long-term follow-up. Efficacy and safety of SEL maintenance therapy were generally comparable across subgroups. A phase 3 trial is ongoing to further investigate SEL as maintenance therapy in pts with advanced/recurrent *TP53*wt EC (ENGOT-EN20/GOG-3083/Xport-EC-042, NCT05611931). Clinical trial information: NCT03555422. Research Sponsor: Karyopharm Therapeutics.

	Placebo, e/n (N = 36)	SEL, e/n (N = 77)	PFS, HR vs placebo (95% CI)
Response to prior therapy: PR	18/20	31/46	0.50 (0.27, 0.92)
CR	9/16	7/31	0.24 (0.09, 0.67)
Disease at time of prior therapy: Primary Advanced	12/17	18/34	0.58 (0.28, 1.21)
Recurrent	15/18	18/41	0.29 (0.14, 0.61)
ECOG: 0	16/22	20/43	0.24 (0.11, 0.53)
1 or 2	11/14	18/34	0.50 (0.20, 1.26)
Histopathological subtype: Endometrioid	22/29	33/65	0.45 (0.25, 0.79)
Non-endometroid	5/7	5/12	0.31 (0.07, 1.34)
Duration of last systemic therapy: 12 to <24 weeks	20/27	28/60	0.45 (0.25, 0.81)
≥24 weeks	7/9	10/17	0.66 (0.25, 1.74)

CI, confidence interval; CR, complete response; ECOG, Eastern Cooperative Oncology Group; e/n, patients with events/(patients with events + patients censored); HR, hazard ratio; PR, partial response.

5609 Poster Session

The role of platinum-free interval in advanced endometrial cancer treatment: A real-world study of 843 patients. First Author: John K. Chan, Palo Alto Medical Foundation, California Pacific Medical Center Research Institute, San Francisco, CA

Background: Time between completion of last platinum-based chemotherapy (PBC) and recurrence is predictive of outcomes in recurrent ovarian cancer; however, its applicability to endometrial cancer (EC) remains uncertain. This retrospective real-world study assessed (1) platinum-free interval (PFI) duration between first-line (1L) PBC and second-line (2L) therapy for EC, (2) differences in patient (pt) and clinical characteristics by PFI, and (3) the association between PFI and outcomes. **Methods:** Using the US Flatiron Health electronic health record–derived deidentified database, we analyzed pts with advanced or recurrent EC who received 1L PBC between 1/1/2013 and 8/31/2022. PFI was defined as the time between completion of PBC and the start date of any 2L therapy. Overall survival (OS), time to treatment discontinuation (TTD), and time to next treatment (TTNT) were analyzed using Kaplan-Meier methods. The association between PFI and clinical outcomes was examined using Cox regression models. **Results:** Of 843 pts, 575 (68%), 147 (17%), and 121 (14%) had a PFI of <6, ≥6 to <12, and ≥12 months (mo), respectively. Pts with advanced disease, carcinosarcoma histology, or a history of surgery or radiation were more likely to have shorter PFI; those with a body mass index of ≥40 kg/m^2 or PD-L1 negative/not detected were more likely to have longer PFI ($P<.05$ for all). Pts with a PFI of <6, ≥6 to <12, or ≥12 mo had a median OS of 12.7, 17.9, or 30.5 mo and median TTNT of 9.8, 8.3, or 12.6 mo, respectively. Compared with pts with a ≥12-mo PFI, those with shorter PFI had a significantly higher risk of death, after adjusting for potential confounders (HR, 1.71 [95% CI, 1.27-2.29] for PFI of <6 mo; HR, 1.57 [95% CI, 1.12-2.20] for PFI of ≥6 to <12 mo). Median OS, TTD, and TTNT, and their association with PFI, are summarized in the Table. **Conclusions:** Our data suggest that platinum sensitivity is an applicable concept in advanced or recurrent EC and is associated with OS. These results may have implications for treatment selection and informing clinical trial designs in EC. Research Sponsor: GSK.

OS, TTD, and TTNT from the start of 2L treatment by PFI duration.

	Total (N=843)	PFI <6 mo (n=575)	PFI ≥6 to <12 mo (n=147)	PFI ≥12 mo (n=121)
OS, median (95% CI), mo	**14.9 (13.3-17.3)**	**12.7 (11.3-14.4)**	**17.9 (14.7-23.9)**	**30.5 (19.0-41.3)**
OS association with PFI, HR (95% CI)[a]		1.71 (1.27-2.29)[b]	1.57 (1.12-2.20)[b]	REF
TTD, median (95% CI), mo	**3.9 (3.6-4.2)**	**3.6 (3.2-3.9)**	**4.4 (3.7-5.2)**	**5.1 (4.2-6.5)**
TTD association with PFI, HR (95% CI)[a]		1.26 (1.02-1.56)[b]	1.09 (0.84-1.41)	REF
TTNT, median (95% CI), mo	**10.1 (9.0-11.1)**	**9.8 (8.5-11.3)**	**8.3 (6.9-10.3)**	**12.6 (10.3-15.9)**
TTNT association with PFI, HR (95% CI)[a]		1.20 (0.91-1.59)	1.44 (1.04-2.00)[b]	REF

[a]Cox regression models adjusted for prespecified potential confounders: PFI, race, age, ECOG performance status, histology, disease stage and grade at diagnosis, body mass index, MMR/MSI status, and receipt of 2L immunotherapy. [b]$P<.05$ vs REF.

5610 Poster Session

Adverse effects of immune checkpoint inhibitors in advanced endometrial cancer: A systematic review and meta-analysis. First Author: Fizza Mohsin, Maimonides Medical Center, Brooklyn, NY

Background: Immune checkpoint inhibitors (ICIs) in combination with chemotherapy have become a standard first-line treatment for advanced endometrial cancer with increased response rate and progression free survival. While immune-related adverse effects (irAEs) are expected, it is interesting to know the rate of all treatment-related adverse effects (TRAEs). This meta-analysis evaluates the spectrum of adverse effects related to ICIs. **Methods:** Search of the PubMed, EMBASE and Cochrane Library for publications up to December 2024 yielded six randomized controlled trials (RCTs), namely RUBY, NRG-GY018, DUO-E, KEYNOTE-B21, AtTend, and MITO END-3 for this analysis. Uniformly, the experiment arms were ICIs plus paclitaxel and carboplatin, while the control arms were same chemotherapy agents, except the DUO-E trial included Olaparib in one of the experimental arms. The primary outcomes of this study were the pooled events of TRAEs and irAEs, analyzed using a random-effects model with RevMan 5.4. **Results:** A total of 3952 patients were included from 6 RCTs. The use of ICI was associated with irAEs, such as hypothyroidism, hyperthyroidism, rash and pneumonitis(Table). It was also associated with increased incidence of serious TRAEs (RR 1.64, 95%CI 1.09-2.48, p=0.02) and higher treatment discontinuation rates (RR 1.44, 95%CI 1.13-1.83, p=0.004). There was greater risk of hematologic toxicities, including anemia (RR:1.25, 95% CI 1.05-1.49), leukopenia (RR:1.40, 95% CI 1.10-1.77), and thrombocytopenia (RR:1.43, 95% CI 1.06-1.93) in ICI arm. ICI arm was at greater risk of hepatotoxicity (RR: 4.47, 95% CI 1.17-17.15), vomiting (RR: 1.43, 95% CI 1.19-1.73) and hypertension (RR:1.93, 95% CI 1.11-3.36). There were no significant differences in peripheral neuropathy (RR:0.96, 95%CI 0.89-1.04), fatigue (RR:1.04, 95%CI 0.95-1.13), infusion related reactions (RR: 1.11, 95% CI 0.51-2.39), arthralgias (RR:0.58, 95% CI 0.21-1.57), or fatal TRAEs between the two treatment groups(RR: 1.21,95% CI 0.69-2.12). **Conclusions:** Advanced endometrial cancer treatment with ICIs is linked to a diverse array of adverse effects. Patients in the ICI and chemotherapy arm demonstrated an increased risk of hematologic toxicity, hepatotoxicity, irAEs and higher treatment discontinuation rate compared to chemotherapy alone. However, no notable difference was observed in fatal TRAEs. Research Sponsor: None.

	Events	Number of studies (n)	Number of patients included (N)	Risk Ratio, 95% Confidence Interval	P value
TRAEs	Any grade	6	3830	1.00 [0.99-1.00]	0.25
	Serious	5	2095	1.64 [1.09-2.48]	0.02
	Leading to discontinuation of treatment	4	2524	1.44 [1.13-1.83]	0.004
Immune mediated	Fatal	5	2095	1.21 [0.69-2.12]	0.51
	Any irAE	4	2524	2.30 [1.59-3.31]	<0.00001
	Rash	4	2159	2.96 [1.31-6.69]	0.009
	Hyperthyroidism	4	2802	3.32 [2.22-4.97]	<0.00001
	Hypothyroidism	6	3830	3.98 [2.87-5.52]	<0.00001
	Pneumonitis	4	2802	2.48 [1.18-5.18]	0.02

5611 Poster Session

The impact of prior neoadjuvant/adjuvant chemotherapy (NACT/ACT) on fruquintinib plus sintilimab outcomes in advanced endometrial cancer (EMC) patients with pMMR status: A subgroup analysis of FRUSICA-1. First Author: Jing Wang, Hunan Cancer Hospital, Changsha, China

Background: FRUSICA-1 (NCT03903705) was an open-label, single-arm, pivotal phase 2 study to evaluate the efficacy and safety of fruquintinib (F, a highly selective VEGFR inhibitor) plus sintilimab (S, an anti-PD-1 monoclonal antibody) in previously treated advanced EMC patients (pts) with pMMR (proficient mismatch repair) status. The primary results of FRUSICA-1 have demonstrated encouraging efficacy (objective response rate [ORR]: 35.6%; median progression-free survival [PFS]: 9.5 mo; median overall survival [OS]: 21.3 mo) in the overall population (Wu X, et al; 2024 ASCO). In this updated exploratory analysis (data cutoff: May 15, 2024), we evaluated the association between prior NACT/ACT and clinical outcomes in this study. **Methods:** Pts who had histologically confirmed advanced EMC with pMMR status confirmed by central lab and had progression on 1 standard systemic therapy were eligible. They received F (5 mg QD, 2 weeks on/1 week off, orally) plus S (200 mg, IV, Q3W) in 21-day cycles until disease progression or unacceptable toxicity. The efficacy subgroup analysis was performed by prior NACT/ACT (Yes vs No). **Results:** As of May 15, 2024, a total of 98 EMC pts with pMMR status were enrolled and received the treatment with the median follow-up of 22.0 mo (95%CI: 20.5, 23.7). Based on pts with or without prior NACT/ACT (Yes vs No = 47 pts vs 51 pts), the baseline demographics and disease characteristics were well balanced. Independent Review Committee (IRC)-assessed ORR (34.0% vs 31.4%) and disease control rate (DCR, 85.1% vs 82.4%) were comparable, respectively. Median duration of response (DoR) in pts with NACT/ACT was 11.1 mo while not reached for pts without NACT/ACT. Median PFS were 7.1 mo (95%CI: 4.7, 13.8) vs 9.5 mo (95%CI: 5.5, not estimable), respectively with two 95%CIs highly overlapped. The 6-mo PFS rates were also comparable at 56.8% vs 59.7%. Median OS pending maturity, the 18-mo OS rates were nearly identical (58.7% vs 59.1%). **Conclusions:** In this updated exploratory analysis of pts with advanced EMC enrolled in FRUSICA-1 study treated with F plus S, encouraging outcomes were achieved in the overall population, including patients who had received prior NACT/ACT and those who had not, with durable and clinically meaningful responses. Clinical trial information: NCT03903705. Research Sponsor: HUTCHMED Limited; Innovent Biologics, Inc.

5612 Poster Session

SHR-A1811 in patients (pts) with HER2-expressing advanced gynecological cancers (Gynecol C): A phase 2 study. First Author: Beihua Kong, Qilu Hospital of Shandong University, Jinan, China

Background: SHR-A1811 is a novel an antibody-drug conjugate consisting of a humanized HER2-directed monoclonal antibody, cleavable tetrapeptide-based linker, and DNA topoisomerase I inhibitor. We assessed SHR-A1811 in HER2-expressing advanced Gynecol C. **Methods:** Pts with ovarian cancer (OC) that had recurrence within 6 mo of last platinum-based therapy, and recurrent/metastatic endometrial cancer (EC) or cervical cancer (CC) that failed standard therapy were enrolled. Pts received SHR-A1811 at 4.8 or 6.4 mg/kg (Q3W, IV). The primary endpoint was ORR per RECIST v1.1. **Results:** As of Dec 25, 2024, 108 pts were enrolled (ECOG PS 1: 71.3%, prior VEGFR inhibitors: 53.7%, prior immunotherapies: 24.1%) including 46 pts with OC, 27 EC, and 35 CC. Rate of pts with HER2 IHC 3+ was 10.9%, 14.8%, and 31.4%; IHC 2+ was 54.3%, 70.4%, and 37.1%, respectively. The median follow-up was 8.1 mo (IQR, 4.7–10.7). For pts with OC, EC, and CC, ORR was 56.1%, 50.0%, and 63.6%, and PFS was 8.5 mo (95% CI, 5.7–NR), 5.6 mo (95% CI, 4.1–NR), and 10.7 mo (95% CI, 6.9–NR), respectively. In the 4.8 mg/kg cohort, for OC, EC, and CC, ORR was 56.8%, 52.0%, and 61.3%, and PFS was 8.5 mo (95% CI, 5.6–11.3), 7.2 mo (95% CI, 4.1–NR), and 10.7 mo (95% CI, 6.2–NR), respectively. Among OC, EC, and CC pts, ORR was 66.7% in 30 pts, 43.5% in 23 pts, and 66.7% in 24 pts with HER2 IHC 2+/3+, respectively. Additional antitumor activities are shown in Table. Treatment-related adverse events (TRAEs) of grade ≥3 occurred in 84 (77.8%) pts, with the most common being decreased neutrophil count (62.0%), decreased white blood cell count (48.1%), and anemia (28.7%). No TRAEs leading to discontinuation of treatment or deaths were reported. **Conclusions:** SHR-A1811 showed encouraging activity and manageable safety profile in pts with HER2-expressing advanced Gynecol C. Clinical trial information: NCT05896020. Research Sponsor: Jiangsu Hengrui Pharmaceuticals Co., Ltd.

Antitumor activity.

	4.8 or 6.4mg/kg				4.8 mg/kg			
	OC (N=46)	EC (N=27)	CC (N=35)	Total (N=108)	OC (N=42)	EC (N=26)	CC (N=33)	Total (N=101)
ORR[a]	23 (56.1)	13 (50.0)	21 (63.6)	57 (57.0)	21 (56.8)	13 (52.0)	19 (61.3)	53 (57.0)
DCR[a]	36 (87.8)	24 (92.3)	31 (93.9)	91 (91.0)	33 (89.2)	23 (92.0)	29 (93.5)	85 (91.4)
DOR, mo[b]	8.5 (5.8–NR)	7.0 (2.8–NR)	9.5 (5.7–NR)	8.5 (6.7–NR)	8.5 (5.8–NR)	7.0 (2.8–NR)	9.5 (4.2–NR)	8.5 (6.9–NR)
TTR, median (range), mo[b]	2.7 (1.1–4.4)	1.5 (1.1–5.3)	1.4 (1.2–5.4)	1.4 (1.1–5.4)	2.7 (1.1–4.4)	1.5 (1.1–5.3)	1.4 (1.2–5.4)	1.4 (1.1–5.4)
PFS, mo[c]	8.5 (5.7–NR)	5.6 (4.1–NR)	10.7 (6.9–NR)	8.3 (6.8–11.3)	8.5 (5.6–11.3)	7.2 (4.1–NR)	10.7 (6.2–NR)	8.5 (6.2–11.3)
6-mo OS rate, % (95% CI)[c]	89.5 (74.5–95.9)	85.4 (60.3–95.2)	93.6 (76.8–98.4)	90.2 (82.0–94.8)	91.2 (75.1–97.1)	84.6 (58.4–94.9)	93.2 (75.4–98.3)	90.5 (81.8–95.1)

Data are n (%), median (95% CI), or otherwise indicated.
[a]In pts with baseline and at least one post-baseline assessments; N was 41, 26, 33, 100, 37, 25, 31, and 93.
[b]In pts with confirmed CR or PR; N was 23, 13, 21, 57, 21, 13, 19, and 53.
[c]In full analysis set; N was 46, 27, 35, 108, 42, 26, 33, and 101.

5613 Poster Session

Evaluating the safety and efficacy of CRISPR/Cas9-modified tumor infiltrating lymphocytes (GT300) as monotherapy in advanced solid tumors. First Author: Pin Wang, Grit Biotechnology, Shanghai, China

Background: Adoptive cell therapy using autologous tumor-infiltrating lymphocytes (TILs) has shown promising results in melanoma patients. However, its effectiveness in other solid tumors, especially "cold" tumors, is still being explored. GT300, a next-generation TIL product, is engineered using CRISPR/AaCas12bMax to disrupt two key immunoregulatory targets identified through genome-wide CRISPR screening. This modification aims to enhance TIL function and overcome the suppressive tumor microenvironment, potentially expanding its use to cold tumors like ovarian and colorectal cancer. Therefore, two studies were initiated to assess the preliminary safety and efficacy of GT300 in advanced solid tumors. **Methods:** The first-in-class study aims to enroll patients with advanced, treatment-refractory solid tumors, focusing on gynecological cancers. After determining the optimal biological dose (OBD), a monotherapy expansion phase will begin for patients with various solid tumors. Participants undergo nonmyeloablative (NMA) lymphodepletion and receive an infusion of the G300 TIL product, followed by IL-2 administration. **Results:** As of September 5, 2024, five patients have been enrolled in these two studies, with a median age of 55 years and a median of two prior therapy lines. After FC lymphodepleting chemotherapy, patients received GT300 infusions at doses of $\geq 1 \times 10^9$ viable cells. Four out of five patients subsequently received IL-2. Most adverse events (AEs) were Grade 1 or 2, with Grade 3/4 AEs including fever, rash, dental ulcer, anemia, and decreased platelet count. No DLTs were observed. The ORR was 60% (3/5 evaluable patients). Two patients (40%) achieved CR in cervical cancer and peritoneal papillary serous carcinoma, while one patient (20%) with ovarian cancer had a PR. Despite variations in TIL doses (3.2×10^9 to 1.90×10^{10} cells) and IL-2 regimens (up to 3.0×10^5 IU/kg), robust TIL proliferation was consistently observed post-infusion. Responders showed biphasic CD45+CD3+ T cell expansion, indicating sustained immune activation. An early increase in IFN-γ levels from days 3 to 10 strongly correlated with positive outcomes, suggesting its potential as an early efficacy biomarker. **Conclusions:** In patients with previously treated gynecological cancer, GT300, administered after FC lymphodepleting chemotherapy and followed by higher-dose IL-2, exhibited a manageable safety profile. GT300, a CRISPR/Cas9 dual knockout anti-exhaustion TIL product, showed favorable clinical outcomes with a 60% objective ORR, including 40% CR and 20% PR, with no DLTs observed. The infusion led to robust TIL expansion and IFN-γ secretion. These promising results indicate favorable long-term survival outcomes, durable responses, and no long-term safety concerns associated with GT300. Clinical trial information: NCT06145802, NCT06397963. Research Sponsor: None.

5614 Poster Session

Feasibility of ChatGPT-4o in management of gynecologic oncologic patients in the emergency department. First Author: Junhwan Kim, Center for Gynecologic Cancer, National Cancer Center, Goyang-Si, Korea, Republic of

Background: Recent studies have highlighted the diagnostic and reasoning capabilities of ChatGPT in medicine. This study aims to evaluate the feasibility of using ChatGPT-4o to assist in managing emergency care for gynecologic oncologic patients, focusing on its potential to support physicians and generate patient education materials. **Methods:** We retrospectively reviewed real cases of gynecologic cancer patients who visited the emergency department of the National Cancer Center in Korea between 2005 and 2024 and identified 15 common cases for evaluation. For each case, four physicians (two gynecologic oncologists and two obstetrics and gynecology residents) assessed the cases based on nine criteria: relevance of differential diagnosis, relevance of suggested necessary examinations, speed in suggesting differential diagnoses and necessary examinations, relevance of examination interpretations, relevance of the final diagnosis, relevance of treatment plans, speed in suggesting the final diagnosis and treatment plans, relevance of prescribed orders, and speed of prescribing orders. Each criterion was scored on a scale of 0, 1, or 2, and total scores were calculated along with the total time taken to generate diagnoses, treatment plans, and actual order prescriptions. The same cases were then evaluated using ChatGPT-4o, with prompts specifically developed to enable consistent assessment. In addition to the nine criteria, ChatGPT-4o was also evaluated on the relevance and speed of patient education, with scores assigned on a scale of 0, 1, or 2. Furthermore, physicians provided feedback on their satisfaction with ChatGPT-4o's generated answers and patient education materials using the same scale. **Results:** ChatGPT-4o demonstrated a mean score of 17.1 (range, 14–18) across the 15 cases, outperforming physicians, who achieved a lower mean score of 13.4 (range, 5–17). The mean time taken by ChatGPT-4o to respond to all nine criteria was 108.4 (range, 69–142) seconds, significantly faster than physicians, who required an average of 391.4 (range, 126–786) seconds. For relevance of patient education, ChatGPT-4o achieved a mean score of 1.9 (range, 1–2) across the 15 cases, with response times consistently under 1 minute per cases. Physicians rated their satisfaction with ChatGPT-4o's generated diagnoses, treatment plans, and order recommendations at a mean score of 1.9 (range, 1–2). Similarly, their satisfaction with ChatGPT-4o's patient education materials was rated at a mean score of 1.8 (range, 1–2). **Conclusions:** ChatGPT-4o demonstrates feasibility as a promising supportive tool for managing emergency care in gynecologic oncologic patients, offering fast and relevant diagnoses, treatment plans, and patient education materials. Future research warrants developing practical applications and conducting prospective evaluations to optimize its integration in emergency departments. Research Sponsor: None.

5615 Poster Session

Clinical and demographic profiles and predictors of survival in epithelioid trophoblastic tumors: A population-based analysis. First Author: Zhuoran Xiao, Tulane School of Public Health, New Orlean, LA

Background: Epithelioid trophoblastic tumor (ETT) is a rare form of gestational trophoblastic neoplasia. Existing studies on ETT have been limited by small sample sizes and a lack of robust socioeconomic and demographic analyses. This study aims to characterize the clinical and demographic profiles of ETT patients and evaluate survival outcomes. **Methods:** ETT cases diagnosed between 2000 and 2021 were extracted from the Surveillance, Epidemiology, and End Results (SEER) database. Survival outcomes were analyzed with Kaplan-Meier survival analysis, and the statistical significance of key variables was assessed using the log-rank test. Hazard ratios (HR) were calculated using Cox proportional hazards regression models. This data is compared to what is currently known based on the published literature. **Results:** A total of 100 patients with ETT were identified. The majority of cases (76%) were in patients aged 30 to 49 years. The cohort was predominantly white race (60%), with 72% identifying as Non-Spanish-Hispanic-Latino. Of patients with staging information (57%), 30% had localized disease. Socioeconomic analysis revealed that 60% of patients had a median household income below $80,000 annually, and 71% resided in metropolitan areas with populations exceeding one million. Black patients had risk of mortality compared to white patients [HR = 3.233; 95% CI: (1.021, 10.240), p = 0.046]. Patients with distant metastases or nodal involvement had significantly worse survival outcomes compared to those with localized disease [HR = 11.813; 95% CI: (1.379, 101.190); p = 0.024]. Among treatment modalities, 65% of patients underwent surgery, 33% received chemotherapy, and 3% received radiation therapy. Patients who received chemotherapy demonstrated a higher risk of mortality compared to those who did not [HR = 5.937; 95% CI: (1.788, 19.710); p = 0.004]. **Conclusions:** ETT patients exhibit significant survival differences based on race, distant disease at diagnosis, and chemotherapy use. These findings highlight the importance of addressing racial disparities, early diagnosis, and optimizing treatment strategies to improve outcomes for this rare malignancy. Further research is warranted to refine our understanding and guide clinical management. Research Sponsor: None.

5616 **Poster Session**

Effects of surgery on the prognosis of patients with locally advanced vulva cancer: A retrospective study of the SEER database and a Chinese multi-centre registry. First Author: Yuqin Wang, Clinical Oncology School of Fujian Medical University, Fujian Cancer Hospital, Fuzhou, China

Background: Vulva cancer is a rare gynecologic oncology, and lacks uniform recommendations in current guidelines, especially for locally advanced cases. This study seeks to explore prognostic factors and optimize treatment strategies for vulva cancer. **Methods:** This multicenter, cross-ethnic retrospective study collected patient data from 2003–2023 in the China Multi-center Registry and from 2004–2021 in the SEER database. Only pathologically confirmed cases of vulva cancer were included in the analysis. Patients lost to follow-up, under 20 years of age, were excluded. Survival outcomes were compared using Kaplan-Meier analysis, while prognostic factors were evaluated through the Cox proportional hazards model. Baseline characteristics between groups were balanced using inverse probability of treatment weighting (IPTW). The primary endpoint of the study was overall survival. **Results:** A total of 19,682 patients with vulva cancer were included in the study, comprising 604 patients in the Chinese cohort and 19,078 patients in the SEER cohort. Multivariate Cox regression models (China cohort: HR=0.46,95%CI:0.33-0.64, $P < 0.001$; SEER cohort: HR=0.43,95% CI:0.41–0.46, $P < 0.001$) indicated that surgery was associated with improved prognosis. In both cohorts of patients with locally advanced vulva cancer, surgery remained a protective prognostic factor (China cohort: HR =0.43,95%CI:0.27-0.69, $p < 0.001$; SEER cohort: HR=0.52 ,95%CI:0.47-0.57, $p < 0.001$). And the protective effect of surgery in patients with locally advanced disease remained significant after IPTW (China cohort: HR= 0.38 ,95%CI:0.24-0.63, $p < 0.001$; SEER cohort: HR=0.50 ,95%CI:0.44–0.56, $p < 0.001$). **Conclusions:** Although guidelines recommend non-surgical treatment as the preferred approach for patients with locally advanced vulva cancer, this large-scale, multicenter, cross-ethnic retrospective study demonstrates that surgery significantly improves prognosis and offers new insights for clinical practice. Research Sponsor: None.

5617 **Poster Session**

Temporal and regional mortality trends due to pulmonary embolism in female patients with genital cancers in the United States from 1999 to 2020. First Author: Marcos Alberto Jr., Indiana University Southwest Internal Medicine, Evansville, IN

Background: The involvement of pulmonary vessels by tumor emboli has been described from different primary sites of malignancy. Pulmonary embolism (PE) is a severe and potentially fatal complication in patients with female genital cancers, including ovarian, cervical, uterine, and vulvar malignancies. These cancers, along with associated treatments such as major abdominal surgery, chemotherapy, and hormone therapy, significantly increase the risk of venous thromboembolism (VTE), including PE. While previous studies detail the advancements in cancer detection and treatment, temporal and regional trends of PE-related mortality among female genital cancer patients remain poorly characterized. **Methods:** This retrospective study analyzes national mortality data from the CDC WONDER database to assess mortality trends from 1999 to 2020 across different demographic subgroups in the United States. Patients with a known history of genital cancer were identified and PE related mortality data was retrieved. Age-adjusted mortality rates (AAMRs) per 100,000 individuals were calculated further stratified based on sex, age (15-64 years and >64 years), race and census region. Rstudio was used to perform t-test and Mann Kendall test. **Results:** From 1999 to 2020, a total of 13,692 deaths were reported in female genital cancer associated pulmonary embolism in the US (AAPC: 0.421 (95% CI: 0.414-0.428)). The AAMR has risen from 0.363 in 1999 to 0.590 in 2020, indicating a worsening trend over the study period (τ: 0.680, $p<0.001$). AAMR varied greatly by region, with the Northeast having the highest AAMR (9.928). This was followed by the West (0.488), Midwest (0.43) and South (0.366). Black females had consistently higher AAMR than white females, with rates of 0.763 vs. 0.329 in 1999 and 0.976 vs. 0.523 in 2020, respectively. Females older than 65 years demonstrated a much higher total AAMR (1.506) compared to females between the ages of 15 and 65 (0.212) ($p<0.001$). Within the age group of 15-25 years, black females had higher AAMRs compared to white female ($p<0.001$). Black females of the age group >65 years demonstrated much higher mortality (total AAMR: 2.745) than white females of the same age group (1.419), and the highest AAMR overall ($P<0.001$). **Conclusions:** The analysis of AAMR for female genital cancer associated pulmonary embolism highlights a concerning disparity in this dangerous cancer related complication, particularly after 2015. This underscores the need for greater attention to be directed towards reproductive health and cancer related complications faced by black women and to address systematic inequalities in intervention and healthcare access. This can improve early detection and timely interventions in order to reduce mortality and improve outcomes for these patients. Research Sponsor: None.

TPS5618 **Poster Session**

TroFuse-020/GOG-3101/ENGOT-cx20: A phase 3, randomized, active-controlled, open-label, multicenter study comparing sacituzumab tirumotecan monotherapy vs treatment of physician's choice as second-line treatment for recurrent or metastatic cervical cancer. First Author: Ritu Salani, Department of Obstetrics and Gynecology, University of California Los Angeles, Los Angeles, CA

Background: Sacituzumab tirumotecan (sac-TMT; formerly MK-2870/SKB264) is an antibody–drug conjugate comprising a trophoblast cell-surface antigen 2 (TROP2)–antibody, a hydrolytically-cleavable linker, and the cytotoxic drug KL610023 (average drug/antibody ratio, 7.4). In an ongoing phase 1/2 study (MK-2870-001), sac-TMT monotherapy showed promising antitumor activity in participants with locally advanced unresectable/metastatic solid tumors that were refractory to standard therapies. This phase 3, randomized, open-label, multicenter study (NCT06459180) evaluates the efficacy and safety of sac-TMT monotherapy vs treatment of physician's choice (TPC) as second-line treatment in participants with recurrent/metastatic cervical cancer. **Methods:** Eligible participants are aged ≥18 years with progressive recurrent/metastatic cervical cancer, measurable per RECIST version 1.1 by the investigator, and had received 1 prior line of platinum doublet chemotherapy (±bevacizumab) and anti–PD-1/anti–PD-L1 therapy as a part of cervical cancer regimens. Participants must provide tissue from a core or excisional biopsy of a not previously irradiated tumor lesion. Approximately 666 participants will be randomly assigned 1:1 to receive either sac-TMT 4 mg/kg intravenously (IV) Q2W or TPC (pemetrexed 500 mg/m^2 IV Q3W; tisotumab vedotin 2 mg/kg IV Q3W; topotecan 1 or 1.25 mg/m^2 on days 1–5 of each 3-week treatment cycle; vinorelbine 30 mg/m^2 on days 1 and 8 of each 3-week treatment cycle; gemcitabine 1000 mg/m^2 on days 1 and 8 of each 3-week treatment cycle; or irinotecan 100 or 125 mg/m^2 on days 1, 8, 15, and 22 of each 6-week treatment cycle). Tumor imaging will be performed ≤28 days before treatment allocation/randomisation, then Q9W until week 54 and Q12W thereafter. The primary endpoint is OS; secondary endpoints include PFS assessed by blinded independent central review, objective response, duration of response, safety, time to deterioration, and patient-reported outcomes. Enrollment began in Q3 2024. Clinical trial information: NCT06459180. Research Sponsor: Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA.

TPS5619 **Poster Session**

Randomized phase II study to evaluate treatment with induction therapy with nivolumab plus ipilimumab, followed by nivolumab with chemoradiotherapy versus standard of care with chemoradiotherapy for women with locally advanced cervical cancer. First Author: Henrique Alkalay Helber, HIAE, Sao Paulo, Brazil

Background: Cervical cancer (CC) is one of the leading cause of death in developing countries, largely due to insufficient HPV vaccination coverage. The majority of patients are diagnosed with locally advanced disease. Current standard of care (SOC) for those patients is cisplatin-based chemoradiotherapy (P-XRT). Recent advances have shown improved overall survival (OS) with addition of pembrolizumab administered concurrently with P-XRT and as adjuvant therapy (Lorusso, Domenica et al., KN A18 - LANCET, 2024) as well as neoadjuvant chemotherapy with carboplatin and paclitaxel (McCormick et al, LANCET, 2024). In the metastatic setting, the phase I/II CheckMate 358 trial demonstrated high responses rates with the combination of nivolumab (N) and ipilimumab (I) (Oaknin Ana et al, LANCET, 2024). Currently, no trials have evaluated the use of immune checkpoint inhibitors as a neoadjuvant and concurrent strategy with P-XRT in locally advanced CC. Therefore, we hypothesized that induction N/I followed by nivolumab and P-XRT in locally advanced CC can improve clinical outcomes with a manageable toxicity profile. **Methods:** This is a phase II, randomized, clinical trial, including 116 patients with locally advanced cervical cancer (FIGO stages IIB-IVA). Treatment arms: Patients who are eligible for the study was randomized to one of the following treatment arms: - Experimental: Induction Nivolumab (N) 1mg/kg IV plus Ipilimumab (I) 3mg/kg IV every 3 weeks x 4 cycles followed by N 240mg every 2 weeks concurrently with P-XRT. - Control: P-XRT. Endpoints: Primary endpoint: 3-year Progression-Free Survival (PFS). Secondary endpoints: 3-year overall survival (OS), complete response rate (CRR), objective response rate (ORR), duration of response (DoR), health related quality of life (HRQoL) and toxicity profile. Statistics considerations: A total of 116 participants were randomized 1:1 (experimental arm Vs SOC), considering a dropout rate of 10%. A two-sided log-rank test at a 0.05 significance level provides 80% power to detect a difference between a 3-year PFS rate of 75% in the experimental arm versus 50% in the control arm. This calculation assumes a recruitment period of 24 months, and a total study duration of 60 months (up to 24 months of recruitment and 36-month follow-up after the end of treatment). Current Status: The study is ongoing, and the recruitment phase has been completed. The first patient was enrolled in September 2022, and the last patient in April 2024. All participants have finished the treatment phase and are currently in the follow-up phase. Final study results are expected by mid-2028 Clinical trial information: NCT05492123. Research Sponsor: BRAVA institute (BRAZIL).

TPS5620 **Poster Session**

A prospective, randomized control trial of concurrent paclitaxel and carboplatin along with radiotherapy versus concurrent cisplatin along with radiotherapy in carcinoma cervix patients at a tertiary care hospital of central India. First Author: Praghnya Subhash Tejale, Government Medical College, Nagpur, India

Background: In India, cervical cancer accounted for 9.0% of all cancers and 18.3% (127,526) of new cases in 2022 as per GLOBOCAN. It is leading cause of cancer-related deaths in women in low and middle-income countries. Concurrent chemoradiotherapy (CCRT) with Cisplatin is standard for LACC but is often limited by nephrotoxicity & ototoxicity. Hence, the combination of paclitaxel and carboplatin has been explored for its potentially favorable toxicity profile and effectiveness. Thus comparative analysis of two concurrent chemoradiotherapy regimens examining their efficacy, toxicity profiles and suitability for patients. is assessed. The results can have significant implications for clinical practice, particularly in resource-limited settings where treatment- related toxicity and patient compliance are critical concerns. **Methods:** Simple randomization with open label study conducted to compare the efficacy and toxicity of concurrent radiotherapy with paclitaxel and carboplatin versus concurrent radiotherapy with cisplatin in patients with locally advanced cervical cancer. Conducted in Department of Radiation Oncology, GMC Nagpur from July 2024 to December 2026. Sample size 100 (50 each group assuming 10% dropout) Inclusion criteria: Age 18-70 years, histologically confirmed diagnosis, FIGO stage IB1 to IVA, ECOG 0-3, written informed consent, baseline audiometry. Exclusion criteria: Prior chemo-radiotherapy for cervical cancer, severe comorbid conditions, pregnant or breastfeeding women, and known hypersensitivity to study drugs. Intervention: Arm A: Concurrent Cisplatin with EBRT to pelvis with dose of 45-50 Gy/ 23-25 fractions followed by brachytherapy. Chemotherapy: Cisplatin 40 mg/m² IV weekly for up to 6 cycles. Arm B: Concurrent RT with Paclitaxel and Carboplatin. RT: Same as Arm A. Chemotherapy: Paclitaxel 50 mg/m² and carboplatin AUC 2 IV weekly for up to 6 cycles. Primary Outcomes: Locoregional control (RECIST criteria at 3,6,12 and 24 months post-treatment). Secondary Outcomes: Overall Survival, Progression-Free Survival, Disease-free survival, Toxicity, Quality of Life (EORTC QLQ-C30) questionnaire. Data Collection and Analysis: Baseline assessments-Medical history, physical examination, laboratory tests, imaging studies. During treatment- Weekly clinical assessments, laboratory tests and toxicity evaluations. Follow-up: Clinical assessments, Imaging studies and QoL at 0, 3, 6, 12 and 24 months post-treatment. Ethical Considerations: Ethical approval is obtained from relevant institutional review boards on 04/12/2024. Patients are under accrual. Research Sponsor: None.

TPS5621 **Poster Session**

ANA trial: Development of a diagnostic test and dynamic evaluation of ctDNA to optimize follow-up and tailor treatment in patients with HPV-related cervical and anal tumors. First Author: Renata Colombo Bonadio, Instituto do Câncer do Estado de São Paulo, Faculdade de Medicina da Universidade de São Paulo, São Paulo, Brazil

Background: Cervical and anal cancers treated with definitive radiotherapy (RT), with or without chemotherapy, frequently exhibit persistent disease or recurrence. Post-treatment imaging—the current gold standard for assessing response—faces limitations due to local inflammatory processes, necessitating repeated imaging and invasive biopsies, which increase complexity and costs. Circulating tumor DNA (ctDNA) has emerged as a promising biomarker for assessing recurrence or disease progression in HPV-associated cancers. This study proposes the development of a low-cost HPV ctDNA test. Additionally, it aims to evaluate ctDNA's accuracy compared to standard imaging and its role in guiding immunotherapy for patients at high risk of recurrence. **Methods:** ANA trial seeks to establish a novel, affordable diagnostic approach to optimize follow-up and treatment strategies for HPV-associated cancers, potentially improving outcomes while reducing costs. This is a prospective, single-center study with two components: 1. Non-interventional phase: Development and validation of a low-cost HPV ctDNA test. The test's accuracy will be compared with commercially available ctDNA tests and standard imaging in monitoring patients with HPV-associated cervical and anal cancers post-definitive RT or chemoradiotherapy. 2. Interventional phase (Phase II trial): A single-arm study evaluating the efficacy of early complementary immunotherapy in patients with persistent ctDNA positivity post-treatment. Eligibility criteria include patients with HPV-positive cervical or anal cancers undergoing definitive RT or chemoradiotherapy. The study will enroll 110 participants, stratified into two groups based on post-treatment ctDNA results: 68 ctDNA-negative patients for serial ctDNA monitoring and 16 ctDNA-positive patients for Phase II immunotherapy intervention. In this phase, patients will receive Pembrolizumab 200mg IV every 3 weeks for twelve months. Endpoints: The primary endpoint for the non-interventional phase is the sensitivity and specificity of the HPV ctDNA test compared to commercial ctDNA tests and imaging. Secondary outcome is cost-effectiveness of HPV ctDNA as a follow-up tool. For the interventional phase, the primary endpoint is the 6-month disease progression rate in ctDNA-positive patients receiving immunotherapy. Secondary outcomes include recurrence rates, and survival outcomes. Clinical trial information: NCT06640283. Research Sponsor: National Council for Scientific and Technological Development (CNPq); Process No. 444027/2023-8.

TPS5622 **Poster Session**

A phase II, single-arm, open-label clinical trial to evaluate the combination of cadonilimab injection and gut microbiota modulation in the treatment of persistent, recurrent, or metastatic cervical cancer following second-line therapy. First Author: Qin Xu, Department of Gynecologic Oncology, Clinical Oncology School of Fujian Medical University, Fujian Cancer Hospital, Fuzhou, China

Background: Current treatment options for cervical cancer include surgery, radiotherapy, and chemotherapy. For persistent, recurrent, or metastatic disease, systemic therapies such as targeted agents and immune checkpoint inhibitors (ICIs) play a crucial role. The NCCN 2023.V1 guidelines recommend PD-1/CTLA-4 bispecific antibody Cadonilimab as a second-line option for recurrent or metastatic cervical cancer. In April 2024, China's NMPA accepted an application for Cadonilimab plus platinum-based chemotherapy (± bevacizumab) as second-line treatment, based on the global phase III AK104-303 trial. Cadonilimab monotherapy demonstrated a 33.0% objective response rate (ORR) and a 12% complete response rate (CR) in platinum-resistant cervical cancer, with an ORR of 43.8% in PD-L1+ patients. Recent research highlights the gut microbiome as a key modulator of immunity and ICI responses across multiple cancers. Gut microbiota modulation may enhance antitumor immunity, improve ICI efficacy, and reduce immune-related adverse events. Fecal microbiota transplantation (FMT) has been shown to restore immune homeostasis by increasing short-chain fatty acid (SCFA) production, particularly butyrate, which strengthens the intestinal barrier and suppresses inflammation. Despite promising findings in other malignancies, no clinical studies have assessed the impact of gut microbiota modulation in advanced cervical cancer immunotherapy. Further investigations are needed to evaluate its therapeutic potential and underlying mechanisms, warranting clinical trials in this field. **Methods:** This study is a Phase II, single-center clinical trial conducted at Fujian Cancer Hospital. Patients will receive gut microbiota transplantation combined with intravenous (IV) administration of Cadonilimab. The recommended dosage of Cadonilimab is 10 mg/kg, with a treatment cycle of 21 days. On Day 1, patients will receive gut microbiota transplantation, followed by Cadonilimab administration on Day 3.Imaging assessments will be conducted every six weeks. The primary objective of the study is to evaluate the Objective Response Rate (ORR). Secondary objectives include Progression-Free Survival (PFS), Disease Control Rate (DCR), Duration of Response (DOR), Overall Survival (OS), PFS rate (≥6 months), and safety (assessed by CTCAE v5.0).Inclusion criteria: Patients with recurrent, metastatic, or persistent cervical cancer; histological types including squamous cell carcinoma, adenosquamous carcinoma, or adenocarcinoma, who are not candidates for curative surgery or radiotherapy. Trial status: The study is in the initiation phase, with plans to enroll 20 patients. As of this submission, patient enrollment has not yet begun. Research Sponsor: Joint Funds for the innovation of science and Technology, Fujian province; 2023Y9449.

TPS5623 **Poster Session**

A single-center, open-label, single-arm, phase I study with dose expansion cohort of sacituzumab govitecan in combination with cisplatin for patients with platinum sensitive recurrent ovarian and endometrial cancer. First Author: Melanie Wain Kier, Division of Hematology and Medical Oncology, Icahn School of Medicine at Mount Sinai, New York, NY

Background: Sacituzumab govitecan (SG) is an antibody-drug conjugate (ADC) composed of the irinotecan active metabolite SN-38 (govitecan) covalently linked to a humanized monoclonal antibody (hRS7) targeting trophoblastic cell-surface antigen-2 (Trop-2). Sacituzumab govitecan has demonstrated in vitro and in vivo activity against multiple solid tumors, including ovarian cancer and endometrial cancer. The Basket Trial, a phase I/II study of single agent sacituzumab govitecan in patients with epithelial cancers, showed clinical efficacy in endometrial cancer patients (n = 18) with an ORR of 22.2% (6.4-47.6) and median OS of 11.9 months (4.7 months – NR). Insufficient ovarian cancer patients were enrolled for response parameters to be met. The combination of platinum agents and topoisomerase inhibitors, such as irinotecan, has showed complementary effects in preclinical studies, however, the use in clinical practice has been limited by intolerable toxicity. Early trials have found that compared to irinotecan, a prodrug for SN-38, sacituzumab govitecan allows for improved targeted delivery of SN-38 to tumor tissue and increased therapeutic activity with relatively moderate toxicity. The tempering of the toxicity by this ADC may allow for the combination of cisplatin with sacituzumab govitecan to capitalize on the synergy between platinum agents and topoisomerase I inhibitors. The most common grade ≥ 3 adverse events that are seen with sacituzumab govitecan include leukopenia, neutropenia, and thrombocytopenia, thus the less myelosuppressive platinum agent cisplatin is the preferred platinum choice for this combination. **Methods:** Sacituzumab govitecan is being evaluated in combination with cisplatin in an open-label, non-randomized, dose de-escalation (phase 1) study with a planned dose expansion cohort in platinum sensitive, recurrent epithelial ovarian and endometrial cancer patients. Platinum sensitivity for both cancers is defined as cancer recurrence/progression occurring more than 6 months after the last dose of prior platinum therapy. The safety run in phase utilizes a 3+3 design with a de-escalated dose level if the starting dose of sacituzumab govitecan shows toxicity. The primary endpoint for the safety run-in is to determine the dose-limiting toxicity (DLT) and dose expansion cohort dose of sacituzumab govitecan when administered with a fixed schedule of cisplatin. The dose expansion cohort is designed to indicate proof of concept regarding the ORR, CBR, PFS, and safety of the combination regimen at the dose established in the safety run-in phase of the study. The study began enrolling patients October 2024 at our institution and is currently in phase 1 at the starting dose level of sacituzumab govitecan. Clinical trial information: NCT06040970. Research Sponsor: Gilead Sciences, Inc.

TPS5624 **Poster Session**

Rationale and study design of the KOV-HIPEC-04: A phase III randomized controlled trial in primary stage three and four ovarian cancer after interval cytoreductive surgery (FOCUS). First Author: Myong Cheol Lim, National Cancer Center, Goyang, Gyeonggi, South Korea

Background: The addition of hyperthermic intraperitoneal chemotherapy (HIPEC) during interval cytoreductive surgery increases progression-free and overall survival for patients with stage III ovarian cancer in two randomized controlled trials (OV-HIPEC-01 and KOV-HIPEC-01). This trial aims to identify the survival benefit of HIPEC in stage III & IV ovarian cancer in the era of maintenance therapy of bevacizumab and/or PARP inhibitors. **Methods:** Ovarian cancer patients will be randomized at the time of interval cytoreductive surgery with achieving complete cytoreduction or cytoreduction with no more than 2.5mm size of residual disease to receive HIPEC (41.5 cisplatin 75mg/m^2, 90 minutes) or not (Control arm). After recovery from surgery, patients will receive postoperative platinum-based adjuvant chemotherapy followed by maintenance therapy with PARP inhibitor or bevacizumab. The primary objective of the trial is to evaluate OS in two groups. Secondary objectives are PFS, cancer-specific survival, time to first subsequent therapy (TFST), safety, CA-125 KELIM, and quality of life. Assuming that the enrollment period is 5 years and the follow-up period is 3 years, the total number of events required is 263. Based on the log-rank test, the total number of subjects required to prove HR 0.67 with a two-sided alpha of 0.05 and 90% power is 494. Considering 5% drop-out, 520 patients are finally studied. **Results:** The first patient was randomized on June 06, 2023. Until Jan. 26, 2025, 279 (53%) patients are randomized. There are no available results at the time of submission. **Conclusions:** The role of HIPEC during interval cytoreductive surgery will be discovered in stage III & IV ovarian cancer with this randomized trial (KOV-04, FOCUS) in the era of maintenance therapy of bevacizumab and/or PARP inhibitors for the first time. Clinical trial information: NCT05827523. Research Sponsor: National Cancer Center Korea (NCC2110790, NCC2110770).

TPS5625 **Poster Session**

A phase Ib, open-label trial of MOv18 IgE in patients with advanced ovarian cancer. First Author: Rebecca Kristeleit, Department of Oncology, Guy's and St Thomas' NHS Foundation Trust, London, United Kingdom

Background: All antibodies currently approved for cancer therapy are monoclonal IgGs. MOv18 IgE is a first-in-class therapeutic IgE antibody to have entered the clinic, successfully completing a Phase I trial in patients with advanced solid tumours. MOv18 IgE targets folate receptor alpha (FRa), an antigen present on a variety of cancers including ovarian, endometrial, lung and triple negative breast cancer. In the first-in-human Phase I trial, MOv18 IgE was well tolerated (up to 12 mg), with urticaria the most frequent toxicity [Spicer, J., *et al. Nat Commun* 14, 4180 (2023)]. These results demonstrated the potential of MOv18 IgE as an anti-cancer therapy supporting further clinical development. MOv18 IgE's unique mechanism of action includes high affinity binding to its main cognate receptor, FcεR1, enabling immunosurveillance and potent myeloid cell driven tumour FRa killing. Additionally, IgE antibodies drive modulation of the tumour immune microenvironment to a more pro-inflammatory phenotype, increasing intra-tumoral levels of activated T cells and tumour killing macrophages. **Methods:** EPS101-10-02 is a two-part, Phase Ib, open-label, dose escalation and expansion trial in patients with PROC, whose disease has progressed after ≤4 prior regimens of anti-cancer therapy. Tumours must express FRa at ³5%, (1+, 2+ or 3+ membrane staining on at least 5% of tumour cells by IHC using the BN3.2 antibody), and patients must have a negative basophil activation test to stimulation with MOv18 IgE prior to Cycle 1, Day 1. Approximately 45 patients with measurable disease will be recruited. MOv18 will be given by IV infusion (starting dose 3 mg) on Days 1, 8 and 15 of a 21-day cycle. Treatment will continue until disease progression, unacceptable toxicity, withdrawal of consent or death. A range of translational endpoints will be evaluated. Primary objectives are to evaluate the safety and tolerability of MOv18 IgE and make a preliminary assessment of efficacy in PROC. Clinical trial information: NCT06547840. Research Sponsor: None.

TPS5626 **Poster Session**

SALVOVAR: A pragmatic randomized phase III trial comparing the salvage weekly dose-dense regimen to the standard 3-weekly regimen in patients with poor prognostic ovarian cancers (GINECO-OV130b; ENGOT-ov78). First Author: Benoit You, Centre Hospitalier Universitaire Lyon Sud, Hospices Civils de Lyon, Oullins-Pierre-Bénite, France

Background: The patients with an advanced epithelial ovarian cancer (EOC) treated with a neo-adjuvant platinum-based chemotherapy who are not amenable to a complete interval debulking surgery (IDS) due to a poorly chemosensitive disease (CA-125 KELIM score $<$1.0) have a particular poor prognosis (~20% overall survival at 5 years). Several studies suggested that these patients may have a benefit from a chemotherapy densification with the weekly dose-dense carboplatin-paclitaxel regimen. **Methods:** SALVOVAR trial (NCT06476184) is an academic pragmatic open-label multicentre international randomized phase III trial, including stage III-IV high-grade EOC patients who present 2 poor prognostic features after 3-4 cycles of standard neo-adjuvant chemotherapy with carboplatin-paclitaxel administered every 3 weeks: 1) an unfavorable standardized KELIM score $<$1.0; and 2) a disease considered to be not amenable to a complete IDS. The enrolled patients are randomly allocated (ratio 1:1) to an experimental arm (weekly dose-dense regimen: carboplatin AUC5 and paclitaxel 80 mg/m^2 on day1, day8, and day15, with 3 week cycles) or a control arm (continuation of the standard regimen given every 3 weeks) for 3 cycles. Bevacizumab will be added at investigator discretion. The stratification factors are: Planned administration of bevacizumab (yes, vs no); BRCA mutation (yes, vs no/unknown); and KELIM score strate (moderately unfavorable $\geq$0.7, vs very unfavorable $<$0.7). The objective is to show the superiority of the experimental arm with 2 co-primary endpoints: 1) percentage of patients achieving late complete cytoreductive surgery after chemotherapy densification (15% increase), and of overall survival (Hazard-ratio, 0.61). 250 patients will be randomized. The secondary endpoints include overall response rate, progression-free survival, percentage of patients receiving PARP inhibitor and safety. Social human sciences are planned with assessment of the patient/physician perceptions in the shared-decision-making; quality-of-life/patient-reported-outcomes; medico-economic investigation, along with surgical definition of standardized criteria for non-resectability, and inventory of BRCA/homologous-recombination assays used in real-life. The trial is activated in France and Japan. It will be open in United Kingdom, The Netherlands, Italy, Czech Republic, Slovenia, Hungary, Slovakia, and Israel. The recruitment started in July 2024. On January 15 2024, 62 patients had been pre-screened and 18 patients had been randomized. SALVOVAR trial is funded by a European Union HORIZON-MISS-CANCER-2022-01 research program, sponsored by ARCAGY-GINECO (France), and coordinated by Lyon University Hospital (HCL, France). Clinical trial information: NCT06476184. Research Sponsor: None.

TPS5627 **Poster Session**

A phase 3, open-label, randomized study of rinatabart sesutecan (Rina-S) vs investigator's choice (IC) of chemotherapy in patients with platinum-resistant ovarian cancer (PROC). First Author: Angeles Alvarez Secord, Duke Cancer Institute, Durham, NC

Background: Ovarian cancer (OC) is the fifth leading cause of cancer-related death among women in the United States, with 12,730 estimated deaths in 2025. In patients (pts) with advanced OC, 70% experience recurrence and many develop platinum-resistant OC (PROC) after standard platinum-based treatment. Rinatabart sesutecan (Rina-S) is an antibody-drug conjugate targeting folate receptor alpha (FRα) with a novel hydrophilic protease-cleavable linker and exatecan, a topoisomerase I inhibitor. In cohort B1 of a phase 1/2 trial (NCT05579366), Rina-S 120 mg/m² every 3 weeks (Q3W) showed encouraging anti-tumor activity with a 50% objective response rate (ORR; 95% CI, 26-74), including 1 complete response, and was well tolerated in a heavily pretreated OC population, with $>$90% having PROC. Responses were observed regardless of FRα expression status. Here we report the design of an open-label, randomized, phase 3 study (NCT06619236) to investigate Rina-S vs IC chemotherapy in pts with PROC. **Methods:** This phase 3 study will enroll ~530 pts with platinum-resistant, high-grade serous or endometrioid epithelial OC, primary peritoneal cancer, or fallopian tube cancer regardless of FRα expression status (Table). Pts will be randomized 1:1 to receive Rina-S 120 mg/m² IV Q3W or IC chemotherapy (paclitaxel, topotecan, pegylated liposomal doxorubicin, or gemcitabine). Primary endpoint is progression-free survival. Secondary endpoints include overall survival, ORR, duration of response, CA-125 response, adverse events, and time to second disease progression. Additional endpoints include QTc changes and overall change from baseline and time to deterioration in Global Health Status/Quality of Life, and patient-reported outcomes. Follow-up visits will occur every 12 weeks for up to ~1 year after the treatment period. Clinical trial information: NCT06619236. Research Sponsor: Genmab A/S.

Key study criteria.

Inclusion Criteria	Exclusion Criteria
High-grade serous or endometrioid epithelial OC, primary peritoneal cancer, or fallopian tube cancer	Primary platinum-refractory disease, defined as OC that did not respond to a first-line platinum-containing regimen
Received 1 to 4 prior lines of therapy, including:	OC that progressed ≤91 days after last dose of a first-line platinum-containing regimen
Platinum chemotherapy	History of another malignancy ≤3 years or evidence of residual disease
Bevacizumab	Known active central nervous system metastases or carcinomatous meningitis
PARP inhibitor (if applicable)	
MIRV (if eligible)	
Platinum-resistant disease defined as:	
Pts who received ≥4 cycles of first-line platinum-based therapy who had a response and then progressed 91-183 days after last dose	
Pts who received 2 to 4 lines of platinum-based therapy and have progressed <183 days after last dose	

MIRV, mirvetuximab soravtansine; PARP, poly-ADP ribose polymerase.

TPS5628 **Poster Session**

Rationale and study design of the KOV-HIPEC-02R (RECOVER): A randomized, multicenter, open-label phase III trial of cytoreductive surgery and hyperthermic intraperitoneal chemotherapy in platinum-resistant recurrent ovarian cancer. First Author: Myong Cheol Lim, Center for Gynecologic Cancer, National Cancer Center, Goyang-Si, Korea, Republic of

Background: Hyperthermic intraperitoneal chemotherapy (HIPEC) administered during interval cytoreductive surgery following neoadjuvant chemotherapy has shown to increase progression-free survival (PFS) and overall survival (OS) rates, as indicated by the OV-HIPEC-01 and KOV-HIPEC-01 trials. A recent meta-analysis (Kim SI, Kim JH, et al., GO 2023) demonstrated a survival benefit associated with HIPEC, particularly after recent exposure of chemotherapy. Moreover, in ovarian cancer, HIPEC is suggested to be effective in overcoming chemotherapy resistance. **Methods:** This trial (KOV-02R, RECOVER) is a multicenter, open-label, 1:1 randomized, phase III trial that will enroll 140 patients with platinum-resistant recurrent epithelial ovarian cancer (NCT05316181). After cytoreductive surgery, patients undergo the HIPEC procedure at 41.5°C, with doxorubicin at 35mg/ m^2 and mitomycin at 15mg/m^2. Enrolled patients receive non-platinum compound systemic chemotherapy until disease progression. The primary objective is to evaluate progression-free survival between the HIPEC group and the control group. Secondary objectives include overall survival, cancer-specific survival, and safety and quality of life. Considering a 5-year enrollment period, 2-year follow-up, and a statistical power of 80%, 140 patients are needed, accounting for a 10% dropout rate. As of January 10, 2025, 115 patients (82.1%) have been randomized. Clinical trial information: NCT05316181. Research Sponsor: None.

TPS5630 **Poster Session**

SynKIR-CAR T cell advanced research (STAR)-101 phase 1 clinical trial for patients with advanced mesothelin-expressing ovarian cancer, mesothelioma, or cholangiocarcinoma. First Author: Janos Laszlo Tanyi, University of Pennsylvania Abramson Cancer Center, Philadelphia, PA

Background: Chimeric antigen receptor (CAR) T cells have transformed treatment of hematologic malignancy but have shown limited efficacy in solid tumors due to T cell exhaustion and lack of functional persistence. Second-generation CAR T cells targeting mesothelin via the SS1 scFv demonstrate safety and early tumor reduction but lack durable clinical benefit (1-3). SynKIR-110, a novel natural killer cell-signaling based CAR T therapy, employs a multichain signaling system designed to reduce exhaustion by activating T cells only upon tumor engagement. In vitro, SynKIR-110 matches CD3-based CAR T cells in cytokine production and tumor lysis, and in conventional CAR T-cell-resistant mesothelioma mouse xenograft models, SynKIR-110 eliminates tumors without observed toxicity (4). **Methods:** This first-in-human, Phase 1, multicenter, open-label, dose-escalation study evaluates the safety and feasibility of SynKIR-110 in patients with advanced mesothelin-expressing tumors, including ovarian cancer, cholangiocarcinoma, and mesothelioma. Participants receive non-myeloablative lymphodepletion with cyclophosphamide and fludarabine, followed by a single intravenous infusion of SynKIR-110. Up to six dose cohorts (3+3 design) will establish the maximum tolerated dose (MTD) or maximum feasible dose (MFD), with an expansion cohort at the recommended phase 2 dose to confirm safety and assess activity. Participants are followed for 12 months to evaluate best overall response, survival, drug persistence, immune function and potential correlation with pre-treatment tumor mesothelin levels, through exploratory analyses. Eligible patients must have recurrent or relapsed ovarian cancer, cholangiocarcinoma, or epithelial pleural or peritoneal mesothelioma after at least one prior systemic therapy. Additional eligibility criteria include measurable disease by iRECIST or mRECIST, ECOG performance status of 0-1, and adequate organ and bone marrow function. Cohort 1 completed without dose-limiting toxicities (DLTs). Enrollment in Cohort 2 initiated in 2025 and is ongoing. SynKIR-110 represents a promising approach to overcoming the limitations of CAR T cells in solid tumors. 1. Beatty GL et al. *Cancer Immunol Res*. 2014 Feb;2(2):112-20. PMID: 24579088. 2. Haas AR et al. *Mol Ther*. 2019 Nov 6;27(11):1919-1929. PMID: 31420241. 3. Beatty GL et al. *Gastroenterology*. 2018 Jul;155(1):29-32. PMID: 29567081. 4. Wang E et al. *Cancer Immunol Res*. 2015 Jul;3(7):815-26. PMID: 25941351. Clinical trial information: NCT05568680. Research Sponsor: Verismo Therapeutics.

TPS5631 **Poster Session**

Evaluating zAvatar test-guided chemotherapy vs. standard of care in relapsed ovarian cancer and metastatic breast cancer: A multicenter randomized clinical trial (zAVATAR-FLUIDS). First Author: Marcio Debiasi, Breast Unit, Champalimaud Clinical Centre, Champalimaud Foundation, Lisboa, Portugal

Background: Relapsed ovarian cancer and metastatic breast cancer (MBC) present significant challenges due to tumor heterogeneity and limited treatment efficacy. Despite numerous recent achievements in personalized medicine, we still lack real-time molecular biomarkers to guide therapeutic decision-making, often resulting in multiple lines of trial-and-error chemotherapy (CT), which ultimately exposes patients to unnecessary toxicities. The zAvatar test – a patient-derived zebrafish xenograft model – has shown to accurately predict tumor response to treatment, providing a real-time and non-invasive means of guiding personalized therapy in advanced cancers (Fior R, et al, 10.1038/s41467-024-49051-0). This trial evaluates the clinical utility of zAvatar as a predictive tool to optimize therapeutic decisions for patients with relapsed ovarian cancer or MBC, presenting with malignant pleural effusion or ascites. **Methods:** In this multicenter, open-label, randomized clinical trial, patients with relapsed ovarian cancer or metastatic HER2-negative breast cancer, ECOG performance status 0-2, measurable disease by RECIST 1.1 and 2 or more equally effective CT options, who need drainage of ascites or pleural effusion, are randomized (1:1) into two groups: the control group will receive CT based on physicians´ choice, while the experimental group will receive treatment guided by the zAvatar-test results. Both groups will have zAvatars generated from tumor cells isolated from ascitic or pleural effusion fluids. The trial will include 276 patients (138 per cancer type). The study aims at determining whether zAvatar-guided decisions lead to improved progression-free survival (PFS) compared to standard of care, as primary endpoint. Recruitment started in January 2025, with an anticipated recruitment period of 3 years (2025–2028). The first patient is expected to be randomized in February 2025 and undergo zAvatar-test evaluations in centralized lab. This trial paves the way for an innovative approach for personalized medicine by validating the zAvatar test's ability to tailor treatment options in advanced cancers, which shall in the future bring into practice a real-time, patient-specific decision-making functional test. Clinical trial identification: EU-CTR n. 2023-509598-22. Legal sponsor: Champalimaud Clinical Centre, Lisbon, Portugal. Funding: Liga Portuguesa Contra Cancro. Protocol FC2024-001. Clinical trial information: 2023-509598-22. Research Sponsor: Liga Portuguesa Contra Cancro.

TPS5632 **Poster Session**

Randomized study evaluating optimal dose, efficacy and safety of E7386 + lenvatinib versus treatment of physicians' choice in advanced/recurrent endometrial carcinoma previously treated with anti−PD-(L)1 immunotherapy. First Author: Ramez Nassef Eskander, Division of Gynecologic Oncology, Department of Obstetrics, Gynecology and Reproductive Sciences, University of California, San Diego, Moores Cancer Center, La Jolla, CA

Background: E7386 is an inhibitor of protein-protein interaction between β-catenin and CREB binding protein (CBP). E7386 + lenvatinib has demonstrated manageable safety and promising antitumor activity in the dose-expansion cohort of Study 102 that included patients with advanced endometrial cancer previously treated with immunotherapy (Lee JY et al., *Ann Oncol* 2024). Considering these results, we are conducting a dose-optimization part of Study 102 (NCT04008797) in patients with advanced/recurrent endometrial carcinoma (aEC). **Methods:** Eligible patients (≥18 years) must have a confirmed diagnosis of aEC, and prior treatment with platinum-based chemotherapy and PD-(L)1-directed therapy. Up to 3 prior lines of therapy, regardless of setting, are allowed; prior hormonal therapy and radiation do not count as lines of therapy. Patients will be randomized (1:1:1:1) to E7386 120 mg BID + lenvatinib 14 mg QD (n=30); E7386 60 mg BID + lenvatinib 14 mg QD (n=30); lenvatinib 24 mg QD monotherapy (n=30); or treatment of physician's choice (TPC, doxorubicin 60 mg/m^2 Q3W or paclitaxel 80 mg/m^2 QW [3 weeks on/1 week off]; n=30 in total). Randomization will be stratified by region (Asia/North America/Rest of the World). The primary objective is to determine the optimal dose of E7386 + lenvatinib in aEC; additional objectives include: safety, assessing the contribution of E7386 to the overall treatment effect of E7386 + lenvatinib, and assessing the efficacy of E7386 + lenvatinib relative to TPC. Tumors will be assessed by investigators (per Response Evaluation Criteria in Solid Tumors [RECIST] version 1.1) every 8 weeks from the first dose. Adverse events will be monitored and graded according to Common Terminology Criteria for Adverse Events (CTCAE) version 5.0. This multinational study is actively recruiting. Clinical trial information: NCT04008797. Research Sponsor: Eisai Inc.

TPS5633 **Poster Session**

Sapanisertib and serabelisib (PIKTOR) with paclitaxel and a diet substudy in patients with advanced/recurrent endometrial cancer (GOG-3111). First Author: David Starks, Avera Cancer Institute, Sioux Falls, SD

Background: Patients with advanced/recurrent endometrial cancer have limited 2L+ treatment options. The PI3K/mTOR pathway regulates glucose homeostasis downstream of insulin/insulin receptor signaling and is mutated in >80% of endometrial cancer. Multi-node inhibition of this pathway with the combination of sapanisertib, an mTORC1/2 inhibitor, and serabelisib, a PI3Kα inhibitor, (PIKTOR) achieves more complete PI3K pathway blockade compared to single node inhibition in preclinical models. In a Phase 1b trial (NCT03154294) of triplet combination paclitaxel, serabelisib, and sapanisertib, the combination led to an overall response rate of 80% with 3 CR and 1 PR in 5 patients with advanced, treatment refractory endometrial cancer. This study evaluates whether PIKTOR with paclitaxel improves efficacy outcomes in participants with advanced/recurrent endometrial cancer with mutation(s) in the PI3K/AKT/mTOR pathway and who have failed prior systemic therapies. **Methods:** GOG-3111 is a Phase 2 (ClinicalTrials.gov ID NCT06463028), multi-center, open-label, single-arm trial evaluating the efficacy and safety of PIKTOR plus paclitaxel in participants with advanced/recurrent endometrial cancer. Approximately 40 participants will be enrolled in the main study and up to 50% of participants will have the option to receive triplet combination therapy with a diet. Eligible participants will have histologically confirmed diagnosis of advanced/recurrent endometrioid endometrial carcinoma and documented genetic mutation(s) in the PI3K/AKT/mTOR pathway by next generation tumor testing. Participants must have received >1 but no more than 3 prior systemic therapies for advanced/recurrent disease (ie, including platinum-based therapy and an immune checkpoint inhibitor either together or separately). Study interventions are 28-day cycles with: Paclitaxel: 80 mg/m2 IV weekly on Days 1, 8, and 15; PIKTOR (sapanisertib [1] 3mg and serabelisib [2] 100 mg) oral with food on Days 2-4, 9-11, 16-18, and 23-25. Radiographic imaging and RECIST v1.1 response assessment will be performed every 8 weeks starting at C1D1. The primary objective is to evaluate the objective response rate (ORR) and secondary objective is to evaluate efficacy via progression-free survival (PFS), PFS at 6 months, overall survival, clinical benefit rate, duration of response; and safety/tolerability of PIKTOR + paclitaxel. The substudy rationale is to evaluate the impact of diet on treatment tolerability and efficacy. Clinical trial information: NCT06463028. Research Sponsor: Faeth Therapeutics.

TPS5634 **Poster Session**

Debio 0123, a highly selective WEE1 inhibitor in adult patients with advanced solid tumors: A phase 1 dose escalation and expansion monotherapy study. First Author: Maria M. Rubinstein, Memorial Sloan Kettering Cancer Center, New York, NY

Background: Debio 0123 is an oral, highly selective WEE1 inhibitor. WEE1 inhibition leads to S phase and G2/M cell cycle checkpoint bypass, allowing mitosis to occur without DNA repair, leading to mitotic catastrophe and cell death. This Phase 1 study (NCT05109975) is evaluating Debio 0123 monotherapy in patients with advanced solid tumors who have recurred or progressed following prior therapy and/or without available standard therapy. During the recently completed dose escalation, Debio 0123 was given once daily over a 21-day cycle and had a manageable safety profile with dose proportional pharmacokinetics. The recommended phase 2 dose is 260 mg (Papadopoulos, et al. ASCO2024,#2426). **Methods:** Following selection of RP2D, a 3-arm expansion phase is ongoing and currently enrolling patients, in both biomarker selected and unselected cohorts. Arm A includes patients with recurrent uterine serous carcinoma progressing after at least one prior line of platinum-based chemotherapy. Arm B includes patients with high-grade epithelial ovarian cancer, primary peritoneal cancer, or fallopian tube cancer that recurred to at least one prior line of platinum-based chemotherapy with high cyclin E1. Lastly, a biomarker-driven cohort (arm C) will enroll patients with specific locally advanced or metastatic solid tumors who have recurred or progressed following prior therapy and/or for whom no standard therapy is available. Additional key inclusion criteria are ECOG Performance Status 0-1, and measurable disease per RECIST 1.1. Debio 0123 will be administered once daily until disease progression, unacceptable toxicity, or withdrawal from the study. Primary endpoints are safety and tolerability and overall response rate (ORR) at recommended dose. Secondary endpoints include duration of response (DOR), progression-free survival (PFS), and overall survival (OS). Enrolment is ongoing in Spain, Switzerland and US. Clinical trial information: NCT05109975. Research Sponsor: None.

TPS5635 **Poster Session**

PENELOPE: A randomized phase II trial of first-line carboplatin and paclitaxel in combination with pembrolizumab, followed by maintenance pembrolizumab with or without nesuparib, in patients with newly diagnosed advanced or recurrent MMR-proficient endometrial cancer. First Author: Se Ik Kim, Seoul National University College of Medicine, Seoul, South Korea

Background: Clinical trials have demonstrated antitumor activity of the immune checkpoint inhibitors in endometrial cancer patients. Two landmark phase III RCTs, NRG-GY018 and RUBY, proved that the addition of pembrolizumab or dostarlimab to standard chemotherapy resulted in significantly longer progression-free survival (PFS) than with chemotherapy alone in patients with advanced or recurrent endometrial cancer. Meanwhile, both two trials consistently showed that the effective size of adding an immune checkpoint inhibitor to combination chemotherapy on PFS was smaller in MMR-proficient (pMMR) cohort, compared to those in MMR-deficient (MMRd) cohort. As poly(ADP-ribose) polymerase (PARP) inhibitors enhance the effects of immune checkpoint inhibitors when combined, improvement of PFS is expected by dual maintenance with pembrolizumab and a PARP inhibitor. Although the phase III DUO-E trial demonstrated elongated PFS from paclitaxel/carboplatin plus durvalumab followed by maintenance durvalumab with or without olaparib in patients with advanced or recurrent endometrial cancer, this trial is not designed to prove that addition of olaparib maintenance provides extra survival benefits. Nesuparib is a newly synthesized small-molecule chemical compound that inhibits both PARP-1&2 and tankyrase. The PENELOPE trial will investigate whether the addition of nesuparib to pembrolizumab maintenance after paclitaxel/carboplatin plus pembrolizumab treatment further improves PFS in patients with advanced or recurrent pMMR endometrial cancer. **Methods:** In this multicenter, open-label phase II clinical trial, patients with pMMR, stage III/IV or recurrent endometrial cancer, naïve to first-line chemotherapy, will be enrolled. Six patients will be enrolled in Stage 1 (safety run-in) and treated with TCP (paclitaxel/carboplatin + pembrolizumab 200 mg; q3w for six cycles) followed by maintenance treatment with P (pembrolizumab 400 mg; q6w up to 14 cycles) + N (nesuparib 150mg PO once a day; up to 14 months). The study will proceed to Stage 2 (dose expansion) if less than 33% of patients in Stage 1 experience a dose-limiting toxicity. Otherwise, additional patients will be enrolled in Stage 1 at lower dose level. In Stage 2, 80 patients will be randomized (1:1) to: arm A) TCP followed by maintenance treatment with P; arm B) TCP followed by maintenance treatment with P + N (150mg or 100mg PO once a day; up to 14 months). Patients will receive maintenance treatment until disease progression. Primary endpoint is investigator-assessed PFS (RECIST 1.1) of arm B vs. arm A, and key secondary endpoints are overall survival, overall response rate, disease control rate, duration of response, and safety. Enrollment began in Q4 2024. Clinical trial information: NCT06502743. Research Sponsor: Onconic Therapeutic INC.

TPS5636 **Poster Session**

IMMUNORARE[5]: A national platform of 5 academic phase II trials coordinated by Lyon University Hospital to assess the safety and the efficacy of the immunotherapy with domvanalimab + zimberelimab combination in patients with advanced rare cancers—The Gestational Trophoblastic Tumors Cohort. First Author: Benoit You, Medical Oncology Department, Institut de Cancérologie des Hospices Civils de Lyon, CITOHL, Université Lyon 1, Lyon, France

Background: For patients with rare cancers, there is an unmet medical need to investigate innovative therapeutics beyond standard first-line treatment. These diseases are rarely evaluated in clinical trials. High-risk gestational trophoblastic tumors (GTT) are treated with polychemotherapy (especially EMA-CO) with high cure rate (~95%). However, patients resistant to polychemotherapy have a poor prognosis, and no validated regimen has been defined. Several case reports suggest that immune checkpoint inhibitors (ICIs) may be active, and a phase II trial with Camrelizumab + Apatinib showed a 50% cure rate. There is a strong rationale for concurrent blockade of the TIGIT and PD1 pathways in this disease. **Methods:** IMMUNORARE[5] (NCT NCT06790706) is a platform of 5 single-arm phase II trials testing the efficacy and tolerability of DOMVANALIMAB (anti-TIGIT) and ZIMBERELIMAB (anti PD-1) in 5 independent cohorts of rare cancers. The trial, sponsored by Lyon University Hospital, will be conducted in 15 French centers, in collaboration with the respective French national reference centers. The gestational trophoblastic tumor cohort, led in collaboration with the French Gestational Trophoblastic Disease Center, will enroll 27 patients with resistance or relapse after at least one line of polychemotherapy (e.g. EP low-dose, BEP, EMA-CO), assessable for biological response with serum hCG (human chorionic gonadotropin). Patients previously treated with immunotherapy are not eligible. Patients will receive intravenous DOMVANALIMAB and ZIMBERELIMAB, every three weeks, until hCG normalization followed by 5 consolidation cycles. The primary objective is the successful hCG normalization rate at 6 months. The secondary objectives are the resistance-free survival, overall survival and tolerance. The trial is designed with a two-stage Simon design, with the possibility of early termination for futility (5% one-sided alpha level, 80% power). The treatment will be considered interesting if the percentage of patients experiencing hCG normalization at 6-months is statistically higher than 35% (H0); 60% is expected (H1). Translational research projects will be developed to unravel the cellular and molecular mechanisms involved in treatment response. Moreover, data from the prospectively implemented database of the French Gestational Trophoblastic Disease Center will be analyzed to create a synthetic historical arm representative of the efficacy of the standard treatments in a similar patient population. Clinical trial information: NCT06790706. Research Sponsor: None.

TPS5637 **Poster Session**

Stratification of vulvar squamous cell carcinoma (VSCC) by HPV and P53 status to guide excision: CCTG VU.2 STRIVE study (NCT06358469). First Author: Amy Jamieson, Vancouver Coastal Health, Vancouver, BC, Canada

Background: Early VSCC is treated surgically. The optimal approach to margin re-excision may depend on molecular subtype. HPV associated (HPV-A) VSCC has a good outcome and is radiosensitive; HPV independent (HPV-I) p53 abnormal(p53abn) VSSC has a worse outcome and is less radiosensitive. **Methods:** Prospective, international, multicentre, phase II platform study enrolling participants with VSCC stratified by HPV status: HPV- Associated (HPV-A) vs HPV-Independent (HPV-I). Criteria: Key eligibility: Primary diagnosis VSCC; surgically staged I-II (FIGO 2021), molecular/ tumour features known: HPV, margin assessment for tumour clearance, dVIN (differentiated-type vulvar intraepithelial neoplasia), p53. Key ineligibility: tumour HPV-I p53 wild-type, recurrent VSCC, stage III-IV, non squamous histotype, planned or previous RT or chemotherapy. Treatment arms: Cohort HPV-A: Margin negative for cancer but $<$ 8mm (regardless of high grade squamous intra epithelial lesion): Active surveillance (AS). Cohort HPV-I p53abn margin: negative for cancer but $<$8 mm and/or positive for dVIN and/or positive p53abn: 2:1 randomization to re-excision versus AS. Primary objective: To estimate the 3-year local recurrence rate (LRR) for HPV-A and HPV-I VSCC surgically managed based on dVIN/p53 status, tumour margin clearance. Secondary objectives: recurrence free and disease specific survival, OS, economics, patient reported outcomes. Statistical design: Cohort HPV-A: n=120 enrolled over 3 years; the upper limit of a one-sided 95% CI for 3-year LRR would be 26% when the observed 3-year LRR=20%. Interim analyses (IAs) planned at 12, 24, 36 months after 1st enrollment and final analysis (FA) at 3 years after last enrollment. Cohort HPV-I: n=129, including 10% loss to follow-up, randomized over 3 years to re excision and surveillance arms in 2:1 ratio. 86 on re-excision arm would have at least 85% power with 95% confidence to exclude a 40% 3-year LRR in favour of a lower rate of 25%, while 43 on surveillance arm will enable an estimate of 3-year LRR at an accuracy that the half length of a two-sided 90% CI will be less than 13% when the observed rate is 40%. IA planned at 36 months after 39th patient enrolled to re-excision arm and FA at 3 years after last enrollment. Conduct to Date**:** This trial was activated Oct 1, 2024. Two enrollments as of Jan 19 2025. Supported by CCS grant #707213; CIHR #195984. Clinical trial information: NCT06358469. Research Sponsor: Canadian Cancer Society (CCS); 707213; Canadian Institutes of Health Research (CIHR); 195984.

TPS5638 **Poster Session**

Evaluation of indocyanine green (ICG) and handheld fluorescence imager in the management of early-stage gynecological cancer. First Author: Shalini Rajaram, All India Institute of Medical Sciences (AIIMS), Rishikesh, India

Background: Current management in most early-stage cancers is complete lymphadenectomy for staging. Since surgery is the mainstay of treatment tailoring extent of surgery is vital. Only 15-20% of early-stage gynecologic cancers have lymph node metastases yet complete lymphadenectomy is recommended. Sentinel lymph (SLN) node evaluation is a bridge to avoid morbidity due to lymphadenectomy. Fluorescence imaging utilizing near-infrared (NIR) spectrum (700–900 nm) is a valuable tool for mapping lymphatics and lymph nodes and fluorescence imaging is available on robotic and laparoscopic platforms. However, open surgery is the preferred approach for most early-stage gynecological cancers except endometrial malignancy. This research plans to assess hand-held fluorescence imager using ICG dye for feasibility, ergonomics, accuracy and applicability in all gynecologic cancers. Indocyanine green (ICG) is a valuable agent for NIR lymphatic mapping and is used in routinely for sentinel node mapping of breast, skin and gastrointestinal carcinomas with superior safety profile. **Methods:** This exploratory study plans to recruit 30-50 women with early stage endometrial, cervical, ovarian, and vulvar malignancies for intraoperative evaluation of sentinel nodes using ICG and hand held fluorescence imager with SPY-PHI camera and pinpoint video processor(Stryker). Eligibility criteria include women aged 18 years and older, biopsy proven cases of endometrial, cervical & vulvar cancers. For women with suspected ovarian malignancy, sentinel node mapping will be done after laparotomy but SLN biopsy will be done once frozen section report is available. Indications for SLN biopsy are those with uterine confined malignancy (aggressive and non-aggressive endometrial histotypes), stage I cervical cancer with tumor size less than 4 cm, unifocal vulvar tumors less than 4 cm with negative groin nodes and women with stage I and II ovarian cancers and suspicious ovarian masses planned for hysterectomy and or salpingo-oophorectomy. 25 women of early-stage cancers have been enrolled. Fluorescence is detected by tracing fluorescent lymphatics to sentinel node prior to opening retroperitoneal spaces or incising skin in cases of vulvar cancer. Data is being captured and final analysis awaited. The distribution of cancer types till date are endometrial cancer n=12, cervical cancer n= 6, vulvar cancer n=1 and ovarian masses n=6. Sentinel lymph nodes were mapped in 23 out of 25 cases intra-operatively. Clinical trial information: CTRI/2023/03/051086. Research Sponsor: Indian Council of Medical Research; 9618.

6000 Oral Abstract Session

Phase 3 randomized trial (KEYNOTE-630) of adjuvant pembrolizumab (pembro) versus placebo (pbo) for high-risk locally advanced cutaneous squamous cell carcinoma (LA cSCC) following surgery and radiation (RT). First Author: Shlomo A. Koyfman, Cleveland Clinic, Cleveland, OH

Background: Patients with high-risk LA cSCC are standardly treated with surgical resection followed by postoperative RT. Up to 30% of pts experience recurrence and/or metastasis. PD-1 inhibitors including pembro are approved in the US for recurrent/metastatic or LA cSCC not curable by surgery or radiation. We present results from the randomized, double-blind, phase 3 KEYNOTE-630 trial (NCT03833167) that evaluated the efficacy and safety of the addition of adjuvant pembro for participants (pts) with high-risk LA cSCC. **Methods:** Adults with histologically confirmed LA cSCC with ≥1 protocol-defined high-risk feature who underwent complete macroscropic resection and completed adjuvant RT ≥4 and ≤16 weeks from randomization were randomly assigned 1:1 to receive pembro 400 mg or placebo (pbo) IV Q6W for ≤9 cycles. The primary end point was recurrence-free survival (RFS), defined as the time from randomization to the first event of local or regional recurrence of index lesion, distant metastasis, or death due to any cause. Secondary end points included overall survival (OS) and safety. The data cutoff date was June 28, 2024. **Results:** A total of 450 pts were enrolled (n = 225 in each arm). All pts completed surgery and RT and 224 in each arm received ≥1 dose of adjuvant treatment. Median study follow-up was 28.6 mo (range, 2.0-62.5). The 24-mo RFS rate was 78.3% (95% CI, 71.5-83.7) for pembro vs 68.6% (95% CI, 61.1-75.0) for pbo (HR 0.76 [95% CI, 0.53-1.10] P = 0.07243, which did not cross the p-value boundary of 0.0160 for statistical significance). On subset RFS analysis, pts with extracapsular extension (HR 0.44; 95% CI, 0.24-0.79), pts aged ≥65 years (HR 0.61; 95% CI, 0.41-0.91), and non-smokers (HR 0.58; 95% CI, CI 0.37-0.90) appeared to benefit most from pembro. Locoregional recurrence occurred in 13.8% of pts receiving pembro vs 25.3% receiving pbo; distant metastasis in 4.4% vs 11.6% of pts; and new high-risk primary cSCC in 0% vs 2.7% of pts. The 24-mo OS rate was 87.3% (95% CI, 81.5-91.5) in the pembro arm vs 90.7% (95% CI, 85.2-94.3) in the pbo arm (HR 1.47 [95% CI, 0.87-2.48]). Treatment-related AEs (TRAEs) occurred in 63.8% of pts in the pembro arm and 41.1% in the pbo arm (grade 3-4 in 7.6% and 2.7%). No pts died due to TRAEs. TRAEs led to treatment discontinuation in 5.4% of pts in the pembro arm and in 1.3% in the pbo arm. **Conclusions:** Pembro did not provide significant benefit in the adjuvant setting for pts with resected, high-risk LA cSCC. The safety profile of adjuvant pembro was consistent with reports from similar studies and there were no treatment-related deaths. The study was stopped for futility as the benefit/risk profile did not support continuing the trial based on recommendations from the data monitoring committee. Clinical trial information: NCT03833167. Research Sponsor: Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA.

6001 Oral Abstract Session

Phase 3 trial of adjuvant cemiplimab (cemi) versus placebo (pbo) for high-risk cutaneous squamous cell carcinoma (CSCC). First Author: Danny Rischin, Department of Medical Oncology, Peter MacCallum Cancer Centre, Melbourne, VIC, Australia

Background: Cemiplimab is standard of care for treatment of patients (pts) with advanced (metastatic/unresectable) CSCC. There is no approved systemic treatment for pts with CSCC at high risk of recurrence after definitive local therapy. **Methods:** C-POST, a double-blind, multicenter, phase 3 study (NCT03969004), enrolled pts with local and/or regional CSCC, after surgery and post-operative radiation therapy, deemed to be at high risk of recurrence due to nodal (extracapsular extension with largest node ≥2 cm or ≥3 involved lymph nodes) and/or non-nodal (in-transit metastases, T4 lesion, perineural invasion, or locally recurrent tumor with ≥1 additional risk feature) criteria. Pts were randomized 1:1 to cemi 350mg or pbo every (Q) 3w for 12w, then cemi 700mg or pbo Q6W up to 36w (up to 48w total). Original protocol had cemi 350mg or pbo Q3W up to 48w. Crossover was allowed after disease recurrence. Primary endpoint was disease-free survival (DFS). Secondary endpoints included freedom from local-regional recurrence (FFLRR), freedom from distant recurrence (FFDR), overall survival (OS), and safety. Data cutoff for pre-specified interim analysis 1 (IA1; ~50% of final DFS events) was Oct 4, 2024. Per IDMC, the pre-specified threshold for DFS was crossed at IA1. **Results:** From Jun 2019 to Aug 2024, 415 pts (209/206 cemi/pbo) were randomized: median age, 71 yrs (range 33–95); 84% male; 83% head and neck primary; 58%/42% high-risk nodal/non-nodal categories. Median follow-up was 24 mos (range 2–64). DFS was superior with cemi vs pbo: hazard ratio (HR) 0.32 (95% CI 0.20–0.51); p<0.0001 (Table). Estimated 24-mo DFS was 87% (95% CI 80–92) for cemi and 64% (56–71) for pbo. Cemi improved FFLRR (HR 0.20; 95% CI 0.09–0.40) and FFDR (HR 0.35; 0.17–0.72) vs pbo. At IA1, OS HR for cemi vs pbo was 0.86 (95% CI 0.39–1.90). Grade ≥3 treatment-emergent adverse events (TEAEs) occurred in 23.9% and 14.2% and discontinuations due to TEAEs occurred in 9.8% and 1.5% of pts receiving cemi and pbo, respectively. In exploratory analyses, DFS benefits were observed in pts with tumoral PD-L1 ≥1% (HR 0.28; 95%CI 0.15–0.52; n=309) and <1% (HR 0.32; 0.12–0.86; n=85). **Conclusions:** Cemiplimab is the first systemic therapy to demonstrate a statistically significant and clinically meaningful reduction in disease recurrence as adjuvant therapy for high-risk CSCC, and has an acceptable safety profile in this setting. Clinical trial information: NCT03969004. Research Sponsor: Regeneron Pharmaceuticals, Inc. and Sanofi.

	Cemi n=209	Pbo n=206
Pts with DFS event, n (%)[a]	24 (12)	65 (32)
Disease recurrence	18 (9)	61 (30)
Death	6 (3)	4 (2)
DFS, mos, median (95% CI)[b]	NR (NE–NE)	49.4 (48.5–NE)
HR (95% CI)[c]	0.32 (0.20–0.51)	-
2-sided p-value[d]	< 0.0001	-
24-mo DFS, % (95% CI)[b]	87.1 (80.3–91.6)	64.1 (55.9–71.1)
24-mo FFLRR, % (95% CI)[b]	94.6 (89.1–97.3)	76.7 (69.1–82.6)
24-mo FFDR, % (95% CI)[b]	94.3 (89.0–97.1)	83.8 (76.3–89.0)

NE, not estimable; NR, not reached.
[a]Censored pts: 185 cemi; 141 pbo.
[b]Kaplan-Meier estimate.
[c]Stratified Cox model.
[d]Stratified log-rank test.

6002 Oral Abstract Session

A phase II (Alliance/A091802) randomized trial of avelumab plus cetuximab vs. avelumab alone in advanced cutaneous squamous cell carcinoma (cSCC). First Author: Dan Paul Zandberg, UPMC Hillman Cancer Center, University of Pittsburgh, Pittsburgh, PA

Background: There is a need for continued improvement in outcomes with systemic therapy for advanced cSCC. Pre-clinical data suggest immunologic synergy between IgG1 mAb therapy targeting EGFR and PD-1:PD-(L)1 blockade. **Methods:** Alliance A091802 is a randomized phase II trial of avelumab (AV) (800 mg) plus cetuximab (C) (500 mg/m2) vs. AV alone every 2 weeks for up to 2 years (yrs). C was given for 1 yr in the AV+C arm. Crossover at progression to AV+C was allowed in the AV arm. Randomization was 1:1 and stratified by PD-L1 [+(>1%) vs. -] and HIV status (+ vs. -). Eligible patients (pts) had distant metastatic or unresectable locally advanced cSCC, anti-PD-1/PD-L1 mAb naive, no prior cetuximab in the advanced setting, ECOG PS 0-2, HIV+ if CD4 >200 and VL <200. Pts with CLL, immunosuppression, or active autoimmune diseases were excluded. The primary endpoint was progression-free survival (PFS) (Ho: Median=12 mo vs Ha: 21 mo or a 75% improvement, power of 80% with one-sided alpha 0.2, n=57, 37 PFS events required). Secondary endpoints were overall survival (OS), confirmed response rate (ORR), clinical benefit rate, and toxicity. After 31/37 events, an early unplanned analysis (along with sensitivity analyses) was performed because it became apparent that 37 events would not be reached. These results were submitted to the Alliance Data and Safety Monitoring Board, which recommended releasing the data. Data cutoff was 1/16/25. **Results:** 60 pts were enrolled between 2019-2023; 57 pts were evaluable. Median age was 72 yrs (41–93), 96.5% were white, 91.2% male, all HIV-; 75.4% PD-L1+. 84.2% were head/neck origin, 47.1% had distant metastasis, and there were no differences in baseline characteristics by arm. AV+C significantly improved PFS compared to AV [median 11.1 months (mo) (7.6–not reached (NR)) vs. 4.8 mo (2.8–NR) hazard ratio (HR) 0.53 95% CI (0.26–1.09), one-sided p=0.041]. The median OS of AV+C vs. AV was NR (25.2–NR) vs. 35.8 mo (18.6–NR) HR 0.77 (0.33–1.78) p=0.267. ORR was 31.0% in the AV+C arm and 21.4% in the AV arm. Treatment-related adverse events (TRAE) of any grade (G) occurred in 93% and 78.6%, respectively, and were G>3 in 48.3% and 21.5% of pts in the AV+C [most common G3 TRAEs were rash (20.7%) and infusion-related reaction (20.7%)] and AV arms, respectively. There were no G5 events. Outcomes after crossover and by PD-L1 status will be presented subsequently. **Conclusions:** Avelumab plus cetuximab significantly improved PFS vs. avelumab alone in advanced cSCC pts, without unexpected toxicity. Alliance A091802 supports a larger confirmatory study with combination cetuximab and PD-1:PD-(L)1 blockade. Support: U10CA180821, U10CA180882, U24CA196171; U10CA180868 (NRG Oncology); U10CA180888 (SWOG); https://acknowledgments.alliancefound.org. EMD Serono CrossRef Funder ID: 10.13039/100004755. Clinical trial information: NCT03944941. Research Sponsor: National Cancer Institute/NIH- Alliance for Clinical Trials in Oncology; EMD Serono.

LBA6003 Oral Abstract Session

PD-1 blockade with toripalimab incorporated into induction chemotherapy and radiotherapy with or without concurrent cisplatin in locoregionally advanced nasopharyngeal carcinoma (DIAMOND): A multicenter, non-inferiority, phase 3, randomized controlled trial. First Author: Jun Ma, Department of Radiation Oncology, Sun Yat-sen University Cancer Center, State Key Laboratory of Oncology in South China, Guangdong Key Laboratory of Nasopharyngeal Carcinoma Diagnosis and Therapy, Guangdong Provincial Clinical Research Center for Cancer, Guangzhou, China

The full, final text of this abstract will be available at meetings.asco.org on the day of presentation and in the online supplement to the June 10, 2025, issue of the *Journal of Clinical Oncology*.

6004 Oral Abstract Session

Tagitanlimab versus placebo in combination with gemcitabine and cisplatin as first-line treatment for recurrent or metastatic nasopharyngeal carcinoma (R/M NPC): Results from a randomized, double-blind, phase 3 study. First Author: Yuankai Shi, National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences & Peking Union Medical College, Beijing Key Laboratory of Clinical Study on Anticancer Molecular Targeted Drugs, Beijing, China

Background: The addition of PD-1 inhibitor to gemcitabine and cisplatin (GP) showed promising activity as first-line therapy for R/M NPC. Here, we first report the PD-L1 inhibitor Tagitanlimab (KL-A167) plus GP compared with placebo plus GP in a randomized phase 3 study (KL167-III-08, NCT05294172). **Methods:** Eligible patients (pts) with previously untreated R/M NPC were in 2:1 ratio randomly assigned to receive tagitanlimab or placebo (1200 mg, D1) in combination with cisplatin (80 mg/m^2, D1) and gemcitabine (1000 mg/m^2, D1 and D8) every 3 weeks (Q3W) for up to 6 cycles followed by tagitanlimab or placebo monotherapy Q3W until disease progression, unacceptable toxicity, or withdrawal of consent. After disease progression, pts from the placebo arm could crossover to receive tagitanlimab monotherapy. The primary endpoint was progression-free survival (PFS) assessed by the blinded independent central review (BICR) according to RECIST version 1.1. **Results:** Between Jun 16, 2022, and May 27, 2023, 295 pts were assigned to tagitanlimab plus GP arm (n = 197) or placebo plus GP arm (n = 98). The median age was 52 years, and 79.7% were male. As of Feb 4, 2024, 47.2% of pts in tagitanlimab plus GP arm vs 23.5% of pts in placebo plus GP arm were still on treatment, 36.7% of pts in placebo plus GP arm were crossed to receive tagitanlimab monotherapy after disease progression. The median follow-up time was 11.7 months. The PFS per BICR was met at the prespecified interim analysis with a 53% reduction in risk of progression or death (HR 0.47; 95% CI, 0.33 to 0.66; one-sided P $<$0.0001). The median PFS was not reached (95% CI, 10.9-NE) in tagitanlimab plus GP arm and 7.9 months (95% CI, 6.9-8.3) in placebo plus GP arm; the 12-month PFS rate was 56.7% vs 26.7%. The objective response rate (ORR) per BICR was 81.7% (95% CI, 75.6-86.9) in tagitanlimab plus GP arm and 74.5% (95% CI, 64.7-82.8) in placebo plus GP arm, with a median duration of response (DoR) of 11.7 months (95% CI, 8.2-NE) and 5.8 months (95% CI, 5.6-6.9; HR 0.48, 95% CI, 0.32-0.70), respectively. The overall survival (OS) benefit was observed in tagitanlimab plus GP arm vs placebo plus GP arm (median OS not reached for either arm; HR 0.62, 95% CI 0.32-1.22). The most common $\geq$ grade 3 treatment-related adverse events (tagitanlimab plus GP arm vs placebo plus GP arm) were neutrophil count decreased (57.9% vs 49.0%), white blood cell count decreased (52.8% vs 46.9%), and anemia (38.6% vs 40.8%). **Conclusions:** The addition of tagitanlimab to GP demonstrated superior PFS efficacy compared to GP alone, supporting that tagitanlimab, as a PD-L1 inhibitor, could be the new standard of treatment for pts with R/M NPC in the first-line setting. The safety profile of tagitanlimab combined with GP was manageable and consistent with previous reports, with no new safety signals identified. Clinical trial information: NCT05294172. Research Sponsor: Sichuan Kelun-Biotech Biopharmaceutical Co., Ltd.

LBA6005 Oral Abstract Session

Becotatug vedotin vs. chemotherapy in pre-heavily treated advanced nasopharyngeal carcinoma: A randomized, controlled, multicenter, open-label study. First Author: Fei Han, Radiation Oncology Department, Sun Yat-sen University Cancer Center, Guangzhou, China

The full, final text of this abstract will be available at meetings.asco.org on the day of presentation and in the online supplement to the June 10, 2025, issue of the *Journal of Clinical Oncology*.

6006 Oral Abstract Session

SHR-A1811 in HER2-expressing salivary gland cancers: Preliminary efficacy and safety results. First Author: Guangliang Chen, Department of Head & Neck Tumors and Neuroendocrine Tumors, Fudan University Shanghai Cancer Center, Shanghai, China

Background: Salivary gland cancer (SGC) is a rare and heterogeneous malignancy with limited treatment options in advanced stages. Overexpression of human epidermal growth factor receptor 2 (HER2) is linked to aggressive histological subtypes and poor prognosis in SGC, making HER2 a promising target for precision therapy. This study evaluates the efficacy and safety of SHR-A1811, a HER2-targeted antibody-drug conjugate (HER2-ADC), in patients with advanced SGC through a molecular subtype-guided approach (NCT05924256). **Methods:** Patients with advanced SGC were stratified into four arms based on genetic subtypes. This analysis focuses on Arm 1 (HER2 overexpression: IHC 3+ or IHC 2+/ISH+) and Arm 4 (HER2-low: IHC 1+ or IHC 2+/ISH-). In Arm 1, patients received SHR-A1811 at 4.8 mg/kg IV on Day 1 of a 21-day cycle. In Arm 4, patients received 4.8 mg/kg or 5.6 mg/kg (if tolerated). The study followed Simon's two-stage design, with the primary endpoint of objective response rate (ORR) per RECIST v1.1. Secondary endpoints included disease control rate (DCR), progression-free survival (PFS), overall survival (OS), and safety. **Results:** As of January 1, 2025, 33 patients were enrolled (baseline characteristics in Table 1). In Arm 1 (21 evaluable patients), the ORR was 85.7%, and the DCR was 100%. In Arm 4 (10 evaluable patients), the ORR was 30.0%, and the DCR was 100%. After a median follow-up of 9.9 months (range: 1.2–16.6) for Arm 1 and 6.0 months (range: 4.7–9.2) for Arm 4, neither median OS nor PFS was reached. Only one patient in Arm 4 experienced disease progression. Treatment-related adverse events (TRAEs) occurred in 32 patients (97%). The most common grade 3/4 TRAEs included neutropenia (36%), leukopenia (15%), anemia (12%), and lymphopenia (12%). Two patients (6%) experienced treatment-related serious adverse events (SAEs), and one patient (3%) developed grade 1 interstitial lung disease. No patient discontinued treatment due to TRAEs, and no treatment-related deaths were reported. **Conclusions:** SHR-A1811 demonstrated promising efficacy in both HER2-positive and HER2-low advanced salivary gland cancers, achieving high ORRs and DCRs with an acceptable toxicity profile. Clinical trial information: NCT05924256. Research Sponsor: None.

Baseline characteristics.

	Arm 1 (N=23)	Arm 4 (N=10)
Age (years), Median (range)	58 (26-75)	56 (36-66)
Male : Female	16:7	8:2
HER2 status, n (%)	IHC 3+, 19 (83) IHC 2+/ISH+, 4(17)	IHC 1+, 8(80) IHC 2+/ISH-, 2(20)
Histology		
Salivary duct carcinoma, n (%)	12 (52)	1 (10)
Carcinoma ex pleomorphic adenoma, n (%)	3 (13)	2 (20)
Adenoid cystic carcinoma, n (%)	0	2 (20)
Others, n (%)	8 (35)	5 (50)
Prior treated for patients, n (%)	16 (70)	9(90)
Prior systemic therapy lines, Median (range)	0 (0-3)	1 (0-7)
Anti-HER2 treatment, n (%)	5 (22)	0

6007 Oral Abstract Session

Darolutamide plus goserelin for androgen receptor-positive salivary gland cancers: Results of phase 2 study (DISCOVARY). First Author: Susumu Okano, Department of Head and Neck Medical Oncology, National Cancer Center Hospital East, Kashiwa, Japan

Background: No standard treatment exists for unresectable locally advanced (LA) or recurrent/metastatic (R/M) salivary gland cancer (SGC). Previous findings suggest that combined androgen blockade (CAB) provides promising clinical activity in patients with androgen receptor (AR)-positive SGC. However, no AR-targeted drug is currently approved for SGC. This multi-center phase 2 study investigated two approaches in patients with unresectable LA or R/M SGC: darolutamide monotherapy followed by the combination of darolutamide and goserelin. In the monotherapy phase, darolutamide showed an objective response rate (ORR) of 20.8% as determined by independent central review (ICR) with tolerable toxicity (ASCO 2023). We now report the results from the combination phase. **Methods:** Eligible patients had histologically confirmed AR-positive LA or R/M SGC, ECOG performance status (PS) 0–2, adequate organ function, and no local therapy options. Patients received darolutamide orally at 1,200mg daily, combined with goserelin at 3.6 mg every four weeks. The primary endpoint was ORR by ICR in patients verified to have AR positivity through central assessment. Secondary endpoints included clinical benefit rate (CBR), disease control rate (DCR), progression-free survival (PFS), overall survival (OS), and safety profiles. **Results:** Between Sep 2022 and Aug 2023, 33 patients were enrolled in the combination phase. Median age was 63 years; 26 were male; ECOG PS 0/1/2 in 28/4/1. Histology included salivary duct carcinoma (n=32) or adenocarcinoma not otherwise specified (n=1). Prior treatment included surgery (n=23), radiotherapy (n=21), and chemotherapy (n=15). The ORR by ICR was 45.2% (14/31; 95% CI, 27.3–64.0), meeting the primary endpoint. CBR was 51.6% (95% CI, 33.1–69.8), and DCR was 64.5% (95% CI, 45.4–80.8). At a median follow-up of 13.7 months, the median PFS was 13.1 months (95% CI, 2.0– not calculable [NC]). Thirteen patients continued treatment at the data cutoff (August 9, 2024). Median OS was not reached (95% CI, 20.0–NC), and 12 months OS rate was 87%(95% CI, 68.9–94.9). Treatment was generally well tolerated, with six patients (18.2%) experiencing grade 3 adverse events. **Conclusions:** This is the first prospective CAB trial in SGC which has met its primary endpoint. Darolutamide plus goserelin demonstrated clinically meaningful efficacy and a favorable safety profile, suggesting it may be a compelling option before initiating chemotherapy, which can significantly diminish a patient's quality of life. Clinical trial information: NCT05694819. Research Sponsor: Bayer.

6008 Oral Abstract Session

Neoadjuvant pembrolizumab in combination with dabrafenib and trametinib (DTP) for *BRAF* V600E-mutated anaplastic thyroid cancer (*BRAF*m-ATC): A multicenter phase 2 trial. First Author: Mark Zafereo, The University of Texas MD Anderson Cancer Center, Houston, TX

Background: ATC patients present with advanced, often surgically unresectable disease with historically dismal prognosis. Median PFS and OS of DT without pembrolizumab were 6.7 and 13.5 months, respectively, in the ROAR trial. Neoadjuvant DTP achieved locoregional control without radical surgery in a retrospective series of *BRAF*m-ATC patients, providing rationale to evaluate efficacy and safety in a phase 2 prospective trial. **Methods:** In this single-arm multicenter phase 2 trial, patients with *BRAF*m-ATC stage IVB/IVC were enrolled in 5 US centers. Following a 3-6 week run-in with D (150 mg BID) and T (2 mg daily), P (200 mg Q3W) was added, with restaging every three (21-day) cycles. Post-operatively, patients continued P (or DTP) with radiotherapy or transitioned directly to adjuvant DTP (up to 26 cycles). Primary endpoints included R0/R1 resection rate (historically 5%) and overall survival (OS). Secondary endpoints included RECIST 1.1 response after DTP and progression-free survival (PFS). **Results:** Between 9/2021-1/2025, 42 patients were enrolled; 36 are included in the current analysis (3 not evaluable, 3 pending surgery) (Table). Patients received median 4 (range: 2-7) neoadjuvant DTP cycles, with 26 (72%) achieving radiographic PR/CR. 30 patients (83%) had surgery after neoadjuvant DTP, achieving R0/R1 resection in 29/30 (97%). Mean surgical morbidity score (0-4 scale, 4=unresectable) improved from 3.3 to 1.6 after DTP ($p<0.01$). Complete ATC pathologic response occurred in 20/30 patients (67%), while 10/30 (33%) had residual ATC in the surgical specimen. Postoperatively, 11/30 (37%) received adjuvant neck radiation, and 28/36 (78%) completed a median of 11 (range: 1-26) adjuvant DTP cycles. With median follow up 18 months, 15/36 (42%) patients died. Median OS was 20 months (95% CI: 12.6-NR); 1- and 2-year OS were 71% and 48%. Complete pathologic responders had better 2-year OS than those with residual ATC (69% vs. 22%, p=0.02). Median PFS was 13.9 months (95% CI, 7.5-NR); 1- and 2-year PFS were 57% and 36%. Grade 5 adverse events occurred in 8 patients (22%), including one possible (duodenal perforation), one probable (kidney injury with sepsis), and 6 unlikely/unrelated treatment-related deaths. **Conclusions:** Neoadjuvant DTP enables surgical resection in *BRAF*m-ATC compared with historical controls, and leads to improved PFS and OS. This approach should now be considered a standard of care for *BRAF*m-ATC. Clinical trial information: NCT04675710. Research Sponsor: Merck; Gateway for Cancer Research; G-20-1200; MD Anderson Petrick Philanthropy.

	Total N=36
Age (y), median (range)	67 (46-86)
Stage IVB/IVC, n (%)	15 (42%)/21 (58%)
Best RECIST response neoadjuvant phase, n (%)	
CR	2 (6%)
PR	24 (67%)
SD	6 (17%)
PD	4 (11%)
Percent change target lesion diameter, mean (95% CI)	-44% (-54%, -34%)
Surgical morbidity score change, mean (95% CI)	-1.7 (-2.1, -1.3)

6009 Clinical Science Symposium

Risk-adapted therapy guided by human papillomavirus (HPV) circulating tumor DNA in patients with HPV-positive oropharyngeal cancer (ReACT 1.0). First Author: Glenn J. Hanna, Department of Medical Oncology, Dana-Farber Cancer Institute, Boston, MA

Background: Human papillomavirus-positive oropharyngeal cancer (HPV+ OPC) has favorable outcomes with platinum-based concurrent chemoradiation (CRT), but long-term toxicity can be significant. Various treatment de-intensification strategies have been explored to maintain survival and mitigate treatment-related morbidity. We present the first study using tumor tissue modified viral (TTMV)-HPV DNA in real-time to stratify non-surgical patients (pts) to receive de-intensified, curative-intent CRT. **Methods:** This phase 2 two-cohort, clinical trial (NCT04900623) enrolled pts with AJCC 2017 8th ed. stage I-III (no fixed nodes) HPV+ OPC treated with CRT if they had detectable TTMV-HPV DNA (type 16) pre-treatment (pre-tx). Pts were assigned to the low-risk (LR) arm with T0-3 N0-2 disease, a $\leq$10 pack-year smoking history, and any detectable HPV DNA result pre-tx. Pts were assigned to the intermediate-risk (IR) arm with T4 disease or a $>$10 pack-year smoking history if they had a pre-tx HPV DNA score of $>$200. LR arm pts received de-intensified CRT (54-66 Gy with reduced dose platinum or RT alone). IR arm pts who cleared their pre-tx HPV DNA by $>$95% were also de-intensified; those $\leq$200 pre-tx or who failed to clear received standard 70 Gy CRT with up to 300 mg/m^2 cisplatin. Primary endpoint was 2-year progression-free survival (PFS) among all de-intensified LR and IR pts. Group-sequential testing for non-inferiority (NI) was performed Q4 months after the first 40 pts completed $>$6 months of follow-up. Interim analyses (IAs) were declared NI if the 2-year PFS lower CI bound was $>$80% among de-escalated LR/IR pts (Bootstrap approach; alpha 0.05). Secondary endpoints: safety, overall survival, distant metastasis-free survival, quality of life (QoL) metrics, and exploratory radiomic data. **Results:** From 7/2021 to 5/2024, 138 pts screened, 71 accrued (cohort 1). Most were male (62, 87%) and white (70, 99%) with a median age of 63 (range: 46-80). Forty-four (62%) were assigned to the LR arm (23% had N2 disease) with a median pre-tx HPV DNA of 439 (range: 6-221995). Twenty-seven (38%) pts were assigned to the IR arm (33% T4, 78% smokers) with a median pre-tx HPV DNA of 2346 (range: 207-84971). Among the 27 IR pts, 18 (67%) had $>$95% DNA clearance and were de-escalated. At a median follow-up of 14 months, the 2-year PFS estimate at IA2 was 92% (95%CI, 85-100) among 62 de-escalated LR/IR pts including 18 (29%) T4/smokers and 15 (24%) with N2 disease. Two distant and 2 locoregional plus distant failures occurred; with no isolated locoregional failures. QoL data is forthcoming; 1 patient died from disease. Cohort 2 explores further de-escalation and is ongoing. **Conclusions:** Using HPV DNA-guided CRT de-intensification we achieved our primary endpoint and report a favorable 2-year PFS $>$90%, which included T4 pts and smokers. HPV DNA as a biomarker to guide de-intensification warrants further study. Clinical trial information: NCT04900623. Research Sponsor: Dana-Farber Cancer Institute.

6010 Clinical Science Symposium

Dynamic circulating tumor DNA-driven, risk-adapted systematic therapy in nasopharyngeal carcinoma: The EP-STAR trial. First Author: Ying Sun, Sun Yat-sen University Cancer Center; Collaborative Innovation Center for Cancer Medicine; State Key Laboratory of Oncology in South China; Guangdong Key Laboratory of Nasopharyngeal Carcinoma Diagnosis and Therapy, Guangzhou, Guangdong, China

Background: Circulating tumor-derived Epstein-Barr virus (EBV) DNA (ctDNA) during treatment has been established as a biomarker in nasopharyngeal carcinoma (NPC). However, how this information would facilitate individualized management remains unknown. We designed EP-STAR, a multicentre, phase II, adaptive trial to investigate whether the dynamic on-treatment ctDNA-driven, risk-adapted treatment strategy improved survival for NPC patients. **Methods:** Locoregionally advanced NPC (stage III-IVA) with detectable pretreatment EBV DNA (excluding T3N0 with EBV DNA$<$2000 copy/mL), who received gemcitabine plus cisplatin induction chemotherapy (IC) concurrently with longitudinal on-treatment EBV DNA monitoring were enrolled and classified into different ctDNA risk subgroups. Low-risk patients (EBV $DNA_{post\text{-}IC1\text{-}3}$=0) did not undergo treatment adaptation and continued standard therapy (chemoradiotherapy, CCRT) (No_adaptive_Arm-control). At-risk patients (intermediate/high-risk) underwent risk-based treatment adaptation (Adaptive population): intermediate-risk patients (EBV $DNA_{post\text{-}IC1}>0$, EBV $DNA_{post\text{-}IC3}$=0 or EBV $DNA_{post\text{-}IC1}$=0, EBV $DNA_{post\text{-}IC2}>0$, EBV $DNA_{post\text{-}IC3}$=0) started treatment intensification with addition of adjuvant metronomic capecitabine to CCRT (650 mg/m² orally twice daily) (Adaptive_Arm-I_cap); high-risk patients (EBV $DNA_{post\text{-}IC1}>/=0$, EBV $DNA_{post\text{-}IC3}>0$) started treatment intensification with addition of 12 cycles sintilimab to CCRT (anti-PD-1 drug, 200 mg intravenously every three weeks) (Adaptive_Arm-II_sin). Primary endpoint was failure-free survival (FFS) of adaptive population; co-primary endpoint was FFS of Adaptive_Arm-II. **Results:** A total of 142 patients were enrolled (58 in Adaptive_Arm-I, 52 in Adaptive_Arm-II, 32 in No_adaptive_Arm-control). Primary endpoint was met, 3-year FFS of adaptive population was 89.0% (88.4–89.6%) at a median follow-up of 41.5 months (Table 1). Data compared favorably with historic cohort of the similar populations but did not undergo adaptive therapy (3-year FFS: 74.7% [68.8–80.6%]), Table 1). Toxicity was manageable with grade 3-4 adverse events recorded in 56.1% and 59.6% patients in Adaptive_Arm-I/II during adaptive phase, respectively; no treatment-related death was observed. **Conclusions:** The ctDNA-driven, risk-adapted paradigm was highly likely to result in improved survival outcomes than conventional unchanging treatment strategy in NPC. Clinical trial information: NCT04072107. Research Sponsor: Major Research Plan of the National Natural Science Foundation of China; 92259202.

Summary of FFS in EP-STAR and the similar population in historic control.

	EP-STAR	Historic control (*Prospective, Cancer Cell, 2024*)
Recruitment year	2020-2021	2019-2021
3-year FFS		
Intermediate & high-risk patients with or without adaptive therapy	89.0% (88.4–89.6%)	74.7% (68.8–80.6%)
High-risk patients with or without adaptive therapy	86.5% (77.3–95.7%)	64.8% (55.0–74.6%)
Low-risk patients	93.8% (91.0–100.0%)	90.8% (85.9–95.7%)

6011 Clinical Science Symposium

REMATCH2201: A phase II study on reducing surgical margins in HPV-negative advanced HNSCC with neoadjuvant PD-1 inhibitor and AP chemotherapy. First Author: Kunyu Yang, Cancer Center, Union Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China

Background: The standard of care for resectable HNSCC includes extensive surgical margins to ensure complete oncologic resection, often at the expense of significant functional impairment. Recent advancements in neoadjuvant PD-1 inhibitors with chemotherapy, have shown potential in achieving substantial tumor regressions. This study posits that such neoadjuvant immunochemotherapy can allow for narrower surgical margins without compromising oncological outcomes, potentially preserving vital anatomical structures and function. **Methods:** This single-center, phase II clinical study (NCT05459415) enrolled 52 patients with operable, HPV-negative locally advanced HNSCC. Participants received three cycles of the AP chemotherapy regimen combined with 200 mg of the PD-1 inhibitor Penpulimab. Tumor response was assessed via MRI and laryngoscopy after the second cycle. Patients achieving greater than 50% reduction in tumor size were selected for conservative-margin surgical resection. Surgical Protocol: If imaging or endoscopy identifies residual tumor, margins will be expanded 5-10mm beyond the tumor edges to ensure clear margins, confirmed by intraoperative frozen section analysis by dual pathologists, ensuring maximal oncologic safety and functional preservation. For patients achieving CR, surgical planning relies on prior diagnostic imaging and endoscopic outcomes to guide precise resections of the larynx and hypopharynx. Post-surgical adjuvant treatment was based on final pathology results, including further immunotherapy for nine cycles. **Results:** Of the initial cohort, 50 patients were evaluable for response; the objective response rate (ORR) stood at 96%, and a pathologic complete response (pCR) was observed in 40.7% of patients. Forty-seven patients proceeded to surgery, all maintaining laryngeal function, and 91.5% underwent reduced-margin resection based on deep imaging response, with a pCR achieved in 44.2% of these cases. The study noted clinical adverse events, including three unrelated deaths and two instances of severe postoperative complications. The 12-month and 24-month Event-Free Survival (EFS) rates were calculated at 97.62% and 89.28% respectively. The overall survival (OS) rate at 24 months was 92.85%. **Conclusions:** The REMATCH2201 trial supports the feasibility of reduced-margin surgery in patients with HPV-negative advanced HNSCC following effective neoadjuvant immunochemotherapy, without increasing the risk of oncologic recurrence. This approach importantly spares critical functional anatomy, advocating for a paradigm shift in the surgical management of these tumors. Nevertheless, further research in a multi-center, randomized controlled trial setting is required to substantiate these findings and refine protocols for broader application in clinical practice. Clinical trial information: NCT05459415. Research Sponsor: Chia Tai Tianqing Pharmaceutical Group Co., Ltd.

6012 Rapid Oral Abstract Session

Neoadjuvant and adjuvant pembrolizumab plus standard of care (SOC) in resectable locally advanced head and neck squamous cell carcinoma (LA HNSCC): Exploratory efficacy analyses of the phase 3 KEYNOTE-689 study. First Author: Douglas Adkins, Washington University School of Medicine, St. Louis, MO

Background: The addition of immune checkpoint inhibitors to neoadjuvant/adjuvant SOC has led to efficacy benefits across multiple tumor types. The randomized phase 3 KEYNOTE-689 study (NCT03765918) showed significantly improved event-free survival (EFS) with neoadjuvant/adjuvant pembrolizumab + SOC vs SOC alone for participants (pts) with resectable LA HNSCC independent of PD-L1 combined positive score (CPS ≥10 population: HR 0.66, 95% CI 0.49–0.88, *P*=.00217; CPS ≥1 population: HR 0.70, 95% CI 0.55–0.89, *P*=.00140; all pts: HR 0.73, 95% CI 0.58–0.92, *P*=.00411). We present exploratory efficacy endpoints for the intention-to-treat population of the study. **Methods:** Adults with SCC of the larynx/hypopharynx/oral cavity (stage III/IVA) or oropharynx (stage III/IVA p16− or stage III T4 N0-2 p16+) were randomized 1:1 to SOC (consisting of surgery + postoperative radiotherapy [PORT] ± concurrent cisplatin 100 mg/m^2 Q3W) with or without 2 cycles of neoadjuvant pembrolizumab, 3 cycles of pembrolizumab concurrent with PORT ± cisplatin and 12 cycles of adjuvant pembrolizumab (200 mg IV Q3W). The primary endpoint is EFS per RECIST 1.1 by blinded independent central review. Safety is a secondary endpoint. Prespecified exploratory efficacy endpoints include locoregional control (time from randomization to first locoregional radiographic progression or recurrence by imaging or biopsy), distant metastases-free survival (DMFS; time from randomization to first distant metastasis or death), and incidence of second head and neck or other cancers. **Results:** A total of 714 pts were randomized (363 to pembrolizumab + SOC, 351 to SOC). At first interim analysis (data cutoff date 25 Jul 2024), median follow-up was 38.3 mo (range, 9.0–66.5). In all pts, cumulative incidence of locoregional progression or recurrence at 36 mo was 13.4% with pembrolizumab + SOC and 14.3% with SOC. The HR for risk of a locoregional failure event with pembrolizumab + SOC vs SOC was 0.92 (95% CI 0.61–1.41). Median DMFS was 51.8 mo with pembrolizumab + SOC vs 35.7 mo with SOC (HR 0.71, 95% CI 0.56–0.90). Estimated DMFS rate at 36 mo was 59.1% vs 49.0%, respectively. Second head and neck or other cancers occurred in 9 (2.5%) and 18 pts (5.1%), respectively. Incidence of treatment-related adverse events was similar with pembrolizumab + SOC and SOC (any grade, 81.4% vs 81.9%; grade ≥3, 44.6% vs 42.9%). **Conclusions:** Among all pts with resectable LA HNSCC in KEYNOTE-689, DMFS results and incidence of second cancers favored the addition of neoadjuvant/adjuvant pembrolizumab to SOC surgery and (chemo)radiotherapy, consistent with the primary EFS results of the study. Locoregional control was similar between arms. No new safety signals for pembrolizumab were observed. Clinical trial information: NCT03765918. Research Sponsor: This study was funded by Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA.

6013 Rapid Oral Abstract Session

Long-term results of the randomized, phase 3 KEYNOTE-412 trial of pembrolizumab (pembro) or placebo (pbo) plus concurrent chemoradiotherapy (CRT) for unresected, locally advanced head and neck squamous cell carcinoma (LA HNSCC). First Author: Yungan Tao, Institut Gustave Roussy, Villejuif, France

Background: In the final efficacy analysis of the randomized, double-blind, phase 3 KEYNOTE-412 trial (NCT03040999), pembro + CRT did not significantly improve event-free survival (EFS) vs pbo + CRT (HR 0.83; 95% CI 0.68-1.03) in unresected LA HNSCC. We present results for KEYNOTE-412 with >2 yrs of additional follow-up. **Methods:** Adults with newly diagnosed high-risk unresected LA HNSCC (any T3-T4 [N0-N3] or any N2a-3 [T1-T4] larynx/hypopharynx/oral cavity/p16-negative oropharynx cancers and T4 or N3 p16-positive oropharynx cancer) were randomly assigned to receive CRT (70 Gy in 35 fractions + 3 cycles cisplatin 100 mg/m^2 Q3W) + 17 cycles of pembro 200 mg or pbo IV Q3W: first cycle 1 week prior to CRT, 2 cycles during CRT, then 14 cycles of maintenance. The primary end point was EFS assessed by blinded independent central review. The key secondary end point was overall survival (OS). Efficacy was analyzed in all randomly assigned pts (ITT population). Exploratory analyses included locoregional control (LRC), distant metastasis-free survival (DMFS), incidence of second malignancies in the ITT population, and efficacy in pts with PD-L1 CPS ≥1. **Results:** 402 pts were assigned to each arm; and 398 received ≥1 dose of study treatment in each arm. As of data cutoff date (August 21, 2024), median study follow-up was 74.4 mo (range, 63.7-88.1). EFS was longer with pembro vs pbo (HR 0.79; 95% CI 0.65-0.96). Overall, 186 (46.3%) and 217 (54.0%) EFS events occurred in the pembro and pbo arms, which represents an additional 15 events in the pembro arm and 25 in the pbo arm since the previous analysis. Full efficacy results for the ITT population are in the table. LRC HR was 0.80 (95% CI 0.57-1.14). Overall, 36 pts (9.0%) in the pembro arm and 45 (11.2%) in the pbo arm developed a secondary malignancy. In pts with PD-L1 CPS ≥1 (pembro, n = 339; pbo, n = 346), median EFS was 70.9 mo (95% CI 55.4-not reached [NR]) for the pembro arm and 48.3 mo (95% CI 26.8-66.8) for the pbo arm (HR 0.80; 95% CI 0.64-0.98); median OS was NR (NR; 95% CI NR-NR) for the pembro arm and NR (95% CI 70.0-NR) for the pbo arm (HR 0.84; 95% CI 0.66-1.06). The safety profile was consistent with previously reported adverse events at the time of the final analysis. **Conclusions:** At end of trial, with >2 yrs of additional follow-up, results showed a clinically meaningful EFS benefit with pembro + CRT versus pbo + CRT and no new safety signals in pts with LA HNSCC. Clinical trial information: NCT03040999. Research Sponsor: Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA.

	Pembro + CRT (n = 402)	Pbo + CRT (n = 402)
EFS, median (95% CI), mo	71.8 (55.4-NR)	49.8 (26.8-66.2)
HR (95% CI)	0.79 (0.65-0.96)	
5-yr EFS rate, %	54.7	47.2
OS, median (95% CI), mo	NR (NR-NR)	NR (74.3-NR)
HR (95% CI)	0.86 (0.70-1.07)	
5-yr OS rate, %	64.4	59.8
DMFS, median (95% CI), mo	NR (68.9-NR)	64.3 (49.8-76.0)
HR (95% CI)	0.80 (0.65-0.98)	
5-yr DMFS rate, %	58.6	51.3

6014 Rapid Oral Abstract Session

A randomized, open-label, multicenter, blank-controlled, phase IV clinical trial of Biyan Qingdu Granula in attenuating acute nose and oral damage in patients undergoing radiotherapy for nasopharyngeal carcinoma. First Author: Zhigang Liu, Cancer Center, the tenth Affiliated Hospital of Southern Medical University (Dongguan People's Hospital), Southern Medical University, Dongguan, China

Background: This randomized, open-label, multicenter, blank-controlled, phase IV trial aimed to evaluate the efficacy and safety of Biyan Qingdu Granula (BQG) in attenuating acute radiation-induced nasal and oral injuries in nasopharyngeal carcinoma(NPC) patients receiving radiotherapy, and to explore the potential advantages and application values of BQG through comparison with conventional treatments. **Methods:** This trial was conducted at 30 hospitals in China between July 21st, 2022 and May 21st, 2024.This trial was registered with the Chinese Clinical Trial Registry, ChiCTR2200060900. A total of 1000 NPC patients with first-time radiotherapy or chemoradiotherapy for NPC were randomly assigned (1:3) to receive routine cure (the control group, n=250) or that with additional BQG (the treatment group, n=750). All patients received basic oral hygiene guidance, gargled the oral cavity with normal saline and flushed the nasal cavity with normal saline. The treatment group patients were instructed to take BQG twice daily from the initiation to the end of radiotherapy for 6 weeks. The primary end points were the incidence of nasopharyngeal secretion and the incidence of Oral Mucositis (OM). The second end points were the grade of nasal mucosal congestion, the Visual Analog Scale (VAS) score for sore throat pharyngeal pain, the grade of symptom in dry and burning throat, the incidence of nasal comorbidities, and the incidence of adverse events (AEs). **Results:** 731 patients in the treatment group and 250 patients in the control group completed the trial, baseline patient characteristics were similar. After six weeks, the incidence of severe nasopharyngeal secretion (grade middle or higher)in the treatment group was significantly lower as compared with the control group(12.4% vs 20.0%, P=0.0033). The incidence of severe OM (World Health Organization grade 3 or higher) was significantly lower in the treatment group than in the control group (12.3% vs 22.4%, P=0.0001). The intergroup rate difference and 95% CI of the incidence of OM between the two groups was -10.1% (-15.8%, -4.4%). The upper limit of the 95% CI was greater than -10%, so it could not be concluded that the experimental group was superior to the control group. However, compared with the control group, the treatment group showed a certain trend in reducing oral mucositis. The BQG group also remarkably reduced the incidence of severe VAS score for sore throat pharyngeal pain and the grade of symptom with dry and burning throat compared to the control group. The incidence of AEs were similar between the groups. **Conclusions:** BQG significantly attenuated the incidence of nasal secretions in NPC patients undergoing radiotherapy, improved pharyngeal pain and the symptoms with dryness and burning, with a good safety profile. Clinical trial information: ChiCTR2200060900. Research Sponsor: Supported by Hutchison Whampoa Guangzhou Baiyunshan Chinese Medicine Co., Ltd.

6015 Rapid Oral Abstract Session

Phase 2 open-label study of brentuximab vedotin (BV) + pembrolizumab (pembro) in patients (pts) with treatment (tx)-naive metastatic head and neck squamous cell carcinoma (HNSCC). First Author: Cristina P. Rodriguez, Fred Hutchinson Cancer Center, Seattle, WA

Background: BV, an antibody-drug conjugate (ADC) targeting CD30, is hypothesized to deplete T regulatory cells (Tregs) that express CD30 and resensitize tumors to anti–PD-1 therapy. SGN35-033 (NCT04609566) is an ongoing multicohort study evaluating the efficacy and safety of BV + pembro in pts with solid tumors; we report results for cohort 6 in tx-naive HNSCC with PD-L1 combined positive score (CPS) ≥1, where pembro has historically demonstrated ORR of 19% and mPFS of 3.2 months. **Methods:** Cohort 6 included pts with metastatic HNSCC with PD-L1 CPS ≥1 by local testing and no prior therapy for metastatic disease or exposure to a PD-1/PD-L1 inhibitor. Pts received BV 1.8 mg/kg + pembro 200 mg every 3 wks. The primary endpoint was confirmed ORR assessed by investigator per RECIST 1.1. Secondary endpoints included DOR, PFS, and safety. Exploratory endpoints included OS and biomarker analyses. A genAI tool (01/02/25; Pfizer; GPT-4o) developed the 1st draft; authors assume content responsibility. **Results:**As of 10/25/24, 32 pts received ≥1 dose of BV + pembro. In all pts, the confirmed ORR was 34% (95% CI, 18.6-53.2), with median follow-up duration of 9.7 mo and median DOR not reached (95% CI, 3.9 mo-not estimable [NE]). BOR is in the Table. Responses were seen regardless of HPV status and across PD-L1 CPS ≥1 subgroups, with responses in 11 of 32 (34%) vs 9 of 25 (36%) in CPS ≥1 vs CPS ≥20, respectively. The KM estimate of DOR ≥6 mo was 89%. Median PFS was 7.2 mo (95% CI, 3.2 mo-NE); 6-mo PFS rate was 56%. Biomarker analyses of peripheral blood showed that Tregs expressed relatively higher CD30 vs other T cells. There was a trend of Treg depletion and increased T-cell proliferation and activation after BV + pembro. Observed PK of BV when combined with pembro in HNSCC was similar to that of BV monotherapy. All pts had ≥1 tx-emergent adverse event (TEAE); 24 pts (75%) had a grade ≥3 TEAE; 10 pts (31%) had tx-related grade ≥3 TEAEs. The most common tx-related grade ≥3 TEAEs were lymphocyte count decreased (13%), ALT increased, fatigue, neutropenia, and neutrophil count decreased (6% each). Tx-related serious TEAEs were reported in 2 pts (6%). No new safety signals were identified. **Conclusions:** BV + pembro demonstrated promising clinical efficacy with a safety profile consistent with each individual agent in pts with tx-naive metastatic HNSCC with PD-L1 CPS ≥1. Biomarker analyses support the hypothesized immunomodulatory mechanism of action of BV + pembro. These encouraging data are consistent with prior findings in PD-1–refractory NSCLC and melanoma and support continued investigation of CD30-directed ADCs + anti–PD-1 therapy in solid tumors. Clinical trial information: NCT04609566. Research Sponsor: Pfizer.

	n=32
BOR, n (%)[a]	
Complete response	1 (3)
Partial response (PR)	10 (31)
Stable disease	12 (38)
PD	5 (16)

[a]1 pt (3%) had unconfirmed PR at data cutoff; 3 pts (9%) discontinued tx with no postbaseline response assessment.

6016 Rapid Oral Abstract Session

Randomized phase I trial of adjuvant personalized cancer vaccine TG4050 in resected locally advanced (LA) head and neck squamous cell carcinoma (HNSCC) patients (pts). First Author: Christophe Le Tourneau, Department of Drug Development and Innovation (D3i), Institut Curie, Paris-Saclay University, Paris, France

Background: Approximately one third of pts with resected LA HNSCC recur. T-cells targeting tumor specific mutations drive anti-tumor immune responses. TG4050 is a viral-based personalized cancer vaccine, encoding up to 30 tumor-specific DNA sequences bearing in-silico predicted class I and class II epitopes. We hypothesized that TG4050 prime an adaptive immune response against tumor antigens and prevent relapse in pts with resected LA HNSCC after treatment with curative intent (NCT04183166). **Methods:** The multicenter, open label, randomized, 2-arm Phase I trial evaluated TG4050 in LA HNSCC pts achieving complete remission following surgery and adjuvant radiotherapy +/- chemotherapy. Pts were randomized to receive (Arm A) weekly doses of TG4050 for 6 weeks followed by a maintenance period of one dose every 3 weeks for up to 20 doses or no vaccine (Arm B, vaccination at relapse in combination with SOC). Safety, efficacy and immunogenicity were evaluated. In selected pts, exploratory characterization of the T cell response was performed using tetramer staining, bulk and single-cell (sc)TCR sequencing. **Results:** 33 pts were randomized between January 2021 and April 2023, 17 pts to Arm A and 16 pts to Arm B. Median age was 61 years (26-79 years), tumor location was oral cavity in 24 pts (72.7%), hypopharynx and oropharynx in 4 pts (12.1%), respectively and larynx in one pt (3.0%). TG4050 was safe and well tolerated with only grade 1 or 2 treatment-related adverse events (AEs). The most frequently reported were injection site reactions. After a median follow-up of 28.5 months, all 16 pts receiving TG4050 in Arm A remained disease-free whereas 3 out of 16 pts in Arm B relapsed. Disease Free Survival (DFS) data at 24 months for all patients will be presented. Exploratory qualitative analyses of the neoantigen-specific T cell response by ELISpot were presented previously. In-depth characterization of the neoantigen-specific T cells including clonal expansion by TCR sequencing and longitudinal analysis by tetramer staining will be presented. **Conclusions:** TG4050 is safe and induces immune responses in pts with resected LA HNSCC. No relapse occurred in the vaccine arm as opposed to 19% in the control arm. With the evolution of the landscape, adjuvant anti-PD1 therapy may become standard in resected LA HNSCC. TG4050 warrants further evaluation in combination with anti-PD1 therapy in phase III trials. Clinical trial information: NCT04183166. Research Sponsor: None.

6017 Rapid Oral Abstract Session

Ficerafusp alfa with pembrolizumab in patients with recurrent or metastatic head and neck squamous cell carcinoma: Updated results from an expansion cohort of an open-label, multicenter, phase 1/1b trial. First Author: Christine H. Chung, Moffitt Cancer Center and Research Institute, Tampa, FL

Background: HPV-negative head and neck squamous cell carcinoma (HNSCC) is an aggressive disease characterized by high recurrence, metastasis (R/M), and resistance to standard treatments. While anti–PD-1 therapies have improved outcomes, the prognosis for R/M HNSCC remains poor, necessitating novel approaches to achieve deeper, more durable responses and improved overall survival (OS). Ficerafusp alfa is a first-in-class bifunctional antibody targeting EGFR and TGF-β. **Methods:** This single-arm, multicenter, dose expansion of an ongoing phase 1/1b study (NCT04429542) enrolled patients (pts) aged ≥18 years with treatment-naive, unresectable R/M HNSCC, with a CPS ≥1. Pts received ficerafusp alfa (1500 mg IV on days 1, 8, and 15) combined with pembrolizumab (200 mg IV on day 1) every 21 days. Study objectives included objective response rate (ORR) per RECIST v1.1, duration of response (DOR), progression-free survival (PFS), OS, safety (CTCAE v5), and pharmacodynamic analyses. This report presents updated findings after two years of follow-up. **Results:** As of December 16, 2024, 42 pts were treated (71% male, median age: 63 years [range: 31–84]); 39 were efficacy evaluable (EE). Among the EE pts, the ORR was 54% (21/39; 95% CI: 37–70) in the overall cohort and 64% (18/28; 95% CI: 44–81) in HPV-negative pts. Notably, 21.4% of HPV-negative pts achieved a complete response (CR). A confirmed durable response of ≥6 and ≥12 months was observed in 72% (13/18) and 56% (10/18) of overall and 73% (11/15) and 60% (9/15) of HPV-negative responders, respectively. Median PFS was 7.4 months (95% CI: 2.9–14.5 overall, and 9.8 months (95% CI: 4.4–23.2) in the HPV-negative subgroup. The 12-month OS rate was 61.5% (95% CI: 44.5–75.7) across the cohort and 60.7% (95% CI: 40.4–76.0) for HPV-negative pts. At data cutoff, all evaluable pts had been followed for at least 20 months. Median OS and DOR had not been reached yet in HPV-negative pts, with mOS surpassing 20 months. Safety findings were consistent with the known safety profile of ficerafusp alfa plus pembrolizumab, while pharmacodynamic analyses demonstrated encouraging post-treatment downregulation of pSMAD2 supporting targeted TGF-β inhibition. **Conclusions:** Ficerafusp alfa combined with pembrolizumab continues to show promising efficacy relative to historical data on the current standard of care, particularly in HPV-negative HNSCC. Median PFS and 12-month OS, ORR, and CR rates are encouraging relative to historical benchmarks in pts with HPV-negative HNSCC. 24-month OS and mature OS/DOR outcomes are anticipated. These findings provide compelling rationale for FORTIFI-HN01, the ongoing multicenter, randomized, double-blind phase 2/3 clinical trial evaluating this combination in first-line PD-L1–positive, HPV-negative R/M HNSCC. Clinical trial information: NCT04429542. Research Sponsor: Study funded by Bicara Therapeutics Inc. with access to pembrolizumab in collaboration with Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA (NCT04429542).

6018 Rapid Oral Abstract Session

Neoadjuvant PD-1 inhibitor combined with Nab-paclitaxel and cisplatin in resectable locally advanced head and neck squamous cell carcinoma (NCT05522985): A randomized, controlled, open label, phase II clinical trial. First Author: Hongling Wang, Department of Maxillofacial and Otorhinolaryngological Oncology, Tianjin Medical University Cancer Institute and Hospital, Key Laboratory of Cancer Prevention and Therapy, Tianjin Cancer Institute, National Clinical Research Center of Cancer, Tianjin, China

Background: More than 60% of head and neck squamous cell carcinoma (HNSCC) patients (pts) were locally advanced at diagnosis. Many previous clinical trials have confirmed that induction chemotherapy can improve the functional retention rate of HNSCC and improve the quality of life. However, pts have no long-term survival benefits from it. In recent years, immunotherapy has brought hope for long-term survival to pts with recurrent and metastatic HNSCC. The exploration of neoadjuvant immunotherapy in HNSCC is also gradually carried out. **Methods:** This was a randomized, controlled, open label, phase II study. 122 pts were panned to enrolled. Key inclusion criteria: pts aged ≥18 years; histologically or cytologically confirmed stage III or IV resectable HNSCC; without prior system anticancer therapy; ECOG≤1. Eligible pts were randomized 1:1 to receive toripalimab (240mg, D1, q3w) in combination with nab-paclitaxel (260 mg/m2,d1,q3w) and cisplatin (75mg/m^2,q3w) for 3 cycles (experimental arm) or nab-paclitaxel (260 mg/m^2,d1,q3w) and cisplatin (75mg/m^2, q3w) for 3 cycles (control arm). Then surgery and pathological remission evaluation was performed. The primary endpoint was pathologic complete response (pCR) rate. Secondary endpoints were major pathological response (MPR), objective response rate (ORR), 2-year progression-free survival (PFS) rate, 2-year overall survival (OS) rate, and safety. **Results:** A total of 122 pts were enrolled (experimental 61, control 61). Median age was 59.5 years (range: 34–83) and 80.33% were male. After neoadjuvant treatment, 88 pts underwent surgery (experimental 45, control 43). pCR rate was significantly different between the two arms (experimental 57.78%, control 34.88%, p = 0.03). More pts achieved MPR (experimental 82.22%, control 53.46%, p = 0.004) in experimental arm. In experimental arm, 2-year DFS (experimental 86.67%, control 71.95%) and 2-year OS (experimental 90.61%, control 77.74%) were higher, the statistical significance was undetermined. The proportion of Grade ≥3 treatment-related adverse events (TRAEs) in the experimental and control arms were 16.39% and 9.84%, respectively. The most common TRAEs are Agranulocytosis, Nausea, Alopecia and Vomiting. No new safety signals were observed and no TRAEs leading to death. There was no significant difference in TRAEs of two arms. **Conclusions:** Comparing to chemotherapy, neoadjuvant immunochemotherapy can significantly improve the pCR and MPR rate of HNSCC. Moreover, adverse events are controllable. And immune neoadjuvant therapy demonstrates a trend towards improving survival. Clinical trial information: NCT05522985. Research Sponsor: None.

6019 Rapid Oral Abstract Session

An open-label, phase Ib trial of the SIRPα inhibitor BI 765063 in combination with the PD-1 inhibitor ezabenlimab and cetuximab in patients (pts) with head and neck squamous cell carcinoma. First Author: Katerin Ingrid Rojas L, Hospital Universitari Vall d'Hebron, Barcelona, Spain

Background: BI 765063 is a first-in-class, humanized IgG4 monoclonal antibody that binds the V1 allele of signal regulatory protein α (SIRPα) and blocks the 'don't eat me' signal of the SIRPα/CD47 axis. This leads to reactivation of innate antitumor responses, restoring phagocytosis and antigen presentation. In a Phase Ia/Ib trial in pts with advanced solid tumors (NCT03990233), BI 765063 ± ezabenlimab was well tolerated with no dose-limiting toxicities and preliminary efficacy was observed (Kotecki et al, ESMO 2021). This Phase Ib study (NCT05249426) is investigating the efficacy and safety of BI 765063 in combination with ezabenlimab + cetuximab (Cohort A) or ezabenlimab + chemotherapy (Cohort B) in pts with recurrent/metastatic (R/M) head and neck squamous cell carcinoma (HNSCC), or in combination with ezabenlimab ± BI 836880 (anti-VEGF/Ang2) in pts with hepatocellular carcinoma. Here, we focus on pts with HNSCC who received BI 765063 combined with ezabenlimab + cetuximab (Cohort A). **Methods:** In Cohort A, adult pts with R/M HNSCC who had received 1 previous systemic therapy (excluding immune checkpoint inhibitors) were eligible. Other inclusion criteria included SIRPα V1/V1 homozygosity (detected in plasma), ≥1 measurable lesion (RECIST v1.1) and ECOG performance status of 0/1. Pts received BI 765063 (24 mg/kg every 3 weeks [q3w]), ezabenlimab (240 mg q3w) and cetuximab (per local guidelines). Primary endpoint was confirmed objective response (OR; RECIST v1.1). Secondary endpoints included disease control (DC) and treatment-emergent adverse events (TEAEs). **Results:** At data cut-off (Dec 2, 2024), 18 pts had been enrolled to Cohort A and received BI 765063 plus ezabenlimab + cetuximab (1 pt was subsequently found to be ineligible). Of the 17 eligible pts, median age was 51 years (range, 33–81), 88% were male and all had received 1 prior therapy. Eight pts (47%) achieved a confirmed OR (3 complete and 5 partial responses) and a further 7 (41%) achieved stable disease to give a DC rate of 88%. Median duration of DC was 7.6 months. TEAEs were reported in all 17 pts. Most common TEAEs were acneiform dermatitis (any grade/grade ≥3, 53%/0%), anemia (35%/24%), hypokalemia (29%/6%), hypothyroidism (29%/0%) and rash (29%/0%). Most common BI 765063 treatment-related AEs (TRAEs) were hypothyroidism (24%) and acneiform dermatitis (18%), all grade 1/2. Grade 3 TRAEs (asthenia, cardiac failure, epistaxis, hypoalbuminemia, lymphopenia, mouth hemorrhage, post-procedural hemorrhage and suspected drug-induced liver injury) were each reported in 1 pt. There were no grade 4/5 TRAEs. **Conclusions:** These preliminary data indicate that BI 765063 in combination with ezabenlimab and cetuximab has a manageable safety profile and promising efficacy as second-line treatment in pts with R/M HNSCC. Biomarker data will be presented at the meeting. Clinical trial information: NCT05249426. Research Sponsor: Boehringer Ingelheim.

6020 Rapid Oral Abstract Session

Dose expansion data from iintune-1, a phase 1/2 study of the STING agonist dazostinag plus pembrolizumab as first-line (1L), in patients with recurrent/metastatic squamous cell carcinoma of the head and neck (RM-SCCHN). First Author: Jérôme Fayette, Centre Léon Bérard, Lyon, France

Background: Checkpoint inhibitors (CPIs) such as pembrolizumab (pembro) can lead to improved outcomes and durable responses in patients (pts) with RM-SCCHN. However, only a subset of pts with RM-SCCHN experience this benefit, and an unmet need for better treatments remains. STimulator of INterferon Genes (STING) agonism enhanced the response to CPIs preclinically. Dazostinag (dazo) is a small molecule STING agonist that has shown antitumor activity and activation of innate and adaptive immune responses in pts with solid tumors in the dose escalation part of iintune-1, with a recommended dose for expansion of 5 mg in combination with pembro. We report data from the ongoing dose expansion cohort 2A of iintune-1 in the first 30 pts with incurable 1L RM-SCCHN with a PD-L1 combined positive score (CPS) $\geq$1, treated with dazo in combination with pembro (NCT04420884). **Methods:** Pts receive dazo 5 mg IV on Days 1, 8, 15 plus pembro 200 mg IV on Day 1, in 21-day cycles. Primary endpoints are safety and tolerability. Secondary endpoints include investigator-assessed overall response rate (ORR) per RECIST 1.1 and duration of response (DOR). Dose optimization is planned as part of expansion. **Results:** As of Dec 16, 2024, 30 pts had been enrolled and received treatment. Median age was 64 years and 73% of pts were male. The most common primary tumor locations were oral cavity (n=10, 33%), oropharynx (n=8, 27%), and larynx (n=6, 20%). Median CPS score was 13.5 (range, 1–101). A median of 4.5 treatment cycles (range 1–15) were received. Treatment-emergent adverse events (TEAEs) occurred in all pts (grade $\geq$3 in 37%); the most common were fatigue (40%), nausea (27%), cough (23%), and headache (20%). Dazo-related TEAEs occurred in 80% of pts (grade $\geq$3 in 13%); the most common was fatigue (30%). Cytokine release syndrome was reported in 4 pts (13%; all dazo-related and grade 1–2). TEAEs led to dazo discontinuation in 1 pt. No treatment-related deaths were reported. Among 29 response-evaluable pts, 1 had a confirmed complete response and 7 had confirmed partial responses (+2 unconfirmed), for an ORR of 34%. Median DOR was not reached. Pharmacodynamic analyses revealed biomarker changes consistent with the expected mechanism of action and dose escalation data, including induction of a STING gene signature, cytokine induction, peripheral immune cell activation and CD8+ T cell recruitment to the tumor. Analyses of changes in peripheral ctDNA pre- and post-treatment are ongoing. **Conclusions:** This early study of dazo 5 mg IV in combination with pembro showed a manageable safety profile with an encouraging ORR in pts with RM-SCCHN. Pharmacodynamic findings demonstrate peripheral and intratumor changes consistent with STING agonism. Clinical trial information: NCT04420884. Research Sponsor: Takeda Development Center Americas, Inc. (TDCA), Lexington, MA.

6021 Poster Session

Real world utilization of comprehensive genomic profiling (CGP) in head and neck squamous cell carcinoma (SCCHN). First Author: Connie Jiayu Zhou, University of California, San Francisco, San Francisco, CA

Background: In Head and Neck Cancer, practice trends of utilizing comprehensive genomic profiling (CGP) vary depending on physician preference and test availability. Here, we examined the impact of CGP on treatment decision-making and patient outcomes in SCCHN at a single institution. **Methods:** Patients with suspected SCCHN underwent tumor-based CGP using the UCSF500 or TEMPUS xT NGS panel. In addition to demographic and clinicopathologic data, we obtained the reason for CGP when noted, disease stage and line of therapy at the time of CGP, CGP results, and post-CGP treatments. OncoKB was used to annotate actionable mutations in Head and Neck Cancer, in addition to other biomarkers when available (microsatellite instability (MSI), tumor mutation burden (TMB), and EGFR amplification). **Results:** Between January 2016 and December 2023, 301 unique patient tumor specimens underwent CGP in the setting of suspected or known SCCHN. Sequencing was performed to refine a diagnosis in 57 samples (18.9%). CGP influenced the determination between cutaneous and mucosal primary in 35 samples, clarified the histology in 9, and clarified the origin of a metastatic lesion in 13. For patients with confirmed SCCHN (N = 246), CGP was performed for therapy selection in 193 (78.5%) of patients. Of these, 19 (9.8%) patients were TMB-high (TMB$>$10), 2 (1.0%) patients were MSI-high, 77 (39.9%) patients were found to have actionable genomic alterations, and clinicians had access to OncoKB-specified agents for 50 (25.9%) of the patients. Anti-PD-1 antibody therapy was administered to 15/20 (75%) of TMB-high and/or MSI-high patients compared to 38 (53.5%) with low TMB or MSI-stable disease. The most common actionable individual gene alterations were in *CDKN2A* (37.3%), *PIK3CA* (14.5%), *PTEN* (7.2%), *FBXW7* (6.0%), and *HRAS* (6.0%) genes. Six of 77 (7.8%) patients with actionable genomic alterations received targeted therapy based on drug availability and the clinical discretion of the treating physician.In these, the overall response rate was 50% (3/6), and the median PFS was 2.6 months. Thus, at this site, the number needed to treat to gain one response in SCCHN patients undergoing sequencing for oncogene-targeted options was 64.5 patients. **Conclusions:** CGP in HNSCC was used most commonly to increase diagnostic accuracy, often providing diagnostic information that guided therapeutic decision-making. It was used infrequently for therapy selection, but in the few patients selected for targeted therapy based on NGS, objective responses were observed. Research Sponsor: None.

6022 Poster Session

Pembrolizumab plus nab-paclitaxel and platinum as first-line treatment in patients with recurrent or metastatic nasal cavity and paranasal sinus squamous-cell carcinoma: A prospective phase II study. First Author: Yuquan Qian, National Cancer Center, National Clinical Research Center for Cancer, Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China

Background: Patients with recurrent or metastatic sinonasal squamous-cell carcinoma (R/M SNSCC) lack standardized systemic treatment protocols and prospective studies. While pembrolizumab with platinum and fluorouracil is established as first-line treatment for R/M head and neck squamous-cell carcinoma, and its combination with carboplatin and paclitaxel shows promise, we evaluated the efficacy and safety of pembrolizumab with nab-paclitaxel and platinum in R/M SNSCC. **Methods:** This is a single-arm phase 2 study, patients with R/M SNSCC received pembrolizumab 200mg, nab-paclitaxel 260mg/m^2 plus cisplatin 75 mg/m^2 or carboplatin AUC5 on day 1 every 21 days for up to six cycles followed by pembrolizumab maintenance therapy until progression or unacceptable toxicity or 35 cycles, whichever occurred first. The primary endpoint was objective response rate (ORR). Secondary endpoints were disease control rate (DCR), progression-free survival (PFS), overall survival (OS) and safety. Immunohistochemistry and high-resolution sequencing of the tumor samples were performed. **Results:** From 10 March 2022 to 31 October 2024, 20 patients were enrolled. The ORR was 60% (95%CI: 0.36-0.81) and two patients (2/20, 10%) achieved CR. The DCR was 100%. Median follow-up was 18.05 months(range:5.2-31.7), with a median PFS of 12.2 months (95%CI: 9 months-not estimated) and an unreached median OS. Patients with PD-L1 CPS $\geq$20 exhibited better ORR (80% vs 28.6%, p=0.144), median PFS (not reached vs 7 months, p=0.0137), and median OS (not reached vs 17.8 months, p=0.0401) compared to those with PD-L1 CPS $<$ 20. ORR was 50% (2/4) in HPV-positive patients and 53.8% (7/13) in HPV-negative patients. The most common genetic alterations were TP53, EGFR, CDKN2A mutations and amplifications in the 11q13 region (including CCND1, FGF19, FGF4, and FGF3 genes). Median TMB was 4 mut/Mb (range 2-13), with no significant difference observed between responders and non-responders. Grade 3/4 Treatment-Related Adverse Events (TRAEs) only accounted for 30% (6/20), and all come from hematologic toxicity. Hypothyroidism was the most common irAEs (12/20, 60%). **Conclusions:** Pembrolizumab plus nab-paclitaxel and platinum shows promising antitumor activity and manageable safety in first-line R/M SNSCC patients. Clinical trial information: ChiCTR2200057343. Research Sponsor: Beijing Hope Run Special Fund of Cancer Foundation of China; LC2022A30; CAMS Innovation Fund for Medical Sciences (CIFMS); 2023-I2M-C&T-B-072; Capital's Funds for Health Improvement and Research; 2024-2-40212.

6023 Poster Session

Phase 2 trial of dual EGFR inhibition with cetuximab and afatinib in patients with recurrent/metastatic head and neck squamous cell cancers (HNSCC). First Author: Aarti K. Bhatia, Yale School of Medicine and Yale Cancer Center, New Haven, CT

Background: Cetuximab is a monoclonal antibody targeting the epidermal growth factor receptor (EGFR) but its clinical activity is limited by resistance mechanisms. Our previous HNSCC trial of chemotherapy, cetuximab and erlotinib demonstrated a 62.5% objective response rate (ORR) including 2 durable complete responses (CR), with greater inhibition of phosphorylated EGFR in post-treatment biopsies. Because human epidermal growth factor receptor (HER)-2 and HER3 are overexpressed in cetuximab-resistant HNSCC, we postulated that the combination of cetuximab and afatinib, an irreversible, pan-HER inhibitor, would overcome resistance by inhibiting EGFR/HER dimers and inhibiting nuclear translocation and resulting non-canonical EGFR activities in R/M HNSCC. **Methods:** The primary objective of this single-arm phase II trial was ORR to the combination of cetuximab and afatinib in patients with R/M HNSCC refractory to platinum-based chemotherapy and/or immune checkpoint therapy. Cetuximab was administered at standard doses weekly/bi-weekly. Afatinib was initially dosed at 40 mg orally daily, amended to 30 mg orally daily after 25 patients, to improve tolerability. Key secondary endpoints were median progression-free survival (mPFS), median overall survival (mOS) and toxicity. Radiographic tumor assessment was performed, using RECIST version 1.1 every 8 weeks. Biopsy was obtained at baseline, 4 weeks after treatment initiation and at end of treatment, where medically feasible. **Results:** The study protocol was approved by the institutional review board and written informed consent was obtained from all participants. Fifty patients were enrolled between 7/3/2017 and 10/16/2024 at Yale Cancer Center, 47 were evaluable for response. Median age was 63 years (range 43-81 years), 39 (83%) were male, 21 (44.7%) had p16 positive tumors, 26 (55.3%) were p16 negative. Most common primary tumor location was oropharynx (n, %: 21, 44.7). ORR was 23.4% (2 complete responses, 9 partial responses, 95% CI: 12.3%-38%) for the entire population, 10 responses were in p16- patients (ORR 38.5%) and 1 response (4.8%) in a patient with p16+ disease. Median PFS was 3.8 months (95% CI: 2.1-not reached) for p16- patients and 1.8 months (95% CI: 1.7-8.9) for p16+ patients. Median OS was 7.5 months (95% CI: 4.8-12). Commonest adverse events (n, %) were diarrhea (19, 40), anemia (17, 36) rash (14, 30) and fatigue (13, 28). Correlative analyses are underway. **Conclusions:** This trial of dual EGFR targeting demonstrated high clinical efficacy, especially in the p16- population. Adverse events were consistent with those associated with EGFR inhibitor treatment. Clinical trial information: NCT02979977. Research Sponsor: NCCN; Boehringer Ingelheim.

6024 **Poster Session**

Petosemtamab (MCLA-158) with pembrolizumab as first-line (1L) treatment of PD-L1+ recurrent/metastatic (r/m) head and neck squamous cell carcinoma (HNSCC): Phase 2 trial. First Author: Carla M.L. van Herpen, Department of Medical Oncology, Radboud University Medical Center, Nijmegen, Netherlands

Background: EGFR is a known oncogenic driver in HNSCC, and the leucine-rich repeat-containing G-protein coupled receptor 5 (LGR5) is associated with cancer stem cells in solid tumors and expressed in HNSCC. Petosemtamab is a human, common light chain, IgG1 bispecific antibody with ADCC-enhanced activity, targeting EGFR and LGR5. Promising interim data from this phase 2, single-arm trial of petosemtamab 1500 mg every 2 weeks (Q2W; 28-day cycles) with pembrolizumab (400 mg Q6W) as 1L treatment in PD-L1+ HNSCC (NCT03526835) demonstrated a 67% overall response rate (ORR) in 24 efficacy evaluable patients (pts) [Fayette, ASCO 2024]. **Methods:** Primary endpoints are investigator-assessed ORR (RECIST v1.1) and safety. Secondary endpoints include duration of response (DOR), progression-free survival (per investigator), and overall survival (OS). Key eligibility criteria were r/m HNSCC with no prior systemic therapy in the r/m setting, PD-L1 combined positive score $\geq$1, ECOG PS 0–1, measurable disease, and primary tumor location in oropharynx (regardless of p16 status), oral cavity, hypopharynx, or larynx. **Results:** A total of 45 pts were treated; as of a September 16, 2024 data cutoff, 18 pts continuing on therapy. Median age was 64 years (range 23–80), ECOG PS 0/1 in 16/29 pts, and 78% were male. The most frequent primary tumor locations were oropharynx (31%), oral cavity (31%), larynx (16%), and hypopharynx (11%). A median of 8 cycles (range 1–17) were administered. Among 43 pts evaluable for efficacy (pts with $\geq$1 dose and $\geq$1 post-baseline scan, or who discontinued early due to progressive disease or death), the ORR was 60% (26/43) with 5 complete responses; median DOR was 11 months with 17 responders still on treatment at data cutoff. Of the 8 pts with p16+ oropharyngeal disease, 4 had confirmed responses (ORR 50%). The median follow-up for OS was 9.6 months; median OS was not reached. Kaplan–Meier estimate of OS at 6 months was 93%. The combination was well tolerated, and no significant overlapping toxicities were observed. Treatment-emergent adverse events (AEs) were reported in 45 pts, most were Grade (G) 1 or 2 in severity; one previously reported unrelated G5 AE occurred. The most frequent AEs (all G/G$\geq$3) were acneiform dermatitis (49%/7%), asthenia (49%/7%), and rash (44%/0%). Infusion-related reactions (composite term) were reported in 38% (all G) and 7% (G3) of pts, mainly occurred at first infusion, and all resolved. Updated data to be presented. **Conclusions:** Petosemtamab, a first-in-class EGFR x LGR5 bispecific antibody, in combination with pembrolizumab continues to demonstrate promising clinical efficacy and a well-tolerated safety profile as 1L treatment for pts with r/m PD-L1+ HNSCC. A global phase 3 trial, LiGeR-HN1 (NCT06525220), is ongoing to evaluate petosemtamab in combination with pembrolizumab in 1L PD-L1+ r/m HNSCC. Clinical trial information: NCT03526835. Research Sponsor: Merus N.V.

6025 **Poster Session**

Using longitudinal spatial-omics to demonstrate in-situ Epstein-Barr virus reduction in responders to immunotherapy treated nasopharyngeal cancer. First Author: Yang Wu, Institute of Molecular and Cell Biology (IMCB), Agency for Science, Technology and Research (A*STAR), Singapore, Singapore, Singapore

Background: Epstein-Barr virus (EBV) related nasopharyngeal cancer (NPC) is endemic in Southern China and Southeast Asia. Limited studies of tumor-immune microenvironment (TIME) modulated by dual checkpoint inhibitors (CPI) exist in relation to intratumoral EBV viral load. **Methods:** Spatial-omic analysis on longitudinally collected fresh frozen tissue from a phase 2 study of nivolumab/ipilimumab in NPC (NCT03097939) was done. Serial sections (10 μm) were cut for both H&E staining, and Stereo-seq assay (BGI, USA) that uses DNA nanoballs to capture mRNA which is amplified & reverse transcribed into cDNA, and then sequenced to a depth of 1 billion reads. Sequencing data was mapped to the human genome GRCh38.p14 and EBV-1 genome to identify Unique Molecular Identifiers (UMI), summarized into BIN100 niches (50μm by 50μm), processed into counts per million (CPM) and normalized for analysis. Cell type composition was estimated for each BIN100 using EBV+ NPC scRNA-seq datasets and *cell2location*. EBV viral load and the proportions of different cell types were associated with pre/post CPI in responders (R) and non-responders (NR) using Generalized Estimation Equation to account for repeated measures in the same slide. Colocalizations of different cell types within each BIN100 were also evaluated, adjusting for cell type proportions across all samples. P-value $<$ 0.05 on two sided testing was considered statistically significant. **Results:** Samples were collected at baseline pre-treatment, and 2 weeks into treatment, and associated with clinical response. Although 21/40 patients were biopsied, only 7 pairs of pre- and on-treatment samples (3R vs 4NR) had sufficient tissue quality for analysis. The most abundant EBV genes were RPMS1, EBNA1.1, LMP2B, LMP2A, and LMP1 (using mean expression). In pre/post treatment comparisons, the EBV viral load significantly reduced in R, as reflected by EBNA1.1 (p=4.9E-11) and LMP2A (p=7.4E-23), controlling for the proportion of epithelial cells (EC), but it did not change in NR. In R, a significant reduction of B cells (p=8.2E-71) and increase of myeloid (p=1.3E-3) and natural killer cells (p=3.1E-3) was observed, while no changes in cell composition were seen in NR. Colocalization analysis of EC with two immune cell (IC) types, CD4+ T cell and CD8+ T cell, identified significantly increased colocalization only in NR (CD4+ T cell: p=4.1E-7; CD8+ T cell: p=4.6E-4), suggesting IC infiltration is induced by CPI in NR but insufficient for cell kill. **Conclusions:** This is the first study to suggest intratumoral viral transcriptional activity reflected by reduction in EBNA1.1 and LMP2A on CPI treated NPC correlates with response and changes in immune cell composition and colocalization. Validation of these findings at protein level using multiplex IHC/IF and spatial analysis of the virus and epithelial/immune cell neighborhood is being completed. Clinical trial information: NCT03097939. Research Sponsor: A*STAR Biomedical Engineering Programme; C211318003; National Medical Research Council (NMRC), Singapore; MOH-001448-00; National Medical Research Council (NMRC), Singapore; MOH-000323; National Medical Research Council (NMRC), Singapore; OFLCG18May-0028; National Medical Research Council (NMRC), Singapore; NMRC OF-LCG-18May-0028; Ministry of Health, Singapore.

6026 **Poster Session**

Cetuximab plus dalpiciclib in patients with HPV-negative, anti-PD-1-resistant recurrent or metastatic head and neck squamous cell carcinoma. First Author: Houyu Ju, Shanghai Ninth People's Hospital Affiliated to Shanghai Jiao Tong University School of Medicine, Shanghai, China

Background: Human papillomavirus (HPV)-negative head and neck squamous cell carcinoma (HNSCC) is characterized by hyperactivation of the cyclin-dependent kinase 4/6 (CDK4/6) pathway. As immunotherapy has become the first-line treatment for HNSCC, resistance to anti-programmed death-1 (PD-1) agents has emerged as a pivotal challenge. This phase II study evaluated the efficacy and safety of dalpiciclib, a CDK4/6 inhibitor, combined with cetuximab in patients with anti-PD-1-resistant, HPV-negative recurrent or metastatic (R/M) HNSCC. **Methods:** Patients diagnosed with p16-negative R/M HNSCC resistant to first-line anti-PD-1 therapy and cetuximab-naïve were enrolled. Patients received oral dalpiciclib 150 mg daily for 21 consecutive days and intravenous cetuximab (400 mg/m² on day 1 of cycle 1, followed by 250 mg/m² weekly) in 28-day cycles. The primary endpoint was the objective response rate (ORR). Secondary endpoints included safety, progression-free survival (PFS), and overall survival (OS). Simon's two-stage design was used, with study termination planned if $\leq$1 response was observed among the first 14 patients. If met, an additional 12 patients were enrolled. **Results:** A total of 28 patients were enrolled, with a median age of 58 years (range 30-75 years). Among 28 evaluable patients, 3 had disease progression, 6 had stable disease, and 19 achieved partial response. The ORR was 67.9% (95% confidence interval [CI], 49.0%-82.0%), and the disease control rate was 89.3% (95% CI, 72.0%-97.0%). As of December 31, 2024, 9 patients remained on treatment. With a median follow-up of 7.34 months, the median PFS was 5.3 months (95% CI, 1.33-9.27), and the median OS was 17.0 months. Treatment-related adverse events (TRAEs) occurred in all patients, predominantly grade 1-2. The most common TRAEs were neutrophil count decreased (25/28, 89.3%), white blood cell count decreased (25/28, 89.3%), and acneiform rash (16/28, 57.1%). Grade 3 TRAEs included neutrophil count decreased (9/28, 32.1%) and white blood cell count decreased (9/28, 32.1%). No grade 4/5 TRAEs were observed. **Conclusions:** Dalpiciclib combined with cetuximab was well-tolerated and demonstrated potentially favorable efficacy in patients with anti-PD-1-resistant, HPV-negative R/M HNSCC. Clinical trial information: NCT05721443. Research Sponsor: Clinical Research Special Project of Shanghai Municipal Health Commission.

6027 **Poster Session**

Analysis of gene mutations, TMB, and PD-L1 in relation to ICI response in HNSCC. First Author: Daniel Beau Stamos, Wake Forest Baptist Medical Center, Winston-Salem, NC

Background: Immune checkpoint inhibitors (ICI) have changed the treatment of incurable advanced, recurrent, or metastatic (R/M) head and neck squamous cell carcinoma (HNSCC). Yet only a subset of patients respond, and predicting response remains challenging. We analyzed tumor genomic profiles and PD-L1 expression in a retrospective cohort of R/M HNSCC patients treated with ICI to evaluate the association with treatment response. **Methods:** We evaluated a single-institution cohort of 119 patients with R/M HNSCC treated with PD-1 inhibitors as monotherapy or in combination with palliative radiotherapy or chemotherapy, and who had genomics tested in tumor (tDNA) and/or in blood (ctDNA) samples. We analyzed clinical characteristics, treatment outcomes, PD-L1 expression, tumor mutation burden (TMB), and genomic profiles. Treatment response was assessed using iRECIST criteria. Responders were defined as complete response (CR), partial response (PR) $\geq$ 6 months, or stable disease (SD) $\geq$1 year. TMB and tDNA were tested by FoundationOne and ctDNA by Guardant. PD-L1 IHC used DAKO 22C3 antibodies. **Results:** Of 119 patients, 43 (36.1%) were considered responders (24 CR, 11 PR, and 8 SD $\geq$ 1 year). 97 patients had tDNA and TMB and 93 patients had ctDNA tested. 91 patients had PD-L1 results. In binary analysis, TMB $\geq$ 10 was significantly associated with response (P = 2.15e-5), while PD-L1 $\geq$ 20 was not (P = 0.83). A combined analysis of tDNA and/or ctDNA evaluated 273 genes. Univariate analysis showed that mutations in DNMT3A (P = 0.005), RET (P = 0.021), FAM123B (P = 0.021), and KDM6A (P = 0.043) were significantly associated with response. In a Lasso Logistic Regression model of the 27 most frequently mutated genes, 7 genes were significantly mutated in responders: DNMT3A (P = 0.0001), MAP2K4 (P = 0.025), FANCA (P = 0.036), ASXL1 (P = 0.019), EGFR (P = 0.0008), STK11 (P = 0.022), and BARD1 (P = 0.042), while TP53 was significantly mutated in non-responders (P = 0.010). Adding TMB to the multivariate model retained the significant association of DNMT3A (P = 0.021) and MAP2K4 (P = 0.015) mutations with response, and included ERBB4 (P = 0.037) mutations and TMB (P = 0.001) as additional significant indicators of response. DNMT3A was mutated only in responders (4 CR and 1 PR), with a positive predictive value of 1.00 and a negative predictive value of 0.74. In the multivariate analyses for tDNA and ctDNA, DNMT3A remained the only gene mutation significantly associated with response (P = 0.004 and P = 0.012). **Conclusions:** In this cohort of 119 patients with R/M HNSCC treated with PD-1 inhibitors, TMB, but not PD-L1, was associated with treatment response in univariate and multivariate analysis. Multivariate models identified eight genes significantly associated with treatment response. DNMT3A was the most remarkable gene, consistently associated with response in univariate and multivariate models. Further, larger studies are needed to validate these findings. Research Sponsor: None.

6028 Poster Session

Personalized biomarker-based treatment strategy in patients with recurrent/metastatic squamous cell carcinoma of the head and neck: Results of the biomarker-driven cohorts of the EORTC-HNCG-1559 trial (UPSTREAM). First Author: Rachel Galot, Service d'oncologie médicale, Laboratoire d'Oncologie médicale (IREC/MIRO/ONCO), Brussels, Belgium

Background: Platinum-refractory recurrent/metastatic squamous cell carcinoma (R/M SCCHN) has a poor prognosis. Several molecular pathways are dysregulated in SCCHN, providing potential targets for treatment. The UPSTREAM trial aimed to develop a personalized treatment strategy for R/M SCCHN. **Methods:** UPSTREAM was a biomarker-driven umbrella trial for post-platinum R/M SCCHN, investigating the activity of targeted agents in patients (pts) with tumors harboring pre-defined biomarker(s) identified on a fresh biopsy. Five biomarker-driven (B) cohorts were conducted as distinct phase 2 trials. The first 4 cohorts focused on p16-negative disease: cohort B1 investigated afatinib in pts with *EGFR* amp/mut and/or *HER2* amp/mut and/or PTEN high; cohort B2 investigated afatinib in cetuximab-naïve pts; cohort B3 investigated palbociclib in pts with *CCND1* amp and cohort B4 investigated niraparib in platinum-sensitive disease. Cohort B5 investigated niraparib in p16 positive oropharyngeal carcinoma. Cohorts B1, B2 and B3 were randomized (versus physician's choice of treatment) with progression-free survival rate at 16 weeks (PFSR 16W) as primary endpoint. Cohorts B4 and B5 were single-arm trials with objective response rate (ORR) over the first 16 weeks as primary endpoint. **Results:** A total of 250 pts were enrolled in UPSTREAM across 5 European countries, of whom 152 were allocated to a biomarker-driven cohort. Only B1 met its primary endpoint. In B1 (n=38 under afatinib), the PFSR 16W was 34.2%. B2 cohort experienced slow recruitment, with only 8 patients treated with afatinib, the PFSR 16W was 12.5%. In B3 (n=12 under palbociclib), PFSW 16W was 16.7%. In B4 (n=28) and B5 (n= 33), the ORR with niraparib was 3.6% (1/28) and 6.1% (2/33), respectively. More detailed results are shown in the table. **Conclusions:** UPSTREAM demonstrated the feasibility of conducting a biomarker-driven clinical trial in R/M SCCHN. The clinical activity observed across the biomarker-driven cohorts is limited. Potential explanations for these results include the absence of clearly identified high-level drivers in SCCHN, the limited evidence supporting some biomarkers (mainly derived from genomic data), and the use of single-agent treatment approaches. These findings highlight the need for further research to identify and refine biomarkers to explore new treatment strategies. Clinical trial information: NCT03088059. Research Sponsor: Boehringer Ingelheim; Pfizer; GSK.

Cohort	Biomarker	Drug	N evaluable patients	ORR	Median PFS (months)	Median OS (months)
B1	p16- and *EGFR* amp/mut or *HER2* amp/mut or PTEN high	afatinib	38	10.5%	2.2	7.2
		physician's choice	17	5.9%	2.4	5.0
B2	p16- and cetuximab-naïve	afatinib	8	0%	2.6	10.7
		physician's choice	4	0%	4.0	4.0
B3	p16- and *CCND1* amp	palbociclib	12	8.3%	1.9	4.3
		Physician's choice	6	0%	1.9	5.1
B4	p16- and platinum-sensitive	niraparib	28	3.6%	2.0	6.8
B5	P16 pos OPC	niraparib	33	6.1%	1.8	6.9

6029 Poster Session

Retlirafusp alfa-a bifunctional anti-PD-L1/TGF-βRII agent plus nab-paclitaxel and carboplatin in pre-treated recurrent/metastatic head and neck squamous cell carcinoma (R/M HNSCC): A prospective, single-arm, phase II clinical trial. First Author: Dongmei Ji, Department of Medical Oncology, Fudan University Shanghai Cancer Center, Shanghai, China

Background: Treatment for pre-treated patients (pts) with recurrent/metastatic head and neck squamous cell carcinoma (R/M HNSCC) is an important unmet clinical need. Dual blockade of PD-L1 and TGF-β could reshape the tumor microenvironment. The aim of this study is to evaluate the efficacy and safety of retlirafusp alfa (SHR-1701, a bifunctional anti-PD-L1/TGF-βRII agent) plus nab-paclitaxel and carboplatin in platinum-refractory R/M HNSCC pts. **Methods:** Patients with R/M HNSCC who received ≥1 line of prior systemic anti-tumor therapy were included. Pts received retlirafusp alfa 30mg/kg, once every 3 weeks, combined with nab-paclitaxel (125mg/m^2) and carboplatin (AUC=1.5), on day 1 and day 8 of a 21-day cycle for up to six cycles, followed by retlirafusp alfa maintenance therapy. The primary endpoint was objective response rate (ORR). Secondary endpoints comprised progression free survival (PFS), overall survival (OS), disease control rate (DCR) and safety. **Results:** From September 5, 2023 to September 25, 2024, 12 eligible pts were enrolled. The median age was 60 (range: 35-72). Among these 12 patients, 11 (91.7%) had received prior immune checkpoint inhibitors (ICIs) and 8 (66.7%) had undergone at least two previous lines of treatment. The median follow-up was 5.45 (95%CI 3.93-6.97) months, and data cutoff was December 31, 2024. All the 12 pts had at least one post-baseline assessment, and 4 pts achieved partial response with a confirmed ORR of 33.33% (95%CI 13.81%-60.93%). Disease control was observed in 8 patients resulting in a DCR of 66.67% (95%CI 39.07%-86.19%). The median PFS was 4.21 (95%CI 0.59-7.83) months. The median OS was immature. Treatment-related adverse events (TRAEs) occurred in 11 (91.67%) pts, mainly grade 1-2. The most common TRAEs (≥30%) were anaemia (8/12, 66.67%), white blood cell count decreased (5/12, 41.67%), hypoalbuminaemia (5/12, 41.67%), haemoptysis (5/12, 41.67%) and epistaxis (4/12, 33.33%). Grade 3-4 TRAEs were observed in 4 (33.33%) pts, with more than 1 patient experiencing white blood cell count decreased (3/12, 25%), neutrophil count decreased (2/12, 16.67%) and anaemia (2/12, 16.67%). **Conclusions:** Even as most pts have progressed on ICIs before enrollment, retlirafusp alfa plus nab-paclitaxel and carboplatin demonstrated promising anti-tumor efficacy and manageable toxicities in pre-treated R/M HNSCC. Long-term efficacy needs to be confirmed by further follow-up. Clinical trial information: ChiCTR2300070675. Research Sponsor: None.

6030 Poster Session

Camrelizumab combined with cetuximab and chemotherapy in recurrent or metastatic head and neck squamous cell carcinoma (R/M HNSCC): 1-year outcomes from the phase II trial. First Author: Dongmei Ji, Department of Medical Oncology, Fudan University Shanghai Cancer Center, Shanghai, China

Background: Pembrolizumab or cetuximab combined with platinum-based-chemo are standard first-line regimen for R/M HNSCC, but the efficacy is far from optimal. We conducted an open-label, single-arm, Simon' s two-stage, phase II study of camrelizumab (PD-1 monoclonal antibody) with cetuximab and cisplatin-based chemotherapy as first-line treatment in R/M HNSCC (NCT05673577). The outcomes from the 1st stage showed promising efficacy. **Methods:** Eligible patients with R/M HNSCC not amenable to curative treatment were enrolled. Patients were treated with camrelizumab 200mg Q3W, cetuximab 400mg/m^2 loading dose followed by 250mg/m^2 weekly, cisplatin 75mg/m^2 Q3W, and nab-paclitaxel 125mg/m^2 on d1, d8 (21-day cycle), for up to 6 cycles. Maintenance therapy with camrelizumab 200mg Q2W, cetuximab 500mg/m^2 Q2W were given until intolerable toxicity or disease progression. Primary endpoint of this study is objective response rate (ORR). Secondary endpoints include progression-free survival (PFS), overall survival (OS), disease control rate (DCR), adverse events (AEs) (CTCAE v5.0) andmolecular biomarkers will be tested as exploratory endpoints. **Results:** Between April 2023 and September 2024, 41 patients were enrolled. The confirmed ORR per RECIST 1.1 was 90.0% (95% CI: 75.0-97.0), which met the prespecified criteria for the primary endpoint of ORR. The confirmed DCR was 100.0%. With the median follow-up duration of 14.5 months, the median PFS was 13.2 months (95% CI: 9.3-NR). The 1-year PFS rate was 54.6% (95% CI: 39.1-76.1). The median OS was not reached. The 1-year and 2-year OS rates were 88.4% (95% CI: 78.2-100.0) and 84.6% (95% CI: 72.8-98.3), respectively. The most common grade 3-4 AEs related to chemotherapy included neutropenia (16.7%), anemia (7.1%). Possible grade 3-4 targeted therapy-related AE was rash (7.1%). Additionally, 14.3% of the patients were administered anti-angiogenic medications to treat reactive cutaneous capillary endothelial proliferation mucositis that was specifically induced by camrelizumab. These AEs were manageable with dose modification. **Conclusions:** Camrelizumab combined with cetuximab and cisplatin-based chemotherapy showed encouraging efficacy and tolerability in the scenario of first-line R/M HNSCC. Further evaluation including a phase III study is warranted. Clinical trial information: NCT05673577. Research Sponsor: Clinical Research Project of Shanghai Municipal Health Commission in Health Industry, 202340122, (2023-2026); National Health Commission: Special Research Project for Clinical Studies of Innovative Drugs After Market Launch, WKZX2024CX01206, (2004-2007)).

Demographics and baseline characteristics.

		N=41 (100%)
Age	Median (range)	59 (34-72)
Sex-n (%)	Male/Female	36/5 (87.8% vs. 12.2%)
HNSCC Primary site of disease	Larynx	15 (36.5%)
	Oral Cavity	14 (34.1%)
	Oropharynx	4 (9.8%)
	HPV-pos	1 (25.0% of Oropharynx)
	HPV-neg	2 (50.0% of Oropharynx)
	unclear	1 (25.0% of Oropharynx)
	Hypopharynx	4 (9.8%)
	Others	4 (9.8%)
Distant metastasis-n (%)		19 (46.3%)
ECOG Performance Status-1 vs. 2 (%)		39 vs. 2 (95.1% vs. 4.9%)

6031 Poster Session

Combination of Tim-3 blockade TQB2618 with penpulimab and chemotherapy in the first-line treatment of recurrent/metastatic nasopharyngeal carcinoma (R/M NPC): A multicenter, single-arm, two-cohort, phase 2 study. First Author: Cheng Xu, Sun Yat-sen University Cancer Center; Collaborative Innovation Center for Cancer Medicine; State Key Laboratory of Oncology in South China; Guangdong Key Laboratory of Nasopharyngeal Carcinoma Diagnosis and Therapy, Guangzhou, China

Background: T cell immunoglobulin and mucin domain molecule 3 (Tim-3) is an inhibitory immune checkpoint receptor that negatively regulates the immune response. This multicenter, single-arm, two-cohort, phase 2 study (NCT05563480) aimed to explore the efficacy and safety of TQB2618, a novel monoclonal antibody blockading Tim-3, plus PD-1 blockade penpulimab as subsequent-line treatment in immunotherapy-resistant R/M NPC (cohort 1) or as first-line treatment by incorporating into chemotherapy in treatment-naïve R/M NPC (cohort 2). Here, we report the results of cohort 2. **Methods:** Eligible pts were ECOG PS 0–1, aged 18–70, diagnosed with histologically confirmed R/M NPC with ≥ 1 measurable lesion. Previous systemic treatment was not allowed, except as a part of curatively intended treatment for locoregionally advanced NPC and develop disease progression at least 6 months after last dose. TQB2618 and penpulimab were administered intravenously at doses of 1200 mg and 200 mg, respectively, on the first day of a 21-day cycle until disease progression or unacceptable toxicity while gemcitabine (1000 mg/m^2, d1&8) and cisplatin (75mg/m^2, d1) were given intravenously for the first 4–6 cycles. The primary endpoint is progression-free survival (PFS). **Results:** Between February 2023 and October 2023, 30 pts were enrolled (median [range] age, 52 [33–70] years; 16.7% women). Seventeen were diagnosed with metastatic disease at the first visit and others developed disease recurrence after definitive treatment. Liver metastasis was found in 10 pts. Median follow-up was 12.5 months (mo) (95% CI: 12.4–NE) at the data cut-off date on December 20, 2024. The median PFS reached 10.8 mo (95% CI, 9.6–16.4) and the 12 mo- and 15 mo-PFS were 40.9% and 34.1%, respectively. For the 17 pts with PD-L1 positive expression, the median PFS was 13.6 mo (95% CI: 8.4–16.6). The tumor response was complete response in 4 pts (13.3%), partial response in 21 pts (70.0%), stable disease in 4 pts (13.3%), and 1 could not be estimated, giving an objective response rate of 83.3%. A total of two pts died, both due to disease progression after 7.9 mo of enrollment. All pts experienced at least one adverse event (AE) and 25 pts (83.3%) were observed ≥ grade 3 (G3) AEs. The most common AEs of all grades (G1–4) or ≥ G3 were chemotherapy-related, including leukopenia (G1–4: 96.7%; ≥ G3: 40.0%), neutropenia (G1–4: 90.0%; ≥ G3: 36.7%), and anemia (G1–4: 93.3%; ≥ G3: 33.3%). **Conclusions:** To our knowledge, this is the first study to evaluate the addition of Tim-3 blockade to the standard first-line treatment of R/M NPC. The results demonstrated that this combination therapy provided clinical benefits comparable to those observed in the historical cohort treated with PD-1 blockade plus chemotherapy, while maintaining a manageable safety profile. Clinical trial information: NCT05563480. Research Sponsor: Chia Tai TianQing Pharmaceutical Group Co., Ltd; Basic and Applied Research Project of Science and Technology of Guangzhou city.

6032 **Poster Session**

The molecular landscape of immunotherapy treatment and advanced disease in head and neck squamous carcinoma (HNSCC). First Author: George Laliotis, University of Jamestown, Jamestown, ND

Background: Advanced head and neck squamous cell carcinoma (HNSCC) exhibits variable responses to immunotherapy, highlighting the need to understand its complex molecular landscape. While immune checkpoint inhibitors show promise, optimizing treatment and predicting outcomes requires deeper molecular insights. Here, we leverage the cBioPortal for Cancer Genomics, analyzing ~800 HNSCC genomic and transcriptomic profiles, to investigate the molecular landscape influencing immunotherapy response in advanced disease. **Methods:** In this retrospective study, we analyzed publicly available data from 825 HNSCC patients treated with immunotherapy, enrolled in participating institutions between 2017 and 2022, sourced from the cBioPortal for Cancer Genomics. We investigated the frequency of most common mutations, copy number alterations, and mRNA expression levels, along with clinicopathological factors and overall survival (OS). **Results:** Genomic analysis of 809 HNSCC samples revealed TP53 as the most frequently mutated gene (63.5%, 514/809), followed by TTN (37.4%), FRG1BP (20.7%), FAT1 (19.3%), and CDKN2A (19.0%). Other genes were mutated at frequencies between 18.7% and 15.2%. Copy number alterations analysis (n=673) showed frequent homozygous deletions in 9p21.3, affecting CDKN2A-AS1 (30.3%, 158/673) and CDKN2A (26.0%, 175/673), and amplifications in 11q13.3, including PPFIA1 (25.7%), FADD (25.3%), CTTN (25.1%), and ANO1 (25.1%). Notably, TP53 mutations and CDKN2A-AS1 deletions were associated with inferior OS (log-rank $P < 0.001$; mOS mutated vs wild-type 45.93 vs 156.37 months and $P = 0.006$; mOS altered vs non-altered 35.45 vs 65.77 months, respectively). Transcriptomic and GSEA profiling linked these alterations to dysregulation of oncogenic pathways, including DNA replication stress, p21 activation, apoptosis, and immune evasion. **Conclusions:** This study of immunotherapy-treated advanced HNSCC provides a valuable resource for understanding the complex genomic landscape of this disease. We identified frequent mutations and copy number alterations which were associated with inferior OS and linked to dysregulation of key oncogenic pathways. These findings underscore the potential of this to facilitate biomarker discovery and the development of personalized medicine approaches to improve outcomes in advanced HNSCC. Research Sponsor: None.

6033 **Poster Session**

Initial safety and efficacy of PDL1V (PF-08046054), a vedotin-based ADC targeting PD-L1, in combination with pembrolizumab in patients with recurrent or metastatic (R/M) HNSCC. First Author: Maura L. Gillison, The University of Texas MD Anderson Cancer Center, Houston, TX

Background: PDL1V is a novel investigational antibody-drug conjugate that delivers monomethyl auristatin E (MMAE) to cells that express programmed cell death ligand 1 (PD-L1) without anticipated checkpoint blockade. Immunogenic cell death via the MMAE payload can be further amplified by traditional immune checkpoint inhibitors, providing strong scientific rationale for combination with pembrolizumab. The objective of Part D of the phase 1 trial is to assess the safety/tolerability and preliminary antitumor activity of PDL1V and pembrolizumab combination in patients with R/M HNSCC. **Methods:** C5851001 (NCT05208762) includes a phase 1 safety run-in cohort (Part D) enrolling patients with untreated R/M HNSCC with PD-L1 CPS $\geq$1 and no prior therapy with anti-PD-1/PD-L1 antibodies in any setting. Measurable disease per RECIST v1.1 and ECOG PS $\leq$1 were required. The first patient group received PDL1V 1.25 mg/kg on days 1 and 8 every 21 days (2Q3W) using adjusted ideal body weight (AIBW). Once safety was demonstrated, a second cohort was initiated at 1.5 mg/kg 2Q3W AIBW. All patients received pembrolizumab 200 mg every 3 weeks. The primary objectives of this study are safety/tolerability and pharmacokinetics. A secondary objective is antitumor activity. **Results:** As of December 20, 2024, 14 patients were dosed; median age was 61 years (range 36–76). Eight patients received 1.25 mg/kg and 6 received 1.5 mg/kg; 92.9% were male, 71.4% had ECOG PS 0, 64.3% were P16 positive oropharyngeal, and 57.1% had CPS 1–<20. Eight patients remain on active therapy at the data cut time. No dose-limiting toxicities (DLTs) were observed. The most frequent PDL1V treatment-related adverse events (TRAEs) were fatigue and nausea (50.0% each), peripheral sensory neuropathy (35.7%), diarrhea (28.6%), and anemia, constipation, decreased appetite, muscle spasms, pneumonitis, and pyrexia (14.3% each); pembrolizumab TRAEs were fatigue (42.9%), diarrhea, and nausea (28.6% each); and abdominal pain, decreased appetite, peripheral sensory neuropathy, pneumonitis, and pyrexia (14.3% each). The most frequent grade $\geq$3 TRAEs for either agent were diarrhea (14.3%) and anemia, decreased appetite, fatigue, and neutropenia (7.1% each). Treatment-related immune-mediated AEs by investigator assessment were observed in 7.1% of patients; 7.1% grade 3. Investigator-assessed, objective response rate at this time for 14 response-evaluable patients was 50.0%; complete response (CR) rate was 21.4%. The median duration of response has not been reached. **Conclusions:** The combination of PDL1V and pembrolizumab was generally well tolerated with no DLTs. Early encouraging objective responses were observed in half of the patients treated, including 21.4% with a CR. Enrollment in multiple combination expansion cohorts in PD-L1 expressing tumors is ongoing. Clinical trial information: NCT05208762. Research Sponsor: Pfizer Inc.

6034 **Poster Session**

A prospective, single-arm, phase II study of adebrelimab plus carboplatin and albumin-bound taxanol as neoadjuvant therapy in patients with resectable locally advanced head and neck squamous cell carcinoma. First Author: Yilin He, Yat-sen Memorial Hospital of Sun Yat-sen University, Guangzhou, China

Background: Currently, clinical studies have shown that patients with tumor remission after preoperative induction chemotherapy have a higher survival rate and a lower risk of distant metastasis, but the pathological complete remission rate of tumor after surgery is low. With the rise of tumor immunology, more and more immunotherapy methods have been applied to the treatment of clinical tumors. In terms of head and neck squamous cell carcinoma, we hereby investigate the efficacy of a PD-L1 inhibitor (Adebrelimab) combined with chemotherapy in patients with resectable advanced head and neck squamous cell carcinoma. **Methods:** This study hypothesized that preoperative induction of PD-L1 inhibitors combined with chemotherapy in patients with resectable advanced head and neck squamous cell carcinoma was superior to conventional chemotherapy regiments recommended by NCCN guidelines. As a course of treatment every three weeks, albumin-bound paclitaxel 260 mg/m2, carboplatin AUC=5 and Adebrelimab 1200 mg were given intravenously on the first day of every three weeks. After three doses, surgery was performed and radiotherapy was performed according to the stage of the tumor. The main index observed in this study was postoperative pathological complete response rate (PCR), and the secondary index was major pathological response rate (MPR) and 2-year survival rate (OS). **Results:** As of December 31, 2024, a total of 30 patients were enrolled in the study. Among them, the median age was 52 years, and 23 patients were male. During immunochemotherapy, the most common adverse reactions were alopecia (100%, 30/30), pruritus (16%, 5/30), and limb weakness (60%, 18/30). At present, 26 patients have completed all preoperative neoadjuvant therapy and successfully received surgical treatment. By comparing the MRI imaging images of these patients before and after medication, the efficacy evaluation of 14 patients was PR (53.9%, 14/26), 1 patient was CR (3.8%, 1/26), 1 patient was PD (3.8%, 1/26), and 10 patients was SD (38.5%, 10/26). In postoperative pathological specimens, 12 patients achieved pathological complete response (PCR: 46%, 12/26) and 3 patients achieved major pathological response (MPR: 11.5%, 3/26). We will follow up these patients and calculate their 2-year survival rate (OS). This study is still ongoing. **Conclusions:** In terms of head and neck squamous cell carcinoma, Phase I clinical studies have confirmed the therapeutic safety and tumor activity of PD-L1 inhibitors. In this Phase II study, the PD-L1 inhibitor (Adebrelimab) demonstrated a favorable therapeutic response to locally advanced head and neck squamous cell carcinoma, and we look forward to final therapeutic data. Clinical trial information: NCT06016413. Research Sponsor: Jiangsu Hengrui Pharmaceutical Co., Ltd.

6035 **Poster Session**

Survival for head and neck squamous cell carcinoma treated with versus without neoadjuvant systemic therapy: A national propensity score–matched analysis. First Author: Vanessa Helou, Department of Otolaryngology-Head and Neck Surgery, University of Pittsburgh, Pittsburgh, PA

Background: Neoadjuvant systemic therapies, including immunotherapy and chemotherapy, offer a promising approach for treating head and neck squamous cell carcinoma (HNSCC). These therapies aim to reduce tumor burden and enable personalized treatment. While pivotal studies like KEYNOTE 689 may redefine therapeutic paradigms, the survival outcomes associated with neoadjuvant systemic therapies in HNSCC remain underexplored. **Methods:** A retrospective cohort analysis using the National Cancer Database evaluated patients with HNSCC surgically treated with versus without neoadjuvant systemic therapies from 2015 to 2022. Overall survival (OS) was compared by using a Cox proportional hazards regression model. Propensity score matching was performed to adjust for stage, age, sex, race, insurance status, urban/rural, Charlson–Deyo score. **Results:** Among 3,569 patients (74% male, 26% female), 1,311 received neoadjuvant chemotherapy, 632 received neoadjuvant immunotherapy, 114 received a combination of neoadjuvant chemotherapy and immunotherapy, and 1,512 were matched HNSCC patients who did not receive any neoadjuvant therapy prior to surgery. Most patients had overall stage IVa/b (59%) tumors of the oral cavity (62%). On univariate analysis, neoadjuvant immunotherapy alone was associated with a 43% reduced the risk of mortality, compared to neoadjuvant chemotherapy alone (HR: 0.57; 95% CI: 0.48–0.68, $P < .001$). Combination therapy was not significantly associated with lower mortality than chemotherapy alone (HR: 0.87; 95% CI: 0.63–1.21, $P = .41$). After adjustment using a propensity matched cohort of patients with HNSCC treated without neoadjuvant therapy, neoadjuvant immunotherapy was associated with significantly improved OS (HR: 0.55; 95% CI: 0.35-0.75, $P < .001$). However, neoadjuvant chemotherapy (HR: 1.07; 95% CI: 0.96–1.18, $P = .23$) and combination therapy (HR: 0.84; 95% CI: 0.49-1.19, $P = .33$) were not significantly associated with improved OS. **Conclusions:** Neoadjuvant immunotherapy may potentially provide improved survival in HNSCC. Further research is needed to assess these findings through prospective trials. Research Sponsor: None.

Overall survival for patients with head and neck squamous cell carcinoma treated with versus without neoadjuvant systemic therapy.

Overall Survival	HR (95% CI)	P
No neoadjuvant therapy	Ref.	
Neoadjuvant chemotherapy	1.07 (0.96–1.18)	0.23
Neoadjuvant combination therapy	0.84 (0.49-1.19)	0.33
Neoadjuvant immunotherapy	0.55 (0.35-0.75)	<0.001

HR, hazard ratio; CI, confidence interval.

6036 Poster Session

ctDNA-based clinicogenomic analysis of advanced head and neck cancer patients treated with immune checkpoint inhibitors. First Author: Atul Bharde, OneCell Dx, Pune, India

Background: Head and Neck cancer (HNC) is among the diverse group of malignancies affecting the head and neck region including the oral cavity. Being the most prevalent malignancy in Southeast Asia, it has a high mortality rate. Despite the advancement in treatment, 5 years survival rate for HNC remains below 50%, and the majority of Pts receiving frontline therapy experience locoregional or incurable metastatic relapse. Immune checkpoint inhibitors (ICI) are recommended for relapsed patients, but only 20% of patients show measurable response. Currently, no predictive biomarkers are available to predict ICI response and there is an urgent need for genomic markers to predict ICI outcomes. Here we report comprehensive genomic profiling (CGP) of advanced HNC patients receiving ICI. **Methods:** ctDNA from 69 advanced HNC patients receiving combinational immune-chemotherapy were serially profiled at the baseline (BL) and post-treatment (Tx) by targeted, hybridization-based CGP using OncoIndx comprehensive gene panel (CGP) comprising 1080 genes. The ctDNA differential features at BL and post-Tx as well as among responders (R) and non-responders (NR) were correlated with Progression-free survival (PFS) and Overall survival (OS) using Kaplan-Meier statistics and multivariate analysis. **Results:** Among total patients, 58% (40/69) were responders (R) while the remaining were non-responders (NR). At the population level, HRR pathway tumor suppressors and epigenetic modifiers were the most frequent pathogenic variants. At BL, the NR population was enriched with oncogenic gene mutations compared to the R population. TP53 and BRCA pathway mutations (mTP53 + BRCA) showed a strong association with progression-free survival (PFS) and overall survival (OS). Pts with cooccurring mTP53 + BRCA had significantly lower PFS (median PFS: 2.77 months for mTP53 + BRCA pathway vs 9.1 months for wt TP53 + BRCA pathway. P=$<$0.0001, HR=3.2-11.6) and OS (median OS: 4.67 months for mTP53 + BRCA pathway vs 12.63 months for wtTP53 + BRCA pathway. P=$<$0.0001, HR = 11.18-55.27). NOTCH 1 or 2 variants were enriched in R population, with a beneficial effect on survival outcomes. Elevated ctDNA alterations and Tumor fraction (TF) concentrated in the NR population disproportionately contained subclonal potential drivers of immunotherapy resistance including NF1, STAT5 B, and STK11 mutations, and were associated with short survival. Univariate and multivariate analysis suggested that ctDNA mutations, TF, and high mutational heterogeneity emerged as risk factors for shorter PFS and OS. In contrast, total Indel burden and NOTCH mutations had beneficial effects on PFS and OS. **Conclusions:** Minimally invasive plasma ctDNA CGP showed heterogenous actionable mutations at BL and post Tx and identified immunotherapy resistance conferring genomic markers for stratifying potential responders for immunotherapy guidance. Research Sponsor: None.

6037 Poster Session

Versatile-002: Overall survival of HPV16-positive recurrent/metastatic head and neck squamous cell carcinoma patients treated with T cell stimulating immunotherapy PDS0101 and pembrolizumab. First Author: Jared Weiss, The University of North Carolina at Chapel Hill, Chapel Hill, NC

Background: The incidence of HPV-associated head and neck squamous cell carcinoma (HNSCC) continues to rise with over 90% of cases being driven by HPV16. Median overall survival (OS) with pembrolizumab in first-line recurrent/metastatic (R/M) HNSCC is 12.3 months in subjects with CPS $\geq$1, 10.8 months for CPS $\geq$1-19, and 14.9 months for CPS $\geq$20. There is an urgent need to improve survival rates in the growing population of HPV16-positive R/M HNSCC. PDS0101 (Versamune HPV) is an investigational T cell stimulating immunotherapy that unleashes a potent, durable attack against HPV16-positive cancers and is being studied in combination with pembrolizumab. Preliminary results were presented at ASCO 2023. (Price KAR, et al. ASCO 2023. Abstract 6012). **Methods:** VERSATILE-002 is a single-arm phase 2 study evaluating PDS0101 and pembrolizumab for first-line HPV16-positive R/M HNSCC with CPS $\geq$1. Subjects received pembrolizumab 200 mg IV Q3W with PDS0101 1 mL SC administered concurrently during Cycles 1, 2, 3, 4, and 12 and pembrolizumab alone for all other Cycles up to Cycle 35 (approx. 2 years). The primary study endpoint is confirmed objective response rate (ORR) per RECIST 1.1. Secondary endpoints include progression-free survival (PFS), OS, and safety. **Results:** The median follow-up is 18.4 months (range 0.2-42.7 months). The efficacy population consists of 53 subjects: 32 (60%) with CPS $\geq$1-19 and 21 (40%) with CPS $\geq$20. The median OS for subjects with CPS $\geq$1 is 30 months (95% CI 23.9, NE). For the CPS $\geq$1-19 subgroup, the median OS is 29.5 months (95% CI 15.3, NE). For the CPS $\geq$20 subgroup, the median OS is 39.3 months (95% CI 18.4, NE). Confirmed response rates by investigator assessment are shown in the Table. Twenty-three subjects are still on study: 3 on treatment and 20 in long-term follow-up. No new safety signals have emerged. The most common TRAEs are injection site reactions, fatigue, headache, and pruritus. Only 19% of subjects experienced Grade $\geq$3 TRAEs. No subject had a Grade 5 TRAE. **Conclusions:** These data represent one of the most extended follow-up periods to date of subjects receiving an HPV16-targeted therapy for HPV16-positive R/M HNSCC. The PDS0101 and pembrolizumab combination is well tolerated and has demonstrated deep and durable clinical responses. Median OS is promising in light of historic expectations, both overall and relative to PD-L1 subgroup, and remains durable with continued follow up. The results support further evaluation in a randomized phase 3 study with OS as the primary endpoint. Clinical trial information: NCT04260126. Research Sponsor: PDS Biotechnology Corporation.

Summary of results.

	CPS ≥1-19 (N=32)	CPS ≥20 (N=21)	CPS ≥1 (N=53)
ORR, %	28.1	47.6	35.8
DCR, %	75.0	81.0	77.4
Median DOR, months (95 % CI)	21.8 (4.2, NE)	NE (5.6, NE)	21.8 (11.5, NE)
Median PFS, months (95% CI)	5.1 (2.4, 8.1)	14.1 (2.1, NE)	6.3 (3.5, 9.0)
Median OS, months (95% CI)	29.5 (15.3, NE)	39.3 (18.4, NE)	30.0 (23.9, NE)

6038 Poster Session

Assessing the safety and efficacy of GT201: A first-in-class autologous tumor-infiltrating lymphocyte monotherapy in advanced solid tumors. First Author: Pin Wang, Grit Biotechnology, Shanghai, China

Background: For patients with unresectable recurrent or metastatic solid tumors that progress after chemotherapy, immune checkpoint inhibitors (ICIs), or targeted therapy, treatment options are limited. GT201, featuring membrane-bound IL-15 (mbIL-15) expressed on TILs, aims to enhance immune activation in the tumor microenvironment and may demonstrate efficacy and durable responses in these advanced cases. We present data from nine patients enrolled in open-label, single-arm studies to investigate the safety and efficacy trends of GT201 therapy. **Methods:** The GT201 study's primary endpoint was to assess TEAEs, including SAEs and AEs, using the CTCAE version 5.0 grading scale. The secondary endpoint focused on preliminary efficacy parameters, including ORR, DCR, PFS, DOR, OS following RECIST v1.1 guidelines. **Results:** As of January 15, 2025, nine patients have been enrolled in the study, with a median age of 52 years and a median of two prior therapy lines. Among them, one patient had bone metastases, two had liver metastases, and one had brain metastases. After standard FC lymphodepletion, patients received GT201 infusions at doses of $\geq 5\times10^9$ viable cells. Seven patients subsequently received IL-2 post-infusion. Most adverse events (AEs) were Grade 1 or 2. Grade $\geq$3 AEs, related to lymphodepleting chemotherapy and IL-2, included decreased lymphocyte, neutrophil, and white blood cell counts, pyrexia, and tachycardia. All Grade $\geq$3 AEs resolved or downgraded to Grade $\leq$2 within 14 days. Among the nine response-evaluable patients with various cancers, including head and neck squamous cell carcinoma (HNSCC), non-small-cell lung cancer (NSCLC), melanoma, cervical cancer, and ovarian cancer, the objective ORR was 55.6% (5/9), and the disease control rate (DCR) was 77.8% (7/9). One patient (11.1%) achieved complete response (CR), four (44.4%) had partial responses (PR), and two (22.2%) had stable disease (SD) as their best response. Notably, in the HNSCC subgroup, both patients achieved objective responses (CR and PR) (2/2, 100%). In the NSCLC subgroup, all three patients achieved disease control (SD $\geq$24 weeks or PR) (3/3, 100%). GT201 cells were detected in all patients, indicated by IL15RA protein staining on peripheral T cells and transgene copy number in peripheral white blood cells. GT201 cells expanded robustly and persisted in peripheral blood for at least six months post-infusion. **Conclusions:** In patients with heavily pretreated advanced or metastatic solid tumors, GT201, infused after FC lymphodepleting chemotherapy and high-dose IL-2, exhibited a manageable safety profile. GT201 demonstrated a favorable clinical profile in HNSCC, with an encouraging objective response rate and durable responses. No Grade $\geq$3 adverse events related to GT201 treatment were observed, supporting its potential as a treatment option worth further exploration. Clinical trial information: NCT05729399, NCT06190275. Research Sponsor: None.

6039 Poster Session

Two cycles of neoadjuvant therapy with low-dose radiotherapy, PD-1 inhibitor tislelizumab, albumin-bound paclitaxel, and cisplatin for resectable locally advanced head and neck squamous cell carcinoma (NeoRTPC02): A phase II, open-label, single-arm trial. First Author: Zhigang Liu, Cancer Center, the tenth Affiliated Hospital of Southern Medical University (Dongguan People's Hospital), Southern Medical University, Dongguan, China

Background: Despite standard treatments, mortality rates remain high in locally advanced head and neck squamous cell carcinoma (LA HNSCC). Neoadjuvant immunotherapy combined with chemotherapy has improved response rates, but further enhancement is needed. Recent studies suggest that low-dose radiotherapy (LDR) can reprogram the tumor microenvironment, reversing immune suppression and improving the efficacy of PD-1 inhibitors. This study aims to evaluate the safety and efficacy of neoadjuvant LDR combined with tislelizumab and chemotherapy in LA HNSCC. **Methods:** This was an open-label, single-arm, phase II clinical trial for patients with untreated, histologically confirmed stage III-IVB HNSCC. Patients received neoadjuvant low-dose radiotherapy (1 Gy/1F, days 1, 2, 8, and 15, Q3W) combined with tislelizumab (200 mg, day 1, Q3W), albumin-bound paclitaxel (100 mg/m^2, days 1, 8, and 15, Q3W), and cisplatin (25 mg/m^2, days 1, 8, and 15, Q3W) for two cycles. Afterward, patients underwent radical surgery approximately 4 weeks later. The primary endpoint was the pathological complete response (pCR) rate, while secondary endpoints included major pathological response (MPR) rate, ORR, R0 resection rate, safety, and treatment-related surgical delay rate. The exploratory endpoints were the 3-year progression-free survival and 3-year overall survival. To further investigate the underlying mechanisms of treatment effects, we used single-cell RNA sequencing (scRNA-seq) to explore how this combination modulates the tumor microenvironment(TME) in HNSCC. **Results:** A total of 37 patients were assessed for eligibility, of which 28 patients were enrolled and received the assigned neoadjuvant treatment. A total of 23 patients proceeded to surgery, and pathological response evaluation was conducted in these patients. Among the 23 patients, 14 (60.9%) achieved pCR, and the MPR and pCR/MPR rates were 21.7% and 82.6%, respectively. The ORR was 64.3% (18/28), including 2 (7.1%) complete response and 16 (57.1%) partial response. The R0 resection rate was 100%. Treatment-related adverse events (TRAEs) were manageable, with grade 3 or 4 TRAEs occurring in 12 (42.9%) patients. The main side effects included neutropenia and decreased white blood cell count. No surgical delays were observed. ScRNA-seq results suggested that this neoadjuvant regimen may reshape the HNSCC TME by enhancing adaptive immunity and potentially increasing FOLR2$^+$ macrophage infiltration. **Conclusions:** Neoadjuvant LDR combined with tislelizumab, albumin-bound paclitaxel, and cisplatin resulted in an impressive pCR rate and demonstrated promising efficacy with manageable toxicity in patients with resectable LA HNSCC. Long-term survival data are still follow-up. Clinical trial information: NCT05343325. Research Sponsor: Beijing Xisike Clinical Oncology Research Foundation.

6040 Poster Session

Effect of induction chemo-immunotherapy on the chance for re-irradiation in high-risk recurrent nasopharyngeal carcinoma: A prospective, single-arm, phase II trial. First Author: Jingjing Miao, Department of Nasopharyngeal Carcinoma, Sun Yat-Sen University Cancer Center, State Key Laboratory of Oncology in South China, Guangdong Key Laboratory of Nasopharyngeal Carcinoma Diagnosis and Therapy, Guangdong Provincial Clinical Research Center, Guangzhou, China

Background: The PRANCIS model has been shown to be robust for identifying patients with recurrent nasopharyngeal carcinoma (rNPC) who are at high risk of treatment-related adverse events from re-irradiation (reRT). Here, we investigate the efficacy of combination doublet gemcitabine-cisplatin (GP) and PD-1 inhibitor (Toripalimab) to down-classify PRANCIS high risk (>252) to low-risk post-3 cycles of treatment, and the survival outcomes of these patients. For patients who converted to low-risk, reRT may be considered (NCT03930498). **Methods:** Eligibility criteria included diagnosed as local ± regional recurrence after ≥1 year of radical treatment, not suitable for surgery, histologic or clinically diagnosis of NPC, stage rII-IVa (AJCC/UICC 8th), PRANCIS model > 252 points. All patients received 3 cycles of GP + PD-1 inhibitor, then received reRT (GTV, 60-66Gy, 1.8-2.0Gy/f) plus PD-1 inhibitor if got CR/PR (reRT group), or received another 3 cycles of GP+PD-1 inhibitor if got SD (no reRT group), finally all got 4 cycles of PD-1 inhibitor maintenance. Primary end point was 2-year overall survival (OS). **Results:** Between Mar 2020 to Nov 2023, 68 high-risk patients were recruited (Table 1). After 3 cycles of GP + PD-1 inhibitor, 44 (64.7%) patients got PR (34 down-classify to low-risk and 10 still high-risk) and received full-course reRT, 22 (32.4%) got SD (all high-risk) and kept receiving GP + PD-1 inhibitor, and 2 (2.9%) could not be evaluated due to 1 died of COVID-19 and 1 withdrew after 2 cycles of treatment. 56 (82.4%) patients finished the scheduled treatment, and 12 discontinued chemo-immunotherapy. With a median follow-up time of 32.7 months, the 2-year OS of whole cohort was 67.2%, and 73.8% vs 51.2% (P = 0.019) in reRT group vs no reRT group. The 2-year progression-free survival (PFS) of whole cohort was 47.9%, and 61.0% vs 24.3% (P < 0.0001) in reRT group vs no reRT group. The most common ≥grade 3 toxicities included neutropenia (30.9%), lymphopenia (22.1%), and xerostomia (16.2%). The incidences of grade 3 nasopharyngeal necrosis was 5.9%. Two (2.9%) patients died of massive nasal bleeding. **Conclusions:** Induction chemo-immunotherapy offered the chance of reRT for high-risk rNPC patients and improved their overall survival with acceptable toxicities. Clinical trial information: NCT03930498. Research Sponsor: National Natural Science Foundation of China for Young Scholars; Sun Yat-sen University Young Teachers Cultivation Program; Sun Yat-sen University Cancer Center 308 Program.

Basic information.

Variables	Whole cohort	reRT group	no reRT group
Age†, year	52.0 (43.0 - 58.0)	54.5 (42.8 - 58.8)	47.0 (43.0 - 54.8)
Sex			
Male	51 (75.0)	30 (68.2)	21 (87.5)
Female	17 (25.0)	14 (31.8)	3 (12.5)
rT stage			
T3	36 (52.9)	28 (63.6)	8 (33.3)
T4	32 (47.1)	16 (36.4)	16 (66.7)
rN stage			
N0	36 (52.9)	25 (56.8)	11 (45.8)
N1-3	32 (47.1)	19 (43.2)	13 (54.2)
rTNM stage			
III	35 (51.5)	27 (61.4)	8 (33.3)
IVa	33 (48.5)	17 (38.6)	16 (66.7)
pre-treatment EBV DNA, copy/ml			
0	23 (33.8)	14 (31.8)	9 (37.5)
>0	41 (60.2)	27 (61.4)	14 (58.3)
Missing	4 (5.9)	3 (6.8)	1 (4.2)
PRANCIS model†, points	295.3 (264.1 - 321.8)	270.8 (258.1 - 340.5)	309.2 (297.5 - 319.4)

†median (IQR).

6041 Poster Session

Optimal maintenance therapy strategy for metastatic nasopharyngeal carcinoma: Insights from a cohort study in an endemic region. First Author: Zhuoying Luo, Sun Yat-sen University Cancer Center, Guangzhou, Guangdong, China

Background: Managing metastatic nasopharyngeal carcinoma (mNPC) remains challenging due to its high incidence and mortality rates. While maintenance therapy shows promising potential, the optimal strategy remains unclear. A prior ranking question is if combined therapy of anti-PD-1 antibodies and capecitabine an effective maintenance strategy for mNPC patients who achieved disease control after first-line therapy. **Methods:** Eligible patients with mNPC who achieved disease control following first-line therapy and subsequently received maintenance therapy were included at Sun Yat-sen University Cancer Center between 2018 to 2023. Progression-free survival and overall survival were analyzed using the Kaplan–Meier method and log-rank test. Cox proportional hazards model and inverse probability of treatment weighting analysis were applied to adjust for confounders. Based on interaction effects, stratification analysis was performed. A sensitivity analysis was based on the E-value from the weighted Cox proportional hazards model. **Results:** This cohort study included 300 mNPC patients receiving maintenance therapy with monotherapy (n=211), anti-PD-1 immunotherapy (n=94) or capecitabine (n=117), and their combination (n=89). 234 patients (78.0%) were male, and the median age was 45 years (interquartile range [IQR]: 36–54). At median follow-up of 37.8 months (IQR: 35.6–40.1), combination maintenance significantly improved progression-free survival (PFS) compared to single-drug maintenance [median PFS: not reached *vs* 27.0 months; weighted hazard ratio (HR): 0.569, 95% Confidence Interval (CI): 0.368-0.878, *P* = 0.011; E-value, 2.32], though no improvement in overall survival was observed. Stratification analysis revealed enhanced efficacy of combination maintenance in patients without prior local treatment (HR: 0.411, 95% CI: 0.266–0.748, *P* = 0.004) or with elevated pre-maintenance Epstein-Barr virus (EBV) DNA levels (HR: 0.312, 95% CI: 0.106–0.917, *P* = 0.034). No significant difference in prognosis was observed between capecitabine and anti-PD-1 monotherapy groups. Combination regimen obtained significantly superior progression-free survival compared to either monotherapy alone. The safety profile was similar between combination maintenance and single-drug groups. **Conclusions:** Combined anti-PD-1 and capecitabine maintenance therapy significantly improved prognosis in mNPC with disease control after first-line therapy, particularly in patients with elevated premaintenance EBV DNA levels or those without local treatment. Research Sponsor: National Natural Science Foundation of China; 822029005; National Natural Science Foundation of China; 82172863; National Natural Science Foundation of China; 82002855; Natural Science Foundation of Guangdong Province; 2023B1515020044; Guangzhou Basic and Applied Basic Research Project; 2023A04J2136; Guangzhou Basic and Applied Basic Research Project; 2023A04J2142.

6042 Poster Session

Major pathological response to neoadjuvant immune-related therapy and influence on long-term survival in patients with locally advanced oral squamous cell carcinoma. First Author: Lai-ping Zhong, Department of Oromaxillofacial Head and Neck Surgery, Center for Oromaxillofacial Head and Neck Disorders, Huashan Hospital, Fudan University, Shanghai, China

Background: In neoadjuvant immune-related therapy (NAIT) for patients with locally advanced oral squamous cell carcinoma (LAOSCC), it has been highly anticipated whether major pathological response (MPR) can translate into long-term survival benefits. The aim of this study was to demonstrate the relationship between MPR to NAIT and long-term survival in LAOSCC. **Methods:** Two single-arm trials were included in this study on NAIT of neoadjuvant immunochemotherapy (NAICT) with Toripalimab plus albumin paclitaxel/cisplatin (NCT04473716) or neoadjuvant immunotarget therapy (NAITT) with Camrelizumab plus Apatinib (NCT04393506) in LAOSCC patients at clinical stage III and IVA (AJCC 2018). The patients received two cycles (21 days each) of NAICT with intravenous albumin paclitaxel (260mg/m^2), cisplatin (75mg/m^2) and Toripalimab (240mg) on day 1 and day 22; or three cycles of NAITT with intravenous Camrelizumab (250mg) on d1, d15, d29, and oral Apatinib daily, initiating on d1, ending on the 5th day before surgery. Then, radical surgery and post-operative radiotherapy/chemoradiotherapy was performed. Primary tumors were assessed for the percentage of residual viable tumor that was identified on HE staining, and tumor with no more than 10% viable tumor cell was considered as MPR. **Results:** From April 2020 to April 2021, 40 patients received NAIT and radical surgery. The rate of CPS>10 in the biopsy and the MPR rate was 20% and 60% in the NAICT group, 24% and 40% in the NAITT group, respectively. The follow-up period ranged from 45 to 53 months. The 4-year OS and DFS rate was 90% and 85% in the NAICT group, 90% and 80% in the NAITT group. In the patients archived MPR, the 4-year OS and DFS rate was 100% and 95%, in the non-MPR patients, the 4-year OS and DFS rate was 80% and 70%. In the nine patients with CPS>10, they were all alive without local tumor recurrence or metastasis. **Conclusions:** NAICT and NAITT are safe and effective, the LAOSCC patients with CPS>10 or archiving MPR could have long-term survival benefit from NAIT. Clinical trial information: NCT04473716, NCT04393506. Research Sponsor: None.

6043 Poster Session

Neoadjuvant immunotherapy in combination with chemotherapy in resectable locally advanced head and neck squamous cell carcinoma: A randomized, open label, phase II clinical trial. First Author: Lei Liu, Division of Head & Neck Tumor Multimodality Treatment, Cancer Center, West China Hospital, Sichuan University, Chengdu, China

Background: The efficacy and safety of neoadjuvant immunotherapy (NAI) for resectable locally advanced head and neck squamous cell carcinoma (LAHNSCC) remain unclear, requiring further exploration. While PD-1 inhibitors combined with chemotherapy have shown promise, most regimens focus on single-target inhibitors. Dual-target inhibitors, such as PD-1/CTLA4 or PD-1/VEGF combinations, demonstrated superior efficacy in recurrent/metastatic HNSCC. This study aims to compare the efficacy and safety of single- and dual-target NAI combined with chemotherapy for resectable LAHNSCC to identify the optimal strategy. **Methods:** This phase II randomized trial will enroll resectable LAHNSCC patients eligible for surgery. Patients will be randomized into three cohorts: Cohort 1 will receive ivonescimab (PD-1/VEGF antibody, 10 mg/kg), Cohort 2 will receive cadonilimab (PD-1/CTLA-4antibody, 6 mg/kg), and Cohort 3 will receive penpulimab (PD-1 antibody, 200 mg), all in combination with cisplatin and nab-paclitaxel. Dose adjustments are allowed based on toxicity, and surgery will be performed within 2-4 weeks after 3 cycles of neoadjuvant treatment. Patients achieving pCR will receive 16 cycles of adjuvant immunotherapy. Those without pCR will undergo adjuvant radiotherapy or chemoradiotherapy, followed by 16 cycles of adjuvant immunotherapy. The primary endpoints were pCR and safety. Secondary endpoints include MPR, ORR, EFS and OS. **Results:** A total of 24 patients were enrolled, with 13 evaluable for analysis. The median age was 58 (range 34-70). The primary site included oral cavity (n=7), oropharynx (n=2, including 1 HPV-positive), and larynx (n=4). The clinical stages were as follows: T2 (n = 3), T3 (n = 6), T4a (n = 5), and cN0/1 (n = 3), cN2 (n = 9), cN3 (n = 1). The pCR rates were 80% (4/5), 0% (0/2), and 66.7% (4/6) in Cohort 1, 2, and 3, respectively. The major pathologic responses (MPR) rates were 80% (4/5), 100% (2/2), and 66.7% (4/6) in Cohort 1, 2, and 3, respectively. Pathological non-response (pNR) occurred more frequently in Cohort 3 (2/6) and absent in Cohorts 1 (0/5) and 2 (0/2). The ORR was 100% in Cohort 1 (CR: 3/5, PR: 2/5) and Cohort 2 (100%, PR: 2/2), while Cohort 3 showed a lower ORR of 83.3% (CR: 3/6, PR: 2/6, SD: 1/6). There were no Grade ≥3 TRAEs or unexpected surgical delays/complications. **Conclusions:** Neoadjuvant single- or dual-target immunotherapy combined with chemotherapy showed promising pathological responses in resectable LAHNSCC. While dual-target therapy showed potential benefits, the small sample size limits definitive conclusions. The treatment was well-tolerated, with no serious TRAEs. Further analyses will be conducted as patient enrollment continues in larger cohorts. Clinical trial information: NCT06444009. Research Sponsor: None.

RECIST and pathologic response.

	RECIST				Pathologic Response		
	CR	PR	SD	PD	MPR	pPR	pNR
					pCR		
Cohort 1	3	2			4	1	
Cohort 2		2			2		
Cohort 3	3	2	1		4		2

6045 Poster Session

Spatial transcriptomics analysis to predict response to immune checkpoint blockade (ICB) in recurrent or metastatic head and neck squamous cell cancer (RM-HNSCC). First Author: Grégoire Marret, Division of Medical Oncology and Hematology, Princess Margaret Cancer Centre, University Health Network, University of Toronto, Toronto, Canada

Background: Spatial transcriptomics (ST) revealed conserved malignant leading edge (LE) and tumor core (TC) architectures in primary oral squamous cell carcinoma (OSCC) with potential for biomarker discovery. Spatial organization of tumor cells, as well as composition and prognostic significance of neighboring stromal cells in RM-HNSCC remain unknown. **Methods:** 21 tumor biopsy samples (14 baseline, 7 paired on-treatment) from 14 ICB-naive RM-HNSCC patients (pts) treated with pembrolizumab in INSPIRE (NCT02644369) were profiled using 10x Visium. Spatial organization was refined by scoring LE and TC gene sets identified in OSCC (Arora and Bose et al. Nat Comm 2023). Malignant (2,671 spots) and nonmalignant (8,177 spots) subclusters were annotated, with the latter classified into five cell subtypes using canonical markers: tumor-associated macrophages (TAMs) (*CD68*, *CD14*, *SCF1R*), regulatory stromal cells (reg) (*KRT17*, *COL10A1*, *SRBP1*), plasma cells (*CD38*, *IRF4*, *PRDM1*), T cells (*CD3D*, *CD3E*, *PTPRC*), and cancer-associated fibroblasts (CAFs) (*FAP*, *COL1A1*, *PDGFRB*). Neighborhood analyses compared normalized counts of stromal cells adjacent to LE and TC, accounting for variations in cell density and sampling differences. A signature was built through *k*-means clustering of the five cell subtypes. Pts were stratified into high/low signature-score groups using the median cutoff and tested for association with progression-free survival (PFS). **Results:** Spatial organization revealed conserved malignant subclusters (C0 and C1) in 19/21 samples from 13 pts (11 non-responders). Top C0 genes were *COL21A1*, *S1PR3*, *LIFR*, and *ZEB1*. Top C1 genes were *KRT6B*, *KRT6C*, *KRTDAP*, and *LCN2*. Pathway analysis predicted activation of cell cycle and glycoprotein 6 in C0, and keratinization and neutrophil degranulation in C1. Comparative expression of OSCC-related gene sets revealed LE correlation with C0, and TC correlation with C1 (both $p <$ 0.0001); stronger overlap was seen with the latter highlighting TC as a more conserved feature in HNSCC. Among non-responders, dominant communication patterns in LE and TC included claudins, cadherins, WNT, and IL-6, linked to cell adhesion, migration/invasion, and immune evasion. Signature generated by neighborhood analysis was enriched in TAMs and T cells, depleted in CAFs and reg near LE and TC, while plasma cells were depleted near LE but enriched near TC. Pts with high signature scores (6/13) exhibited improved PFS compared to low scores (7/13), median PFS 6.0 months [95% CI, 2.3-NA] versus 1.9 months [95% CI, 1.8-NA] (p = 0.059). **Conclusions:** To our knowledge, this is the first report using ST analysis to characterize LE and TC architectures in RM-HNSCC, along with heterogeneous neighboring stromal cells with prognostic potential for ICB. Ongoing cohort expansion will elucidate the clinical significance of these findings. Research Sponsor: G. M. is supported by CRIS-Princess Margaret Cancer Centre Drug Development Fellowship Program.

6046 Poster Session

Effect of fusion of radiomic, pathomic, and clinical biomarkers on multi-scale tumor biology and OS stratification in HNSCC receiving standard of care (SOC). First Author: Omid Haji Maghsoudi, Picture Health Inc., Cleveland, OH

Background: SOC immunotherapy (IO) for head and neck squamous cell carcinoma (HNSCC) has limited efficacy with inadequate biomarkers (BMs), necessitating improved strategies. Routine radiology and pathology scans provide underutilized tumor data that can address this need. BMs built from these scans can be integrated - along with existing BMs and clinical data - into multimodal predictors for improved stratification by clinical benefit. We evaluated (1) separate BMs using radiomics, pathomics, or clinical data, (2) their cross-modality correlations, and (3) a fused multimodal predictor of overall survival (OS). **Methods:** 100 HNSCC patients (96% male; mean age: 55 yrs; mean BMI: 22.6) treated primarily with pembrolizumab or nivolumab $\pm$ chemotherapy in 1L setting were analyzed. Radiomic and pathomic features were extracted via the Picture Health Px Platform. Tumors and adjacent vessels were segmented on pre- and on-treatment CT. Radiomic features (shape, texture, quantitative vessel tortuosity) were extracted, and longitudinal changes were distilled into feature clusters. Pathomics features of tumor and immune cell nuclei morphology and spatial interactions were extracted from baseline H&E whole-slide images. Clinical variables included: PD-L1 CPS, local/regional/distant recurrence, M stage, oral/non-oral cavity site, P16 status, and BMI. Uni- and multimodal models were trained and evaluated by cross-validation to predict OS. **Results:** Radiomics and pathomics models outperformed the clinical model, P16 (HR=0.9, p=0.82) and PD-L1 status (HR=0.7, p=0.08) alone. A fused multimodal model of 6 radiomic clusters, 10 pathomic features, and 6 clinical variables achieved strongest OS stratification (Table 1). High pathomic tumor-immune cell interaction - indicating immune activation - was associated with PD-L1 (p=0.020) and P16 status (p$<$1e-5), and tied to on-treatment decreases in radiomic wavelet-entropy features of heterogeneity (r=-0.30, p=0.044) and increases in radiomic structural homogeneity (r=0.27, p=0.024). Despite these correlations, each modality contributed independently to the multimodal prediction (R2$<$0.03), emphasizing complementarity. **Conclusions:** A multimodal BM integrating radiology and pathology to capture tumor properties (heterogeneity, angiogenesis, immune infiltration, nuclei morphology) refined understanding of tumor behavior and IO outcome. Findings suggest an interpretable multimodal BM may better identify high-risk patients who would benefit from alternative therapies, enabling more personalized and effective HNSCC management. Research Sponsor: Genmab.

Model summaries by modality.

Modality	N	Low risk N	High risk N	High Risk HR (p-value)	Median Shortened OS (yrs)
Clinical	100	47	53	1.8 (0.049)	1.09
Pathology	85	62	23	2.4 (0.012)	3.04
Radiology	68	54	14	3.2 (0.0004)	3.06
Multimodal	57	33	24	6.3 (0.0001)	4.20

6047 Poster Session

ctDNA tumor fraction (TF) to predict response to nivolumab in recurrent or metastatic (R/M) head and neck squamous cell carcinoma (HNSCC): An analysis of the multicentric phase 2 TOPNIVO trial. First Author: Filippo Gustavo Dall'Olio, Institut Gustave Roussy, Villejuif, France

Background: Anti-PD1 provides clinical benefits in HNSCC, yet biomarkers of response remain poorly defined. In other cancer types, measures of ctDNA shedding, such as TF, have been shown to correlate with treatment outcomes. Little is known about ctDNA shedding in HNSCC and its prognostic role. TOPNIVO was a single-arm phase 2 trial designed to assess the tolerability of nivolumab in pretreated R/M HNSCC. The aim of this study is to explore plasma estimation of TF with plasmatic ctDNA and its prognostic role in HNSCC patients receiving nivolumab at 2nd line or later. **Methods:** Plasma samples were obtained at baseline in the phase 2 TOPNIVO study (NCT03226756), just before treatment initiation. Genomic copy number alteration and TF were investigated using low-pass Whole Genome Sequencing performed with ctDNA extracted from plasma. Bioinformatic analysis was based on the ichorCNA (V0.2.0). TF $>$ 3% was considered positive. For Tumor Volume (TV) assessment, primary and secondary lesions were analyzed. When available, all lesions were included if fewer than five were present; otherwise, at least five per organ were manually delineated by two experienced physicians. Volume of each lesion were extracted using LIFEx software V.3.44 (Local Image Feature Extraction, www.lifexsoft.org). Patient's TV was then defined by the sum of the volume of all measured lesions. Primary endpoint was overall survival (OS). **Results:** Plasma samples were available for 86 out of 343 patients, with no major differences compared to the overall cohort in terms of baseline characteristics. In particular, 65 (76%) were male, 12 (14%) had an ECOG PS of 2, 42 (49%) had locally recurrent disease only, and 9 (10%) had HPV-positive oropharyngeal disease. ctDNA TF was positive in all patients (median TF 7.4%, range 4.8% to 35.9%). Median OS of the selected population was 7.4 months (95% CI 5.4 - 11.2). TF was correlated with TV (Spearman 0.31, p = 0.008). Moreover, it was higher in patients with liver metastasis (n = 8, median TF 14% vs 7 %,) and, for oropharynx, higher in patients with HPV positive disease (n= 9 vs 30, median TF 17% vs 6.7%,). TF was correlated with OS both in univariate (Hazard Ratio - HR 1.9, p = 0.015) and multivariate Cox models (HR 3.12, p = 0.003). **Conclusions:** In HNSCC patients of the TOPNIVO study, ctDNA TF was always detectable and depends on tumor volume and on the biology of the disease. TF retains independent prognostic validity. More translational data will be presented on biological correlates of ctDNA shed. Research Sponsor: None.

Multivariable Cox model for overall survival.

Variable	p	HR	95% CI
Sex (male vs female)	0.34	1.40	0.70 - 2.83
Age (> 70)	0.87	1.06	0.53 - 2.11
ECOG PS (2 vs 0-1)	0.97	1.02	0.40 - 2.59
Metastatic only disease vs local recurrence	0.028	0.43	0.20 - 0.91
HPV+ oropharynx vs other	0.99	1	0.39 - 2.52
Log TV	0.78	1.03	0.82 - 1.31
Log TF	0.0032	3.12	1.46 - 6.65

6048 Poster Session

Phase 2 trial of ozuriftamab vedotin (BA3021), a conditionally binding ROR2-ADC, in patients with heavily pretreated squamous cell carcinoma of the head and neck. First Author: Douglas Adkins, Washington University School of Medicine, St. Louis, MO

Background: Recurrent or metastatic squamous cell carcinoma of the head and neck (R/M SCCHN) represents a marked unmet need. ROR2 is a cell-surface transmembrane receptor protein tyrosine kinase highly expressed in several tumor types including HNSCC. Ozuriftamab vedotin is a conditionally binding ROR2 antibody-drug conjugate designed to reduce off-tumor toxicity and improve pharmacokinetics by conditionally binding to ROR2 under low-pH conditions (pH$<$6.7) of the tumor microenvironment, thus sparing normal tissue. This novel mechanism avoids tissue-mediated drug disposition and improves pharmacokinetics. The recommended Phase 2 dose of 1.8 mg/kg was determined from the Phase 1 trial (NCT03504488). **Methods:** This multi-center, open-label, single-arm Phase 2 trial evaluated ozuriftamab vedotin in patients (pts) with R/M SCCHN previously treated with anti-PD-1 agents. Patients with SCCHN were enrolled and received 1.8 mg/kg of ozuriftamab vedotin given in 2 schedules: once every two weeks (Q2W) or days 1 and 8 of a 21-day cycle (2Q3W). Tumor assessments were conducted by CT or MRI every 6 weeks from Cycle 1 Day 1 until week 12, then every 8 weeks up to 1 year. Evaluable pts included those with at least one post-treatment scan. ROR2 expression was characterized by immunohistochemistry. Additional assessments included pharmacokinetic, pharmacodynamic, immunogenicity, and biomarker evaluations to characterize efficacy and safety. **Results:** As of May 31, 2024, 31 pts received ozuriftamab vedotin either Q2W (n=12) or 2Q3W (n=19) for a median of 84 days. Pts had a median of 3 prior lines of therapy, and all had experienced failure of anti–PD-1 therapy. Among 28 evaluable pts (evaluable as defined as having complete 1 post dose tumor assessment) for best overall response, there were 10 responders (36%; 1 confirmed complete response, and 5 confirmed/4 unconfirmed partial responses, and 14 stable disease. A disease control rate of 86% was observed. Median duration of response for all confirmed responders has not been reached ($>$3.6 months; 95% CI, 0.4–NE). Most adverse events (AEs) were grade 1-2, with fatigue (59%), anemia (34%), and nausea (34%) being the most frequent. Six pts (19%) experienced grade 3 treatment-related AEs (TRAEs). Two pts experienced a grade 4 TRAE (1 pt with hyponatremia in 2Q3W cohort, and 1 pt with neuropathy in Q2W cohort). No grade 5 TRAEs were observed. **Conclusions:** Pts treated with ozuriftamab vedotin achieved a high rate of disease control with acceptable tolerability. Shows promising efficacy, including in pts refractory to anti-PD1 and warrants further evaluation in SCCHN. Clinical trial information: NCT03504488. Research Sponsor: None.

6049 Poster Session

Establishment and validation of a dynamic prognostic model using serial circulating tumor DNA (ctDNA) for endemic EBV-related nasopharyngeal carcinoma (NPC): A secondary analysis of EP-SEASON. First Author: Zi-Cheng Zhen, Department of Radiation Oncology, Sun Yat-sen University Cancer Center, State Key Laboratory of Oncology in South China, Guangdong Key Laboratory of Nasopharyngeal Carcinoma Diagnosis and Therapy, Guangdong Provincial Clinical Research Center for Cancer, Guangzhou, China

Background: Published risk prediction tools have focused on pretreatment factors, whereas the accuracy remains challenging in cancer care. Emerging evidences emphasize the dynamic rather than static recurrence risks during treatment course, and non-invasive diagnostics tools have advanced opportunities for serial tumor assessments. Here, we present an effective dynamic risk individualized prediction model (NPC-DRIM) incorporating serial ctDNA data, using the endemic EBV-related NPC as a model. **Methods:** This study included 1000 patients (pts) enrolled from a prospective biomarker study EP-SEASON, with complete longitudinal ctDNA data at 11 timepoints across treatment: after each neoadjuvant chemotherapy (NAC) circle (T1-3), every week during radiotherapy (T4-T9), within 1 week after radiotherapy (T10), and 1-3 months after radiotherapy (T11). Pts were divided into subcohort$_{NAC}$ (n=752) and subcohort$_{no\text{-}NAC}$ (n=248) according to receiving NAC or not, and randomly 70/30% split into training and validation cohort. Time-series and statistical features characterizing the dynamic change of ctDNA at each timepoint were extracted. The NPC-DRIM at T3-T11 were developed using the features selected via Cox univariate analysis in training cohort and then validated. The performance of NPC-DRIM was determined by C-index, time-dependent AUC, calibration curves, and decision curves, and compared with existing models. **Results:** The NPC-DRIM incorporated 4 clinical variables, 8 time-series features and 10 statistical features of ctDNA data. The C-index for predicting recurrence increased with time: 0.64 at T2, 0.69 at T3-T4, 0.70 at T5, 0.71 at T6, 0.73 at T7-T9, 0.77 at T10, and 0.76 at T11 in subcohort$_{NAC}$; 0.70 at T5, 0.68 at T6, 0.82 at T7, 0.78 at T8, 0.73 at T9, 0.74 at T10, and 0.83 at T11 in subcohort$_{no\text{-}NAC}$. The NPC-DRIM at T11 had statistically improved outcome prediction compared to other dynamic models (Landmark Cox and Joint Model), and static models (AHR_Chen, RPA_Guo, RPA_Lee, and AJCC_8th staging system) (Table). For individualized dynamic risk prediction, we developed a web-based calculator to visualized the estimated changing recurrence risks. In addition, we showed that the high-risk pts identified by NPC-DRIM benefit from immune checkpoint inhibitors (ICI), while the low-risk pts did not. **Conclusions:** We introduce for the first time that the dynamic risk prediction model NPC-DRIM outperformed the conventional models, facilitating personalized therapeutic paradigms. Clinical trial information: NCT03855020. Research Sponsor: National Natural Science Foundation of China; 92259202; National Natural Science Foundation of China; 82441026; Science and Technology Projects in Guangzhou; 2024B01J1301; Noncommunicable Chronic Diseases-National Science and Technology Major Project; 2024ZD0520700; Guangzhou Municipal Health Commission; 2023P-GX02; Cancer Innovative Research Program of Sun Yat-sen University Cancer Center; CIRP-SYSUCC-0010.

	Subcohort$_{NAC}$		Subcohort$_{no\text{-}NAC}$	
	C-index	*p* value	C-index	*p* value
NPC-DRIM	**0.76**		**0.83**	
Landmark Cox	0.65	0.01	0.63	<0.01
Joint Model	0.63	<0.01	0.61	0.01
AHR Model (Chen et al. 2021)	0.61	<0.01	0.57	<0.01
RPA Model (Guo et al. 2019)	0.59	<0.01	0.59	<0.01
RPA Model (Lee et al. 2019)	0.59	<0.01	0.66	0.02
AJCC_8th	0.56	<0.01	0.57	<0.01

6050 Poster Session

Mechanisms of resistance to anti-PD1 treatment in recurrent and/or metastatic squamous cell carcinoma of the head and neck: A multi-omics IMMUCAN/EORTC analysis. First Author: Athenais van der Elst, Université Catholique de Louvain, Bruxelles, Bruxelles, Belgium

Background: Anti-PD1 therapies improve overall survival (OS) in recurrent/metastatic (R/M) squamous cell carcinoma of the head and neck (SCCHN), but only a minority of patients (pts) achieve durable responses. The mechanisms driving resistance to anti-PD1 in SCCHN remain poorly understood. **Methods:** Using the IMMUcan multi-omics workflow combining WES, RNAseq, multiplex immunofluorescence and Imaging mass cytometry, we characterized the molecular and immune profiles of R/M SCCHN progressing on anti-PD1 treatment and compared them to an anti-PD1-naïve cohort. **Results:** 74 R/M SCCHN patients who progressed on PD1 inhibitors at the time of tumor biopsy were analysed and compared to a different cohort of 79 R/M SCCHN patients naïve of any anti-PD1 treatment. Among the 74 anti-PD1 resistant patients, 60 patients had primary resistance, and 14 had secondary resistance. Compared to anti-PD1 naïve SCCHN, tumor biopsies from anti-PD1 resistant SCCHN patients exhibited significantly more *EGFR*, *MYCL* and *RRAGC* amplifications, and more genomic alterations of the MYC pathway. Tumor samples harboring MYC pathway alterations were characterized by lower T cell infiltration compared to MYC pathway wild type (WT) tumors, and those harboring an amplification of *EGFR* had less B cells and dendritic cells in the tumor microenvironment compared to *EGFR*-WT. Moreover, transcriptomic and proteomic analyses revealed that secondary resistant SCCHN had increased CD8+ T cell infiltration and higher levels of immune exhaustion markers compared to anti-PD1 primary resistant and to anti-PD1-naïve SCCHN. 48 pts from the anti-PD1-naïve cohort were subsequently treated with PD(L)1 inhibitors. In this subgroup, pts with high B2M expression on tumor cells had better OS. SCCHN with high B2M expression on tumor cells also showed greater T cell infiltration compared to SCCHN with low B2M expression. **Conclusions:** Our data provide a rational to guide the development of therapeutic strategies aimed at reversing acquired resistance to PD-1 blockade in SCCHN. Our data suggest the potential use of B2M expression on tumor cells as predictive biomarker of response to anti-PD1 therapy. Research Sponsor: None.

Clinical characteristics.

	Anti-PD1 naïve cohort (N=79)	Anti-PD1 resistant cohort (N=74)
Substance abuse		
Smoker and/or drinker	68 (86.1%)	62 (83.8%)
HPV-status		
Positive	11 (13.9%)	10 (13.5%)
Primary disease location		
Oral cavity	19 (24.1%)	17 (23.0%)
Oropharynx	34 (43.0%)	33 (44.6%)
Hypopharynx	14 (17.7%)	14 (18.9%)
Larynx	12 (15.2%)	10 (13.5%)
Disease extent at the time of tumor biopsy		
Locoregional only disease	32 (40.5%)	26 (35.1%)
Distant metastatic disease	47 (59.5%)	48 (64.9%)
Number R/M treatment lines prior to biopsy		
0	57 (72.2%)	5 (6.8%)
1	17 (21.5%)	23 (31.1%)
2+	5 (6.4%)	46 (62.2%)

6051 Poster Session

Comprehensive profiling of circulating tumor DNA and microbial landscapes in nasopharyngeal cancer across Asia: NCCH1905/A-TRAIN study. First Author: Thinh Huy Nguyen, Ho Chi Minh City Oncology Hospital, Ho Chi Minh City, Viet Nam

Background: Nasopharyngeal cancer (NPC), a malignancy of the nasopharynx, is strongly associated with Epstein-Barr virus (EBV) infection. Although rare in Western countries, NPC is significantly more prevalent in Southeast Asia, likely due to a combination of environmental and dietary factors, though these remain incompletely understood. Current treatments, primarily radiation and chemotherapy, may not fully address the unique challenges posed by NPC. This study aims to conduct a comprehensive genomic analysis, including circulating tumor DNA (ctDNA), and microbial analysis to clarify NPC pathogenesis by examining patient backgrounds in Asian populations. **Methods:** This is an Asian multicenter prospective observational study conducted by nine institutions in Japan, Philippines, Malaysia, Thailand, Singapore, Taiwan and Vietnam. Eligible patients had histological diagnosis of NPC with metastatic and/or recurrent disease. ctDNA will be analyzed in blood samples collected at newly initial diagnosis of metastatic disease and/or at disease progression. Genomic profiling will be analyzed using TruSight Oncology 500 ctDNA for plasma (Illumina) and TruSight Oncology 500 (Illumina) for tumor tissue, respectively. Furthermore, we analyzed more than 3,000 viral genes using tumor tissue. **Results:** Seventy-two samples from 72 NPC patients were analyzed. The median age of the patients was 52 years old (range, 25-78), with 53 (73.6%) males. All the patients were Asian, and the details are as follows: 23 Vietnamese, 15 Chinese, 7 Thai, 6 Taiwanese, 5 Iban, 4 Filipino, 3 Japanese and 3 Malay. The number of patients with a history of surgery and radiotherapy was 10 (13.9%) and 45 (62.5%), respectively. Forty-nine patients (68.1%) had a history of chemotherapy, and all had a history of platinum-based drug administration, while eight (11.1%) had a history of immuno-checkpoint inhibitors administration. Pathogenic variants in ctDNA were detected in 40 out of 72 patients (55.6%). The most frequently deleterious mutations were *TP53, NRAS* and *TGFBR2*. Copy number alteration was observed in 33 patients (45.8%). Comprehensive viral and bacterial analysis was available in 20/72 patients (27.8%), with EBV found in 17 patients and none of the viruses in 3 patients. Actinomyces was dominant in all cases, although the bacterial flora was somewhat different. **Conclusions:** In this study, we conducted comprehensive genomic and microbial analyses of samples collected from NPC patients in Asia, and detected various genomic features as well as elucidating the characteristics of the microbial flora present in the background. As a result, it was shown that anaerobic bacteria may be involved in the pathogenesis of NPC. These bacterial groups form a tumor microenvironment through inflammation and immune modulation, and it is suggested that they promote tumor formation. Clinical trial information: NCT05099978. Research Sponsor: AMED (Japan Agency for Medical Research and Development).

6052 Poster Session

Characterizing the prevalence and prognostic significance of MTAP loss in endemic nasopharyngeal cancer using immunohistochemistry (IHC) versus fluorescent in situ hybridization (FISH). First Author: David Johnson, Department of Clinical Oncology, State Key Laboratory of Translational Oncology, Charlie Lee Precision Immunooncology program, Sir Y.K. Pao Centre for Cancer, The Chinese University of Hong Kong, Hong Kong, Hong Kong

Background: Methylthioadenosine phosphorylase (MTAP) loss has been associated with poor outcomes in various cancers, including nasopharyngeal carcinoma (NPC). Homozygous deletion of the MTAP locus is one of the most frequent somatic changes in NPC, creating opportunities for therapeutic targeting. However, the concordance between MTAP IHC and FISH for detecting MTAP loss, and the prognostic impact of partial MTAP loss, has not been fully explored. This study evaluated the prevalence of MTAP loss, correlation between IHC and FISH, and association of MTAP expression with time to progression (TTP), progression-free survival (PFS) and overall survival (OS). **Methods:** MTAP expression was analyzed by IHC, and locus loss was confirmed using FISH in tumors M0 (non-metastatic) NPC patients. Correlations between MTAP IHC and FISH results were analyzed to assess concordance, sensitivity, and specificity. Kaplan-Meier survival curves and log-rank tests compared survival distributions, while Cox proportional hazards models were applied for univariate and multivariate analyses. Subgroup analyses were performed by tumor, nodal and overall stage (AJCC 8th edition). **Results:** Among 175 patients, 65 (36.0%) exhibited IHC 0 and FISH-negative MTAP loss. Concordance rate between IHC 0 and FISH-negative was 94.9%. MTAP loss was significantly correlated with higher N2–3 and stage III–IVA disease (Pearson correlation coefficients: 0.81 and 0.73, respectively; $p < 0.0001$). Based on receiver operating curve (ROC) analysis, the optimal MTAP cutoff for progression was 110. Partial MTAP loss (MTAP 0–109) was significantly associated with shorter TTP compared to MTAP 110–300 (median TTP: 4.6 years vs. 15.8 years; p = 0.04). In multivariate analysis, MTAP <110 remained significant for TTP (HR = 0.65; CI 0.48-0.98 p = 0.04) after adjusting for grouped N stage. Subgroup analyses demonstrated that MTAP <110 was significantly associated with shorter PFS in N2–3 patients (HR 0.5 CI 0.28-0.9 p = 0.02) and shorter TTP in stage III–IVA patients (HR 0.61 CI 0.37-1.0 p = 0.05). **Conclusions:** Partial MTAP loss (IHC <110) is associated with worse outcomes in NPC, particularly shorter TTP and PFS, with significant prognostic value in advanced nodal and overall stage disease. High concordance between IHC and FISH supports IHC as a reliable diagnostic tool. These findings highlight MTAP expression as a potential prognostic biomarker for NPC, warranting further validation and exploration of targeted therapies. Research Sponsor: Viracta Therapeutics and ScinnoHub Pharmaceutical Co., Ltd.

6053 **Poster Session**

Tracking circulating tumor DNA through liquid biopsy after radiotherapy for dynamic risk monitoring in cancer patients. First Author: Renyuan Huang, Sun Yat-sen University Cancer Center; Collaborative Innovation Center for Cancer Medicine; State Key Laboratory of Oncology in South China; Guangdong Key Laboratory of Nasopharyngeal Carcinoma Diagnosis and Therapy, Guangzhou, Guangdong, China

Background: Circulating tumor DNA (ctDNA) analysis provides a useful tool for non-invasive tumor burden assessment. However, the management of detectable ctDNA without clinical or radiographic evidence of disease during follow-up remains poorly studied and clinically challenge. Here, we explored whether monitoring ctDNA dynamics can differentiate phenotypes in these patients. Nasopharyngeal carcinoma (NPC) is an ideal model for the sensitive detection of cell-free Epstein-Barr virus DNA (cfEBV DNA). **Methods:** The study analyzed medical records of 14,611 non-metastatic NPC cases treated with definitive radiotherapy with or without chemotherapy from two cohorts: a discovery cohort (n = 4,485) and an independent validation cohort (n = 10,126). Cox regression and recursive partitioning analysis (RPA) were used for survival analyses and patient stratification. **Results:** In the discovery cohort, 23.1% of cases presented detectable cfEBV DNA during follow-up and experienced significantly worse survival compared to those with longitudinally undetectable cfEBV DNA (5-year DFS: 39.1% vs. 91.5%, $p< 0.001$). Pre-treatment cfEBV DNA level ($\geq$2000 vs. $<$ 2000 copies/ml) and the maximum level during follow-up ($\geq$500 vs. $<$ 500 copies/ml) were significantly associated with disease failure. Based on the longitudinal dynamic changes, patients with bounce of cfEBV DNA after its clearance had worse survival than those without bounce (HR_{DFS}= 4.3 [3.1-6.0], $p< 0.001$), and patients with persistent cfEBV DNA had the worst survival (HR_{DFS} = 11.5 [8.3–15.9], $p< 0.001$). RPA was then conducted incorporating other clinical prognostic factors and four distinct prognostic phenotypes were identified (Table). The model showed a significantly higher positive predictive value (96.6% vs. 60.5%) and similar negative predictive value (67.4% vs. 65.8%) compared to single-point cfEBV DNA assessments. Patients who had clearance of low cfEBV DNA burden had a favorable prognosis (5-year DFS, 83.4%). In contrast, most patients with persistent cfEBV DNA had disease failure (5-year DFS, 8.0%); this subgroup can be defined as molecular relapse. The results were consistent in the validation cohort. Notably, patients in the molecular relapse group benefited from early salvage therapy with improved DFS, whereas patients in other phenotypes responded poorly. **Conclusions:** Tracking longitudinal ctDNA dynamics after definitive treatment can enable more precise risk assessment and facilitate risk-adapted, individualized patient management. Research Sponsor: None.

Prognostic phenotypes based on RPA and cfEBV DNA dynamics.

	HR_{DFS}	
Group	**Discovery cohort**	**Validation cohort**
Clearance of low cfEBV DNA burden (<500 copies/ml)	Reference	
Clearance of high cfEBV DNA burden (≥500 copies/ml)	3.0 [1.9-4.7]	1.6 [1.1-2.2]
Bounce after clearance	5.9 [4.1-8.7]	3.5 [2.5-4.7]
Persistent cfEBV DNA	15.7 [10.8-22.7]	13.0 [9.6-17.7]
	$p<0.001$	$p<0.001$

6054 **Poster Session**

Induction chemotherapy followed by chemoradiotherapy with cisplatin or cetuximab for unresectable locally advanced head and neck cancer (TTCC-2007-01 trial): Analysis of genomic biomarkers by next-generation sequencing after long-term outcomes. First Author: Alejandro Olivares Hernández, Medical Oncology Department, University Hospital of Salamanca, Biomedical Research Institute of Salamanca (IBSAL), Salamanca, Spain

Background: Induction chemotherapy (ICT) may provide survival benefit in some patients (pts) with unresectable locally advanced squamous head and neck carcinoma (LA-SCCHN). Objective: Study the benefit of ICT followed by radiotherapy plus cetuximab versus (vs) cisplatin (RT/CET vs RT/CDDP) by profiling predictor biomarkers of response from pts of TTCC-2007-01 trial (NCT00716391). **Methods:** Design TTCC-2007-01: studied the non-inferiority of RT/CET (70Gy + 400mg/250mg/m2 weekly) vs RT/CDDP (70Gy + 100mg/m2 d1-22-43) after ICT (docetaxel 75mg/m2 + platinum 75mg/m2 + 5-FU 750mg/m2 d1-5) in unresectable LA-SCCHN (Oral Oncology, 2022 Nov:134:106087). A cohort of samples were analyzed after DNA extraction and processed using OncoScan platform and TruSight Panel (next-generation sequencing). Survival analysis was performed using Kaplan-Meier (log-rank or Breslow test, survival in months 'm') and Cox regression (HR 95% CI). Statistical significance was $p<0.05$ (SPSSv28). **Results:** In total, 70 pts (male 90% / female 10%) were analyzed in RT/CDDP arm (mean age 55 [45-68]) versus 72 pts (male 88,9% / female 11.1%) in RT/CET arm (mean age 60 [32-70]). The most frequent localizations in RT/CDDP arm were oropharynx (44.3%) and hypopharynx (21.4%). In RT/CET were oropharynx (37,5%) and hypopharynx (23,6%). In RT/CDDP arm HPV was positive in 17.1% of tumors versus 13,1% in RT/CET. In RT/CDDP arm the median overall survival (OS) was 65m [25.6-105.4] vs 36.8m [14.3-59.2] in the RT/CET arm. The progression-free survival (PFS) was 33.2m [16.2-50-1] in the RT/CDDP arm vs 18.3m [9.1-28.6] in the RT/CET arm. *TP53* was the most frequent mutation without differences in OS in either arm. However, mutations were associated with unfavorable PFS in the RT/CDDP arm (22.6 vs 66.2; p=0.025 Breslow), with no difference in RT/CET arm (20.1 vs 15.2; p=0.885 Breslow). HPV+ tumors were associated with better OS (83.9 vs 33.2; p=0.027 Breslow) in RT/CDDP arm. There was no difference in the RT/CET arm (28.1 vs 23.9; $p>0.05$). In the RT/CDDP arm the chromosomal biomarker that was associated with worse OS was 18q12.2- (22.7 vs 85.6; HR 3.3 [1.6-6.6]). Focal alterations 3p14.2- had superior OS (83.9 vs 22.9m; HR 0.1 [0.04-0.30]). In the RT/CET arm the 6p25.3+ biomarker was associated with superior OS (not reached vs 26.6m; HR 0.42 [0.2-0.8]). In terms of PFS in RT/CDDP arm, gains in 2p were associated with worse PFS (12.0 vs 41.7m; HR 2.9 [1.4-6.2]). 6p25.3+ alterations had better PFS in the RT/CET arm (38.8 vs 11.5; HR 0.40 [0.2-0.8]). **Conclusions:** ICT plus RT/CDDP was shown most beneficial in pts with *TP53* wild type, HPV+ and 3p14.2-. In contrast, ICT plus RT/CET is not influenced by *TP53* or HPV. 6p25.3+ is a robust biomarker of response in RT/CET arm in terms of OS and PFS. Correct pts selection may allow for further standardization of ICT in LA-SCCHN. Research Sponsor: Carlos III Health Institute; PI18/01476.

6055 **Poster Session**

Characterization of dynamic changes in tumor-infiltrating lymphocytes (TIL) after neoadjuvant administration of CUE-101, an HPV16 E7-HLA-IL2 fusion protein, to patients with HPV+ locally advanced oropharyngeal squamous cell carcinoma (LA-OPSCC). First Author: Jesse M Zaretsky, Department of Medicine, Division of Oncology, Washington University School of Medicine, St. Louis, MO

Background: CUE-101 is a novel fusion protein designed to selectively engage and expand HPV16-specific T-cells to promote an anti-tumor immune response in HPV+ malignancies. CUE-101 is comprised of the HPV16 $E7_{11-20}$ epitope, HLA-A*0201, and a reduced affinity human IL2. In this single-arm Phase 2 trial (NCT04852328), CUE-101 is administered to HLA-A*0201+ patients with HPV16+ LA-OPSCC in three schedules (A, B, and C) before curative-intent surgery and adjuvant therapy or definitive chemoradiation therapy. Primary endpoints were safety of CUE-101 and changes in the frequency of HPV16 $E7_{11-20}$-specific CD8+ T cells in blood and tumor. Correlates in TIL for Schedules A and B are presented here. **Methods:** CUE-101 (4 mg/kg IV) was administered 14 days (Schedule A), 14 and 7 days (Schedule B), or 7 days (Schedule C) before curative-intent treatment. Biopsies of the primary tumor were collected before CUE-101 administration and within 2 days prior to curative-intent therapy. Single-cell RNA and T-cell receptor (TCR) sequencing (scRNAseq, 10X Genomics) was performed on fresh sorted CD8 T-cells. HPV16 $E7_{11-20}$ dextramer staining and flow cytometry assessed reactivity to HPV E7. Multiplex immunofluorescent (mIF) tissue staining with a 30-marker Phenocycler panel (Akoya Biosciences) assessed tumor, myeloid, and T-cell states. Changes in T-cell clonal frequency were significant if fold change >2 and fisher exact test adjusted p <0.05. Changes in cell populations after treatment were evaluated by two-tailed paired student's t-test. **Results:** Of 20 total patients enrolled, paired biopsies from 13 of sufficient quality were analyzed by scRNAseq, flow cytometry, and mIF. In a joint analysis of Schedules A (n=7) and B (n=6), we identified multiple T-cell clones that significantly expanded following CUE-101 treatment, representing 4-51% (mean 18.3%) of tumor-infiltrating CD8 cells by scRNAseq. Among these, we found significant enrichment for phenotypes of chronic T cell activation (PD1+CD39+, often associated with tumor reactivity, p =0.041). In agreement with this finding, flow cytometry of TIL showed increased CD8+CD39+ cells (mean 10.9%, p =0.026) among CD45 cells, and a small increase in NK cells (1.7%, p =0.005). Absolute cell counts by mIF confirmed these trends. Direct dextramer staining of TIL samples has not specifically identified HPV $E7_{11-20}$ reactive T cells pre- or post-treatment, therefore cloning of TCRs from expanded T-cells is being performed to enable functional testing of HPV reactivity. **Conclusions:** Significant clonal expansion of intra-tumoral CD8 T-cells with signatures associated with tumor reactivity were observed within 2 weeks of CUE-101 administration in HPV16+ LA OPSCC. Studies in blood and of T-cell specificities are ongoing. Clinical trial information: NCT04852328. Research Sponsor: CUE Biopharma.

6056 **Poster Session**

Survival association of PIK3CA in HPV-driven head and neck squamous cell carcinoma (HNSCC). First Author: Kelly Bridgham, Department of Otolaryngology Head & Neck Surgery, Thomas Jefferson University, Philadelphia, PA

Background: Across many solid tumor malignancies, including head and neck squamous cell carcinoma (HNSCC), clinical trial data has supported the integration of PD1 Immune Checkpoint Inhibitors (ICIs) into treatment algorithms; however, durable response to single agent therapy occurs in only a fraction of patients. Thus, there is a great need to understand the molecular underpinnings of response and resistance mechanisms. PIK3CA mutation is a common driver of HPV+ mediated malignancy. We sought to understand the prevalence and clinical impact of PIK3CA mutation in HPV+ and HPV- cancer by applying a multi-omics approach to a large, clinically appended dataset. **Methods:** HNSCC (N = 1901) patient who underwent DNA (592-gene or whole exome) and RNA (whole transcriptome) sequencing at Caris Life Sciences (Phoenix, AZ) was queried to identify HPV+ and HPV- HNSCC cohort. Tumor mutational burden (TMB) was measured by totaling all somatic mutations (mt) per tumor (TMB-H: $>$ 10 mt/MB). Real-world overall survival (rwOS) was obtained from insurance claims data, calculated from either time of biopsy (OS) or start of immunotherapy ($_{IO}$OS) to last contact, or time on ICI ($_{IO}$TOT). Mann-Whitney U and X^2/Fisher-Exact tests were applied, with *p*-values adjusted ($p < .05$). **Results:** Compared to HPV- samples, PIK3CA mutation was highly associated with HPV+ primary (28.5% vs 11.4%, p <0.01) and metastatic (23.8% vs 11.2%, $p<0.01$) lesions. The prevalence of TMB-H was significantly higher in both HPV+ (30.7% vs 7.9%, $p<0.01$) and HPV- (30.7% vs 18.2%, $p<0.01$) with PIK3CA mutation compared to WT. HPV- disease showed significantly worse survival as expected (HR = 0.63, $p<0.001$), while PIK3CA mut /wt status was not associated with differences in OS among HPV+ (HR = 1.05, p = 0.78) or HPV- cohorts (HR = 1.11, p = 0.44). However, irrespective of tumor site and metastatic status, mutPIK3CA HPV+ patients' trend towards an increased $_{IO}$OS (HR = 0.64, p =0.176) and increased $_{IO}$TOT compared to wtPIK3CA patients (HR = 0.72, p = 0.073). In contrast, mutPIK3CA HPV- HNSCC showed worse $_{IO}$OS (HR = 1.65, $p<0.001$) and a trend toward decreased $_{IO}$TOT (HR = 1.20, p=0.248) compared to wtPIK3C patients. **Conclusions:** Data from this cohort indicate potential survival association for PIK3CA mutation, with differing impact in HPV+ and HPV- HNSCC. Further research is needed to explore the mechanism underlying these findings and identify other molecular factors that might contribute to the observed outcomes. Research Sponsor: None.

6057 **Poster Session**

Evaluation of plasma methylated DNA markers for detection HPV-positive oropharyngeal squamous cell carcinoma: A case control study. First Author: Kathryn M. Van Abel, Department of Otorhinolaryngology, Mayo Clinic, Rochester, MN

Background: The incidence rate of human papillomavirus associated oropharyngeal squamous cell carcinoma (HPV(+)OPSCC) has persistently increased over the past decade and is anticipated to rise further over the next decade. Cost effective, accurate, and less invasive screening options for HPV(+)OPSCC have remained stagnant leading to the interrogation of circulating tumor DNA in liquid biopsies such as plasma. We hypothesized that candidate methylated DNA markers (MDMs), previously described by our group, would be present in the plasma of patients with HPV(+)OPSCC and absent in controls. **Methods:** HPV(+)OPSCC cases were enrolled from a high-volume referral practice. Cancer-free control patients were identified from the surrounding 7-county catchment area and frequency matched to cases by age and alcohol use. cfDNA was extracted from 4 mL of plasma and bisulfite converted prior to Target Enrichment Long-probe Quantitative Amplified Signal assays for 15 MDMs. Strand counts for individual MDMs were normalized to a methylated genomic reference marker. An MDM score was derived via random forest modeling of the 15 MDMs. Area under the receiver operator characteristic curve (AUC) for discriminating cases from controls was evaluated for individual markers and for the MDM score. The sensitivity of the MDM score at 95% specificity was also evaluated. **Results:** The study consisted of 96 HPV(+)OPSCC and 100 cancer-free controls. The study population was predominately white (95%) with a median age of 61 yrs (IQR: 52-69 yrs). Eighty-nine percent of the cases were male with cancers affecting either the tonsil in 50 (52%) or base of the tongue in 46 (48%) patients; by design 50% of controls were male. Stage I:II:III:IV disease was present in 66%:22%:9%:3% of the cases. The median (IQR) AUC across the 15 MDMs was 0.83 (0.82-0.85) overall: 0.78 (0.77-0.83) for stage I disease and 0.92 (0.91-0.93) for stage II-IV disease. The MDM score for the combined panel of 15 MDMs achieved a cross-validated AUC of 0.93 (CI: 0.89-0.97) overall: 0.90 (CI: 0.84-0.96) for stage I disease and 0.98 (CI: 0.97-1.00) for stage II-IV disease. At 95% specificity, the cross-validated sensitivity of the MDM score for HPV(+)OPSCC was 80% (CI: 71-87%) overall: 73% (CI: 60-83%) for stage I disease and 94% (CI: 78-99%) for stage II-IV disease. **Conclusions:** We validated a set of previously discovered MDM markers in HPV(+)OPSCC in a robust case control cohort using plasma. The MDMs were detected in both early and late-stage disease. Additional prospective studies in larger intended use cohorts are needed to validate our results for clinical use. Research Sponsor: None.

6058 **Poster Session**

Evidence of a role for oropharyngeal cancer cells with low HPV gene expression in treatment failure. First Author: Devraj Basu, University of Pennsylvania, Philadelphia, PA

Background: A subset of tumor cells with reduced HPV gene expression, here termed HPV-lo cells, are proposed contribute to therapy resistance in HPV+ oropharyngeal cancers (OPCs). However, the biologic and clinical significance of this cell state is unclear because it has been analyzed in relatively few HPV+ OPCs and total tumor cells and remains to be directly linked to therapy resistance and recurrence. We aimed to evaluate HPV-lo cells for their biologic traits, cytotoxic drug responses, and association with recurrence. **Methods:** Single cell mRNA sequencing (scRNAseq) was performed on 64,822 tumor cells from five HPV+ OPC PDXs, and HPV-lo cells were defined by presence of $<$1.0 normalized HPV mRNA reads. Expression profiles distinguishing HPV-lo cells were assessed by gene set enrichment analysis. Changes in HPV-lo cell frequency and gene expression were examined by scRNAseq after two weeks of *in vivo* cisplatin treatment in NSG mice. To test for association of HPV-lo cells with recurrence, a single institution cohort of 851 therapy-naïve p16+ OPC patients receiving primary surgery was used to curate 50 pT1/2 tumors that later recurred (cases) and match 50 tumors that were cured (controls) for pathologic stage, smoking history, and adjuvant therapy. A clinical *in situ* hybridization (ISH) assay was used to probe for HPV E6/E7 in the case-control cohort. Digital image analysis segmented the ISH(+) vs. ISH(-) cells in tumor regions plus the subset of ISH(-) cells comprised of CD45-IHC(+) tumor infiltrating leukocytes (TILs). The ISH(-) tumor cell fraction was estimated by calculating total % ISH(-) cells - %TILs. **Results:** Content of HPV-lo cells in PDXs ranged from 32% to 65%. These cells showed significant downregulation of E2F target genes and upregulation of p53 target genes, supporting presence of reduced HPV E6/E7 activity. Their relative quiescence was further supported by transcriptional inference of fewer cells in the $S/G_2/M$ cell cycle fractions. HPV-lo cell content in the PDXs negatively correlated with cisplatin response measured by T/C ratio (r=-0.96, p=0.007), and the size and gene expression profile of this fraction were largely unaltered by cisplatin. In the case-control cohort, the HPV ISH(-) tumor cell fraction was larger in cases ($p<0.001$), which often contained large tumor regions devoid of ISH(+) cells. The %ISH(-) tumor cells provided favorable discrimination of cases vs. controls based on an area under the ROC curve of 0.77 ($p<0.001$, OR=66, 95% CI=11-547). **Conclusions:** HPV+ OPCs contain a subset of tumor cells with reduced HPV gene expression and a relatively quiescent phenotype, and increased size of this cell fraction appears predictive of recurrence. Cell state dynamics maintaining this fraction during cytotoxic therapy may contribute treatment failure. Thus, HPV-lo cells merit evaluation for generalizability as a biomarker and mechanistic interrogation as an etiology for tumor recurrence. Research Sponsor: None.

6059 **Poster Session**

Risk factors for aspiration pneumonia related to postoperative chemoradiotherapy for high-risk head and neck cancer: A supplementary analysis of a phase II/III JCOG1008 trial. First Author: Tomoya Yokota, Shizuoka Cancer Center, Shizuoka, Japan

Background: A randomized phase II/III trial (JCOG1008) suggested that postoperative chemoradiotherapy (POCRT) with weekly cisplatin is a treatment option for patients with postoperative high-risk locally advanced squamous cell carcinoma of the head and neck (LA-SCCHN). Aspiration pneumonia (AP) is one of the most important toxicities associated with CRT. This study investigated the clinical risk factors for AP during and after POCRT. **Methods:** Patients enrolled in JCOG1008 were analyzed to evaluate the incidence of AP, to identify the clinical risk factors for AP during and after POCRT, and to assess the influence of AP on treatment outcomes. AP was defined as a clinical condition meeting all of the following criteria: (i) patients had both subjective and objective symptoms suggesting pneumonia, (ii) the presence of aspiration was suspected clinically or by endoscopic or video-fluorographic examinations, (iii) no evidence of micro-organisms that cause atypical pneumonia. Analyses were performed by logistic regression model. **Results:** Of 251 patients who underwent POCRT, 100 patients who underwent laryngectomy was excluded. Among the 151 patients who received POCRT, 93 (61.6%), 85 (56.3%), and 113 (74.8%) developed AP during, after, and overall period of POCRT, respectively. The multivariable analyses identified two independent risk factors for AP occurring during or after POCRT: PS 1 [vs. PS 0; odds ratio (OR) 3.416, 95% CI (1.192-9.789), p = 0.0222] and dysphagia $\geq$grade 3 (vs. grade 1-2; OR 46.333, 95% CI (2.901-740.080), p = 0.0067). The multivariable analyses also identified two independent risk factors for AP occurring after POCRT: dysphagia $\geq$grade 3 (OR 3.995, 95% CI (1.538-10.375), p = 0.0045) and reconstruction surgery (OR 3.452, 95% CI (1.616-7.374), p = 0.0014). Charlson comorbidity score $\geq$4 and the use of sleeping pills at the end of POCRT were marginally associated with the onset of AP after POCRT (OR 2.699, 95% CI (0.919-7.926), p = 0.0708, OR 2.107, 95% CI (0.918-4.837), p = 0.0788, respectively). The occurrence of AP was not significantly associated with overall survival, relapse-free survival, and local relapse-free survival. **Conclusions:** PS 1, dysphagia $\geq$grade 3, and prior reconstruction surgery were associated with the onset of POCRT-related AP. Careful attention should be paid to these risk factors for AP in patients with LA-SCCHN undergoing POCRT. Clinical trial information: jRCTs031180135. Research Sponsor: National Cancer Center Research and Development Funds; Grant-in-Aid for Clinical Cancer Research; The Japan Agency for Medical Research and Development.

6060 **Poster Session**

Anti-programmed death-1 inhibitors and nimotuzumab in combination with induction chemotherapy for locoregionally advanced nasopharyngeal carcinoma: A propensity score-matched analysis. First Author: Chunyan Chen, Department of Radiation Oncology, Sun Yat-sen University Cancer Center, State Key Laboratory of Oncology in South China, Guangdong Key Laboratory of Nasopharyngeal Carcinoma Diagnosis and Therapy, Guangdong Provincial Clinical Research Center for Cancer, Guangzhou, China

Background: The poor prognosis of locoregionally advanced nasopharyngeal carcinoma (LANPC) due to the high incidence of metastasis necessitates effective treatment strategies. Synergistic effects have been observed when anti-programmed death-1 (anti-PD-1) inhibitors are combined with chemotherapy or targeted therapy. **Methods:** In total, 319 patients with LANPC were retrospectively enrolled between December 2017 and November 2022. The primary endpoint was progression-free survival. Propensity score matching was performed to adjust for potential confounders. **Results:** Overall, 150 patients were included after propensity score matching. The immunotherapy + nimotuzumab + chemotherapy (INC) group (n=50) had a higher 3-year progression-free survival rate (96.6% [95% confidence interval (CI): 93.2–100.0]) than the nimotuzumab + chemotherapy (NC) group (n=100) (79.8% [95% CI: 75.6–84.0]). The INC group had a hazard ratio of 0.16 (95% CI: 0.02–1.22; P=0.04). The objective response rates were 100% and 99% for the INC and NC groups, respectively. Grade $\geq$3 treatment-related adverse events were reported in eight (5.3%) patients, and hyponatremia (2.0%) was the most common. Grade $\geq$3 immune-related adverse events (rash and reactive capillary proliferation) were reported in two (4.0%) patients. **Conclusions:** Neoadjuvant therapy with anti-PD-1 inhibitors and nimotuzumab combined with chemotherapy demonstrates promising anti-tumor activity with acceptable safety for LANPC. More well-designed randomized trials with larger patient cohorts are needed to confirm long-term efficacy. Research Sponsor: None.

Short-term efficacy of three months after the end of treatment.

Response evaluation	INC group [n = 50 (%)]	NC group [n = 100 (%)]
CR	38 (76.0)	19 (19.0)
PR	12 (24.0)	80 (80.0)
SD	0	1 (1.0)
PD	0	0
ORR (95% CI)	100% (92.9%, 100%)	99% (94.6%, 100%)
DCR (95% CI)	100% (92.9%, 100%)	100% (96.4%, 100%)

CI, confidence interval; CR, complete response; DCR, disease control rate; IC, induction chemotherapy; ORR, objective response rate; PD, progressive disease; PR, partial response; SD, stable disease.

6061 Poster Session

Initial results of MC200710 investigating therapeutic vaccine (PDS0101) alone or with pembrolizumab prior to surgery or radiation therapy for locally advanced HPV associated oropharyngeal carcinoma, a phase 2 window of opportunity trial. First Author: David M. Routman, Department of Radiation Oncology, Mayo Clinic, Rochester, MN

Background: PDS0101 is a T cell stimulating immunotherapy (therapeutic vaccine) targeting HPV16. The combination of PDS0101 + pembrolizumab (5 cycles) has shown durable clinical responses in HPV-positive recurrent/metastatic HNSCC. MC200710 is a window of opportunity study in patients with HPV-associated oropharyngeal squamous cell carcinoma (HPV+ OPSCC). This prospective phase II trial utilized 2 cycles of neoadjuvant PDS0101 aloneor in combination with pembrolizumab prior to surgical resection or chemoradiotherapy (CRT). Herein, we report the initial results, including primary endpoint of ctDNA response. **Methods:** Between June 2022 and September 2024, 20 patients (10 per Arm) with locally advanced HPV+ OPSCC were enrolled in a sequential alternating design. Arm A received 2 cycles of PDS0101 and Arm B received 2 cycles of PDS0101 and pembrolizumab with all patients undergoing subsequent surgery or CRT. Assessments were done at baseline, post cycle 1, and post cycle 2 (prior to surgery or CRT). The coprimary endpoint of ctDNA response was defined as a $\geq$50% decline in ctDNA post cycle 2 compared to baseline as quantified using NavDx (TTMV fragments/mL). Radiologic objective response rate (ORR) was assessed as per RECIST 1.1. Toxicity through the neoadjuvant period was assessed using CTCAE criteria and recurrence rates following surgery or CRT are reported. **Results:** Patients were similar between arms: male 90%, median age 61 years, cT1/T2 70%, cN1 65%, and no smoking history 65%. All patients completed both cycles of therapy with 13 (65%) undergoing primary operative management and 7 CRT (35%). The most common toxicity was injection site reaction 85% grade 1, 15% grade 2, 0% grade 3, consistent with prior studies. One patient experienced grade 2 pneumonitis during the neoadjuvant window (Arm B). There was one grade 3 toxicity (5%) possibly attributable to study intervention with one patient experiencing transient hepatitis requiring hospitalization (Arm A). Zero of 10 patients in Arm A had a $\geq$50% decline in ctDNA from baseline while 5 of 10 patients (50%) met this primary endpoint in ARM B (p=0.03). After Cycle 2, based on RECIST 1.1, no Arm A patients had a partial response (PR), with 7 having stable disease (SD); Arm B had 2 patients with PR and 8 with SD. With median follow up of 6 months, 2 patients in Arm A recurred and 0 patients in Arm B. **Conclusions:** The combination of PDS0101 and pembrolizumab met the trial's primary endpoint of ctDNA response and shows promise for further evaluation. ctDNA can be used to assess early response and future studies could use ctDNA to adapt neoadjuvant therapy. Based on these findings, a neoadjuvant dose optimization study in HPV16+ oropharyngeal carcinoma is warranted and evaluation of PDS0101 and pembrolizumab in comparison to pembrolizumab alone. Clinical trial information: NCT05232851. Research Sponsor: PDS Biosciences.

6062 Poster Session

Efficacy of definitive radiotherapy with concurrent and adjuvant immune checkpoint inhibitors in patients with locally advanced head and neck squamous cell carcinoma (LA HNSCC). First Author: Hazem Aboaid, Department of Internal Medicine, Kirk Kerkorian School of Medicine at UNLV, Las Vegas, NV

Background: Head and neck squamous cell carcinoma (HNSCC) is the most common type of head and neck cancers, associated with a high incidence and mortality. In 2019, the FDA approved pembrolizumab for the treatment of recurrent/metastatic (RM) HNSCC. While many promising results were noted in the RM setting, unfortunately this was not the case for locally advanced HNSCC (LA HNSCC). Multiple studies have yielded negative results. This meta-analysis aims to further explore the efficacy of immune checkpoint inhibitors (ICIs) in the treatment of LA HNSCC. **Methods:** MEDLINE and EMBASE databases were systematically searched up to December 31, 2024. Randomized controlled trials (RCTs) evaluating ICIs in patients with LA HNSCC were included. The primary outcome was 2-year progression-free survival (PFS). A generic inverse variance method was used to calculate the estimated pooled hazard ratio (HR) for PFS with 95% confidence interval (CI). Heterogeneity was assessed with Cochran's Q test. Fixed effects model was applied. **Results:** A total of 1,687 patients from 2 phase III RCTs (KEYNOTE-412, JAVELIN Head and Neck 100) and 1 phase II/III RCT (NRG-HN004) were analyzed. NRG-HN004 compared durvalumab + radiotherapy (RT) vs cetuximab + RT, while KEYNOTE-412 and JAVELIN Head and Neck 100 compared pembrolizumab or avelumab + chemoradiotherapy (CRT) vs CRT alone, respectively. In PD-L1 positive cohort, longer PFS was noted in the ICIs arm (HR 0.81; 95% CI: 0.67-0.99; P=0.04), while in PD-L1 negative cohort, we noted the opposite with a shorter PFS in the ICIs arm (HR 1.34; 95% CI: 1.02-1.76; P=0.03). PFS was not different between the two treatment arms in the overall population and all the other subgroups, including HPV negative, HPV positive, males, and females. We conducted a subset analysis of cisplatin-eligible (CE) LA HNSCC including KEYNOTE-412 and JAVELIN Head and Neck 100 trials to assess the addition of ICIs to definitive CRT. We also noted increased PFS in PD-L1 positive cohort in the ICIs arm (HR 0.78; 95% CI: 0.63-0.97; P=0.02). However, in PD-L1 negative cohort, PFS was near significant to be decreased in the ICIs arm (HR 1.31; 95% CI: 0.99-1.75; P=0.06). **Conclusions:** This study showed that definitive radiotherapy with concurrent and adjuvant ICIs in LA HNSCC was associated with increased PFS in the PD-L1 positive group but decreased PFS in the PD-L1 negative arm. NRG-HN004 trial demonstrated that immunoradiotherapy was inferior to radiation plus cetuximab in cisplatin-ineligible LA HNSCC. In the subset analysis of CE LA HNSCC, addition of ICIs to standard CRT has more pronounced significant PFS in the PD-L1 positive cohort, while there is a trend towards decreasing PFS in the PD-L1 negative cohort. Further studies are needed in the future to evaluate the efficacy of ICIs addition to standard definitive CRT in PD-L1 positive or high LA HNSCC. Research Sponsor: None.

6063 Poster Session

Prognostic impact of preoperative imaging-detected extranodal extension in head and neck squamous cell carcinoma treated with postoperative chemoradiotherapy. First Author: Yuta Hoshi, Department of Head and Neck Medical Oncology, National Cancer Center Hospital East, Kashiwa, Japan

Background: In 2024, the Head and Neck Cancer International Group (HNCIG) newly defined imaging-detected and pathological extranodal extension (iENE/pENE). We previously reported the utility of iENE in induction chemotherapy followed by definitive chemoradiotherapy (Onaga R, et al. ASCO Annual Meeting, 2024). However, the significance of iENE in surgically treated head and neck squamous cell carcinoma (HNSCC) remains unclear, particularly in high-risk populations with positive pENE. We aimed to investigate the prognostic value of iENE in patients treated with completed surgery and postoperative chemoradiotherapy (poCRT) due to pENE-positivity. **Methods:** We retrospectively analyzed patients with HNSCC (oral cavity, oropharynx, hypopharynx, or larynx) who underwent surgical resection between 2013 and 2023 at our hospital. pENE-positive patients who received poCRT (cisplatin $\geq$ 200 mg/m² and radiation therapy $\geq$ 60 Gy) were included, excluding those with positive surgical margins of the primary site. iENE grading on preoperative CT or MRI and pENE assessment in surgical specimens were re-evaluated according to HNCIG consensus recommendations. Relapse-free survival (RFS) and Overall survival (OS) were analyzed using the log-rank test. **Results:** We identified 95 patients with a median age of 62 years (range: 16-76). The primary tumor sites included oral cavity (58 patients), hypopharynx (29), larynx (5), and oropharynx (3). iENE grades were 0/1/2/3 in 24/29/13/29 patients, and pENE was categorized as minor ENE/major ENE/soft tissue metastasis (STM) in 40/20/35 patients. With a median follow-up of 42.1 months, 43 patients developed recurrence (local/regional/distant/regional and distant: 1/7/30/5). In the iENE classification, the 5-year RFS for iENE Grades 0/1/2/3 was 77.8%, 60.3%, 35.9%, and 33.4% (p=0.003), and the 5-year OS was 88.8%, 70.5%, 37.8%, and 63.0% (p=0.021), respectively. When iENE grades were grouped into Grade 0/1 and Grade 2/3, the latter group had significantly shorter RFS (5-year RFS: 68.0% vs. 34.2%, $p < 0.001$) and OS (5-year OS: 78.3% vs. 55.9%, p = 0.008). In the pENE classification, no significant differences in RFS and OS were observed among minor ENE, major ENE, and STM (p=0.380 for RFS, p=0.617 for OS). **Conclusions:** Our study revealed for the first time that preoperative iENE was a significant prognostic factor for pENE-positive patients treated with poCRT. Specifically, patients with iENE grade 2/3 exhibited a poor prognosis, emphasizing the need for additional treatment strategies tailored to this very high-risk group. Research Sponsor: None.

Prognosis based on iENE grades and pENE category.

		N=95	5-year RFS	p-value	5-year OS	p-value
iENE	Grade 0	24	77.8%	0.003	88.8%	0.021
	Grade 1	29	60.3%		70.5%	
	Grade 2	13	35.9%		37.8%	
	Grade 3	29	33.4%		63.0%	
pENE	Minor ENE	40	60.9%	0.380	70.6%	0.617
	Major ENE	20	56.4%		70.1%	
	Soft tissue metastasis	35	45.1%		66.6%	

6064 Poster Session

Concurrent chemoradiotherapy with or without nimotuzumab in induction chemotherapy resistant locoregionally advanced nasopharyngeal carcinoma: An open-label randomised, controlled, phase 2 trial. First Author: Li-Ting Liu, Department of Nasopharyngeal Carcinoma, Sun Yat-Sen University Cancer Centre, Guangzhou, China

Background: Induction chemotherapy (IC) followed by concurrent chemoradiotherapy (CCRT) is the current standard of care for locoregionally advanced nasopharyngeal carcinoma (LA-NPC). Patients resistant to IC have a high risk of treatment failure. Nimotuzumab, a humanized anti-epidermal growth factor receptor (EGFR) antibody, has shown potential efficacy in combination with CCRT. This randomized phase 2 trial aimed to evaluate the efficacy and safety of nimotuzumab plus CCRT compared to CCRT alone in IC-resistant LA-NPC. **Methods:** We conducted an open-label, randomized phase 2 trial at Sun Yat-sen University Cancer Center, Guangzhou, China. Eligible patients (aged 18–70) had untreated, non-keratinizing, IC-resistant stage II–IVa (the 8th edition of the American Joint Committee on Cancer classification system) LA-NPC, defined as detectable plasma Epstein-Barr virus (EBV) DNA and/or stable/progressive disease after two cycles of IC. Other inclusion criteria were ECOG performance status of 0–1, positive EGFR expression and adequate organ function. Patients were randomized (1:1) to receive CCRT plus nimotuzumab or CCRT alone. Cisplatin (100 mg/m²) was given on days 1, 22, and 43 of intensity-modulated radiotherapy in both groups. In the experimental group, nimotuzumab (200 mg) was administered weekly during CCRT. Randomization was done using a computer-generated code random number code with a block size of six, stratified by disease stage. The primary endpoint was 2-year progression-free survival (PFS) in the intention-to-treat population. Safety was assessed in all participants who received at least one dose of the assigned treatment. The study was registered at ClinicalTrials.gov (NCT04223024), and patients are under follow-up. **Results:** Two hundred forty-six patients were enrolled and randomized (121 to CCRT plus nimotuzumab, 125 to CCRT alone). At a median follow-up of 47 months (IQR 44–50), the 2-year PFS was 81.0% (95% CI 72.8–86.9) in the CCRT plus nimotuzumab group and 80.8% (95% CI 72.7–86.7) in the CCRT group (stratified HR 0.93 [95% CI 0.59–1.47], p=0.70). The most frequent grade 3–4 adverse events were mucositis (24 [20.2%] vs 22 [17.6%]), leukopenia (23 [19.3%] vs 21 [17.2%]), and nausea (14 [11.8%] vs 16 [13.8%]) in the CCRT plus nimotuzumab group compared with CCRT group. A higher frequency of grades 1–2 rash was observed in the CCRT plus nimotuzumab group (15 [12.6%] vs 6 [4.9%]). Late adverse events were predominantly mild, with no grade 4 events reported in either group. No treatment-related deaths occurred in either group. **Conclusions:** In IC-resistant LA-NPC, the addition of nimotuzumab to CCRT did not provide a significant survival benefit. Further research into predictive biomarkers and novel combinations is needed to optimize treatment for high-risk populations. Clinical trial information: NCT04223024. Research Sponsor: None.

6065 Poster Session

Patient-reported outcomes (PROs) in the C-POST trial of adjuvant cemiplimab (cemi) vs placebo (pbo) for high-risk cutaneous squamous cell carcinoma (CSCC). First Author: Annette May Ling Lim, Peter MacCallum Cancer Centre, Melbourne, Australia

Background: C-POST is a phase 3, double-blind, pbo-controlled trial (NCT03969004) of adjuvant cemi for treatment of patients (pts) with CSCC at high risk of recurrence after surgery and radiation therapy. Positive results for the primary endpoint of disease-free survival (DFS) at interim analysis 1 are reported in a separate ASCO abstract. Here we evaluate adjuvant cemi vs pbo on PROs as exploratory endpoints. **Methods:** Pts (N=415) were randomized 1:1 to adjuvant cemi or pbo for up to 48 weeks (4 cycles). The European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (QLQ-C30) was administered at Day 1 of every cycle, end of treatment, and during follow-up. The pre-specified PRO analysis focused on 6 QLQ-C30 scales of global health status (GHS)/QoL; 3 functional scales (physical [PF], role [RF], emotional [EF]); and 2 symptom scales (fatigue [FA], pain [PA]). Overall changes from baseline across treatment cycles were analyzed using mixed effects models for repeated measures; if 95% CIs did not cross zero, differences were considered of nominal statistical significance (α=0.05) as no adjustment was made for multiplicity. PRO responder analysis used a published threshold of 10 points for clinically meaningful change across scales; median time to first deterioration was determined using Kaplan–Meier analyses. **Results:** QLQ-C30 completion rates from baseline through all cycles were >88% in both arms. Baseline scores showed moderate-to-high GHS/QoL and functioning and low symptom burden (Table). Overall changes from baseline on QLQ-C30 GHS/QoL, functioning, and symptom scores were small and similar between arms (Table). In the PRO responder analysis, most pts in both arms reported maintenance or clinically meaningful improvement in QoL in all scales across all cycles (cemi: 55.9–86.8%; pbo: 55.5–88.2%). Median time to first deterioration was also similar between arms in all scales (cemi: 5.3–25.6 months; pbo: 8.3–22.2 months). **Conclusions:** QoL was maintained during treatment with adjuvant cemi, with no clinically meaningful worsening vs pbo. These PRO results complement the observed improvement in DFS and support the favorable risk profile of adjuvant cemi for pts with high-risk CSCC. Clinical trial information: NCT03969004. Research Sponsor: Regeneron Pharmaceuticals, Inc.

	Baseline mean (SD)		Overall LS mean change from baseline (95% CI)		
QLQ-C30 scale	Cemi (n=209)	Pbo (n=206)	Cemi (n=209)	Pbo (n=206)	Difference (95% CI)
GHS/QoL	75.4 (17.5)	75.8 (17.4)	−2.0 (−4.3, 0.4)	−1.0 (−3.4, 1.4)	−0.9 (−3.7, 1.8)
PF	87.1 (16.0)	90.6 (13.9)	−1.4 (−3.2, 0.5)	−1.9 (−3.9, 0.0)	0.5 (−1.7, 2.7)
RF	83.8 (24.8)	84.2 (20.8)	−4.2 (−7.3, −1.2)	−1.6 (−4.8, 1.5)	−2.6 (−6.2, 0.9)
EF	84.6 (18.7)	85.1 (16.7)	0.2 (−2.2, 2.7)	−0.4 (−2.9, 2.1)	0.7 (−2.2, 3.5)
FA	20.9 (19.9)	20.5 (20.1)	5.0 (2.2, 7.7)	4.2 (1.4, 7.0)	0.8 (−2.4, 4.0)
PA	14.7 (21.2)	13.1 (20.4)	3.2 (−0.1, 6.5)	2.1 (−1.3, 5.6)	1.1 (−2.8, 5.0)

6066 Poster Session

Osteoradionecrosis as a complication following intensity-modulated radiation therapy or proton therapy in the treatment of oropharyngeal carcinoma. First Author: Edward Christopher Dee, Department of Radiation Oncology, Memorial Sloan Kettering Cancer Center, New York, NY

Background: Osteoradionecrosis (ORN) is a late complication of head and neck radiotherapy (RT) that negatively impacts survivorship. Although there is an abundance of literature reporting on ORN for photon-based RT, few studies have investigated the correlation between proton therapy and ORN; also, the current literature on ORN incorporates a broad mix of head and neck subsites. Therefore, we report our 10-year institutional experience to assess rates of ORN in a homogenous and consecutive cohort of patients with oropharyngeal squamous cell carcinoma (OPSCC) treated with curative-intent radiotherapy, representing the largest available institutional series. **Methods:** A consecutive cohort of 1564 OPSCC patients (1344 definitive, 220 post-operative) who received at least 50Gy were treated at our institution between 2013 and 2023 were included in this study. Patients were treated with either IMRT or proton therapy. CTCAE version 5 was used for ORN grading. **Results:** Overall ORN rate was 4.35%. Of 1389 patients who underwent IMRT, 56 (4.03%) developed ORN, vs 12/175 (6.86%) treated with proton therapy (hazard ratio [HR] 2.62, 95%CI 1.39–4.93, P=0.003). Median time to ORN in the IMRT arm was 25mo (range, 2mo–91mo). Median time to ORN in the proton arm was 23.5mo (2mo–45mo). Post-operative vs definitive treatment setting was not associated with the rate of ORN (univariate Cox HR 1.00, 95% CI 0.51–1.95, P=0.99). On subset analysis of the 1344 patients treated in the definitive setting, 47/1210 (3.88%) patients treated definitively with IMRT developed ORN as compared to 11/134 (8.21%) patients treated definitively with protons (univariable Cox HR 3.62, 95% CI 1.85–7.09, P<0.001). On multivariable analysis including treatment modality and use of chemotherapy, proton therapy was associated with increased hazard of ORN (HR 2.75, 95%CI 1.46–5.19, P=0.002). Concurrent chemotherapy was also independently associated with increased hazard of ORN (HR 3.34, 95%CI 1.05–10.65, P=0.041). A total of 10 out of 1564 (0.64%) patients developed CTCAE grade 3 ORN. The rates of grade 3 ORN were 2/175 (1.14%) in the proton cohort and 8/1389 (0.58%) in the IMRT cohort. This difference was not statistically significant on univariable Cox analysis (HR 2.44, 95%CI 0.51–11.60, P=0.26). **Conclusions:** The overall prevalence of ORN was 4.35%; the prevalence of >/= grade 3 ORNs was 0.64% in this consecutive cohort of patients with OPSCC treated with either IMRT or proton therapy. The overall prevalence of ORN of any grade was statistically higher for protons versus IMRT, a difference that was more pronounced in the definitive setting. Given the uncertainties with relative biological effectiveness calculations in proton therapy, avoidance of hot-spots, frequent replanning, and use of empirical proton-specific normal tissue constraints may help to reduce rates of ORN. Future work should explore the role of combination proton and photon treatment, especially in the definitive setting. Research Sponsor: National Cancer Institute/U.S. National Institutes of Health; P30 CA008748.

6067 Poster Session

Efficacy analysis of neoadjuvant PD-1 inhibitor combined with chemotherapy in various subanatomical sites of locally advanced and recurrent resectable head and neck squamous cell carcinoma: A retrospective real-world study. First Author: Haolei Tan, Head and Neck Surgery Department I, Hunan Cancer Hospital and The Affiliated Cancer Hospital of Xiangya School of Medicine, Central South University, Changsha, China

Background: Clinical research on Head and Neck Squamous Cell Carcinoma (HNSCC) often considers the disease as a whole. However, the therapeutic outcomes may vary significantly across different subanatomical sites, as well as between locally advanced (LA) and recurrent resectable (RR) HNSCC. Therefore, we stratified HNSCC according to specific anatomical sites and initial diagnosed versus recurrent tumors, and analyzed the efficacy of neoadjuvant PD-1 inhibitor + chemotherapy. **Methods:** Retrospectively analyzed patients with LA and RR HNSCC admitted to Hunan Cancer Hospital from October 2021 to December 2024, who received neoadjuvant PD-1 inhibitor and chemotherapy. Post-treatment efficacy was evaluated using imaging, endoscopy, or pathology. Differences in efficacy outcomes between different subanatomical sites and between LA and RR tumors were classified and statistically analyzed. **Results:** 1) A total of 482 patients were included: 434 with LA HNSCC(90.04%) and 48 with RR HNSCC (9.96%), 453 males (93.98%) and 29 females (6.02%). Patient ages ranged from 17 to 77 years, with a mean age of 52.43 $\pm$ 9.83 years. 2)The top three types of LAHNSCC that underwent neoadjuvant therapy were: tongue (N=157, 36.180%), buccal oris (N=105, 24.19%),and hypopharynx (N=92, 21.20%). 3)The objective response rates (ORR) following neoadjuvant therapy were as follows: 90.32% for oropharyngx, 83.33% for gingiva, 80.25% for tongue, 79.35% for hypopharynx, 68.57% for buccal oris, and 56.25% for RR HNSCC. The highest pathological deep response rates (pCR+MPR) was observed in tongue (34.40%), followed by oropharynx (29.04%), gingiva (26.67%), and only 33% for RR HNSCC. **Conclusions:** There are significant variations in the sensitivity of HNSCC to neoadjuvant immunotherapy + chemotherapy across different subanatomical sites. Oropharynx exhibits the highest response to this regimen, whereas RR cases demonstrate relatively poor responsiveness. In terms of pathological deep response, tongue, oropharynx, and gingiva show favorable response rates, while RR cases exhibit significantly lower response rates. Research Sponsor: Hunan Provincial Major Science and Technology Project, Research and Application of Key Technologies for Oral Cancer Prevention and Treatment; 2023ZJ1120; Hunan Provincial Natural Science Foundation Project; 2024JJ9264.

Disease status	Tongue	Buccal oris	Hypopharynx	Oropharynx	Gingiva	Others	Recurrent Resectable HNSCC
Number	157	105	92	31	30	19	48
CR	31(19.75%)	12(11.43%)	13(14.13%)	8(25.81%)	3(10.00%)	7(36.84%)	4(8.33%)
MPR	23(14.65%)	13(12.38%)	7(7.61%)	1(3.23%)	5(16.67%)	0(0.00%)	0(0.00%)
PR	72(45.86%)	47(44.76%)	53(57.61%)	19(61.29%)	17(56.67%)	10(52.63%)	23(47.92%)
SD	20(12.74%)	18(17.14%)	11(11.96%)	2(6.45%)	1(3.33%)	0(0.00%)	16(33.33%)
PD	8(5.10%)	11(10.48%)	7(7.61%)	0(0.00%)	3(10.00%)	0(0.00%)	10(10.42%)
NA	3(1.91%)	4(3.81%)	1(1.09%)	1(3.23%)	1(3.331%)	2(10.53%)	0(0.00%)
ORR	126(80.25%)	72(68.57%)	73(79.35%)	28(90.32%)	25(83.33%)	17(89.47%)	27(56.25%)

6068 Poster Session

Functional and survival outcomes in HPV positive oropharyngeal squamous cell cancer treated with response-adaptive de-escalation: A pooled analysis. First Author: Faith Abodunrin, Section of Hematology and Oncology, Department of Medicine, University of Chicago, Chicago, IL

Background: Human papillomavirus (HPV) positive OPSCC is known to have a favorable prognosis compared to its HPV negative counterparts. It is thus important to limit treatment-related toxicity while preserving functional and survival outcomes. In this pooled study, we report functional and survival outcomes across prospective cohorts treated with chemotherapy-response-adaptive dose and volume de-escalation of radiation. **Methods:** Patients with non-metastatic HPV positive OPSCC were sequentially treated at an academic center on either an interventional de-escalation trial: OPTIMA 1 (NCT02258659); OPTIMA II (NCT03107182); (NCT04572100) or off-protocol in a prospective registry. Eligible patients had N1-3 or T3-4 (AJCC 8th edition) disease. Very low-risk patients T0-2N0-1 (single lymph node <3cm) were excluded. Patients were stratified as low risk (LR) or high risk (HR) according to T/N stage and smoking history. Following chemotherapy (carboplatin and paclitaxel or *nab*-paclitaxel) with or without nivolumab, patients received de-escalated treatment with low dose arm (LDA; radiation [RT] alone to 50Gy or transoral robotic surgery), intermediate dose arm (IDA; chemoRT [CRT] to 45-50Gy) or regular dose arm (CRT to 70-75Gy). To analyze functional outcomes, we compared swallowing performance scores (SPS), trismus, percutaneous endoscopic gastrostomy (PEG) tube placement obtained from pre- and post-(C)RT. Comparisons across risk categories and treatment arms using Chi-square, Fisher, and Student t-tests. Survival outcomes were compared using log-rank statistic. **Results:** Eligible patients (n=242) started treatment between 2014 and 2024: 116 LR and 126 HR patients; 83% received de-escalated treatment (LDA/IDA) and 17% received standard dose (RDA). Post-treatment SPS (p=0.0002) and trismus scores (p=0.0013) was better among de-escalated versus non-de-escalated patients. Lower PEG placement rates were observed among de-escalated patients 33/196 (16.8%) vs 27/39 (69.2%) (p<.0001). With median follow-up of 48 months, no statistically significant differences in overall survival or progression free survival were observed between treatment arms. OS (95.1% (95% CI 90.8%-97.4%) vs 93.7%(95% CI 77.72%- 98.4%), P=0.185) and PFS (92.2% (95% CI 87.1%-95.2%) vs 90.7% (95% CI 73.9% - 96.9%, p=0.202) were similar in deescalated and non-deescalated patients at 3 years. Low risk individuals also had better OS (97.1% vs 92.1%, p=0.01) and PFS (96.1% vs 88.3%, p=0.004) at three years. **Conclusions:** Improved functional outcomes including posttreatment swallowing function, trismus, and lower PEG placement rates were observed with chemotherapy-response-adaptive radiation de-escalation with excellent survival in the largest prospective cohort reported to date. Response-adaptive de-escalation warrants further comparative study. Research Sponsor: Chicago Institute of Translational Medicine.

6069 **Poster Session**

Neoadjuvant chemoimmunotherapy with afatinib for locally advanced head and neck squamous cell carcinoma (neoCHANCE-2): An open-label, single-arm, phase 2 study. First Author: Zhigong Wei, Department of Biotherapy, Cancer Center, West China Hospital, Sichuan University, Chengdu, China

Background: Neoadjuvant chemoimmunotherapy has been an emerging hotspot for the treatment of locally advanced head and neck squamous cell carcinoma (LA-HNSCC), but the treatment response still requires improvement. Given the potential synergistic anti-tumor effects of dual inhibition of the PD-1/L1 and EGFR pathways, we proposed a novel neoadjuvant treatment regimen combining chemoimmunotherapy with EGFR-TKI, followed by adjuvant immunotherapy treatment, and evaluated the efficacy and safety of this approach. **Methods:** This open-label, single-arm, phase 2 trial was done at a tertiary hospital in China. Patients were eligible if they were aged at least 18 years old; had pathologically confirmed HNSCC with locally advanced disease according to the AJCC 8th Edition; had an ECOG performance status of 0−1; had at least one measurable target lesion according to RECIST 1.1 criteria; and had sufficient organ function. Patients with LA-HNSCC received two cycles of tislelizumab (200mg) and TP (nab-paclitaxel and cisplatin) chemotherapy, administrated on day one of each three-week cycle, along with afatinib (30mg) during the intermittent period between chemoimmunotherapy cycles, followed by 15 cycles of adjuvant tislelizumab treatment. The primary endpoint was the complete pathologic response (pCR) rate, defined as the percentage of patients with no detectable RVT cells in the resected primary tumor. **Results:** A total of 40 patients were enrolled and received neoadjuvant treatment, 32 of whom proceeded to surgical resection and achieved a pCR rate of 40.6% (95% CI: 23.7−59.4%). The overall response rate (ORR) was 82.5% (95% CI: 67.2−92.7%). The median follow-up time was 14.4 months (range: 2.4−27.6 months) . The estimated 1-year overall survival (OS) was 96.7% (95%CI: 90.5%−100%). No deaths occurred among patients who achieved pCR/MPR. The most common treatment-related adverse events (TRAEs) of any grade were alopecia (100%), followed by nausea (62.5%), lymphopenia (57.5%), diarrhea (55%), and rash (55%). The most common TRAE of grade 3−4 was lymphopenia (5/40, 12.5%). No treatment-related surgical delays were observed. Neoadjuvant treatment induced a significant increase in the proportion of peripheral CD8+ T cells, along with a reduction in B cells. TP53 wild-type patients were more likely to achieve a more favorable pathologic response compared to those with a TP53 mutation. A significant difference in oral microbial composition was found between patients with different pathologic responses. **Conclusions:** This study firstly reported the promising efficacy and acceptable safety profile of neoadjuvant chemoimmunotherapy combined with apatinib in the treatment of patients with LA-HNSCC. Further evaluation in large-scale clinical trials with longer follow-up periods is needed. Clinical trial information: NCT05516589. Research Sponsor: None.

6070 **Poster Session**

Induction pembrolizumab plus cisplatin and 5-FU chemotherapy followed by chemoradiotherapy in locally advanced squamous cell cancer of oropharynx, hypopharynx or larynx: Results of multicenter prospective phase II study. First Author: Ilya Pokataev, Moscow City Oncological Hospital No. 1 Named After S.S. Yudin, Moscow, Russian Federation

Background: Chemoradiation with cisplatin or induction chemotherapy with docetaxel, platinum agent and 5-FU are associated with high toxicity. We hypothesized that immunochemotherapy with pembrolizumab and platinum-based chemotherapy followed by chemoradiotherapy (CRT) might be associated with higher clinical efficacy along with a lower likelihood of adverse effects (AE). **Methods:** We conducted the multicenter single-arm phase II study (NCT05551767), including patients (pts) with stage III-IV, PD-L1 positive (CPS≥1), squamous cell carcinoma of larynx, oropharynx or hypopharynx. Pts with ECOG > 2 were excluded. All enrolled pts received 3 cycles of induction therapy with pembrolizumab 200 mg on day (d) 1, cisplatin 100 mg/m^2 on d1 and 96-hour infusion of 5-FU 1000 mg/m^2/d followed by CRT. We aimed to evaluate response rate, survival, safety and incomplete CRT rate after induction therapy. **Results:** Since 2022 to August 2024 120 pts were enrolled, including 82 (72.5%) with oropharyngeal, 21 (17.5%) hypopharyngeal and 12 (10%) laryngeal cancer. The median age was 60 (range 35 - 75), most patients were male (87.5%) and 108 (90%) had ECOG 0-1. Objective response rate (ORR) by RECIST 1.1 was assessed after induction therapy in 116 of 120 pts: 73 (62.9%) pts had response including 19 pts (16.4%) with complete responses (CR). The median change of target lesions was -55% (from -100% to 65%). ORR after CRT was assessed in 102 pts: 84 (82.4%) responders were identified with a 71.6% CR rate. Only 8 (6.7%) pts did not start CRT after induction therapy. Among other 112 pts 92.9% received radiation dose ≥66Gy. With a median follow-up 16.6 months 1-year progression-free survival was 73.5% and 1-year overall survival was 80%. There were no treatment-related deaths on induction therapy although 6 (5%) pts required hospital readmission due to adverse events (AE). The incidence of grade 3-4 AE by CTC AE v.5.0 was 30.8% with asymptomatic neutropenia grade 3-4 being the most frequent AE (23.3%). **Conclusions:** The study demonstrated promising ORR, progression-free survival rate and acceptable safety profile of induction therapy with pembrolizumab, cisplatin and 5-FU in head and neck cancer. High response rate to induction therapy was associated with a high number of CRT completion. Clinical trial information: NCT05551767. Research Sponsor: Moscow Center For Healthcare Innovations.; #2112-10/22.

6071 **Poster Session**

Primary results from IChoice-02, a phase 2 trial of induction chemoimmunotherapy followed by response-adapted de-escalation of chemoradiation in HPV-associated oropharyngeal cancer. First Author: Xueguan Lu, Department of Radiation Oncology, Fudan University Shanghai Cancer Center, Shanghai, China

Background: Despite multiple attempts to de-intensify treatments in HPV-associated oropharyngeal cancer (OPC), data with incorporation of immunotherapy remain scarce. Neoadjuvant platinum-based chemotherapy and anti-PD-1 therapy has shown promising pathological response after radical surgery. In IChoice-02 trial, we evaluated the efficacy of induction chemoimmunotherapy followed by response-adapted de-escalation of radiotherapy and omission of concurrent chemotherapy in HPV-associated OPC. **Methods:** IChoice-02 trial enrolled T1-2/N1-3M0 (excluding T1N1M0 patients with single and≤3cm lymph node) or T3-4N0-3M0 (UICC/AJCC 8th staging system) HPV+ OPC. Following two cycles of induction toripalimab (240mg), docetaxel (75mg/m2) and cisplatin (75mg/m2) every 3 weeks, patients with deep response (CR or ≥50% PR per RECIST in both oropharynx and nodes) were subjected to de-intensified radiotherapy (60Gy) alone with no concurrent chemotherapy, while those otherwise received standard-dose radiation to 70Gy with two cycles of concurrent cisplatin (80mg/m2 every three weeks). The primary endpoint was 2-year progression-free survival (PFS). **Results:** 97 patients were enrolled from March 2021 until July 2024, including 44 (45.3%) stage I, 28 (28.9%) stage II and 25 (25.8%) stage III. Following induction chemoimmunotherapy, 60.8% (59/97) achieved radiological deep response. 53/73 (72.6%) of stage I-II and only 6/25 (24%) of stage III patients underwent subsequent de-escalation. With 16.5 months median follow-up, 2/59 patients had loco-regional relapse (both in-field) in the de-escalation arm, and 6/38 in the standard arm experienced treatment failure (3 locoregional, 2 distant and 1 with both). 1-year PFS was 92.9%, 96.1% and 87.8% in the full cohort, de-escalation arm and standard arm, respectively. 1-year overall survival (OS) was all 100%. There were no treatment-related deaths. Unexpectedly, two cases of second primary malignancy (one with intracranial lymphoma and the other with melanoma) were observed within 4 months after treatment completion. **Conclusions:** Induction toripalimab in combination with platinum-based doublet chemotherapy followed by de-escalation of chemoradiation to lower radiation dose with omitted concurrent chemotherapy yielded outstanding 1-year survival. Long-term survival is awaited with further follow-up. Clinical trial information: NCT04867330. Research Sponsor: Shanghai Junshi Biosciences.

6072 **Poster Session**

Preoperative steroid for enhancing patients' recovery after head and neck cancer surgery with free tissue transfer reconstruction: Phase III, placebo-controlled, randomized, double-blind study (J-SUPPORT 2022, PreSte-HN Study). First Author: Kohtaro Eguchi, Department of Head and Neck Surgery, National Cancer Center Hospital, Chuo-Ku, Japan

Background: The enhanced recovery after surgery (ERAS) pathway integrates evidence-based protocols to optimize recovery during the perioperative period. It has recently been applied to head and neck cancer surgery with free tissue transfer reconstruction (HNS-FTR). While preoperative corticosteroid administration has shown benefits in reducing postoperative pain and nausea/vomiting in certain surgeries, its role in the ERAS pathway for HNS-FTR remains unclear. This study aimed to assess the impact of adding preoperative corticosteroid administration on the quality of postoperative recovery within the ERAS pathway for HNS-FTR. **Methods:** This phase III, placebo-controlled, randomized, double-blind trial included 180 patients undergoing HNS-FTR. Patients were randomly assigned (1:1) to receive either 8.0 mg of dexamethasone phosphate in 100 mL of saline or placebo (100 mL of saline) as a single intravenous dose preoperatively. All patients received standardized perioperative care under the multicenter ERAS pathway for HNS-FTR. The primary endpoint was the quality of postoperative recovery, assessed by the area under the curve (AUC) for the total scores of the Japanese version of the Quality of Recovery Score (QOR-40J) on postoperative days 2 and 4. Key secondary endpoints included the AUC of visual analog scale (VAS) scores for pain and nausea on postoperative days 1 to 3. Complications were analyzed using the Clavien-Dindo classification. **Results:** Data from 87 and 91 patients in the dexamethasone and placebo groups, respectively, were evaluated. ERAS pathway completion rates were 97.7% and 97.8% for the dexamethasone and placebo groups, respectively. The estimated AUC for QOR-40J total scores on postoperative days 2 and 4 was 295.7 in the dexamethasone group and 299.8 in the placebo group, with no significant difference (p = 0.665). Similarly, no significant differences were observed in VAS scores for pain (p = 0.829) and nausea (p = 0.649). While there were no significant differences in complications of Grade 2 or higher (p = 0.584) or wound-related complications (p = 0.938), a significant difference was found in postoperative bleeding, with no cases observed in the placebo group (p = 0.039). **Conclusions:** Preoperative corticosteroid administration in the ERAS pathway for HNS-FTR did not yield clinically significant benefits. Ensuring the successful implementation of the ERAS pathway is crucial. Clinical trial information: jRCTs031210593. Research Sponsor: AMED.

6073 **Poster Session**

Association of AI-informed biomarkers of spatial organization of tumor-infiltrating lymphocytes with loco-regional recurrence in laryngeal squamous cell cancer. First Author: Sahil Hasit Patel, Case Western Reserve University, Cleveland, OH

Background: Laryngeal Squamous Cell Carcinoma (LaSCC) has varying outcomes based on the stage of cancer patients present with. Currently, a high proportion of patients are diagnosed with advanced-stage LaSCC complicating the treatment landscape and over-treating low risk patients. Risk stratification of LaSCC can help tailor treatment plans. Numerous studies have identified spatial architecture of tumor-infiltrating lymphocytes (TILs) as a prognostic biomarker in oral cavity and oropharyngeal SCC. In this work, we evaluate the prognostic value of an artificial intelligence (AI)-leveraged approach that characterizes the spatial architecture of TILs on digitized hematoxylin and eosin (H&E)-stained slides from patients with LaSCC. **Methods:** H&E slides from 192 patients with LaSCC were collected from Baylor Medical Center. This dataset was randomly divided into two equal cohorts, A and B. The slides were digitized as whole slide images at 40x magnification. The nuclei of all cells were automatically segmented using a deep-learning model (Hover-Net). Each nucleus was then classified as TIL or non-TIL based on morphological features. TILs and non-TILs were clustered based on proximity, and features related to the density and spatial distribution were extracted. The top features, determined by the least absolute shrinkage and selection operator, were used to train a Cox Proportional Hazards regression model that assigned a risk score for recurrence of cancer to each patient in cohort A. For validation, the model was applied to patients in cohort B. The 25th percentile training risk score was used as a cutoff for classifying patients as high or low risk. The performance of the model in prognosticating loco-regional recurrence (LRR) was evaluated using survival analysis. **Results:** Patients in Cohort B identified as "high risk" by the model based on spatial organization of TILs had a significantly shorter survival time. Univariate survival analysis showed this model was prognostic for DFS with a hazard ratio of 2.57 (95% Confidence Interval: 1.12-5.89, p-value=0.048), meaning that patients classified as "high risk" are approximately 2.5 times more likely to develop LLR. **Conclusions:** We used computational pathology to characterize the architecture of TILs and develop a model to predict risk of LLR in LaSCC. With additional validation, this approach can be used to assist clinicians with making clinical decisions. Research Sponsor: None.

Multivariate analysis.

Variable	Reference vs Comparison	Pr(>|z|)	HR (95% CI)
Race	Black vs Caucasian	0.93	0.92 (0.40 - 2.31)
N	N0 vs N+	0.67	1.80 (0.12 - 26.06)
T	1-2 vs 3-4	0.83	1.28 (0.13 - 12.38)
Chemo	Yes vs No	0.38	3.49 (0.21 - 56.90)
Tobacco	Yes vs No	0.26	2.08 (0.58 - 7.47)
Alcohol	Yes vs No	0.43	1.53 (0.54 - 4.35)
TIL Architecture Risk	High vs Low	0.03 *	0.26 (0.08 - 0.89)

6074 **Poster Session**

Decision analysis of PD-1 inhibitor combined with chemotherapy in neoadjuvant therapy of resectable locally advanced head and neck squamous cell carcinoma (LA HNSCC). First Author: Xiaohong Chen, Beijingshijitan hospital Capital medical university, Beijing, China

Background: Neoadjuvant therapy (NAT) with PD-1 inhibitors plus chemotherapy has been shown to have a high pathological response rate in LA HNSCC, but there is controversy over factors such as the number of treatment cycles and biomarkers. This trial explored multiple factors that may affect NAT and provided patients with an individualized treatment strategy. **Methods:** Untreated pts with AJCC 8th edition stage III-IVB (HPV-positive oropharyngeal : stage II-III) LA HNSCC were selected between 2021 and 2024. After enrollment, pts received 2 cycles of PD-1 inhibitors combined with chemotherapy, and RT was used when CR was achieved on imaging. If PR, SD or PD was achieved, direct surgery or RT could be chosen, or 1-2 cycles of PD-1 inhibitors plus chemotherapy could be received again before curative treatment. The primary endpoint was 1y-DFS. The sample size was N=80, which provided 0.8 power based on Exact Test at One-Sided alpha level of 0.05. **Results:** A total of 82 pts were included. Median age was 59 yrs (23-76), and 81 (98.8%) were male. Location: oropharyngeal was 22 (26.8%) (HPV-positive was 61.9%), laryngeal was 10 (12.2%), hypopharynx was 48 (58.5%), nasal cavity and sinuses was 2 (2.4%). T3 +T4 was 55.3%, N2+N3 was 44.7%. CPS of pts who underwent testing was 89.0% (73/82), and 48.0% pts were CPS$\geq$20. Pts received 2 cycle (45.1%), 3cycle (50%), 4 cycle (4.8%) NAT. Median follow-up time was 15.9 months, 1y-PFS was 95.9% and 1y-OS was 98.4%. The PFS of pts with pCR or (CR+PR) were both significantly higher than that of pts with non-pCR or (SD+PD)(p=0.049 and p=0.024). The ORR was 84.1%, and ORR of 2-cycle was lower than muti-cycle (81.1% vs 86.7%,p=0.544) . 49.1% pts achieved pCR of primary lesion. pCR of 2-cycle was little higher than muti-cycle (53.3% vs 44.4%, p=0.867). However, the T3-4 in the 2-cycle group was significantly lower than that in the multi-cycle group (43.2% vs 68.9%, p=0.037). In T3-4 pts, pCR in multiple cycles was higher than that in 2 cycles (56.3% vs 38.5%, p=0.339). In addition, pCR of CPS $\geq$ 20 was significantly higher than that of CPS $<$ 20 (66.7% vs 34.6%, p=0.028). In T1-2 population, pCR of CPS$\geq$20 vs $<$20 was 81.8% vs 28.6% (p=0.006), while no significant different in T3-4 population. Poorly differentiated patients with CPS $\geq$ 20 vs. moderately/highly differentiated pts was 85% and 30.6% ($p<0.001$). 1y - laryngeal function preservation rate was 98.3% (1/58). The overall TRAEs incidence rate was 72%, the most common Grade 3-4 TRAEs were myelosuppression (8.9%). **Conclusions:** Increasing the number of cycles may be beneficial for T3-4 pts. In addition, CPS$\geq$20 pts can achieve higher pCR, especially in T1-2 pts. CPS is also associated with worse pathological differentiation type. Clinical studies (NCT06100497) are currently underway to further explore the efficacy and safety of PD-1 inhibitors combined with chemotherapy in poorly differentiated LA HNSCC. Research Sponsor: None.

6075 **Poster Session**

Efficacy and safety of Sapylin versus dexamethasone atomized inhalation for CCRT-induced oral mucositis in patients with nasopharyngeal carcinoma: A randomized, parallel design, and non-inferiority clinical trial. First Author: Haiqing Luo, Affiliated Hospital of Guangdong Medical University, Zhanjiang, China

Background: Radiation-induced oral mucositis (RIOM) is a common adverse reaction to radiotherapy and chemotherapy in patients with nasopharyngeal carcinoma (NPC). Sapylin is an immune adjuvant with anti-tumor effects in multiple malignancies. This study investigated the efficacy and safety of Sapylin versus dexamethasone for treating RIOM in patients with NPC. **Methods:** This prospective, parallel-design, non-inferiority randomized study aims to investigate the effects of inhaling atomized Sapylin versus dexamethasone on the incidence and severity of RIOM in patients with NPC undergoing concurrent chemoradiotherapy (CCRT). A total of 100 patients were enrolled and randomized in a 1:1 ratio into the intervention (Sapylin) and control (dexamethasone) groups. Both groups received cisplatin-based CCRT. The Sapylin and dexamethasone groups received Sapylin (1 KE) and dexamethasone (10 mg), respectively, both via atomized inhalation once daily. Both treatments commenced on the first day of CCRT and continue until the conclusion of radiotherapy. **Results:** Comparisons among groups showed no statistically significant differences in patient characteristics after randomization of patients. Compared to the dexamethasone group, the Sapylin group demonstrated a lower incidence of RIOM (78.9% vs. 83.6%, $P < 0.05$) and a significantly reduced incidence of severe RIOM (grades III-IV) (37.1% vs. 42.5%, $P < 0.05$). The onset times for grades I, II, III, and IV RIOM in the Sapylin group were later than those observed in the dexamethasone group ($P < 0.05$). From baseline to the conclusion of radiotherapy (RT), the changes in Body Mass Index (BMI) in both groups were statistically significant ($P < 0.001$). During RT, the decrease in BMI was less pronounced in the Sapylin group, with a mean change of 0.97 ± 0.76 (mean $\pm$ SD), compared to a larger decrease in the dexamethasone group, which had a mean reduction of 2.02 ± 0.81 (mean $\pm$ SD). A significant positive correlation was found between changes in BMI and the severity of RIOM ($r = 0.671$, $p < 0.003$). No significant difference in the incidence of adverse reactions was observed between the two groups ($P > 0.05$). **Conclusions:** Compared to dexamethasone group, Sapylin group resulted in a decrease in the incidence and severity of RIOM in patients with NPC without obvious side effects. The use of Sapylin atomized inhalation regimen is both safe and effective, and it positively influences the improvement of nutritional status. Clinical trial information: ChiCTR2200064576. Research Sponsor: None.

6076 **Poster Session**

Use of early EBV DNA clearance to select optimal induction chemotherapy cycles for locoregional advanced nasopharyngeal carcinoma. First Author: Wanping Guo, Sun Yat-sen University Cancer Cener, Guangzhou, China

Background: Based on 3 cycles of induction chemotherapy (IC) followed by concurrent chemoradiotherapy (CCRT) is the standard treatment for locoregional advanced nasopharyngeal carcinoma (LA-NPC). However, it remains unclear whether all patients benefit from 3 cycles of IC. Epstein-Barr virus (EBV) DNA is a key biomarker for NPC, and changes of cell-free EBV DNA (cfEBV DNA) may reflect tumor dynamics. This study aims to use early cfEBV DNA clearance to guide optimal IC cycle selection for LA-NPC patients. **Methods:** We included 1541 LA-NPC patients treated with IC+CCRT between 2010 and 2023, all with early cfEBV DNA data (pre-treatment, and after 1st IC cycle). Independent prognostic factors were identified by COX regression, and predictive accuracy was assessed using receiver operating characteristic (ROC) curves. Propensity score matching (PSM) balanced covariates between groups receiving different IC cycles. The primary outcome, progression-free survival (PFS) was analyzed using Kaplan-Meier and log-rank tests. **Results:** After the 1st IC cycle, 693 (44.97%) patients had undetectable cfEBV DNA. cfEBV DNA after the 1st IC (p=0.014) and N stage (p=0.048) were significant predictors of PFS. The combination of N stage and cfEBV DNA after the 1st IC cycle had a higher AUC for 5-year PFS (0.610) compared to N stage, cfEBV DNA after 1st IC, or TNM stage alone (0.543, 0.588, 0.557). Based on these two factors, patients were divided into high-risk (N2-3 and detectable cfEBV DNA after 1st IC) and low-risk (N0-1 or undetectable cfEBV DNA after 1st IC) groups. The 5-year PFS for low-risk and high-risk groups was 81.2% vs. 65.1% ($p<0.001$). After PSM, low-risk patients receiving 3 cycles of IC showed significantly better PFS compared to those receiving 2 cycles (5-year PFS: 86.0% vs. 72.5%, $p<0.001$). However, high-risk patients showed similar PFS regardless of IC cycles (5-year PFS: 66.1% vs. 63.7%, p=0.306). **Conclusions:** EBV DNA clearance after the first cycle of IC is a sensitive predictor of outcomes in LA-NPC. Low-risk patients may benefit from an additional cycle of IC, while high-risk patients require alternative strategies such as immunotherapy or earlier initiation of CCRT. Research Sponsor: National Natural Science Foundation of China; National Natural Science Foundation of China; Science and Technology Program of Guangzhou.

6077 **Poster Session**

Induction chemotherapy with or without toripalimab followed by concurrent chemoradiotherapy for locoregionally advanced nasopharyngeal carcinoma: A multicenter, open-label, randomized, controlled, phase 2 trial. First Author: Kai Hu, Department of Radiation Oncology, the First Affiliated Hospital of Guangxi Medical University, Nanning, Guangxi, China

Background: Although nasopharyngeal carcinoma (NPC) treatment has entered the era of immunotherapy, the optimal treatment model for locoregionally advanced nasopharyngeal carcinoma (LANPC) remains unclear. This trial aimed to evaluate the efficacy and safety of adding toripalimab to induction chemotherapy (IC) in patients with LANPC. **Methods:** Patients with LANPC (T4NanyM0 or TanyN2/N3M0, AJCC 8th edition) were enrolled at 8 centers across China and randomized (1:1) into two arms: the standard arm (gemcitabine and cisplatin IC followed by cisplatin concurrent chemoradiotherapy [CCRT]) and the toripalimab arm (toripalimab plus IC followed by CCRT). Both arms received intravenous gemcitabine (1g/m²) on days 1 and 8, and cisplatin (80 mg/m²) on day 1, every 3 weeks for 3 cycles, followed by standard CCRT (cisplatin 100 mg/m² every 3 weeks for 3 cycles). In the toripalimab arm, patients also received intravenous toripalimab (240 mg) on day 1 every 3 weeks for 3 induction cycles. The primary endpoint was failure-free survival (FFS). Secondary endpoints included complete response (CR) rate after neoadjuvant treatment, locoregional failure-free survival (LRRFS), distant metastasis-free survival (DMFS), overall survival (OS), and toxicity. Response evaluation was conducted according to RECIST 1.1, and adverse events (AEs) were assessed by CTCAE v5.0. This study is registered with ClinicalTrials.gov (NCT05340270), and follow-up is ongoing. **Results:** Between July 2022 and March 2024, 150 patients (mean age 47 years, 72% male) were randomized to the toripalimab arm (n = 75) and the standard arm (n = 75). As of November 30, 2024, the median follow-up duration was 23.4 months, and 15 patients had reached the primary endpoint. Long-term efficacy data are still awaited. The CR rate after neoadjuvant treatment was 36.0% (27 of 75) in the toripalimab arm and 13.3% (10 of 75) in the standard arm (P= 0.001). The overall response rate (ORR) after neoadjuvant treatment was 94.7% (71 of 75) in the toripalimab arm and 85.3% (64 of 75) in the standard arm (P= 0.042). Grade 3-4 acute treatment-related adverse events (trAEs) occurred in 50 (66.7%) patients in the toripalimab arm and46 (61.3%) patients in the standard arm (P= 0.496), with immune-related AEs (irAEs) reported in 5 (6.7%) patients in the toripalimab arm and none (0.0%) in the standard arm (P= 0.058). All grade 3-4 irAEs were manifested as rashes and pruritus. **Conclusions:** Adding toripalimab to standard IC followed by CCRT resulted in a superior CR rate and ORR compared to IC-CCRT alone, with manageable toxicity profiles in patients with LANPC. Further follow-up is needed to confirm long-term efficacy, and this combination may offer an optimal, cost-effective therapeutic model for LANPC. Clinical trial information: NCT05340270. Research Sponsor: None.

6078 **Poster Session**

Radiotherapy plus nimotuzumab versus cisplatin in low-risk locoregionally advanced nasopharyngeal carcinoma who had favorable response to induction chemotherapy: A randomised, phase III, non-inferiority trial. First Author: Hai-Qiang Mai, Department of Nasopharyngeal Carcinoma, Sun Yat-Sen University Cancer Centre, Guangzhou, China

Background: Patients with low-risk locoregionally advanced nasopharyngeal carcinoma (LA-NPC) have high survival when treated with radiotherapy (RT) plus cisplatin after induction chemotherapy (IC). Whether replacement of cisplatin with nimotuzumab—a humanized antibody against the epidermal growth factor receptor (EGFR)—can preserve high survival and reduce treatment toxicity is unknown for patients with good response to IC. Therefore, we assessed whether nimotuzumab plus RT was non-inferior to cisplatin plus RT in low-risk LA-NPC with favorable response to IC. **Methods:** The study was a randomised, non-inferiority, phase 3 trial at Sun Yat-sen University Cancer Centre, China. Adult patients (aged 18–70 years) with non-keratinizing stage II-IVA (except N3 category; the eighth edition of the American Joint Committee on Cancer classification system) NPC, with pre-treatment plasma EBV DNA$<$1500 copies/mL, positive EGFR expression and an Eastern Cooperative Oncology Group performance status of 0–1, were treated with 2 cycles of paclitaxel-cisplatin-fluorouracil IC, those achieved CR/PR with undetectable EBV DNA were randomly assigned (1:1) to receive either intravenous nimotuzumab at a dose of 200 mg weekly or cisplatin 100 mg/m² on days 1, 22 and 43 of intensity-modulated radiotherapy. Randomization was done using a computer-generated code random number code with a block size of six, stratified by overall stage. The primary endpoint was 2-year progression-free survival (PFS) in the intention-to-treat population. Safety was assessed in all participants who received at least one dose of the assigned treatment. This study is registered with ClinicalTrials.gov, number NCT 04456322. **Results:** Of the 381 patients who underwent randomization, 191 were assigned to RT plus nimotuzumab and 190 to RT plus cisplatin. After median follow-up duration of 39.5 months, in the evaluation of 2-year PFS, RT plus nimotuzumab was noninferior to RT plus cisplatin (94.2% and 95.8%, respectively; absolute difference, 1.6 percentage points; 95% CI, −2.8 to 6.0, [noninferiority margin, -10 percentage points], $P_{noninferiority}$=0.0001). The most common grade 3-4 acute toxicities were leucopenia (37 [19.5%] of 190 patients in the cisplatin group vs. 2 [1.1%] of 189 patients in the nimotuzumab group), mucositis (36 [18.9%] vs. 28 [14.8%]), and vomiting (21 [11.1%] vs. 0). No patients died during treatment. Patients in the cisplatin group also showed more grade 1-2 auditory or hearing loss and peripheral neuropathy in late adverse events, and impaired long-term quality of life. **Conclusions:** Our findings show that nimotuzumab plus RT represents an alternative concurrent treatment strategy for patients with low-risk LA-NPC with a favorable response to IC. Clinical trial information: NCT04456322. Research Sponsor: None.

6079 **Poster Session**

5-year survival outcomes after perioperative pembrolizumab (pembro) in patients with human papillomavirus (HPV)-unrelated, locally advanced head and neck squamous cell carcinoma (LA-HNSCC): A multi-center, two-cohort, phase 2 trial. First Author: Edward S. Sim, Dana-Farber and Brigham and Women's Cancer Center, Boston, MA

Background: A phase 2 trial (NCT02296684) demonstrated that perioperative pembro added to standard of care (SOC) surgery/adjuvant radiation-based therapy resulted in frequent pathologic tumor responses (pTR) and favorable 2-year survival relative to historical rates in patients with HPV-unrelated, LA-HNSCC (Uppaluri et al., CCR 2020; Oliveira et al., Sci Immunol 2023). The early results of this institutional phase 2 trial provided necessary rationale for the Merck-sponsored, KEYNOTE-689 phase 3 trial that compared perioperative pembro with SOC versus SOC in patients with resectable LA-HNSCC. Here, we report 5-year survival outcomes from the phase 2 trial. We also evaluated the effect of two pembro dosing schedules and the presence or absence of pTR at the primary tumor site on long-term survival outcomes. **Methods:** Cohort 1 received one dose of neoadjuvant pembro (200 mg IV) and, in patients with high-risk pathology, six doses of adjuvant pembro. Cohort 2 received two doses of neoadjuvant but no adjuvant pembro. $pTR_{primary}$ was defined as the proportion of the resected primary site tumor bed that exhibited pathologic response: 0 ($<$10%), 1 (10%-49%), and 2 ($\geq$50%). Event-free survival (EFS), defined as the time from surgery to disease progression, recurrence, or death, and overall survival (OS) was analyzed by the Kaplan-Meier method with log-rank testing for significance. **Results:** Sixty-five patients enrolled (36 in cohort 1 and 29 in cohort 2). The median follow-up was 48.4 months (IQR: 30.1-60.9). The 5-year OS for all patients was 73% (95% CI: 62-85%) and the EFS was 71% (95% CI: 61-83%). A comparison of patients in cohort 2 versus 1 showed no significant differences in OS (HR = 0.39; 95% CI: 0.12-1.20; p = 0.09) or EFS (HR = 0.72; 95% CI: 0.28-1.84; p = 0.48). For all patients, those with $pTR_{primary}$ 1 or 2 versus 0 had significantly better EFS (HR = 0.34; 95% CI: 0.11-1.02; p = 0.04), but not OS (HR = 0.42; 95% CI: 0.14-1.3; p = 0.10). **Conclusions:** Among patients with HPV-unrelated, LA-HNSCC treated with perioperative pembro and SOC, the 5-year OS and EFS were favorable relative to historical results (~40-50% 5-year OS and EFS) with SOC alone. While OS was numerically better in cohort 2 compared to cohort 1, and among patients with $pTR_{primary}$1 or 2 compared $pTR_{primary}$ 0, the differences did not reach statistical significance, possibly due to the small sample size. $pTR_{primary}$ after neoadjuvant pembro was significantly associated with better EFS, suggesting its potential utility as an early surrogate marker for EFS. Clinical trial information: NCT02296684. Research Sponsor: "Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA provided pembrolizumab and financial support for the study".

6080 **Poster Session**

AI-based classification of laryngeal dysplasia and lymphocytic activity quantification from routine histology. First Author: Adam Shephard, University of Warwick, Coventry, West Midlands, United Kingdom

Background: Laryngeal Dysplasia (LD) is a premalignant condition arising in the lining of the larynx. It is graded based on cytological and architectural features present in the epithelium of H&E-stained histology images. However, LD grading suffers from high inter- and intra-rater variability and is not always predictive of malignant transformation. Additionally, distinguishing LD from other laryngeal lesions, such as squamous cell carcinoma (SCC) or benign polyps, remains challenging. Artificial intelligence (AI) offers a solution by enabling objective classification of lesion types, whilst identifying key features associated with LD progression, including lymphocytic infiltration. We propose an AI model using weakly-supervised deep learning to classify LD and highlight potential diagnostic features. **Methods:** We used 109 H&E-stained whole slide images (WSIs) from 82 cases (UHCW and Dundee) scanned at 40$\times$ magnification (0.12 microns-per-pixel, mpp) using a Pannoramic 250 whole-slide scanner. The dataset comprised 50 LD cases (65 WSIs), 20 laryngeal SCC cases (28 WSIs), and 12 benign polyp cases (16 WSIs). Using a pre-trained H-optimus-0 model, we extracted patch-level (224$\times$224 pixels) features from the slides (20$\times$ magnification, 0.5 mpp), with a TransMIL aggregator predicting slide-level classifications for dysplasia, SCC, and polyps. Additionally, we derived slide-level intra-epithelial lymphocyte (IEL) and peri-epithelial lymphocyte (PEL) scores using HoVer-NeXt based lymphocyte segmentation, in and around the epithelium (segmented by HoVer-Net+) in LD cases, and compared these scores across WHO LD grades using Mann-Whitney U tests. **Results:** In Monte Carlo cross-validation experiments (10 repeats), the model achieved an average one-versus-all AUROC of 0.85 and AUPRC of 0.73 for lesion classification (dysplasia vs SCC vs polyp). In LD cases, both IEL and PEL scores were significantly higher in severe dysplasia cases compared to moderate (IEL: r_{rb} = 0.09, p = 0.02; PEL: r_{rb} = 0.36, p = 0.02) and mild dysplasia (IEL: r_{rb} = 0.09, p = 0.01; PEL: r_{rb} = 0.36, p = 0.003). This suggests a potential link between increased lymphocyte presence (activity) and higher grades of dysplasia. **Conclusions:** We present a novel AI model for classifying laryngeal lesions and quantifying lymphocytic activity in LD. Our findings suggest the diagnostic potential of AI in identifying LD, whilst highlighting peri- and intra-epithelial lymphocyte density as a potential biomarker, which has not been previously linked to dysplasia grade. Further validation in large, multi-centric datasets is required. Research Sponsor: None.

6081 **Poster Session**

Examining age-specific trends in the incidence of human papillomavirus-associated oropharyngeal cancer in the United States. First Author: Joshua Elbridge Chan, Stanford University School of Medicine, Stanford, CA

Background: The incidence of human papillomavirus (HPV) infection-associated oropharyngeal cancer (OPC) has been steadily rising in the United States, with HPV surpassing behavioral risk factors like tobacco and alcohol use as the leading cause of OPC, particularly in men. We examined the impact of the HPV vaccine on the incidence of OPC, accounting for age, gender, and lifestyle behavior. **Methods:** Cancer incidence was extracted from the United States Cancer Statistics Public Use Database (USCS). Data on alcohol and tobacco consumption were obtained from the Substance Abuse and Mental Health Services Administration (SAMHSA). The Behavioral Risk Factor Surveillance System (BRFSS) was employed to collect HPV vaccination and screening information. Information on HPV infection and number of sexual partners was provided by the National Health and Nutrition Examination Survey (NHANES). The Joinpoint Regression Program (National Cancer Institute) and Pearson correlation coefficients were used for statistical analyses. **Results:** Between 2001 and 2021, oropharyngeal cancer (OPC) incidence rates increased in males by 2.3% ($p<0.001$) compared to a 0.74% annual increase in females (p=0.002). Compared to the rising incidence of OPC in older men, the younger cohort showed a significant decrease in the incidence of OPC. Specifically, younger males 35-39 years old and 40-44 years old had a 1.86% decrease (p=0.004) and 1.37% decrease (p=0.005) in OPC incidence per year, compared to a rising incidence of 1.66% ($p<0.001$) and 2.56% ($p<0.001$) annually among males 60-64 years old and 65-69 years old, respectively. With the 2009 approval of the HPV vaccine for young men, we investigated whether this was associated with decreased OPC incidence. Indeed, HPV vaccination showed a significant negative correlation with OPC incidence in men younger than 45 (r=-0.818; p=0.001). We then evaluated whether substance use and sexual practices, both risk factors for OPC, have changed during this time. Among 18-25 year olds surveyed in SAMHSA from 2003 to 2021, we found that overall consumption of alcohol decreased by 11.0% ($p<0.05$) and tobacco use decreased by 22.8% ($p<0.05$), even though alcohol and tobacco use were initiated at higher rates in this younger age cohort. Using the NHANES database from 2009-2016, we found that the rate of oral HPV infection, assessed via oral cavity rinses, has not significantly changed (7.6% to 7.2%; p=0.896). Similarly, there was no change in the proportion of people with more than four lifetime oral sex partners (36.0% to 39.0%; p=0.684). **Conclusions:** This study reveals a strong inverse relationship between HPV vaccination rates and OPC incidence in men under 45 years, suggesting that vaccination efforts may be effectively reducing cancer risk in this group. The decreasing rate of alcohol and tobacco consumption in this age group may also contribute to our findings. Research Sponsor: None.

6082 **Poster Session**

AI-driven reflectance confocal microscopy for noninvasive diagnosis and accurate surgical margin assessment intra-operatively in oral cavity squamous cell carcinoma. First Author: Farideh Hosseinzadeh, Department of Surgery, Head and Neck Service, Memorial Sloan Kettering Cancer Center, New York, NY

Background: Oral cavity squamous cell carcinoma (SCC) remains a common malignancy in the head and neck region, with challenges in tumor resection and recurrence prevention. Traditional methods like frozen-section analysis are limited by time delays, sampling errors, and tissue distortion. Reflectance Confocal Microscopy (RCM) provides a noninvasive alternative for real-time, high-resolution imaging, but interpreting RCM images accurately requires expert knowledge. Integrating artificial intelligence (AI) could improve the accuracy and reliability of RCM image interpretation for diagnosing SCC and assessing surgical margins. The integration of machine learning and artificial intelligence (AI) has the potential to enhance the accuracy and reliability of RCM image interpretation, providing a more efficient tool for diagnosing oral cavity SCC and assessing surgical margins in real-time during surgery. **Methods:** We developed an AI model using Google Cloud's AutoML platform to classify RCM images for diagnosing oral cavity SCC and evaluating tumor margins. The dataset comprised 4,090 RCM images from 83 patients, including 1,998 images of benign tissue and 2,092 images of malignant tissue. The dataset was divided into training (80%), validation (10%), and test (10%) sets. A single-label classification approach was employed to differentiate benign and malignant tissue. Model performance was evaluated using sensitivity, specificity, accuracy, F1 score, and negative predictive value. **Results:** The AI model achieved an area under the curve (AUC) of 0.99, sensitivity of 98.09%, specificity of 95.00%, accuracy of 96.58%, and an F1 score of 96.70%. In comparison, expert human readers in our prior study achieved accuracies of 90.91% for normal tissue and 81.7% for tumor detection, highlighting the accuracy of the AI model's diagnostic performance. **Conclusions:** The combination of RCM imaging with AI-powered analysis provides an accurate, noninvasive method for real-time diagnosis and surgical margin assessment in oral cavity SCC. The AI-driven model has excellent sensitivity, specificity, and overall accuracy, offering a potentially efficient and reliable modality for the real-time evaluation of digital RCM images. This approach can reduce the time required for intraoperative margin assessment, minimize patient anesthesia time, and overcome challenges related to conventional histopathology, ultimately improving surgical outcomes in patients with oral cavity SCC. Research Sponsor: None.

6083 **Poster Session**

Artificial intelligence-powered real-time model for predicting recurrence and survival in head and neck squamous cell carcinoma after curative intent surgery. First Author: Hyun Ae Jung, Division of Hematology-Oncology, Department of Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, South Korea

Background: Head and neck squamous cell carcinoma (HNSCC) accounts for approximately 5.3% of cancer-related mortality worldwide, with an estimated 660,000 new diagnoses and 325,000 deaths annually. Curative-intent surgery or definitive chemoradiotherapy remain the only two curative treatment modalities for patients with HNSCC but recurrence rates vary from 10-50% and survival is still limited for some patients emphasizing the need for accurate predictive and prognostic models. This study developed and validated an AI model that integrates clinical, pathological, laboratory, and radiologic data to predict recurrence and survival in HNSCC, aiming to optimize patient outcomes and personalize treatment strategies. **Methods:** The model was developed using XGBoost and Cox regression, internally validated, and tested using data from Samsung Medical Center (SMC). Data in the model included baseline data collected at the time of surgery and longitudinal laboratory data gathered during surveillance. An 80/20 ratio was applied to randomly allocate patients to the developing set and internal validation sets from the SMC dataset. The dataset included patients with HNSCC who underwent curative intent surgery between January 2008 and August 2024. Two models were developed: one to predict progression-free survival (PFS) and overall survival (OS) within 12 months after the surgery, and another to predict PFS and OS within 12 months of the surveillance monitoring point, thus creating a real-time prediction model. External validation was conducted using data from Massachusetts General Hospital (MGH). **Results:** A total of 1,062 patients with HNSCC (oral cavity cancer, oropharyngeal cancer, and laryngeal cancer) were included in the study. The AUC for predicting 12-month PFS after surgery was 0.804 (sensitivity: 82.4%, specificity: 77.3%), with a C-index of 0.802 for RFS. For predicting OS at 12 months after surgery, the AUC was 0.875 (sensitivity: 100%, specificity: 73.1%), with a C-index of 0.862 for RFS. For external validation using MGH data, the AUC for predicting 12-month PFS was 0.875, with a C-index of 0.793 for RFS. The C-index for OS in the MGH dataset was 0.75. In the longitudinal surveillance model, the AUC for predicting 12-month PFS at each monitoring point was 0.883, while the AUC for 12-month OS was 0.902. **Conclusions:** This study successfully developed and validated an AI-powered model for predicting RFS and OS in HNSCC patients, achieving strong performance in both internal and external validations. These findings highlight the potential of AI-based approaches to support personalized treatment strategies and improve prognostic accuracy in HNSCC. Research Sponsor: None.

6084 **Poster Session**

Pathologic response to neoadjuvant sequenced, lymphatic-sparing SBRT plus pembrolizumab in HPV-negative head and neck squamous cell carcinoma. First Author: Richard Bryan Bell, Providence Cancer Institute, Portland, OR

Background: The Neoadjuvant Immuno-Radiotherapy Trial (NIRT-2) is a phase II study, conducted at 2 institutions, that evaluated in patients (pts) with locoregionally advanced HPV-negative head and neck squamous cell carcinoma (HNSCC) whether the combination of neoadjuvant sequenced, lymphatic sparing stereotactic body radiation therapy (SBRT) delivered to gross tumor volume (GTV) plus pembrolizumab is effective in enhancing major pathologic response (MPR) compared to historical controls of anti-PD-1 alone. **Methods:** 27 pts with resectable clinical stage III-IVA HPV-negative HNSCC who would warrant adjuvant RT per the investigators were enrolled. Neoadjuvant therapy consisted of SBRT 8Gy X 3 delivered over 1 week (GTV +/-3mm) followed by 3 cycles of pembrolizumab (200mg) prior to definitive surgical resection + neck dissection at week 7. Standard of care adjuvant RT +/- chemotherapy was administered based on pathologic staging, followed by adjuvant pembrolizumab for 6 months (14 doses). The primary endpoint was MPR (defined as $</=10\%$ viable tumor cells), assessed using a single-arm Simon Two-stage design to test the hypothesis that SBRT would improve MPR to pembrolizumab from 22%, rejecting the null hypothesis if 10 or more responses (37%) are observed in 27 pts (Type 1 error 5%, 90% power, alternative rate 50%). Secondary endpoints included pathologic down-staging allowing for surgical de-escalation and omission of adjuvant RT. **Results:** The study completed enrollment (N=27) on January 17, 2025, at which time 22 pts had completed surgery. 22/27 (81%) pts enrolled were clinically staged as T3/T4 and 8/27 (30%) were N2b/c (AJCC 8th Ed). Pathologic down-staging was observed in 16/22 (73%) pts, which permitted surgical de-escalation (no tracheostomy or free flap, $>50\%$ organ preservation) in 11 pts (50%). 16/22 (73%, one-sided 95% CI =53%-100%, $p<.0001$) had a MPR, of which 6 had a pathologic complete response (pCR), thus meeting the study's primary endpoint of 10 MPR. Adjuvant RT was omitted in 17/22 (77%) pts. All pts remain disease-free at a median follow-up of 8.5 months (IQR=3.9, 21.2; range=0-32). **Conclusions:** Neoadjuvant sequenced, lymphatic sparing SBRT followed by pembrolizumab led to notable pathologic down-staging allowing for surgical de-escalation and omission of adjuvant RT. Clinical trial information: NCT04938609. Research Sponsor: Providence Portland Medical Center Foundation.

6085 **Poster Session**

Omission of concurrent chemotherapy in and out of a phase III randomized controlled trial for stage II nasopharyngeal carcinoma. First Author: Yuting Wang, Department of Radiation Oncology, Sun Yat-sen University Cancer Center, State Key Laboratory of Oncology in South China, Guangdong Key Laboratory of Nasopharyngeal Carcinoma Diagnosis and Therapy, Guangdong Provincial Clinical Research Center for Cancer, Guangzhou, China

Background: In the era of intensity-modulated radiotherapy (IMRT), the precision of radiotherapy has been greatly enhanced, allowing for more precise targeting of tumor tissue while minimizing damage to surrounding normal tissues. Therefore, whether radiotherapy alone can replace the traditional chemoradiotherapy regimen, which may cause substantial side effects, particularly hematologic toxicity, gastrointestinal adverse reactions, and immune suppression, has become a key focus of current clinical research. This investigation explores the potential benefits of IMRT as a standalone treatment, particularly its ability to offer similar efficacy in terms of overall survival and disease control while sparing patients from the added toxicities associated with chemotherapy. **Methods:** In a parallel-group, multicenter, randomized, controlled phase III trial, we compared cisplatin-based concurrent chemoradiotherapy with radiotherapy alone. Stage II NPC patients (2010 UICC staging) were randomly assigned in a 1:1 ratio to receive concurrent chemoradiotherapy (IMRT combined with cisplatin, 100 mg/m² every 3 weeks for 3 cycles) or IMRT alone. The primary endpoint was overall survival in the intention-to-treat population. Secondary endpoints included progression-free survival, locoregional relapse-free survival, distant metastasis-free survival, and safety. **Results:** A total of 211 patients were enrolled (106 in the IMRT alone group, 105 in the concurrent chemoradiotherapy group). The median follow-up time was 37 months. The 3-year overall survival rate was 96.3% for the IMRT alone group and 98.2% for the concurrent chemoradiotherapy group (HR = 0.650, 95% CI: 0.109-3.889; p-value = 0.637). No significant differences were observed between the groups in progression-free survival, locoregional recurrence, or distant metastasis (all p-values $>$ 0.05). The incidence of grade 3-4 adverse events was significantly lower in the IMRT alone group (p-value $<$ 0.05), including hematologic toxicity (leukopenia) and non-hematologic toxicity (hypokalemia). **Conclusions:** In stage II NPC patients, IMRT alone can achieve comparable 3-year overall survival to concurrent chemoradiotherapy, while significantly reducing side effects, which may provide a feasible treatment option for these patients, particularly for those with early-stage II nasopharyngeal carcinoma, where radiotherapy alone offers high therapeutic potential and lower treatment risks. Clinical trial information: NCT02610010. Research Sponsor: Sun Yat-sen University Clinical Medical Research 5010 Program.

6086 **Poster Session**

The use of docetaxel as a radiosensitizer in patients with head and neck cancer unsuitable for cisplatin based chemoradiation: Landmark 3-year survival analysis of a randomized phase III trial (DHANUSH). First Author: Sneha Dhar, Tata Memorial Hospital, Mumbai, India

Background: Patients with cisplatin-ineligible locally advanced head and neck squamous cell carcinoma (LA-HNSCC) have limited guideline-recommended treatment options. DHANUSH (CTRI/2017/05/008700), an open-label, phase II/III randomized controlled trial, was among the first studies to demonstrate superior disease-free survival (DFS) and overall survival (OS) in this patient population. Here, we present the 3-year landmark survival analysis update of our study cohort. **Methods:** This was a single-centre, open-label, randomized controlled phase II/III study conducted at our institute between July 2017 and May 2021. Cisplatin-ineligible patients with LA-HNSCC who were planned for definitive or adjuvant chemoradiation in the multidisciplinary joint clinic were enrolled. Patients were randomly assigned in a 1:1 ratio to receive either radiation therapy alone or concurrent weekly docetaxel (15 mg/m²) for up to seven cycles. The primary endpoint of the study was 2-year disease-free survival (DFS). Here, we present the 3-year landmark survival update, including disease-free (DFS) and overall survival (OS), as of January 25, 2025. **Results:** The study recruited 356 patients, with 179 receiving concurrent docetaxel and 177 receiving radiation therapy alone. The median follow-up for the entire cohort was 67.9 months (95% CI, 65.7–70.3). At the time of the median follow-up, 123 deaths occurred in the concurrent docetaxel arm compared to 136 deaths in the radiation therapy alone arm. The median DFS in the concurrent docetaxel arm was 11.9 months (95% CI, 8.3–21.7) compared to 5.9 months (95% CI, 4.9–8.2) in the radiation therapy alone arm (p = 0.003). Similarly, the median OS was 23.1 months (95% CI, 17.4–30.6) in the concurrent docetaxel arm versus 15.3 months (95% CI, 13.9–22.3) in the radiation therapy alone arm (p = 0.048). The 3-year DFS was 36.3% (95% CI, 29.9–44.1) in the concurrent docetaxel arm versus 23.2% (95% CI, 17.7–30.3) in the radiation therapy alone arm. Similarly, the 3-year OS was 40.2% (95% CI, 33.7–48.1) in the concurrent docetaxel arm compared to 28.8% (95% CI, 22.9–36.3) in the radiation therapy alone arm. **Conclusions:** The addition of concurrent docetaxel to radiation therapy significantly improved survival outcomes (DFS and OS) in cisplatin-ineligible LA-HNSCC patients at the 3-year survival landmark. Clinical trial information: CTRI/2017/05/008700. Research Sponsor: None.

6087 **Poster Session**

Neoadjuvant APG-157 monotherapy in patients with locally advanced squamous cell carcinoma of head and neck: A phase IIA, single arm trial. First Author: Marilene Beth Wang, Department of Head and Neck Surgery, David Geffen School of Medicine at UCLA, Los Angeles, CA

Background: Newly diagnosed, locally advanced squamous cell carcinoma of the head and neck (SCCHN) poses significant treatment challenges due to its infiltrative nature, and high recurrence risk. From diagnosis to definitive curative-intent therapy, patients may experience rapid disease progression leading to a poor prognosis. A safe and effective therapy to halt tumor growth during this period is critical to improve patient outcomes. **Methods:** APG-157, a first-in-class immuno-oncology drug was evaluated in Phase 2A trial (NCT05312710) of 24 patients with stage I–IVA SCCHN in oral cavity (54.2%) and oropharynx (45.8%). Fifty percent had stage III & IVA disease. 91% of oropharyngeal cases were HPV+. APG-157 was administered orally as a soft lozenge - 200 mg, 3X a day before meals - for 4-6 weeks between initial diagnosis and definitive therapy. The primary and secondary endpoints included overall response rate (ORR) using RECIST v1.1 and safety, respectively. The exploratory endpoints included changes in tissue biomarkers, circulating tumor DNA (ctDNA), salivary cytokines, and post-hoc analysis of Event-Free Survival (EFS). **Results:** APG-157 was well tolerated with no treatment-related Grade 3 or 4 adverse events. There was no delay in subsequent definitive therapy. Of 13 oral cavity patients, 10 completed surgery, 3 had post-operative radiotherapy, and all achieved R0 resection. 11 patients with oropharyngeal cancer had chemoradiation (n=10) or radiation alone (n=1). APG-157 showed antitumor activity as 77% of the subjects achieved pathological responses (23% near-complete, 23% major, 31% partial), while 15% had stable disease and 8% showed progression. Among the patients undergoing surgery as definitive therapy, 46% demonstrated clinical-to-pathological downstaging, while 8% experienced upstaging. The (ORR) was 16.7% (n=24), with tumor reduction observed in 45% of the patients. No primary tumor progression occurred, achieving a 100% disease control rate (DCR) with 2 complete responses (CRs), 2 partial responses (PRs), and 20 cases of stable disease (SD). Median EFS was not reached at 2 years. All patients remain alive with no recurrence except one subject who died from a non-cancer-related cause. Pre- and post-treatment multiplex IHC analysis showed APG-157 reduced Ki-67+ tumor cells, increased CD8+ infiltration, and reprogrammed macrophages to the M1 phenotype. Post-treatment ctDNA clearance correlated with complete (30%) and partial (70%) disease control, resulting in ORR of 100% (Gouda MA, et al. Liquid Biopsy Response Evaluation Criteria in Solid Tumors (LB-RECIST). Ann Oncol. 2024 Mar;35(3):267-275). **Conclusions:** APG-157 is a safe and effective oral therapy addressing a critical unmet need in SSCHN. It is a convenient neoadjuvant treatment option with a strong safety profile and durable long-term outcomes after curative-intent therapy. Clinical trial information: NCT05312710. Research Sponsor: Aveta Biomics, Inc.

6088 **Poster Session**

Induction chemotherapy (IC) followed by concomitant radiotherapy and weekly cisplatin (CCRT) versus CCRT alone in patients with locally advanced (LA) nasopharyngeal carcinoma (NPC): Twenty-year follow-up of a randomized phase II study conducted by the Hellenic Cooperative Oncology Group (HeCOG) with biomarker evaluation. First Author: Amanda Psyrri, National and Kapodistrian University of Athens, Athens, Attiki, Greece

Background: Non-endemic NPC is associated with inferior outcomes compared to the endemic form. HeCOG conducted a randomized phase II study to compare IC followed by CCRT with CCRT alone in patients with LA NPC. Here, we report the 20-year follow-up data with biomarker analysis. **Methods:** Patients were randomly allocated 1:1 to CCRT alone or 3 cycles of IC with Epirubicin, Paclitaxel, and Cisplatin followed by CCRT. Random assignment was stratified by histology (type I versus type II+III) and stage (IIB+III versus IV). The primary objective of this analysis was to identify clinical and molecular features associated with PFS and OS. Clinical (141 cases /72 Group A, 69 Group B) and biomarker data (IHC / CISH: 109 Cases, NGS: 61 Cases / 29 Group A; 32 Group B) were analyzed using descriptive statistics, traditional survival Analysis techniques (Kaplan-Meier, Cox) and machine learning approaches (random survival forest). **Results:** Regarding the clinicopathological characteristics, only age at the beginning of the study (HR=1.05, 95%CI=(1.03, 1.06), p$<$0.001) and the CCRT response was associated with OS (PD: HR=20.03, 95%CI=(9.02, 44.48), p$<$0.001; SD: HR=5.17, 95%CI=(2.01, 13.32), p=0.001, respectively). For NGS mutational status, irrespective of effect, only *MSH2* (HR=3.37, 95%CI=(1.27, 8.92), p=0.015) and *PIK3CA* (HR=2.71, 95% CI=(1.03, 7.12), p=0.043) displayed significant association with OS, while random survival forest additionally yielded significant associations for *BRCA1*, *CD274*, *TSC1*, *KRAS* and *KIT*. Considering pathogenic mutations only, *CD8B*, *KDM4A, MLH1*, *MSH6*, and *RANBP2* displayed significant association with OS. Concerning IHC, ECADH (HR=1.16, 95%CI=(1.03, 1.32), p=0.018), GSK3B (HR=1.21, 95%CI=(1.01, 1.44), p=0.036) and AE1AE3 (HR=0.13, 95%CI=(0.02, 0.96), p=0.018), displayed significant association with OS, with higher values of ECADH and GSK3B indicating worse outcome, whereas AE1AE3 expression indicates better outcome. **Conclusions:** Age at diagnosis and response to CCRT emerge as the most important clinical factors forlong-term survival in LA non-endemic NPC.We identified potential molecular correlates for long-term outcomes to be validated in prospective studies. Clinical trial information: ACTRN 12609000730202. Research Sponsor: None.

6089 Poster Session

Transoral robotic surgery (TORS) and de-escalated adjuvant therapy for human papillomavirus-related oropharyngeal carcinoma (HPVOPC): Long-term follow up of the Sinai Robotic Surgery (SIRS) trial (NCT02072148). First Author: Marshall R. Posner, Tampa General Hospital Cancer Institute/Cancer Center of South Florida, Palm Springs, FL

Background: De-escalation therapy for HPVOPC remains undefined and controversial. Definitive and postoperative chemoradiation are associated with significant toxicity. Efforts to de-intensify treatment with CRT only, such as HN002 and HN005, were unsuccessful. A previous investigation by this group (SIRS 1.0) and E3311 have highlighted the potential value of TORS with pathological risk stratification of patients for de-escalated adjuvant therapy. Our early work demonstrated that TORS, in combination with reduced-dosed adjuvant therapy for early and intermediate HPVOPC, resulted in equivalent progression-free survival (PFS) and overall survival (OS) while reducing toxicity in the first two years of treatment. Here we report the 5-year results for SIRS. **Methods:** This is a nonrandomized phase II trial for early-stage molecularly confirmed HPVOPC patients (n=63) treated with TORS followed by reduced-dose adjuvant therapy based on pathological risk-stratification into one of three groups: Group 1 (n=31) with no adjuvant therapy, Group 2 (n=15) with 50-Gy radiotherapy, and Group 3 (n=17) with 56-Gy chemoradiotherapy concurrent with weekly cisplatin. Patient demographics, baseline tumor characteristics, clinical outcomes, and adverse events during treatment and surveillance were recorded across the full 5-year study period. **Results:** Among the 63 total patients, median follow-up is 58 months (IQR 43—76 months). In the first two years following TORS, 5 patients experienced locoregional recurrence (7.9%); of these, one later had distant metastasis and one had a second HPV+ recurrence in the ipsilateral neck. All were salvaged by TORS, neck dissection, and/or chemoradiation. No patients had an HPVOPC recurrence between years 2 to 5 of follow-up. Two patients, one each from Group 1 and Group 2, developed a molecularly proven HPV+ contralateral second primary tumor at the tonsils approximately 5 years following TORS. Both patients were successfully salvaged and remain disease-free. Two patients (one each in Group 2 and 3) died from causes unrelated to cancer. The five-year OS is 96.8% (61/63) and the disease-specific survival (DSS) is 100% (63/63). Five-year PFS is 87.1% (27/31) for Group 1, 86.7% (13/15) for Group 2, 94.1% (16/17) for Group 3, and 88.9% (56/63) for the full cohort. **Conclusions:** Long-term follow-up of SIRS demonstrates de-escalation TORS and pathologic risk stratification is safe and effective in molecularly proven HPVOPC and reduces the lethal and morbid long-term side effects of full dose radiation and CRT. All recurrences occurred in the first two years postoperatively and were salvaged. Multidisciplinary decision-making utilizes the benefits of each specialty to optimize outcomes in de-escalation. Clinical trial information: NCT02072148. Research Sponsor: None.

6090 Poster Session

Which systemic regimen to choose in cisplatin-ineligible patients with concurrent radiation therapy for head and neck cancers: carboplatin/5-flurouracil or carboplatin/paclitaxel? First Author: Parth J. Sampat, SUNY Upstate Medical University, Syracuse, NY

Background: For locally advanced head and neck cancer, concurrent chemotherapy-radiation therapy (ChemoRT) is mainstay of treatment. Carboplatin and 5-Flurouracil (CF) is category 1 recommendation per NCCN guidelines and used mainly in Cisplatin ineligible patients. In this study we aim to compare the outcomes of concurrent radiation therapy with either CF or Carboplatin/Paclitaxel (CP). **Methods:** TrinetX, a global federated research network that provides a dataset of electronic medical records from different healthcare organizations (HCOs), was utilized. Initial query was made to isolate patients who had head and neck cancer (ICD 10 codes C02, C03, C04, C05, C06, C09, C10, C12, C13, C14, C32) and received radiation therapy, concurrently either with CP or CF. Further, propensity score matching (PSM) was carried out to match age, sex, and race. Outcomes of all-cause mortality (ACM), sepsis, septic shock, neutropenia, nausea/vomiting (NV), diarrhea were evaluated. **Results:** 8,310 cases were identified who received ChemoRT, of whom 26% (2,160) received CF. Caucasians were the predominant race in both groups, but Asians received more CF (14% vs 4%, $p<0.0001$). Patients receiving CF were younger (61.4 $\pm$ 9.87 vs 63.5 $\pm$ 10.4, $p<0.0001$). It was seen that patients who received CF had higher ACM rate (51.54% vs 48.52%, p=0.0163; median overall survival (OS) 571 days vs 781 days, p=0.0007). Risk of sepsis (21.24% vs 17.05%, $p<0.0001$), septic shock (7.11% vs 5.24%, p=0.0014), neutropenia (21.98% vs 17.05%, $p<0.0001$), NV (32.79% vs 28.58%, p=0.0003) was more with CF compared to CP, while no difference in neuropathy and diarrhea. After PSM, though elevated but no statistical difference was seen in ACM (50.95% vs 48.75%, p=0.1593), septic shock (7.09% vs 5.77%, p=0.0852), and neutropenia (22.10% vs 19.66%, p=0.0544), while there was still difference in sepsis (21.17% vs 17.8%, p=0.0065), and NV (33.74% vs 29.73%, p=0.0059). **Conclusions:** Concurrent chemoRT with CP offers similar efficacy compared to CF, with less toxicity and can be established as to go chemotherapy regimen with radiation therapy in patients who are ineligible for Cisplatin. Research Sponsor: None.

6091 Poster Session

Circulating tumor HPV-DNA dynamics and neoadjuvant chemotherapy with or without nivolumab in viral-mediated oropharyngeal cancer. First Author: Maha AT Elsebaie, University of Chicago, Department of Hematology/Oncology, Chicago, IL

Background: Human papillomavirus-associated (HPV+) oropharyngeal carcinoma (OPC) is linked to favorable survival outcomes, prompting efforts to de-intensify treatment strategies. Circulating tumor HPV-DNA (ctHPV-DNA) is a promising biomarker for assessing treatment response and guiding de-escalation strategies. This study evaluates how patient characteristics influence ctHPV-DNA dynamics during neoadjuvant therapy across two de-escalation clinical trials. **Methods:** Patients with non-metastatic HPV+ OPC enrolled across two trials of neoadjuvant carboplatin/paclitaxel (NCT04572100) or carboplatin/*nab*-paclitaxel/nivolumab (OPTIMA II, NCT03107182), with ctHPV-DNA available at baseline and post-neoadjuvant, were eligible. All participants received three cycles of neoadjuvant therapy followed by response-adapted de-escalated locoregional treatment. ctHPV-DNA values (copies per ml plasma) were measured at baseline and after 2-3 cycles of neoadjuvant therapy, and percentage reductions were calculated. We defined "ctHPV-DNA clearance" as $\geq$ 95% reduction from baseline and compared data distribution between patients who achieved clearance and those who did not using Kruskal-Wallis, Pearson's $\chi 2$, or Fisher's exact tests. Overall survival (OS) and progression free survival (PFS) probabilities were compared using log-rank test. **Results:** The study included 84 patients. The mean age was 60.9 years. 93% of patients with neoadjuvant nivolumab/chemotherapy achieved ctHPV-DNA clearance compared to 82% with chemotherapy alone, p=0.298. Patients with T1-T2 tumors (AJCC 8th edition) were significantly more likely to achieve ctHPV-DNA clearance compared to those with T3-T4 tumors (p=0.0254). Age, race/ethnicity, smoking history, tumor site (e.g., tonsil), and risk group were not significantly associated with ctHPV-DNA clearance rates. ctHPV-DNA clearance by cycle 2-3 of neoadjuvant therapy predicted radiographic response per RECIST v1.1 (p=0.001), and significantly improved OS (p=0.025) and PFS ($p<0.001$). Survival outcomes were similar across OPTIMA II and NCT04572100 as previously reported. **Conclusions:** Earlier T-stage tumors were associated with rapid ctHPV-DNA clearance by cycle 2 with a trend towards higher clearance rate with neoadjuvant nivolumab/chemotherapy. Rapid clearance predicts radiographic response, OS, and PFS, supporting ctHPV-DNA as a useful biomarker for treatment monitoring with neoadjuvant treatment in HPV+ OPC. Clinical trial information: NCT03107182. Research Sponsor: American Cancer Society; University of Chicago Cancer Center.

ctHPV-DNA % reduction between baseline and follow up at cycle 2-3.

	≥ 95% reduction N (%)	< 95% reduction N (%)	*p*
Age, (mean ± sd)	60.4 ± 10	61.3 ± 8.5	0.656
Gender (Male)	59 (86.8)	9 (13.2)	1
Race (Caucasian)	54 (86)	9 (14)	0.583
Risk (High)	34 (92)	3 (8)	0.309
T1 stage	**12 (75)**	**4 (25)**	**0.0254**
T2 stage	**30 (97)**	**1 (3)**	
T3 stage	**8 (89)**	**1 (11)**	
T4 stage	**3 (60)**	**2 (40)**	
Tumor shrinkage (median %, range)	**-64.2 (-23, -100)**	**-42 (-14, -71)**	**0.001**

6092 Poster Session

Evolving beyond the "unknown primary": Investigating histopathology after diagnostic transoral robotic surgery for microscopic HPV-associated oropharyngeal carcinoma. First Author: Nikita Bedi, Division of Head and Neck Surgery, Department of Otolaryngology, Stanford University, Palo Alto, CA

Background: Squamous cell carcinoma metastatic to the head and neck arising from an unknown primary tumor (hnSCCUP) is a common presentation for HPV-associated oropharyngeal carcinoma. Previously, with traditional approaches, rates of primary site identification for hnSCCUP were low. Using diagnostic transoral robotic surgery (TORS), primary tumors are now routinely found. In this report, we evaluate the histopathology and oncologic outcomes of these tumors. **Methods:** A retrospective review was conducted on 100 patients referred to Stanford University for hnSCCUP evaluation between October 2013 and April 2022. A final cohort of 80 patients who remained classified as hnSCCUP after comprehensive multidisciplinary review was analyzed. Surgical excision followed a standardized protocol targeting oropharyngeal subsites, and specimens were meticulously analyzed by three H&N pathologists. **Results:** The primary site was identified in 66 of 80 patients (83%), with a mean tumor size of 6 mm (range: 2–20 mm). Among the identified tumors, 97% were staged as T1, and 71% measured $\leq$1 cm, confirming their predominantly microscopic nature. The most common tumor locations were the palatine tonsil (26%), lateral tongue base (24%), glossopharyngeal sulcus (21%), and midline tongue base (18%). Histologically, most tumors exhibited a pushing pattern embedded within lymphoid stroma, while 29% demonstrated a pagetoid growth pattern, spreading in a ribbon-like distribution along the superficial lymphoepithelium. Following diagnostic TORS, 23 patients (29%) underwent further surgery, including 10 with surgery alone and 13 with adjuvant therapy. Radiation alone was administered to 15 patients (19%), while 42 patients (53%) underwent chemoradiation. At a median follow-up of 38 months (range: 12–101 months), 77 patients (97%) were alive with no locoregional tumor recurrence. Two patients (2.5%) developed distant metastases, with one death, and one patient (1.2%) experienced persistent regional disease after chemoradiation. Functional swallowing outcomes declined temporarily across all treatment groups. At six months, patients who underwent surgery alone had the least decline in Functional Oral Intake Scale (FOIS) scores, while those receiving chemoradiation experienced the greatest impact. By one year, all patients showed significant recovery, with no long-term feeding tube dependence. **Conclusions:** With a systematic surgical technique for p16+ oropharyngeal carcinoma, diagnostic TORS has revealed a unique pattern of small-volume, often microscopic primary tumors often initially mistaken as hnSCCUP. In many cases, it seems the unknown primary represents a T1-microscopic tumor measuring $<$ 1 cm in maximum diameter with a prominent pattern of submucosal spread. Research Sponsor: The Isackson Family Fund for Research; The Stanford Head and Neck Surgery Research Fund.

6093 Poster Session

Dabrafenib and trametinib in the treatment of BRAF-mutated anaplastic thyroid cancers (ATC). First Author: Irini Yacoub, New York Proton Center/Memorial Sloan Kettering Cancer Center, New York, NY

Background: ATCs are rare, aggressive tumors with poor median overall survival (OS). Approximately 45% harbor BRAF V600 mutations driving tumor progression. We evaluated the outcomes of BRAF-V600E-mutated ATC treated with dabrafenib and trametinib (D/T), with or without local therapy. **Methods:** Consecutive ATC patients with BRAF-V600E mutations treated at our institution from 2016-2024 that received D (150 mg twice daily) and T (2 mg once daily) as a component of their multiple lines of therapies were included. Locoregional therapies included surgery alone, surgery and radiation, or radiation alone. We reported the OS of these patients. **Results:** Out of 82 BRAFV600E mutated ATC patients, 61 pts. (74%) were metastatic at the time of D/T initiation. Median age was 71 years (range 47-86 yrs). Locoregional therapies given: surgery only (n=8); surgery and RT (n=24); RT only (n=23). Median follow-up for all patients is 10 months, and 19 months for alive patients. Median OS for all patients is 14 months. Among those who had surgery only (n=8), the median OS was not reached. Patients who had surgery and radiation had a median OS of 22 months. Lastly, the patients who had RT only as local therapy had a median OS of 14 months. Patients without residual ATC after surgery had a median OS of 39 months versus 21 months for those with residual neck disease. 14 patients who received D/T prior to surgery had a median OS of 39 mo. Table 1 provides details of outcomes by metastatic status. **Conclusions:** This is the largest study to date reporting on outcomes of patients with BRAF V600 mutated ATC receiving D/T. This regimen demonstrates highly favorable results. Our data suggests that patients should undergo surgery when feasible and that D/T should be given prior to surgical intervention. However, the optimal timing, integration as well as the types of local therapy should be prospectively evaluated. Research Sponsor: None.

Patient outcome by metastatic status.

	Overall Survival	
	M0 (N=21)	**M1 (N=61)**
All Patients		
Median Follow-up (all)	15 months (range 2-49)	9 mo (range 0-71)
Median Follow-up (alive)	34 mo. (range 7-49)	16 mo. (range 0-71mo)
Median OS	22 mo. (95% CI 4-40mo.)	10 mo. (95% CI 5-15mo.)
12-month	66%	48%
18-month	55%	37%
Surgery (vs. No surgery)	N=13 versus N=8	N=19 versus N=42
Median OS	22 mo. versus 10 mo.	28 mo. versus 9 mo.
12-month	77% versus 47%	68% versus 38%
18-month	68% versus 47%	61% versus 25%
Surgery* (No residual neck disease versus residual)	N=5 versus N=8	N=15 versus N=4
Median OS	Not reached versus 22 mo.	39 mo. versus 9 mo.
12-month	80% versus 75%	73% versus 50%
18-month	53% versus 47%	65% versus 50%
Radiation (vs. No RT)	N=6 versus N=2	N=17 versus N=25
Median OS	7 mo. versus 10 mo.	9 mo. versus 6 mo.
12-month	50% versus 0%	41% versus 36%
18-month	50% versus 0%	29% versus 22%
Surgery + RT	N=6	N=12
Median OS	22 mo.	21 mo.
12-month	75%	58%
18-month	55%	58%
Order of D/T		
Before Surgery	N=3	N=11
Median OS	Not reached	28 mo.
12-month	100%	82%
18-month	67%	72%

*Surgery with or without RT.

6094 Poster Session

Efficacy and safety of larotrectinib in patients with TRK fusion thyroid carcinoma: An updated analysis. First Author: Marcia S. Brose, Department of Medical Oncology, Sidney Kimmel Cancer Center, Thomas Jefferson University Hospital, Philadelphia, PA

Background: *NTRK* gene fusions are oncogenic drivers in various tumor types, including thyroid carcinoma (TC). Larotrectinib (laro) is the first-in-class, highly selective, central nervous system-active TRK inhibitor, approved for tumor-agnostic use in patients (pts) with TRK fusion cancer. Here, we report updated long-term efficacy and safety data in pts with TRK fusion TC treated with laro. **Methods:** Pts with TRK fusion TC enrolled in 3 laro clinical trials (NCT02576431, NCT02122913, NCT02637687) were included. Laro was administered at 100 mg twice daily (BID) to adults; 2 pediatric pts received 100 mg/m^2 BID (maximum dose 100 mg BID). Responses were independent review committee-assessed per RECIST v1.1. Data cutoff: July 20, 2024. **Results:** At data cutoff, 31 pts were enrolled; 24 (77%) had differentiated TC (DTC) and 7 (23%) had anaplastic TC (ATC). Median age was 60 years (range 6–80). Median time since initial cancer diagnosis was 5 years (range 0–46). Seventeen pts (55%) were systemic treatment-naïve in the metastatic/unresectable setting, 6 (19%) received 2 or more prior therapies, and 24 (77%) received prior radioiodine. All *NTRK* gene fusions were identified by next-generation sequencing. Overall response rate (ORR) was 65% (95% confidence interval [CI] 45–81): 3 (10%) complete responses, 17 (55%) partial responses (PR), 5 (16%) stable disease (SD), 4 (13%) progressive disease (PD), and 2 (6%) not evaluable. For pts classified as DTC, ORR was 79% (95% CI 58–93). For pts classified as ATC, ORR was 14% (95% CI 0–58). Three (10%) pts had poorly differentiated TC, 1 classified as DTC (PR) and 2 as ATC (1 SD for $>$36 months and 1 PD). Median time to response for all pts was 1.9 months (range 1.6–16.2). Median duration of response, progression-free survival, and overall survival (OS) were 35 months (95% CI 19–not estimable [NE]), 39 months (95% CI 17–NE), and not reached (NR; 95% CI 28–NE), respectively, at median follow-ups of 48, 42, and 68 months. Median OS was NR (95% CI 56–NE) in DTC and 9 months (95% CI 3–NE) in ATC. The 6-year OS rate for all pts was 60% (95% CI 41–79). The 6-year OS rate was 71% (95% CI 50–91) for pts with DTC and 17% (95% CI 0–46) for pts with ATC. Median duration of treatment was 31 months (range 1–88). At data cutoff, 7 (23%) pts remained on treatment, 5 of whom had disease control. Treatment-related adverse events (TRAEs) were predominantly Grade 1/2. Grade 3/4 TRAEs were reported in 5 (16%) pts. There were no discontinuations due to TRAEs. **Conclusions:** Laro demonstrates rapid and durable responses, extended survival, and a favorable safety profile in pts with TRK fusion DTC. Limited single-agent activity is observed in pts with ATC. This supports the use of a TRK inhibitor to treat TRK fusion DTC and the importance of testing for *NTRK* gene fusions in patients with advanced TC needing systemic therapy. Clinical trial information: NCT02576431, NCT02122913, NCT02637687. Research Sponsor: These studies were funded by Bayer HealthCare Pharmaceuticals, Inc.

6095 Poster Session

Comparative transcriptomic analysis to identify similarities and therapeutic vulnerabilities in olfactory neuroblastoma (ONB), sinonasal neuroendocrine carcinoma (SNEC) and sinonasal undifferentiated carcinoma (SNUC). First Author: Elisabetta Xue, Center for Immuno-Oncology, Center for Cancer Research, National Cancer Institute, Bethesda, MD

Background: ONB, SNEC and SNUC are rare sinonasal epithelial/neuroepithelial tumors, underserved by clinical trials, with few treatments available despite novel therapeutic agents against surface targets approved or in clinical development. Transcriptomic similarities of ONB with small cell lung cancer (SCLC), pheochromocytoma (PH), paraganglioma (PG), glioblastoma (GB) and low-grade glioma (LGG) are reported, but not for SNUC or SNEC. We examined the transcriptome of ONB, SNUC, SNEC, neuroendocrine (NE) and central nervous system tumors from a real-world (RW) patient cohort to identify similarities and uncover therapeutic vulnerabilities. **Methods:** Tumor specimens (pathology per referring clinician) tested (Caris Life Sciences, Phoenix, AZ) included ONB (n = 26), SNUC (n = 9), SNEC (n = 6), SCLC (n=1751), pancreatic NE tumors (PNET, n=16), PH (n=23), PG (n=50), LGG (n=657), GB (n=4524) and neuroblastoma (NB, n=47). RNA sequencing data were processed to obtain transcripts per million (TPM) values. Clustering was performed with a random subset of 50 samples for tumor types with n$>$100. ONBs were subtyped to neural and basal (Classe *et al.* 2018). RW overall survival (rwOS) was calculated from insurance claims (tissue collection to last contact), compared with log-rank test; Cox proportional hazard model was used for hazard ratio (HR). Selected genes encoding surface targets included *DLL3*, *PMEL*, *PVRL4*, *TACSTD2*, *ERBB2*, *F3*, *CLDN18*, *EGFR*, *ERBB3*, *MET*, *GPC3*, *CD276*, *VTCN1* and *FOSL1*. Median TPM values for genes of interest in ONB, SNUC and SNEC were examined. **Results:** There were 5 transcriptomic clusters (C1-5) (Table). Across clusters, median rwOS was worse for C1 (11.6 mo) and C3 (16.6 mo) vs. C2, C4, and C5 (all not reached), (p = 0.0) and was numerically better in neural (C4) vs. basal ONB (C0) (HR = 0.388, p=0.199). Highest expression for *F3* (34.5), *CD276* (15.6), *GPC3* (7.2) and *CLDN18* (1.1) was in ONB; *ERBB2* (16.4), *TACSTD2* (13.9), *EGFR* (9.2), *PVRL4* (6.2), *PMEL* (2.0) and *FOLR1* (1.5) in *SNUC*; *ERBB3* (83.3), *MET* (32.4), *DLL3* (3.5) and *VTCN1* (1.7) in SNEC. **Conclusions:** We show that neural ONBs cluster independently and basal ONBs co-cluster with SCLC and PNET, joined also by SNUC and SNEC. In our dataset, this cluster is associated with worse rwOS. We also show expression of surface target genes in ONB, SNUC and SNEC, indicating the presence of actionable subsets with existing drugs approved in other tumor types. Our findings provide targets for protein expression validation and expansion of therapeutic options for patients with these rare tumors. Research Sponsor: None.

Cluster	Tumor type, samples over N
C1	**ONB basal, 6/7**
	SNUC, 9/9
	SNEC, 5/6
	SCLC, 48/50
	PNET, 15/16
	NB, 2/47
C2	**ONB neural, 2/18**
	SNEC, 1/6
	PH, 22/23
	PG, 47/50
	NB, 4/47
C3	LGG, 50/50
	GBM, 50/50
	PG, 1/50
C4	NB, 41/47
	PG, 1/50
	PH, 1/23
C5	**ONB neural, 16/18**
	ONB basal, 1/7
	PG, 1/16

6096 Poster Session

Efficacy and safety of anlotinib in neoadjuvant treatment of locally advanced differentiated thyroid cancer (DTC): A multicenter, single-arm, phase II study. First Author: Dapeng Li, Department of Thyroid and Neck Oncology, Tianjin Medical University Cancer Institute and Hospital, Tianjin, Tianjin, China

Background: Neoadjuvant therapy is often necessary for patients with locally advanced inoperable or locally recurrent thyroid cancer without chance of surgery. Anlotinib is a small molecule multi-targeted tyrosine kinase inhibitor that can inhibit tumor angiogenesis while simultaneously inhibiting tumor growth, and has demonstrated significant benefit in radioiodine (RAI)-refractory differentiated thyroid cancer (DTC). Our study aims to evaluate the efficacy and safety of anlotinib in the preoperative neoadjuvant therapy with unresectable DTC. **Methods:** The study (ChiCTR2100048077) was a single-arm, open-label, multicenter phase II study. Eligible patients were between 18-75 years old with histopathological confirmed locally advanced differentiated thyroid cancer at high surgical risk and susceptible to postoperative recurrence. Patients with locally advanced DTC with distant metastasis and potential for local resection were also included. Patients received 12mg of anlotinib once daily on a schedule of 2 weeks on and 1 week off until surgery or disease progression and treatment discontinuation. The primary endpoint was objective response rate (ORR). The secondary endpoints included time to response (TTR), disease control rate (DCR), actual surgery rate, rate of R0 resection and safety. The objective response was evaluated according to RECIST 1.1. Here we report the results of this study. **Results:** 50 patients (20 males vs. 30 females) were enrolled from 3/2022 to 12/2023, with a median age was 56.5 (range: 26.0-74.0), 52% of patients had undergone previous surgery and 14% of patients had received radioiodine (iodine-131) treatment. At the cutoff date (November 30th, 2024), out of 43 patients with assessable efficacy, no CR occurred, 18 patients achieved PR, 24 patients achieved SD and 1 patients had PD.ORR and DCR was 41.86% (95%CI:27.01-57.87) and 97.67% (95%CI: 87.71-99.94) respectively. 21 patients underwent surgery, 57.1% (12/21) achieved R0 resection. Median time to response was 2.84 months (range: 1.31-5.16 months). In patients who did not undergo surgical treatment, the median progression-free survival (mPFS) had not yet reached. The 6-month progression-free survival rate (PFS rate) was 95.83% (95%CI:73.92-99.40). 76%(38/50) of patients had experienced anlotinib treatment-related adverse events (TRAEs), Grade 3+ TRAEs were observed in 9 patients (18%, most common hypertension). 16% (8/50) of patients were discontinued due to TRAEs. No deaths attributable to adverse events (AEs) were observed. **Conclusions:** The study indicated that anlotinib was safe and effective as a neoadjuvant therapy for patients with locally advanced DTC. Clinical trial information: ChiCTR2100048077. Research Sponsor: None.

6097 Poster Session

Updated efficacy, safety and biomarker analysis of a phase 2 study of LBL-007 (alcestobart, an anti-LAG-3 mAb) combined with tislelizumab (an anti–PD-1 mAb) and chemotherapy in previously untreated recurrent or metastatic nasopharyngeal carcinoma (R/M NPC). First Author: Dongchen Sun, Department of Medical Oncology, State Key Laboratory of Oncology in South China, Guangdong Key Laboratory of Nasopharyngeal Carcinoma Diagnosis and Therapy, Guangdong Provincial Clinical Research Center for Cancer, Sun Yat-Sen University Cancer Center, Guangzhou, China

Background: For the first time weevaluated LBL-007 in combination with tislelizumab and chemotherapy in previously untreated R/M NPC in a prospective, multi-center phase 2 study. Preliminary findings indicated this combination had encouraging ORR in this patient population (2024 ASCO, abstr 6033). Here we present the updated efficacy, safety and biomarker analysis of this study focusing on previously untreated R/M NPC (NCT05516914). **Methods:** Untreated R/M NPC patients received gemcitabine at 1 g/m² on days 1 and 8, cisplatin at 80 mg/m² on day 1 (GP) in combination with LBL-007 600 mg and tislelizumab 200 mg on day 1 of every 3 weeks, the chemotherapy was up to 6 cycles, followed by LBL-007 and tislelizumab on day 1 of every 3 weeks as maintenance therapy. The primary endpoint was efficacy, and the secondary endpoints included safety and biomarker analysis. **Results:** As of January 13, 2025, 42 patients with NPC were enrolled and received LBL-007 in combination with tislelizumab plus chemotherapy as first-line treatment. The median follow-up was 17.1 months. Out of 41 efficacy evaluable patients, the ORR and DCR were 85.4% and 100%, the mPFS was 15.0 months and the mDoR was 14.7 months. mOS is not mature. A favorable trend of improved efficacy with LBL-007 combined with tislelizumab plus chemotherapy was observed compared to tislelizumab plus chemotherapy (mPFS 9.6 months, mDoR 8.5 months; NCT03924986). All-grade TRAEs occurred in 39 patients (92.9%), with grade ≥3 TRAEs in 29/42 patients (69.0%). Treatment permanent discontinuance due to LBL-007 TRAEs occurred in 2 (4.8%) patients. 16 patients (38.1%) experienced LBL-007 treatment related SAEs. TRAEs leading to death occurred in 1 patient and infusion-related reaction happened in 4 patients. No new safety signal was observed. Patients with LAG-3 expression ≥5% potentially had improved efficacy compared to those with <5% (Table 1). **Conclusions:** LBL-007/tislelizumab combined with GP chemotherapy has shown encouraging ORR, PFS and DoR in R/M NPC as first-line treatment with favorable safety profiles. These findings support a pivotal phase III study comparing LBL-007/tislelizumab plus GP with tislelizumab plus GP in R/M NPC in 1L setting. The correlation between higher LAG-3 expression and improved efficacy was observed, which warranted further validation in larger population. Clinical trial information: NCT05516914. Research Sponsor: Nanjing Leads Biolabs Co., Ltd.

Clinical outcomes of efficacy evaluable patients.

	LAG-3 < 5% N=10[a]	LAG-3≥5% N=27[a]	Total N=41
ORR, N(%)	7 (70%)	25 (92.6%)	35 (85.4%)
DCR, N(%)	10 (100%)	27 (100%)	41 (100%)
mPFS (95%CI), months	12.1 (3.3, NE)	15.8 (9.7, NE)	15.0 (9.7, NE)
mDoR (95%CI), months	8.8 (3.2, NE)	14.7 (8.3, NE)	14.7 (8.6, NE)
15-month PFS rate, % (95%CI)	40.0% (12.3%, 67.0%)	53.9% (33.4%, 70.7%)	49.8% (33.6%, 64.1%)

[a]LAG-3 was evaluated in 37 patients.

6098 Poster Session

Results from a phase I study of KL590586 in patients with advanced RET-mutant medullary thyroid cancer. First Author: Xiangqian Zheng, Tianjin Medical University Cancer Institute and Hospital, Tianjin, China

Background: *RET* mutations occur in 70% of medullary thyroid cancers (MTC). KL590586 (A400/EP0031) is a potent next-generation brain-penetrant selective RET inhibitor (SRI) with activity against acquired resistance mutations to first-generation SRIs (Zhou et al. 2023, Garralda et al. 2024). Here we present the preliminary safety and efficacy data of KL590586 in patients (pts) with advanced RET-mutant MTC from the phase I part of a phase I/II study completed in China (KL400-I/II-01, NCT05265091). **Methods:** The phase I part, comprising a dose-escalation phase and a dose-expansion phase, was conducted to evaluate the safety, pharmacokinetics, and efficacy of KL590586 in pts with RET-altered solid tumors. Eligible pts with advanced RET-mutant MTC were enrolled to receive KL590586 once a day (QD) until disease progression or unacceptable toxicity. Tumor assessments were performed every 8 weeks as per RECIST v1.1. **Results:** As of September 20, 2024, 27 advanced RET-mutant MTC pts without prior SRIs were enrolled and treated in the phase I part across 4 dose levels (20 to 90 mg QD). The median age was 49 years, and 66.7% of pts were male. Among these 27 pts, 8 were treatment-naïve, and 19 had received previous systemic treatment, with 84.2% of them treated with multikinase inhibitors (MKIs). The median follow-up was 19.0 months. Adverse events were reported for all pts. The most common adverse events considered treatment related (TRAEs, ≥ 35%) were increased ALT (77.8%), increased AST (70.4%), headache (48.1%), increased blood creatine phosphokinase (40.7%), increased blood lactate dehydrogenase (37.0%), and hyperuricaemia (37.0%), with grade ≥3 TRAEs occurring in 22.2% of pts. The most frequent grade ≥ 3 TRAEs (≥ 5%) were increased ALT (7.4%) and increased GGT (7.4%). No TRAEs led to treatment discontinuation or death. At data cut-off, the confirmed objective response rate (cORR) was 63.0% (17/27) and the disease control rate was 100% for overall population. The cORR was 56.3% (9/16) and 62.5% (5/8) in pts with prior MKI or treatment naïve, respectively. Median duration of response was not reached (95% CI, 7.4 to NE), with the longest duration still ongoing at 25.8 months. Similarly, median progression-free survival (PFS) was not reached, with the 24-month PFS rate of 77.8%. **Conclusions:** KL590586 was well tolerated in pts with advanced RET-mutant MTC, exhibiting a safety profile consistent with that previously reported in NSCLC (Zhou et al. 2023). In MTC pts with or without previous MKIs, KL590586 demonstrated robust clinical activity with durable responses. The findings support further investigation of KL590586 as a potential therapeutic alternative for this patient population. Phase II trials are evaluating KL590586/EP0031 in China and US/Europe/UAE. Clinical trial information: NCT05265091. Research Sponsor: Sichuan Kelun-Biotech Biopharmaceutical Co., Ltd.

6099 Poster Session

***BRAF*-V600E papillary thyroid cancer: Updated analysis of real-world patient data.** First Author: Martina Chirra, University of Cincinnati Medical Center, Cincinnati, OH

Background: Papillary thyroid cancer (PTC) is the most common type of thyroid cancer, usually characterized by a good prognosis after surgery with or without radioactive iodine therapy (RAI). However, ~5-15% of patients become RAI refractory, and some require systemic therapy, often with multi tyrosine kinase inhibitors (mTKIs).*BRAF*-V600E, the most common mutation in PTC (~60% of patients), is associated with poor outcomes. The effectiveness of mTKIs compared to BRAF-targeted therapy (BRAF/MEKi) and immunotherapy (IO) remains unclear in the *BRAF*-V600E mutant (*BRAF*-m) population. Therefore, we conducted an updated analysis comparing real-world (rw) survival and molecular/transcriptional signatures in patients with *BRAF*-m and *BRAF*-wildtype (WT) PTC. **Methods:** Differentiated thyroid cancer (DTC) tumor samples underwent DNA/RNA next-gen sequencing at Caris Life Sciences. Tumor microenvironment (TME) cell fractions were estimated by RNA deconvolution using QuanTIseq. A transcriptional IFNγ signature score associated with response to IO was calculated. PD-L1$^+$ (SP142) was defined as ≥2$^+$ in stain intensity and ≥5% of tumor cells stained. Insurance claims data was used to infer rw overall survival (rwOS) from the time of initial diagnosis to death/last contact, and time on treatment (TOT) was assessed from the first to last date of treatment, with hazard ratios (HR) and p-values calculated using the Cox proportional hazards model and log-rank test, respectively. **Results:** A total of 1,348 patients with DTC were identified, of which 82% (n=1,102) were PTC and 18% (n=246) were follicular thyroid cancer (FTC). The majority (95%) of PTC patients were naïve to mTKIs or BRAF/MEKi. *BRAF*-V600E mutations were present in 68% (n=754) PTC patients and only 0.8% (n=2) FTC patients. *TERT* promoter mutations were the most common mutation overall in PTC (72%), more prevalent in *BRAF*-m *vs* *BRAF*-WT PTC (79% *vs* 54%, p<0.001). Mutations in *NRAS*, *HRAS* and *KRAS* were largely exclusive to *BRAF*-WT PTC (22%, 9% and 6% *vs* 0.1%, 0% and 0% in *BRAF*-m PTC, p<0.001), as were *RET*, *BRAF*, and *ETV6* gene fusions (24%, 5% and 5% *vs* 0%, 0.4% and 0% in *BRAF*-m PTC, p<0.01). *BRAF*-m PTC were more often PD-L1$^+$ (33% *vs* 18%, p<0.001), consistent with higher IFNγ scores. This was accompanied by higher Treg and M1 macrophage TME fractions, and lower M2 macrophage, T cell (CD4$^+$ and CD8$^+$), NK cell, monocyte and myeloid dendritic TME fractions compared to *BRAF*-WT PTC (p<0.05). There was no difference in rwOS between *BRAF*-m and *BRAF*-WT PTC (HR=0.845, 95% CI 0.654-1.092, p=0.197), nor per treatment received in *BRAF*-m PTC (BRAF/MEKi *vs* mTKIs, BRAF/MEKi *vs* IO, IO *vs* mTKIs). Similarly, TOT for BRAF/MEKi, mTKIs and IO were similar between *BRAF*-m and *BRAF*-WT PTC. **Conclusions:** *BRAF*-m PTC is associated with a more pro-inflammatory TME milieu compared to *BRAF*-WT PTC. However, in this limited data set, treatment choice was not associated with differences in overall survival in *BRAF*-m PTC. Research Sponsor: CARIS Life Sciences.

6100 Poster Session

Anti-TROP2 ADC ESG401 in a master protocol clinical trial for salivary gland cancer based on molecular typing. First Author: Xiaojuan Zheng, National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, Beijing, China

Background: Salivary gland carcinomas (SGC) are rare, with limited prospective clinical outcome data. There is no standard of care or FDA-approved systemic therapy for recurrent and/or metastatic (R/M) disease. Precision therapy targeting specific gene alterations is emerging as a promising approach for SGC. We designed a single-center, open-label, master protocol clinical trial evaluating the efficacy and safety of molecular subtype-guided precision neoadjuvant/transformative or rescue therapy for SGC. This report focuses on the preliminary results of the TROP2-targeted group. **Methods:** Pts with locally advanced/recurrent SGC received neoadjuvant/transformative therapy, while pts with locally advanced/recurrent who could not tolerate or refused surgery/radiotherapy and pts with symptomatic, rapidly progressive metastatic SGC received rescue therapy. Pts were divided into molecular subtypes (HER2, NTRK, AR, TROP2) or assigned to chemotherapy if no molecular alterations were detected. Trop2-positive pts were assigned to the TROP2 group and treated with ESG401 (16 mg/kg i.v. on days 1, 8, and 15 of each 28-day cycle). The primary endpoint was ORR per RECIST1.1; secondary endpoints included AEs, DCR, PFS, and OS. **Results:** As of Jan 22, 2025, 14 Trop2-positive pts were enrolled, including 4 receiving neoadjuvant/transformative therapy and 10 receiving rescue therapy. Among the 12 efficacy-evaluable pts, pathological types included salivary duct carcinoma (n=3), adenoid cystic carcinoma (n=5), and others (n=4). Safety findings were consistent with the ESG401-101 study, with no new safety signals observed. Among 4 pts receiving neoadjuvant/transformative therapy, 2 achieved decreased SD, though not meeting PR criteria. Among 8 pts receiving rescue therapy, 4 achieved PR with ORR was 50% (4/8). For 12 efficacy-evaluable pts, DCR was 100% (12/12). Three pts with brain metastases achieved IC-PR/CR, yielding an IC-ORR of 100%. **Conclusions:** ESG401 demonstrated promising efficacy in Trop2-positive SGC, providing a rationale for molecular subtype-based targeted therapy in this population and warranting further investigation in larger studies. Clinical trial information: NCT06145308. Research Sponsor: None.

6101 Poster Session

Amivantamab for recurrent/metastatic adenoid cystic carcinoma: A multicenter, single-arm, phase 2 clinical trial. First Author: Olga Zamulko, University of Cincinnati Cancer Center, Cincinnati, OH

Background: Adenoid cystic carcinoma (ACC) is a rare salivary gland cancer with heterogenous clinical behavior. ACC typically presents with locoregional disease and is treated with curative intent surgery and adjuvant radiation, but many patients develop locally recurrent/metastatic (R/M) disease even years later. Two recognized molecular subtypes exist: ACC 1 (37%), characterized by *MYC* amplification and *NOTCH*-activating mutations and a poor prognosis, and ACC 2 (63%), which demonstrates P63 expression and upregulated EGFR and MET and a better prognosis. There is no standard treatment for R/M ACC, but multi-targeted tyrosine kinase inhibitors are a mainstay of treatment despite their limited efficacy. Amivantamab is a bispecific antibody that binds to the extracellular domains of EGFR and MET, causing immune-directed destruction of cancer cells. Since MET expression renders EGFR inhibitors ineffective, we hypothesized that amivantamab would overcome resistance especially in the ACC 2 subtype. This multicenter, single arm, Phase 2 clinical trial (NCT05074940) evaluated the efficacy of amivantamab in patients with R/M ACC supported by Janssen Pharmaceuticals. **Methods:** Eligible patients were ≥18 years of age with R/M ACC and had progressive disease (PD) within 6 months of enrollment, ECOG ≤1, with adequate organ and marrow function. Patients received amivantamab 1050 mg or 1400 mg (≥80kg) IV weekly for 4 weeks then Q2 weeks until PD or unacceptable toxicity. The primary end point was overall response rate (ORR) assessed by RECIST 1.1. Among 18 treated patients the lower limit of a one-sided 90% exact binomial CI would be >14% if ≥5 patients respond. Adverse events (AEs) were assessed by CTCAE v5. Secondary end points included progression- free survival (PFS) and overall survival (OS). Key exploratory end points were P63 and MYC expression. **Results:** We enrolled 21 patients with 17 evaluable for response at time of submission. Most were male (14, 67%) non-Hispanic (20, 95%), and White (19, 90%) with a median age of 61 (range, 36-76) years. The majority received prior treatment. The best ORR was 6% (1 partial response), while 9 (53%) had stable disease (SD) and 7 (41%) PD. Median duration of SD was 5.4 months. The most common treatment-related AEs (TRAEs) were acneiform rash (17, 81%), infusion related reaction (16, 76%), and fatigue (15,71%). Grade 3 TRAEs occurred in 3 patients (14%) including acneiform rash, oral mucositis, and elevated alkaline phosphatase with no Grade ≥4 TRAEs. Median PFS and OS were 4.8 (95% CI, 1.84-7.64) and 10.4 months (95% CI, 5.48-NR), respectively. There was no correlation between tumor P63 or MYC levels and clinical benefit (PR+SD). **Conclusions:** While amivantamab did not achieve the target ORR, the safety profile was manageable and clinical benefit was observed in 59% of patients. Clinical trial information: NCT05074940. Research Sponsor: Janssen Pharmaceuticals.

6102 Poster Session

A phase 2 study of novel MDM2 inhibitor alrizomadlin (APG-115) with or without toripalimab in patients (pts) with advanced adenoid cystic carcinoma (ACC) or other solid tumors. First Author: Ye Guo, Department of Medical Oncology, Shanghai East Hospital, School of Medicine, Tongji University, Shanghai, China

Background: Alrizomadlin, an investigational MDM2 inhibitor, has shown a manageable safety profile with preliminary efficacy in liposarcoma (LPS) and ACC and in combination with a PD-1/PD-L1 inhibitor in advanced solid tumors. **Methods:** This multicenter trial (APG115XC102) assessed alrizomadlin (± toripalimab) in pts with advanced ACC, malignant peripheral nerve sheath tumor (MPNST), LPS, biliary-tract cancer (BTC), or other solid tumors in China. Enrolled pts had an ECOG PS 0-1 and were without central nervous system metastases. Alrizomadlin was administered orally at 50, 100, or 150 mg every other day for 2 weeks, with 1 week off, in repeated 21-day cycles, and combined with toripalimab 240 mg IV for 30 minutes on Day 1 of repeated 21-day cycles until disease progression or unacceptable toxicity. The primary endpoint was RP2D for the combination. ORR was assessed per RECIST v1.1. **Results:** As of January 5, 2025, 54 pts were enrolled. In the monotherapy arm, 22 pts were treated with alrizomadlin 150 mg; common treatment-related adverse events (TRAEs) included nausea (68.2%), decreased appetite (45.5%), thrombocytopenia (40.9%), white blood cell count decreased (40.9%), neutropenia (36.4%), and hypoalbuminemia (22.7%). Grade ≥ 3 TRAEs included neutropenia (13.6%) and thrombocytopenia (9.1%). No treatment-related serious adverse events (SAEs) were reported. In the combination arm, 32 pts were treated with alrizomadlin at 50 (n = 3), 100 (n = 3), or 150 mg (n = 26). No DLT was observed; the expansion dose was 150 mg plus toripalimab. Common TRAEs at 150 mg included nausea (73.1%), thrombocytopenia (65.4%), neutropenia (50.0%), decreased appetite (42.3%), and anemia (38.5%). Grade ≥ 3 TRAEs included thrombocytopenia (38.5%) and neutropenia (34.6%). Treatment-related SAEs were reported in 8 pts, including 6 thrombocytopenia, 1 neutropenia, 1 intestinal fistula, and 1 peptic ulcer. One pt (3.8%) discontinued treatment because of grade 4 thrombocytopenia; no treatment-related death was reported. Regarding efficacy, in the monotherapy arm, 14 pts were evaluable, with 2 unconfirmed partial responses (PRs) in 9 pts with ACC (ORR 22.2%, DCR 100%). All 5 pts with MPNST achieved SD (DCR 100%). In the combination arm, 28 pts were evaluable: 1 of 5 pts with BTC had a confirmed PR, and the ORR (CR + PR) was 20% and DCR 80%; 1 unconfirmed PR was reported in 6 pts with LPS, for an ORR of 16.7% and DCR of 66.7%. Pts with MPNST had an ORR of 14.3% and a DCR of 53.6%, and 2 pts with MPNST had confirmed PRs with prolonged PFS (1 pt > 60 weeks, 1 > 96 weeks). **Conclusions:** Alrizomadlin monotherapy showed promising antitumor activity in pts with advanced ACC or MPNST. Alrizomadlin combined with toripalimab was also well tolerated, showing antitumor activity in MPNST, BTC, and LPS and an acceptable safety profile (NCT04785196). Clinical trial information: NCT04785196. Research Sponsor: Ascentage Pharma Group Corp Ltd. (Hong Kong).

6103 Poster Session

A phase II study of lenvatinib plus pembrolizumab in patients with recurrent/metastatic salivary gland cancers. First Author: Alan Loh Ho, Memorial Sloan Kettering Cancer Center, New York, NY

Background: Recurrent/metastatic (R/M) salivary gland cancers (SGCs) are rare diseases without standard therapies. Based on the hypothesis that VEGFR inhibition can enhance immune checkpoint-induced responses against SGCs, we conducted a phase II trial of the multikinase inhibitor lenvatinib (len) plus the programmed death-1 (PD-1) inhibitor pembrolizumab (pem) in two R/M SGC cohorts: adenoid cystic carcinoma (ACC) and non-ACC histologies. Here we report results from the completed non-ACC cohort. **Methods:** Patients (Pts) with R/M SGC (except ACC) were enrolled. RECIST v1.1 measurable disease was required; prior therapies were allowed. Pts with acinic cell carcinoma (AcCC) were required to have progression of disease (PD) or worsening disease-related symptoms. Len 20 mg oral daily and pem 200 mg intravenously every 3 weeks was given. The primary endpoint was best overall response (BOR) rate using a minimax Simon two-stage design. In the first stage, >1 confirmed complete and/or partial responses (CRs, PRs) was required among 18 pts to enroll 14 more pts. >4 responses among 32 pts would be considered positive (BOR 5% vs 20%, 1-sided alpha 0.1, power 0.9). Secondary objectives were progression-free survival (PFS) and safety/tolerability per CTCAE v5.0. **Results:** 27 pts with R/M SGC pts were enrolled; 26 evaluable for the study endpoints. Among evaluable pts, the median age was 62 and 15 were men. SGC histologies included 9 AcCC, 8 salivary duct carcinoma (SDC), 4 myoepithelial carcinoma, 2 mucoepidermoid carcinoma, and 1 each of polymorphous adenocarcinoma, epithelial-myoepithelial carcinoma, and mucinous adenocarcinoma. 5/26 (19.2%) had confirmed PR. 18 pts had stable disease (SD), 1 PD as best response; 2 evaluable pts did not reach first scan assessment. As of 1/20/25, median PFS was 47 weeks. Among the 9 AcCC pts, 4 (44.4%) had PR and 5 SD; 8/9 pts had tumor regression in target lesions. For the 8 SDC pts, 1/8 (12.5%) had PR. Per protocol, 2 pts (AcCC and SDC) stopped treatment after 2 years; both resumed treatment when PD occurred, achieving SD and PR, respectively. Six deaths were observed, 4 possibly related to treatment: 3 SDC (respiratory failure due to pneumonitis vs. cancer progression [1]; cardiac arrest after polymyositis/myocarditis/aspiration pneumonia [1]; stroke [1]) and 1 myoepithelial carcinoma (respiratory failure due to pneumonitis vs. infection [1]). **Conclusions:** Trial enrollment was completed after 26 evaluable pts given the study was positive for the primary BOR endpoint and the grade 5 events observed. Len+pembro may be active and safe among pts with AcCC, though further study is needed. This combination may be less promising for SDC given the grade 5 events and low response rate observed. (Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA provided lenvatinib and pembrolizumab for the study.) Clinical trial information: NCT04209660. Research Sponsor: Merck; U.S. National Institutes of Health.

6104 Poster Session

Trop2-targeted PET/CT with ^{68}Ga-MY6349 for detecting metastatic lesions in metastatic thyroid cancer: Prospective comparison of diagnostic accuracy with ^{18}F-FDG PET/CT. First Author: Hao Fu, The First Affiliated Hospital of Xiamen University, Xiamen, Fujian, China

Background: Trophoblast cell surface antigen 2 (Trop2) targeted molecular imaging with ^{68}Ga-MY6349 has been proposed as a potential modality for visualizing cancerous lesions, but its utility for identifying metastatic thyroid cancer (TC) is not well-established in the literature. This study aims to evaluate the clinical utility of ^{68}Ga-MY6349 PET/CT for detecting metastatic TC and to compare the results with those of ^{18}F-fluorodeoxyglucose (FDG) PET/CT. **Methods:** This was a prospective, single-center, open-labeled, single-arm comparative imaging trial. Patients with clinically suspected or confirmed metastatic TC were prospectively enrolled and underwent paired ^{68}Ga-MY6349 and ^{18}F-FDG PET/CT from November 2023 to January 2024. Histopathology and clinical follow-up (mean 12 months ± 0.7 [standard deviation] (range: 11-13 months) were used as reference standards for the final diagnosis. ^{18}F-FDG and ^{68}Ga-MY6349 uptake were compared by using the Wilcoxon signed-rank test. The McNemar test was used to compare the diagnostic efficacy of the two techniques, and the influence of various clinicopathological characteristics on ^{18}F-FDG and ^{68}Ga-MY6349 uptake was evaluated by Mann-Whitney and Kruskal-Wallis tests. **Results:** In total, 55 participants (median age, 51 years [interquartile range, 35-61 years]; 17 men) were evaluated. In all 55 participants, the ^{68}Ga-MY6349-derived SUV_{max} was higher than the ^{18}F-FDG-derived SUV_{max} in the local recurrence (24.9 vs. 10.7, P = .026), metastatic central compartment (12.7 vs. 4.9, P < .001), metastatic lateral compartment (11.0 vs. 5.4, P < .001), and mediastinal lymph nodes (LNs) (9.5 vs. 4.6, P = .012). ^{68}Ga-MY6349 PET/CT had a higher sensitivity than ^{18}F-FDG PET/CT for detecting neck lesions (88% vs. 56%; P < .001). **Conclusions:** ^{68}Ga-MY6349 PET/CT was superior to ^{18}F-FDG PET/CT for detecting metastatic TC, especially in local recurrence and LNs metastases. Clinical trial information: NCT06465017. Research Sponsor: None.

Comparison of ^{18}F-FDG and ^{68}Ga-MY6349 uptake in metastatic thyroid cancer.

Site of Disease	^{18}F-FDG Uptake (SUV max)	^{68}Ga-MY6349 Uptake (SUV max)	*P* value
Local recurrence	10.7±7.6	24.9±23.7	0.026
Central compartment LNs	4.9±4.6	12.7±10.9	<0.001
Lateral compartment LNs	5.4±6.4	11.0±10.23	<0.001
Mediastinal LNs	4.6±2.8	9.5±7.5	0.012
Pulmonary metastases	2.4±0.7	3.4±1.5	0.175
Other sites*	8.5±3.8	14.2±17.1	0.691

LNs, lymph nodes; Other sites include bone and subcutaneous metastasis.

6105 Poster Session

Dual immune checkpoint inhibition in advanced incurable radioiodine-refractory differentiated thyroid carcinoma (RAIR DTC), anaplastic (ATC), and medullary thyroid carcinoma (MTC): Long-term survival results from phase II clinical trial. First Author: Kartik Sehgal, Dana-Farber Cancer Institute, Boston, MA

Background: Immunoprofiling and preclinical studies with patient derived organotypic tumor spheroids supported therapeutic targeting of programmed death (PD)-1 and cytotoxic T lymphocyte antigen (CTLA)-4 pathways in thyroid tumors. We previously presented initial results of a phase 2 clinical trial evaluating dual immune checkpoint inhibition with nivolumab (N) and ipilimumab (I) in advanced incurable thyroid carcinoma (TC) (ASCO 2020, PMID: 39446365) with data cutoff at 24 months (mo) follow up. **Methods:** This nonrandomized phase 2 clinical trial evaluated N (3 mg/kg every 2 weeks) + I (1 mg/kg every 6 weeks) in the primary patient population of RAIR DTC, with exploratory cohorts in ATC and MTC. Primary endpoints were objective response rate (ORR), with secondary endpoints of safety, progression-free survival (PFS), and overall survival (OS). Here, we present long term results (data cutoff 12/27/24), with median follow up of 75.3 mo for the overall population. **Results:** 49 patients (32 RAIR DTC, 10 ATC, and 7 MTC) were evaluable, 51% female, with median age of 65 years (range 30-88). Median duration of follow up (by cohorts) for this analysis was 74.9 mo (range 12.7 - 82.1) for RAIR DTC, 67.6 mo (29.9 - 84.4) for ATC and 81.1 mo (75 - 82.1) for MTC. ORR was 9.4% (in RAIR DTC), 30% (ATC), and 0% (MTC), all partial responses. Previously unreported, median duration of response (DoR) was 30 mo (range: 18.1 – 69.7) for RAIR DTC, and 23.2 mo (9.1 - 73.1) for ATC. Updated median PFS was 4.9 mo (95% CI 2.1, 17.0) for RAIR DTC, 4.3 mo (0.5, NA) for ATC, and 2.1 mo (0.9, 4.0) for MTC. 5-year PFS rates were 14.6% (95% CI 4.3%, 30.9%) for RAIR DTC, and 26.7% (4.8%, 56.3%) for ATC. Updated median OS was 44.6 mo (95% CI 24.6, NA) for RAIR DTC, 13.8 mo (1.2, NA) for ATC, and 46.1 mo (12.2, NA) for MTC. 5-year OS rates were 39.0% (95% CI 22.2%, 55.4%) for RAIR DTC, 30.0% (7.1%, 57.8%) for ATC, and 42.9% (9.8%, 73.4%) for MTC. **Conclusions:** Exceptionally durable responses were observed in the exploratory cohort of ATC (median DoR: 23.2 mo). To the best of our knowledge, this is the longest follow up reported for patients with aggressive thyroid carcinoma treated with immunotherapy. 5-year OS rate of 30% in incurable ATC is congruent with one prior report of 25.7% at another large volume cancer center (PMID: 3597734), but compares favorably with the historical rates reported for ATC in the SEER database (8% for all stages and 4% for distant metastatic disease). Biomarker studies are currently underway to identify exceptional responders and long-term survivors. Clinical trial information: NCT03246958. Research Sponsor: Bristol Myers Squibb.

	RAIR DTC (N=32)	ATC (N=10)
Median PFS (95% CI), mo	4.9 (2.1, 17.0)	4.3 (0.5, NA)
5 year PFS (95% CI)	14.6% (4.3%, 30.9%)	26.7% (4.8%, 56.3%)
Median OS (95% CI), mo	44.6 (24.6, NA)	13.8 (1.2, NA)
5 year OS (95% CI)	39.0% (22.2%, 55.4%)	30.0% (7.1%, 57.8%)

6106 Poster Session

A phase II study of pemetrexed and pembrolizumab in patients (pts) with recurrent and/or metastatic (R/M) salivary gland cancer (SGC): Results from non-adenoid cystic cohort. First Author: Katharine Andress Rowe Price, Department of Oncology, Mayo Clinic, Rochester, MN

Background: Treatment options for pts with R/M SGC are limited. Responses to chemotherapy (CT) are low with high toxicity and responses to immune checkpoint inhibition (ICI) are $<$10%. Pemetrexed (PTX) is safe and tolerable with responses reported in pts with R/M SGC.[1] Given enhanced responses with PTX and pembrolizumab (PMB) for lung cancer, we hypothesized that PTX and PMB will have activity for SGC. Herein we present the efficacy results in pts with non-adenoid cystic carcinoma (ACC). **Methods:** MC200708 is a single arm phase II study of PTX and PMB in pts with R/M SGC (NCT04895735). Pts were treated in 2 cohorts: ACC (cohort A) and non-ACC (cohort B). Key eligibility criteria: $\geq$18 years, ECOG 0-1, measurable disease. Prior ICI and/or PTX was allowed. Key exclusion criteria: serious comorbidities, autoimmune disease, and brain metastases. Simon's 2-stage design was used for each cohort. Primary endpoint was overall response rate (ORR). Secondary endpoints: progression free survival (PFS), overall survival (OS), and toxicity. All pts received PTX 500 mg/m2 IV + PMB 200 mg IV q3 weeks until progression or treatment intolerance. Imaging was q3 cycles. **Results:** 25 pts were enrolled Aug 2021-Feb 2024; 1 cancelled prior to treatment. Of 24 eligible and treated pts, median age was 59.5 years (46-77), 66.7% male, performance status 0 (62.5%) or 1 (37.5%). Histologies were salivary duct carcinoma (SDC, 11), acinic cell carcinoma (8), mucoepidermoid carcinoma (MEC, 3), myoepithelial carcinoma (1), and carcinoma NOS (1). 7 pts had no prior therapies (29.2%). The remaining pts had 1 (33.3%), 2 (29.2%), or $\geq$ 3 lines of therapy (8.3%). 83.3% of pts had no prior ICI. Median cycles of treatment was 8 (2-34), and duration of response was 12.5 months (4.1-20.6). 9 of 24 pts had a confirmed partial response (PR) for ORR of 37.5% (CI: 18.8-59.4). PRs were seen in 7 pts with SDC (7 of 11, 63.6% PR), 1 with MEC, and 1 with acinic cell. Stable disease (SD) was seen in 5 (20.8%), progressive disease in 8 (33.3%), and 2 didn't have post-baseline imaging, but were considered non-responders per protocol. Clinical benefit rate was 58.3% (CI: 36.6-77.9). With median follow-up of 12.0 months (2-34.7), median OS is 20.7 months (CI: 17.3-not reached) and median PFS is 6.2 months (CI: 2.1-17.3). 1-year OS and PFS rate is 76.3% (95% CI: 59.9-97.2) and 36.1% (CI: 21.01-62.2), respectively. Common toxicities were grade 1 fatigue and nausea. 6 pts (25.0%) had $\geq$1 grade 3-4 toxicity possibly related to treatment, mostly hematologic. The 4 pts with grade 3-4 non-heme toxicity had grade 3 fatigue, rash, and heart failure, and 1 grade 4 hypokalemia. Correlative studies investigating biomarkers of response are underway. **Conclusions:** PTX and PMB has activity in pts with R/M SGC, with promising responses in pts with SDC and median response duration of 1 year. [1] Viscuse et al. *Head Neck* 2019;41(6):E99-103. Clinical trial information: NCT04895735. Research Sponsor: Merck.

6107 Poster Session

A multisite randomized trial of an advanced pneumatic compression device vs usual care for head and neck cancer related lymphedema: Short-term results. First Author: Barbara Murphy, Vanderbilt University Medical Center, Nashville, TN

Background: Lymphedema is common in head and neck cancer survivors (HNCS). Published data indicate that an Advanced Pneumatic Compression Device (APCD) is an effective intervention for lymphedema refractory to Therapist Guided Lymphedema Treatment (TGLT). It may also address barriers to TGLT. We therefore conducted a study in which HNCS with previously untreated lymphedema were randomized to APCD or Usual Care. We report short-term, two-month outcomes. **Methods:** This was a six-month, multi-site (community/academic), stratified, randomized effectiveness trial. Eligible patients were lymphedema therapy naïve HNCS with internal or external lymphedema on exam or imaging and at least 1 moderate ($\geq$ 4/10) lymphedema associated symptom. Participants were randomized (1:1) to APCD or Usual Care. Those randomized to APCD were to use the device for 32 minutes per day. Participants randomized to Usual Care were referred for lymphedema therapy per institutional standards. The primary outcome was improvement in lymphedema associated symptom severity. Additional outcomes included anatomical measures, patient reported biopsychosocial outcomes, barriers to care, and patient satisfaction. **Results:** 236 participants were enrolled (119 APCD group, 117 Usual Care group). At two-months there was a similar decrease in lymphedema associated symptom burden and internal soft tissue swelling in both groups. We demonstrated a statistically significant external soft tissue swelling benefit favoring the APCD group as measured by the Head and Neck Cancer Related Lymphedema and Fibrosis Grading score (p=0.016). Digital photography identified a reduction in number of grids with swelling (p=$<$0.001) in the APCD group only. No reduction of internal swelling was noted in either group by imaging measures. 95% of APCD participants and 71% of Usual Care participants received assigned therapy. Time to therapy initiation was 29.8 days (SD 23.5) for Usual Care and 17.86 days (SD 10.53) for APCD. **Conclusions:** We demonstrated that APCD therapy is an effective treatment modality in lymphedema therapy naïve HNCS. Furthermore, participants experienced significant barriers to TGLT which may be effectively addressed with use of the APCD. A hybrid multi-modal approach to treatment associated lymphedema may further optimize patient outcomes. Clinical trial information: NCT04797390. Research Sponsor: Tactile.

6108 Poster Session

Outcomes with 177 lutetium-dotatate (177Lu-dotatate) in olfactory neuroblastoma (ONB): A case series. First Author: Mateus Trinconi Cunha, Department of Thoracic/Head and Neck Medical Oncology, The University of Texas MD Anderson Cancer Center, Houston, TX

Background: Olfactory neuroblastoma (ONB) is a rare malignant tumor of the nasal cavity with a high recurrence rate after local therapy. Effective treatments for recurrent/metastatic (R/M) ONB are lacking. ONB frequently expresses somatostatin receptor (SSTR). Radionuclide bound to somatostatin analogues is an established treatment for SSTR-expressing gastrointestinal and pancreatic neuroendocrine tumors. This study reports the efficacy and survival outcomes of ONB patients treated with 177Lu-dotatate at a comprehensive cancer center. **Methods:** We conducted a retrospective analysis of ONB patients treated with 177Lu-dotatate at MD Anderson Cancer Center through NOV 1 2024, with a follow-up cutoff date of DEC 1 2024. Time-to-event outcomes were estimated with the Kaplan-Meier method, and comparisons of survival were done with the log-rank test. Objective response rate (ORR) to 177Lu-dotatate was assessed by RECIST v1.1 and PERCIST criteria adapted to Ga-60 Dotatate PET-CT. The magnitude of effect was estimated with Cox proportional hazards model, with statistical significance set at p$<$ 0.05. **Results:** Thirteen R/M ONB patients were identified, 8 were female, and the median age at first dose of 177Lu-dotatate was 54 years. Overall, 6 (46%) ONB tumors were Hyams grade 2, 5 (38%) were grade 2-3, 1 (8%) grade 3, and 1 (8%) grade 4. All patients had distant metastasis prior to 177Lu-dotatate treatment, with the most common sites being bone (76%), and dura (38%), while 6 (46%) also had locoregional disease. Six (46%) patients received 177Lu-dotatate as first line therapy, 4 (31%) as second line, and the remaining 3 (23%) in later lines. Prior therapies included somatostatin analogues (n=4), chemotherapy plus PD-L1 inhibitor (n=1), Lenvatinib (n=1), and clinical trials with experimental drugs (n=3). Among 10 patients with post-treatment restaging scans, PERCIST showed partial response in 7 (70%) and stable disease in 3 (30%). Of these pts, 7 were evaluable per RECIST, demonstrating partial responses in 4 (57%) and stable disease in 3 (43%). At a median follow-up of 19.8 months from starting 177Lu-dotatate, the median progression-free survival (PFS) was 17.43 mo. (95%CI 8.29-NE). For patients treated with 177Lu-dotate in second-line or beyond, the median PFS significantly shorter at 4.18 mo. (95%CI 1.35-NE); hazard ratio (HR) 0.22 (95%CI 0.08-0.60; p = 0.001). Median time-to-progression for 177Lu-dotatate was not achieved. There was no statistical difference in PFS between first or later lines 177Lu-dotatate use (HR 1.74; 95%CI 0.38-7.86; p = 0.47). **Conclusions:** 177Lu-dotate demonstrates activity in R/M ONB, with a favorable PFS compared to previously administered lines of systemic therapy. This case series, the largest reported to date to our knowledge, supports the growing evidence supporting for the use of 177Lu-dotate in this orphan disease. Research Sponsor: None.

TPS6109 **Poster Session**

HexAgon-HN: Phase 2/3, randomized study of the hexavalent OX40 agonist INBRX-106 in combination with pembrolizumab vs pembrolizumab alone as first-line treatment for recurrent/metastatic head and neck cancer with a PD-L1 combined positive score of ≥20. First Author: Jong Chul Park, Massachusetts General Hospital, Boston, MA

Background: Pembrolizumab (pembro) ± chemotherapy is a standard-of-care first-line treatment option for recurrent/metastatic (R/M) head and neck squamous cell carcinoma (HNSCC). Pembro monotherapy is commonly used in patients with a PD-L1 combined positive score (CPS) of ≥20, with an objective response rate (ORR) of <25% and median overall survival (OS) of <15 months.[1] Therefore, a high unmet need exists for more effective, non–chemotherapy-based treatment options. INBRX-106 is a novel, hexavalent OX40 agonist designed to promote higher-order clustering of the costimulatory receptor OX40, leading to more potent agonism than the bivalent first generation of OX40 agonists. Combining INBRX-106 with pembro may amplify and prolong the antitumor immune response. In an ongoing phase 1/2 study (NCT04198766), INBRX-106 + pembro has demonstrated robust pharmacodynamics, a favorable safety profile, and promising clinical activity in multiple tumor types, including R/M HNSCC. These findings supported the initiation of HexAgon-HN (NCT06295731), a phase 2/3, randomized study evaluating INBRX-106 + pembro vs pembro alone as first-line treatment for R/M HNSCC with a PD-L1 CPS of ≥20. **Methods:** Eligible patients must have biopsy-confirmed R/M HNSCC that is considered incurable; a primary tumor in the oral cavity, oropharynx, hypopharynx, or larynx; no previous receipt of therapy for R/M disease; a centrally confirmed PD-L1 CPS of ≥20; measurable disease per RECIST 1.1; and an Eastern Cooperative Oncology Group performance status (ECOG PS) of 0 or 1. Prior curative-intent treatment for locoregionally advanced HNSCC is allowed if progressive disease occurred ≥6 months (≥12 months if immunotherapy) after completion of treatment. Up to 410 patients will be randomized 1:1 (stratified by locoregional advanced vs distant metastatic disease, HPV status, and ECOG PS) to INBRX-106 + pembro 200 mg every 3 weeks or pembro (alone in the open-label, phase 2 part or in combination with placebo in the double-blind, phase 3 part). If the phase 2 part (N≈60) shows favorable results for the primary efficacy endpoint (ORR) and secondary safety and efficacy endpoints (eg, duration of response [DOR], progression-free survival [PFS] rate at 6 months, and clinical benefit rate [CBR]), the study can seamlessly proceed to the phase 3 part. The phase 3 part (N≈350) has dual primary efficacy endpoints of PFS and OS; secondary endpoints include ORR, DOR, CBR, time to chemotherapy, safety, and patient-reported quality of life. This study is currently enrolling in the US (30 sites), Europe (40 sites), and Asia-Pacific region (15 sites). 1. Burtness B, et al. *Lancet*. 2019;394:1915-1928. Clinical trial information: NCT06295731. Research Sponsor: Inhibrx Biosciences, Inc.

TPS6110 **Poster Session**

A phase II study of ACR-368 and low dose gemcitabine combination therapy in patients with recurrent and/or metastatic head and neck squamous cell carcinoma. First Author: Robin Park, Department of Head and Neck-Endocrine Oncology, Moffitt Cancer Center, Tampa, FL

Background: Safe and efficacious therapeutic options for patients with recurrent and/or metastatic head and neck squamous cell carcinoma (R/M HNSCC) beyond the 1st line palliative treatment, for which the standard of care is PD-1 inhibitor with/without chemotherapy, are limited. Therefore, developing novel therapeutic strategies in this setting remains a critical unmet need. ACR-368 (prexasertib) is a potent, selective CHK1/2 inhibitor which impairs DNA damage repair (DDR) and induces cancer cell apoptosis. ACR-368 has shown single agent activity in a phase Ib trial of patients with advanced squamous cell carcinomas including heavily treated R/M HNSCC. Pre-clinical studies suggest down-regulation of DDR pathways downstream to CHK1/2 is a major resistance mechanism to ACR-368 that can be overcome with low doses of nucleoside analogs that increase replication stress. Work conducted at Acrivon Therapeutics using their AP3 platform uncovered protein signaling features linked to ACR-368 resistance that demonstrated low-dose gemcitabine (LDG) may sensitize cancer cells to ACR-368 treatment. Furthermore, combining LDG with ACR-368 induces synergistic cancer cell regression in *in vitro* and *in vivo* models of HNSCC. Therefore, combined ACR-368 and LDG warrant further evaluation. **Methods:** This is a multi-center, parallel-arm, open-label, phase II trial evaluating combined ACR-368 with LDG in patients with R/M HNSCC. Eligible patients must have been treated with 1 prior line of PD-1/L1 inhibitor with/without chemotherapy with no limitation on the number of prior therapies received in the R/M setting. Patients must agree to a biopsy after the lead-in LDG infusion and at disease progression or end of treatment. OncoSignature is a proprietary predictive biomarker designed to predict response from ACR-368 that will be evaluated as a companion diagnostic. Lead-in LDG 10 mg/m2 IV will be administered before Cycle 1 only followed by ACR-368 105 mg/m2 IV Q2W and LDG 10 mg/m2 Q2W until discontinuation due to disease progression, intolerance, or consent withdrawal. Patients with HPV-unrelated R/M HNSCC will be assigned to Cohort A and patients with HPV-related R/M HNSCC to Cohort B. Primary objective is to determine objective response rates (ORR) in Cohort A and Cohort B, respectively. Study will enroll 14 patients in Cohort A and 29 patients in Cohort B to detect an increase in ORR from 0 to 19% and 5 to 22%, in respective cohorts (type I, II errors, both 10%). Secondary objectives include safety, duration of response, progression-free survival, and overall survival. Exploratory objectives include evaluating potential predictive biomarkers and the effect of lead-in LDG on OncoSignature by comparing pre- and post-LDG tumors. Since recruitment began 09-25-2024, 5 of planned 43 patients have been enrolled as of 01-22-2025. Clinical trial information: NCT06597565. Research Sponsor: Acrivon.

TPS6111 **Poster Session**

VERSATILE-003: A phase 3, randomized, open-label trial of PDS0101 and pembrolizumab compared with pembrolizumab for first-line treatment of patients with HPV16-positive recurrent/metastatic head and neck squamous cell carcinoma. First Author: Katharine Andress Rowe Price, Mayo Clinic, Rochester, MN

Background: Human papillomavirus (HPV)-related head and neck squamous cell carcinoma (HNSCC) has surpassed cervical cancer as the most common HPV-related cancer in the US, with the majority being caused by HPV16. Persistent expression of HPV16 oncoproteins E6 and E7 by host genome may promote HNSCC. HPV16-positive HNSCC may be associated with poor clinical outcomes in the recurrent/metastatic (R/M) setting. PDS0101 (Versamune HPV) is an HPV16-immunotherapy that generates a potent, targeted T cell attack against HPV16 E6 & E7. In a Phase 2 study, PDS0101 plus pembrolizumab has shown encouraging safety and survival benefit in patients with HPV16-positive R/M HNSCC. (Weiss J et al. ESMO 2024. Poster 879P. NCT04260126). **Methods:** VERSATILE-003 is a global Phase 3, randomized, controlled, open-label study evaluating PDS0101 plus pembrolizumab vs. pembrolizumab in patients with HPV16-positive R/M HNSCC with PD-L1 positive disease (CPS ≥1). Key eligibility criteria include age ≥18-years-old, histologically- or cytologically-confirmed diagnosis of R/M HNSCC with primary tumor location of oropharynx, oral cavity, hypopharynx, or larynx and no prior systemic anticancer treatment in the R/M setting, HPV16 tumor positivity (centrally tested), PD-L1 positivity defined as CPS ≥ 1 using FDA-approved PD-L1 IHC 22C3 pharmDx kit, and measurable disease based on RECIST 1.1 confirmed by blinded independent central review (BICR). Patients will be randomized 2:1 to receive pembrolizumab 200 mg IV Q3W with PDS0101 1 mL SC administered concurrently during Cycles 1, 2, 3, 4, and 12 (investigational arm), or pembrolizumab 200 mg IV Q3W alone (control arm). The primary objective is to compare overall survival (OS) between the investigational and control arms. Secondary objectives include objective response rate (ORR), disease control rate (DCR), duration of response (DOR), and progression-free survival (PFS) using RECIST 1.1 and assessed by BICR. Exploratory objectives include tumor response assessed by investigator and by irRECIST, PFS2, quality of life as assessed by EQ-5D, QLQ-C30, and QLQ H&N35, and assessment of ctHPVDNA. Updated enrollment data will be provided. Clinical trial information: NCT06790966. Research Sponsor: PDS Biotechnology Corporation.

TPS6112 **Poster Session**

A phase 2 study of fianlimab (anti–LAG-3) plus cemiplimab (anti–PD-1) versus cemiplimab plus placebo in patients with recurrent/metastatic head and neck squamous cell carcinoma (HNSCC) with positive PD-L1 expression. First Author: Danny Rischin, Peter MacCallum Cancer Centre, Melbourne, Australia

Background: Concurrent blockade of lymphocyte activation gene 3 (LAG-3) may enhance the efficacy of anti–programmed cell death-1 (PD-1) therapies. In a multicohort study, fianlimab (anti–LAG-3) plus cemiplimab (anti–PD-1) showed signs of clinical activity with durable responses and a generally manageable safety profile in patients with recurrent/metastatic (R/M) head and neck squamous cell carcinoma (HNSCC) warranting further investigation. **Methods:** This randomized, multicenter, Phase 2 study (NCT06769698) will investigate fianlimab (anti–LAG-3) plus cemiplimab (anti–PD-1) versus cemiplimab plus placebo in patients with R/M HNSCC with positive programmed cell death-ligand 1 (PD-L1) expression. The primary objective is to evaluate investigator-assessed objective response rate (ORR) with combination therapy (fianlimab + cemiplimab) versus cemiplimab monotherapy (cemiplimab + placebo). Key inclusion criteria: (1) aged ≥18 years; (2) histologically confirmed R/M HNSCC; (3) primary tumor location of oral cavity, oropharynx, larynx, or hypopharynx; (4) confirmed positive PD-L1 expression status with a Combined Positive Score of ≥1 based on a previous immunohistochemistry (IHC) test performed on a surgical/core biopsy specimen; (5) for patients with oropharynx disease, human papillomavirus (HPV) status must be established by p16 IHC or HPV DNA or RNA *in situ* hybridization (ISH) test; biopsy can be from primary tumor or nodal/distant metastasis; (6) for patients with squamous cell carcinoma of neck node with occult primary, a positive HPV DNA or RNA ISH test; (7) measurable disease per Response Evaluation Criteria in Solid Tumors version 1.1; (8) Eastern Cooperative Oncology Group performance status of ≤1; (9) adequate bone marrow, hepatic, and renal function. Key exclusion criteria: (1) patients who have progressive disease within 6 months of completion of curatively intended systemic treatment for locoregionally advanced HNSCC; (2) patients who have received prior systemic anticancer therapy in the R/M HNSCC setting. Approximately 120 patients will be enrolled across two cohorts. Patients will receive fianlimab + cemiplimab intravenously (IV) every 3 weeks (Q3W) or cemiplimab (350 mg) + placebo IV Q3W. Cohort 1 (n=60, HPV positive HNSCC) will be randomized 1:1 to receive: a) fianlimab + cemiplimab, b) placebo + cemiplimab. Cohort 2 (n=60, HPV negative HNSCC) will be randomized 1:1 to receive: a) fianlimab + cemiplimab, b) placebo + cemiplimab. The primary endpoint is ORR per investigator assessment. The secondary endpoints are progression-free survival, disease control rate, duration of response, safety, pharmacokinetics, and immunogenicity. Clinical trial information: NCT06769698. Research Sponsor: Regeneron Pharmaceuticals, Inc.

TPS6113 **Poster Session**

A multicenter, randomized, double-blind, phase 2/3 study of ficerafusp alfa (BCA101) or placebo in combination with pembrolizumab for first-line treatment of PD-L1-positive, recurrent or metastatic head and neck squamous cell carcinoma: The FORTIFI-HN01 study. First Author: Renata Ferrarotto, The University of Texas MD Anderson Cancer Center, Houston, TX

Background: HPV-negative head and neck squamous cell carcinoma (HNSCC) is an aggressive disease characterized by high rates of recurrence, metastasis, and resistance to standard treatments. Over 80% of HPV-negative HNSCC cases overexpress TGF-β, a key driver of poor survival and treatment resistance. Ficerafusp alfa, a first-in-class bifunctional antibody, targets epidermal growth factor receptor (EGFR) while neutralizing TGF-β in the tumor microenvironment. In a Phase 1/1b trial (NCT04429542), ficerafusp alfa demonstrated promising efficacy and a manageable safety profile in first-line recurrent/metastatic (R/M) HNSCC. The ongoing FORTIFI-HN01 study (NCT06788990) is a randomized, double-blind, placebo-controlled Phase 2/3 trial designed to assess the efficacy and safety of ficerafusp alfa combined with pembrolizumab versus placebo plus pembrolizumab in patients with PD-L1 positive first-line R/M HPV-negative HNSCC. **Methods:** Eligible patients must have histologically confirmed R/M HNSCC with primary lesions in the oral cavity, larynx, or hypopharynx, or OPSCC, excluding HPV-positive OPSCC confirmed by central laboratory testing. Additional criteria include no prior systemic therapy for R/M disease, PD-L1 positive tumors (CPS $\geq$1), measurable disease per RECIST v1.1 assessed by BICR, and ECOG performance status of 0 or 1. The Phase 2 objective is to determine the optimal biological dose (OBD) of ficerafusp alfa through an integrated analysis of safety, tolerability, PK, PD, and efficacy. Subjects will be randomized 1:1:1 to receive high-dose ficerafusp alfa, low-dose ficerafusp alfa, or placebo, each combined with pembrolizumab. Randomization is stratified by PD-L1 CPS (1-19 vs. $\geq$20) and disease extent (local/regional recurrence only, distant metastasis only, or both). After OBD determination, the trial will transition seamlessly into Phase 3 with a 2:1 randomization (OBD vs. control).Patients will receive pembrolizumab (200 mg i.v. every 3 weeks for up to 35 cycles) and either ficerafusp alfa (1500 mg or 750 mg) or placebo weekly until disease progression or unacceptable toxicity. Tumor imaging will occur every 6 weeks during the first year and every 9 weeks thereafter. The primary endpoints are objective response rate (ORR) per RECIST v1.1 (BICR) and overall survival (OS). Secondary endpoints include safety, additional efficacy measures, and patient-reported outcomes (PROs). The trial is actively recruiting, with a planned enrollment of (NCT06788990). Clinical trial information: NCT06788990. Research Sponsor: Study funded by Bicara Therapeutics Inc.

TPS6114 **Poster Session**

A phase II study of AK117 combined with cetuximab or AK104 in the treatment of recurrent or metastatic head and neck squamous cell carcinoma after the failure of PD-1 (L1) inhibitors and/or platinum-based therapy. First Author: Jun Wang, Division of Head & Neck Tumor Multimodality Treatment, Cancer Center, West China Hospital, Sichuan University, Chengdu, China

Background: The administration of first-line pembrolizumab monotherapy or pembrolizumab combined chemotherapy has been shown to improve survival among patients with recurrent or metastatic head and neck squamous cell carcinoma (R/M HNSCC). However, over 80% of the patients still experience disease progression within a year. Upon progression, treatment options are notably limited. Therefore, there is a dearth of a standardized treatment for R/M HNSCC after the failure of PD-1 (L1) inhibitors and/or platinum-based therapy. This study aims to assess the safety and efficacy of AK117 (anti-CD47) combined with Cetuximab or AK104 (PD-1/CTLA-4 Bispecial Antibody) in this patient subset. **Methods:** This is a non-randomized, two-group, phase II study. The inclusion criteria include: 1) Pathological or radiological diagnosis of R/M HNSCC (including oral cavity, oropharynx, larynx, and pharynx) and cannot be cured by local treatment; 2) Failure of PD-1 (L1) inhibitors and/or platinum-based therapy; 3) Eastern Cooperative Oncology Group (ECOG) Performance Status (PS) 0-1 and expected survival $\geq$3 months. Key exclusion criteria are active autoimmune diseases, use of immunosuppressive drugs, or any severe or uncontrolled systemic disease. We group the patients based on the duration of first-line PD-1 (L1) inhibitors from start to failure (Group 1: the duration $\leq$ 3 months; Group 2: the duration $>$ 3 months). Group 1 patients receive AK117 (45mg/kg, day 1, every 3 weeks) in combination with Cetuximab (initial dose 400mg/m^2, subsequent doses of 250mg/m^2, day 1, every week) maintained for one year or until progression or intolerable toxicity occurred. Group 2 patients are treated with AK117 (45mg/kg, day 1, every 3 weeks) in combination with AK104 (10mg/kg, day 1, every 3 weeks) maintained for one year or until progression or intolerable toxicity occurred. The primary endpoints are incidence of adverse events and overall survival. Secondary endpoints are objective response rate, progression free survival, disease control rate, and duration of response. Clinical trial information: NCT06508606. Research Sponsor: Akeso, Inc.

TPS6115 **Poster Session**

FIERCE-HN: A multicenter, randomized, double-blind, placebo-controlled, phase 3 study of ficlatuzumab (HGF/cMET MAb) in combination with cetuximab in participants with recurrent or metastatic (R/M) HPV negative head and neck squamous cell carcinoma (HNSCC). First Author: Julie E. Bauman, GW Cancer Center, George Washington University, Washington, DC

Background: Patients with HPV-negative R/M HNSCC have a worse median overall survival (OS) than HPV-positive patients and current treatments options are limited.[1] Ficlatuzumab is a humanized IgG1 MAb that binds HGF, the ligand for the c-MET tyrosine kinase receptor. HGF/c-MET pathway dysregulation is frequently observed in HPV-negative HNSCC, and has been linked to EGFR inhibitor resistance, limiting the potential efficacy of EGFR-targeting drugs like cetuximab. In a phase 2 study, both pathways were targeted using ficlatuzumab plus cetuximab in patients with HPV-negative R/M HNSCC resistant to cetuximab, platinum, and anti-PD1 immune checkpoint inhibitors (ICI) who have a very poor historical prognosis. A PFS of 4.1 months, median OS of 7.4 months, and overall response rate (ORR) of 38% (6/16; 2 CR, 4 PR) was observed.[2] FIERCE-HN compares the efficacy/safety of ficlatuzumab+cetuximab vs placebo+cetuximab in patients with R/M HPV-negative HNSCC. **Methods:** This is an international, multicenter, randomized, double-blind, placebo-controlled phase 3 study. Major enrollment criteria include confirmed diagnosis of R/M HNSCC primary tumors of the oropharynx (p-16 negative only), oral cavity, hypopharynx, or larynx. Participants must have progressed on, or be intolerant to, previous anti-PD-1/PD-L1 ICI and platinum-based chemotherapy; have 2 or fewer prior lines of anticancer therapy; and have no prior treatment with cetuximab/alternative EGFR inhibitors in the R/M setting. Patients with feeding tubes are eligible. The primary endpoint is OS; key secondary endpoints include PFS and ORR. Other secondary endpoints are DCR, DoR, safety, PK, immunogenicity and QoL. Patients will receive cetuximab 500mg/m2 and are randomized 1:1:1 to Arm A: ficlatuzumab 10mg/kg, Arm B: ficlatuzumab 20mg/kg, or Arm C: placebo. Treatments will be on Days 1 and 15 of a 28-day cycle. This is an adaptive study with two interim analyses (IAs). IA 1 will be conducted after 70 OS events, when futility and optimal dose assessments will be performed. Participants enrolled after IA 1 will be randomized 1:1 to the optimal ficlatuzumab dose or placebo, plus cetuximab. IA 2 will be conducted after 163 OS events to assess whether an event count re-estimation is needed. The final analysis will occur after 232 (or up to 279) OS events, depending on the re-estimation outcome. The study has statistical power of 80%, assuming a true OS hazard ratio of 0.667. Between 410 to 500 patients will be enrolled. The study is ongoing and actively recruiting in North America, Europe, United Kingdom, and Asia-Pacific. Clinical trial information: NCT06064877 (collaborator Eli Lilly provided cetuximab). 1. Cohen E et al., JITC. 2019;7:184. 2. Bauman JE et al., JCO. 2023. 41:3851. Clinical trial information: NCT06064877. Research Sponsor: AVEO Oncology.

TPS6116 **Poster Session**

Reduction of postoperative radiotherapy in head and neck squamous cell carcinoma: A single-arm, phase II trial (REPORT-HNSCC study). First Author: Chunyan Chen, Department of Radiation Oncology, Sun Yat-sen University Cancer Center, State Key Laboratory of Oncology in South China, Guangdong Key Laboratory of Nasopharyngeal Carcinoma Diagnosis and Therapy, Guangdong Provincial Clinical Research Center for Cancer, Guangzhou, China

Background: Postoperative radiotherapy (PORT) significantly enhances the prognosis for high-risk patients with locally advanced squamous cell carcinoma of the head and neck (LA HNSCC). However, elective nodal irradiation (ENI) in low-risk areas can lead to serious acute and long-term toxicities, which negatively impact quality of life. In a study by Contreras (NCT00593840), 72 patients with LA HNSCC experienced a remarkable 97% regional control rate at five years after eliminating PORT to the pathologically negative (pN0) neck. Additionally, patients who responded well to neoadjuvant therapy showed better local control rates, suggesting a possible reduction in the need for radiotherapy. The RAVD study (NCT01133678) demonstrated that the elimination of ENI in patients with good response to neoadjuvant chemotherapy did not appear to compromise outcomes and resulted in significantly decreased late toxicity. Preclinical studies have also suggested that the elimination of ENI may preserve beneficial T cells in normally draining lymph nodes, enhancing the efficacy of radioimmunotherapy. The study was designed to evaluate regional control rates and quality of life in LA HNSCC patients undergoing sequential elimination of ENI to the pN0 neck by neoadjuvant chemo-immunotherapy. **Methods:** REPORT-HNSCC is a phase 2, single-arm, single-center trial assessing patients with newly diagnosed LA HNSCC. Patients receive neoadjuvant chemo-immunotherapy (flexibility in regimens and cycles). This trial targets patients with an ipsilateral and/or bilateral pN0 neck, while surgical resection will be guided by the surgeon's discretion. Key treatment components include 60 to 66 Gy to the primary tumor bed (CTVtb), 60 Gy to CTV1, and 54 to 60 Gy to CTV2, with appropriate expansion margins to optimize target volume. Eliminating ENI (that is, CTV2) to the pN0 neck. A symmetric 0.3-cm expansion around the CTV defined the corresponding planning target volume (PTV). Radiation doses were prescribed to the PTV. Intensity-modulated radiotherapy (IMRT) will be administered to all patients, while select patients with positive surgical margins or extranodal extension receive concurrent chemotherapy. The primary endpoint is 2-year region-free recurrence survival rate. Secondary endpoints include 2-year PFS, 2-year OS, 2-year DMFS, 2-year LRFS, acute and late toxicities, and quality of life. We will also explore predictive biomarkers for better understanding of responses and survival. As of January 2025, we have enrolled 14 of the planned 50 patients since the study began in October 2024, with results expected by December 2029. Clinical trial information: NCT06630780. Research Sponsor: None.

TPS6117 **Poster Session**

Phase II trial of neoadjuvant chemotherapy (NAC) docetaxel-cisplatin alone (DC) or with anti-human papillomavirus (HPV) gene therapy PRGN-2009 (DCP) followed by surgery in patients (pts) with newly diagnosed HPV-associated oropharyngeal cancer (HPV-OPC). First Author: Charalampos S. Floudas, Center for Immuno-Oncology, Center for Cancer Research, National Cancer Institute, National Institutes of Health, Bethesda, MD

Background: HPV-OPC is caused primarily by HPV16. Prognosis following standard-of-care (SOC) treatment, (surgery followed by adjuvant radiotherapy (RT), or concurrent chemoRT (CRT)) is favorable, with >80% 5-year recurrence-free survival (RFS). However, RT toxicity including tissue fibrosis results in long-term swallowing dysfunction and impacts quality of life (QOL). NAC treatment (DC) followed by surgery has resulted in clinical-to-pathologic downstaging or pathologic complete response (pCR) and avoidance of RT in most pts, with >90% 5-year survival, and induces HPV-specific T cell immunity. PRGN-2009 is a gorilla adenoviral vector based gene therapy harboring a DNA payload designed to induce HPV specific T-cell responses. This trial will evaluate the rate of pCR with NAC (DC) alone or combined with PRGN-2009 (DCP) in pts with newly diagnosed HPV-OPC. **Methods:** This is an investigator-initiated, single-center, randomized controlled phase II trial. Newly diagnosed HPV-positive OPC pts of stage I (cT1-2, N0-1) or II (T1-3, N0-2), M0 (AJCC Cancer Staging Manual, 8th ed.) planned for SOC surgery will be randomized to 2 treatment arms of 30 patients each, DC and DCP, to evaluate if PRGN-2009 may be associated with an increased rate of pathological CR (pCR) following neoadjuvant chemotherapy. DC consists of 3 cycles of intravenous cisplatin 75 mg/m^2 and docetaxel 75 mg/m^2 every 21 days (dose reductions allowed). DCP also includes PRGN-2009 induction dose pre-cycle 1, and one dose after each DC cycle (total 4 doses). Supportive measures include pre-infusion dexamethasone, antiemetics, neutropenia primary prophylaxis. Imaging (FDG PET, CT) will be performed at baseline. Research blood samples will be collected longitudinally. Mandatory research primary tumor biopsy will be performed at baseline and post-treatment tumor/tumor bed biopsy will be at the time of surgical resection. On-treatment tumor biopsies will be offered (optional). Study treatment and procedures will be performed at the NIH Clinical Center (Bethesda, MD). After treatment completion, pts will have surgery at their primary institution; adjuvant treatment determined per established risk factors. Primary endpoint is the rate of pCR in each arm. Secondary endpoints include safety and 2-year RFS in each arm. Exploratory objectives include assessment of changes in hearing (audiograms baseline/post-treatment), swallowing function (MD Anderson Dysphagia Inventory) and QOL (Functional Assessment of Cancer Therapy – Head & Neck); associations between changes in imaging, pathologic response, and circulating cell-free HPV DNA; changes in the tumor microenvironment and in HPV-specific T cell immunity. 8 of 60 pts planned have been enrolled. Clinical trial information: NCT06223568. Research Sponsor: NCI, NIH.

TPS6118 **Poster Session**

A phase III randomized controlled trial comparing palliative stereotactic body radiotherapy vs. palliative standard radiotherapy in patients with advanced head and neck cancer (NCT06641791). First Author: Ian Poon, Sunnybrook Health Sciences Centre, Toronto, ON, Canada

Background: The optimal radiotherapy (RT) treatment regimen for patients with advanced head and neck cancer (AHNC) unsuitable to receive curative intent RT is undefined. Stereotactic body radiotherapy (SBRT) is a promising technique but rigorous multicentre evaluation is required prior to adoption. **Methods:** This is a Phase III randomized controlled trial comparing palliative SBRT to palliative standard RT (SRT) in participants with advanced mucosal, squamous cell head and neck cancer unable to tolerate curative intent RT. Key eligibility criteria: Unsuitable for curative intent therapy, no evidence of metastatic disease, stages TX or T0-T4/N0-N3, geriatric 8 score [1] ≤14. Treatment arms: (Experimental) SBRT 4500 cGy/ 5fr (twice a week to primary and nodal GTV (BED_{10}85) OR 4000 cGy /5 fr twice a week if organs at risk (BED_{10}-72) versus (standard) 2400 cGy/ 3fr (day 0/7/21 (BED_{10}43) or 2500 cGy/ 5fr over 1 week (BED_{10}38). Primary objective: To compare OS between arms. Secondary objectives evaluate progression-free survival (PFS), locoregional failure-free survival, distant metastases-free survival, response rates, acute and long-term toxicity (CTCAE v5.0), treatment compliance, patient-reported outcomes (PRO-CTCAE, FACT-HN), resource utilization, and health utilities. Statistical design: The trial aims to enroll 196 patients with a 2:1 randomization ratio (SBRT:SRT). The study is powered at 80% with a two-sided alpha of 0.05 to detect a difference in 1-year OS of 40.3% vs. 22% (HR = 0.6), assuming a 15% drop-out/lost to follow-up rate. Conduct to Date: This trial was activated on October 31, 2024. Supported by CCS grant #707213; CIHR #175014. [1] Takahashi M, Takahashi M, Komine K, Yamada H, Kasahara Y, Chikamatsu S, et al. (2017) The G8 screening tool enhances prognostic value to ECOG performance status in elderly cancer patients: A retrospective, single institutional study. PLoS ONE 12(6): e0179694. https://doi.org/10.1371/journal.pone.0179694. Clinical trial information: NCT06641791. Research Sponsor: Canadian Cancer Society (CCS); 707213; Canadian Institutes of Health Research (CIHR); 175014.

TPS6119 **Poster Session**

TRENT-002: A prospective, multicenter, randomized controlled phase II study to evaluate the efficacy and safety of salvage preoperative PD-1 inhibitor combined with chemotherapy neoadjuvant therapy in recurrent laryngeal/hypopharyngeal squamous cell carcinoma (L/HPSCC). First Author: Xiaohong Chen, Beijing Tongren Hospital, Capital Medical University, Beijing, China

Background: Salvage surgery is considered the standard of care for patients with resectable recurrent L/HPSCC. However, salvage surgery achieves durable disease control in only 20% to 50% of patients. The PATHWay study showed that the subgroup that received salvage therapy indicated that adjuvant pembrolizumab could significantly improve PFS compared with placebo, but there is no OS data. This muti-center, prospective, randomized controlled phase II study will evaluate efficacy and safety of PD-1 inhibitors plus chemotherapy as neoadjuvant therapy in recurrent L/HPSCC. **Methods:** Patients who meet the inclusion criteria will be divided into groups according to whether they had received radiotherapy in the past. Arm 1 and Arm 2 are the groups that had not received radiotherapy in the past (N=100), and Arm 3 and Arm 4 are the groups that had received radiotherapy (N=160). Arm 1 and Arm 2 will be randomly assigned at a 1:1 ratio. Arm 1 will receive 3 cycles of pembrolizumab + nab-paclitaxel + cisplatin, followed by surgery. After surgery, patients will be stratified according to the presence or absence of high-risk factors (extranodal extension or positive margins). The high-risk group will receive concurrent chemoradiotherapy + pembrolizumab maintenance therapy (up to 15 cycles), and the low-risk group will receive radiotherapy + pembrolizumab maintenance therapy (up to 15 cycles). Arm 2 will undergo surgery directly, followed by concurrent chemoradiotherapy/radiotherapy. The total radiation dose is 60-66 Gy, 2.0 Gy/fraction for high-risk group and 44-50 Gy, 2.0 Gy/fraction for low-risk group. Similarly, Arm3 and Arm4 will be randomly assigned in a 1:1 ratio. Arm 3 will receive 3 cycles of pembrolizumab + nab-paclitaxel + cisplatin, followed by surgery, and pembrolizumab maintenance treatment after surgery. Arm 4 will be directly given surgery, and after surgery, the doctor will choose observation / re-radiotherapy or chemoradiotherapy. Eligibility criteria will include patients with squamous cell carcinoma of the larynx and hypopharynx confirmed by histology and/or cytology; patients with recurrence of primary tumor or second primary tumor after receiving curative treatment; At least 6 months after the last platinum-containing treatment; ECOG performance status 0-1. Primary end points is 2y-PFS. Secondary end points include ORR, pCR, 3y-OS, safety. Recruitment is ongoing and will continue until 260 patients are enrolled. Clinical trial information: NCT06793761. Research Sponsor: None.

TPS6120 **Poster Session**

A phase II randomized trial of nano-crystalline megestrol acetate for nutritional improvement in postoperative head and neck squamous cell carcinoma undergoing radiotherapy. First Author: Lei Liu, Division of Head & Neck Tumor Multimodality Treatment, Cancer Center, West China Hospital, Sichuan University, Chengdu, China

Background: Head and neck squamous cell carcinoma (HNSCC) patients frequently experience malnutrition and weight loss, exacerbated by cancer cachexia and treatment-related side effects during concurrent radiotherapy. Nano-crystalline megestrol acetate (NMA) improves bioavailability and efficacy compared to conventional formulations, demonstrating enhanced appetite, weight gain, and quality of life (QoL) in cancer cachexia. **Methods:** This randomized, parallel-controlled Phase II trial evaluates the efficacy and safety of NMA in improving nutritional outcomes in HNSCC patients undergoing postoperative CCRT. The study enrolls 96 HNSCC post-surgery patients. Participants are stratified by pre-treatment weight loss (>5% vs. ≤5%) and standard treatment regimen (radiotherapy vs. concurrent chemoradiotherapy), then randomized 1:1 to receive NMA (625 mg/day) plus standard treatment or standard treatment alone. The novel aspects of this design include the use of a nano-crystalline formulation to overcome absorption challenges, allowing effective drug delivery in fasting states. Additionally, comprehensive endpoints assess appetite status (A/CS-12 score), weight changes, lean body mass, inflammatory and nutritional markers, and QoL, providing an integrated evaluation of nutritional and clinical benefits. 12 of planned 96 patients have been enrolled. Clinical trial information: NCT06772428. Research Sponsor: None.

TPS6121 **Poster Session**

A phase 2 clinical trial of preoperative pembrolizumab and chemotherapy followed by adjuvant pembrolizumab in resectable locoregionally recurrent head and neck squamous cell carcinoma. First Author: Kartik Sehgal, Dana-Farber Cancer Institute, Boston, MA

Background: Locoregional recurrence is a major cause of death in squamous cell carcinoma of head & neck (HNSCC) initially treated with curative intent approaches. While salvage surgery may still provide a chance for cure, disease-free survival (DFS) and overall survival (OS) rates remain low for this high-risk population. Neoadjuvant programmed death (PD)-1 inhibitor based approaches have shown promising clinical outcomes compared to upfront surgery in multiple cancer types, e.g. melanoma and non-small cell lung cancer. Recently, a randomized placebo-controlled phase III (KEYNOTE-689) trial evaluating perioperative pembrolizumab in treatment-naïve locally advanced HNSCC met its primary endpoint of event-free survival. Since our trial is targeted at a higher risk patient (pt) population of locoregionally recurrent resectable HNSCC (already managed with curative intent once), we are evaluating the combination of pembrolizumab with chemotherapy in the neoadjuvant setting followed by adjuvant pembrolizumab therapy. **Methods:** This investigator-initiated non-randomized open-label phase 2 clinical trial is enrolling pts with resectable locoregionally recurrent HNSCC, with primary sites in oral cavity, oropharynx, larynx or hypopharynx. Pts must have documented duration of $\geq$6 months from completion of prior curative intent treatment for HNSCC (surgery and/or radiation therapy with/without platinum chemotherapy or cetuximab targeted therapy) to diagnosis of local or locoregional recurrence, and must have resectable disease. Study treatment plan consists of three phases: pre-operative phase, curative intent surgery, and adjuvant phase. In the pre-operative phase, pembrolizumab, cisplatin (or carboplatin) and docetaxel will be administered every 3 weeks for 2 treatment cycles. This will be followed by surgery within 6 weeks of cycle 2 day 1 in pre-operative phase. Adjuvant phase consists of pembrolizumab every 3 weeks until total of 15 cycles, disease recurrence, or intolerable adverse events. The primary endpoint of the trial is major pathological response (mPR) in surgical specimens after pre-operative treatment, defined as $\leq$ 10% residual invasive SCC within the resected primary tumor specimen and all sampled regional lymph nodes. Key secondary endpoints include safety, DFS, and OS. Correlative biomarker analyses are planned as exploratory endpoints. We hypothesize that treatment with pre-operative pembrolizumab and chemotherapy will lead to mPR rate of 15% compared to null hypothesis of 2%. If we find $\geq$2 pts with disease in mPR among 25 evaluable pts, the Simon two-stage design (14 pts in first stage) will have a power of 85.5% with a type I error rate of 7.4%. Safety rule is built in to monitor delays in surgery. 12 of planned 28 pts have been enrolled as of January 2025 (ClinicalTrials.gov NCT05726370). Clinical trial information: NCT05726370. Research Sponsor: Merck.

TPS6122 **Poster Session**

A phase 3 randomized study of ASP-1929 photoimmunotherapy in combination with pembrolizumab versus standard of care in locoregional recurrent head and neck squamous cell carcinoma (HNSCC). First Author: Anastasios Maniakas, The University of Texas MD Anderson Cancer Center, Houston, TX

Background: Recurrent (r) HNSCC carries a poor prognosis and a low survival rate. Locoregional (LR) progression significantly contributes to both morbidity and mortality in these patients, underscoring the importance of LR disease control. The approval of anti-PD-1 inhibitors (pembrolizumab, nivolumab) has expanded treatment options for rHNSCC, but response rates with monotherapy remain low. ASP-1929 photoimmunotherapy (PIT), a novel drug-device treatment, combines cetuximab with a light-activatable dye (IR700) to selectively target EGFR-expressing cancer cells and cause cell membrane destruction and rapid tumor necrosis after activation with local light illumination. Preclinical data have demonstrated that ASP-1929 PIT-mediated tumor necrosis and immunogenic cell death induces antitumor immunity and when combined with anti-PD-1 therapy, synergistically enhances anticancer activity. In an interim evaluation of a multicenter, phase 1/2a, open-label study of 19 patients with metastatic and/or rHNSCC, the combination of ASP-1929 PIT and pembrolizumab showed promising efficacy with a manageable safety profile.[1] The objective of this pivotal phase 3 study is to further evaluate the efficacy and safety of ASP-1929 PIT in combination with pembrolizumab in rHNSCC. **Methods:** The ASP-1929-381is a global phase 3, multi-center, randomized, open-label, controlled study of ASP-1929 PIT in combination with pembrolizumab vs pembrolizumab-based standard of care (SOC) in the first line treatment of LR rHNSCC with no distant metastases. Key inclusion criteria: rHNSCC patients without distant metastases who are candidates for SOC first-line treatment with pembrolizumab + chemotherapy; anti-PD-1 and anti-PD-L1-treatment naïve; at least one lesion accessible for PIT light treatment and RECIST 1.1 measurable; age $\geq$18 years; ECOG score 0 or 1. Key exclusion criteria: diagnosis and/or treatment of additional malignancy within 2 years of randomization; history of $\geq$ grade 3 cetuximab infusion reactions; prior allogeneic tissue/solid organ transplant; life expectancy $<$3 months. The study will enroll ~408 patients and begin with a 2:2:1 randomization into three arms (ASP-1929 PIT 320 mg/m^2 plus pembrolizumab vs ASP-1929 PIT 640 mg/m^2 plus pembrolizumab vs physicians' choice pembrolizumab-based SOC regimen). The SOC arm will include pembrolizumab monotherapy, or pembrolizumab in combination with platinum (cisplatin or carboplatin) + 5-fluorouracil or taxane (paclitaxel or docetaxel). The primary endpoint is overall survival (OS). Key secondary endpoints include complete response rate (CRR) and overall response rate (ORR). The study is currently enrolling in the US, with plans to expand to Taiwan, Japan, and other territories (NCT06699212). 1. Cognetti et al. J Clin Oncol 42, 2024 (suppl 16; abstr 6083). Clinical trial information: NCT06699212. Research Sponsor: Rakuten Medical, Inc.

TPS6123 **Poster Session**

RIBBON-UM: Treatment individualisation by EBV stratification in nasopharyngeal carcinoma (NPC): A phase 2, multi-arm umbrella platform trial. First Author: Melvin L.K. Chua, National Cancer Centre Singapore, Duke-NUS Medical School, Singapore, Singapore

Background: Induction chemotherapy (IC) and chemoradiotherapy (CRT) is the current standard of care (SOC) for locoregionally advanced NPC (LA-NPC). However, CRT alone or CRT and adjuvant chemotherapy (AC) are also first-line SOC options. Plasma Epstein-Barr virus (EBV) DNA is an archetypal biomarker for endemic NPC, and has been assessed for pre-and on-treatment clinical stratification. RIBBON-UM is a phase 2, multi-arm umbrella trial investigating pre- and on-treatment plasma EBV DNA assessment to individualise treatment of patients with LA-NPC. **Methods:** Patients who are newly-diagnosed, biopsy-proven NPC of TNM-stage III-IVA by AJCC/UICC 8th ed and have DETECTABLE EBV DNA pre-treatment are eligible. RIBBON-UM incorporates a 2-tier stratification by TN-status and EBV DNA levels – (1) First, patients will be stratified into low- (LR) and high-risk (HR) based on pre-treatment EBV DNA cut-off 4000 copies/mL AND/OR T4N+ or N2-3 disease; (2) Second, for the HR patients who are assigned to IC (gemcitabine-cisplatin), patients will be further stratified into HR and very-high risk (VHR) depending on their EBV DNA clearance post-3 cycles of IC. RIBBON-UM consists of 3 treatment arms (NCT05517135): Arm I will enroll LR patients (T3N0-1, T4N0 AND EBV DNA $<$4000 copies/mL) to upfront CRT (cisplatin/carboplatin) $\pm$ AC (cisplatin and 5-fluorouracil or capecitabine based on physician's discretion). HR patients (T4N+ OR N2-3 OR EBV DNA $\geq$4,000 copies/mL) will receive upfront IC, and if UNDETECTABLE EBV DNA post-IC, they will be assigned to Arm II – CRT $\pm$ AC. For patients with a DETECTABLE EBV DNA post-IC (VHR), these patients are assigned to Arm III – a single-arm, phase 2 trial investigating experimental AC (NCT06093061), embedded within the RIBBON-UM protocol. Currently, VHR patients enrolled into Arm III will receive CRT + 1-y combined tislelizumab (200 mg IV 3-weekly) and metronomic capecitabine at 650 mg/m^2 bidaily (RIBBON-LA-01, NCT06093061) or 1-y metronomic capecitabine (if they decline). Statistical plan of RIBBON-UM consists of 2 analyses: (1) we will evaluate if our risk-stratification strategy by TN-status and pre- and on-treatment EBV DNA levels improves 2-y disease-free survival (DFS) rate of patients with LA-NPC from 65% (historical) to 75% for the modular platform trial; (2) we hypothesise that AC intensification (Arm III) will improve 2-y DFS of the VHR cohort from 60% (historical) to 75%. 133 and 62 patients are required to test these hypotheses at 5% 1-sided significance level with 80% power, respectively. The risk-stratified treatment individualisation and AC intensification strategies will be deemed successful if 96 of 133 (from Arms I-III) and 44 of 62 patients (Arm III) remain disease-free at 2 y. From Nov 2022 to Jan 2025, we have enrolled 93 and 51 patients into RIBBON-UM and RIBBON-LA-01, respectively. We expect enrolment to RIBBON-UM to complete by Jun 2025. Clinical trial information: NCT05517135, NCT06093061. Research Sponsor: BeiGene; NMRC Singapore Open-Fund Large Collaborative Grant; NMRC Singapore Clinical Trials Grant.

TPS6124 **Poster Session**

A phase 2 clinical trial of adjuvant ado-trastuzumab emtansine (T-DM1) for patients with HER2-positive salivary gland cancer. First Author: Glenn J. Hanna, Department of Medical Oncology, Dana-Farber Cancer Institute, Boston, MA

Background: Salivary gland carcinomas (SGCs) represent a rare, but unique group of histologically and molecularly distinct head and neck cancers. Despite aggressive locoregional management with surgery and adjuvant (chemo)radiation, distant metastatic spread is not infrequent, particularly among high-risk subtypes like salivary duct carcinoma. Strong surface expression of HER2 has been observed in 60-80% of high-risk SGCs. This is the first clinical trial exploring the early addition of concurrent and adjuvant HER2-directed therapy to improve both locoregional and distant disease control rates in a HER2-overexpressing high-risk SGC population. **Methods:** This phase 2 open-label, clinical trial (NCT04620187) is enrolling patients (pts) with newly diagnosed SGC of any histology arising in the head and neck whose tumor overexpresses HER2 (2-3+ by IHC expression or *ERBB2* amplification/select mutations) treated with upfront definitive surgery. Pts must have adequate organ and cardiac function, with stage II-IVB (AJCC 2017 8th ed.) disease (stage II requires positive margins). Enrollment following surgery is permitted. Once registered post-op, adjuvant T-DM1 (3.6 mg/kg IV every 21-days) starts within 3-7 weeks of surgery prior to radiation (RT). Four to 8 weeks post-op pts receive standard RT (photon or particle) with concurrent weekly cisplatin (40 mg/m^2) for 6-weeks. T-DM1 continues every 3-weeks during RT and up to 1-year following surgery. The primary endpoint is 2-year disease-free survival (DFS). Secondary endpoints include safety and tolerability, overall survival, distant metastatic-free survival, and correlation between HER2 expression and outcomes. We hypothesize that treatment with adjuvant T-DM1 will improve historical 2-year DFS from 60 to 72%. When 24 DFS events are observed among N=47 pts who are eligible and receive protocol treatment, the design has 80% power to detect a 35% reduction in the DFS hazard to 0.1660 (using a one-sided 10% type I error rate; Wald's test). The study opened to accrual in October 2020 and is now accruing at four academic medical centers throughout the U.S. Sixteen of 47 planned subjects have been enrolled as of December 2024. Clinical trial information: NCT04620187. Research Sponsor: Genentech.

6500 Oral Abstract Session

Ropeginterferon alfa-2b versus anagrelide for the treatment of essential thrombocythemia: Topline results of the phase 3 SURPASS-ET trial. First Author: Ruben A. Mesa, Atrium Health Wake Forest Baptist Comprehensive Cancer Center, Wake Forest University School of Medicine, Winston-Salem, NC

Background: *BCR::ABL1*-negative myeloproliferative neoplasms (MPNs), including essential thrombocythemia (ET), polycythemia vera (PV) and myelofibrosis (MF). No new treatments have been approved for ET in the US since anagrelide in 1997. Ropeginterferon alfa-2b (ropeg) is an anti-clonal interferon-based therapy approved by the FDA and globally for PV, providing the rationale for evaluation in ET and other MPNs. **Methods:** SURPASS ET is an open-label, multicenter, Phase III trial comparing ropeg with anagrelide over 12 months in patients with ET who were hydroxyurea-resistant or-intolerant. A total of 174 patients were randomized in a 1:1 ratio to receive ropeg or anagrelide. Ropeg was administered at 250 mcg at Week 0 titrating to 350 mcg at Week 2 and 500 mcg from Week 4 if tolerated. The primary endpoint was the rate of response, as defined by the Modified European LeukemiaNet response criteria, at both Months 9 and 12. Secondary endpoint assessments included *JAK2*V617F allele burden, MPN-associated symptoms, thromboembolic events, spleen size, and safety. **Results:** Baseline patient characteristics were balanced across treatment arms (Table 1). The primary endpoint was achieved in 42.9% of patients in the ropeg arm versus 6.0% in the anagrelide arm (p=0.0001). Ropeg showed response improvements by each parameter: 1) Platelets $\leq 400 \times 10^9$/L and white blood cells $< 9.5 \times 10^9$/L: 56.0% vs. 6.0%. 2) Improvement or stabilization of splenomegaly: 87.9% vs. 54.2%. 3) Symptom improvement or stabilization: 71.4% vs. 33.7%. 4) Absence of hemorrhagic/thrombotic events: 84.6% vs. 51.8%. ET-related major thrombotic and cardiovascular events occurred in 1 (1.1%), and 0 patients in the ropeg arm vs. 7 (8.8%) and 6 (7.5%) patients, respectively, in the anagrelide arm. Mean *JAK2*V617F allelic burden decreased from 33.7% at baseline to 25.3% at 12 months (ropeg arm) vs. 39.7% to 37.3% (anagrelide arm). Ropeg showed lower rate of adverse event (AE)-related discontinuation (5.5% vs.18.8%) and treatment-related serious AEs (2.2% vs. 10.0%). **Conclusions:** Ropeg showed superior efficacy and safety compared to anagrelide as second-line therapy for ET. It represents a potential new therapeutic option for ET. Clinical trial information: NCT04285086. Research Sponsor: PharmaEssentia Corporation.

Patient demographics and baseline characteristics.

	Ropeg (n*=91)	Anagrelide (n=83)	Total (N=174)
Age, y	61 (21-80)	64 (20-83)	63 (20-83)
Race, x (%)			
Caucasian	5	2	7
Asian	86	81	167
Gender, x (%)			
Female	47 (52)	44 (53)	91 (52)
Male	44 (48)	39 (47)	83 (48)
Total symptom score at baseline (MPN-SAF)	9 (0, 71)	9 (0, 74)	9 (0. 74)
Spleen length by ultrasound, cm	13.1 (5.2-16.3)	15.2 (9.2-23.4)	13.9 (5.2-23.4)
Leukocytes, $x10^9$/L	11.4 (7.2-47.7)	11.6 (7.2-75.9)	11.5 (7.2-75.9)
Platelets, $x10^9$/L	942 (384-2132)	870 (406-4199)	925 (397-4199)
***JAK2*V617F, x (%)**	72 (79)	70 (84)	142 (82)
***CALR* exon 9, x (%)**	11 (12)	10 (12)	21 (12)

*n (%) presented for categorical variables. Median (range) for continuous variables.

6501 Oral Abstract Session

Primary endpoint results of the phase 3b ASC4START trial of asciminib (ASC) vs nilotinib (NIL) in newly diagnosed chronic phase chronic myeloid leukemia (CML-CP): Time to treatment discontinuation due to adverse events (TTDAE). First Author: Andreas Hochhaus, Klinik für Innere Medizin II, Universitätsklinikum Jena, Jena, Germany

Background: ASC, the first BCR::ABL1 inhibitor to Specifically Target the ABL Myristoyl Pocket, recently received FDA Accelerated Approval for newly diagnosed CML-CP based on major molecular response (MMR) rates in the ASC4FIRST trial (NCT04971226). We present results from ASC4START (NCT05456191), with the primary objective of assessing the tolerability of ASC vs second-generation tyrosine kinase inhibitor NIL in patients (pts) with newly diagnosed CML-CP. **Methods:** Adults were randomized 1:1 to receive ASC 80 mg once daily or NIL 300 mg twice daily, stratified by ELTS risk category. The primary endpoint is TTDAE. Events included AEs leading to treatment (tx) discontinuation and deaths due to AEs. Secondary endpoints include molecular response and safety. **Results:** Pts were recruited by 120 participating sites across 24 countries and randomized to ASC (n=284) or NIL (n=284). Two pts who did not receive NIL were excluded from safety analyses. Median follow-up was 9.7 mo. At cutoff (Sep 3, 2024), 10.9% and 17.3% of pts discontinued ASC and NIL, respectively, most commonly due AEs (4.9% vs 11.6%) and unsatisfactory therapeutic effect (2.5% vs 2.8%). The study met its primary endpoint, showing statistically significant difference in TTDAE in favor of ASC with a cause-specific hazard ratio of 0.45 (95% CI, 0.25-0.81; *P*=.004). Fewer pts discontinued due to AEs with ASC (16/284 [5.6%]) vs NIL (34/282 [12.1%]). There were 3 deaths on study due to AEs (ASC: cardiac arrest and suicide, n=1 each; NIL: cardiac arrest, n=1). Median duration of exposure was 39.1 wk with ASC vs 38.0 wk with NIL. Mean relative dose intensity was 94.8% vs 92.6%, respectively. Any-grade AEs occurred in 80.3% of pts with ASC vs 86.5% with NIL. Grade $\geq$3 AEs occurred in 25.0% and 31.9% of pts, respectively. AEs leading to dose adjustment/interruption occurred in 24.3% of pts with ASC vs 30.1% with NIL. Most frequent any-grade AEs ($\geq$10%) with ASC vs NIL were thrombocytopenia (15.1% vs 13.8%), headache (10.2% vs 13.1%), myalgia (10.2% vs 8.2%), rash (8.5% vs 16.3%) and increased alanine aminotransferase (3.2% vs 12.4%). AEs of special interest included arterial occlusive events (0.7% vs 2.1%), acute pancreatitis (clinical events; 0.4% vs 2.5%), and hepatotoxicity (including laboratory terms; 8.1% vs 24.8%). *BCR::ABL1*^{IS} $\leq$10% (89.8% vs 82.0%), *BCR::ABL1*^{IS} $\leq$1% (69.0% vs 52.5%), MMR (22.9% vs 10.2%), MR^4 (4.6% vs 1.1%), and MR$^{4.5}$ (2.5% vs 0.4%) rates by wk 12 were higher with ASC vs NIL. **Conclusions:** The study met the primary endpoint with ASC showing significantly superior tolerability vs NIL based on TTDAE. The study is ongoing with additional analyses planned for tolerability and efficacy. The findings further support the potential for ASC to be a preferred therapy for newly diagnosed CML-CP, allowing more pts to meet tx goals without requiring tx switch. Clinical trial information: NCT05456191. Research Sponsor: Novartis Pharma AG.

6502 Oral Abstract Session

Efficacy and safety of pivekimab sunirine (PVEK) in patients (pts) with blastic plasmacytoid dendritic cell neoplasm (BPDCN) in the CADENZA study. First Author: Naveen Pemmaraju, The University of Texas MD Anderson Cancer Center, Houston, TX

Background: BPDCN is a rare, clinically aggressive hematological malignancy primarily involving the skin, bone marrow, and lymph nodes. CD123 (IL-3Rα) is highly overexpressed on the surface of all BPDCN blasts making it an ideal target for novel immunochemotherapy. PVEK is a first-in-class antibody-drug conjugate comprising a high-affinity CD123 antibody, cleavable linker, and an indolinobenzodiazepine pseudodimer payload. Here, we present the primary analysis of efficacy and safety from CADENZA. **Methods:** In the open-label, multicenter, phase 1/2 CADENZA study, adults with BPDCN received PVEK monotherapy intravenously on day 1 of a 21-day cycle, as a <30-min outpatient infusion. Primary endpoint was the rate of composite complete response, defined as complete response (CR) + clinical CR (CR with minimal skin abnormality [CRc]) in frontline (1L) pts. Key secondary endpoints were duration of CR + CRc, median overall survival (OS), overall response rate (ORR), % of pts who were bridged to stem cell transplantation (SCT) after PVEK, and safety and tolerability. **Results:** At primary analysis (data cutoff: October 2, 2024), CADENZA enrolled 84 pts with CD123-positive BPDCN who received PVEK at the recommended phase 2 dose (RP2D) of 0.045 mg/kg every 21 days, including 33 pts with 1L BPDCN (median age, 73.0 [range, 48-84]; $\geq$65 years, 91%; male, 82%) and 51 pts with relapsed/refractory (R/R) BPDCN (median age, 69.0 [range, 19-85]; $\geq$65 years, 59%; male, 82%). Pts with R/R BPDCN had received 1-3 prior systemic therapies; 57% had prior tagraxofusp. Median follow-up was 21.5 mo for 1L pts and 24.1 mo for the R/R group. Among 1L pts, CR + CRc was 70% (95% CI, 51.3-84.4) and median duration of CR + CRc was 9.8 months (mo) (95% CI, 4.6-Not Reached [NR]); ORR was 85%. Median OS was 16.6 mo (95% CI, 11.4-NR). Among 13 (39%) 1L pts bridged to SCT, CR + CRc was 92% (95% CI, 64.0-99.8) and median OS was NR. In the R/R group, CR + CRc was 14% and median duration of CR + CRc was 9.2 mo (95% CI, 2.4-NR); ORR was 35%. Median OS was 5.8 mo (95% CI, 3.9-8.4) and 12% of pts bridged to SCT. Median (IQR) PVEK treatment exposure was 5 (4-9) cycles for the 1L group and 3 (2-5) cycles for the R/R group. Safety was assessed in all 84 pts. The most common treatment-emergent adverse event (TEAE) was peripheral edema (any grade, 54%; grade $\geq$3, 12%). TEAEs led to discontinuation in 9% and 7% of pts with 1L and R/R BPDCN, respectively. No capillary leak syndrome (CLS) events or treatment-related deaths were reported, and 2 (2%) pts experienced veno-occlusive disease of grades 2 and 3 after cycles 4 and 8, respectively, which resolved. **Conclusions:** PVEK treatment demonstrated promising efficacy, with high and durable CR + CRc responses. PVEK was tolerable at the RP2D. The safety profile was manageable, with no CLS events. These results support PVEK as a potential new treatment option for adult pts with BPDCN. Clinical trial information: NCT03386513. Research Sponsor: AbbVie.

6503 Oral Abstract Session

Phase II study of cladribine, low-dose cytarabine, and venetoclax, alternating with azacitidine and venetoclax, in higher-risk chronic myelomonocytic leukemia and myelodysplastic syndromes. First Author: Guillermo Montalban-Bravo, The University of Texas MD Anderson Cancer Center, Houston, TX

Background: Responses to hypomethylating agents (HMAs) in patients (pts) with higher-risk myelodysplastic syndromes (HR-MDS) and chronic myelomonocytic leukemia (CMML) are short-lived, with a high risk of transformation to acute myeloid leukemia (AML). Cladribine (CDA) induces monocyte apoptosis and is active in AML when combined with low dose cytarabine (LDAC) and venetoclax (VEN). We aimed to evaluate the safety and activity of CDA, LDAC and VEN in HR-MDS and CMML. **Methods:** We designed a phase II clinical trial (NCT05365035) for pts with newly diagnosed (ND) or relapsed/refractory (R/R) HR-MDS or CMML. Induction consisted of CDA 5 mg/m^2 daily IV on days 1-3, LDAC 20 mg s.c bid days 1-5 and VEN 400 mg daily days 1-5 followed by azacitidine 75 mg/m^2 daily days 1-7 with VEN 400 mg daily days 1-7 or CDA 5 mg/m^2 days 1-3, LDAC 20 mg s.c bid days 1-5 and VEN 400 mg days 1-5 alternating every 2 cycles. The primary end point was to evaluate safety and efficacy of the combination. **Results:** Between 10/2022 and 01/2025, 50 pts have been treated (19 [38%] ND and 31 [62%] R/R). Thirty pts (60%) had MDS, and 20 (40%) had CMML. Thirty-seven (74%) pts had high/very high IPSS-Molecular risk and 5 (10%, 4 R/R, 1 ND) pts had biallelic *TP53* (*biTP53*) loss. The median age was 75 years (range 52-83). Among R/R pts, the median number of prior therapies was 1 (range 1-4) with 6 (19%) having received prior VEN treatment and 2 (4%) having undergone allogeneic stem cell transplant (SCT). The median number of cycles received was 2 (range 1-15). The 4- and 8-week mortality was 2% and 4%, respectively. Overall, the combination was well tolerated with thrombocytopenia (n=17, 35%), febrile neutropenia (n=6, 13%) and neutropenia (n=5, 10%) being the most common grade $\geq$3 adverse events. Among the 48 pts with evaluable responses, the overall response rate (ORR) based on the IWG 2006 response criteria was 43% (complete response [CR] rate of 13% [n=4]) in R/R pts and 72% (CR rate of 39% [n=7]) in ND pts. Based on the IWG 2023 response criteria, the ORR was 40% (n=12, CR: 5 [17%]) and 72% (n=13, CR: 10 [56%]) in R/R and ND pts, respectively. Median number of cycles to best response was 1 (range 1-5). Among responders, 85% and 73% of pts demonstrated neutrophil ($>1 \times 10^9$/L) and platelet ($>100 \times 10^9$/L) recovery after cycle 1 after a median of 27 and 21 days, respectively. Eight (16%) pts required dose reductions due to cytopenias. Fifteen (30%) pts underwent subsequent SCT. After a median follow up of 15.1 months, the median overall survival (OS) was 5.8 months and not reached in R/R and ND pts, respectively. The median leukemia-free survival was 4.1 months and not reached in R/R and ND pts, respectively. Among R/R pts, *biTP53* was associated with shorter OS (3.1 vs 12.3 months, p=0.0344). **Conclusions:** CDA, LDAC and VEN is safe in pts with HR-MDS and CMML, demonstrating promising results in ND pts. Clinical trial information: NCT05365035. Research Sponsor: None.

6504 Oral Abstract Session

An all-oral regimen of decitabine-cedazuridine (DEC-C) plus venetoclax (VEN) in patients (pts) with newly diagnosed acute myeloid leukemia (AML) ineligible for intensive induction chemotherapy: Results from a phase 2 cohort of 101 pts. First Author: Amer Methqal Zeidan, Yale University School of Medicine, New Haven, CT

Background: In pts with AML aged ≥75 years and ineligible for induction chemotherapy, the combination of the Bcl-2 inhibitor VEN plus azacitidine (AZA) was approved based on the Phase 3 VIALE-A trial (complete remission [CR] rate, 36.7%; median CR duration, 17.5 months; median overall survival [OS], 14.7 months). However, monthly seven-day clinic injections of parenteral AZA until progression impose a significant burden on pts. Further, multiple adjusted comparisons have demonstrated similar clinical efficacy between AZA and decitabine. Oral DEC-C (decitabine 35 mg and cedazuridine 100 mg) has equivalent pharmacokinetic (PK) area under the curve exposure to intravenous decitabine. This Phase 1/2 trial was designed to evaluate the all-oral regimen of DEC-C plus VEN in pts with AML aged ≥75 years or with comorbidities precluding first-line intensive induction chemotherapy (NCT04657081). Here, we report results from the pivotal Phase 2 part of the trial. **Methods:** Eligible pts received oral DEC-C on Days 1–5 plus VEN 400 mg daily in 28-day cycles after Cycle 1 VEN ramp up (100 mg Day 1, 200 mg Day 2, 400 mg Day ≥3). Bone marrow examination during Cycle 1 was optional, with VEN and/or DEC-C dose adjustments based on response and count recovery. The primary endpoint was CR rate, based on European LeukemiaNet (ELN) 2017 response criteria. The sample size was calculated based on the lower limit of the 95% confidence interval (CI) of the target CR rate exceeding the clinically meaningful historical rate of 17.9%, with a one-sided α of 0.025, which required ~100 pts to ensure ≥95% power. **Results:** As of September 30, 2024, 101 pts were enrolled and had completed a median of 4 (range, 1–15) cycles. Median age was 78 years. ELN 2017 classification was favorable, intermediate, and adverse in 31.7%, 33.7%, and 29.7% of pts, respectively. Median follow-up was 11.2 months. The CR and CR/CR with incomplete hematologic recovery rates were 46.5% (95% CI, 36.5%–56.7%) and 63.4% (95% CI, 53.2%–72.7%), respectively. Median time to CR was 2.4 months. Median CR duration was not reached; among pts who achieved CR, 80.0% remained so at 6 months and 75.3% at 12 months. Median OS was 15.5 (95% CI, 7.6–not estimable) months. Grade ≥3 treatment-emergent adverse events were reported in 98.0% of pts, most commonly febrile neutropenia (49.5%), anemia (38.6%), and neutropenia (35.6%). The 30- and 60-day mortality rates were 3.0% and 9.9%, respectively. PK data confirmed no drug-drug interactions between oral DEC-C and VEN. **Conclusions:** The all-oral regimen of DEC-C plus VEN resulted in comparable safety, response, and survival rates to parenteral AZA plus VEN in pts with newly diagnosed AML ineligible for intensive induction chemotherapy. These data support the potential use of DEC-C plus VEN as a treatment option for these pts. Clinical trial information: NCT04657081. Research Sponsor: Taiho Oncology, Inc.

6505 Oral Abstract Session

Phase 1b/2 study of lisaftoclax (APG-2575) combined with azacitidine (AZA) in patients (pts) with treatment-naïve (TN) or prior venetoclax (VEN)-exposed myeloid malignancies. First Author: Michael Francis Leahy, Royal Perth Hospital, Perth, Western Australia, Australia

Background: Lisaftoclax (LISA), an investigational, orally active small molecule BCL-2 inhibitor, has shown enhanced treatment responses when combined with AZA in preclinical and clinical studies. We evaluated the safety and efficacy of LISA plus AZA in pts with myeloid malignancies. **Methods:** This open-label, multicenter study enrolled pts with TN or relapsed/refractory (R/R) AML/MPAL or high-risk (HR) MDS/CMML. Prior VEN treatment was permitted. In Part 1, LISA was administered at escalating doses (200, 400, 600, or 800 mg once daily [QD]) and combined with AZA to assess DLTs and determine the MTD. Part 2 evaluated the safety and efficacy of LISA 200, 400, or 600 mg QD over 28 or 14 days of 28-day cycles, combined with AZA at the standard dose (75 mg/m^2 on days 1-7 or 1-5 and 8-9 of each cycle). Safety and efficacy assessments were conducted for all pts receiving at least one dose of LISA. **Results:** As of January 6, 2025, 97 pts were enrolled, with a median treatment duration of 2 (0-16) cycles. Pt distribution included: 49 R/R AML; 20 R/R HR-MDS; 14 TN HR-MDS; 7 TN AML; 4 R/R CMML; 2 R/R MPAL; and 1 TN CMML. The median (range) age was 71 (23-89) years, with 59.8% of pts being male and 73.2% having an ECOG PS ≥ 1. Pts with R/R AML/MPAL D1-28, D1-14, and MDS/CMML had median prior therapies of 2.0 (1.0-8.0), 1.0 (1.0-3.0), and 1.0 (1.0-2.0), respectively, with prior VEN exposure in 46.2% (12/26), 50.0% (5/10), and 14.3% (2/14), respectively. There were no DLTs, and the MTD was not reached. The RP2D for TN HR-MDS was AZA (standard dose) + LISA 600 mg on days 1-14; for TN AML, it was AZA (standard dose) + LISA 600 mg on days 1-28. Common grade 3/4 TEAEs included neutropenia (40%), febrile neutropenia (31%), and thrombocytopenia (22%). Others included sepsis (9%), pneumonia (7%), and lower-respiratory-tract infections (3%). Febrile neutropenia was the most frequently reported SAE (26.8%). Only 3% of pts had neutropenia leading to a dose reduction of LISA, with no 60-day mortality reported. In 14 efficacy-evaluable pts with TN-MDS/CMML, the ORR was 64%, with CR and marrow CR achieved by 29% and 36% of pts, respectively; no PRs were observed. In pts with R/R AML treated with LISA for either 28 (n = 18) or 14 days (n = 8) of repeated 28-day cycles, the ORRs were 39% and 50%, respectively, including CR rates of 28% and 37.5%, respectively. In 20 pts refractory to VEN, the ORR was 17% (3/18) in pts with AML/MPAL and 50% (1/2) in pts with HR-MDS; 11% of pts with AML/MPAL and 50% with MDS had bone marrow blasts < 5%. **Conclusions:** LISA at different dose regimens combined with AZA provides promising treatment options for pts with HR-MDS or AML. No DLTs occurred. The MTD was not reached. The combination was efficacious and well tolerated, with few dose modifications and low infection rates, supporting further clinical development of this regimen in these populations (APG2575AU101; NCT04964518). Clinical trial information: NCT04964518. Research Sponsor: Ascentage Pharma Group Corp Ltd. (Hong Kong).

6506 Oral Abstract Session

Ziftomenib in relapsed/refractory (R/R) *NPM1*-mutant acute myeloid leukemia (AML): Phase 1b/2 clinical activity and safety results from the pivotal KOMET-001 study. First Author: Eunice S. Wang, Roswell Park Comprehensive Cancer Center, Buffalo, NY

Background: *NPM1*-m drives leukemogenesis in ~30% of AML. Despite current risk stratification, nearly half will have R/R disease within a year, after which outcomes are poor with <10% complete response following chemotherapy. Ziftomenib – a potent, highly selective, oral, investigational menin inhibitor – has shown clinical activity as monotherapy and in combination for adults with R/R *NPM1*-m and *KMT2A*-r AML, with 600 mg once-daily (QD) as the recommended phase 2 monotherapy dose for *NPM1*-m. Here we present the primary analysis for *NPM1*-m patients (pts) treated with ziftomenib 600 mg QD in the pivotal KOMET-001 study. **Methods:** KOMET-001 (NCT04067336) is a multicenter, open-label phase 1/2 study of ziftomenib in adults with R/R AML. In phase 2, pts with *NPM1*-m R/R AML received ziftomenib 600 mg QD. Phase 2 primary endpoint: complete remission with full/partial hematologic recovery (CR/CRh); key secondary endpoints: composite complete remission (CRc), durations of CR/CRh and CRc, and safety. The analyses below include *NPM1*-m pts pooled from phase 1b/2. **Results:** The phase 2 primary endpoint was met (p=0.0058). As of 20 Dec 2024, 112 pts were enrolled (51% US/Canada, 49% Europe/UK) in phase 1b/2 and treated with ziftomenib 600 mg QD, with a median follow-up of 4.2 months. Median age was 69 yrs (range 22–86), 56% female, 83% ECOG PS 0–1, median of 2 prior therapies (range 1–7), including 60% prior venetoclax (VEN) and 23% prior transplant. CR/CRh rate in all phase 1b/2 pts was 25% (28/112; 95% CI 17–34) and overall response rate was 35% (39/112; 95% CI 26–44). In phase 2 pts, 23% (21/92; 95% CI 15–33) achieved CR/CRh (Table), with 67% (10/15) MRD negativity among CR/CRh responders tested (local). Comparable CR/CRh rates were observed in both VEN-naïve and exposed pts (21% vs. 24%). Ziftomenib was well tolerated with 3% (3/112) discontinuing due to treatment-related adverse events (TRAEs). 40% (45/112) of pts had Grade (Gr) ≥3 TRAEs, including 13% differentiation syndrome (all Gr3), ≤5% each anemia, febrile neutropenia and thrombocytopenia, and 2% QTc prolongation (Gr3). Updated clinical activity and safety data will be presented. **Conclusions:** In the pivotal KOMET-001, the phase 2 primary endpoint was met: Ziftomenib achieved deep and durable responses in R/R *NPM1*-m AML, regardless of prior VEN. Ziftomenib was well tolerated with limited myelosuppression and only 3% ziftomenib-related discontinuations. Taken together, these data support the potential use of ziftomenib monotherapy as a new treatment option for R/R *NPM1*-m AML. Clinical trial information: NCT04067336. Research Sponsor: Kura Oncology, Inc.

Response, n (%)	Phase 2 600 mg QD N=92	Phase 1b/2 600 mg QD N=112
CR	13 (14)	20 (18)
CR/CRh	21 (23)	28 (25)
CRc	24 (26)	32 (29)
Median duration, months (95% CI)		
CR/CRh	3.7 (1.9–NE)	3.7 (1.9–7.7)
CRc	4.6 (2.8–11.4)	5.1 (2.8–8.1)
Restricted mean duration, months (95% CI)		
CR/CRh	4.3 (3.1–5.6)	5.2 (3.6–6.7)
CRc	5.9 (4.0–7.7)	6.4 (4.6–8.1)

6507 Oral Abstract Session

γ9δ2 T-cell activation (γδTCA) with ICT01 combined with azacitidine-venetoclax (AV) for older/unfit adults with newly diagnosed (ND) AML: Preliminary efficacy and dose selection in phase 1/2 study EVICTION. First Author: Pierre Yves Dumas, CHU, Bordeaux, France

Background: AML impairs immunosurveillance bypassing target recognition and subsequent cytotoxic T cell responses. Immunomodulatory and cytotoxic effects of AV and γδTCA with ICT01 have shown synergistic efficacy in an in-vivo AML model with adoptive γδTC transfer. ICT01 is a first-in-class humanized, Fc-disabled anti-butyrophilin 3A mAb selectively inducing γδTCA for direct anti-leukemic cytotoxicity and IFNγ/TNFα release. γδTC are known to drive anti-leukemic efficacy in the post-transplant setting and intratumor presence of γδTCs is prognostic. γδTCA by ICT01 was dose dependent, safe, and tolerable. Here, ICT01-mediated γδTCA added to AV has been investigated in a dose-optimization Phase 1/2 study. **Methods:** ND-AML pts ≥ 75 years old or unfit to receive intensive chemotherapy were randomized 1:1 to AV plus either 10 mg (ICT01^{LOW}) or 75 mg ICT01 (ICT01^{HIGH}) Q4W. We assessed cytogenetics, NGS, pharmacodynamics (PD) in peripheral blood (PB) and bone marrow (BM), safety, and anti-tumor efficacy. **Results:** Of 45 pts randomized, 33 had conclusive disease assessments as of 20-Jan-2025, median age was 75 yrs (range 51–87), the minority (30%) had favorable risk (ELN 2024) and 55% had abnormalities of uncertain risk, some of which are suggestive of a poor response to AV. Median number of BM blasts at diagnosis was 38% (range 5–98%). No DLT was reported, and all pts had at least one adverse event; 30-day mortality was 3%. Grade 3/4 febrile neutropenia was seen in 19 (42%) and neutropenia in 32 pts (71%). ICT01 reproducibly induced rapid γδTCA in PB and BM, followed by increased serum IFNγ/TNFα reflective of downstream immune-cell effects. γδTC counts rapidly dropped in both PB and BM upon first ICT01 dosing and returned to near baseline values during ICT01^{LOW} dosing but became almost undetectable during continued ICT01^{HIGH} dosing. ICT01^{LOW} exhibited a favorable benefit–risk profile with 90% CR/CRi (71% CR, 19% CRi) and lower rates of neutropenia/febrile neutropenia than both ICT01^{HIGH} and published data, while PD effects seen with ICT01^{HIGH} suggestive of activation-induced γδTC death upon repeated dosing were associated with less efficacy (75% CR/CRi [42% CR, 33% CRi]). Notably, response rates were high (particularly with ICT01^{LOW}) both in pts with adverse (CR 40% / CR/CRi 60% for *TP53/CK*; N=10), intermediate/uncertain (CR 47% / CR/CRi 95% for *MECOMr, NRAS, ASXL1*, *JAK2*, *DNMT3A*, *SF3B1*, *U2AF1*, *SRSF2*, *RUNX1*, *STAG2*; N=19) and favorable (CR 80% / CR/CRi 90% for *NPM1*, *IDH1/2*; N=10) risk mutations per ELN 2024. **Conclusions:** For AV combination, the recommended Phase 2 dose is 10 mg ICT01 Q4W. Both ICT01 regimens were safe and very well tolerated and generated very high CR and CR/CRi rates in older/unfit ND-AML pts. The high response rates seen in adverse risk pts warrant further clinical investigation. Clinical trial information: NCT04243499. Research Sponsor: ImCheck Therapeutics.

6508 Oral Abstract Session

Long-term outcomes of patients surviving beyond 2 years post–allogeneic stem cell transplantation. First Author: Nihar Desai, Princess Margaret Hospital, Toronto, ON, Canada

Background: Advances in hematopoietic stem cell transplantation (HSCT) have been driven by progress in supportive care, conditioning regimens, and graft-versus-host disease (GvHD) prophylaxis. Post-transplant morbidity and mortality are most pronounced in the first two years after HCT. Long-term outcomes have been previously described in a CIBMTR study, which reported a 10-year survival of 85% for those who survived the first two years. Post-transplant cyclophosphamide (PTCy) has revolutionized transplant outcomes. However, its impact on long-term survival remains unclear. **Methods:** We included patients undergoing HSCT from Jan 2015 to Dec 2023 who were alive and without relapse two years after HSCT. We aimed to compare long-term outcomes in patients receiving PTCy-based GvHD prophylaxis to previous conventional GvHD prophylaxis strategies. Overall survival (OS) was calculated using the Kaplan–Meier method. The incidence of non-relapse mortality (NRM) and relapse were estimated using Fine & Gray's competing risk analysis. **Results:** Of the 1,401 patients, we included 571 patients alive and relapse-free two years after HCT (Table 1). The median follow-up post-HSCT was 4.8 years (3-5.9). The 5-year OS was 91% (95% CI: 88 – 94). The causes of death were: disease recurrence (17, 3%), infection (8, 1.4%), GvHD (4, 0.7%), second primary malignancies (3, 0.5%), and cardiac complications (3, 0.5%). The use of PTCy was associated with improved OS, 91.7% (95% CI: 88 – 95) vs. 88.7% (95% CI: 81 – 93), p=0.05. NRM at 5 years was 4.9% (95% CI: 3 – 7) and was significantly lower in patients receiving PTCy (2.9 % vs. 10.4%, p<0.001). Relapse risk at 5 years was 9.2% (7 – 13) and was not significantly different between the groups, 10.6% in recipients of PTCy vs. 5.6%, p=0.06. On MVA accounting for confounding variables, PTCy was independently associated with improved OS [HR: 0.46 (0.2 – 0.8), p=0.01], and NRM [HR: 0.23 (0.1 – 0.5), p<0.001]. Age >60 years at HSCT was associated with increased mortality [HR: 2.8 (1.5 – 5.3), p=0.001]. The development of chronic GvHD was protective against relapse [HR: 0.5 (0.3 – 0.9), p=0.04] (Table 1). **Conclusions:** The long-term outcomes for patients alive and relapse-free 2 years after HSCT are excellent. Relapse remained the most common cause of death even after 2 years. PTCy-based GvHD prophylaxis was associated with improved NRM and OS without an impact on disease relapse. Research Sponsor: None.

Baseline characteristics and multivariable analysis.

	PTCy	Others	p
Age, years, median (IQR)	57 (40 – 64)	52 (37 – 62)	0.04
Diagnosis, n (%)			
AML	231 (54)	60 (43)	
MDS	57 (13)	19 (14)	0.78
MF	46 (11)	5 (4)	
Donors, n (%)			
HLA-matched sibling	90 (21)	69 (49)	<0.01
HLA-matched unrelated	220 (51)	60 (43)	
HLA-mismatched unrelated	38 (9)	8 (7)	
Haploidentical	84 (19)	2 (1)	
GVHD prophylaxis, n (%)			
Cnl + MTX	-	43 (31)	
ATG + Cnl + MTX	-	73 (52)	-
Alemtuzumab + Cnl	-	24 (17)	
PTCy-ATG-Cnl	383 (89)	-	
PTCy- Cnl – MMF	48 (11)	-	
Cryopreservation, n (%)	100 (23)	52 (36)	0.004
CD34⁺ x 10^6/kg, median (IQR)	7.2 (6 – 8.1)	7.3 (5.9 – 7.6)	0.76
MVA			
OS	**HR**	**95% CI**	**p**
Age >60 years (vs <60 years)	2.84	1.5 – 5.3	0.001
PTCy (vs non-PTCy)	0.45	0.2 – 0.8	0.01
NRM			
Age more than 60 years (vs <60 years)	2.50	1 – 6.2	0.04
PTCy (vs non-PTCy)	0.23	0.1 – 0.5	<0.01
Relapse			
Age >60 years (vs <60 years)	1.47	0.7 – 3.0	0.29
PTCy (vs non-PTCy)	1.54	0.4 – 5.4	0.49

AML: Acute myeloid leukemia; ATG: anti thymocyte globulin; BM: bone marrow; Cnl: calcineurin inhibitor; MDS: Myelodysplastic syndrome; MF: myelofibrosis; MTX: methotrexate; MMF: mycophenolate mofetil; PTCy: post-transplantation cyclophosphamide; RIC: Reduced-intensity conditioning; IQR: interquartile range (25% - 75%); TBI: total body irradiation.

6509 Rapid Oral Abstract Session

A phase I study of asciminib in combination with dasatinib, prednisone, and blinatumomab for Ph-positive acute leukemia in adults. First Author: Marlise R. Luskin, Dana-Farber Cancer Institute, Boston, MA

Background: Treatment of Ph+ acute lymphoblastic leukemia (ALL) requires potent BCR:ABL1 inhibition. Acquired resistance to the ATP-competitive ABL1 inhibitor dasatinib (DAS) justifies combination with the allosteric inhibitor asciminib (ASC) to deepen responses and prevent mutational resistance. Our phase 1 study (NCT03595917) confirmed the safety and preliminary efficacy of DAS 140 mg/day(d) and ASC 80 mg/d (Luskin *Blood* 2024). Blinatumomab (blin), a bispecific CD19-CD3 T-cell engager, is effective consolidation for Ph+ ALL. Here we report a 15-patient (pt) expansion cohort testing the safety of DAS, ASC and blin. **Methods:** Pts ≥18 years (yrs) with Ph+ ALL or chronic myeloid leukemia (CML) blast crisis, no prior DAS or ASC treatment or ABL1 T315I were eligible. Induction: DAS 140 mg/day (d), ASC 80 mg/d and prednisone 60 mg/m^2/d (max 120) 1-24 (tapered d 25-32). Consolidation: DAS 140 mg/d, ASC 80 mg/d, and blin (28 mcg/d d1-28 of a 42-d cycle) for 5 cycles. DAS and ASC are administered indefinitely. Dose-limiting toxicity (DLT) was CTCAEv5 non-heme toxicity grade (gr) 3+ during the first DAS, ASC, and blin combination cycle. **Results:** The 15-pt (9 male, 6 female) cohort accrued 08/2023-09/2024 (data cut 11/15/24). Median age was 62 yrs (range 25 – 83; 87% [13] ≥60). All pts were newly diagnosed: median WBC 11.1x10^3/μL (20% [3] ≥50), transcript type p190 (11, 73%) vs p210 (4, 27%), *IKZF1*^{plus} in 36% (5/14). Most (87%, 13/15) were trackable by clonoSEQ. Median time to blin was 33 days (range 28 – 77). There were no DLTs during the 6-pt safety run-in so 9 additional pts enrolled with all completing at least 1 cycle of ASC, DAS, plus blin. DAS dose reductions were common (n=7) for pleural effusion (n=3), transaminitis (n=1), and other (n=3). ASC dose reduction to 40 mg/d was required in 1 pt (asymptomatic gr3 lipase increase). One pt (age 81) discontinued protocol after 1 blin cycle due to general health decline. Five pts were transplanted per physician discretion after 2 (n=2), 3 (n=2), or 4 (n=1) blin cycles (suspected CML n=2; high-risk genetics n=2; persistent *BCR::ABL1* n=1). All others (n=9) have completed 4 or 5 blin cycles, or blin is ongoing. Responses deepened after the first cycle of blin (Table). No pt has progressed (median follow-up 238 days, 95% CI 112-420). **Conclusions:** Dual ABL1 inhibition with ASC and DAS can be safely combined with blin in Ph+ acute leukemia. An additional 25-pt cohort is planned with blin in combination with DAS and ASC at optimized doses. Clinical trial information: NCT03595917. Research Sponsor: Novartis.

Response kinetics.

	Induction (ASC, DAS, prednisone)	Consolidation Cycle 1 (ASC, DAS, blin)
Hematologic CR	**100%** (15/15)	**100%** (14/14)
Cytogenetic CR	**86%** (12/14)	**100%** (14/14)
Flow Negative (<10^{-4})	**79%** (11/14)	**100%** (14/14)
***BCR::ABL1* Molecular Response (MR)**		
MR1	**87%**(13/15)	**100%**(14/14)
MR2	**60%**(9/15)	**100%**(14/14)
MR3	**20%**(3/15)	**57%** (8/14)
MR4	**7%**(1/15)	**43%**(6/14)
clonoSEQ Response		
<10^{-4}	**67%**(6/9)	**67%**(6/9)
<10^{-6} (0 transcripts)	**11%**(1/9)	**11%**(1/9)

6510 Rapid Oral Abstract Session

MRD negativity after end of induction in the phase 3 PhALLCON trial: A post hoc analysis. First Author: Ibrahim Aldoss, City of Hope – Duarte, Duarte, CA

Background: The phase 3 PhALLCON trial (NCT03589326) in adults with newly diagnosed Ph+ ALL met its primary endpoint, showing a significantly higher rate of minimal residual disease negativity (MRDneg; *BCR::ABL1*^{IS} ≤0.01%) with complete remission (CR) at end of induction (EOI) with ponatinib (PON) vs imatinib (IMA; 34.4% vs 16.7%; *P*=0.002) and safety comparable to IMA. We report post hoc analyses of patients (pts) who did not reach MRDneg by EOI. **Methods:** Pts were randomized 2:1 to PON (30 mg QD reduced to 15 mg upon MRDneg CR at EOI) or IMA (600 mg QD) plus 20 cycles (C) of reduced-intensity chemotherapy (induction C1–3; consolidation C4–9; maintenance combination C10–20) then PON/IMA monotherapy until disease progression or unacceptable toxicity. Cumulative molecular response rates, event-free survival (EFS; defined as any-cause death, no CR by EOI, or relapse from CR), and safety were evaluated in pts with *BCR::ABL1* p190/p210 confirmed by central lab at baseline who did not reach MRDneg by EOI and those achieving MRDneg post-cycle 4 day 1 (C4D1). Data cutoff: Aug 12, 2022. **Results:** Of 232 pts (PON/IMA: n=154/78) with p190/p210, 140 (86 [56%]/54 [69%]) did not have MRDneg by EOI (median age: 54 y; ≥60 y: 37%; female: 55%; ECOG 0/1: 44%/49%; p190/p210: 66%/34%). Of these, 113 pts (PON/IMA: 73/40) continued treatment after EOI, 48 of whom (35 [48%]/13 [33%]) reached MRDneg (MR4 or better) post-C4D1 (Table). Of those 48 pts (median age: 54 y; ≥60 y: 33%; female: 60%; ECOG 0/1: 46%/54%; p190/p210: 71%/29%), median duration of MRDneg (95% CI) was not reached (NR; 13.0 mo–NR) with PON and 3.8 mo (2.3–NR) with IMA; 16 pts (PON/IMA: 10/6) had HSCT. In the 140 pts without MRDneg by EOI, median EFS (mEFS; 95% CI) was NR (NR–NR) with PON and 24.8 mo (21.3–NR) with IMA; 2-y EFS (95% CI) was 82% (69–90) and 62% (41–77), respectively. In the 48 pts with MRDneg post-C4D1, mEFS was NR (NR–NR) and NR (21.3 mo–NR); 2-y EFS was 88% (68–96) and 80% (20–97), respectively. In the 140 pts without MRDneg by EOI, treatment-emergent adverse event (TEAE) rates with PON/IMA were 100%/98% (gr ≥3: 91%/94%); dose modification due to TEAEs: 71%/54% (discontinuation: 15%/9%; reduction: 16%/28%; interruption: 66%/41%). In the 48 pts with MRDneg post-C4D1, TEAE rates with PON/IMA were 100%/100% (gr ≥3: 91%/100%); dose modification due to TEAEs: 69%/62% (discontinuation: 6%/0%; reduction: 11%/46%; interruption: 69%/38%). **Conclusions:** Among pts without MRDneg by EOI, more pts who continued the study achieved deep and durable molecular response after C4D1, and 2-y EFS appeared to be better with PON than IMA. These data support the clinical benefit and tolerability of continuing PON in pts without MRDneg by EOI. Clinical trial information: NCT03589326. Research Sponsor: Takeda Development Center Americas, Inc.

Response in pts without MRDneg by EOI who continued treatment post-C4D1, n (%)	PON (n=73)	IMA (n=40)
MRDneg	35 (48)	13 (33)
By end of C9	28 (38)	11 (28)
By end of C20	30 (41)	12 (30)
MR4.5 (*BCR::ABL1*^{IS} ≤0.0032%)	27 (37)	4 (10)
By end of C9	17 (23)	2 (5)
By end of C20	23 (32)	3 (8)

6511 Rapid Oral Abstract Session

Reduced dose PTCy in patients with acute myeloid leukemia receiving matched unrelated donor allogeneic hematopoietic stem cell transplantation. First Author: Nihar Desai, Princess Margaret Hospital, Toronto, ON, Canada

Background: Post-transplant cyclophosphamide (PTCy) at 50 mg/kg on D+3 & +4 after allogeneic hematopoietic cell transplantation (HCT) is established for graft-versus-host disease (GvHD) prophylaxis. PTCy causes significant toxicities, including bloodstream infections (BSI), delayed engraftment, viral reactivations, hemorrhagic cystitis (HC), cardiotoxicity, and fluid overload (FO), contributing to increased non-relapse mortality (NRM). **Methods:** In July 2024, we initiated a pilot to evaluate reduced (35 mg/kg on D+3 & +4) PTCy dosing (PTCy70). We included patients with AML receiving 10/10 matched unrelated donor peripheral blood grafts. All patients received fludarabine and busulfan conditioning. GvHD prophylaxis included anti-thymocyte globulin (ATG 2 mg/kg), a calcineurin inhibitor, & PTCy70. Outcomes were compared with a contemporary cohort receiving PTCy 100. **Results:** From July-Dec 2024, 30 patients received PTCy70. Baseline characteristics were comparable except for conditioning intensity (Table 1). Median follow up was 497 days (316 – 733) & 80 days (56 – 119) for PTCy100 & PTCy70, respectively. No graft failure occurred in PTCy70 group vs one in PTCy100 group. Median time to neutrophil engraftment was comparable, 20 days (19–21). Median time to platelet engraftment was shorter in the PTCy70 group (14 vs. 16 days, p=0.01). At D+30, the incidence of platelet engraftment was significantly higher in the PTCy70 group (87% vs. 81%, p=0.01).D+30 incidence of BSI was much lower in the PTCy70 group (30% vs. 59%, p=0.005). Most BSIs in both groups were caused by gram-positive organisms (71% vs. 77%, p=0.7). CMV at D+100 was 7.2% (95% CI: 1.2 – 21) in PTCy70 and 18.7% (95% CI: 12 – 27) in the PTCy100 group (p=0.14). None of the patients receiving PTCy70 developed HC vs. 11 in the PTCy100 group. FO occurred in 16 (53%) patients (grade 1: 12; grade 2: 4) receiving PTCy70, with none developing >grade 2 FO. There was no difference in the median duration of admission (31 days, p=0.9).Six patients receiving PTCy70 developed grade II-IV aGvHD. Four had grade II skin GvHD & responded to topical steroids. At D+100, there was no significant difference in grade II-IV (18.7% vs. 29%, p=0.29), grade III-IV acute GvHD (4.8% vs. 3.3%, p=0.80), and NRM (5.3% vs 1.8%, p=0.62). **Conclusions:** PTCy70 is associated with faster platelet engraftment & lower BSI, with no increase in aGVHD. PTCy70 also seems to reduce HC and viral reactivation. Extended follow-up is necessary to examine longer term outcomes. Research Sponsor: None.

Baseline characteristics.

	PTCy 100	PTCy 70	p
Age, years, median (IQR)			
Recipient	59 (49 – 66)	63.5 (57 – 67)	0.07
Myeloablative conditioning, n (%)	46 (41)	5 (17)	0.01
CMV serostatus, n (%)			
D+/R+	57 (51)	14 (47)	
D+/R-	35 (31)	6 (20)	0.13
D-/R+	4 (4)	4 (13)	
D-/R-	16 (14)	6 (20)	
CD34+ cell dose x 10^6/kg, median (IQR)	7.5 (6.3 – 8.1)	6.7 (5.3 – 8)	0.07

6512 Rapid Oral Abstract Session

Overall survival (OS) and duration of response for transfusion independence (TI) in erythropoiesis stimulating agent (ESA)–naive patients (pts) with very low-, low-, or intermediate-risk myelodysplastic syndromes (MDS) treated with luspatercept (LUSPA) vs epoetin alfa (EA) in the COMMANDS trial. First Author: Guillermo Garcia-Manero, University of Texas MD Anderson Cancer Center, Houston, TX

Background: In the phase 3 COMMANDS trial (NCT03682536), LUSPA was superior in improving red blood cell (RBC)-TI ≥12 wks with concurrent hemoglobin increase ≥1.5 g/dL in Wks 1 to 24 vs EA and had durable clinical benefit in pts with ESA-naive transfusion-dependent (TD) lower-risk MDS (LR-MDS; Della Porta MG, et al. *Lancet Haematol*. 2024; Garcia-Manero G, et al. *ASH*. 2024). Here, we report updated results including OS and duration of response. **Methods:** Eligible pts (≥18 yrs; ESA-naive; RBC TD; very low/low/intermediate-risk MDS) were randomized 1:1 (stratified by baseline [BL] RBC transfusion burden [TB], serum erythropoietin [EPO] level, and ring sideroblast [RS] status) to receive LUSPA (1.0-1.75 mg/kg) SC Q3W or EA (450-1050 IU/kg; max dose 80,000 IU) SC QW for ≥24 wks. Secondary endpoints included OS, duration of RBC-TI ≥12 wks, and safety. **Results:** As of Nov 4, 2024, median follow up (FU) was 29.0 and 27.1 mos for the LUSPA (n=182) and EA (n=181) groups, respectively. Median OS for LUSPA was not reached (NR) and was 46.7 mos for EA (HR, 0.86; 95% CI, 0.60-1.24); 3-yr OS rates were 63.8% and 62.2%, respectively, and 5-yr OS rates were 54.0% and 41.8%. In subgroups, similar OS trends were observed (Table). Overall, RBC-TI ≥12 wks (Wk 1 to end of treatment [EOT]) was reached by 76.4% (139/182) of pts in the LUSPA group and 55.8% (101/181) in the EA group. Median cumulative duration (95% CI) of RBC-TI ≥12 wks (sum of all durations of RBC-TI ≥12 wks episodes from Wk 1 to EOT) was 187.3 (119.6-NE) wks for LUSPA vs 94.9 (73.1-179.0) wks for EA (HR, 0.51; 95% CI, 0.34-0.77). Median duration (95% CI) of longest RBC-TI ≥12 wks period (from Wk 1 to EOT) was 126.6 (81.0-184.4) vs 86.7 (55.9-111.1) wks (HR, 0.64; 95% CI, 0.44-0.93). At cutoff, 24.7% of LUSPA pts and 11.2% of EA pts were on treatment; 84.6% and 82.7%, respectively, had ≥1 dose escalation. With longer FU, no new safety concerns emerged. Deaths occurred in both groups on- (10.4% vs 9.5%) and post-treatment (20.9% vs 26.3%). Progression to acute myeloid leukemia was comparable between groups (3.8% vs 4.4%). **Conclusions:** LUSPA led to improvements in response rate and duration, with a positive OS trend requiring further evaluation through more extended follow up. LUSPA signifies a new standard of care for anemia in first-line LR-MDS. Clinical trial information: NCT03682536. Research Sponsor: Bristol Myers Squibb.

Median OS, mos	LUSPA	EA	HR (95% CI)
Overall (ITT)	(n=182)	(n=181)	0.86
	NR	46.7	(0.60-1.24)
Stratification subgroup			
BL TB <4 U	(n=118)	(n=111)	0.87
	NR	46.7	(0.55-1.38)
BL TB ≥4 U	(n=64)	(n=70)	0.74
	NR	48.2	(0.42-1.31)
RS+	(n=133)	(n=130)	0.77
	NR	48.2	(0.50-1.19)
RS−	(n=49)	(n=50)	0.93
	NR	46.2	(0.50-1.75)
BL EPO ≤200 U/L	(n=145)	(n=144)	0.84
	NR	51.4	(0.55-1.27)
BL EPO >200 U/L	(n=37)	(n=37)	0.81
	NR	35.4	(0.40-1.64)

ITT, intention-to-treat; U, units.

6513 Rapid Oral Abstract Session

Efficacy of macrophage checkpoint Clever-1 inhibition with bexmarilimab plus azacitidine in myelodysplastic syndrome: Results from the ph1/2 BEXMAB study. First Author: Naval Guastad Daver, Department of Leukemia, The University of Texas MD Anderson Cancer Center, Houston, TX

Background: Treatment of higher-risk (HR) myelodysplastic syndrome (MDS) represents an unmet medical need. Hypomethylating (HMA) agents, including azacitidine, are used in the frontline setting for HR MDS patients with complete remission rate reported as 16% (Hasegawa et al., 2023) After HMA-failure, including primary refractory disease or relapse after frontline treatment (r/r MDS), the reported median overall survival (mOS) is <6 months (Prébet et al., 2011). Bexmarilimab, a first-in-class macrophage checkpoint inhibitor, blocks Common lymphatic and vascular endothelial receptor-1 (Clever-1) to enhance macrophage antigen presentation and T cell activation. In the MDS bone marrow (BM), Clever-1 is also abundant on malignant blasts. Translational data suggest that by inhibiting blast Clever-1, bexmarilimab hampers the energy production of the malignant cells. Thus, bexmarilimab may alter the BM immune microenvironment and make the blasts susceptible to other cytotoxic agents, such as HMAs, thereby enhancing their effectiveness in patients with HR MDS, both in frontline and r/r setting. **Methods:** The Phase 1/2 (Ph1/2) BEXMAB study investigates safety, tolerability and preliminary efficacy of bexmarilimab in combination with standard-of-care, azacitidine, in HR MDS. Key inclusion criteria include indication for azacitidine treatment with a risk score of >3 based on the revised International Prognostic Scoring System (IPSS-R) and for r/r MDS, failure to achieve response to or disease progression during treatment with HMA or HMA containing regimen. In Ph1, Bayesian optimal interval (BOIN) design was used for dose escalation to identify recommended dose for expansion (RDE). Ph1 studied 1, 3 and 6mg/kg bexmarilimab, administrated weekly in 28-day cycles, in combination with a standard regimen of azacitidine (75 mg/m^2 D1-7 each cycle). r/r MDS was selected as the first population for Ph2 dose optimization and expansion following a Simon's 2-stage design, with subjects randomized to RDE (6mg/kg) and RDE-1 (3mg/kg). After dose escalation, Ph1 expansion cohorts were used to enrich frontline MDS population at RDE and RDE-1. **Results:** Safety and efficacy data from 20 frontline HR MDS and 35 r/r MDS patients, comparing bexmarilimab dose levels, will be reported. Previous analysis per IWG2006 criteria indicated an overall response rate (ORR) of 100% in 5 frontline MDS patients and 80% in 20 r/r MDS patients (65% per IWG2023). Simultaneously, a median overall survival estimate of 13.4 months, was reported for the r/r MDS population. During dose escalation, no dose limiting toxicities (DLT) were reported during the 28-day DLT period. Ongoing safety follow-up indicates a total of 277 treatment-emergent adverse events, of which 38 (13.7%) are considered bexmarilimab-related. **Conclusions:** Enrolment for both dose finding and randomized dose optimization parts (n=55) of the BEXMAB Phase 1/2 study has been completed. Safety and efficacy results for both populations will be reported for the first time. Clinical trial information: NCT05428969. Research Sponsor: Faron Pharmaceuticals.

6514 Rapid Oral Abstract Session

Dosing decitabine and venetoclax for terminal differentiation to improve outcomes in TP53 mutant MDS and AML. First Author: Bradley Rockwell, Montefiore Einstein Comprehensive Cancer Center, Bronx, NY

Background: Mutations in the tumor suppressor TP53 gene are common in elderly patients with myelodysplastic syndrome (MDS) and acute myeloid leukemia (AML) and confer resistance to conventional chemotherapeutic DNA damaging agents. Venetoclax (Ven) added to the hypomethylating agents (HMA) of Decitabine or Azacitidine is the current standard of care for elderly patients with AML and is frequently used in high-risk MDS (HR-MDS). Currently approved dosing schedules of HMA/Ven rely on cytotoxicity and have not improved outcomes in the TP53 mutant population. The efficacy and tolerability of metronomic weekly dosing of Decitabine and Ven in HR-MDS and AML were previously described (Goldfinger et al, Blood 2024). Mechanistically, metronomic dosing relies on terminal differentiation, rather than cytotoxicity making it an attractive regimen for TP53 mutant MDS/AML. **Methods:** Patients with histologically confirmed AML or MDS and a TP53 mutation received a once-weekly dose of decitabine 0.2 mg/kg subcutaneously and one dose of Ven 400 mg on days 1, 8, 15 and 22 of a 28-day cycle. **Results:** Between April 2020 and January 2025, 40 patients with TP53 mutated myeloid malignancies were treated with metronomic weekly low-dose Decitabine/Ven (14 AML, 26 MDS). Twenty-four patients were followed prospectively as part of a clinical trial (NCT05184842), and 16 were treated off-trial and had data collected retrospectively. Median age at diagnosis was 76.5 years, 13 (32%) were from minority backgrounds, 28 (70%) had complex cytogenetics and 31 (82%) had biallelic TP53 mutations (median VAF 36%). All AML patients were ELN-poor risk, 21 MDS patients (82%) were R-IPSS high or very high risk. The median time on therapy was 5.8 months, with 10 (25%) patients still on therapy at time of data cut-off. Four patients in the AML and five in the MDS cohorts were not evaluable (2 withdrew consent, 1 lost to follow-up and 6 did not have a BM biopsy for evaluation). Of the evaluable AML patients, 7 (70%) achieved a complete remission (CR), 3 (30%) did not respond. In the evaluable MDS patients, 9 (43%) achieved a CR and 3 (15%) a marrow CR, 4 (19%) with stable disease, 5 (24%) with no response. Of the 26 patients who were transfusion-dependent at the start of therapy, 15 (58%) became transfusion-independent. For the entire cohort (n=40), the median overall survival (OS) was 11.3 months. For the AML and MDS cohorts, the OS was 11.6 and 9.9 months, respectively. In patients who underwent allogeneic stem cell transplant (n=6), OS was 16 months. Non-heme therapy-related adverse events of ≥ grade 3 was seen in 13 (54%) of patients. **Conclusions:** In this cohort, of elderly patients with poor risk TP53 mutated MDS and AML the use of a non-cytotoxic dosing schedule of Decitabine and Ven resulted in over half the patients achieving a CR and transfusion independence. The median OS of 11.3 months compares favorably to currently approved cytotoxic dosing of HMA/Ven. Clinical trial information: NCT05184842. Research Sponsor: None.

6515 Rapid Oral Abstract Session

IMproveMF update: Phase 1/1B trial of imetelstat (IME)+ruxolitinib (RUX) in patients (pts) with intermediate (INT)-1, INT-2, or high-risk (HR) myelofibrosis (MF). First Author: John Mascarenhas, Tisch Cancer Institute, Icahn School of Medicine at Mount Sinai, New York, NY

Background: IME, a first-in-class, direct, and competitive inhibitor of telomerase activity, showed potential survival improvements and disease-modifying activity in the phase 2 IMbark MF trial (NCT02426086). Preclinical evidence demonstrated IME+RUX reduced disease burden better than either agent alone. IMproveMF (NCT05371964) aims to evaluate IME+RUX in pts with INT-1/INT-2/HR MF. **Methods:** IMproveMF is an open-label, single-arm, phase 1/1b trial (part 1: dose escalation; part 2: dose confirmation and expansion) of IME+RUX in adults with DIPSS INT-1, INT-2, or HR MF. In part 1 (up to 21 pts), RUX was required for ≥12 wk with a stable dose for ≥4 wk immediately before adding IME; pts received IME via intravenous infusion at each dose level cohort (4.7, 6.0, 7.5, and 9.4 mg/kg IME sodium; equivalent to 4.4, 5.6, 7.1, and 8.9 mg/kg active dose, respectively) every 28 d based on Bayesian Optimal Interval design to identify the recommended part 2 dose (RP2D). Pts in part 1 were dose adjusted to the RP2D as needed in part 2, with 2 dose reductions allowed. Part 2 of the trial will enroll pts who are RUX naive. Primary endpoints are adverse events (AE), including dose-limiting toxicity (DLT), in part 1 and AEs and 24-wk response rate (≥50% reduction in MF total symptom score [TSS]) in part 2. Secondary endpoints include pharmacokinetics (PK) and clinical activity. Total planned enrollment is ≈41 pts. **Results:** As of 11/04/2024, 17 pts were enrolled in part 1 with a median age of 67 y (71% aged ≥65 y); 7 had INT-1, 9 INT-2, and 1 HR MF. Respective to the dose levels in the Methods, 3, 3, 4, and 7 pts received the corresponding IME dose level. No DLTs were reported for IME; 2 pts had dose reductions due to neutropenia. Five pts discontinued IME (none due to AEs). Four pts had RUX dose reductions (due to AEs and other, n=2 each). AEs were experienced by 15 pts; 8 experienced grade 3 events of anemia (n=4), neutropenia (n=3), leukopenia (n=2), abdominal pain, fatigue, epistaxis, and pneumonia (n=1 each; the latter 2 and 1 anemia event were considered serious AEs). There were no grade 4/5 AEs. There was an overall reduction in TSS from baseline (median, −5 points in maximum absolute reduction up to wk 24) with IME regardless of dosing, and a trend of dose-dependent spleen volume decrease. A reduction in variant allele frequency of several driver mutations was also observed. Hematologic, PK, and additional mutational data will be included in the presentation, as available. **Conclusions:** In part 1 of IMproveMF, no DLTs were observed and the RP2D dose of 9.4 mg/kg IME was determined. AEs were consistent with those observed in other IME clinical trials, and preliminary efficacy was positive, demonstrating the potential of IME+RUX in this pt population with high unmet needs. Part 2 of this trial is ongoing across the US at 6 sites. Clinical trial information: NCT05371964. Research Sponsor: This study was funded by the Geron Corporation. All authors contributed to and approved the abstract; writing and editorial support were provided by Jeremy J. Henriques, PhD, CMPP, of The Lockwood Group (Stamford, CT, USA), funded by the Geron Corporation.

6516 **Rapid Oral Abstract Session**

Efficacy and safety of asciminib (ASC) in patients (pts) with chronic-phase chronic myeloid leukemia (CML-CP) after 1 tyrosine kinase inhibitor (TKI): Interim analysis (IA) of the phase 2 ASC2ESCALATE trial. First Author: David Jacob Andorsky, Rocky Mountain Cancer Centers, US Oncology Research, Boulder, CO

Background: ASC2ESCALATE (NCT05384587) is the first prospective trial of ASC in CML-CP after 1 TKI (2L) with dose escalation for pts with suboptimal response; ASC is also being assessed in a separate newly diagnosed (1L) cohort. A previous IA of the 2L cohort reported ASC's safety (n=71) and wk 24 efficacy (n=28; *BCR::ABL1*^{IS} ≤1%, 85.7%; major molecular response [MMR], 42.9%). We report updated safety (n=101) and wk 24 efficacy (n=63) results. **Methods:** ASC2ESCALATE is a phase 2, single-arm, open-label US study of ASC in adults with 1L or 2L CML-CP without the T315I mutation. In the 2L cohort, eligible pts had discontinued their prior TKI due to warning or failure per ELN2020 or intolerance with *BCR::ABL1*^{IS} >0.1% at screening. Pts received ASC 80 mg once daily (QD). If *BCR::ABL1*^{IS} >1% at wk 24, dose was increased to 200 mg QD. If *BCR::ABL1*^{IS} >0.1% at wk 48, dose was increased from 80 to 200 mg QD or from 200 mg QD to 200 mg twice daily, or pts could be taken off study. If pts had any grade 3/4 or persistent grade 2 toxicity refractory to optimal management, they were ineligible for dose escalation at wk 24 and/or 48 and continued the same dose. **Results:** This IA included all 101 pts enrolled with 2L CML-CP; all pts had received ≥1 ASC dose by the cutoff (Nov 15, 2024). Prior treatment (Tx) included dasatinib (44.6%), imatinib (42.6%), nilotinib (9.9%), or bosutinib (5.0%); 66.3% of pts had received prior Tx for ≥12 mo. Pts discontinued prior Tx due to lack of efficacy (56.4%) or intolerance (43.6%). By the cutoff, 92 pts (91.1%) remained on ASC; 9 pts (8.9%) discontinued ASC, mostly due to adverse events (AEs; n=4) and pt decision (n=3). Median duration of ASC exposure was 26.1 (range, 6-100) wk. Pts evaluable for all efficacy analyses completed assessments for the respective timepoint or discontinued earlier (wk 4, n=94; wk 12, n=86; wk 24, n= 63). At wk 4, 12, and 24, 46.8%, 84.9%, and 82.5% pts, respectively, had *BCR::ABL1*^{IS} ≤1%. Deeper responses were also achieved at wk 12 (MMR, 39.5%; MR^4, 11.6%; MR$^{4.5}$, 2.3%) and 24 (MMR, 44.4%; MR^4, 25.4%; MR$^{4.5}$, 9.5%). Seven pts had dose escalation from 80 to 200 mg QD per their response level at wk 24 (n=3) and 48 (n=4). All-grade AEs ≥20% were headache (22.8%) and nausea (20.8%). Grade ≥3 AEs ≥5% were hypertension (8.9 %), thrombocytopenia (6.9%), and neutropenia (5.9%). AEs led to dose adjustment/interruption in 27 pts (26.7%). AEs led to discontinuation in 4 pts; 1 of these AEs occurred >30 d after last ASC dose. No arterial-occlusive events or on-Tx deaths occurred. **Conclusions:** 2L ASC demonstrated high molecular response rates at wk 24 and safety consistent with previously established ASC data across Tx lines; no new or worsening safety signals arose. ASC was tolerable with few AEs leading to discontinuation. These IA results support ASC as a Tx option in 2L CML-CP. The impact of dose escalation continues to be explored. Clinical trial information: NCT05384587. Research Sponsor: Novartis Pharmaceuticals Corporation.

6517 **Rapid Oral Abstract Session**

Age-related macular degeneration in individuals with clonal hematopoiesis. First Author: Keishla Marie Arce-Ruiz, McGraw/Patterson Center for Population Sciences, Dana-Farber Cancer Institute, Boston, MA

Background: Clonal hematopoiesis (CH), an age-related condition involving somatic mutations in blood stem cells, increases the risk of myelodysplastic syndrome (MDS), blood cancers and cardiovascular disease through inflammatory pathways. Age-related macular degeneration (AMD), the leading cause of blindness in the developed world, is also characterized by chronic inflammation. An increased prevalence of AMD has been observed in older adults with MDS, but the association between CH and AMD remains unexplored. Understanding this relationship could reveal shared inflammatory mechanisms in age-related diseases and guide prevention strategies. **Methods:** This retrospective cohort study used exome sequencing and electronic medical records (EMRs) from 467,200 adults ≥40 years of age in the UK Biobank (UKB), recruited between 2006–2010 and followed until 2020. Participants with prevalent blood cancer, AMD, or with missing AMD diagnosis dates were excluded. CH was defined as pathogenic somatic mutations with a variant allele fraction (VAF) ≥0.02. Incident AMD was identified using ICD-10 codes (H35.3). Kaplan-Meier estimates and log-rank tests assessed cumulative incidence, while Cox regression models calculated hazard ratios (HRs), adjusted for age, sex, smoking and hypertension. A separate cohort of 4,079 patients from Dana-Farber Cancer Institute (DFCI) validated findings and enabled granular clinical data abstraction from EMRs. **Results:** CH was detected in 29,550 (6.8%) individuals of the UKB. The 12-year cumulative incidence (C.I.) of AMD was higher in individuals with CH (n=671, C.I. 2.45%) compared to those without (n=6,728, 1.61%; p<2x10-16). In unadjusted Cox models, individuals with CH had a 51% higher risk of AMD compared to those without (HR =1.51 (95% CI: 1.39–1.63; $p < 2\times10^{-16}$), remaining significant after adjusting for covariates (p=0.023). CH genotypes most associated with AMD risk included *ASXL1* (HR: 1.32; p = 0.0146) and splicing factors (HR: 1.54; p = 0.0345). Individuals with CH and AMD had a 33% higher risk of progressing to blindness compared to those without CH, though this was not statistically significant (p = 0.242). In the DFCI cohort (n= 4,079), CH was present in 1,028 (25.2%) individuals. 86 (8.37%) individuals with CH had AMD diagnoses compared to those without CH (n= 86, 3.21%; $p = 2.53\times10^{-10}$), with exudative AMD, a more severe subtype, being more prevalent in CH patients (n=11; $p = 1.1\times10^{-5}$). **Conclusions:** There is a significant association between CH and AMD, suggesting that AMD prevalent in individuals with MDS is related to presence of CH in the pre-MDS state. Real world data support these findings, highlighting a trend towards severe AMD subtypes in individuals with CH. The identification of specific genes linked to AMD incidence suggests that certain CH genotypes may confer a higher risk for AMD, highlighting the role of AMD screening in individuals with myeloid malignancy precursor conditions. Research Sponsor: Conquer Cancer - The ASCO Foundation.

6518 **Poster Session**

Outcomes in patients (pts) younger than 50 years old (yo) with treatment-naïve blastic plasmacytoid dendritic cell neoplasm (BPDCN) treated with tagraxofusp (TAG): Subanalysis of a phase 1/2 trial. First Author: Anthony Selwyn Stein, City of Hope, Duarte, CA

Background: BPDCN is an aggressive, orphan hematologic malignancy characterized by cells expressing CD123 and other markers. In BPDCN pts <50 yo, including in the adolescent and young adult (AYA) population (ie, pts 15-39 yo), data are limited. TAG, a first-in-class CD123-targeted therapy, is the only drug approved for adults (US/EU) and pediatric pts aged ≥2 yo (US only) with BPDCN. TAG has a well-characterized and manageable safety profile, with transient adverse events (AEs) occurring mostly in cycle 1, no cumulative long-term toxicity, and no myelosuppression. While not approved, multi-agent chemotherapy is used in AYAs, resulting in short- and long-term toxicity, including myelosuppression. Here we report the safety and efficacy of 1L TAG treatment, with prespecified/multi-system response criteria, for BPDCN pts <50 yo from a subgroup analysis of the phase 1/2 TAG monotherapy study (NCT02113982). **Methods:** We analyzed outcomes in treatment-naïve pts <50 yo who received 1L TAG 12 μg/kg intravenously on days 1-5 of a 21-day cycle. Assessed outcomes included best response, time to best response, duration of response (DOR), overall survival (OS), treatment-related adverse events (TRAEs), and capillary leak syndrome (CLS). **Results:** Ten pts (median age of 31.5 yo [range 22-45]) were included in this analysis, including 6 AYA pts. All pts had ECOG PS of 0-1, 20% had bone marrow involvement, and 60% had ≥2 sites of BPDCN disease. Pts received a median of 4 cycles (range 2-7) of TAG. In cycle 1, pts received a median of 5 TAG doses (range 3-5) in line with the USPI dosing. At a median follow-up of 34 months, the CR/CRc rate was 70%, with a 41-day median time to CR/CRc. DOR was not reached (range 8.4-51.8 months); median OS was 38.4 months. All pts were bridged to stem cell transplantation (SCT), including 2 autologous SCTs: 7 pts with CR/CRc following TAG treatment (median time from last TAG dose to SCT, 38 days) and 3 pts with PR or SD were bridged to SCT following subsequent multi-agent chemotherapy. Most common Grade 3-4 TRAEs were thrombocytopenia and ALT/AST elevation; the majority of TRAEs resolved with resolution in the same cycle; no grade 5 TRAEs occurred. No pts had a dose reduction or discontinuation due to a TRAE. No investigator-assessed CLS was reported, although some pts required dose interruption due to weight gain or hypoalbuminemia. **Conclusions:** In treatment-naïve BPDCN pts <50 yo, including AYAs, TAG, a chemotherapy-free option, induced high rates of CR/CRc (70%) and allowed all pts who achieved CR/CRc to bridge to SCT. TAG was well tolerated with no cumulative AEs or cumulative myelosuppression. No investigator-assessed CLS was observed in these younger pts. Overall, TAG is an effective front-line therapy, including in pts <50, with durable (median not reached) responses and prolonged survival. Clinical trial information: NCT02113982. Research Sponsor: Menarini Group.

6519 **Poster Session**

Decoding immune dysregulation in AML: Insights from integrated genomic and transcriptomic analysis. First Author: Harsh Goel, All India Institute of Medical Science (AIIMS), New Delhi, India

Background: Acute Myeloid Leukemia (AML) is an aggressive hematologic malignancy marked by abnormal proliferation of myeloid progenitor cells, often leading to poor outcomes and high relapse rates. While the genetic underpinnings of AML are well-documented, the role of immune dysregulation in its progression remains underexplored. This study integrates whole exome sequencing (WES) and transcriptome analysis to identify genetic mutations, transcriptional alterations, and immune regulatory disruptions, with a focus on their contributions to hematopoiesis and immune dysfunction. **Methods:** WES and RNA sequencing were performed on 10 AML patient samples to investigate somatic mutations, differential gene expression, and immune-related pathways. WES data were analyzed to detect mutations in AML-associated genes, while transcriptomic analysis compared gene expression profiles between AML cells and normal hematopoietic stem cells (HSCs). Bioinformatic tools, including differential expression analysis, Gene Set Enrichment Analysis (GSEA), and pathway mapping, were employed to identify key regulatory networks. Single-cell RNA sequencing (scRNA-seq) was conducted to assess cellular heterogeneity and differentiation dynamics, with a focus on immune cell subsets and pathways involved in immune evasion. **Results:** Analysis revealed recurrent mutations and dysregulation in genes critical to hematopoiesis, apoptosis, and immune regulation, including *RUNX1, FLT3, CEBPA, TP53, WT1, GATA2,* and *TET2*. Transcriptomic profiling highlighted distinct gene expression patterns in AML cells, with significant disruption in cell cycle control, differentiation, and apoptosis. Dysregulated immune pathways, such as IL-7R and PD-1, were identified as key contributors to immune cell activation impairment and immune tolerance. scRNA-seq data provided insights into the cellular heterogeneity of AML, uncovering altered lineage differentiation and immune subset composition, which may facilitate immune evasion and disease progression. **Conclusions:** This integrative analysis illuminates the interplay between genetic mutations, transcriptional dysregulation, and immune dysfunction in AML. The findings underscore the pivotal role of immune pathways, such as IL-7R and PD-1, in AML pathogenesis, presenting them as potential therapeutic targets. By linking genetic and immune alterations, this study advances our understanding of AML biology and highlights the need for therapies addressing both genetic and immune dysfunctions to improve clinical outcomes. Research Sponsor: None.

6520 **Poster Session**

V-RULES: Real-world effectiveness and safety of CPX-351 in patients with secondary acute myeloid leukemia (AML). First Author: Thomas William LeBlanc, Department of Medicine, Duke University School of Medicine, Durham, NC

Background: CPX-351 was approved for newly diagnosed (ND) therapy-related AML (t-AML) or AML with myelodysplasia-related changes (AML-MRC) following the pivotal phase 3 trial, which demonstrated improved CR/CRi (47.7% vs 33.3%) and median OS (9.56 vs 5.95 months [mo]), and comparable safety vs conventional 7+3 in adults aged 60-75 years. The Vyxeos Real-world US Long-term Effectiveness and Safety Study (V-RULES) evaluated real-world (RW) clinical outcomes and safety of CPX-351 in US patients with ND t-AML or AML-MRC. **Methods:** V-RULES is a retrospective, multicenter, single-arm study based on medical records of patients with ND t-AML or AML-MRC who were treated with CPX-351 since its FDA approval in August 2017. Primary endpoints were CR/CRi/CRh and OS. **Results:** Overall, 161 patients (t-AML, n=47; AML-MRC, n=114) received $\geq$ 1 induction of CPX-351 (1 cycle, n=142; 2 cycles, n=19) and 50 patients received consolidation (1 cycle, n=40; 2 cycles, n=10). Median age at AML diagnosis was 60 years (range: 21-78); 78 (48%) patients were aged $<$60 years. Of patients with available cytogenetic data, 88/154 (57%) were classified as adverse-risk per Grimwade 2010 and 49/155 (32%) had complex karyotype. Notably, 33/134 patients (25%) had *TP53* mutations (*TP53*m) and 57/91 patients (63%) had myelodysplasia-related gene mutations (MRm). Median follow-up time (IQR) was 9.7 mo (4.1, 27.8). CR (including minimal residual disease negativity)/CRi/CRh at any time was 63% in 149 evaluable patients (t-AML, 85%; AML-MRC, 53%). Median OS was 12.9 mo (95% CI: 8.9, 19.7) and estimated 4-year OS was 29% (95% CI: 21%, 38%). Survival was longer in patients aged $<$60 vs $\geq$ 60 years: median OS was 17.8 (95% CI: 9.6, 45.4) vs 10.6 mo (95% CI: 6.7, 13.8) and estimated 4-year OS was 37% (95% CI: 24%, 49%) vs 22% (95% CI: 12%, 34%). Compared with the overall population, median OS was shorter in patients with *TP53*m (5.3 mo [95% CI: 2.3, 7.4]) and longer in patients with MRm (17.8 mo [95% CI: 11.4, 38]). Patients who underwent hematopoietic cell transplantation (HCT) after CPX-351 treatment (38%) had a median OS post-HCT of 45.6 mo (95% CI: 24.9, not estimated). In patients with CR/CRh/CRi, median time to neutrophil ($\geq$ 500/μL) and platelet ($\geq$ 50,000/μL) recovery in induction 1 was 35 days (n=76) and 36 days (n=72), respectively. Infection (52%) and febrile neutropenia (42%) were the most common grade $\geq$ 3 adverse events (AEs); 2 patients had a serious AE of cardiac events. **Conclusions:** These results highlight the effectiveness and safety of CPX-351 for the treatment of t-AML and AML-MRC in the US RW setting, consistent with the pivotal trial and published RW data. Notably, this study demonstrated favorable outcomes for younger patients ($<$60 years) who were not included in the pivotal trial. Patients who received HCT also had improved outcomes, as did those with MRm. These results support the continued use of CPX-351 as the standard of care for ND t-AML or AML-MRC. Research Sponsor: Jazz Pharmaceuticals; N/A.

6521 **Poster Session**

Venetoclax as cytoreductive therapy in high-risk acute promyelocytic leukemia: A potential alternative to anthracyclines. First Author: Ravi Teja Banda, Continental Hospitals, Hyderabad, India

Background: High-risk acute promyelocytic leukemia (APL) presents a significant mortality risk during induction therapy, primarily due to complications like disseminated intravascular coagulation (DIC) and treatment-related toxicities. Anthracyclines, traditionally used for cytoreduction, can cause cardiotoxicity, increase DIC risk, and induce severe neutropenia. Venetoclax has demonstrated efficacy in relapsed/refractory APL. This study explored the feasibility of using venetoclax for cytoreduction in high-risk APL patients, particularly those contraindicated for anthracyclines (cardiac issues, advanced age and in select patients based on physician discretion). **Methods:** We evaluated the safety and efficacy of venetoclax in high-risk APL patients unsuitable for anthracycline-based induction therapy. Venetoclax was initiated at 100 mg and gradually increased to 400 mg over a week. Treatment duration was determined by the patient's leukocyte count, with the goal of achieving a count below 4000/mm^3. All patients received standard ATRA (All-Trans Retinoic Acid) + ATO (Arsenic Trioxide) induction. **Results:** Ten patients received venetoclax for cytoreduction. The median age was 45 years (range: 26-70). The median duration of venetoclax therapy was 8 days (range:6-12). All patients achieved complete hematological remission within 31 days of induction and molecular remission by 28 days of the first consolidation cycle. Two patients experienced laboratory tumor lysis syndrome, and one developed differentiation syndrome which was effectively managed with continued venetoclax therapy. No patients required interruption of ATRA or ATO. Notably, no patients experienced prolonged neutropenia ($>$ 28 days), severe mucositis (Grade 3 or 4), cardiotoxicity, or DIC. **Conclusions:** This study demonstrates the feasibility of using venetoclax for cytoreduction in high-risk APL patients. Venetoclax effectively reduced tumor burden while minimizing the risks associated with anthracyclines. These encouraging results warrant further investigation into the potential role of venetoclax in high-risk APL to improve patient outcomes and mitigate treatment-related toxicities. Research Sponsor: None.

Patient characteristics.

Patient Age/ Sex	WBC(10^3/ μL)	Platelet(10^3/ μL)	Hb (g/ L)	BM blast (%)	WBC max (10^3/ μL)	No of days venetoclax used	Cardiac comorbidity	Time to achieve HCR (days)
45/M	15000	30000	9	30	25000	9	CAD	26
40/F	13000	25000	8.8	55	19000	7	NIL	24
33/M	12000	35000	8.1	45	18000	7	NIL	28
31/F	25000	45000	9.6	40	25000	9	NIL	30
65/M	17000	10000	7.5	33	19000	9	NIL	30
45/F	15000	10000	8.5	25	16000	8	RHD	28
66/M	22000	20000	9.7	60	24000	7	CAD	29
70/F	38000	25000	7.8	34	45000	10	CAD	31
46/M	16000	10000	7	33	18000	8	CAD	30
26/F	13000	45000	9.7	30	17000	8	NIL	28

BM -Bone Marrow; WBC max- Maximum WBC before starting venetoclax; CAD-Coronary Artery Disease; RHD-Rheumatic Heart Disease; HCR-Hematological Complete Response.

6523 **Poster Session**

Use of BAFFR CAR-T to treat B cell leukemia/lymphoma and auto-immune diseases. First Author: Min Luo, Guangzhou Bio-gene Technology Co., Ltd., Guangzhou, China

Background: BAFFR (B-cell Activating Factor Receptor) is a member of the tumor necrosis factor (TNF) receptor superfamily and is almost exclusively expressed on B cells. Meanwhile, BAFFR is found to be highly expressed on the surface of lymphoma cells. In addition, blocking the BAFF/BAFFR interaction can inhibit the maturation of B cells, which is beneficial for alleviating autoimmune diseases, such as psoriasis, inflammatory bowel disease, multiple sclerosis, and rheumatoid arthritis. These characteristics make BAFFR a promising target for B-cell malignancies and autoimmune diseases. It has been reported that BAFFR CAR-T (PMB-CT01) treated six non-Hodgkin lymphoma (NHL) patients, and all of these patients achieved CR and showed tolerable safety profile. **Methods:** In the current study, we screened out three different BAFFR antibodies (1312, 1313, and 1315) and constructed them into second-generation CARs, consisting of BAFFR scFv, 4-1BB co-stimulatory domain and CD3ζ. The preclinical efficacy of BAFFR CAR-T cells was evaluated *in vitro* and *in vivo*. **Results:** *In vitro* experiments showed that all three CAR-T cells effectively killed Raji tumor cells, with 1312-CAR-T demonstrating the strongest cytokine release and cytotoxicity. *In vivo* tumor-bearing mouse experiments using Raji cells showed that 1312-CAR-T could effectively clear tumor cells in the mice. While the control group all mice died by day 33, and the experimental group remained fully alive. In addition, SLE model using MRL/MpJ-Fas^{lpr} mice showed that BAFFR CAR-T cells could decrease the dsDNA-IgG levels in the serum. **Conclusions:** The results of this study suggest that BAFFR is an active and promising immunotherapeutic target for B-cell malignancies and auto-immune diseases. In the future, BAFFR CAR-T clinical trials will be conducted to treat B-ALL, lymphoma, and autoimmune diseases. It would be interesting to see whether BAFFR CAR-T can achieve similar or even better results than CD19 CAR-T in treating these diseases. Research Sponsor: National Natural Science Foundation of China; No. 82202034.

6524 **Poster Session**

The IRAK4 long isoform as widely upregulated in non-splicesome mutated acute myeloid leukemia and as altered by hypomethylating agent therapy. First Author: Eric J. Vick, University of Cincinnati, Cincinnati, OH

Background: IRAK4, a kinase effector of MyD88 signaling downstream of Toll-Like Receptor and IL-1 receptor pathways, has recently been shown to function independently of MyD88 in Myelodysplastic Syndrome (MDS) and AML leukemic cells. Our previous research demonstrated that AML leukemic stem and progenitor cells (LSPC) rely on signaling through IRAK4. Notably, AML LSPCs express a hypermorphic long splice isoform of IRAK4 (IRAK4-L) resulting from the inclusion of exon 4. IRAK4 inhibitors, currently in clinical trials for the treatment of MDS and AML, show improved efficacy in spliceosome mutants, which preferentially express IRAK4-L. However, in patients without known spliceosome mutations, the extent of IRAK4-L expression remains unclear. Additionally, the impact of IRAK4-L levels in Venetoclax and Azacitidine treatment is unknown in refractory or unfit AML. **Methods:** Umbilical cord vein blood stem cells expressing MLL-AF9 and NRAS^{G12D} (CD34+MA9.NRAS) were maintained in vitro using supplemented media. Venetoclax and Azacitidine doses were incrementally increased in combination until cells tolerated co-treatment with up to 1 μM of each compound with minimal cell death. Patient-derived xenograft (PDX) samples were obtained from the Cincinnati Children's Biobank and included AML samples from diverse genetic backgrounds, relapsed/refractory cases, and pediatric populations (ages 1-20). Cell lysates were normalized to total protein and analyzed using a chemiluminescent capillary-based immunoblotting system, which requires minimal lysate quantities. An IRAK4 C-terminus antibody was used to detect both the shorter and longer IRAK4 protein isoform. RNA sequencing was performed, and transcripts were normalized per million counts. IRAK4 transcript ratios were calculated by dividing the total long isoform transcripts by the short isoform transcript for each condition in duplicate. **Results:** Analysis of PDX and human AML cell lines revealed that 8/9 PDX preferentially expressed the IRAK4-L isoform ($>$70% of IRAK4-L), with 4/9 PDX samples and 5/6 previously uncharacterized cell lines producing it almost exclusively ($>$95% IRAK4-L). MA9.NRAS cells predominantly express IRAK4-L, but transiently shifted to IRAK4-S during treatment with AZA/VEN (27% IRAK4-S), an effect reversed upon recovery from treatment. **Conclusions:** IRAK4-L is widely expressed in AML patient-derived samples, including those with complex karyotypes and TP53 mutations, suggesting that IRAK4 inhibitors may be useful beyond splicing factor-mutant MDS/AML. Our models demonstrate that changes in IRAK4-L expression during treatment with hypomethylating agents may be useful as a biomarker to guide therapy strategies. Further research is needed to understand how prolonged treatment and other standard of care therapies affect IRAK4-L expression and sensitivity to IRAK4 inhibitors. Research Sponsor: Conquer Cancer, the ASCO Foundation; Leukemia and Lymphoma Society; Harris Scholar Award.

6525 **Poster Session**

A phase I study of allogeneic anti-CD19 CAR-T therapy for patients with CD19+ relapsed/refractory acute B-lymphoblastic leukemia. First Author: Sun Guangyu, The First Affiliated Hospital of University of Science and Technology of China, Hefei, China

Background: Acute B-lymphoblastic leukemia (B-ALL), characterized by CD19 expression, responds well to CD19-targeted CAR-T therapy. However, autologous CAR-T is limited by cost and accessibility. We've developed RD06-03, an allogeneic CAR-T product engineered with TCR/Gene-X knockout and NK inhibitory molecule overexpression, exhibiting resistance to allogeneic rejection and enhanced anti-tumor effects without inducing graft-versus-host disease (GvHD). Our phase 1 trial (NCT06307600) aims to assess the safety and efficacy of RD06-03 in R/R B-ALL patients, offering a novel "off-the-shelf" solution. **Methods:** Patients aged 3-70 years with CD19+ R/R B-ALL were eligible and enrolled in a dose escalation study with dosing groups (CAR+ T cells/kg) of DL1: 1×10^5, DL2: 3×10^5, DL3: 5×10^5 and EDL (exploratory dose level): 6.5×10^5. All patients received lymphodepletion with fludarabine (30mg/m^2/day) and cyclophosphamide (500mg/m^2/day) for 3 days before CAR-T infusion. Dose-limiting toxicity (DLT) and the maximum tolerated dose (MTD) were evaluated using accelerated titration and "3+3" escalation, followed by case expansion at the appropriate dose. **Results:** As of December 15, 2024, six R/R B-ALL patients were enrolled (DL1: 1, DL2: 3, DL3: 1 and EDL: 1) with a median age of 37.5 years (range, 18-63) and a median of 3 prior therapies (range, 2-8+). One patient relapsed after unrelated umbilical cord blood transplantation. Baseline median bone marrow blasts were 41.9% (range, 10%-88.5%). RD06-03 was well tolerated with no DLT, neurotoxicity or GvHD observed. CRS occurred in 4 of 6 patients (66.7%, all Grade 1) with a median duration of 2.5 days (range, 1-4). For doses above DL2, all 5 patients achieved CR/CRi (100%) with undetectable MRD, indicating a deep remission. The majority of responders remain in remission, with the longest remission duration reaching 147 days and a median follow-up of 128 days (range, 60-175). Robust expansion was observed in all patients receiving doses above DL2, with rapid expansion occurring at a median of 4 days post-infusion. The median peak expansion exceeded 1 million copies/μg DNA, with a median persistence of 28 days and the longest persistence surpassing 3 months. **Conclusions:** The phase I trial of RD06-03 confirms its safety and efficacy in patients with R/R B-ALL. Notably, RD06-03's engineered TCR/Gene-X and NK inhibitory molecules enhance its resistance to rejection and antileukemic activity without GvHD. RD06-03 demonstrates robust persistence, achieving a 100% CR/CRi rate in medium- to high-dose groups, which is even lower than that of autologous CAR-T, while maintaining a manageable safety profile under standard lymphodepletion. This aligns with its genetic modifications designed for optimal immune rejection resistance. Further studies are essential to solidify these findings and explore RD06-03's therapeutic potential. Clinical trial information: NCT06307600. Research Sponsor: None.

6526 **Poster Session**

TLR9 agonists as a potential therapeutic option for B-ALL patients with low P53 expression. First Author: Ling Bai, First Affiliated Hospital of Jilin University, Changchun, China

Background: B-cell acute lymphoblastic leukemia (B-ALL) is a highly malignant hematologic cancer with poor prognosis, especially in relapsed or refractory cases. Abnormal P53 expression is more prevalent in relapsed/refractory B-ALL and is associated with increased drug resistance. B-ALL cells in the bone marrow (BM) promote the survival of malignant cells by suppressing P53 accumulation. Therefore, identifying drugs that can reactivate P53 signaling may provide novel therapeutic strategies for patients with low P53 expression, particularly by targeting BM-resident B-ALL cells. **Methods:** Building on our previous findings that TLR9 agonists can activate the P53 signaling pathway and preferentially eliminate BM-resident B-ALL cells over peripheral B-ALL cells, we investigated the mechanisms by which TLR9 agonists regulate glucose metabolism through P53 to induce B-ALL apoptosis. We constructed P53 knockdown cell lines, conducted seahorse assays to analyze glucose metabolism, and performed RNA sequencing to identify key molecules. Mechanistic studies focused on the regulation of glucose metabolism and its P53-dependent pathways. Furthermore, we elucidated the role of glucose metabolism in TLR9 agonist-induced reactive oxygen species (ROS) production and mitochondrial apoptosis. **Results:** TLR9 agonists preferentially eliminate BM-resident B-ALL cells via P53-dependent pathways. Specifically, TLR9 agonists suppress glycolysis while enhancing oxidative phosphorylation and ROS generation through the P38-P53-TIGAR signaling axis. Elevated ROS levels further facilitate the formation of the BAX/BAK/TOM20 complex, promote TOM20 oxidation and accumulation, and activate BAX. The P53-TIGAR-ROS-MOMP axis was identified as the critical mechanism underlying TLR9 agonist-induced apoptosis in B-ALL. Additionally, patient-derived xenograft models confirmed that ROS generation is key to the efficient clearance of BM-resident B-ALL cells by TLR9 agonists. **Conclusions:** As P53-reactivating agents, TLR9 agonists selectively eliminate B-ALL cells while preserving immune cell anti-tumor function. This study highlights the role of glucose metabolism in the TLR9 agonist-mediated clearance of BM-residual B-ALL cells, providing a potential maintenance or combination therapy strategy for relapsed/refractory B-ALL patients, particularly those with low P53 expression. Research Sponsor: Science and Technology Department Science and Technology Development Plan Project in Jilin Province; YDZJ202301ZYTS425; National Natural Science Foundation of China; 82303732; the First Hospital of Jilin University; JDYYCB-2023003.

6527 **Poster Session**

Real-world patient management practices in responders to venetoclax for newly diagnosed acute myeloid leukemia. First Author: Ofir Wolach, Rabin Medical Center, Petach Tikva, Israel

Background: Venetoclax (VEN) is approved for adult patients (pts) with newly diagnosed (ND) acute myeloid leukemia (AML) in combination with hypomethylating agents (HMAs) or low dose cytarabine. This abstract describes real-world pt management practices among pts with ND AML who respond to VEN+HMA. **Methods:** The AML Real world evidenCe (ARC) Initiative is a multicenter chart review study of adults with ND AML treated with VEN at 17 academic sites in the US, Israel, and Canada. Pts ineligible for intensive chemotherapy (IC; ie, aged ≥75 years or ≥1 Ferrara criteria comorbidity) who initiated VEN+HMA on or after April 2016 were included (ie, before and after release of product label). Pt management practices in first-line VEN treatment and related impact on duration of response (DoR; assessed with Kaplan-Meier analyses) were examined among pts achieving composite complete remission (CRc; ie, CR or CR with partial hematologic recovery or incomplete count recovery). **Results:** Among IC-ineligible VEN-treated pts, 116 (60.4%) achieved CRc (median age 73.0 years, 37.9% female, 53.4% European LeukemiaNet 2017 adverse risk, 24.2% Eastern Cooperative Oncology Group grade ≥2). Median DoR was 11.0 months (95% confidence interval: 8.8; 15.2). Most pts (75.9%) received VEN + azacitidine. Median observed VEN treatment duration was 5.8 months and 31.9% remained on VEN as of data entry; 12.1% received hematopoietic stem cell transplant post-VEN. Almost all pts (93.6%) had ≥1 marrow assessment post-VEN initiation, usually in cycle 1 (68.0%) or 2 (19.4%). During VEN treatment, 44.8% received granulocyte colony stimulating factor. Antifungals were used in cycle 1 by 68.1% (83.5% prophylactic; 63.3% strong CYP3A4 inhibitor); DoR did not differ by antifungal use. Most pts (68.1%) had VEN dose ramp-up, from a median of 100 mg to 400 mg daily over 3 days. In cycle 1, 59.5% started with 28 VEN dosing days; this proportion declined in subsequent cycles. Among pts still treated, 48.6% and 54.8% had ≤21 dosing days in cycles 2 and 3, respectively. Most pts achieved CRc in cycle 1 (58.6%) or 2 (21.6%); median DoR did not differ significantly between these pts vs later responders. Among 93 pts treated for ≥1 cycle post-response, most (87.1%) had a dose hold before initiating the next cycle; 51.6% of these 93 pts had a dose hold up to 14 days. Of 50 pts remaining on 28 dosing days until CRc, 26.0% reduced to ≤21 dosing days in the next cycle. Neither postremission dosing days modifications nor between-cycle dose holds significantly impacted DoR. **Conclusions:** Among VEN-treated ND pts with AML achieving CRc in real-world academic settings, most achieved CRc by the end of cycle 2, consistent with clinical trial results. Nevertheless, timing of response did not appear to affect DoR. Postremission dosing days modifications and between-cycle dose holds were common in clinical practice and did not appear to impact DoR. Research Sponsor: AbbVie; Genentech.

6528 **Poster Session**

Nucleophosmin (*NPM1*) genomic alterations (GA) in acute myeloid leukemia (AML): A genomic landscape study. First Author: Osama Batayneh, SUNY Upstate Medical University, Syracuse, NY

Background: *NPM1* GA characterize a clinically important subset of AML cases which relapse in more than 50% of treated patients despite being generally sensitive to conventional chemotherapy regimens. In AML, the interactions between GA in *NPM1*, *KMT2A* and menin protein have been linked to leukemogenesis and represent new potential targets for anti-tumor therapies. **Methods:** 4,206 cases of AML underwent comprehensive genomic profiling from 2019 through 2024, using the FoundationOne Heme combined hybrid capture based DNA and RNA sequencing assay. All classes of relevant GA were evaluated. The tumor mutation burden (TMB), homologous recombination deficiency signature (HRDsig) and microsatellite Stability (MSS) status were determined from the sequenced data. **Results:** 633 (15.1%) of the 4,206 AML featured *NPM1* GA (NPM1mut). Short variant mutations were found in >99% of the NPM1mut AML with the W288fs*12 frameshift base substitution accounting for 92.4% of cases. An *NPM1 - MLF1* fusion was identified in 1.3% of NPM1mut cases. The NPM1mut+ were more frequently associated with female patients (53.4% vs 41.5%; p<.0001) and had a slightly higher median age compared to the NPM1 wild type (NPM1wt) AML patients (62yrs vs 60yrs; p<.0001). Majority of patients (>60%) were from European decent. There were greater NPM1 GA in patients with European (77.1% vs 68.5%; p<.0001) and lower with African ancestry (9.2% vs 10.2%; p<.0001). MSI High (0% in both groups) status, HRDsig+ (0–0.1%) and elevated TMB (median < 1 mutation/Mb) were extremely uncommon in both groups. GA more frequent in NPM1mut AML compared to the NPM1wt AML cohort included *DNMT3A* (39.2% vs 12.6%; p<.0001), *FLT3* (54.5% vs 14.7%; p<.0001), *IDH1* (16.1% vs 5.6%; p<.0001), *IDH2* (19.0% vs 9.0%; p<.0001), *TET2* (23.4% vs 13.5%; p<.0001) and *WT1* (12.5% vs 9.4% p=.02). GA more frequent in NPM1wt AML included *ASXL1* (17.1% vs 3.6%; p,.0001), *BCOR* (7.5% vs 1.6%; p<.0001), *KMT2A* (14.7% vs 0.2%; p<.0001), *RUNX1* (22.5% vs 1.9%; p-,.0001), *STAG2* (6.9% vs 1.6%; p<.0001) and *TP53* (19.1% vs 4.1%; p<.0001). **Conclusions:** The development of menin inhibitors has recently identified GA in *NPM1* as a promising target of therapy for AML patients. Other therapy targets in AML such as *FLT3* and *IDH1/2* are more frequently identified in NPM1mut than NPM1wt AML, while *KMT2A* is more frequently identified in NPM1wt AML. This genomic landscape study reveals significant differences in important GA associated with AML in NPM1mut and NPM1wt cases which may enrich our understanding of the molecular profile in AML and identify additional targets for therapy. Research Sponsor: None.

Pathogenic genomic alterations in NPM1mut and NPM1wt AML.

	NPM1wt AML (n=3573)	NPM1mut AML (n=633)	P-value
ASXL1	17.1%	3.6%	<.0001
CEBPA	6.4%	8.2%	NS
DNMT3A	12.6%	39.2%	<.0001
FLT3	14.7%	54.5%	<.0001
IDH1	5.6%	16.1%	<.0001
IDH2	9.4%	19.0%	<.0001
KMT2A	14.7%	0.2%	<.0001
RUNX1	22.5%	1.9%	<.0001
TET2	13.5%	23.4%	<.0001
TP53	19.1%	4.1%	<.0001

6529 Poster Session

Real-world outcomes of inaticabtagene autoleucel in Chinese patients with B-ALL. First Author: Hongsheng Zhou, Southern Medical University Southern Hospital, Guangzhou, China

Background: Inaticabtagene autoleucel (Inati-cel) is a CD19-specific chimeric antigen receptor (CAR) T-cell product, featuring a CD19 scFv derived from the clone HI19α and a 4-1BB/CD3-ζ costimulatory domain, which was approved in China for adult patients with relapsed or refractory B-acute lymphoblastic leukemia (r/r B-ALL) in November 2023. **Methods:** We conducted the multi-center, non-interventional real-world study (NCT06450067) to evaluate Inati-cel for adult B-ALL patients. Between November 20, 2023, and November 13, 2024, 62 patients received Inati-cel and were evaluable. The median age was 37.5 (range, 14-76) years, with 13 patients aged≥60 years. At screening, 16 cases relapsed after hematopoietic stem cell transplantation (HSCT), 4 cases were primary refractory, and over 70% of patients carried high-risk genetic abnormity. The median infusion dose was 0.60 (range: 0.46-0.9) $\times 10^8$CAR-T live cells. **Results:** The data as of December 30, 2024, with a median follow-up of 3.8 months (range: 0.5–12.4 months), 89.5% achieved MRD-negative ORR after Inati-cel in r/r patients, including 31 with CR and 3 with CRi (table1). Nine patients with MRD-positive at screening, the MRD-negativity rate reached 100% after Inati-cel. After Inati-cel, 26 patients had MRD results detected by q-PCR, and 92.3% obtained negative results. After achieving CR/CRi, 4 patients subsequently underwent allo-HSCT in remission. The median DOR, OS and RFS have not been reached with and without censoring patients at subsequent allo-HSCT. Among the evaluable patients, the 1-year RFS and DOR rates were 76.2% and 74.1%, respectively. Seven patients experienced relapses, including 3 CD19+ relapses, 2 CD19- relapses, and 2 with unclear CD19 status. It is worth noting that in 6 cases of extramedullary disease, 4 cases were effective, but 2 cases relapsed within 3 months after Inati-cel. All patients who received the Inati-cel infusion were alive, except for one death from disease progression. The most common adverse events (AEs) of special interest were cytokine release syndrome (CRS) and immune effector cell-associated neurotoxicity syndrome (ICANS). Fifty-one percent of patients developed CRS, but grade 3 or higher CRS and ICANS only occurred in 3.2% and 1.6% of patients, respectively; all patients recovering without sequelae, no AE-related deaths. **Conclusions:** The real-world use of Inati-cel demonstrates a high MRD-negative ORR in adult B-ALL. The safety profile was manageable, with a low incidence of grade ≥3 CRS and ICANS in the real-world setting. Longer follow-up data will be presented. Clinical trial information: NCT06450067. Research Sponsor: None.

Efficacy profiles treated with Inati-cel.

Response	r/r B-ALL at enrollment , n=32	isolated extramedullary disease, n=6	MRD-pos, n=4	MRD-neg, n=20
CR or CRi (No. of patients)	30	4	-	-
Rate	93.7%	66.7%	-	-
CR, No. (%)	27(84.3%)	4(66.7%)	-	-
CRi, No. (%)	3 (9.4%)	-	-	-
MRD-neg rate, No. (%)	30/30 (100%)	-	4/4 (100%)	-
1-year DOR rate	67.4%		93.3%	
1-year RFS rate	68.2%		93.8%	

6530 Poster Session

Comparable efficacy of venetoclax 50mg with posaconazole versus venetoclax 400mg in newly diagnosed AML patients: A prospective study of pharmacokinetics, toxicity, and clinical outcomes. First Author: Gaurav Prakash, PGIMER, Chandigarh, Nehru Hospital, Chandigarh, India

Background: Metabolism of Venetoclax(VEN) by CYP3A enzymes gives a unique opportunity to administer it at a lower dose with a CYP3A inhibitor. Azoles are strong CYP3A inhibitors & they are commonly used for antifungal prophylaxis during AML induction. Current data suggest that VEN 100mg with posaconazole achieves comparable clinical efficacy but is associated with higher myelotoxicity. We prospectively explored further dose reduction of VEN to 50 mg with posaconazole & compared it with VEN 400 mg with respect to pharmacokinetics, response rates & toxicity. **Methods:** We conducted an open-label, prospective study & enrolled 31 AML patients unfit for intensive chemotherapy. Patients received either VEN 50 mg with posaconazole (VEN50 cohort, n=20) or VEN 400 mg without posaconazole (VEN400 cohort, n=11). Pharmacokinetic parameters, including C0, Cmax, & AUC(0–24), were assessed using high-performance liquid chromatography. Clinical outcomes: overall response rate (ORR), composite complete response (CRc), measurable residual disease (MRD), & hematological recovery time-were analysed. **Results:** The median age of patients was 50 years (IQR: 35.5–60). Under the ELN2024 model, 74% of VEN50 patients & 63.6% of VEN400 patients were favourable-risk, while 26% & 36.4% were intermediate-risk, respectively. The ORR was 80% in the VEN50 cohort & 81.8% in the VEN400 cohort. CRc rates were comparable between the VEN50 (60%) & VEN400 (63.6%) cohorts, with similar MRD negativity rates (30% vs. 36.3%). Pharmacokinetic analysis revealed significantly lower systemic drug exposure in the VEN50 cohort [AUC(0–24):17.88 μg·h/mL vs. 48.05 μg·h/mL, p=0.002] with C0 levels of 0.42 μg/mL vs. 1.08 μg/mL (p=0.004) & Cmax levels of 1.435 μg/mL vs. 3.63 μg/mL (p=0.002). Patients in VEN50 cohort experienced shorter neutropenic phase (17.5 vs. 24 days). Adverse events, including febrile neutropenia (60% vs. 72.7%, p=0.501) & culture-positive infections (20% vs. 27.2%, p=0.569), were comparable between the two cohorts. No treatment-related death occurred in either of the group. **Conclusions:** Our findings suggest that lower plasma levels achieved with VEN50 can lead to comparable CR rate & MRD negative rate in comparison with VEN400 with lesser myelotoxicity. Research Sponsor: None.

Comparison of baseline characteristics and outcomes.

Category	VEN 50mg + Posaconazole)	VEN 400 mg	P-Value
Median Age (IQR)	50 (35–59)	39 (35–52)	0.32
ECOG (0–2) (%)	90	91	0.29
C0 (μg/mL, Median)	0.42 (0.17–1.57)	1.08 (0.4–2.78)	0.004
Cmax (μg/mL, Median)	1.435 (0.54–5.51)	3.63 (1.27–6.92)	0.002
AUC0-24 (μg·h/mL, Median)	17.88 (8.09–81.47)	48.05 (19.96–94.79)	0.002
Overall Response Rate (ORR) (%)	80	81.8	1.0
CRc (CR + CRi) (%)	60	63.6	1.0
MRD Negativity (%)	30	36.3	0.98
Febrile Neutropenia (%)	60	72.7	0.501
Neutropenia Recovery (days, Median)	17.5	24	0.4
Culture-Positive Infections (%)	20	27.2	0.569

6531 Poster Session

Subgroup analysis by fitness criteria of patients (pts) with blastic plasmacytoid dendritic cell neoplasm (BPDCN) treated with first-line (1L) tagraxofusp (TAG). First Author: Naveen Pemmaraju, The University of Texas MD Anderson Cancer Center, Houston, TX

Background: BPDCN, an aggressive orphan hematologic neoplasm, expresses CD123 and presents in skin, bone marrow, blood, and viscera. For pts eligible to undergo hematopoietic cell transplantation (HCT), the 1L treatment goal is to rapidly induce a durable complete response (CR) before HCT. TAG is a first-in-class CD123-targeted therapy with a well-characterized and manageable safety profile without cumulative myelosuppression and the only drug approved to treat BPDCN. In 1L pts with a median age of 68 yrs, TAG has demonstrated, in a phase 1/2 pivotal trial with prespecified/multisystem response criteria, a 75% overall response rate, 24.9-month (mo) median duration of CR/clinical CR (CRc), and the ability to bridge 51% of pts with CR/CRc to HCT (Pemmaraju, JCO 2022). Notably, multi-agent intensive chemotherapy (IC) prior to HCT is still used, particularly in young fit pts, despite short- and long-term toxicity/myelosuppression and despite short durations of response (DOR). Also, many pts with BPDCN are ineligible for IC before HCT. We assess outcomes, based on pretreatment comorbidity burden, across HCT-specific comorbidity index (HCT-CI; Sorror, JCO 2007) fitness groups for pts who received 1L TAG for BPDCN in the pivotal trial (NCT02113982). **Methods:** Pts who received 1L TAG 12 μg/kg IV on days 1-5 of a 21-day cycle (C) were retrospectively assigned to categories by HCT-CI score (0 [low], 1-2 [intermediate; int] and 3+ [high]) per baseline medical history, concomitant medications, and labs. Outcomes included best response, time to response (TTR), DOR, overall survival (OS), HCT rate, treatment-related adverse events (TRAEs), and capillary leak syndrome (CLS). **Results:** 65 pts were scored as HCT-CI low (n=15), int (n=22), or high (n=28). Median age was 61, 67.5, and 70 yrs, respectively; disease was more extensive in high-risk pts. Objective responses (80%, 68%, 79%) were high regardless of HCT-CI group, with CR/CRc rates of 73%, 59%, and 46%. Median TTR was similar; median DOR was longer in low and int (24.9 mo/not reached [NR]) vs high (3.9 mo). HCT rates were 33%, 45%, and 21%; pre-transplant CR/CRc rates were 100%, 90%, and 83% with median DOR NR. Median OS in HCT pts was 38.4 mo, NR, and NR. In each group, most common Grade 3-4 TRAEs were thrombocytopenia and increased ALT/AST; most were in C1 and transient. Two deaths due to CLS occurred in int pts. Grade 3-4 CLS occurred in 0%, 9%, and 4% of pts; all CLS events were in C1 and all grade 1-4 CLS events resolved. **Conclusions:** 1L TAG BPDCN treatment yielded high response rates regardless of HCT-CI fitness, with a similar safety profile across HCT-CI groups. TAG enabled bridge to HCT across all fitness groups, including pts with high risk possibly ineligible for IC, as TAG is not associated with prolonged myelosuppression seen with IC. These results affirm TAG as the SOC in 1L treatment for the majority of pts with BPDCN. Clinical trial information: NCT02113982. Research Sponsor: Menarini Group.

6532 Poster Session

Detection of KMT2A partial tandem duplication (PTD) in AML by whole genome sequencing (WGS): Addressing limitations of traditional techniques in the era of revumenib approval. First Author: Robert Huether, Tempus AI, Inc., Chicago, IL

Background: The menin inhibitor revumenib was recently FDA approved for treating patients with relapsed or refractory KMT2A-rearranged (rKMT2A) acute leukemias. Cytogenetics, FISH, and targeted next-generation sequencing (NGS) frequently miss KMT2A 11q23 partial tandem duplications (KMT2A-PTD)). Although KMT2A-PTDs have expression signatures similar to rKMT2A, they were excluded from revumenib's registration trial. Preclinical models have shown that menin inhibitors may also be effective for KMT2A-PTD, highlighting the need for precise breakpoint and KMT2A fusion product detection. Here, we evaluated the effectiveness of high-resolution WGS to identify a diverse array of KMT2A-PTD. **Methods:** Using a WGS assay (Tempus xH) optimized for comprehensive profiling of myeloid neoplasms, we capture the entire KMT2A locus at base pair resolution. DNA was extracted from blood or bone marrow aspirates and was used to construct paired-end libraries via tagmentation. Sequencing was performed on the Illumina NovaSeq-X platform, achieving a mean coverage of 80X. Data were analyzed using the DRAGEN Platform with custom post-processing filters. Exon copy number calls from a targeted NGS assay and exon capture RNAseq NGS assay (Tempus xT and xR, respectively) were used for verification. **Results:** WGS from 230 hematopoietic neoplasms (68% AML, 18% MDS, 12% CML, and 2% others) identified 13 specimens (5.6%) containing a KTM2A-PTD, with variant allele frequencies (VAFs) between 9-66%. All PTDs contained breakpoints within known intron boundaries: one breakpoint in intron 1 (13/13) with terminal breakpoints located in intron 8 (6/13) or intron 10 (7/13). RNA data was available for 11 of 13 specimens and contained direct support for the presence of all the KMT2A-PTDs (100%). Using an NGS-targeted panel, exon-level copy calls were assessed for all 13 specimens with PTDs. Although unvalidated, we observed exon level gains in 9 of the 13 specimens (69%). As shown in prior studies, KMT2A-PTDs were mutually exclusive to other translocations, including rKMT2A. However, other high-frequency mutations for myeloid disease were present in select samples including mutations in IDH1, DNTM3A, WT1, and RUNX1. **Conclusions:** WGS is an effective tool for detecting KMT2A alterations that may be missed by traditional techniques such as NGS targeted capture, FISH or cytogenetics. 100% concordance was observed between WGS and RNAseq for KMT2A-PTDs, supporting the reliability of WGS. The FDA approval of menin inhibitors for KMT2A-rearranged AML/ALL suggests potential clinical opportunities for broad tests (WGS) to identify other rearrangements, including KMT2A-PTDs, highlighting the need for further research into targeted anti-leukemia therapies. Research Sponsor: Tempus AI, Inc.

6533 **Poster Session**

Mitoxantrone hydrochloride liposome combined with cytarabine (MA) for patients with newly diagnosed secondary acute myeloid leukemia. First Author: Stephen Yang Liang, Department of Hematologic Oncology, State Key Laboratory of Oncology in South China, Guangdong Provincial Clinical Research Center for Cancer, Sun Yat-Sen University Cancer Center, Guangzhou, China

Background: Secondary acute myeloid leukemia (sAML) is an aggressive subset typically characterized by unfavorable biological features. CPX-351, a dual-drug liposomal formulation of cytarabine and daunorubicin, has demonstrated improved remission rates and overall survival (OS) in sAML; however, its use remains limited in China. Mitoxantrone hydrochloride liposome (Lipo-MIT), a pegylated liposomal formulation of mitoxantrone, provides enhanced anti-tumor efficacy and reduced toxicity. Here we report the outcomes of a novel regimen combining Lipo-MIT and cytarabine (MA) for patients (pts) with newly diagnosed sAML. **Methods:** This is a single-arm, prospective, exploratory study. Eligible pts were aged 18 to 75 years and had newly diagnosed therapy-related AML, AML with antecedent myelodysplastic syndrome (MDS) or chronic myelomonocytic leukemia (CMML), or de novo AML with MDS-related cytogenetic abnormalities. Patients received MA regimen consisting of Lipo-MIT (24mg/m^2 on day 1) and cytarabine (100mg/m^2/d from days 1 to 7) every four weeks for up to 2 cycles. The primary endpoint was CRc (complete remission (CR)+CR with incomplete neutrophil or platelet recovery (CRi)). The secondary endpoints included the rate of CRc with negative minimal residual disease (MRD), overall response rate (ORR), overall survival (OS) and safety. **Results:** As of January 20, 2025, a total of 13 pts were enrolled with a median age of 53 years (range, 24.0-65.0), including 8 with therapy-related AML and 5 with AML arising from antecedent MDS. According to the 2022 edition of the European Leukemia Network recommendations, 2 (15.4%) pts were classified as a favorable prognosis, 2 (15.4%) as intermediate, 8 (61.5%) as adverse, and 1 (7.7%) as unknown. The most commonly mutated gene and abnormality karyotype was TP53 and del(7q), respectively, both occurring in 23.1% (3/13). Of 13 pts, 5 were assessed as CR, 3 as CRi and 1 as PR. The CRc rate was 61.5% (8/13) and the ORR was 69.2% (9/13). Among 8 pts who achieved CRc, the rate of negative MRD was 75% (6/8). With a median follow-up of 3.4 months, the 1-year OS rate was 88.9% (95% CI, 43.3-98.4) while the median OS was not reached. The median duration of absolute neutrophil count $<$500 cells/μL was 21.0 days (range, 7.0-29.0) and platelet count $<$50000 platelets/μL was 20.0 days (range, 14.0-61.0) in pts who achieved CRc after initial induction. The non-hematological treatment-emergent adverse events (TEAEs) graded at 3 were febrile neutropenia (46.2%), fever (7.7%), sepsis (7.7%), pulmonary infection (7.7%), oral mucositis (7.7%), anaphylaxis (7.7%) and pruritus (7.7%). No non-hematological TEAEs of grade 4 or worse were observed and the 60-day mortality rate was 0%. **Conclusions:** The MA regimen demonstrated encouraging remission rates and a superior safety profile, indicating its potential as a treatment option for newly diagnosed sAML. Clinical trial information: ChiCTR2300076618. Research Sponsor: None.

6534 **Poster Session**

Co-mutational landscape of Indian core binding AML: An answer to the unfavorable outcome in a favorable AML? First Author: Rahul Bhargava, Fortis Memorial Research Institute, Gurugram, India

Background: Core binding factor AML, which encompasses RUNX1/RUNX1T1 and CBFB/MYH11, comprise 10-15% of all AML, currently classified as favorable risk in the 2022 European LeukemiaNet Risk Stratification. The Indian CBF AML cohort as reported in earlier studies tends to be younger, with extramedullary disease and with higher number of co-mutations. Also due to unavailability of the anti CD33 gemtuzumab ozogamicin in India, the outcomes to standard therapies tend to be dismal when compared to the West. This raises a dilemma for the ELN risk stratification of this entity as a favorable risk. **Methods:** 165 patients of CBF AML were accrued, from two different centers. Non-disclosure consents from the participating centers were obtained. Patients with documented CBF AML who have undergone NGS based testing were included. Descriptive statistical analysis was done for continuous and ordinal data. The analysis was done using SPSS version 24. A two tailed p value of $<$5% was considered significant. The data from TCGA studies was compared which was accessed through www.cbioportal.org and all studies of AML were included. **Results:** A total of 165 patients of CBF AML were included in the study. Median age was 33.4 years (range 16-45) with a clear male predilection (male to female ratio of 3.1:1).RUNX1/RUNX1T1 rearrangement was detected in 70% (116) cases and 49 (30%) cases harbored the CBFB/MYH11 gene rearrangement. At least one additional mutation was detected in 70% cases with RUNX1/RUNX1T1 rearrangement and 80% cases of CBFB/MYH11.The most frequent co-occurring alteration was NRAS (32% cases across both subtypes, more common in CBFB/MYH11). Another statistically significant finding was patients with inv(16) manifested a significantly higher frequency of Spliceosome mutations (p = 0.028) and WT1 mutations (p = 0.021) compared to t(8;21). Two patients harbored concomitant TP53 mutations predicted to be pathogenic based on ClinVar database as well as IARC TP53 database. Both these patients also had a complex karyotype along with RUNX1/RUNX1T1 fusion. Mutation in DNA methylation genes occurred more in CBFB/MYH11 vs RUNX1/RUNX1T1 cases ($p<0.06$). The patients with CBFB/MYH11 also depicted a higher prevalence of mutations in the polycomb repressor genes ASXL1 and ASXL2 when compared to RUNX1/RUNX1T1($p<0.06$).Another feature was higher prevalence of cohesin complex gene mutations involving SMC1A and SMC3 which were seen in 20% cases overall. The inv(16) group showed a lower predilection compared to the t(8;21) group ($p<0.061$). **Conclusions:** The presence of higher number of additional mutations in the Indian cohort underscores the need of larger studies/controlled trials of this subset, which otherwise has been stratified as favorable. The access to standard of care like GO is a necessity and there is a need to formulate national/regional guidelines for the Indian subset. Research Sponsor: None.

6535 **Poster Session**

Outcomes of Ph-like B-lineage acute lymphoblastic leukemia in the era of novel therapies. First Author: Hamed Rahmani Youshanlouei, University of Chicago, Chicago, IL

Background: Ph-likeALL) is a high-risk subset of B-ALL with poor treatment response and high relapse rates. We examined outcomes of Ph-like B-ALL pts (pts) treated at a large academic center in the current era of novel therapies. **Methods:** We retrospectively analyzed 68 adults with Ph-like B-ALL treated at the University of Chicago (2014-2023). Ph-like status was classified per WHO 2022 criteria using FISH, DNA and RNA sequencing. **Results:** Median age at diagnosis was 34 years (range, 18-74), 68% were male. We found CRLF2 rearrangements (CRLF2-r) in 75%, JAK2-r in 10%, ABL1-r in 6%, FGFR-r in 3%, and rearrangements in ABL2, CSF1R, PDGFR and ROS1 at 1.5% each. Most common co-occurring somatic gene mutations involved IKZF1 (41%), CDKN2A (37%), JAK2 (37%), KRAS (16%), PAX5 (12%) and NRAS (10%). First-line therapy was chemo alone in 80% of pts with the following distribution: CALGB 10403 in 43%, hyper-CVAD in 28% and other chemo in 9%. The remaining 20% of pts received novel therapies in first-line setting, including C10403 + inotuzumab (InO) in 7%, ino + blinatumomab (blin) in 6%, hyperCVD + venetoclax in 4% and C10403 + imatinib in 3%. Post-induction flow cytometry-based measurable residual disease (MRD) negativity rate was significantly higher in pts who received novel therapies upfront vs pts who received standard chemo (55% vs 20%, p= 0.02). This is lower than our non-Ph-like B-ALL pts, for whom the MRD-negative CR rate after chemo induction was 62% ($p< 0.01$). We also observed higher 5-year relapse-free survival (RFS) rate for pts who received novel therapies upfront vs standard chemo alone (65% vs 20%, $p< 0.01$). We did not detect a significant difference in overall survival (OS) for pts treated with novel therapies vs standard of care (p= 0.52), which is likely due to the utilization of novel therapies as salvage regimens after relapse. Of note, 5 pts received kinase inhibitors (ruxolutinib, dasatinib, imatinib) in salvage setting, but did not achieve remission. There were no differences in OS or RFS outcomes when pts were stratified based on CRLF2-r vs non-CRLF2-r. Among co-occurring gene alterations, we observed higher risk for relapse in cases with KRAS mutations (HR= 4.29, 95% CI= 1.3-13.4), which was independent from the type of first-line therapy. 7% received anti-CD19 CAR-T cell therapy. 32% had allogeneic transplant (HCT), which was done in CR1 in 31%, while 69% received HCT after salvage (CR2 or CR3). 64% received myeloablative conditioning (TBI-based regimens) with the following distribution of donors: 46% matched unrelated, 27% mismatched unrelated, 18% matched related, 9% haplo-cord. Median OS after HCT was 10 months. **Conclusions:** Ph-like B-ALL pts treated with standard chemo have lower CR and RFS rates. Adding novel agents (InO, blin, venetoclax) to upfront regimens may improve outcomes. Future studies should focus on optimal first-line combinations and higher-risk groups such as KRAS-mutated Ph-like B-ALL. Research Sponsor: None.

6536 **Poster Session**

Potential benefits of using a different donor for transplantation consolidation after donor-derived CD7 CAR T. First Author: Jing Pan, State Key Laboratory of Experimental Hematology, Boren Clinical Translational Center, Department of Hematology, Beijing Gobroad Boren Hospital, Beijing, Beijing, China

Background: Stem cell transplantation (SCT) is often used in patients with relapsed or refractory T-cell acute lymphoblastic leukemia (r/r T-ALL) after CD7 CAR T therapy, in order to consolidate efficacy or promote immune reconstitution to reduce the risk of infection. Previous studies have shown that consolidatory SCT may be able to prolong the survival of patients after CD7 CAR T. However, infections after SCT raise concerns. Here, we explored optimization strategies for SCT consolidation after newly HLA-matched donor-derived CD7 CAR T therapy in r/r T-ALL patients. **Methods:** This is a retrospective analysis of SCT consolidation following donor-derived CD7 CAR T therapy, based on a phase 1 trial (ChiCTR2000034762) and a phase 2 trial (NCT04689659) approved by the Institutional Review Board (IRB) of Beijing Goboard Boren Hospital, and a phase 1/2 trial (NCT06316427) approved by the IRB of Beijing Goboard Hospital. The analysis was aimed to evaluate the impact of using different donors for CAR T therapy and the subsequent SCT, compared to using the same donor. **Results:** A total of 19 patients were included in this analysis, including four from the phase 1/2 trial who used different donors for CAR T therapy and SCT consolidation (Group A), and 15 patients who used the same donor for CAR T therapy and SCT consolidation (Group B, 7 from the phase 1 trial and 8 from the phase 2 trial). The median age of the 19 patients was 11 (range 2-43). 16 patients (84%) were male, and three (16%) were female. The median interval from CAR T cell infusion to stem cell infusion was 32 days (range, 26-34) for group A, and 39 days (range 32-48) for group B. After stem cell infusion, all patients in group A had no detectable CAR T cells in the peripheral blood. However, in group B, six of the 13 patients evaluated had detectable CAR T cells in the peripheral blood, whereas the other seven did not. Within three months after stem-cell infusion, no patients in group A had CMV or EBV activation, while nine patients (60%) in group B had CMV or EBV activation. Two patients (50%) in group A and 10 patients (67%) in group B had any type of viral activation. Compared to group B, patients in group A tended to have a higher chimerism rate in the peripheral blood at two months and in the bone marrow at three months after stem cell infusion. **Conclusions:** In post-CD7-CAR patients, the risk of viral activation (especially CMV/EBV activation) after SCT using the same donor as CAR T was high. This may be partly related to the persistence of CAR T cells after SCT. The results showed that using a different donor from CD7 CAR T for subsequent SCT may contribute to the timely clearance of CAR T cells from patients and simultaneously reduce the rate of CMV/EBV activation after stem cell infusion. In addition, the chimerism rate was slightly increased at some time points. These results will be further evaluated in an ongoing phase 1/2 study at our center. Clinical trial information: NCT04689659, NCT06316427, ChiCTR2000034762. Research Sponsor: None.

6537 **Poster Session**

Overcoming acquired venetoclax resistance in acute myeloid leukemia through cell metabolism targeting. First Author: João Agostinho Machado-Neto, Department of Pharmacology, Institute of Biomedical Sciences, University of São Paulo, São Paulo, Brazil

Background: Venetoclax is a selective inhibitor of the anti-apoptotic protein BCL2, often overexpressed in acute myeloid leukemia (AML), contributing to cell survival and resistance to standard therapies. It has expanded treatment options, especially for elderly or chemotherapy-ineligible patients. However, acquired resistance to venetoclax is a significant challenge, limiting long-term effectiveness. Understanding the mechanisms of resistance is crucial for improving therapeutic strategies and identifying biomarkers for personalized treatment. This study investigates these mechanisms by analyzing cellular phenotype, metabolic changes, BCL2 family gene/protein expression, and signaling pathways in venetoclax-resistant AML cell lines. **Methods:** Venetoclax-sensitive AML cell lines, MOLM-13 and MV4-11, were exposed intermittently to increasing concentrations of the drug to induce resistance. Cell viability was assessed using MTT assays, clonogenicity by colony formation, and apoptosis, mitochondrial damage, and DNA content by flow cytometry. Metabolic profiles were analyzed with Seahorse XF96, and signaling pathways were studied by Western blotting, qPCR, and global proteomics. Synergy assays were conducted with metformin (mitochondrial complex I inhibitor) and KPT-9274 (NAMPT inhibitor). **Results:** Intermittent exposure to venetoclax selected for resistant clones, MV4-11VR (IC_{50} > 1000 nM; parental cells IC_{50} = 2.5 nM) and MOLM-13VR (IC_{50} = 723 nM; parental cells IC_{50} = 3.3 nM). Venetoclax-induced apoptosis, mitochondrial damage, and DNA fragmentation were absent in resistant cells. Metabolic analysis showed increased mitochondrial metabolism in MOLM-13VR cells and enhanced glycolysis in MV4-11VR cells. Molecularly, MV4-11VR cells exhibited downregulation of BCL2L10, BAX, BCL2L11, BBC3, BIK, and BNIP3, while MOLM-13VR cells showed reduced BID, PMAIP1, BAD, BMF, and BECN1, along with increased MCL1. MOLM-13VR cells displayed enhanced MAPK signaling, and both resistant models had activation of the PI3K/AKT/mTOR pathway and upregulation of BCL-XL. Proteomic analysis revealed enhanced metabolic activity, with MV4-11VR cells enriched in fatty acid biosynthesis and carbohydrate metabolism pathways, while MOLM-13VR cells showed upregulation of aerobic respiration and ATP metabolism. Both parental and resistant cells exhibited comparable sensitivity to metformin and KPT-9274. The combination of these inhibitors with venetoclax resulted in synergistic effects, with KPT-9472 and venetoclax eliminating over 95% of resistant cells. **Conclusions:** This study provides key insights into the mechanisms of venetoclax resistance in AML. Targeting cellular metabolism with metformin or KPT-9274, combined with venetoclax, offers promising synergistic effects and potential strategies to overcome resistance, improving treatment outcomes in resistant AML cases. Research Sponsor: Fundação de Amparo à Pesquisa do Estado de São Paulo (FAPESP); 2023/12246-6.

6538 **Poster Session**

Should we treat TP53-mutated high-risk myeloid neoplasms in older patients? First Author: Talha Badar, Mayo Clinic, Jacksonville, FL

Background: *TP53* mutated (*TP53*^{mt}) high-risk myeloid neoplasm (HR-MN) confers a dismal prognosis in the contemporary era with only a subset of eligible patients (pts) able to achieve long-term remission with allogeneic stem cell transplantation (allo-HCT). Owing to poor outcomes, many physicians believe it is futile to treat older pts with disease-directed therapy, since curative intent allo-HCT cannot be offered. We sought to describe the outcomes of older pts with *TP53*^{mt} HR-MN receiving disease directed treatment. **Methods:** We conducted a multicenter observational study in collaboration with 11 U.S. academic centers under the COMMAND consortium. We reviewed the data of 451 older (≥ 60 years [yrs]) *TP53*^{mt} HR-MN (n= 282 acute myeloid leukemia [AML], n= 91 MDS transformed AML, n= 50 myeloproliferative neoplasm blast phase (MPN-BP) and n= 28 high-risk myelodysplastic syndromes [HR-MDS]) pts to analyze their outcome with disease directed treatment. **Results:** The median age was 70 yrs (range [R],60-90) and 58% were male. Proportions of pts with age ≥ 70 yrs were 47.5%. Eastern Cooperative Oncology Group Performance Status (ECOG-PS) was available in 68% (n= 306) of pts; 10.5%, 49%, 32% and 8.5% had ECOG-PS 0-3, respectively. The median bone marrow (BM) blast % was 32 (R, 5-99) and *TP53* variant allele frequency (VAF) was 45% (R, 2-97). The proportion of pts with multi-hit (MH) *TP53*^{mt} and complex cytogenetics (CG) was 83% and 82%, respectively. 43 %, 31%, 20% and 6% received hypomethylating agent (HMA) + venetoclax, intensive chemotherapy, HMA and other low-intensity therapy, respectively. The complete remission rate with or without count recovery (CR/CRi) amongst evaluable patients (n= 356) was 37%. The median duration of response was 6.7 months (mo) (R, 5.9-7.5). Amongst 56 (12%) pts who underwent allo-HCT, the median overall survival (mOS) from time of allo-HCT was 21.9 mo. The mOS among pts ≥ 70 yrs was 6.5 mo. The mOS in mo was better in HR-MDS (16.4), compared to *de novo* AML (6.5), MDS transformed AML (7.1) and MPN-BP (5.27), p= 0.003. We conducted multivariable analysis for OS using baseline variables that were significant/ showed trend towards significance, on univariate analysis (p<0.1). HR-MDS (HR; 0.43, 95% CI: 0.23-0.82, p= 0.01), CR/CRi (HR; 0.55, 95% CI: 0.39-0.77, p= <0.001) and allo-HCT (HR; 0.28, 95% CI: 0.16-0.47, p= <0.001) positively impacted OS. Whereas age ≥ 70 yrs showed trends towards inferior OS (HR; 1.31, 95% CI: 0.95-1.80, p=0.09). Complex CG (HR; 1.63, 95% CI: 0.83-3.21, p=0.15) and MH*TP53*^{mut} (HR; 1.30, 95% CI: 0.67-2.52, p= 0.42) did not retain significance for OS. **Conclusions:** Our multicenter study suggests that disease directed treatment in older *TP53*^{mt} HR-MN leads to modest response rates with short durations of response in the absence of allo-HCT. 12% of pts were able to receive allo-HCT with improvement in OS close to 2 yrs. The decision to treat this poor risk gp of pts should be based on individual pt characteristics and desires. Research Sponsor: None.

6539 **Poster Session**

Cytomolecular mechanisms of relapse after frontline FLT3 inhibitor (FLT3i)-based therapy in FLT3-mutated (mut) acute myeloid leukemia (AML). First Author: Sankalp Arora, Division of Cancer Medicine, The University of Texas MD Anderson Cancer Center, Houston, TX

Background: Data regarding the mechanisms of relapse and outcomes with salvage therapies in patients (pts) with *FLT3* mut AML after frontline FLT3i-based therapy are limited. **Methods:** This is a retrospective study of pts with *FLT3* mut AML who received frontline FLT3i-based therapy at our institution. Molecular and cytogenetic (CG) testing was compared between diagnosis and relapse. **Results:** 272 pts received frontline treatment with FLT3i from 9/2013-7/2024: 214 *FLT3*^{ITD}, 27 *FLT3*$^{ITD+TKD}$ and 31 *FLT3*^{TKD}. Induction therapy was intensive chemotherapy (IC) in 107 pts and low intensity therapy (LIT) in 165 pts [including HMA+venetoclax(VEN)+FLT3i in 93 pts]. FLT3i's used were gilteritinib (n=105), sorafenib (n=96), quizartinib (n=54), midostaurin (n=16), and crenolanib (n=1). Composite complete remission (CRc = CR + CRi) was attained in 203 pts (75%). 97 pts (36%) underwent allogenic stem cell transplant (ASCT) in 1st remission. After a median (med) follow-up of 46 months (mos), 80 pts (35% of responders) relapsed. Post-ASCT relapses occurred in 22/97 pts (23%). Relapse rates in pts receiving IC+FLT3i, HMA+VEN+FLT3i, and LIT+FLT3i (no VEN) were 23% (p<0.01), 31% (p<0.01), and 65% (ref), respectively. At relapse, loss of a *FLT3* mut (ITD and/or TKD) was noted in 34/72 tested pts (47%), with similar rates among transplanted and non-transplanted pts. *FLT3* loss at relapse was more common in pts who received IC+FLT3i or HMA+VEN+FLT3i *vs* LIT+FLT3i (no VEN): 57% vs 32% (p=0.05). Among 55 pts with comprehensive molecular testing at relapse, 24 (44%) had a newly detectable non-*FLT3* mut, most commonly *RAS* pathway (8, 15%), *WT1* (7, 13%), *TET2* (4, 7%), and *IDH1/2* (4, 7%). New mutations at relapse were less common in post-ASCT pts (19% vs 59%; p<0.01). Among *FLT3*^{ITD} pts, new *FLT3*^{TKD} mut at relapse occurred in 8/58 tested pts (14%): 7 had received frontline type 2 FLT3i. New CG abnormalities at relapse occurred in 27/65 tested pts (42%), most commonly trisomy in 11 pts (17%). No *BCR::ABL1* was observed at relapse. 51 pts received 1st salvage therapy after relapse (22 *FLT3*^{wt} and 29 *FLT3*^{mut} relapses). *FLT3*^{wt} relapses had higher CRc rates (41% vs 10%, p=0.02), and a trend to higher med OS (8.6 mos vs 5.7 mos, p=0.13) with salvage therapy compared with *FLT3*^{mut} relapses. **Conclusions:** Loss of *FLT3* mut at relapse occurred in almost 50% of pts receiving frontline FLT3i and was more common in pts receiving IC+FLT3i or HMA+VEN+FLT3i. Common mechanisms of clonal evolution included emergent mutations in *RAS* pathway, *WT1*, and DNA methylation genes (*TET2*, *IDH1/2*). Mutational clonal evolution was less frequent in post-ASCT relapses. Persistent *FLT3* mut at relapse was associated with a worse prognosis. Research Sponsor: MD Anderson Cancer Center Leukemia Specialized Programs of Research Excellence (SPORE) Grant CA1100632.

6540 **Poster Session**

Initial results from a phase II study of dose-adjusted etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin (DA-EPOCH) ± rituximab (R) + tafasitamab (tafa) for adults with newly-diagnosed (ND) Philadelphia chromosome negative (Ph-) B lymphoblastic leukemia (B-ALL). First Author: Noam Edward Kopmar, Fred Hutchinson Cancer Center, Seattle, WA

Background: For adults with ND Ph- B-ALL, treatment consists of intense multiagent chemotherapy, with outcomes linked to early measurable residual disease negativity (MRD-). The addition of blinatumomab to frontline chemotherapy improves survival, but regimens used are limited by toxicity and complexity. DA-EPOCH ± R is well-tolerated, effective (32% MRD- after cycle [C]1), and relatively simple to administer for ND B-ALL. Tafa is a CD19 monoclonal antibody with activity in B-cell lymphomas. We hypothesized that adding tafa to DA-EPOCH ± R in adults with ND Ph- B-ALL would improve rates of early MRD- without an increase in toxicity. **Methods:** This is a phase II investigator-initiated trial of DA-EPOCH ± R + tafa in adults with ND CD19+ Ph- B-ALL who are not candidates for pediatric-inspired therapy: age >40, unable to receive all care in specialized center, etc. (NCT05453500). The primary endpoint is MRD- (<0.01%) by multiparameter flow cytometry (MFC) after C1; secondary endpoints include rates of MRD- by C4, incidence of grade 3+ non-hematologic adverse events (AEs) by CTCAE v5, and event-free (EFS) and overall survival (OS). Exploratory endpoints include high-throughput sequencing (HTS)-based MRD detection in marrow and cerebrospinal fluid (CSF) by clonoSEQ. DA-EPOCH (+ R if CD20+) with intrathecal chemo given on days (D) 1-5 every 21 D for up to C8 (Cassaday, et al. *Leuk Lymphoma*, 2023). Tafa is given at 12 mg/kg IV on D 1, 8, and 15 in each C. Risk and response are assigned per NCCN. We used a Simon 2-stage design based on results with DA-EPOCH alone: if ≥5/15 pts (33%) achieved MRD- after C1, we would enroll up to 30 pts. **Results:** From 3/2023 to 1/2025, 17 pts have enrolled: 15 are evaluable (2 on treatment without sufficient time to categorize response), with 1 pt removed during C1 for AE (grade 4 AST elevation). Median age was 67 (range: 44-84), and 67% (12/16) had poor-risk cytogenetics. Six pts (38%) received R. In those with sufficient follow-up (f/u), complete response rate was 80% (12/15); MRD- by MFC after C1 was 40% (6/15) and 71% (10/14) by C4. In pts MRD- by MFC, 56% (5/9) were MRD- by HTS. Initial CSF evaluation demonstrated disease by MFC in 3 pts; HTS on CSF was positive in those pts, plus 3 more (6 total). There were 2 grade 4 AEs (reported as serious AEs): sepsis and intracranial hemorrhage. Grade 3 AEs seen in > 1 pt were fibrinogen decreased (5), infections (5), febrile neutropenia (4), hypotension (3), and syncope (2). With the longest f/u at 21 mo (range 0.6-21), 0 pts have relapsed. Four pts have died: 3 from non-relapse mortality unrelated to study treatment (2 following allogeneic transplantation) and 1 from refractory ALL. **Conclusions:** In a cohort of ND Ph- B-ALL, the addition of tafa to DA-EPOCH ± R led to rates of MRD- that are higher than historical rates, with similar toxicity. Since the target C1 MRD- rate was reached in part 1 of the 2-stage design, the trial is proceeding to part 2 and accrual will be completed. While f/u is short, no relapses have been seen. HTS is feasible on CSF and extends the level of detection beyond MFC. Clinical trial information: NCT05453500. Research Sponsor: Incyte.

6541 Poster Session

Outcomes in patients with B-cell precursor acute lymphoblastic leukemia receiving inotuzumab ozogamicin stratified by body mass index. First Author: Wendy Stock, University of Chicago, Chicago, IL

Background: Inotuzumab ozogamicin (InO) is approved for the treatment of adults for relapsed/refractory B-cell precursor acute lymphoblastic leukemia (R/R B-ALL). In previous studies, elevated body mass index (BMI) has been associated with worse outcomes in adult patients treated for ALL. We report the efficacy and safety of InO in adult patients with R/R B-ALL, stratified by BMI. **Methods:** Data from three previous studies, NCT01363297/B1931010 (InO: 0.8–1.8 mg/m^2/cycle [Ph1], 1.6–1.8 mg/m^2/cycle [Ph2]) NCT01564784/B1931022 (InO: 1.5–1.8 mg/m^2/cycle) and, NCT03677596/B1931030 (InO: 0.9–1.2mg/m^2 or 1.5–1.8mg/m^2 per cycle) were pooled, participants (pts) were grouped by formal BMI definitions: <25 kg/m^2 (healthy), 25–30 kg/m^2 (overweight) and >30 kg/m^2 (obese). Data presented as descriptive statistics only. A genAI tool was used with author review to develop the first draft (8 Jan 2025; Pfizer; GPT-4o); authors take full responsibility for the content. **Results:** Data from 338 pts (18–79 years; median age 44, 41% female) were analyzed, with 155 pts in the <25 kg/m^2 group, 116 pts in the 25–30 kg/m^2 group and 67 pts in the >30 kg/m^2 group. Across the <25, 25–30 and >30 kg/m^2 BMI groups, CR/CRi was achieved in 108 (70%), 88 (76%) and 46 (69%) of pts, and MRD negativity observed in 87 (56%), 73 (63%) and 35 (52%) of pts, respectively. At 24 months, the probability of progression-free survival (95% CI) was 19.9% (13.2, 27.5), 12.8% (7.2, 20.1) and 10.9% (4.2, 21.1), and the probability of survival (95% CI) was 28.1% (21.0, 35.6), 22.1% (14.8, 30.3) and 17.5% (9.2, 27.8) in the <25, 25–30 and >30 kg/m^2 BMI groups, respectively. Most pts experienced TEAEs, and incidence was similar across BMI groups (97%–99%). Common hepatic Grade ≥3 TEAEs were sinusoidal obstruction syndrome (SOS) (10 %, <25 kg/m^2; 6%, 25–30 kg/m^2; 9%, >30 kg/m^2) and GGT increase (7 %, <25 kg/m^2; 5%, 25–30 kg/m^2; 5%, >30 kg/m^2). Overall, 143 pts (42%) proceeded to hematopoietic stem cell transplantation (HSCT) after InO treatment, sixty-seven (43%) in the <25 kg/m^2 group, 49 (42%) in the 25–30 kg/m^2 group, and 27 (40%) in the >30 kg/m^2 group. Post-HSCT, non-relapse mortality within 100 days was estimated to be 22% in the <25 kg/m^2 group, 22% in the 25–30 kg/m^2 group and 19% in the >30 kg/m^2 group. Post-HSCT SOS was observed in 18 pts (27%) in the <25 kg/m^2 group, 7 pts (14%) in the 25–30 kg/m^2 group and 6 pts (22%) in the >30 kg/m^2 group, with grade 3–4 SOS observed in 10 (15%), 7 (14%) and 5 pts (19%), respectively. **Conclusions:** In this pooled analysis of pts treated with InO for R/R B-ALL, efficacy and safety outcomes were broadly consistent across BMI groups. However, lower PFS and OS rates at 24 months were noted in pts with higher BMI. Research Sponsor: Pfizer.

Summary of outcomes.

%	<25 kg/m^2 (N=155)	25–30 kg/m^2 (N=116)	>30 kg/m^2 (N=67)
CR/CRi	70	76	69
CR	33	36	40
CRi	37	40	28
MRD-negativity	56	63	52
PFS (24 months)	20	13	11
OS (24 months)	28	22	18

6542 Poster Session

Novel potent and selective inhibitors targeting FLT3 for AML therapy. First Author: Gauthier Errasti, PMC Isochem, Paris, France

Background: Acute Myeloid Leukemia (AML) is a malignancy frequently driven by mutations in the FMS-like tyrosine kinase 3 (FLT3) gene. The FLT3 internal tandem duplication (ITD) and tyrosine kinase domain (TKD) mutations, particularly D835 and F691, appear in approximately 30% of AML patients, often leading to poor prognosis and resistance to existing therapies. Gilteritinib and Quizartinib are two FDA-approved FLT3 inhibitors, with the former approved only for relapsed/refractory AML and the latter approved only for newly diagnosed AML. Quizartinib does not target TKD resistance mutations, whereas Gilteritinib's efficacy on FLT3-ITD-D835Y is limited and it is not effective against FLT3-ITD-F691L. Consequently, there is a critical need for next-generation FLT3 inhibitors that can address all of these mutations. **Methods:** We have characterized efficacy of two novel FLT3 inhibitors, CCM-405 and CCM-445. *In vitro* enzymatic binding affinities were determined by the KdELECT assay, and cellular IC_{50}s were determined by the Cell-Titer Glo assay. *In vivo* antitumor activity of CCM-405 / 445 was evaluated in mutant cell line-derived xenograft (CDX) models of AML. Tumor growth inhibition (TGI) was measured in the FLT3-ITD luciferase-expressing MV4-11 (MV4-11-luc) systemic xenograft model as well as subcutaneous xenograft models of FLT3-ITD F691L and D835Y mutants. Efficacy of novel inhibitors was compared with Gilteritinib. *In vitro* efficacy was compared with experimental FLT3 TKD mutant inhibitor Luxeptinib. **Results:** Enzymatically, CCM-405 / 445 inhibit FLT3-ITD, FLT3-ITD-D835V and FLT3-ITD-F691L with K_ds of 12 nM / 4.1 nM, 1.9 nM / 0.39 nM and 1.6 nM / 0.4 nM, respectively (Luxeptinib K_ds: ITD-D835V: 550 nM; ITD-F691L: 97 nM). CCM-405 / 445 inhibit the proliferation of Ba/F3 FLT3-ITD and FLT3-ITD D835Y cell lines with potency comparable to Gilteritinib, and FLT3-ITD F691L with potency superior to Gilteritinib, and are significantly less toxic to Ba/F3 FLT3 WT than to the mutants (Luxeptinib: negligible cellular mutant/WT selectivity). CCM-405 / 445 are also potent against human AML cell lines MV4-11 and MOLM-13. *In vivo*, in the systemic FLT3-ITD model, CCM-405 induced ~90% tumor regression (> 100% TGI) and was significantly more effective than Gilteritinib ($p < 0.001$), which did not regress the tumor, when these agents were administered orally at doses corresponding to equal fractions of their maximum tolerated doses (MTDs). In both FLT3-ITD-F691L and FLT3-ITD-D835Y CDX models, CCM-405 induced almost complete tumor regression (>100% TGI). Both novel inhibitors were significantly more efficacious than Gilteritinib (45% and 4% TGI, respectively). **Conclusions:** Novel FLT3 inhibitors have been developed that can both target FLT3-ITD and potentially overcome mutational resistance to FDA-approved FLT3 inhibitors. These agents are significantly more effective than Gilteritinib and have potential clinical applications. Research Sponsor: CCM Biosciences.

6543 Poster Session

Brexucabtagene autoleucel (Brexu-cel) as consolidation treatment in adults with B-cell acute lymphoblastic leukemia. First Author: Niranjan Khaire, University of Texas MD Anderson Cancer Center, Houston, TX

Background: Brexu-cel is a CD19 CAR T cell approved for adult patients with R/R B-cell ALL. We aimed to evaluate toxicity/efficacy in adult pts with marrow blasts <5%. **Methods:** We retrospectively analyzed pts (≥18y) with B-ALL who received brexu-cel (not on clinical trials) at MDACC, Houston. Pts were included if they had marrow blasts <5% and without any clinical (and imaging) evidence of extra-medullary disease (EMD) at the time of LD. CAR T levels were monitored post infusion in PB using flow cytometry. **Results:** 46 pts received Brexu-cel from Feb 2022 to Dec 2024. Baseline characteristics are as in table 1. 36/46 pts were NGS MRD negative (30 had undetectable disease at 10^{-6} sensitivity and 6 had disease detectable < LLOD of the assay; clonoSEQ). 10/36 pts were positive at values ranging from 3-3283 cells/million. Post infusion peak CAR T expansion was noted at a median of 8 days from infusion and the median peak expansion was 13.5 cells/μL [range <1-2222]. A peak CAR T expansion threshold of 15 cells/μL was identified as an optimal predictor for RFS with a neg predictive value of 97%. 23/46 (50%) pts of the whole cohort had a peak CAR T expansion of ≥15 cells/μL. Amongst the 10 pts who were NGS MRD positive at the time of CAR T infusion, the median peak CAR T expansion was 77.5 cells/μL [range 3-573] and 7/10 (70%) had a peak expansion of ≥15 cells/μL. Amongst those (n=36) who were NGS MRD negative at the time of CAR T infusion, the median peak CAR T expansion was 10 cells/μL [range <1-2222] and 16/36 (44%) had a peak expansion of ≥15 cells/μL.Among the 23 pts who had a peak expansion of ≥15 cells/μL, 1 had a relapse, 1 died while in MRD negative remission and the remaining 21 (91%) are alive in remission. In contrast, among the 23 pts with a peak expansion of <15 cells/μL, 8 pts had a molecular/clinical relapse while 15/23 (65%) were alive in remission. With a median follow-up of 12.8 mos (range 1-27), the 12-mo RFS is 71% for the whole cohort (86% in the CAR T expansion ≥15 cells/μL; 58% in the peak CART expansion <15 cells/μL). The 12-mo OS is 94% for all pts. 6 pts had a subsequent allo-SCT after the CAR T infusion at the treating physician's discretion at a median of 3.6 mos (range 2.8-8.8) from the cell infusion. Among the 3 pts with G3-4 CRS/ICANS, (table1) the peak CAR T expansion was 102, 1270 and 2222 cells/μL. **Conclusions:** Brexu-cel CAR T expansion was observed even in pts with no morphologic disease. CAR T expansion threshold of ≥15 cells/μL could identify pts with durable RFS. Rates of G3-4 CRS/ICANS were low when brexu-cel was used as consolidation. Research Sponsor: None.

Parameters		N (%), median [range] N=46
Age		38 [20-84]
	≥60 years	9 (20)
Gender	Male	29 (63)
Disease / Prior Therapy	Median lines of therapy	2 [1-4]
	CART infusion in CR1	12 (26)
	Prior blinatumomab	44 (94)
	Prior inotuzumab	35 (76)
	Prior allo-SCT	7 (15)
	Ph positive ALL	15 (33)
	Ph like ALL	10 (28)
Post CAR T complications	G3 CRS	3 (7)
	G4 CRS	0
	G3 ICANS	1 (2)
	G4 ICANS	1(2)

6544 Poster Session

Impact of *TP53* mutations and variant allelic frequency on survival in adults with newly diagnosed acute lymphoblastic leukemia. First Author: Roberta Santos Azevedo, Department of Leukemia, The University of Texas MD Anderson Cancer Center, Houston, TX

Background: *TP53* mutations are associated with poor outcomes in acute lymphoblastic leukemia (ALL); however, a variant allele frequency (VAF) cutoff (mutation burden) which may more accurately predict overall survival (OS) has not been identified. **Methods:** We retrospectively analyzed adult patients (pts) with newly diagnosed ALL with *TP53* mutation status tested at diagnosis. The maximum log-rank test was used to evaluate the impact of *TP53* VAF. **Results:** Among 654 pts, 115 (18%) harbored *TP53* mutations. *TP53* mutations were more common in B-cell ALL (19% vs. 6% in T-cell ALL, p=0.003), older age (61 vs. 45 years, p<0.001), low hypodiploid/near-triploid (Ho-Tr) karyotype (98% vs. 10%, p<0.001), and therapy-related ALL (20% vs. 9%, p<0.001). 11 pts (10%) harbored ≥2 *TP53* mutations. The median *TP53* VAF was 42% (range, 1-94%) and was higher in pts with Ho-Tr karyotype (54%) compared to diploid karyotype (41%, p=0.02). *TP53*-mutated ALL was associated with significantly inferior OS in pts ≥60 years of age (2-year OS 55% vs. 69%; p=0.03). In the older pts, *TP53* VAF was associated with worse OS and the optimal cutoff was 45%. Among pts ≥60 years, *TP53* VAF ≥45% had a 2-year OS of 37% compared to 71% for those with VAF <45% (p=0.01), which was driven by higher rates of both relapse and non-relapse mortality. In older pts who received frontline inotuzumab ozogamicin (InO) and/or blinatumumab (Blina), *TP53* VAF ≥45% remained a strong predictor of OS (2-year OS 37% vs. 75% for VAF <45%; p=0.04). By multivariate analysis (MVA) in pts aged ≥60 years, *TP53* VAF ≥45% (HR 1.8, 95% CI 1.0-3.2, p=0.03) and complex karyotype (HR 2.9, 95% CI 1.2-7.3, p=0.02) were associated with inferior OS, while frontline InO and/or Blina trended toward improved OS (HR 0.6, 95% CI 0.3-1.0, p=0.07). *TP53*-mutated ALL was associated with a trend towards inferior OS in pts <60 years of age (2-year OS 66% vs. 88%; p=0.06), despite higher rates of allo-SCT in pts with *TP53*-mutated ALL (47% vs. 22% for *TP53* wild type; p<0.001). In these younger pts, *TP53* VAF was not prognostic (2-year OS 72% vs. 61% for VAF ≥45% vs. <45%; p=0.6). Outcomes were similar in younger pts with *TP53* VAF≥45%, irrespective of allo-SCT status (2-year OS of 68% vs. 74% for those with VAF≥45% who underwent allo-SCT vs. those who did not; p=1.0). By MVA in younger pts, Ph-like was associated with worse OS (HR 2.1, 95% CI 1.3–3.1, p=0.002), while frontline InO and/or Blina significantly improved outcomes (HR 0.5, 95% CI 0.3–0.7, p<0.001). Neither *TP53* mutation status nor VAF impacted OS on MVA. **Conclusions:** *TP53* mutations were associated with worse outcomes in both younger and older adults with ALL. VAF ≥45% can risk stratify pts aged ≥60 years but did not impact OS in younger pts. Incorporating frontline InO and/or Blina into therapy might improve outcomes of *TP53*-mutated ALL. Research Sponsor: None.

6545 Poster Session

A phase 2 study of olutasidenib in relapsed/refractory acute myeloid leukemia: Outcomes by number of prior treatment regimens. First Author: Eunice S. Wang, Roswell Park Comprehensive Cancer Center, Buffalo, NY

Background: A subset of patients (7-14%) with acute myeloid leukemia (AML) have mutations in the isocitrate dehydrogenase 1 gene (m*IDH1*). Olutasidenib (OLU), a selective, potent, oral inhibitor of mIDH1, is approved for treatment of relapsed/refractory (R/R) m*IDH1* AML. Results from the phase 2 pivotal cohort (NCT02719574) demonstrated clinical efficacy and tolerability of OLU, with a complete remission/complete remission with partial hematological recovery (CR/CRh) rate of 35% for a median duration of 25.9 months. Here we evaluated the efficacy and safety of OLU in patients with R/R AML grouped by the number of prior regimens. **Methods:** The pivotal cohort of the phase 2 study assessed OLU 150 mg BID in adult patients and included efficacy endpoints of CR/CRh, overall response rate (ORR), duration of response (DOR), and overall survival (OS). This post hoc analysis evaluated outcomes based on when patients received OLU: after 1-2 or ≥3 prior lines of therapy. **Results:** There were 147 patients in the efficacy evaluable analysis set (1-2 prior regimens, n=93; ≥3 prior regimens, n=54). Median age was 72 years in patients with 1-2 prior regimens and 66.5 years in those with ≥3 prior regimens. Forty-three percent and 33% of patients had prior treatment with a hypomethylating agent, and 11% and 4% received prior venetoclax therapy (1-2 and ≥3 prior regimens groups, respectively). In patients with ≥3 prior regimens, 31% had prior hematopoietic stem cell transplantation vs none in those with 1-2 prior regimens. Those in the 1-2 prior regimens group had a higher ORR and CR/CRh rate and longer median OS, with a larger percentage of patients achieving CR, than those in the ≥3 prior regimens group (Table 1). All patients experienced ≥1 treatment-emergent adverse event (TEAE). Serious TEAEs were reported in 73% (68/93) and 77.8% (42/54) of patients in the 1-2 and ≥3 prior regimens groups, respectively, and TEAEs ≥grade 3 occurred in 89.2% (83/93) and 90.7% (49/54). The most common TEAEs included nausea, decreased red blood cell count, and fatigue. No new safety signals were identified. **Conclusions:** Higher response rates (including CR and CRh) and greater survival were observed in patients receiving OLU following 1-2 versus ≥3 prior treatment regimens, providing rationale for initiating OLU earlier in the R/R treatment paradigm. Clinical trial information: NCT02719574. Research Sponsor: Forma Therapeutics, Inc; Rigel Pharmaceuticals, Inc.

Efficacy of OLU stratified by number of prior regimens.

	1-2 Prior Regimens n=93	≥3 Prior Regimens n=54
ORR, n (%); 95% CI	50 (54); 43.1, 64.2	21 (39); 25.9, 53.1
DOR, median months (95% CI)	14.8 (7.4, 25.9)	16.6 (5.8, NR)
CR rate, n (%); 95% CI	35 (38); (27.8, 48.3)	12 (22); (12.0, 35.6)
DOR, median months (95% CI)	21.3 (12.0, NR)	NR (8.7, NR)
CR/CRh rate, n (%); 95% CI	38 (41); 30.8, 51.5	13 (24); 13.5, 37.6
DOR, median months (95% CI)	25.3 (12.0, NR)	NR (8.7, NR)
OS, median months (95% CI)	13.0 (9.3, 18.9)	8.9 (5.8, 14.9)

NR, not reached.

6546 Poster Session

Matching-adjusted indirect comparison (MAIC) of olutasidenib (OLU) and ivosidenib (IVO) in isocitrate dehydrogenase 1 (IDH1)-mutated relapsed/refractory (R/R) acute myeloid leukemia (AML). First Author: Justin M. Watts, University of Miami, Sylvester Comprehensive Cancer Center, Miami, FL

Background: OLU and IVO are allosteric type II IDH1 inhibitors approved by the FDA and recommended by NCCN for *IDH1*^{mut} R/R AML patients based on single-arm trials. In the absence of a head-to-head trial, a MAIC was performed to estimate relative treatment effects of OLU vs. IVO in *IDH1*^{mut} R/R AML. **Methods:** Analyses used registrational data for OLU (Study 2102-HEM-101; N=147; individual-level data) and IVO (AG120-C-001; N=174; study-level data). A logistic propensity score model was used to estimate weights based on the first moment for Study 2102-HEM-101 patients to match AG120-C-001, including the following characteristics identified from a literature review, validated by clinical experts: number of prior systemic therapies, age, prior stem cell transplant, AML type, relapse type, cytogenetic risk, ECOG PS, and *IDH1* mutation. Complete remission (CR) and CR + CR with partial hematological recovery (CRh) were summarized as odds ratios (ORs) and 95% confidence intervals (CIs). Duration of CR (DoCR), duration of CR+CRh, and OS were summarized in terms of difference in medians and 95% CIs. OS was also summarized in terms of hazard ratios (HRs) and restricted mean survival time (RMST). A simulated treatment comparison (STC) was performed as a sensitivity analysis. **Results:** Table 1 summarizes MAIC-adjusted estimates. Naïve and adjusted rates of CR and CR+CRh for OLU vs. IVO were comparable, but point estimates favored OLU for CR. Differences in median DoCR were not statistically significant but favored OLU over IVO. OLU had a significantly longer duration of CR+CRh than IVO. For OS, the naïve comparison suggested OLU was better than IVO (HR=0.72; 95% CI 0.55, 0.92), whereas the MAIC was uncertain but favored OLU. STC results were consistent with the MAIC. **Conclusions:** Naïve and adjusted rates of response for OLU vs. IVO were comparable (adjusted point estimate favored OLU for CR and IVO for CR+CRh), while a longer duration of CR+CRh was observed with OLU. Adjusted OS was similar between the two groups, although the HR favored OLU, and could not be estimated by response category given lack of patient characteristics and reduction in effective sample size (ESS). Results rely on the assumption of no unmeasured confounders which reflects a limitation of the methodology. Research Sponsor: Rigel Pharmaceuticals, Inc.

MAIC results.

Outcome	OLU – adjusted (95% CI)	IVO – observed (95% CI)	MAIC OLU vs. IVO (95% CI)	N	ESS
CR	27%	25%	OR=1.12 (0.61, 2.08)	147	73.03
CR + CRh	29%	33%	OR=0.83 (0.46, 1.50)	147	73.03
DoCR, median mos	21.3 (12.0, NE)	10.1 (6.5, 22.2)	Diff=11.18 (-4.30, 22.72)	47	17.76
Duration of CR+CRh, median mos	17.5 (12.0, 29.1)	8.2 (5.6, 12.0)	Diff=9.84 (3.24, 22.28)	51	21.06
OS, median mos	9.7 (5.6, 16.4)	9.0 (7.4, 10.2)	HR=0.75 (0.53, 1.07)	147	73.03
OS, RMST mos	15.6 (12.1, 19.2)	12.2 (10.6, 13.9)	Diff=3.39 (-0.51, 7.29)	147	73.03

N, sample size; NE, not estimable.

6547 Poster Session

Investigating age of onset and prognosis of p53 mutant myeloid malignancies in African Americans. First Author: Brendon Fusco, Montefiore Einstein Comprehensive Cancer Center, Bronx, NY

Background: TP53 mutations drive poor outcomes in Myelodysplastic Syndrome (MDS) and Acute Myeloid Leukemia (AML), aggressive hematologic malignancies characterized by clonal abnormalities in myeloid hematopoiesis. Prognostic scoring systems incorporate cytogenetic and molecular abnormalities based on data from majority White populations and have limited applicability to minorities. Racial disparities in survival are well-known, with Black patients experiencing worse outcomes. While TP53 mutations are associated with poor outcomes, there is limited data about their implications in minority populations. Objective: To study TP53 mutation status, variant allele frequency (VAF), and co-mutations on outcomes in MDS and AML between White and minority populations in the Bronx, a racially diverse region. **Methods:** This retrospective cohort study analyzed 84 patients diagnosed with TP53 mutated AML and MDS between 2014 and 2024 at Montefiore Medical Center. Data included race/ethnicity (Black, White, Hispanic), age, age at diagnosis, gender, diagnosis, first-line chemotherapy, and bone marrow blast percentage. Molecular data included TP53 mutation status (bi- vs. mono-allelic), variant allele frequency (VAF), and co-mutations. Co-mutation patterns will be presented at the meeting. Comparisons were made using descriptive statistics, and survival outcomes were analyzed using Cox proportional hazards models adjusted for age and gender. **Results:** Black patients were diagnosed at a younger age than White or Hispanic patients (mean: 63.7 vs. 72.6 vs. 65.9 years, p = 0.029) and had shorter median overall survival (3.9 vs. 16.4 vs. 10 months, p = 0.014). Black patients had higher mean VAF (48.1 vs. 31.9 vs. 38.2, p = 0.047) and were more likely to have co-mutations than isolated TP53 mutations, though this was not significant (OR 4.21, p = 0.06). Patients with VAF above the median had a threefold increased risk of death (aOR 3.14, p = 0.019), independent of age or gender. **Conclusions:** Black patients with TP53 mutant MDS and AML present younger and have worse outcomes than White patients, associated with a higher TP53 VAF and more frequent co-mutations. This is to our knowledge the largest dataset of TP53 in minorities with MDS and AML; highlighting the need for personalized prognostic models that incorporate minorities to overcome racial disparities in myeloid malignancies. Research Sponsor: None.

6548 Poster Session

Socioeconomic and clinical predictors of 30-day readmissions in AML patients undergoing allogeneic stem cell transplantation. First Author: Aditi Sharma, Barbara Ann Karmanos Cancer Institute, Detroit, MI

Background: 30-day readmissions among acute myeloid leukemia (AML) undergoing allogeneic hematopoietic stem cell transplantation (allo-HCT) are a key quality metric, contributing to morbidity, mortality, and healthcare costs. We analyzed age-specific characteristics and factors associated with readmissions. **Methods:** Using the 2016–2021 National Readmissions Database, we identified adult AML hospitalizations for allo-HCT, stratified into <45, 45–65, and >65 years. Patient demographics, hospital factors, comorbidities, complications and outcomes were analyzed. Multivariable Cox regression determined adjusted hazard ratios for 30-day readmissions. **Results:** Of 15,757 admissions, 3,743 were <45, 8,169 were 45–65, and 3,844 were >65 years. The younger cohort had a higher proportion of females (53% vs. 47% vs. 39%, p<0.001). Overall infection rates, acute graft-versus-host disease, and use of total body irradiation were similar across groups (p>0.05). Mean LOS was 29 vs. 32 days for >65 and <45 years (p<0.001). Inpatient mortality was 4%, 5% and 6% in young, middle-aged and older group (p=0.02), while readmission rates (27% vs. 27% vs. 30%, p=0.16) and mortality during readmission (5% vs. 7% vs. 7%, p=0.42) were comparable. Mean time to readmission was 12 days, primarily driven by infections (34%), GI/hepatobiliary complications (10%), active AML (5%), & kidney dysfunction (5%). Lower-income quartiles vs. wealthiest and Medicare vs. private insurance were linked to higher readmission risk. Depression further elevated risk, whereas home-health care lowered it. Among clinical variables, GVHD, chronic kidney disease, and acute respiratory failure each predicted higher readmission (see Table). **Conclusions:** Our findings highlight disparities in 30-day readmissions after allo-HCT for AML, driven by socioeconomic, clinical, and mental health factors. Targeted interventions, such as optimizing post-discharge care and providing psychosocial support, may help reduce the readmission burden in high-risk patients. Research Sponsor: None.

Factors associated with 30-day readmissions	Adjusted Hazard Ratio	95% Confidence Interval	p value
Year of Admission (2021 vs. 2016)	0.71	0.53-0.95	0.02
Median household income			
Quartile 1 (poorest)		Reference	
Quartile 2	0.84	0.74-0.96	0.011
Quartile 3	0.83	0.72-0.95	0.006
Quartile 4 (wealthiest)	0.74	0.65-0.85	<0.001
Private Insurance vs. Medicare	0.86	0.76-0.97	0.018
Large Metro Hospital vs. Others	1.25	1.03-1.52	0.023
Home-health care vs. Routine discharge	0.88	0.78-0.99	0.027
Acute Respiratory Failure	1.32	1.06-1.65	0.013
Fluid-electrolyte imbalance	1.11	1.01-1.22	0.034
Cardiac arrhythmia	1.17	1.02-1.33	0.021
Acute graft-versus-host disease	1.21	1.05-1.39	0.007
Chronic kidney disease	1.45	1.18-1.78	0.001
Depression	1.16	1.02-1.32	0.021
Length of Stay			
≤30 days		Reference	
31-40 days	1.28	1.13-1.46	<0.001
>40 days	1.29	1.11-1.51	0.001

6549 **Poster Session**

Outcomes of therapy-related AML (T-AML) with venetoclax-based therapies. First Author: Jennifer Croden, The University of Texas MD Anderson Cancer Center, Houston, TX

Background: T-AML refers to AML in patients (pts) with prior exposure to cytotoxic chemotherapy (CT) and/or radiotherapy (RT) and is often associated with adverse risk (AR) genomics. Evaluation of outcomes of T-AML with respect to type of prior therapy exposure, AML genomics, and contemporary AML therapy, especially with venetoclax (VEN), is warranted. **Methods:** We retrospectively analyzed pts aged ≥18 years with newly diagnosed T-AML. Pts with an antecedent myeloid disorder (MDS/CMML) prior to AML diagnosis were excluded; thus, including only pure T-AML. Composite complete response (CRc) included CR and CRi and overall response (OR) included CRc + morphologic leukemia free state. **Results:** From 1/2012 to 12/2023, 317 pts were included; median (med) age was 69 years (range 21-92). Overall, 120 (38%) received prior CT alone, 77 (24%) received prior RT alone (RT), and 114 (36%) received both (CRT). The most common prior malignancy was non-Hodgkin lymphoma (37%) in the CT group, prostate cancer (60%) in the RT group, and breast cancer (45%) in the CRT group.Among 286 pts with complete cytogenetic data, 180 (63%) were adverse, of whom 132 (46%) had complex karyotype (CK; 42% of CT, 48% of RT, and 61% of CRT groups). *TP53* was mutated in 113/286 patients (40%) tested (36% of CT, 35% of RT, and 47% of CRT groups). Stratified by type of CT received, CK and *TP53* mutation were seen in 5/5 (100%) and 3/5 (60%) of PARP inhibitor-exposed, 98/184 (53%) and 78/183 (43%) of alkylator-exposed, and 21/36 (58%) and 16/37 (43%) of topoisomerase inhibitor-exposed. Overall, 217/304 (71%) were ELN 2017 AR. In total, 251 pts (79%) received low-intensity AML therapy (LIT). CRc and OR was achieved in 122 (49%) and 146 (58%) pts treated with LIT (vs 58% and 65% with LIT+VEN). In pts treated with intensive chemotherapy (IC), the CRc and OR rate was 64% and 68% (vs 68% and 73% with IC+VEN). Overall, med RFS was 7.2 months (mos; 95% CI 5.6-8.9), and med OS was 11.8 mos (10.0-13.7). Med OS was 5.7 vs 9.0 mos (p=0.02) with LIT and LIT+VEN, respectively (resp), and med OS was 10.9 vs 48.9 mos (p=0.03) for IC vs IC+VEN, resp. Among pts treated with LIT+VEN, med OS was 14.0, 12.4, and 9.6 mos in those who had received prior CT, RT and CRT, resp; when stratified by ELN 2017 criteria, med OS was 24.6, 9.4 and 4.8 mos in the favorable, intermediate and AR groups, resp. Sixty-seven (21%) pts underwent HSCT with a landmarked comparison showing improved OS with HSCT (28.5 months vs 9.4, p<0.001). On multivariate Cox analysis in the LIT+VEN group, with forward model selection, using variables age </≥ 60, adverse cytogenetics, *ASXL1, IDH1/2, FLT3-ITD, RAS, RUNX1, TP53* status, HSCT, and prior therapy group, HSCT was favorable (HR=0.19, 95% CI 0.01-0.37), along with *IDH2* and *NPM1* mut, while *RAS* and *TP53* mut was associated with higher hazards of death. Other factors were not significant. **Conclusions:** Venetoclax improves outcomes in T-AML. In LIT+VEN treated patients, ELN 2024 risk stratification is prognostic. Research Sponsor: None.

6550 **Poster Session**

Impact of clinical trial treatment and area deprivation index in the outcomes of adolescent and young adult patients with acute myeloid leukemia. First Author: James Wesley Hill, Department of Internal Medicine, McGovern Medical School, The University of Texas Health Science Center at Houston (UTHealth Houston), Houston, TX

Background: Socioeconomic status (SES) is an independent prognostic factor in patients (pts) with acute myeloid leukemia (AML). Adolescent and young adult (AYA, age 15-39) pts with AML traditionally have better outcomes than older adult pts. Prior studies have shown that SES adversely impacts outcomes in AYA pts. Area Deprivation Index (ADI) is one of the most advanced SE tools, incorporating 17 SE factors to rank neighborhoods based on disadvantaged status. Higher ADI score corresponds to more disadvantaged neighborhoods. Here, we report the largest cohort of AYA pts with AML treated at a single institution with molecular, cytogenetic (CG) and ADI data. **Methods:** AYA pts with AML treated at MD Anderson Cancer Center from 3/2013 to 3/2023 were included. ADI data was downloaded from https://www.neighborhoodatlas.medicine.wisc.edu. Backward elimination was applied to the multivariable model, removing variables sequentially until only variables with p<0.1 remained. **Results:** 190 AYA pts were included (non-Hispanic White, NHW-139, non-Hispanic Black-24, Hispanic-16, Asian-11). Median age was 31 years (17-39). 81 pts (43%) had adverse risk by ELN 2022 and 135 (71%) were treated in clinical trials. Both median overall survival (OS) and relapse-free survival (RFS, not censored for transplant (SCT)) was 85.4 months, respectively. ADI national rank 61-100 (HR 1.906, 1.069-3.396, p=0.029), complex CG (HR 2.854, 1.530-5.324, p=0.001), intermediate risk (HR 2.514, 1.160-5.449, p=0.020), and adverse risk (HR 4.257, 1.975-9.177, p<0.001) adversely affected OS. Notably, treatment in clinical trials (HR 0.499, 0.309-0.806, p=0.005) and SCT (HR 0.499, 0.288-0.862, p=0.013) led to longer OS. Only complex CG and adverse risk negatively impacted RFS. **Conclusions:** AYA pts from disadvantaged neighborhoods (ADI national rank 61-100) had an inferior OS. Our data showed that treatment in clinical trials and SCT led to longer OS. These results underscore the importance of treatment in clinical trials and SCT for improving OS in AYA, particularly for AYA pts from disadvantaged neighborhoods. Efforts to improve access to clinical trials and SCT, especially for AYA pts from disadvantaged neighborhoods are needed. Research Sponsor: None.

Results of Cox regression analysis for overall survival (p value cutoff 0.100 for MVA).

	Univariate			Multivariate		
	HR	95% CI	P	HR	95% CI	P
ADI state 1-6	ref	ref	ref	ref	ref	ref
7-10	1.558	0.964-2.517	0.070	1.178	0.625-2.221	0.612
ADI national 1-60	ref	ref	ref	ref	ref	ref
61-100	1.918	1.232-2.986	0.004	**1.906**	**1.069-3.396**	**0.029**
CG: Complex	5.046	3.021-9.428	<0.001	**2.854**	**1.530-5.324**	**0.001**
Favorable	ref	ref	ref	ref	ref	ref
Intermediate	2.162	1.005-4.650	0.049	**2.514**	**1.160-5.449**	**0.020**
Adverse	4.640	2.347-9.175	<0.001	**4.257**	**1.975-9.177**	**<0.001**
Clinical trial	0.495	0.315-0.779	0.002	**0.499**	**0.309-0.806**	**0.005**
SCT (time-dependent)	0.643	0.389-1.062	0.085	**0.499**	**0.288-0.862**	**0.013**

6551 **Poster Session**

Phase II trial of 10-day ASTX727 (decitabine/cedazuridine) in combination with venetoclax for relapsed or refractory acute myeloid leukemia. First Author: Mehmet Uyanik, Department of Leukemia, The University of Texas MD Anderson Cancer Center, Houston, TX

Background: The disease outcomes in relapsed refractory acute myeloblastic leukemia (R/R AML) remain dismal. We previously demonstrated safety and encouraging activity of 10-day regimen of IV decitabine with venetoclax (VEN) in R/R AML. In this prospective clinical trial, we investigate the efficacy of a novel 10-day induction regimen with fully oral combination therapy for pts with R/R AML. **Methods:** We conducted a phase II trial in pts with R/R aged ≥18 y with ECOG performance status ≤2 was eligible for enrollment. Exclusion criteria included GI conditions affecting absorption of the drugs, active GvHD, and APL. For induction, pts received oral ASTX727 (100mg/35mg) D1-10 and VEN 400mg D1-28. In subsequent cycles, ASTX727 was reduced to D1-5 in pts achieving CR/Cri (NCT04975919). **Results:** Between December 2021 and March 2024, 20 were enrolled on this trial. The median age was 65 (39-76), 25% of pts (n=5) had therapy-related AML. 60% pts (n= 12) had prior VEN exposure. Eighty-five percent of the pts were either and/or harbored complex karyotype. Median duration of the treatment was 1.7 m (0.5-9.5) and median no of cycles was 1 (range 1-6). The composite CR/CRi/MLFS rate was 40% (n=8), with best response achieved at median 1.3 m. Duration of response in responders was 8.5 m (2.9-30.8). MRD was negative in 25% (2/8) of responding pts, and 3 pts (15%) proceeded to stem cell transplantation (SCT). Two transplanted patients (67%) were in CR before SCT, while 1 patient (33%) was in MLFS. The median OS was 8.6 m. VEN-naive pts showed longer OS (10.5m vs 4.4m with prior VEN, p=0.12). Responding pts who could be bridged to SCT had better OS benefit (not reached vs 6.6m, p=0.01). The median OS of pts with $TP53^{mut}$ was 3.1 m vs 8.6 m in pts who were $TP53^{WT}$ (p=0.60). The 4-week mortality rate was 6%, and the 8-week mortality rate was 17%. Treatment-emergent adverse events of Gr 3/4 were observed in 81% of pts (17), with infections and febrile neutropenia being the most frequent complications (35% each). After a median follow up of 8.7 m (0.5-30.8), 80% of pts (16) died. Among the deaths, 40% were attributed to disease progression, and 25% to bacterial infections. None of the deaths were associated with bacterial infections occurred in patients with CR. **Conclusions:** The 10-day ASTX727-VEN combination showed safety profile comparable to other HMA-VEN regimens in salvage setting. TP53 wild type, VEN-naïve pts and those who could be bridged to SCT had better outcomes. Novel therapies are needed to improve outcomes in R/R AML. Clinical trial information: NCT04975919. Research Sponsor: MD Anderson Cancer Center.

6552 **Poster Session**

Factors associated with frailty in vulnerable hematopoietic cell transplantation candidates. First Author: Hyunhae Lee, University of Washington, Seattle, WA

Background: Allogenic hematopoietic cell transplantation (allo-HCT) is increasingly offered to older patients and those with comorbidities. Frailty, characterized by reduced muscle strength and functional decline, is associated with lower quality of life, increased mortality, and higher hospitalization after allo-HCT. However, frailty prior to allo-HCT remains understudied. The study investigated factors associated with frailty in allo-HCT candidates prior to transplant. **Methods:** This cross-sectional analysis utilized data from the ACE-BMT study, an ongoing longitudinal, unblinded, randomized seamless phase II/III trial, that enrolled adult patients allo-HCT candidates either age of ≥65 years, with HCT comorbidity index (HCI-CI) score of ≥3, or 4-meter walk speed test <0.8 m/s. We classified frailty in participants at baseline using the Fried frailty phenotype: 1) unintentional weight loss, 2) low energy (Patient Health Questionnaire 9-item [PHQ-9]), 3) grip strength or stand-up time below standard, 4) 4-meter walk test < 0.8m/s, and 5) the lowest 20% of physical functioning (Medical Outcomes Study Physical Health). Participants were classified as frail (≥3), pre-frail (1-2), or not frail (0). We assessed pre-HCT variables including demographics, comorbidities, and self-reported social support (ENRICHED Social Support Instrument), symptom severity and interference with daily life (MD Anderson Symptom Inventory), depression (PHQ-9), cognitive impairment (Bless Orientation Memory Concentration), quality of life (Euro Quality of Life 5-Dimensions), and functional status (Karnofsky Performance Status). We compared baseline characteristics based on frailty status and conducted a multivariable logistic regression to identify the factors associated with frailty. **Results:** Among 381 patients (mean age 65.49, 38.32% female) included in the analysis, 81.7% were pre-frail and frail at baseline. Compared to non-frail, participants as frail were younger (mean age 66.49 vs 61.49), more likely to be female (35.7% vs. 48.7%), to have cardiovascular disease (1.3% vs. 9.2%) and diabetes (9.8% vs. 23.7%), and a HCT-CI score ≥3 (39.3% vs. 61.8%). They also self-reported greater depression, symptom severity and interference, cognitive impairment, and poorer quality of life. In a multivariable logistic regression model, older age (OR: 0.98, 95% CI: 0.95, 1.00), higher symptom interference (OR: 1.04, 95% CI: 1.01-1.08), and depression (OR: 1.14, 95% CI: 1.03-1.27) were significantly associated with frailty. **Conclusions:** Frailty prior to allo-HCT is associated with symptom burden and depression, underscoring the importance of addressing these factors pre-HCT. These findings provide preliminary support for psychological screening and symptom-focused interventions. Future analyses will examine the incidence and risk factors of post-HCT frailty and its association with clinical outcomes. Research Sponsor: NIH, NCI; R01CA227092.

6553 Poster Session

Allogeneic hematopoietic cell transplantation for acute leukemia patients not in complete remission. First Author: Shlomo Elias, Hadassah University Hospital Jerusalem Israel, Jerusalem, Israel

Background: Current guidelines support allogeneic hematopoietic cell transplantation (allo-HCT) in patients with acute leukemia who achieve complete remission (CR) and are at high risk for relapse. Patients with primary refractory disease or those refractory to re-induction therapy after relapse have a poor prognosis without allo-HCT. While several studies have explored the role of allo-HCT in this setting, most have focused on patients receiving myeloablative conditioning (MAC) and have not included contemporary transplant patients or accounted for the impact of molecular genetic risk factors. Consequently, the benefit of allo-HCT in this patient population remains unclear. **Methods:** This study evaluated the outcomes of patients with acute leukemia from two centers who underwent allo-HCT between 2009 and 2020 while not in CR at the time of transplant, receiving either myeloablative conditioning (MAC) or reduced-intensity conditioning (RIC) regimens. **Results:** Our cohort included 196 patients who underwent transplantation between 2009 and 2020, with the majority (86%) diagnosed with acute myeloid leukemia (AML). At 36 months post-transplant, the probability of overall survival (OS) was 24% (95% CI: 19-31). In multivariable analysis, the presence of circulating blasts, recipient CMV seropositivity, and low pre-transplant albumin levels were associated with reduced OS. The cumulative incidence of relapse was 54% (95% CI: 47-61) at 36 months, with the presence of circulating blasts being significantly associated with an increased incidence of relapse. Among AML patients, the presence of at least one high-risk mutation (TP53, RUNX1, ASXL1, or FLT3-ITD, historically considered high-risk per National Comprehensive Cancer Network [NCCN] criteria version 3.2021) was also associated with an increased incidence of relapse. **Conclusions:** Allo-HCT provides a durable remission in a select group of patients with relapsed or refractory acute leukemia, with an overall survival of 24% at 36 months. The presence of circulating blasts, CMV seropositivity, and low albumin levels at the time of allo-HCT were associated with increased relapse and inferior OS in this retrospective analysis. The impact of these factors should be further investigated in larger, prospective cohorts to better identify patients with acute leukemia not in CR who would benefit from allo-HSCT. Research Sponsor: None.

6554 Poster Session

Exploratory analyses of immune reconstitution biomarkers from a Ph1b study of an investigational, oral, live biotherapeutic, SER-155, in adult allo-HCT. First Author: Emily Walsh, Seres Therapeutics, Cambridge, MA

Background: SER-155 is an investigational, oral, live biotherapeutic product (LBP) comprised of 16 bacterial strains designed to decolonize gastrointestinal (GI) pathogens, improve epithelial barrier integrity, and modulate immune responses to prevent bloodstream infections (BSI). In the placebo-controlled cohort 2 of the phase 1b study, SER-155-001 (NCT04995653), SER-155 was generally well tolerated with a safety profile similar to placebo and the incidence of BSIs, a secondary endpoint, was significantly lower after treatment with SER-155 when compared to placebo. We report exploratory analyses of biomarkers of T cell expansion relevant for immune reconstitution after HCT. **Methods:** Participants were randomized 1:1 to receive 4 days of oral vancomycin (for microbiome conditioning) and 10 days of SER-155 or placebo/placebo administered pre-HCT (course 1) and post-neutrophil engraftment (course 2). Primary endpoints were safety and SER-155 strain engraftment (PK). Exploratory endpoints included plasma cytokine concentrations measured by ELISA and analysis of peripheral blood mononuclear cells (PBMCs) by flow cytometry. **Results:** Demographics were comparable across treatment arms. 34 of 45 randomized participants were treated and received allo-HCT (SER-155, 20; placebo, 14); 28 received course 2 (SER-155, 19; placebo, 9). SER-155 strain engraftment was observed in the peri-transplant period (median 11.5 strains after course 1) and post-HCT (median 11 strains after course 2 and HCT Day 100). Significant differences and trends in cytokines of systemic inflammation and immune homeostasis were observed relative to placebo prior to HCT Day 0 and post-HCT. On HCT Day 0, both arms had similar concentrations of IL7 and IL15 (Table 1). However, after course 2, and at HCT Day 100, significantly higher concentrations of IL7 were observed in the SER-155 arm relative to placebo (p=0.02, and p=0.003, respectively). In a preliminary analysis of PBMCs from a subset of participants, a high frequency of CD4+ T cells were observed in the SER-155 arm at the same timepoints. For homeostatic cytokine IL15, no significant differences were observed between arms. **Conclusions:** The significantly higher concentrations of IL7 with SER-155 treatment and observed frequency of CD4+ T cells support the potential role of the GI microbiome in promoting homeostatic expansion of peripheral T cells and immune reconstitution important for successful HCT. Clinical trial information: NCT04995653. Research Sponsor: Seres Therapeutics.

Median plasma IL7 and IL15 (pg/mL), SER-155 vs. placebo (generalized linear model).

HCT Day or event	SER-155 IL7	Placebo IL7	SER-155 IL15	Placebo IL15
D0	13.8	13.0	31.9	30.4
D7	15.1	14.6	50.9	62.6
D14	12.8	15.5	56.6	69.8
Post-neutrophil engraftment	13.4	9.0	16.3	15.4
Post-course 2	7.4*	3.9	6.2	9.1
D100	7.1**	3.5	6.2	6.2

*$p<0.05$, **$p<0.01$.

6555 Poster Session

Peripheral blood cell-free DNA testing as a predictor for relapse post-allogeneic stem cell transplant for AML. First Author: Vanisha Patel, Hackensack University Medical Center, Hackensack, NJ

Background: Allogeneic stem cell transplantation (allo-SCT) is a curative option for acute myelogenous leukemia (AML), but relapse is a challenge. Monitoring minimal residual disease post-transplant through tumor-derived circulating cell-free DNA (cfDNA) in peripheral blood (PB) and bone marrow is an emerging strategy. Persistent mutations in cfDNA may be prognostic indicators of relapse. **Methods:** This single-center retrospective study included 120 AML patients who received allo-SCT from 2018 to 2022, with PB cfDNA collected between Days 30-200. Samples were analyzed by commercial assays (Liquid Trace or Hematology Profile Plus), that use next generation sequencing, Sanger Sequencing, and fragment length analysis to identify molecular abnormalities in DNA of 179 genes associated with hematologic neoplasms. cfDNA positivity was determined by identifying gene amplifications, deletions, single nucleotide variations and indels, including reported variant allele frequency (VAF) above 0. cfDNA negativity was defined by absence of genomic alterations. The primary endpoints were the association of cfDNA presence with overall survival (OS) and relapse-free survival (RFS). A secondary endpoint was the association of mutation risk (adverse/intermediate) with OS and RFS. **Results:** Patients were grouped by cfDNA presence at Day 45 ± 15 (n=30, median survival time 1.173 years) and Day 150 ± 50 (n=90, median survival time 1.4822 years). Kaplan-Meier analysis revealed that patients positive for PB cfDNA at Day 150 ± 50 had significantly worse OS ($p<0.0001$) and RFS ($p<0.0001$) compared to cfDNA negative. Similarly, cfDNA positivity at Day 45 ± 15 also correlated with worse OS ($p<0.01$) and RFS ($p<0.0007$). Regarding mutation risk, adverse mutations at Day 150 ± 50 were linked to worse OS ($p<0.0001$) and RFS ($p<0.0001$). Multivariate analysis revealed that adverse-risk mutations were significantly associated with relapse (odds ratio [OR] 29.48, 95% CI 4.306-350.4, $p<0.002$), RFS (hazard ratio [HR] 12.62, 95% CI 3.541-44.35, $p<0.0001$), and OS (HR 19.24, 95% CI 5.242-75.73, $p<0.0001$). Intermediate-risk mutations also correlated with relapse (OR 13.27, 95% CI 2.818-89.91, $p<0.002$), RFS (HR 9.325, 95% CI 2.748-35.25, $p<0.0005$), and OS (HR 11.48, 95% CI 3.279-45.61, $p<0.0002$). Transplant age, donor type, CMV status, and GvHD regimen were not statistically significant. **Conclusions:** This study demonstrates that cfDNA detection in PB post-allo-HSCT is strongly associated with increased relapse and mortality in AML patients. Persistent high-risk mutations correlate with increased risk of relapse and poor survival outcomes. These findings highlight the potential of PB cfDNA as a predictive marker, potentially enabling earlier intervention to alter post-transplant treatment strategies. Research Sponsor: None.

6557 Poster Session

The impact of the use of hypomethylating agents prior to reduced intensity conditioning allogeneic bone marrow transplant among patients with MDS. First Author: Yanal Mufeed Alnimer, University of Kentucky, Lexington, KY

Background: Allogeneic transplantation is the only potential cure for patients with myelodysplastic syndrome (MDS). It is unclear whether cytoreduction with hypomethylating agents (HMAs) prior to reduced intensity conditioning (RIC) transplantation in patients with 5–10% bone marrow blasts impact transplant outcomes. **Methods:** We utilized the publicly available CIBMTR dataset from the publication *"Alternative Donor Transplantation for Myelodysplastic Syndrome: Haploidentical Relative and Matched Unrelated Donor"* to evaluate the differences in relapse-free survival (RFS), transplant-related mortality (TRM), and overall survival (OS) between recipients and non-recipients of pretransplant HMAs among MDS patients undergoing RIC Allo-SCT. The two groups were matched on confounding variables, including donor type, blast percentage at diagnosis and at the time of transplant, age, sex, race, IPSS-R score, CMV donor status, conditioning regimen, time to transplant, and year of diagnosis. Matching was performed using the inverse probability of treatment weights (IPTW) method. Weighted Kaplan-Meier curves were used to evaluate OS, RFS, and TRM between the two groups. Additionally, a doubly robust Cox regression model was constructed to estimate hazard ratios (HR) for the effect of pretransplant HMA use on OS and RFS. **Results:** A total of 603 patients were included in our analysis. The median age was 67.1 years (IQR 63.1–70.5), and the median follow-up was 21.8 months (0.95 CI 13.1–NR). In the weighted data. The 0.75 quantile for RFS was 7.57 months (0.95 CI 6-NR months) for the non-HMA group versus 5.79 months (0.95 CI 4.14–6 months) for the HMA group (P = 0.027). Similarly, the 0.75 quantile for OS was 9.54 months (0.95 CI 7.96–NR) for the non-HMA group versus 5.79 months (0.95 CI 4.38–7.43 months) for the HMA group (P = 0.005). There was no significant difference in the incidence of acute or chronic GVHD or TRM. In doubly robust Cox regression model. Pretransplant HMA was associated with worse RFS and OS with a HR of 0.66 (0.95 CI 0.44-0.97, P value =0.035) and HR of 0.60 (0.95 CI 0.42-0.90, P value< 0.01) respectively. **Conclusions:** Pretransplant use of HMA in MDS patients with less than 10% bone marrow blasts is associated with worse RFS and OS following allogeneic SCT with RIC. Notably, this detrimental impact is most pronounced in patients with less than 5% blasts, raising critical questions about the role of pretransplant HMA in this low-risk subgroup and emphasizing the need for refined treatment strategies. Research Sponsor: None.

Doubly robust (weighted) Cox-regression model on RFS.

Variable	Estimate	Lower .95 CI	Upper .95 CI	P-Value
No-Hypomethylating agents before Transplant (Reference=HMA pretransplant)	0.66	0.44	0.97	**0.035**
Sex (Reference=Male)	1.27	0.89	1.80	0.186
MUD VS Haploidentical	0.92	0.42	2.02	0.84
Poor cytogenetics (Reference=very good and good)	3.9	2.66	5.82	**<0.01**

6558 **Poster Session**

Allogeneic stem cell transplantation in chronic myelomonocytic leukemia: Analysis of post-transplant survival and risk factors in 138 Mayo Clinic patients. First Author: Ali Alsugair, Mayo Clinic, Rochester, MN

Background: Allogeneic stem cell transplantation (ASCT) is currently the only curative therapy in chronic myelomonocytic leukemia (CMML). **Methods:** A Mayo Clinic enterprise-wide database search identified 138 CMML cases who underwent ASCT. Conventional statistical methods were used for analyses. **Results:** 138 CMML patients (transplanted between 1995-2024) were included (median age 63 years; males 62%);104 (group A) received ASCT before and 34 (group B) after blast transformation (BT). At initial diagnosis, CMML-1/CMML-2 and dysplastic/proliferative representations were 78%/22% and 54%/46%; 31% displayed abnormal karyotype and most frequent mutations were *ASXL1* (56%), *TET2* (44%) and *SRSF2* (38%). At time of initial diagnosis, CPSS-Mol risk categories were low (17%), intermediate-1 (11%), intermediate-2 (40%), and high (32%). Median time from diagnosis to ASCT was 11 months (range 0-201). Median overall survival (OS) from the time of initial diagnosis was 67 months (range 4-239) and from the time of ASCT 54 (range 0-212) months. Occurrence of BT before ASCT was associated lower post-transplant survival (PTS; 16 vs 95 months, P=0.01, HR 1.9, 95%CI 1.2-3.2). Bone marrow (BM) blasts, at the time of ASCT, $<$5%, 5-9%, and 10-19% correlated with median OS of 171, 81, and 18 months in group A (p=0.01) and 50, 25, and 13 months in group B (P=0.07), respectively. Pre-ASCT hypomethylating agent exposure was associated with lower PTS in group A (P=0.02). PTS was also adversely affected by *DNMT3A* and *SETBP1* mutations. In group A, PTS was the longest with myeloablative busulfan-based (median not reached) and the shortest (median 22 months) with Cy-TBI-based conditioning (p=0.1). Donor type did not impact PTS: matched unrelated (63%), matched sibling (23%), mismatched unrelated (7%), or haploidentical (7%). Post-transplant cyclophosphamide was associated with a numerically lower median PTS (22 months), compared to other forms of GVHD prophylaxis (107 months; p=0.1) and significantly higher non-relapse mortality (p=0.02). Documentation of morphologic CR at day 100 was associated with significantly longer PTS in both groups A (92%,164 vs. 18 months; p=0.01) and B (84%, 42 vs. 11 months; p=0.01). The presence of abnormal karyotype at day 100 was associated with shorter PTS in group A (p=0.01). Grade $\geq$3 acute and moderate to severe chronic GVHD occurred in 20% and 34%, respectively, in group A patients and in 26% and 44% in group B. GRFS at 1/3 years were 42/21% in group A and 31/16% in group B. At last follow up, 44% in group A and 65% in group B were dead. Causes of death were relapse/non-relapse related in 36/64% in group A and 39/61% in group B. **Conclusions:** ASCT is effective in securing long-term survival in CMML, especially when the procedure is performed prior to BT and in the setting of $<$5% BM blasts/promonocytes. Response assessment at day 100 was highly informative of outcome. Research Sponsor: None.

6559 **Poster Session**

Allogeneic hematopoietic stem cell transplantation in T-cell acute lymphoblastic leukemia adults in complete remission: A systematic review and meta-analysis. First Author: Muhammad Umair Mushtaq, Division of Hematologic Malignancies & Cellular Therapies, University of Kansas Medical Center, Kansas City, KS

Background: There is limited data on the outcomes of allogeneic hematopoietic stem cell transplantation (allo-HCT) in T-cell acute Lymphoblastic Leukemia (T-ALL) patients. This study aims to assess complications, recurrence rates, and survival outcomes in T-ALL patients in clinical remission receiving allo-HCT. **Methods:** Following PRISMA guidelines, a comprehensive literature search was conducted across PubMed, Embase, Cochrane, and the clinicaltrials.gov registry from inception to December 2024 using keywords related to T-ALL and allo-HCT. Out of 1161 identified search results, 8 studies were included in this meta-analysis. Data was analyzed for outcomes including overall survival (OS), leukemia-free survival (LFS), relapse rates, non-relapse mortality (NRM), and graft-versus-host disease (GVHD) of Allo-HSCT in adult T-ALL patients in clinical remission. R version 4.4.2 was used to conduct a proportional meta-analysis using an inverse variance, random effects model. **Results:** This study included eight retrospective studies involving 3,280 T-ALL patients undergoing allo-HCT, with a median age of 32 years (range: 17–49) and a median follow-up of 37 months (range: 28–44). Seventy-one percent of the patients were male. Donor types included matched sibling (48.3%), matched unrelated (33.7%), haploidentical (10.2%), and mismatched unrelated (7%). Most grafts were from peripheral blood (75.8%), with the remainder from bone marrow. A myeloablative conditioning regimen was used in 86% of patients. At the time of HSCT, 92.16% of patients were in clinical remission. The pooled 2-year overall survival (OS) for patients in clinical remission was 63.2% (95% CI: 47.2–79.2; p$<$0.0001; I^2 = 89.4%), and 53.5% at 5 years (95% CI: 25.9–81.1; p$<$0.0001; I^2 = 93.7%). Similarly, the pooled leukemia-free survival (LFS) was 64.5% at 2 years (95% CI: 51.9–77.1; p$<$0.0213; I^2 = 74%) and 62.7% at 5 years (95% CI: 26.9–99.4; p$<$0.0003; I^2 = 92.5%). The pooled relapse rate was 23.4% at 2 years (95% CI: 9.6–37.2; p$<$0.0001; I^2 = 89.4%) and 53.3% at 4 years (95% CI: 0.0–100; p$<$0.0001; I^2 = 98.5%). The pooled non-relapse mortality (NRM) rate was 14.5% at 1 year (95% CI: 9.1–19.6; p = 0.0695; I^2 = 69.6%), 20.8% at 4 years (95% CI: 17.9–23.8; p = 0.4907; I^2 = 0%), and 26% at 5 years (95% CI: 18.6–29.9; I^2 = 0%). The pooled incidence of chronic graft-versus-host disease (cGVHD) was 34.3% (95% CI: 27.0–41.5; p = 0.6564; I^2 = 75.8%). **Conclusions:** T-ALL patients in clinical remission at allo-HCT showed favorable survival outcomes, though relapse remains a significant concern, particularly over time. Non-relapse mortality stabilizes after the first year but continues to pose a challenge. Chronic graft-versus-host disease prevalence remains high, underscoring the importance of long-term management strategies. Research Sponsor: None.

6560 **Poster Session**

Factors associated with outcomes following reduced intensity conditioning haploidentical hematopoietic cell transplantation in acute myeloid leukemia. First Author: Muhammad Umair Mushtaq, Division of Hematologic Malignancies & Cellular Therapies, University of Kansas Medical Center, Kansas City, KS

Background: Allogeneic hematopoietic cell transplantation (HCT) is a curative therapy for high-risk acute myeloid leukemia (AML). Elderly patients can undergo HCT using a reduced-intensity conditioning (RIC) regimen. When HLA-matched donors are unavailable, haploidentical (Haplo) family donors can be used, offering outcomes similar to those with matched donors. This study investigates factors influencing outcomes following RIC haplo HCT with posttransplant cyclophosphamide (PT-Cy)-based GVHD prophylaxis. **Methods:** A retrospective multicenter study was conducted using the CIBMTR registry (2012-2017, P-5737 dataset, Ustun et al.) to assess AML patients undergoing first RIC haplo-HCT. Outcomes included overall survival (OS), disease-free survival (DFS), relapse, non-relapse mortality (NRM), acute and chronic GVHD, GVHD-free relapse-free survival (GRFS), and engraftment. Patient- and transplant-related factors were analyzed with Chi-square and Wilcoxon tests. Kaplan-Meier and univariate and multivariate Cox regression analyses were conducted. Hazard ratios (HR) with 95% confidence intervals (CI) were calculated. Statistical significance was defined as p$<$0.05. **Results:** We included 185 AML patients undergoing the first RIC haplo-HCT with PT-Cy-based GVHD prophylaxis. The median age was 63.8 years, 58% were male, and 70% were Caucasians. Graft sources were peripheral blood (55%) and bone marrow (45%), with a graft cell dose of$>$2 million CD34 cells/kg in 82% of patients. HCT-Comorbidity index (CI) was three or higher in 45% of patients, and Karnofsky's performance status was $<$90% in 53% of patients. The median follow-up was 4 years, and 36% were alive at the last follow-up. The median OS, DFS, and GRFS were 1.59, 0.76, and 0.31 years, respectively. Primary disease (33.5%), organ failure (9%), and infection (8%) were the leading causes of death. Relapse, acute (grade II-IV), chronic GVHD, and NRM occurred in 52%, 36%, 30%, and 20.5% of patients, respectively. Neutrophil engraftment occurred over a median of 17 days. In multivariate analyses, high disease risk independently predicted inferior OS (HR 1.72, p=0.012), inferior DFS (HR 1.49, p=0.136), higher relapse (HR 1.88, p=0.028), and higher NRM (HR 2.12, p=0.011). Higher HCT-CI predicted inferior OS (HR 1.88, p=0.041), higher NRM (HR 5.21, p=0.043), and delayed neutrophil engraftment (HR 0.37, p$<$0.001). Asians, compared to Caucasians, had superior GRFS (HR 0.46, p=0.040). **Conclusions:** In AML patients undergoing RIC haploidentical HCT, favorable outcomes were observed, and key determinants were high disease risk and comorbidities. Relapse remains the leading cause of treatment failure. These findings suggest pre-transplant assessments and post-transplant strategies to mitigate relapse risk for optimizing outcomes in this patient population. Research Sponsor: None.

6561 **Poster Session**

Myeloablative fractionated busulfan conditioning regimen with sorafenib for allogeneic stem cell transplant in AML: Results of a phase 1/2 study. First Author: Uday R. Popat, Department of Stem Cell Transplantation and Cellular Therapy, The University of Texas MD Anderson Cancer Center, Houston, TX

Background: Myeloablative conditioning for allogeneic stem cell transplant (allo-SCT) can be given safely to older patients by extending the duration of busulfan (Bu) administration. This allows the addition of agents like sorafenib for a 3-week period to synergize with the conditioning. Here, we studied 4 doses of sorafenib with myeloablative fludarabine and fractionated Bu (f-Bu) in a phase 1/2 study (NCT03247088). **Methods:** From 3/2018-9/2023, 59 AML patients 18-70 years old with 8/8-HLA matched donors were enrolled prospectively. Sorafenib dose finding was done in phase 1 with a Bayesian Model Averaging Continual Reassessment Method with target toxicity probability .30 and cohort size 3, with DLT defined as grade $>$3 regimen-related toxicity occurring on days -24 to 30. Subsample sizes were 3 patients at 200, 400, and 600mg, and 50 patients at the highest tolerated dose of 800mg (400mg bid), given daily on days -24 to -5. The f-Bu dose targeted an area under the concentration vs time curve of 20,000 $\pm$ 12% μmol.min, given over 3 weeks. The first 2 doses (80 mg/m2 each) were given outpatient on days -20 and -13. The last 4 pharmacokinetically guided doses were given inpatient after Flu 40mg/m2 on days -6 to -3. GVHD prophylaxis was cyclophosphamide 50mg/kg on days 3-4 and tacrolimus. Unrelated donor graft recipients also received MMF. All patients were eligible for sorafenib maintenance for 1 year post-transplant. 30 (51%) patients began this maintenance and 13 (21%) completed 1 year. **Results:** Median age was 53 years (range, 24-70). Disease status at SCT was CR1 in 42 (71%) patients, CRi in 6 (10%), and advanced disease in 11 (19%). 34 (58%) had ELN22 adverse risk disease, 31 (53%) were MRD+, 17 (29%) had FLT3 ITD, donor was unrelated in 37 (63%), and peripheral blood was the graft source in 53 (90%). The cohort's 2-year overall survival (OS) was 74.9% (95% credible interval (CrI) 61.8-84.8%), with a median follow-up in 43 surviving patients of 2.2 years. A fitted Bayesian Weibull regression model for OS showed a higher risk of death with MRD+ disease (posterior mean HR = 3.13, 95% CrI 1.01–12.03) and age $>$ 60 (posterior mean HR = 2.22, 95% CrI 0.76–6.91). No association was seen with OS or PFS and comorbidity score, remission status, or ELN22 risk group. Outcomes were similar in FLT3 ITD and wild type patients. **Conclusions:** The f-Bu regimen with sorafenib results in promising outcomes for AML patients. Clinical trial information: NCT03247088. Research Sponsor: National Cancer Institute.

Outcomes (n=59).

	1 year	2 years
OS	86%	75%
PFS	83%	69%
Relapse	12%	22%
NRM	10%	10%
		Percent
Acute GVHD II-IV, day 100		36%
Acute GVHD III-IV, day 100		3%
Chronic GVHD, 2 years		14%
Mod/Severe Chronic GVHD		9%
		Median (range) days
Neutrophil Engraftment		15 (12-28)
Platelet Engraftment		23 (14-164)
T Cell Chimerism, day 30		100 (33-100)
Myeloid Chimerism, day 30		100 (91-100)
Grade 3-5 toxicity, day 100 (>10%)	**Events**	**Percent**
Febrile Neutropenia	24	41%
Bacterial infection	21	36%
Pneumonitis/IPS	8	14%
Rash	6	10%

6562 **Poster Session**

Association between pre-transplant biological aging markers and clinical outcomes in allogeneic hematopoietic cell transplant recipients. First Author: Kelly E. Rentscher, Medical College of Wisconsin, Milwaukee, WI

Background: Cancer and its treatments can accelerate the aging process, placing survivors at increased risk for poor outcomes. Hematopoietic cell transplant (HCT) recipients may show variations in biological aging before HCT due to previous treatment exposures; however, pre-transplant transcriptomic markers of biological aging have not yet been investigated as predictors of clinical outcomes. We used data from the Center for International Blood and Marrow Transplant Research (CIBMTR) to examine the hypothesis that recipients with greater pre-transplant expression of molecular processes in the cellular senescence pathway—a fundamental mechanism of aging—would have worse clinical outcomes. **Methods:** Participants included 261 adults (M_{age}=41.3 years) that received an HLA-matched unrelated donor myeloablative HCT between 1995–2005 for acute myelogenous leukemia (AML) in complete remission and had pre-transplant blood samples available in the CIBMTR Repository. Whole-genome RNA sequencing of recipient peripheral blood mononuclear cells (PBMCs) was used to derive molecular senescence markers, including the DNA damage response (DDR; 29-gene composite), cellular senescence signals $p16^{INK4a}$ and p21 (*CDKN2A* and *CDKN1A*, respectively), the pro-inflammatory senescence-associated secretory phenotype (SASP; 60-gene composite) and the SenMayo senescence gene set (125-gene composite). We examined acute and chronic graft-versus-host disease (GVHD), transplant-related mortality (TRM), relapse, leukemia-free survival (LFS), and overall survival (OS) as clinical outcomes. **Results:** Transcriptomic composites were examined as continuous variables. Cox proportional hazard models adjusting for patient, disease, and transplant characteristics and major cell subsets in the PBMC pool revealed that elevated SASP and SenMayo expression were associated with increased risk of TRM (*HR*=3.56, *p*=.005 and *HR*=6.88, *p*=.002, respectively) and OS (*HR*=2.31, *p*=.03 and *HR*=4.50, *p*=.004, respectively). However, enhanced expression of senescence signal p21 was associated with decreased risk of relapse (*HR*=0.52, *p*=.01) and LFS (*HR*=0.70, *p*=.03). The DDR and senescence signal $p16^{INK4a}$ did not significantly relate to clinical outcomes. **Conclusions:** Transcriptomic markers of biological aging assessed in allogeneic HCT recipients before transplant are predictive of relapse and survival outcomes. Specifically, findings suggest that enhanced expression of pro-inflammatory SASP and SenMayo genes may represent a pre-transplant molecular risk profile, whereas elevated expression of p21 may serve as a protective prognostic indicator in the HCT setting. Given the heterogeneous nature of senescent cells, research that examines these transcriptomic markers following HCT as well as how recipient and donor profiles may interact to influence outcomes is warranted. Research Sponsor: NIH National Institute on Aging.

6563 **Poster Session**

Pre-transplant measures of geriatric assessment domains and outcomes of allogeneic hematopoietic cell transplantation in adults aged 75 and older. First Author: Amar Harry Kelkar, Dana-Farber Cancer Institute, Boston, MA

Background: The upper age limit for allogeneic hematopoietic cell transplantation (HCT) has risen over time, yet prior studies indicate worse outcomes—particularly non-relapse mortality (NRM)—in patients over 70 compared to younger patients (Shahzad, *Transplant Cell Ther* 2025). As the population ages, we expect the transplant-eligible age range to extend, underscoring the need to identify reliable predictors of outcomes in older adults. **Methods:** We conducted a retrospective study of all adults aged ≥75 who underwent HCT at Dana-Farber Cancer Institute from January 2008 to August 2024. We evaluated overall survival (OS), progression-free survival (PFS), NRM, and cumulative incidence of relapse (CIR). Guided by geriatric assessment (GA) domains, clinical health data were collected from pre-HCT consent session notes. Log-rank (OS, PFS) and Gray's tests (NRM, relapse) were used for group comparison; Cox (OS, PFS) and Fine-Gray (NRM, relapse) models were used for multivariable analysis. **Results:** Sixty-seven patients (median age 76 years, range 75-80) were analyzed; 73.1% were male and 86.6% were White. Acute myeloid leukemia (46.3%) and myelodysplastic syndromes (35.8%) were the most common HCT indications. Neutrophil engraftment occurred in 94% of patients by a median of 15 days (range 3-40). Median follow-up for survivors was 21 months (range 11-125), and median OS was 33 months (95% CI: 18-55). At 18 months, OS was 61% (95% CI: 48-72%), PFS 54% (95% CI: 41-66%), NRM 11% (95% CI: 4.9-21%), and CIR 34% (95% CI: 23-46%). In univariable analysis, age ≥77 (p=0.0095), number of medications ≥15 at HCT consent (p=0.0078), and post-HCT bacterial or fungal infection (p=0.039) were associated with worse OS; similar factors affected PFS (e.g., for patients with bacterial or fungal infection, p=0.049). Diabetes (p=0.0001) and ≥15 medications at time of HCT consent (p=0.001) correlated with higher NRM. On multivariable analysis, age ≥77 (HR 2.44; p=0.028) and ≥15 medications (HR 2.68; p=0.019) significantly predicted worse OS; both factors also predicted inferior PFS. **Conclusions:** In this relatively large cohort of the oldest HCT recipients, older age, polypharmacy, and comorbidities emerged as likely predictors of worse clinical outcomes. Interestingly, relapse—rather than NRM—was the primary cause of treatment failure, aligning with established links between advanced age and the biology of myeloid malignancies. While the expanding upper age limit for HCT is a promising development for patients ≥75, our data are vital to facilitate informed consent discussions. These findings also underscore the need for robust pre-HCT evaluations, such as assessment of other GA domains via dedicated functional assessments (e.g., IADLs and gait speed) to improve risk stratification. Investigation in a larger cohort (≥70 years) is underway to further explore these results. Research Sponsor: None.

6564 **Poster Session**

Assessment of long-term toxicities of imatinib in CML: Experience from a tertiary care cancer centre in south India. First Author: Akhil Santhosh, MVR Cancer Centre & Research Institute, Calicut, India

Background: Imatinib has been the standard 1st line drug for chronic myeloid leukemia (CML) in chronic phase for decades. Literature is replete with data regarding acute toxicities of imatinib, but chronic long-term effects of the drug on cardiac, renal, endocrine, skin and bone health are less explored. In rare cases, imatinib has been postulated to cause left ventricular dysfunction, impairment in bone mineral density, thyroid hormone abnormalities and sensorineural hearing loss. **Methods:** We conducted a prospective study on CML patients aged 18 and above who had taken Imatinib for a minimum duration of 10 years. All patients were subjected to a detailed skin examination, laboratory tests including complete blood count, liver/renal function tests, thyroid profile, 2D echo, bone densitometry and pure tone audiometry. All tests were organized in accordance with a camp conducted for CML patients in our center. Children, pregnant women, patients who had not achieved major molecular remission and patients in accelerated phase/blast crisis were excluded. **Results:** 100 patients (males n=60, females, n=40) participated in the study. Median age was 45years (IQR 30-60). All patients were in major molecular remission with excellent drug compliance. Regarding the rarer side effects, 2D echo revealed left ventricular dysfunction in 4 patients (4%, n=1 moderate, n=3 mild). After interruption of drug, ejection fraction improved in all 3 patients with mild LV dysfunction (repeat 2d echo after 3 months). Pure tone audiometry revealed bilateral sensorineural hearing loss in 5 patients (5%, moderate n=3, severe n=2). Repeat testing done after 3 months post drug discontinuation showed improvement for 2 out of 3 patients with moderate sensorineural hearing loss (conversion to mild degree). 10 patients had osteopenia and 2 patients had osteoporosis in bone densitometry scans. Drug was not discontinued for the same. Patients were started on calcium+ vitamin D supplementation for osteopenia and 6 monthly zoledronic acid injections for osteoporosis. Cutaneous side effects were reported in 43%(N=43). Hyperpigmentation was the most common, seen in 30%(n=30) followed by hypopigmentation in 11% and chronic malar flush in 2%. Menstrual irregularities were reported in 10 females (n=10, 25%), most common being oligomenorrhea(n=7). 4 males (6.66%) had gynecomastia on examination. Anemia was seen in 25% (n=25,10 males and 15 females). Hypophosphatemia and elevated TSH were seen in 12 (12%) and 7 patients (7%) respectively. **Conclusions:** CML is now equated to a chronic disease with patients attaining a near normal life expectancy which makes it very important for clinicians to be well versed with both acute and chronic toxicities of imatinib. Through our study, we were able to highlight certain rare toxicities like ejection fraction abnormalities, hearing loss and bone mineral density changes that may be seen with imatinib. Research Sponsor: None.

6565 **Poster Session**

Early predictors of treatment-free remission in chronic myeloid leukemia. First Author: Aziz Farhat, The University of Texas MD Anderson Cancer Center, Houston, TX

Background: Tyrosine kinase inhibitors (TKIs) have significantly improved outcomes for chronic myeloid leukemia (CML), allowing most patients to achieve near-normal life expectancy. This has shifted treatment goals toward achieving treatment-free remission (TFR), particularly important for younger patients. Current criteria for TFR rely on sustained deep molecular remission after years of therapy, but early predictors are lacking. We aimed to identify factors predictive of TFR eligibility. **Methods:** We screened 780 patients with newly diagnosed chronic phase CML treated at The University of Texas MD Anderson Cancer Center from January 2012 to December 2023. Among them, 412 patients (53%) met the NCCN criteria for TFR (sustained MR4.5 for 2 years following 3 years of therapy). Thirty patients (4%) were excluded due to insufficient treatment duration. The remaining 338 patients (43%) formed the control cohort. We compared these cohorts and evaluated predictive factors for TFR eligibility using univariate and multivariate logistic regression, including factors with $P < 0.1$ in the multivariate model. **Results:** Patients in the TFR cohort were older (median age 51 vs. 46 years, P = 0.007) and had a different distribution of Sokal risk categories (P = 0.037): 67% low risk, 27% intermediate, and 6% high risk, compared to 64%, 25%, and 11% in the control group. TKI usage also differed (P = 0.01), with 32% vs. 41% receiving imatinib, 43% vs. 33% dasatinib, 19% receiving nilotinib in both groups, and 6% vs. 8% receiving ponatinib. *BCR::ABL* transcript distribution was significantly different ($P < 0.001$). The e13a2 transcript was more common in the control group (51% vs. 33%), while the e14a2 transcript predominated in the TFR group (46% vs. 32%). Co-occurrence of both transcripts was similar (21% vs. 16%), but other variants were rare and only observed in the control group (1% vs. 0%). Resistance mutations in the ABL gene were exclusively detected in the control group (13%, 44 patients). Univariate analysis identified older age (OR: 1.02; P = 0.001), BCR::ABL halving-time <30 days (OR: 4; $P < 0.001$), and achieving molecular milestones—transcript levels <10% IS at 3 months (OR: 11.4; $P < 0.001$), <1% IS at 6 months (OR: 10.5; $P < 0.001$), and <0.1% IS (MMR) at 1 year (OR: 6.5; $P < 0.001$)—as predictive factors for TFR eligibility. The e14a2 transcript (OR: 2.2; $P < 0.001$), co-occurrence of both transcripts (OR: 1.9; P = 0.001), and treatment with newer-generation TKIs vs. imatinib (OR: 1.5; P = 0.008) were also significant predictors. Multivariate analysis confirmed that older age (OR: 1.2; P = 0.045), halving-time <30 days (OR: 2; P = 0.041), achieving MMR at 1 year (OR: 5.6; $P < 0.001$), and the e14a2 transcript (OR: 1.6; P = 0.049) were independent predictors. **Conclusions:** Early predictors of TFR eligibility include older age, halving-time <30 days, MMR at 1 year, and the e14a2 transcript. These factors could guide prospective trial designs as early surrogates for TFR. Research Sponsor: None.

6566 **Poster Session**

Long-term follow-up of treatment-free remission in chronic myeloid leukemia after discontinuation of tyrosine kinase inhibitor therapy. First Author: Mehmet Uyanik, Department of Leukemia, The University of Texas MD Anderson Cancer Center, Houston, TX

Background: Treatment-free remission (TFR) is an important goal of therapy in patients (pts) with chronic myeloid leukemia in chronic phase (CML-CP). Here, we report our TFR experience in pts with CML-CP after a longer follow-up. **Methods:** Pts with CML-CP who were treated with tyrosine kinase inhibitors (TKIs) and subsequently discontinued therapy between October 2011 and January 2024 were included in this analysis. Molecular responses were assessed by qPCR (MMR, MR4, and MR4.5 defined as *BCR::ABL1* transcripts ≤0.1%, ≤0.01%, and ≤0.0032% on the international scale, respectively). The Kaplan Meier method was used to estimate the probability of TFR. **Results:** A total of 351 pts with CML-CP discontinued TKI therapy after a median treatment duration of 118.5 mo (range, 15.8-303.2). Most of the pts opted for elective discontinuation (70.2%) or discontinued therapy due to adverse events (24.3%). The median duration of sustained MR4.5 before TKI discontinuation was 61.8. mo (range, 1.0-206.8), and the median duration of sustained MR4 before TKI discontinuation was 76.5 mo (range, 1.37-215.1). With a median follow-up of 66.8 mo (range, 4.7-211.4) after TKI discontinuation, 93 pts (26.5%) lost MMR after a median of 7.2 mo (range, 1.2-124.9) from stopping therapy. 88 (93%) pts regained MMR after resuming therapy after a median of 3.6 mo (range, 0.4-36.5). The median TFR duration was not reached, with a 5-year TFR rate of 72.2%. The 5-year TFR rates were 63.0% and 79.2% in pts with a MR4.5 duration of <5 years, and ≥5 years before cessation of the TKI, respectively. The 5-year TFR rates were 54.5%, and 80.4% in pts with a MR4 duration of <5 years, and ≥5 years before cessation of the TKI, respectively. There was no significant difference in the rates of 5-year TFR between pts who received frontline first- or second-generation TKIs (P=0.79). Five-year TFR rates were similar between pts who were treated at standard TKI dose and those treated with TKIs at reducing dosing (p=0.52). There was no significant difference in the TFR rates according to the *BCR::ABL1* transcripts subtypes (p=0.1). **Conclusions:** The long-term follow-up results continue to demonstrate improved TFR rates of approximately 80% in patients who achieve a deep molecular response (MR4 or deeper response) sustained for 5 years or more. Research Sponsor: None.

6567 **Poster Session**

Allogeneic stem cell transplantation-related outcomes in myelodysplastic syndromes. First Author: Alexandre Bazinet, The University of Texas MD Anderson Cancer Center, Houston, TX

Background: Allogeneic stem cell transplantation (SCT) is the only known curative modality in myelodysplastic syndromes (MDS). Its use has historically been limited due to older patient age and comorbidity burden. Recent advances in reduced-intensity conditioning (RIC) have expanded the use of SCT in MDS. **Methods:** This was a retrospective single center database review study to evaluate contemporary outcomes in SCT-treated MDS. We identified all patients with newly diagnosed MDS presenting to our center between Jan 2000 and Mar 2023 and stratified them by receipt of SCT. Biallelic *TP53*-mutated status was defined as 2 *TP53* mutations, VAF ≥ 50%, or concomitant del(17p). Landmark analyses were performed to compare outcomes with or without SCT (median time from diagnosis to SCT as landmark). **Results:** 3649 patients with newly-diagnosed MDS were included. 573 (16%) underwent SCT. 4-week, 8-week, and 100-day mortality were 3%, 6%, and 14%, respectively. Acute GVHD occurred in 64% of patients (14% grade 3/4). Chronic GVHD occurred in 33%. Patients undergoing SCT (ages 18-77) had a median OS of 25 m from SCT day 0. The 5-year cumulative incidences of death and relapse were 21% and 31% with myeloablative conditioning (MAC) and 27% and 36% with reduced-intensity conditioning (RIC). Stratified by IPSS-R, the median OS post-SCT was 136, 40, 92, 103, and 8 m in Very Low, Low, Intermediate, High, and Very High risk. Patients with *TP53*wt, *TP53*mut monoallelic, and *TP53*mut biallelic had a median OS of not reached (NR), 9 m, and 7 m. Patients with non-complex, complex (3 abn), and very complex (> 3 abn) CG had a median OS of 96 m, 14 m, and 7 m. Transplanted patients without *TP53* mutations had 5-year OS of 59% and those without complex CG had 5-year OS of 54%. Immediate pre-SCT blasts <5% and 5-9% were associated with similar post SCT OS (median 29 and 30 m) whereas patients with 10-19% (8 m) and > 20% (12 m) had inferior survival. Multivariate analysis identified bone marrow ring sideroblast %, *TP53* mutations, haplo donor, pre-SCT transformation to AML, and increasing donor age as associated with worse post-SCT OS while receipt of venetoclax pre-SCT and higher Karnofsky score were favorable. By landmark analyses, SCT was associated with improved OS across IPSS-R risk categories. Median OS was 185 m with SCT vs 82 m without SCT in Very Low risk (p<0.01), 107 vs 58 m in Low risk (p<0.01), 103 vs 31 m in Intermediate risk (p<0.01), 108 vs 18 m in High risk (p<0.01), and 16 vs 13 m in Very High risk (p<0.01). No significant benefit of SCT was noted in patients with *TP53* mutations. The median OS was 27 m with SCT vs 17 m without SCT in *TP53*mut monoallelic (p=0.10) and 14 vs 13 m in *TP53*mut biallelic (p=0.16). **Conclusions:** SCT is curative in 50-60% of patients with MDS without *TP53* mutations or complex CG. Efforts should be made to improve accessibility of SCT in this population. Alternative therapies are urgently needed in patients with *TP53* mutations or complex CG. Research Sponsor: University of Texas MD Anderson Cancer Center Support Grant; CA016672.

6568 **Poster Session**

Impact of static and dynamic risk assessment in HMA-treated MDS patients undergoing stem cell transplantation. First Author: Luis E. Aguirre, Dana-Farber Cancer Institute, Boston, MA

Background: MDS risk assessed by the IPSS-R and IPSS-M at diagnosis impacts outcomes post-hematopoietic stem cell transplant (HSCT). Recent EBMT data showed no post-HSCT survival benefit from downstaging IPSS-R scores with hypomethylating agent (HMA) therapy. However, the lack of mutational data precluded evaluating dynamic IPSS-M changes. This study aimed to determine whether evaluating IPSS-M at diagnosis or pre-HSCT more accurately predicts post-HSCT outcomes in pts treated with HMA. Additionally, in the absence of consensus on the role of cytoreductive therapy in the pre-HSCT setting for pts with higher-risk MDS, we investigated whether the dynamic application of IPSS-M offers any advantages for such therapy. **Methods:** We analyzed 176 paired samples from higher-risk MDS pts treated with HMA followed by HSCT at Dana-Farber (n=91) and Moffitt (n=85). Disease risk was assessed by IPSS-M at diagnosis and after HMA therapy pre-HCT. Dynamic assessment was categorized as decrease (improvement), no change, or increase (progression) in IPSS-M risk category from diagnosis to HSCT. The primary outcome was post-HSCT progression-free survival (PFS). **Results:** In the cohort, 60% were male, with a median age of 66 yrs (range 26-79). At diagnosis, 87.5% had MDS with increased blasts and 9.7% had MDS with low blasts. Pts received a median of 4 cycles of HMA prior to HSCT, with 63.1% having MUD donors and 84.1% receiving RIC. At diagnosis, 80% were higher-risk (MH/H/VH) per IPSS-M. Post-HMA, 61.4% improved in IPSS-M, while 24.4% had no change and 14.2% progressed. The 4y PFS for the cohort was 47%, with no significant differences between centers (48% vs 47%, p=0.75). In MVA, there was no difference in prognostic accuracy between IPSS-M estimated at diagnosis and pre-HSCT (c-index: 0.635 vs. 0.645). Dynamic assessment showed a 4y PFS of 50% for both improved/unchanged IPSS-M vs 31% for progressive IPSS-M (c-index: 0.647, p=0.09). Substantial improvement in IPSS-M (≥2.5 score change) yielded a 4y PFS of 38%, comparable to those with progression (23%) and much worse than those with discreet/evident improvement (53%/56%). Pts with substantial improvement in IPSS-M had a higher proportion of VH risk MDS at diagnosis than those with discreet/evident improvement (77% vs. 28%), indicating that adverse disease biology at diagnosis negatively affected outcomes despite favorable response to HMA. **Conclusions:** Pre-HSCT IPSS-M assessment did not enhance post-HSCT outcome predictions compared to evaluation at diagnosis. Worsening IPSS-M correlated with worse outcomes, while improvement did not yield better results than unchanged risk. For those with high-risk disease, improvement in IPSS-M achieved through HMA does not appear to mitigate the adverse risk established at diagnosis. Thus, in HMA-treated pts, downstaging of IPSS-M pre-HSCT should not be a therapeutic goal or an endpoint for response evaluation in MDS trials. Research Sponsor: None.

6569 **Poster Session**

Effect of prior treatment (tx) on the clinical activity of imetelstat (IME) in transfusion-dependent (TD) patients (pts) with erythropoiesis-stimulating agent (ESA), relapsed or refractory (R/R)/ineligible lower-risk myelodysplastic syndromes (LR-MDS). First Author: Rami S. Komrokji, H. Lee Moffitt Cancer Center and Research Institute, Tampa, FL

Background: IME, a first-in-class, direct, and competitive inhibitor of telomerase activity, was approved in the US for the tx of red blood cell (RBC)-TD LR-MDS in pts who are R/R or ineligible for ESA based on the results of the pivotal IMerge trial (NCT02598661). IMerge demonstrated significant and durable efficacy of IME (n=118) versus placebo (n=60) for ≥8-week, ≥24-week, and ≥1-year RBC-transfusion independence (TI), with a generally manageable safety profile in this pt population. Here, we pooled data from the 3 parts of the IMerge trial (phase 2, phase 3, and QTc substudy) to investigate the effect of prior txs on the clinical activity of IME. **Methods:** In IMerge, pts received IME intravenously every 4 weeks at 7.1 mg/kg active dose (7.5 mg/kg IME sodium equivalent). Prior lenalidomide (LEN) and prior hypomethylating agent (HMA) use were exclusion criteria in phase 3 only. In this analysis, pooled data from IME-treated pts (phase 2, phase 3, and QTc substudy) were analyzed by prior tx: ± ESA, luspatercept (LUSP), LEN, and HMA; pts may have received >1 prior tx. Outcomes included ≥8-week, ≥24-week, and ≥1-year RBC-TI, rates of hematologic improvement-erythroid (HI-E) based on the revised International Working Group (IWG) 2018 criteria, transfusion reduction of ≥4 U/8 weeks, and a hemoglobin (Hb) rise of ≥1.5 g/dL for ≥8 weeks. **Results:** The data cutoff dates were 10/13/2023 (phase 2/3) and 10/13/2024 (QTc substudy). A total of 226 IME-treated pts pooled in IMerge were included in this analysis; most pts (n=188) had a high transfusion burden (TB) per revised IWG 2018 at baseline (vs low TB [n=38]; Table). Of all pts, 39% achieved ≥8-week RBC-TI (median duration of response, 55 weeks), and 28% and 18% achieved ≥24-week and ≥1-year RBC-TI, respectively. Among all IME-treated pts, 204 had prior tx with an ESA and 22 were ineligible for ESAs; 36 had prior LUSP, 26 had prior LEN, and 22 had prior HMA. Pt characteristics and efficacy by prior tx are shown in the table. **Conclusions:** Pts who were ESA ineligible or who had prior tx with LUSP, LEN, or HMA, and were largely high TB, in IMerge experienced clinical benefit from IME tx, though the number of pts was small. Given the limited efficacy data available in later lines of tx for LR-MDS, these results have important clinical implications, suggesting that IME has clinical activity regardless of prior txs. Clinical trial information: NCT02598661. Research Sponsor: This study was funded by the Geron Corporation. All authors contributed to and approved the abstract; writing and editorial support were provided by Casandra Monzon, PhD, CMPP, of The Lockwood Group (Stamford, CT, USA), funded by the Geron Corporation.

	ESA ineligible (n=22)	Prior ESA (n=204)	Prior LUSP (n=36)	Prior LEN (n=26)	Prior HMA (n=22)
TB at baseline, n					
Low TB	3	35	5	4	3
High TB	19	169	31	22	19
≤8-week RBC-TI, %					
Median duration of RBC-TI for ≥8-week TI responders, weeks	36	40	31	23	14
≥24-week RBC-TI, %	32	60	70	41	41
≥1-year RBC-TI, %	14	29	22	19	9
HI-E (IWG 2018), %	9	19	14	8	0
Transfusion reduction of ≥4 U/8 weeks (IWG 2006), %	41	44	31	35	23
Hb rise ≥1.5 g/dL for ≥8 weeks (IWG 2006), %	64	64	69	54	50
	27	34	31	19	14

6570 Poster Session

Real-world (RW) outcomes of patients (pts) with lower-risk myelodysplastic syndrome (LR-MDS) receiving first-line (1L) luspatercept (LUSPA) or 1L erythropoiesis-stimulating agents (ESA) in the US. First Author: Idoroenyi Usua Amanam, City of Hope Cancer Center, Duarte, CA

Background: LR-MDS pts receiving ESAs for anemia often experience treatment (tx) resistance or relapse. Evidence from the COMMANDS trial led to LUSPA's US FDA approval in August 2023 as 1L tx for anemia in pts with LR-MDS. This is the first study assessing RW characteristics and outcomes in pts with LR-MDS receiving 1L LUSPA or ESA after 1L LUSPA approval. **Methods:** Interim data from an ongoing, retrospective medical records review of pts with LR-MDS receiving 1L LUSPA or ESA was collected (17 Oct 2024-19 Dec 2024; target sample size = 200 pts per cohort). Eligible adult pts had IPSS/IPSS-R-defined diagnosis of LR-MDS and initiated 1L LUSPA or ESA between 28 Aug 2023-31 Jul 2024 (tx initiation date = index date). Outcomes were descriptively analyzed; pt characteristics and changes in hemoglobin (Hb) and red blood cell (RBC) transfusion requirements during the first 6 months (mos) of 1L anemia tx are reported. **Results:** 103 pts (1L LUSPA: 46; 1L ESA: 57) were included in the interim data.In the LUSPA and ESA cohorts, respectively,median age at index was 67.7 and 62.9 yrs; 63.0% and 66.7% were White; 54.3% and 40.4% were female; 28.3% and 10.5% had *SF3B1* mutation; 93.5% and 68.4% had ECOG 0/1; and median follow-up was 7.9 and 8.4 mos. IPSS/IPSS-R risk status was intermediate-1/intermediate for 21.7% of LUSPA pts and 8.8% of ESA pts. Of pts with known ring sideroblast (RS) level, 62.2% (23/37) of LUSPA pts and 71.8% (28/39) of ESA pts were RS negative. Baseline (BL) sEPO was $<$200 IU/L for 30.6% (11/36) of LUSPA pts and 78.9% (30/38) of ESA pts. Most ptsreceiving 1L LUSPA achieved Hb increase of $\geq$1.5 g/dL (LUSPA: 89.1%; ESA: 56.1%) in the first 6 mos of tx. Of pts who were RBC transfusion-dependent (RBC-TD) at BL, a greater proportion of LUSPA pts became RBC transfusion-independent (RBC-TI) vs ESA pts (91.7% vs 71.4%) in the first 3 mos (Table). Updated results for the full cohort to be presented at the meeting. **Conclusions:** During the first 6 mos of tx,a higher proportion of ptsreceiving 1L LUSPA showed improvement in Hb and a reduced need for RBC compared to those receiving 1L ESA. This analysis corroborates the results of the COMMANDS trial and demonstrates the favorable RW effectiveness of 1L LUSPA vs 1L ESA for anemia treatment in LR-MDS. Research Sponsor: Bristol Myers Squibb.

	1L LUSPA (n=46)	1L ESA (n=57)
Mean (SD) BL Hb,[a] g/dL	7.7 (0.9)	8.2 (1.2)
Pts with Hb increase by ≥1.5 g/dL after tx, n (%)	41 (89.1)	32 (56.1)
Pts with Hb increase by ≥1.5 g/dL for ≥8 wks, n (%)	37 (80.4)	27 (47.4)
Mean (SD) Hb change from BL during first 6 mos of tx, g/dL	1.7 (1.0)	1.0 (1.0)
BL RBC-TD pts with follow-up RBC data known, n	12	14
Became RBC-TI (0 transfusions for ≥8 wks) within first 3 mos of tx, n (%)	11 (91.7)	10 (71.4)
Median time to RBC-TI, mos	0.8	1.9
RBC-TI for ≥12 wks, n (%)	11 (91.7)	9 (64.3)
Decreased RBC need by ≥50% in first 16 wks of tx among pts with ≥1 BL transfusion, n (%)	9 (75.0)	6 (42.9)

[a]Evaluable pts (LUSPA, n=42; ESA, n=53).

6571 Poster Session

An exploratory analysis of myelofibrosis (MF) patient subgroups by baseline hemoglobin levels in the gecacitinib phase 3 trial. First Author: Yi Zhang, The First Affiliated Hospital, Zhejiang University School of Medicine, Hangzhou, China

Background: Anemia is a key prognostic indicator of MF. In the double-blind, randomized phase 3 ZGJAK016 trial, gecacitinib (GCA), a dual JAK/ACVR1 inhibitor, demonstrated superior spleen response over hydroxyurea, and a trend toward improvement in constitutional symptom and anemia associated with MF in JAK inhibitor-naive patients (pts). To further elucidate the impact of GCA on anemia, we conducted a post-hoc analysis of the data from this trial, examining outcomes in relation to the severity of anemia. **Methods:** Pts in the GCA group were categorized post subgroups based on their baseline hemoglobin (Hb) levels: less than 100 g/L (moderate to severe anemia), 100 g/L to lower limit of the normal (LLN) (mild anemia), LLN to upper limit of the normal (ULN) (normal), and more than ULN for (Hb elevated). The primary endpoint was the proportion of pts with a spleen volume reduction of $\geq$ 35% from baseline (SVR35) at week (wk) 24. Secondary endpoints included the proportion of pts with a $\geq$ 50% reduction in Total Symptom Score (TSS50), and transfusion independence (TI) rate at wk 24 (no red blood cell transfusions and no Hb levels of $<$80 g/L in the last 12 wks before wk 24). **Results:** Of all the 71 pts randomly assigned to GCA in the intent-to-treat (ITT) population, 47 (66.2%) were moderately/severely anemic at baseline (including 16 pts [22.5%] with severe anemia [Hb levels of $<$ 80 g/L]), 11 (15.5%) were mildly anemic and 13 (18.3%) were non-anemic (including three pts [3.8%] with Hb levels of $>$ ULN). In the moderately/severely anemic subgroup, a higher proportion of pts were classified as DIPSS high risk, transfusion dependent, and had a diagnosis with primary MF at baseline. Most pts in the mildly anemic group were TI, as were all in the nonanemic subgroup. The three pts with elevated Hb all had post- polycythemia vera MF. Mean Hb levels increased by wk 2 across all GCA subgroups, then remained stable in the anemic subgroups, or slightly decreased but still $>$ 110 g/L in the normal subgroup and markedly decreased in the Hb elevated subgroup. Mean platelet counts decreased by wk 2 except in the Hb elevated subgroup and then maintained stability. In the moderately/severely and mild anemic subgroup, 24 of 36 (66.7%) pts who were TI at baseline maintained this status at wk 24 and 8 of 22 (36.4%) who were non-TI at baseline achieved TI at wk 24. The SVR35 rates and TSS50 rates at wk 24 were comparable across subgroups and consistent with those observed in the ITT population. **Conclusions:** In summary, GCA delivers a threefold benefit in terms of spleen and symptom management, as well as anemia, to JAK inhibitor-naive pts with MF who have mild, moderate/severe, or no anemia at baseline, particularly those with Hb levels below LLN. Clinical trial information: NCT04617028. Research Sponsor: Suzhou Zelgen Biopharmaceuticals Co, Ltd.

	ITT (n =71)	Hb <100 g/L (n =47)	Hb ≥100 g/L to LLN (n =11)	LLN to ULN (n =10)	>ULN (n =3)
SVR35 rate at wk 24	64.8%	59.6%	81.8%	70.0%	66.7%
TSS50 rate at wk 24	62.0%	57.4%	90.9%	50.0%	66.7%
TI rate at wk 24	60.6%	48.9%	81.8%	90.0%	66.7%

6572 Poster Session

Efficacy of BTI615 on malignant cells expansion and bone marrow fibrosis in a myelofibrosis mice model. First Author: Xiaomei Li, Chengdu Brilliant Inspiration Biotherapeutics Co., Ltd., Chengdu, Sichuan, China

Background: Due to the limitation of Janus kinase inhibitors and allogeneic transplant, critical unmet needs are remained in myelofibrosis (MF) patients, particularly for those with cytopenias, non-response or intolerance issues. Novel therapeutic avenues could arise from promoting bone marrow regeneration, which is dysregulated by pro-tumorigenic, fibrotic niche networked by vicious cycle of transforming growth factor β (TGF-β) signaling. Here we verified that BTI615, a synthetic active TGF-β modulating peptide, rescued malignant cells expansion and bone marrow fibrosis to restore hematopoiesis in a romiplostim-induced MF model. **Methods:** Mice (5-6 weeks old C57BL/6J, male) were treated with romiplostim (s.c., 90 μg/kg, Q3D), and simultaneously dosed with BTI615 (i.v., 30 or 120 mg/kg, TIW) for 4 weeks. The bloods, femurs, and spleens were collected for cell counting, Hematoxylin and Eosin staining, Gordon & Sweet's silver staining, immunofluorescence imaging and cytokines quantification. **Results:** In blood, BTI615 restored the declined peripheral red blood cells and hemoglobin, and suppressed inflammatory increase of white blood cells (incl. monocytes and granulocytes). Histological examination of bone marrow and spleen revealed that BTI615 remarkably suppressed megakaryocytes hyperplasia and atypia. Moreover, there was a significant reduction in the deposition of reticular fibers, fibronectin and collagen IV over the femurs by BTI615. Notably, in BTI615 treated bone marrow, the specialized niches erythroblastic islands and total Ter-119 positive cells markedly increased, accompanied by declining trends of splenomegaly. Aligned with those symptom relieves, BTI615 decreased the amount of active TGF-β_1 and the intensity of phospho-Smad2, as well as the expression of interleukin (IL)-1α and monocyte chemoattractant protein (MCP)-1 in bone marrow. **Conclusions:** Given its effective suppression on hyperplasia of atypical megakaryocytes, inflammation, marrow fibrosis and the ultimate recovery of hematopoietic function via modulating TGF-β signaling, BTI615 has a great potential to be the next generation therapeutic approach for MF. Research Sponsor: None.

6573 Poster Session

Ropeginterferon alfa-2b for pre-fibrotic primary myelofibrosis and DIPSS low/intermediate-risk myelofibrosis. First Author: Harinder Gill, Department of Medicine, School of Clinical Medicine, LKS Faculty of Medicine, the University of Hong Kong, Hong Kong, China

Background: There is currently no consensus on the optimal treatment for primary myelofibrosis (PMF) in pre-/early fibrotic stage (pre-PMF) and DIPPS low/intermediate-1 risk MF. Ropeginterferon alfa 2b (Ropeg-IFN-α2b) is a next-generation monopegylated interferon alfa-2b developed specifically to treat myeloproliferative neoplasms (MPN). **Methods:** Key eligibility included morphologically confirmed pre-PMF, and DIPSS low/intermediate-1 risk overt PMF, post-polycythemia vera MF (PPV-MF), and post-essential thrombocythemia MF (PET-MF) in patients requiring cytoreduction. The primary endpoints were responses in hemoglobin (from 10 g/dL to upper reference range), white blood cell (to $<$ 10 x 10^9/L) and platelet (to $\leq$ 400 x 10^9/L) at 24 and 52 weeks. Secondary endpoints included safety (adverse events, AEs), reductions in variant allele frequencies (VAF) of driver and non-driver genes, spleen length by palpation, Myeloproliferative Neoplasm Symptom Assessment Form Total Symptom Score (MPNSAF-TSS), and bone marrow fibrosis. Patients received Ropeg-IFN-α2b at a dose of 250 mcg at Week 0, followed by 350 mcg at Week 2 and 500 mcg every 2 weeks from Week 4 onwards. **Results:** At the data cut-off of 30 June 2024, 71 patients (40 men and 31 women) with a median age of 60 (range: 31-86) years were enrolled. At a median follow up of 119 (10-131) weeks, responses in hemoglobin, white blood cell and platelet counts were 73.9%, 82.6% and 100% at Week 24; and 76.2%, 79.4% and 100% at Week 52, respectively. Reduction in *JAK2*V617F VAF was found in 16 of 47 evaluable patients (34%) at Week 24, and 20 of 41 evaluable patients (44%) at Week 52. Reduction in *CALR* VAF was found in 10 of 19 evaluable patients (53%) at Week 24, and 6 of 14 evaluable patients (43%) at Week 52. Reduction of spleen size was found in 9 of 19 patients (47%) at Week 24, and 9 of 17 patients (53%) at Week 52. Reduction in MPNSAF-TSS of $\geq$50% was found in 27 of 63 evaluable patients (42.9%) at Week 24, and 23 of 57 patients (42.1%) at Week 52. The most common non-hematologic AEs included transaminitis (grade 1-2, N=35, 49.2%); malaise (grade 1-2, N=29, 40.8%; grade 3-4, N=1, 1.4%), and hair loss (grade 1-2, N=24, 33.8%). The most common hematologic AEs were anemia (grade 1-2, N=15, 21.1%; grade 3-4, N=6, 8.5%), neutropenia (grade 1-2, N=15, 21.1%; grade 3-4, N=4, 5.6%) and thrombocytopenia (grade 1-2, N=8, 11.2%; grade 3-4, N=3, 4.2%). Thrombohemorrhagic events or progression to blast-phase MF was not observed during the study. **Conclusions:** Ropeg-IFN-α2b was well-tolerated and induced clinical, hematologic and molecular responses in patients with pre-PMF and low/intermediate-1-risk MF. Clinical trial information: NCT04988815. Research Sponsor: Health and Medical Research Fund (HMRF); 09201046.

6574 **Poster Session**

Safety and efficacy of bromodomain and extra-terminal (BET) inhibitor INCB057643 in patients (pts) with relapsed or refractory myelofibrosis (r/r-MF) and other advanced myeloid neoplasms: A phase (Ph) 1 study. First Author: Justin M. Watts, Sylvester Cancer Center, University of Miami, Miami, FL

Background: BET proteins are epigenetic readers that regulate expression of oncoproteins involved in hematologic malignancies, including MF. The oral, small-molecule BET inhibitor INCB057643 had favorable tolerability and encouraging clinical activity in pts with advanced MF in a previous Ph 1/2 trial. **Methods:** This ongoing Ph 1, open-label 3+3 dose-escalation/expansion study (NCT04279847) is evaluating INCB057643 monotherapy (mono; part 1; 4 mg→12 mg once daily [qd]) in adults with r/r-MF, essential thrombocythemia (ET), myelodysplastic syndrome (MDS), or MDS/myeloproliferative neoplasm (MPN) overlap syndrome, or combination therapy (combo; part 2; 4 mg qd→part 1 maximum tolerated dose) with ruxolitinib (RUX) in adults with MF and suboptimal response to RUX or who were Janus kinase inhibitor (JAKi) naive. Primary endpoint is safety/tolerability. Secondary endpoints: spleen volume (SV) response (≥35% reduction from baseline [BL; SVR35] at Week [Wk] 24), symptom response (≥50% reduction from BL in MPN-Symptom Assessment Form total symptom score [TSS50] at Wk 24), and anemia response (sustained hemoglobin increase ≥1.5 g/dL from BL [if transfusion (TF) independent at BL] or TF independence [if dependent at BL] for ≥12 wks). **Results:** As of 9Sep2024, 18 pts were treated in mono dose escalation, 20 in mono dose expansion, and 23 in combo dose escalation. 48 (79%) pts had MF, 5 (8%) MDS or MDS/MPN, and 8 (13%) ET. Median (range) INCB057643 exposure was 196 (15–812) days (d) in mono dose escalation, 155 (14–341) d in mono dose expansion, and 176 (25–560) d in combo dose escalation. The most common treatment (tx)-emergent adverse event (TEAE) was thrombocytopenia (TCP; 46%). Grade ≥3 TEAEs occurred in 57%, most commonly TCP (26%) and anemia (20%). Serious TEAEs occurred in 31%; 3 (5%) were tx related. No fatal events were tx related. 9 TEAEs lead to discontinuation. 2 dose-limiting toxicities occurred with mono (12 mg, TCP, hyperbilirubinemia) and 1 with combo (6 mg, TCP). 3 pts had acute myeloid leukemia transformation (4-mg mono MDS/MPN, 10-mg mono MDS, 4-mg combo MF). Wk 24 SVR35 was achieved by 3/20 evaluable MF pts treated with any mono dose (3/7 receiving ≥10 mg) and by 4/17 treated with any combo dose. Wk 24 TSS50 was achieved by 7/19 evaluable MF pts treated with any mono dose (5/8 receiving ≥10 mg) and by 8/16 treated with any combo dose. Durable anemia response occurred in 6/22 evaluable mono pts (2 TF-dependent at BL) and 4/20 combo pts. **Conclusions:** INCB057643 mono or combo with RUX was generally well tolerated, with no tx-related fatal events. Improvements in anemia, spleen size, and symptom burden were observed with mono and combo. Dose expansion is ongoing for 6- and 10-mg mono and 4- and 8-mg combo groups (add-on and JAKi naive). A Ph 3 study of INCB057643 mono in advanced post-JAKi MF pts is being initiated. Clinical trial information: NCT04279847. Research Sponsor: Incyte Corporation.

6575 **Poster Session**

A simplified scoring system to predict in-hospital mortality of leukapheresis in patients with leukemia. First Author: Barath Prashanth Sivasubramanian, Northeast Georgia Medical Center, Gainesville, GA

Background: The 2019 consensus guidelines from the American Society for Apheresis recommend leukapheresis as a category II recommendation (acceptable second-line therapy) for patients with symptomatic hyperleukocytosis or leukostasis. Mortality in these patients has been reported to vary between 8-29%. However, no tool is currently available to assess the mortality risk following the procedure. **Methods:** The National Inpatient Sample Database (2016-2021) and ICD-10 coding were utilized to identify adults (age ≥18 years) with leukemia who underwent leukapheresisprocedure. Different types of leukemia were identified along with various demographic and clinical characteristics of patients including symptoms of leucostasis such as acute encephalopathy, respiratory failure, cardiac failure, and renal failure using ICD-10 codes. Also included were complications associated with leukapheresissuch as hemorrhage. Multivariate logistic regression models were constructed to identify independent factors associated with mortality. A scoring system was constructed to identify the risks of mortality using the variables in the model and their associated odds ratio (OR). Splines were used to identify the knots which were used as cutoff values. The cumulative risk score was divided into three strata: low (mortality < 10%), intermediate (10-40%), and high risk (>40%). **Results:** Of the estimated 4,705 patients who underwent leukapheresis, 14.2% had lymphoid leukemia, 6.2% had monocytic leukemia, 52.2% had myeloid leukemia, and 3.6% had other types of leukemia. The overall in-hospital mortality was 24.2% and the median length of hospital stay was 10 days (IQR 5-24). 71.3% received leukapheresiswithin the first 48 hours of hospitalization. Variables identified as significantly associated with mortality included the type of leukemia: monocytic leukemia (OR 3.1), myeloid leukemia (OR 2.6), lymphoid leukemia (OR 1.8) other types of leukemia (OR 3.8). Organ failure associated with hospital mortality included acute respiratory failure (OR 12.7), acute renal failure (OR 2.3), cardiogenic shock (OR 8), acute encephalopathy (OR 2.2), and disseminated intravascular coagulation (OR 1.8). The cumulative mortality score ranged from 0 to 33, categorizing patients into high risk (score ≥ 5), intermediate risk (score 2-4) and low risk (score 0-1). The risk score demonstrated a performance with an area under the curve of 0.79. of note, age, gender, and race were non-contributory in this scoring system. **Conclusions:** A novel simplified scoring tool to predict in-hospital mortality in leukemia patients requiring leukapheresis is proposed. This tool can assist in preprocedural risk assessment and help guide management planning along with consideration for the role of other treatment modalities. Research Sponsor: None.

6576 **Poster Session**

Efficacy and safety outcomes of obecabtagene autoleucel (obe-cel) stratified by age in patients (pts) with relapsed/refractory B-cell acute lymphoblastic leukemia (R/R B-ALL). First Author: Bijal D. Shah, Moffitt Cancer Center, Tampa, FL

Background: CD19 chimeric antigen receptor T-cell therapy (CAR T) exhibits good efficacy in adults with R/R B-ALL but is associated with higher toxicity with increasing age. Obe-cel, an autologous anti-CD19 CAR T, has shown high and durable response rates with low incidence of immunotoxicity in adult R/R B-ALL, and was recently approved by the US FDA. Here, we report a post-hoc analysis of the Phase Ib/II FELIX trial (NCT04404660) evaluating efficacy, safety, and persistence outcomes with obe-cel stratified by pt age. **Methods:** Adult R/R B-ALL pts received obe-cel using a tumor burden-guided dosing strategy to minimize toxicity. Overall remission rate (ORR; complete remission [CR]/CR with incomplete hematologic recovery), event-free survival (EFS), safety, and persistence are reported for pts aged <55 and ≥55 years (yrs; data cut-off: 7 Feb 2024). **Results:** Of 127 obe-cel infused pts, 79 (62.2%) were aged <55 yrs (median 36.0 [range: 20–54]) and 48 (37.8%) were aged ≥55 yrs (median 65.0 [range: 55–81]). A higher proportion of pts aged <55 yrs were Hispanic/Latino (36.7% vs 18.8%), had extramedullary disease at lymphodepletion (LD; 29.1% vs 8.3%), received prior blinatumomab (53.2% vs 22.9%), and prior inotuzumab ozogamicin (35.4% vs 25.0%) than those ≥55 yrs, while a higher proportion of pts aged ≥55 yrs had Philadelphia chromosome-positive disease (47.9% vs 16.5%). Median bone marrow blast burden at LD was higher in pts aged ≥55 yrs (45.5%) vs <55 yrs (30.0%). At 21.5 months' (mos) median follow-up (range: 8.6–41.4), the ORR (95% CI) was 72.2% (60.9–81.7) in pts aged <55 yrs vs 87.5% (74.8–95.3) in pts aged ≥55 yrs. In responders, 84.2% of pts <55 yrs and 83.3% ≥55 yrs with ≥1 post-infusion next-generation sequencing result achieved measurable residual disease-negative remission to 10^{-6} leukemic cells by Month 3. Durable remission at 1 yr post infusion was observed in 68.3% and 51.8% of pts aged <55 and ≥55 yrs, respectively. EFS was comparable in pts aged <55 and ≥55 yrs: median (95% CI) 14.3 mos (6.0–not estimable [NE]) vs 11.7 mos (6.6–NE), respectively. While in remission, 29.8% of pts aged <55 yrs and 2.4% aged ≥55 yrs proceeded to consolidative stem cell transplant (SCT). Incidence of Grade ≥3 cytokine release syndrome (CRS; 2.5% vs 2.1%) and immune effector cell-associated neurotoxicity syndrome (ICANS; 5.1% vs 10.4%) were low for pts aged <55 and ≥55 yrs, respectively. Treatment-related mortality within 3 mos post obe-cel infusion was 0% in pts aged <55 yrs vs 4.2% in pts aged ≥55 yrs. CAR T-cell persistence was similar in both age groups. **Conclusions:** Obe-cel treatment resulted in favorable ORR and EFS with low Grade ≥3 CRS/ICANS incidence in both age groups. These findings indicate that obe-cel is effective and has a positive benefit/risk profile regardless of age, including in older adults with R/R B-ALL despite few receiving consolidative SCT. Clinical trial information: NCT04404660. Research Sponsor: Autolus Therapeutics PLC. Third-party medical writing assistance, under the direction of the authors, was provided by Michaella Hulley, PhD, of Ashfield MedComms, an Inizio company, funded by Autolus Therapeutics PLC.

6577 **Poster Session**

Updated results of a phase 2 study: Timdarpacept (IMM01) combined with azacitidine (AZA) as the first-line treatment in adults with chronic myelomonocytic leukemia (CMML). First Author: Hongyan Tong, The First Affiliated Hospital of Zhejiang University School of Medicine, Hangzhou, Zhejiang, China

Background: Timdarpacept is a recombinant signal regulatory protein α (SIRPα) IgG1 fusion protein that exerts anti-tumor activity via blocking "Don't eat me" signal and activating the "Eat me" signal to induce strong antibody-dependent cellular phagocytosis (ADCP). **Methods:** The study (NCT05140811) assessed the safety and efficacy of Timdarpacept combined with AZA as first-line treatment for newly diagnosed CMML patients. Timdarpacept was administered intravenously at a dosage of 2.0mg/kg/week, while subcutaneous AZA was given at a dosage of 75 mg/m^2 on D1-7 per 28-day cycle. **Results:** At the cut-off date on Dec 31, 2024, 24 patients, with a median age of 62, males 62.5%, and 75.0% ECOG≥1, were enrolled. 33.3% and 66.7% patients were and high risk (HR), respectively. Majority of patients had poor baseline of hematologic conditions with a median hemoglobin (Hb) level of 69.5 (32-132) g/L and a median platelet (PLT) count of 73.5 (5-667)×10^9/L. The median duration of follow-up was 21.0 months (95% CI, 19.3-23.3). Among 22 efficacy evaluable patients, overall response rate (ORR) was 72.7%, including 27.3% complete response (CR), 13.6% marrow CR (mCR) with hematologic improvement (HI), 4.5% HI and 27.3% mCR alone. The median time to response (TTR) was 1.8 months and the median duration of response (DoR) was 16.9 months (95%CI, 5.1-not reached [NR]). The median time to CR (TTCR) was 3.7 months and the median duration of CR (DoCR) was 13.6 months (95%CI, 5.7-NR). The median of progression-free survival (PFS) was 17.8 months (95%CI, 5.3-NR), with an estimated 12-month PFS of 59.0% (95%CI, 33.4-77.6). Median OS has not been reached yet. The most common ≥Grade 3 TRAEs (≥10%) included lymphopenia (66.7%), leukopenia (62.5%), neutropenia (58.3%), thrombocytopenia (50.0%), anemia (29.2%) and pneumonia (16.7%). Without using of a low dose priming regimen, Grade ≥3 hemolysis occurred in 1 patient (4.2%). **Conclusions:** Timdarpacept, without a low-dose priming, combined with AZA, was well tolerated in 1L CMML. The combination, when compared to the historical data of AZA monotherapy, showed promising efficacy results for patients with treatment-naive CMML-1 and -2. Clinical trial information: NCT05140811. Research Sponsor: ImmuneOnco Biopharmaceuticals (Shanghai) Inc., Shanghai, China.

6578 **Poster Session**

Maintenance therapy with azacitidine and valproic acid after allogeneic stem cell transplant in patients with high-risk myelodysplastic syndrome and acute myelogenous leukemia. First Author: Timothy Edward O'Connor, Loyola University Medical Center, Maywood, IL

Background: Relapse is a major cause of death after allogeneic stem cell transplant (allo-SCT) in patients with high-risk myelodysplastic syndrome (MDS) and acute myelogenous leukemia (AML). Chemotherapy maintenance to prevent relapse has had limited success to date, with a phase 3 hypomethylating agent (HMA) study showing no improvement in relapse rate or survival (Oran et al.). A subgroup analysis, however, showed that high-risk patients may indeed benefit (Pasvolsky et al.). We tested a combination of an HMA [azacitidine (AZA)] and a histone deacetylase (HDAC) inhibitor [valproic acid (VPA)] as a novel maintenance following allo-SCT for high-risk AML and MDS patients based on previously reported in vitro synergism between these agents. **Methods:** This investigator-initiated, single-center, phase II trial included only patients with high-risk MDS and AML who were enrolled following day+40 of allo-SCT to receive AZA and VPA for 4, 28 day cycles. Exclusions included no grade 3-4 acute GVHD, active infection, low risk AML in CR1, a neutrophil count $<$ 1500/μl, or platelets $<$ 50 000/μl. Risk was assessed via DRI at time of transplant. AZA was administered at 40 mg/m2 daily for 5 days SQ with daily oral VPA starting at 15 mg/kg and dose-adjusted to achieve a trough level of bound VPA of 100 μg/mL. Tacrolimus and methotrexate were used as GVHD prophylaxis. The primary endpoints were 1-year relapse rate, overall (OS), and progression-free (PFS) survival. **Results:** Fifty patients were enrolled. The median age was 52 with 28 (56%) male. The median hematopoietic cell transplantation-specific comorbidity index was 2. Graft types: 21 (42%) matched related, 21 (42%) matched unrelated, and 8 (12%) cord blood. Thirty grafts were from peripheral blood and 12 marrow. Myeloablative conditioning was used in 36 (72%) and reduced intensity conditioning in 14 (28%). At time of transplant for AML patients, 21 (46%) were in CR1, 5 (11%) in CR2, 2 (4%) in CRi, and 18 (39%) were relapsed/refractory. Four had high grade MDS. Baseline DRI: 42 (84%) were very high risk or high risk and 8 (16%) were intermediate risk. Eight (16%) patients did not receive all four cycles: 5 (10%) due to progression of disease, 1 (2%) due to acute GVHD, 1 each (2%) due to fatigue and cytopenias. One-year PFS and OS were 80% and 86% and 5-year PFS and OS were 47% and 61%, respectively. The one-year relapse rate was 18%. Most toxicities were grade I or II: fatigue, cytopenias, and acute kidney injury. **Conclusions:** The co-administration of AZA and VPA as a short-term maintenance strategy following allo-SCT in patients with high risk MDS and AML is safe and feasible. While a comparative trial is warranted, the use of this HMA+HDAC regimen seems to validate prior data that HMA-based maintenance may improve the outcomes of high-risk MDS and AML patients. Clinical trial information: NCT02124174. Research Sponsor: None.

6579 **Poster Session**

Hydroxyurea vs. hypomethylating vs. other agents in chronic myelomonocytic leukemia: A retrospective inspection of treatment strategies among 457 Mayo Clinic patients. First Author: Muhammad Yousuf, Mayo Clinic, Rochester, MN

Background: Treatment strategies in chronic myelomonocytic leukemia (CMML) are not standardized and include hydroxyurea (HU) and hypomethylating agents (HMA). In a phase 3 study comparing HU and decitabine, in proliferative CMML, response rates were higher for decitabine (56% vs 31%; p$<$0.01) but overall survival was similar (p=0.67) between the two groups (Itzykson, R. JCO, 2023. 41:1888). In the current retrospective study, we examined the survival impact of different treatment strategies among 457 Mayo Clinic patients with CMML. **Methods:** The current study was conducted under institutional review board approved minimum risk protocols allowing retrospective patient data collection and analysis. Diagnostic criteria were according to the International Consensus Classification (Arber et al. Blood 2022. 140:1200). All statistical analyses were conducted using JMP 17 software. For survival analysis, patients were censored at time of allogeneic stem cell transplant (ASCT). **Results:** A total of 457 patients were considered (median age 72 years; 68% males). 209 patients received CMML-directed therapy: HU (N=102), HMA (N=78; azacitidine 32 and decitabine 46). Responses were adjudicated separately for leukocytosis and anemia; normalization of leukocyte count was achieved in 21% vs. 16 % (p$<$0.01) for HU vs. HMA and overall response in anemia in 1% vs. 9% (p=0.02), respectively. Overall survival did not appear to be impacted by different treatment strategies at any stage of CMML; (i) treated vs. untreated (p=0.3), (ii) HU vs. HMA for first-line therapy (p=0.3), and (iii) HU/HMAs vs. other drugs as first-line therapy (p=0.1). Blast transformation-free survival (BTFS) was also similar between HU vs. HMA as well as HU/HMA vs. other drugs. In univariate analysis, BTFS was inferior in patients receiving CMML-directed therapy (p$<$0.01); the particular association (HR 2; 95% CI 1.2-3.3) retained its significance in multivariable analysis that also included other risk factors for BTFS: bone marrow blast $\geq$10% (HR 4.3), circulating blast $\geq$2% (HR 2.7), WBC $\geq$13 x 10^9/L (HR 1.8), and ASXL1 mutation (HR 1.7). **Conclusions:** In the current retrospective study that included a large number of patients with CMML, chemotherapy with HU or HMA did not appear to affect overall survival but might have increased the risk of blast transformation. The study also suggests superiority of HU for the treatment of leukocytosis and HMA for anemia. Research Sponsor: None.

Predictors of blast transformation-free survival (BTFS) in 457 patients diagnosed with chronic myelomonocytic leukemia (CMML).

BTFS	Univariable analysis *p-value* (HR)	Multivariable analysis *p-value* (HR)
CMML-directed therapy	**<0.01** (2.9; 1.8-4.7)	**<0.01** (2; 1.2-3.3)
Bone marrow blasts ≥10%	**<0.01** (12.4)	**0.01** (4.3)
Circulating blasts ≥2%	**<0.01** (5.2)	**<0.01** (2.7)
WBC ≥13 x 10^9/L	**<0.01** (2.9)	**0.02** (1.8)
ASXL1mut	**<0.01** (2.1)	**0.02** (1.7)

TPS6580 **Poster Session**

QuANTUM-Wild: A phase 3, randomized, double-blind, placebo-controlled trial of quizartinib in combination with chemotherapy and as single-agent maintenance in *FLT3*-ITD–negative acute myeloid leukemia (AML). First Author: Pau Montesinos, Hematology, Hospital Universitari I Politécnic La Fe and Programa Español de Tratamientos en Hematología (PETHEMA) Group, Valencia, Spain

Background: Quizartinib (Quiz) is an oral, selective, type-II FLT3 inhibitor with potent activity against wild-type (wt) FLT3, FLT3-ITDs, and other kinase domain variants. Quiz is approved for patients (pts) with *FLT3*-ITD+ newly diagnosed (ND) AML based on results from the QuANTUM-First trial (NCT02668653). Mutations in the *FLT3* gene are observed in ~30% of AML cases, most commonly as ITDs, but they are not the only mechanism affecting FLT3 activation. Elevated expression of the FLT3 receptor is observed in nearly all cases of AML, and high levels of *FLT3* gene expression are detected in 70–100% of AML blasts, independent of the presence of *FLT3* gene mutations, potentially contributing to leukemic cell survival and proliferation. Evidence from preclinical and clinical studies supports Quiz activity in *FLT3*-ITD–negative (*FLT3*-ITDneg) AML. In the phase 2 QUIWI trial, the addition of Quiz to standard chemotherapy and as single-agent maintenance significantly prolonged overall survival (OS) vs placebo (Pbo) in ND *FLT3*-ITDneg AML. QuANTUM-Wild is a global, phase 3, double-blind, Pbo-controlled trial evaluating Quiz with standard induction/consolidation chemotherapy and as maintenance in ND *FLT3*-ITDneg AML (NCT06578247). **Methods:** Eligible pts are aged 18–70 years with *FLT3*-ITD allelic frequency $<$ 5%. Treatment includes standard induction with cytarabine and an anthracycline plus Quiz/Pbo, followed by up to 4 cycles of consolidation (+/− allo-HSCT) with high-dose cytarabine and Quiz/Pbo, and then single-agent maintenance with Quiz/Pbo in 28d cycles for up to 36 cycles. Pts are randomized 2:2:1 into 3 arms: Arm A (Quiz in all phases), Arm B (Pbo in all phases), or Arm C (Quiz in induction/consolidation and Pbo in maintenance). Quiz is administered at 60 mg/day, reduced to 30 mg if combined with strong CYP3A inhibitors. The primary endpoint is OS, and secondary endpoints include event-free survival (EFS), relapse-free survival (RFS), complete remission (CR) rate and duration, measurable residual disease (by *FLT3*-ITD in all pts and by *NPM1* and *CBF* if present), and safety. Planned enrollment is ~700 pts, with 280 each in Arms A and B, and 140 pts in Arm C. The primary OS analysis compares Arms A and B, while Arm C is descriptive. Enrollment is expected to continue through 2028. Clinical trial information: 2023-507936-20-00; NCT06578247. Research Sponsor: Daiichi Sankyo.

TPS6581 **Poster Session**

First-in-human study of autologous chimeric engulfment receptor T-cell CER-1236 targeting TIM-4-I in acute myeloid leukemia (CertainT-1). First Author: Abhishek Maiti, Division of Cancer Medicine, The University of Texas MD Anderson Cancer Center, Houston, TX

Background: Acute myeloid leukemia (AML) is the most common adult acute leukemia. Patients with relapsed or refractory (R/R) disease have dismal outcomes with complete remission (CR) rates of 5%- 15% and median overall survival of 3 to 6 months with best available therapies. In addition, patients in remission with measurable residual disease (MRD) have poor outcomes with no approved therapies. CER-1236 is an autologous chimeric engulfment receptor T cell (CER-T) which fuses external domain of TIM-4 with intracellular domains from T cells and innate immune cells including Toll-like receptor 2 (TLR2), CD28 and CD3ζ. This receptor binds TIM-4-ligand (phosphatidylserine) on tumor cells leading to phagocytosis and lysis of target cells followed by tumor antigen processing and cross-presentation to induce an adaptive immune response. CER-1236 was shown to eliminate AML cell in vitro, and in vivo in a xenograft model. TIM-4 is the key receptor which binds to TIM-4-L and leads to target cell engulfment. TIM-4-L is expressed in 88% of primary patient AML samples, across TP53 mutated and other mutational subgroups, with significantly higher expression than bone marrow from healthy donors. **Methods:** This is an open label phase I study to evaluate the safety and preliminary activity of CER-1236 in patients with R/R AML. We will evaluate 3 doses levels from 1 to 5 x10^6/kg CER+ T cells using a BOIN dose escalation design. Subsequently we will evaluate patients in 3 expansion cohorts including R/R AML, TP53 mutated AML, and AML in composite CR (cCR), i.e., CR/CRi/CRh with positive MRD. For the dose escalation study we will enroll adults with R/R AML or myelodysplastic syndrome (MDS)/AML per ICC 2022 criteria who have exhausted standard therapeutic options and patients with treated secondary AML who have progressed to AML after receiving AML directed therapy for antecedent hematological disorder, e.g, MDS. Patients will need an ECOG performance status of 0 to 1 and adequate end organ function. We will exclude patients with t(15;17), proliferative disease or active infections. For the MRD dose expansion cohorts we will enroll patients with cCR with MRD $\geq$0.1% by validated multi-parametric flow cytometry. Study treatment: Patients will receive lymphodepleting chemotherapy (LDC) with fludarabine 30 mg/m^2/d and cyclophosphamide 400 mg/m^2/d for 3 days followed by a single infusion of CER-1236 2 days later. Patients may receive standard treatments as bridging therapy after apheresis and prior to LDC. The primary objective of the study is the safety of CER-1236 in terms of dose-limiting toxicities, cytokine release syndrome, and Immune effector cell-associated neurotoxicity syndrome. Secondary objectives are to measure objective response rate per the ELN 2022 criteria including CR+CRh+CRi+MLFS, cCR, MRD negativity by flow cytometry, and PK/PD profile and biomarkers of response. Research Sponsor: None.

TPS6582 **Poster Session**

Tagraxofusp and low-intensity chemotherapy for the treatment of CD123-positive relapsed or refractory acute myeloid leukemia. First Author: Wooin Cho, Stanford Cancer Institute, Clinical Trial Office, Stanford University School of Medicine, Palo Alto, CA

Background: The combination of venetoclax and a hypomethylating agent (Ven/HMA) is the standard frontline (1L) therapy for patients with acute myeloid leukemia (AML) who are ineligible for intensive chemotherapy (IC). However, outcomes after Ven/HMA failure are poor, with a median overall survival of only 2-3 months. Cladribine (CLAD) with LDAC has previously been shown to be well-tolerated and effective in IC-ineligible patients with newly diagnosed AML. Resistance to Ven/HMA is commonly driven by mutations in the RAS/MAPK pathway and the presence of monocytic subclones that are less dependent on BCL2, both of which may retain sensitivity to cladribine-based therapy following 1L Ven/HMA. Tagraxofusp (TAG), a CD-123 targeted therapy, selectively induces apoptosis in CD123-expressing cells by irreversibly inhibiting protein synthesis through EF-2 inactivation. CD123 is highly expressed on AML blasts and leukemia stem cells compared to normal hematopoietic stem cells in the majority of AML patients. TAG in combination with Ven/HMA has shown efficacy in 1L adverse-risk AML. With its minimal additive myelosuppression and targeted specificity, TAG represents an ideal partner to combine with traditional cytotoxic chemotherapies such as CLAD and LDAC. This investigator-initiated study aims to determine the safety and tolerability of TAG in combination with CLAD and LDAC for IC-ineligible patients with relapsed or refractory (R/R) CD123 positive AML after 1L treatment with Ven/HMA. **Methods:** This single-center, open-label Phase 1b/2 trial will enroll up to 20 patients. Key inclusion criteria are: age$\geq$18 years, R/R AML after 1L Ven/HMA with no prior salvage therapies with the exception of monotherapy with targeted inhibitors, ECOG 0-2; serum albumin$\geq$3.2g/dL; and adequate cardiac, renal, and liver function. The phase 1b dose-exploration will determine the safety and tolerability of CLAD, LDAC, and TAG. The first 3 patients will all be treated at Dose Level 1, consisting of CLAD 5mg/m2 IV daily on days 1-3, LDAC 20mg/m2 IV daily days 1-5, TAG 12mcg/kg IV daily days 4-6. Dose escalation will proceed as tolerated to a target dose level of Dose Level 3, consisting of CLAD 5mg/m2 IV daily on days 1-5, LDAC 20mg/m2 IV daily days 1-10, TAG 12mcg/kg IV daily days 4-6. Dose-escalation and de-escalation will be determined by the BOIN design. The primary objective is determination of the RP2D based on the safety of TAG+CLAD+LDAC, as assessed by DLT evaluation. Secondary objectives include ORR, CR, composite CR (CR+CRi+CRh), and rate of MRD negativity in responders. Duration of RFS, OS, and responses according to mutational profile, karyotype, CD123 expression, and patient demographics will be reported. Once the RP2D is determined, a dose expansion cohort will begin enrolling. The study began enrolling patients in January 2025 and is actively recruiting. Clinical trial information: NCT06561152. Research Sponsor: None.

TPS6583 **Poster Session**

A phase II open-label study of olutasidenib post-transplant maintenance therapy for patients with IDH1-mutated myeloid malignancies. First Author: Jeremy L. Ramdial, Department of Stem Cell Transplantation and Cellular Therapy, The University of Texas MD Anderson Cancer Center, Houston, TX

Background: Allogeneic hematopoietic stem cell transplantation (alloSCT) remains one of the most effective treatments for patients with myeloid malignancies. Much of the benefit is due to the immune-mediated graft-versus-leukemia effect to prevent relapse. Nevertheless, despite advances in conditioning therapy, disease relapse remains the most important cause of treatment failure after alloSCT. Maintenance therapy post alloSCT aims to reduce relapse incidence and strengthen the potential for cure. With modern treatment regimens, expected complete remission (CR) rates for newly diagnosed AML patients are 60-70%, however, long-term cure rates are only ~30% and improved treatments are needed. IDH1 mutations occur in $>$7% of older patients with AML and up to 4% of patients with high-risk CMML or MDS. A multicenter phase I trial of another IDH1 inhibitor used as maintenance treatment following alloSCT for IDH1-mutated AML demonstrated a two-year progression-free survival (PFS) of 81%, and two-year overall survival (OS) of 88%. The 2-year cumulative incidence of disease relapse was 19% (95% CI, 4%–41%) and the 2-year cumulative incidence of non-relapse mortality (NRM) was 0%. Olutasidenib is a well-tolerated, highly selective, non-cytotoxic, and potent FDA-approved oral inhibitor of mutant IDH1, with an overall response rate in relapsed/refractory AML of 48%. **Methods:** In our single center, investigator-initiated study under the MDACC-Rigel Research Alliance we aim to determine the safety and tolerability of olutasidenib as maintenance post-allo-SCT and to determine the rate of progression-free survival (PFS). Eligibility includes patients 18-75 years old with IDH1 mutation presence at diagnosis with acceptable organ function. Patients must also have a diagnosis of AML, MDS, MPN, or CMML according to World Health Organization (WHO) classification that underwent first or second alloSCT with either peripheral blood or bone marrow hematopoietic stem cell source, regardless of donor type/match, conditioning regimen, or GVHD prophylaxis and is at least 30 days post stem cell transplant until day 120. A safety lead-in phase will be given for the first 6 patients to investigate whether the starting dose of 150 mg BID is safe and tolerable. After the safety lead-in phase, the remaining patients will be enrolled at the same dose and the safety and tolerability will be monitored. We also would like to determine response rate, overall survival (OS), cumulative incidence of relapse, NRM, GVHD relapse-free survival (GRFS), rate and grading of aGVHD grade 2-4 and 3-4 at day 100, incidence and grading chronic GVHD (cGVHD) all grades. The goal enrollment is 25 total patients. The study was activated and enrollment began in December 2024. Clinical trial information: NCT06668584. Research Sponsor: None.

TPS6584 **Poster Session**

Phase 3 study of either ivosidenib monotherapy or azacitidine monotherapy in patients with IDH1-mutant myelodysplastic syndromes who are hypomethylating agent naive (PyramIDH). First Author: Valeria Santini, DMSC, Azienda Ospedaliero-Universitaria Careggi, University of Florence, Florence, Italy

Background: Myelodysplastic syndromes (MDS) are a heterogeneous group of clonal myeloid disorders that occur predominantly in older patients with variable risk of progression to acute myeloid leukemia (AML). According to International Prognostic Scoring Systems, patients with lower-risk MDS (LR-MDS) and cytopenias can be treated with different drugs and in some cases hypomethylating agents (HMAs). However, in higher-risk MDS (HR-MDS), HMAs are the only available standard of care therapy. The complete response (CR) + partial response (PR) rate of azacitidine in treatment-naive MDS ranges between 16% and 22%. These low response rates, combined with the short duration of responses observed with these approaches highlight an unmet medical need for this population. Ivosidenib (IVO) is an oral, targeted small molecule inhibitor of mutant IDH1 that is currently FDA approved in relapsed/refractory MDS with a complete remission (CR) + partial remission (PR) rate of 38.9% (95% CI: 17.3%, 64.3%) with all responses being CR. In the phase 2 IDIOME study, 72% of patients with previously untreated *mIDH1* HR-MDS obtained CR+PR with IVO monotherapy; median OS and DOR were not reached after median follow-up of 25.2 months. The aim of PyramIDH is to confirm the safety and clinical activity of IVO monotherapy in HMA–naive *mIDH1* MDS in a larger cohort. **Methods:** PyramIDH (NCT06465953) is a phase 3, multicenter, open-label, randomized, non-comparative two-arm study of IVO or azacitidine (AZA) monotherapy in patients with HMA-naive *mIDH1* MDS. Key eligibility criteria include diagnosis of HMA-naive *IDH1 R132* mutated MDS. HR-MDS (moderate high-, high- and very-high-risk MDS per IPSS-Molecular (IPSS-M) score), will be eligible if the bone marrow blast count is $<$20% regardless of blood cell counts. LR-MDS (low- and moderate-low-risk MDS per IPSS-M score), must have cytopenias related to MDS, defined as: $<$100 platelets/μL, or absolute neutrophil count (ANC) $<$1000/mm^3, or hemoglobin $<$10g/dL, have a blast count between 5% and 19%, and be eligible for HMA therapy. Very-low-risk MDS per IPSS-M will not be eligible for enrollment. Enrolled patients (n=~48) will be randomized (2:1) to IVO or AZA monotherapy and they will be stratified by IPSS-M risk status (HR versus LR). The primary endpoint is CR+PR at 4 months as per IWG 2006 criteria. Key secondary endpoints include duration of CR+PR per IWG 2006 criteria, time to CR+PR per IWG 2006 criteria, transfusion independence rate, AML transformation rate, and number of patients going to transplant. Other secondary endpoints are CR+PR at 6 months per IWG 2006 criteria; CR+PR at 4 and 6 months per IWG 2023 criteria; overall response rate per IWG 2023 criteria, duration of response, EFS, OS, duration of transfusion independence (TI), time to TI, AML transformation, quality of life, PK/PD, and safety. Clinical trial information: NCT06465953. Research Sponsor: Servier.

TPS6585 **Poster Session**

Phase II study evaluating olutasidenib in patients with *IDH1*-mutated clonal cytopenia of undetermined significance or lower-risk myelodysplastic syndromes/chronic myelomonocytic leukemia. First Author: Kelly Sharon Chien, Department of Leukemia, The University of Texas MD Anderson Cancer Center, Houston, TX

Background: Observational studies have demonstrated that individuals with clonal cytopenia of undetermined significance (CCUS) involving high-risk mutations, such as *IDH1*, are more likely to transform to acute myeloid leukemia (AML), with one study showing a progression rate of 100% in *IDH1/2*-mutated patients after 5 years of follow-up. However, there are no Food and Drug Administration (FDA)-approved strategies for the prevention of hematologic malignancies in the setting of CCUS. *IDH1* mutations are detected in 3-4% of patients with myelodysplastic syndromes (MDS) or chronic myelomonocytic leukemia (CMML). Despite the safety and efficacy of IDH1 inhibitors in acute myeloid leukemia and the recent FDA approval of ivosidenib for relapsed/refractory *IDH1*-mutated MDS, no IDH1-directed therapies are approved in lower-risk, treatment-naïve MDS/CMML. Olutasidenib, an FDA-approved oral, highly selective, potent inhibitor of mutant IDH1, is well-tolerated, non-cytotoxic and effective, with overall response rates in relapsed/refractory AML of 48% as monotherapy. We consequently hypothesize olutasidenib to be effective in both improving hematologic parameters and decreasing the risk of progression to high-risk MDS/CMML and AML in *IDH1*-mutated patients. **Methods:** This multicenter investigator-initiated study under the MDACC-Rigel Research Alliance is a phase II single-arm study evaluating the efficacy of olutasidenib monotherapy in patients with *IDH1*-mutated CCUS or lower-risk MDS/CMML. Eligibility includes adult patients with acceptable organ function and confirmed *IDH1* mutation with CCUS (by World Health Organization criteria) or lower-risk MDS/CMML (by Revised International Prognostic Scoring System [IPSS-R] and Molecular International Prognostic Scoring System [IPSS-M] criteria). The primary objective of the study is to determine the response rate by International Working Group 2018 criteria. Secondary objectives include rates of transfusion independence, safety and tolerability, overall survival, progression-free survival, duration of response, rates of leukemic transformation, and changes in *IDH1* clone size. All patients will receive olutasidenib 150 mg orally twice daily. CCUS patients will receive up to 18 months of olutasidenib, while lower-risk MDS/CMML patients can receive olutasidenib indefinitely. Response assessments will be performed approximately every 3 months for the first year, then yearly thereafter. Once off treatment, survival follow-up will occur every 3 months for 3 years. The goal enrollment is 15 total patients with at least 8 CCUS patients across 5-6 centers in the United States. The study was activated and enrollment began in December 2024. Clinical trial information: NCT06566742. Research Sponsor: None.

TPS6586 **Poster Session**

Phase II study evaluating olutasidenib and azacitidine in patients with *IDH1*-mutated higher-risk myelodysplastic syndromes, chronic myelomonocytic leukemia, or advanced myeloproliferative neoplasms. First Author: Kelly Sharon Chien, Department of Leukemia, The University of Texas MD Anderson Cancer Center, Houston, TX

Background: *IDH1* mutations are detected in 3-4% of patients with myelodysplastic syndromes (MDS) or chronic myelomonocytic leukemia (CMML) and approximately 9% of patients with myeloproliferative neoplasms (MPN). *IDH1* mutations have been associated with shortened survival and increased rates of transformation to acute myeloid leukemia (AML). Despite the use of IDH1 inhibitors in AML and the recent FDA approval of ivosidenib for relapsed/refractory *IDH1*-mutated MDS, no IDH1-directed therapies are approved in MPN or treatment-naïve MDS/CMML, and no combination treatment regimens are commercially available. Olutasidenib, an FDA-approved oral, highly selective, potent inhibitor of mutant IDH1, is well-tolerated, non-cytotoxic and effective, with overall response rates in relapsed/refractory AML of 51% in combination with azacitidine. Olutasidenib alone or with azacitidine demonstrated overall response rates of 86% in treatment-naïve and 47% in relapsed/refractory MDS. We consequently hypothesize olutasidenib to be effective in patients with *IDH1*-mutated higher-risk MDS/CMML or advanced MPN. **Methods:** This multicenter investigator-initiated study under the MDACC-Rigel Research Alliance is a phase II non-randomized study evaluating the efficacy of olutasidenib in combination with azacitidine in patients with *IDH1*-mutated higher-risk MDS/CMML or advanced MPN. Patients will be divided into 2 arms: treatment naïve and previously treated. Eligibility includes adult patients with acceptable organ function and confirmed *IDH1* mutation with higher-risk MDS/CMML (by International Prognostic Scoring System [IPSS], Revised IPSS [IPSS-R], or Molecular IPSS [IPSS-M] criteria) or advanced MPN (with bone marrow blast percentage $\geq$ 10%). The primary objective of the study is to determine the overall response rate by International Working Group 2023 criteria (MDS), 2015 MDS/MPN uniform response criteria (CML), and European Leukemia Network 2017 AML criteria (advanced MPN). Secondary objectives include rates of complete remission, safety and tolerability, overall survival, progression-free survival, duration of response, and changes in *IDH1* clone size. All patients will receive azacitidine 75 mg/m^2 intravenously or subcutaneously daily on days 1-7 of each treatment cycle and olutasidenib 150 mg orally twice daily. Response assessments will be performed after cycle 1, then every 3 cycles up through cycle 12, then every 12 cycles thereafter. Once off treatment, survival follow-up will occur every 3 months for 3 years. The goal enrollment is 45 patients (25 treatment-naïve and 20 previously-treated with no more than 5 MPN patients in each arm) across 5-6 centers in the United States. The study was activated and enrollment began in January 2025. Clinical trial information: NCT06597734. Research Sponsor: None.

TPS6587 **Poster Session**

Shorespan-007: Phase 3 study of bomedemstat versus hydroxyurea in essential thrombocythemia naive to cytoreductive therapy. First Author: Kristen M. Pettit, University of Michigan, Ann Arbor, MI

Background: Lysine-specific demethylase 1 (LSD1) is an enzyme that regulates hematopoietic stem and progenitor cell proliferation and maturation. Bomedemstat (MK-3543) is an LSD1 inhibitor shown to have manageable safety and improve symptoms, durably reduce platelet and white blood cell (WBC) count, and reduce mutation burden in patients with essential thrombocythemia (ET) in a phase 2 study. Here, we describe the methodology of the randomized, double-blind, phase 3 Shorespan-007 study (NCT06456346), which has been designed to evaluate the efficacy and safety of bomedemstat compared with hydroxyurea in participants with ET naive to cytoreductive therapy. **Methods:** Key eligibility criteria include patients aged $\geq$18 years with an ET diagnosis per WHO diagnostic criteria for myeloproliferative neoplasms, an indication for cytoreductive therapy, no prior cytoreductive therapy, a bone marrow fibrosis score of 0 or 1, a platelet count of $>450 \times 10^9$/L, and an absolute neutrophil count of $\geq 0.75 \times 10^9$/L. Key exclusion criteria include a documented increased risk of bleeding or an active infection necessitating systemic therapy. Approximately 300 participants will be enrolled. Participants will be randomly assigned 1:1 to bomedemstat at a starting dose of 50 mg/day by mouth titrated to a target platelet count of $\geq 150 \times 10^9$/L to $\leq 350 \times 10^9$/L or hydroxyurea at a starting dose of 500 mg/day by mouth titrated per the approved product labeling. The primary end point is durable clinicohematologic response, defined as the following: a confirmed reduction of platelet count to $\leq 400 \times 10^9$/L; absence of a WBC count elevation to $>10 \times 10^9$/L locally assessed to be due to ET; and, if WBC count is elevated to $>10 \times 10^9$/L at screening, a reduction of WBC count to $\leq 10 \times 10^9$/L (confirmed by first subsequent visit a minimum of 2 weeks apart, starting by week 24 and maintained for $\geq$24 weeks to at least week 48; absence of any thrombotic or major hemorrhagic events or disease progression to myelofibrosis [MF] or myelodysplastic syndrome [MDS]/acute myeloid leukemia (AML) by week 52). Secondary end points include change in fatigue from baseline per the MFSAF v4.0, change in total fatigue score from baseline per the PROMIS Fatigue SF-7a scale, change in total symptom score from baseline per the MFSAF v4.0, duration of clinicohematologic response, duration of hematologic remission, incidence of thrombotic events, incidence of major hemorrhagic events, transformation to post-ET MF or MDS/AML, and safety and tolerability. Clinic visits will occur every 2 weeks for the first 12 weeks and every 4 weeks thereafter. Adverse events will be monitored throughout the study and for $\leq$30 days after treatment end and will be graded per NCI CTCAE v5.0. Recruitment for Shorespan-007 is ongoing or planned in sites in Asia, Australia, Europe, North America, and South America. Clinical trial information: NCT06456346. Research Sponsor: Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA.

TPS6588 **Poster Session**

IMpactMF, randomized, open-label, phase 3 trial of imetelstat (IME) versus best available therapy (BAT) in patients (pts) with intermediate-2 (INT-2) or high-risk (HR) myelofibrosis (MF) relapsed or refractory (R/R) to Janus kinase inhibitors (JAKi). First Author: John Mascarenhas, Tisch Cancer Institute, Icahn School of Medicine at Mount Sinai, New York, NY

Background: IME is a first-in-class telomerase inhibitor approved in 2024 for pts with transfusion-dependent lower-risk myelodysplastic syndromes who are R/R or ineligible for erythropoiesis-stimulating agents. In the phase 2 IMbark trial (NCT02426086) in pts with MF, IME (9.4 mg/kg every 3 weeks [q3w]; N=59) at wk 24 showed median overall survival (OS) of 29.9 mo (median follow-up, 27.4 mo), total symptom score reduction $\geq$50% in 32% of pts, and spleen volume reduction $\geq$35% in 10% of pts. IME treatment dose-dependently improved bone marrow (BM) fibrosis and reduced MF driver mutation variant allele frequency, which correlated with improved OS. The most common grade $\geq$3 adverse events were thrombocytopenia, anemia, and neutropenia; cytopenias were generally manageable, short-lived, and resolved to grade $\leq$2 in $<$4 wks. These data support further evaluation of IME. **Methods:** IMpactMF (MYF3001; NCT04576156) is a phase 3, open-label, randomized (2:1) trial of IME versus BAT in ≈320 adults with INT-2 or HR MF R/R to JAKi or ineligible for allogeneic stem cell transplantation or further JAKi. Randomization is to IME sodium 9.4 mg/kg (8.9 mg/kg active dose) intravenously q3w or investigator-selected BAT (eg, hypomethylating agents, hydroxyurea, interferon, thalidomide, danazol, chemotherapy, or other non–JAKi-containing therapy, but not hematopoietic stem cell transplantation or splenectomy). Eligibility criteria include peripheral blood and marrow blast counts $<$10% and Eastern Cooperative Oncology Group performance status $\leq$2. Chronic liver disease unrelated to underlying MF, active systemic hepatitis infection, or clinically significant cardiovascular disease are not allowed. Pts are stratified at randomization based on INT-2 or HR MF per the Dynamic International Prognostic Scoring System and baseline platelet count. Crossover to IME may be permitted for pts who meet progressive disease criteria ($\geq$25% increase in spleen volume from baseline) or a palpable increase in splenomegaly after 6 mo of BAT. IMpactMF is the first MF phase 3 trial evaluating OS as the primary endpoint. Secondary endpoints include wk 24 symptom and spleen response rates, progression-free survival, clinical response assessments per modified 2013 International Working Group-Myeloproliferative Neoplasms Research and Treatment criteria, time to and duration of response, reduction in BM fibrosis, safety, pharmacokinetics, and pt-reported outcomes. Biomarkers and mutation analyses will be performed. As of December 2024, 172 sites in North and South America, Europe, Middle East, Australia, and Asia have enrolled ≈75% of pts. The planned interim analysis (when ≈35% of pts planned to be enrolled have died) is expected in early 2026 and final analysis is expected in early 2027. Clinical trial information: NCT04576156. Research Sponsor: This study was funded by the Geron Corporation; writing and editorial support were provided by Meredith Rogers, MS, CMPP, of The Lockwood Group (Stamford, CT, USA), funded by the Geron Corporation.

TPS6589 **Poster Session**

Anti-tumor activity of CoREST inhibitor, JBI-802 (dual epigenetic modifier of LSD1/HDAC6): An opportunity to treat essential thrombocythemia and MPN/MDS patients with thrombocytosis in ongoing phase 1/2 clinical trial. First Author: Melda S. Dolan, Jubilant Therapeutics and Jubilant Radiopharmaceuticals, Yardley, NJ

Background: Lysine specific demethylase 1 (LSD1) and histone deacetylase 6 (HDAC6) are epigenetic proteins associated with several diseases, including cancer. JBI-802 is a highly potent CoREST inhibitor with LSD1/HDAC6 selective dual inhibition that shows superior anti-tumor activity in several pre-clinical models with significant modulation of PD biomarkers that include CD11b, CD86 and acetylated alpha-tubulin. JBI-802 in first-in-human phase I clinical trial (NCT05268666) demonstrated a dose-proportional increase in exposure across cohorts and its correlation with on-target effects in therapy resistant advanced lung cancers patients. 2/2 immunotherapy resistant NSCLC patients displayed improvement in tumor-related symptoms with confirmed partial response (PR) in one NSCLC patient at 10 mg dose. Overall, JBI-802 was well tolerated and showed remarkable safety profile without affecting hemoglobin, with grade 3/4 thrombocytopenia as the only adverse event observed in 38% of patients at the higher dose. Dose-dependent decrease in platelets as a part of MOA of LSD1 and HDAC6 inhibition demonstrated that JBI-802 is pharmacologically active and provided an opportunity to treat patients with hematological malignancies like essential thrombocythemia (ET) and other myelodysplastic/myeloproliferative neoplasms (MDS/MPN) characterized by thrombocytosis. **Methods:** The ongoing phase 1/2 clinical trial will assess the safety and preliminary efficacy of orally administered JBI-802 in ET and MDS/MPN patients with thrombocytosis (ACTRN12624000478516) in a standard 3+3 design in 30 patients in two phases. Part 1: Dose Escalation Phase - Primary objective is to determine the recommended phase 2 dose (RP2D) of JBI-802 and safety in subjects with ET and MDS/MPN neoplasms with thrombocytosis, with dose-limiting toxicity as the primary endpoint during the monitoring period. Secondary objective is to evaluate the overall safety and tolerability, and to determine the preliminary antitumor activity along with characterization of pharmacokinetic (PK) profile of JBI-802 and its metabolites as well as clinical and hematologic responses. Part 2: Dose Expansion Phase – The objective is to obtain preliminary evidence of efficacy as defined by MDS/MPN IWG response criteria, which includes platelet count reduction, and response assessments of spleen size and volume, evaluation of hematology parameters and bone marrow aspiration/biopsy, and to further evaluate the overall safety and tolerability of JBI-802, along with characterization of PK and PD profile and changes in mutant allele frequencies. Study results will provide insights into the clinical potential of JBI-802 in treating ET and MDS/MPN patients relapsed and/or refractory to standard of care therapies. Clinical trial information: ACTRN12624000478516. Research Sponsor: None.

7000 Oral Abstract Session

Prospective validation of end of treatment ctDNA-MRD by PhasED-Seq in DLBCL patients from a national trial. First Author: Steven Wang, Amsterdam UMC Location Vrije Universiteit, Amsterdam, Netherlands

Background: The prognostic utility of circulating tumor DNA measurable residual disease (ctDNA-MRD) detection at end of treatment (EOT) using phased variant (PV) enrichment and detection sequencing (PhasED-Seq) has been demonstrated in patients with diffuse large B-cell lymphoma (DLBCL) receiving first-line (1L) therapy. Prior studies are limited by treatment, patient, and sample heterogeneity. Here, we independently validate the prognostic value of PhasED-Seq in a national, multi-center study of uniformly treated 1L DLBCL patients. **Methods:** ctDNA-MRD was assessed using Foresight CLARITY in LBCL patients enrolled on HOVON-902 from >50 centers in the Netherlands and Belgium. Patients were treated with curative-intent 1L therapy (R-CHOP or DA-EPOCH-R). We evaluated the prognostic significance of MRD status [positive (+), negative (-)] on progression-free survival (PFS) and overall survival (OS). PVs were identified from pretreatment biopsies or plasma with matched normal DNA. EOT plasma samples were used for ctDNA-MRD detection. **Results:** A total of 150 of 156 (96%) eligible patients had successful PV identification. Of included patients, 90%, 9%, and 1% had DLBCL, HGBL, and PBMCL, respectively. IPI distribution was 22% low, 29% low-intermediate, 27% high-intermediate, and 22% high risk; median age was 67.5. The 24-month PFS and OS in this cohort were 74% and 86%, respectively, with 31 months of median follow-up. At the EOT, 76% of patients were MRD- and 24% were MRD+. MRD+ status significantly predicted inferior PFS (2 yr PFS 88 vs 28%; HR 9.7, 95% CI 4.2-22.3, p<0.0001) and OS (2 yr OS 97 vs 50%; HR 10.6, 95% CI 4.1-27.7, p<0.0001). Moreover, in patients without complete response, MRD+ was significantly prognostic for PFS, suggesting an ability to adjudicate imaging results (HR for PFS 7.6, 95% CI 3.6-16.3, p < 0.0001). Among patients who were MRD- and achieved CMR at EOT, 2-year PFS and OS were 91% and 99%, respectively. All patients who failed to achieve CMR and remained MRD+ experienced relapse. ctDNA-MRD was prognostic for outcomes in all subgroups considered, including source of baseline sample (tumor versus plasma), best clinical response, IPI, sex, lactate dehydrogenase, stage, or extranodal disease. In multivariate analysis including ctDNA-MRD, IPI, and best overall response, ctDNA-MRD was significantly and independently prognostic for both PFS [HR for ctDNA: 7.1, 95% CI 3.5-14.3, p<0.0001] and OS [HR for ctDNA: 5.1, 95% CI 2.2-11.9, p=0.00018]. **Conclusions:** We validated the prognostic value of PhasED-Seq-based ctDNA-MRD in a real-world multicenter 1L DLBCL cohort. This highlights the utility of ctDNA-MRD to confirm residual disease in patients without complete response by imaging, as well as the potential to identify patients who may benefit from consolidation therapy. These results support the integration of MRD as a standard component of response evaluation in 1L DLBCL treatment. Research Sponsor: None.

7001 Oral Abstract Session

Revision of staging system for natural killer T-cell lymphoma: A multicenter study from the Chinese Southwest Oncology Group and Asia Lymphoma Study Group. First Author: Tongyu Lin, Phase I Clinical Trial Ward of Medical Oncology Center, Sichuan Clinical Research Center for Cancer, Sichuan Cancer Hospital & Institute, Sichuan Cancer Center, Affiliated Cancer Hospital of University of Electronic Science and Technology of China, Chengdu, China

Background: Natural killer T-cell lymphoma (NKTCL), characterized by extranodal involvement, challenges the efficacy of the Ann-Arbor staging system (AASS) in its precise prognostic stratification. A revised staging system is warranted for precise prognosis prediction in the modern chemotherapy era. **Methods:** A training cohort of patients with newly diagnosed NKTCL was assessed to revise the AASS in the context of the modern chemotherapy era. The results were validated in an independent international cohort that received asparaginase-based chemotherapy. **Results:** Our analysis of 2017 newly diagnosed NKTCL patients from 19 centers across two countries highlights the limitations of the AASS, which demonstrates an uneven patient distribution and insufficient differentiation of outcomes, particularly between stages III and IV. We proposed a revised staging system in which AASS stage I patients with nasal-type disease only were classified as stage I, whereas those with local invasion or limited non-nasal-type disease were reclassified as stage II. AASS stage II patients with regional lymph node involvement were assigned to stage III. Additionally, patients with distant lymph node involvement or extensive skin/subcutaneous soft tissue involvement were classified as stage IVA, those with extensive visceral organ invasion were classified as stage IVB, and those with bone marrow infiltration or hemophagocytic lymphohistiocytosis were classified as stage IVC. This proposal better distinguishes clinical outcomes across different stages, achieves a more equitable distribution of patients, and demonstrates multiple advancements over the AASS. **Conclusions:** The revised staging system is promising for the staging of NKTCL patients with different prognoses and could be useful for decisions regarding the treatment strategy and future clinical trial designs. Research Sponsor: National Natural Science Foundation of China; 82470237; National Natural Science Foundation of China; 82270198; Cancer Innovative Research Program of Sun Yat-sen University Cancer Center; CIRP-SYSUCC-0022.

7002 Oral Abstract Session

Molecular landscape of distinct follicular lymphoma histologic grades: Insights from genomic and transcriptome analyses. First Author: Cong Sun, Department of Lymphoma, Tianjin Medical University Cancer Institute and Hospital, Tianjin, China

Background: The 2022 *World Health Organization Classification of Hematologic Malignancies* classifies follicular lymphoma grades 1-2 (FL1-2) and grade 3A (FL3A) as classical follicular lymphoma (cFL) and reclassifies grade 3B (FL3B) as follicular large B-cell lymphoma (FLBL), without addressing cases of patients with concurrent FL and DLBCL. However, genetic information of FL histologic grading remains limited, and the latest classification lacks sufficient evidence to resolve whether these subgroups represent single or multiple distinct biological entities. **Methods:** This study analyzed clinical data from 831 patients, whole-exome sequencing (WES) from 149 patients, and transcriptome sequencing from 63 patients to explore differences among FL1-2, FL3A, FL3B, and FL/DLBCL. **Results:** A total of 1006 patients were initially identified. After excluding those under 18 years of age, those with histological transformation, and those with incomplete clinical information, 831 patients remained. Among them, 588 (71%) had FL1-2, 84 (10%) had FL3A, 67 (8%) had FL3B, and 92 (11%) had FL/DLBCL. Baseline clinical and tumor characteristics are summarised in table. The Kaplan-Meier survival analysis was performed on 477 FL patients who received R-CHOP treatment. Age > 60, spleen involved, elevated serum LDH, elevated β2-MG and grade 3B were associated with inferior PFS and OS; while ECOG 3-4 and Ann Arbor stage III/IV disease were associated with inferior PFS. Factors that retained significance on multivariable analysis for PFS were grade 3B (HR 2.08, 95% CI 1.22-3.56, p = 0.0076) , ECOG 3-4 (HR 2.49, 95% CI 0.98-6.32, p = 0.05) and elevated serum LDH (HR 1.68, 95% CI 1.05-2.69, p = 0.03), while for OS, it was only grade 3B (HR 4.67, 95% CI 1.95-11.15, p < 0.001). Genomics showed that FL3B and FL/DLBCL lack mutations in epigenetic regulators CREBBP and KMT2D but exhibit additional copy number variations, such as 1p36.32 losses and 3p21.1 gains, which are linked to poor prognosis. Transcriptomics revealed that with increasing histologic grade, immune-related pathway activity decreases, whereas metabolic pathway activity increases, which may be associated with the upregulation of MYC, IRF4, and BATF expression. **Conclusions:** In summary, these findings define FL3B and FL/DLBCL as biologically and clinically distinct B-cell lymphomas, differing from traditional FL. FL1-2 and FL3A differ in their tumor microenvironments rather than genetic profiles. Research Sponsor: None.

Clinical and genetic characteristics among four subgroups.

Clinical characteristics	FL1-2 (%)	FL3A (%)	FL3B (%)	FL/DLBCL (%)	P
No. of patients	588 (71)	84 (10)	67 (8)	92 (11)	
Age					<0.0001
Median years (range)	52 (24-87)	56.5 (28-82)	56 (24-78)	60 (27-87)	
< 60 years	439 (75)	46 (57)	36 (54)	43 (47)	
≥60 years	149 (25)	36 (43)	31 (46)	49 (53)	
ECOG performance status					0.029
< 2	549 (93)	82 (98)	60 (90)	79 (86)	
≥2	8 (1)	0 (0)	3 (4)	4 (4)	
Missing	31 (5)	2 (2)	4 (6)	9 (10)	
B symptoms					0.110
Yes	75 (13)	18 (21)	10 (15)	17 (18)	
No	482 (82)	64 (76)	52 (78)	66 (72)	
Missing	31 (5)	2 (2)	5 (7)	9 (10)	
Ann Arbor stage					0.001
I–II	98 (17)	19 (23)	20 (30)	25 (27)	
III–IV	445 (76)	58 (69)	39 (58)	51 (55)	
Missing	45 (8)	7 (8)	8 (12)	16 (17)	
POD24					0.078
Yes	97 (16)	8 (10)	17 (25)	18 (20)	
No	436 (74)	65 (77)	46 (69)	60 (65)	
Missing	55 (9)	11 (13)	4 (6)	14 (15)	
Lymph nodes <5					<0.0001
Yes	208 (35)	34 (40)	37 (55)	54 (59)	
No	371 (63)	49 (58)	25 (37)	35 (38)	
Missing	9 (2)	1 (1)	5 (7)	3 (3)	
Marrow involved					0.003
Yes	80 (14)	15 (19)	4 (6)	3 (3)	
No	504 (86)	63 (75)	60 (90)	88 (96)	
Missing	4 (1)	5 (6)	3 (4)	1 (1)	
Spleen involved					0.295
Yes	139 (24)	25 (30)	14 (21)	15 (16)	
No	407 (69)	54 (64)	47 (70)	65 (71)	
Missing	42 (7)	5 (6)	6 (9)	12 (13)	
FLIPI					0.269
0–1	141 (24)	18 (21)	24 (36)	24 (26)	
2	220 (37)	22 (26)	10 (15)	19 (21)	
3–5	183 (31)	37 (44)	24 (36)	31 (34)	
Missing	44 (7)	7 (8)	9 (13)	18 (20)	
FLIPI2					0.316
0–1	398 (68)	51 (61)	39 (58)	51 (55)	
2	160 (17)	16 (19)	9 (13)	19 (21)	
3–5	64 (11)	13 (15)	10 (15)	11 (12)	
Missing	26 (4)	4 (5)	9 (13)	11 (12)	
LDH(uL):>UNL					<0.0001
Yes	88 (15)	26 (31)	23 (34)	44 (48)	
No	500 (85)	58 (69)	44 (66)	48 (52)	
β2-MG≥3mg/L					0.943
Yes	411 (70)	61 (73)	46 (69)	64 (70)	
No	172 (29)	23 (27)	20 (30)	28 (30)	
Missing	5 (1)	0 (0)	1 (1)	0 (0)	
Genetic alterations					
No. of patients	99	22	10	18	
KMT2D mutation	50 (51)	8(36)	2 (20)	1 (6)	p<0.001
CREBBP mutation	39 (39)	7 (32)	0 (0)	2 (11)	p<0.001
STAT6 mutation	21 (21)	2 (9)	0 (0)	0 (0)	p=0.045
1p36.32 alteration	21(21)	3(14)	5(50)	6(33)	p=0.096
6p22.1 alteration	27(27)	11(50)	3(30)	11(61)	p= 0.016
7q22.3 alteration	8(8)	3(14)	7(70)	10(56)	p<0.0001
3p21.1 alteration	19(19)	7(32)	4(40)	9(50)	p<0.0001

Note: Differences in patient/disease characteristics among groups (FL1-2, FL3A, FL3B and FL/DLBCL respectively) were analyzed using Fisher's exact test for discrete variables and the Kruskal-Wallis H test for continuous variables. DLBCL, diffuse large B cell lymphoma; ECOG, Eastern Cooperative Oncology Group; POD24, progression of disease within 2 years; FLIPI, Follicular Lymphoma International Prognostic Index; HGB, hemoglobin; LDH, lactate dehydrogenase; CRP, C-reactive protein; β2-MG, β2-macroglobulin.

7003 Oral Abstract Session

A phase 1 study of KITE-363 anti-CD19/CD20 chimeric antigen receptor (CAR) T-cell therapy in patients (pts) with relapsed/refractory (R/R) B-cell lymphoma (BCL). First Author: Saurabh Dahiya, Stanford University School of Medicine, Stanford, CA

Background: Approximately 30% of pts with R/R LBCL who relapse after CAR T-cell therapy experience CD19 antigen escape (Spiegel et al. *Blood.* 2021).KITE-363 is a bicistronic, autologous CAR T-cell therapy that can potentially prevent CD19 escape through upfront dual targeting of CD19 and CD20. Here we report safety and preliminary efficacy from an open-label, multicenter Phase 1 study of KITE-363 in R/R BCL. **Methods:** Eligible adults had LBCL, indolent NHL, nodular lymphocyte-predominant Hodgkin lymphoma (NLPHL), or mediastinal gray zone lymphoma R/R after ≥2 lines of therapy (LoT). Pts with LBCL may have had primary refractory disease after ≥1 LoT. Study included dose escalation (1A) and expansion (1B; LBCL only) cohorts. After lymphodepleting chemotherapy, pts received KITE-363 at dose levels (DLs) 1, 2, or 3 (0.5×10^6, 1×10^6, or 2×10^6 CAR T cells/kg, respectively). Primary endpoints were incidence of dose-limiting toxicities (DLTs; Phase 1A) and investigator-assessed objective response rate (ORR per Lugano; Phase 1B). **Results:** As of 10/14/2024, 41 pts enrolled and 37 received KITE-363 (see table). For pts with LBCL (n = 34), 50% were primary refractory and 44% had IPI 3-4. No DLTs occurred. Grade ≥3 adverse events (AEs) occurred in 76% of treated pts and serious AEs in 49%. Grade 3 cytokine release syndrome (CRS; per Lee et al. 2014) occurred in 1 pt (3%; NLPHL; DL 3); Grade 3 immune effector cell-associated neurotoxicity syndrome (ICANS) occurred in 3 pts (8%; 1 DL 2; 2 DL 3); no Grade ≥4 CRS/ICANS occurred. Median onset of ICANS was 6 d with median duration of 5 d, and median onset of CRS was 4 d with median duration of 5 d. Six pts died (5 to progression; 1 to myelodysplastic syndrome concurrent with LBCL relapse, unrelated to KITE-363). At 7.3 months median follow-up, ORR in CAR-naive pts at DL 3 was 87%; complete response (CR) rate was 78%. Among those, all 7 pts with LBCL who were CAR-naive after ≥2 LoT had a CR. Those in DL 3 who were primary refractory (n = 15) had an 80% ORR (CR rate, 67%). Median duration of response was not reached. In all pts at DL 3 (n = 26), median CAR T-cell expansion peak, area under the curve (AUC), and time to peak were 121.5 cells/μL, 711.1 cells/μL×d, and 10 d, respectively. For CAR-naive pts in DL 3, median peak and AUC were 132.2 cells/μL and 819.2 cells/μL×d; medians in those with prior CAR T-cell therapy (n = 3) were 5.7 cells/μL and 85.7 cells/μL×d, respectively. **Conclusions:** No DLTs occurred in Phase 1A. Safety profile of KITE-363 was tolerable, with no Grade ≥3 CRS in pts with LBCL and 2 cases of Grade 3 ICANS at the highest DL. KITE-363 demonstrated high responses in pts with highly refractory BCL, including those with primary refractory disease. Clinical trial information: NCT04989803. Research Sponsor: Kite, a Gilead Company.

Baseline characteristics.

	Treated Pts (N=37)[a]
Median age, y (range)	62 (25-83)
ECOG 1	59
Stage III/IV	73
≥3 prior LoT	41
Prior CAR T-cell exposure	19

[a]Percent unless otherwise specified.

7004 **Oral Abstract Session**

Multi-virus specific T cells to enhance the activity of bispecific antibodies in lymphoma. First Author: Akiva Diamond, Department of Medicine, Section of Hematology-Oncology, Baylor College of Medicine; Baylor St.Luke's Medical Center; Dan L Duncan Comprehensive Cancer Center, Houston, TX

Background: Although Bispecific Antibodies (BsAbs) have the advantage of an "off the shelf" immune approach, their clinical activity relies on the patients' native T-cell population that is impaired by prior chemotherapy and tumor-induced T cell exhaustion. T-cell dysfunction within the TME is one potential mechanism of BsAb resistance (Falchi, L. et. al. Blood), while continuous exposure to bispecific molecules also induces T-cell exhaustion (Phillipp, N. et. al. Blood). A higher frequency of regulatory T cells and increased markers of T cell exhaustion were seen in BsAb non-responders (Cortes-Selva, D. et. al. Blood). Banks of multi-virus specific T cells (MVSTs) have safely controlled viral infections in allogeneic hematopoietic stem-cell transplantation recipients (Tzannou, et. al JCO). Expanded MVSTs have a differentiated phenotype, exhibit immediate effector functions (cytotoxicity and cytokine secretion) and have not produced severe graft versus host disease in hundreds of recipients. We hypothesized that MVSTs would enhance the antitumor activity of BsAbs. **Methods:** To compare the anti-tumor activity of PBMCs and MVSTs, we cocultured GFP-labeled CD20+ BJAB lymphoma cells alone or with healthy donor PBMCs or MVST at a 1:1 ratio, in the presence or absence of CD3xCD20 BsAb. We evaluated T-cell activation using CD69 and CD25 antibodies using quantitative flow cytometry and tumor cell killing by assessing tumor survival at 24 and 48 hours. **Results:** While the addition of both MVSTs and PBMCs alone reduced tumor cell numbers, PBMCs + BsAbs reduced tumor cells to less than 50% of the cultures at 24 hours but the subsequent increase tumor cell numbers indicated lack of effective control. By contrast, MVSTs reduced the frequency of tumor cells from 42.5% at 24 hours and less than 2% by 48 hours. The number of T-cells in PBMCs decreased by 0.88-fold after 48-hours, while MVSTs increased by 2.16-fold in the presence of 1ng/ml BsAb. The number of T cells expressing CD25 increased 6.25-fold with PBMCs and 456.68-fold with MVST in the presence of BsAb. **Conclusions:** We have demonstrated that in combination with BsAb, MVSTs exhibit more rapid effector function and expansion than similarly cultured PBMCs, suggesting they could enhance tumor response depth. Despite using healthy donor PBMCs, which showed a 6-fold increase in activated T cells with BsAb, MVSTs induced 456-fold increase. This significant boost in T cell activation highlights MVSTs' potential to overcome endogenous T cell exhaustion and enhance BsAb therapy. Research Sponsor: National Cancer Institute; 5 P50 CA126752-12 (Heslop).

Tumor cell and T cell numbers after co-culture with PBMC or MVST +/- BsAb.

	Tumor cell numbers		CD3+ T-cell numbers	CD25+ Activated T-cells
	24 hours	48 hours	48 hours	48 hours
BJAB Alone	104,345	101,992		
+ PBMC	104,632	57,094	30,458	5,058
+ PBMC + BsAb 1ng	17,350	37,621	26,665	31,621
BJAB Alone	51,633	69,183		
+ MVST	52,815	19,858	86,545	419
+ MVST + BsAb 1ng	28,259	1,584	186,737	191,348

7005 **Oral Abstract Session**

WaveLINE-003: Phase 2/3 trial of zilovertamab vedotin plus standard of care in relapsed/refractory diffuse large B-cell lymphoma. First Author: Philippe Armand, Dana-Farber Cancer Institute, Boston, MA

Background: Outcomes for patients relapsed/refractory (R/R) diffuse large B cell lymphoma (DLBCL) remain poor. Zilovertamab vedotin (ZV) is a novel ROR1-targeting antibody-drug conjugate that has shown promising efficacy in patients with DLBCL. Here we present results of the dose confirmation part of the waveLINE-003 (NCT05139017) trial evaluating ZV plus rituximab and gemcitabine-oxaliplatin (R-GemOx) in pts with R/R DLBCL. **Methods:** The phase2/3 trialwaveLINE-003 enrolled adult participants (pts) with confirmed R/R DLBCL after ≥1 lines of therapy (LOT) who were ineligible for chimeric antigen receptor T-cell therapy (CAR-T), autologous stem-cell transplant (ASCT), or failed such therapies (cohort A). In the dose confirmation phase, eligible pts received ZV (1.5, 1.75, or 2.0 mg/kg) plus R-GemOx Q3W for ≥6 cycles. Primary endpoints were safety and recommended phase 2 dose (RP2D). Secondary endpoints were objective response rate (ORR) and duration of response (DOR) per Lugano 2014 response criteria by central review, and overall survival. **Results:** At data cut-off date (August 1, 2024),40 pts had been enrolled in cohort A to receive R-GemOx plus ZV 1.5 mg/kg (n=17), 1.75 mg/kg (n=16), or 2.0 mg/kg (n=7); 22 (55%) were ≥65 years old, and 8 (20%) relapsed >12 mo. Median number of prior LOTs was 2.0 with 7 (18%) pts receiving prior CAR-T, and 7 (18%) receiving prior ASCT. Median follow-up was 9.8 months (mo). Seven DLTs (1 for ZV [1.5 mg/kg], 2 for ZV [1.75 mg/kg], and 4 for ZV [2.0 mg/kg]) were reported. Treatment-related adverse events (AE) were reported in 39 (98%) pts; the most common being diarrhea (n=18 [45%]), nausea (n=15 [38%]), anemia (n=11 [28%]), and platelet count decrease (n=11 [28%]). Grade ≥3 treatment-related AEs were reported in 26 (65%) pts, the most common being neutropenia (n=9 [23%]), neutrophil count decreased (n=9 [23%]), platelet count decreased (n=9 [23%]), and anemia (n=8 [20%]). Two pts discontinued due to AE (sepsis and respiratory failure, both treatment-related), and 1 pt died due to sepsis (treatment related), all in the 2.0 mg/kg dose cohort. The RP2D was determined to be 1.75 mg/kg. ORR was 27% (3 CR, 1 PR [ZV 1.5 mg/kg]), 56% (8 CR, 1 PR [ZV 1.75 mg/kg]), and 57% (3 CR, 1 PR [ZV 2.0 mg/kg]), with median DOR of 14.4 mo, 8.7 mo and not reached (NR), respectively. Median overall survival was 11.5 mo (ZV 1.5 mg/kg), NR (ZV 1.75 mg/kg), and 7.4 mo (ZV 2.0 mg/kg), with 6-month OS rate of 70.0%, 78.8%, and 68.6%, respectively. **Conclusions:** Zilovertamab vedotin in combination with R-GemOx demonstrated promising efficacy and acceptable safety in R/R DLBCL at the RP2D of ZV of 1.75 mg/kg plus R-GemOx. The study is proceeding to the phase 3 portion randomizing patients to ZV-RGemOx versus RGemOx. Clinical trial information: NCT05139017. Research Sponsor: Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA; N/A.

7006 **Oral Abstract Session**

Sintilimab (anti-PD-1 antibody) combined with chidamide (an oral subtype-selective HDACi) followed by P-GemOx regimen in patients with treatment-naïve extranodal natural killer/T cell lymphoma (TN-ENKTL): A multicenter, open-label, single-arm, phase II study (SCENT-2 trial). First Author: Huiqiang Huang, Sun Yat-sen University Cancer Center, Guangdong, China

Background: ENKTL is a highly aggressive NHL with a higher incidence in Asia. P-GemOx regimen is one of standard first-line treatment with mildly toxicities. We confirmed that Sintilimab plus Chidamide (SC) is safe and efficacious in patients(pts) with relapsed or refractory (r/r) ENKTL in previous study (SCENT trial). Initiation of SC prior to r/r might further optimize pts outcomes. Therefore, we conducted a prospective study to investigate the efficacy and safety of SC followed by P-GemOx for TN-ENKTL (NCT04994210). Here we present the preliminary results of pts with early stage. **Methods:** This is an investigator-initiated study,eligible pts were aged 18-80 years with histologically confirmed TN-ENKTL. Pts received 2 cycles of SC (SC×2) with standard doses (part A). Once pts had a CR or PR, 2 cycles of P-GemOx (P-GemOx×2) were administered (part B). If they got SD or PR, pts received P-GemOx×4. All pts accepted involved field radiotherapy (IFRT) after part B. The primary endpoint is the CR rate (CRR) of part A+B. Key secondary endpoints include CRR of part A, duration of CR (DoCR), PFS, OS and safety. According to historical data of P-GemOx, we expected a CRR of 80% and a minimum CRR of 60% after part A + B. A sample size of 47 was required. Pretreatment FFPE tumor and blood samples were analyzed by capture-based NGS targeting lymphoma relevant genes. **Results:** From Aug 2022 to Dec 2024, 47 eligible pts were enrolled from 3 centers in China. Two pts remained on treatment. All pts underwent PET/CT for efficacy evaluation. Across the 46 efficacy-evaluable pts after SC×2, 36 (78.2%) achieved response, including 29(60.3%) CR pts. Median cycles of P-GemOx were 2(1-4). After part B, among the 42 response-evaluable pts, the CRR was 95.2% (40/42), and the ORR was 97.6% (41/42). The median follow-up time was 12.4 (0.2-23.7) months. The 1-year DoCR, PFS, OS rates were 96.2% (95%CI, 75.7-99.5), 97.5% (95%CI, 83.6-99.6), 95.3% (95%CI, 82.2-98.8), respectively. The most common myelotoxicities were neutropenia (97.8%), lymphopenia (89.4%), anemia (74.5%), thrombocytopenia (58.7%), and non-myelotoxicities including appetite (38.3%), nausea (38.3%), lipase increased (31.9%). Most toxicities came from P-GemOx. Three patients died, 2 due to disease progression and 1 due to accident. Tumor DNA data in relation to efficacy will be presented at the meeting. **Conclusions:** Preliminary results from SCENT-2 trial exceeded expected efficacy. It may be a promising chemo-reduced therapeutic and manageable toxicities for this population. Further investigation is needed. Clinical trial information: NCT04994210. Research Sponsor: None.

7007 **Oral Abstract Session**

Sintilimab (anti-PD-1) plus ifosfamide, carboplatin, and etoposide (ICE) in second-line classical Hodgkin lymphoma (cHL): Results of a multicenter, randomized, controlled, double-blind phase 3 study (ORIENT-21). First Author: Peng Liu, National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences & Peking Union Medical College, Beijing Key Laboratory of Clinical Study on Anticancer Molecular Targeted Drugs, Beijing, China

Background: Sintilimab monotherapy for cHL in third-line setting and beyond has been evaluated in a single-arm, phase 2 study ORIENT-1. Here, we present results of the phase 3 study ORIENT-21 evaluating sintilimab plus ICE versus placebo plus ICE as the second-line treatment for cHL. **Methods:** This study enrolled cHL pts who have failed first-line standard chemotherapy. The study has a safety run-in phase to enroll pts receiving sintilimab plus ICE, followed by a randomized phase in which pts were assigned in a 1:1 ratio to receive either sintilimab plus ICE (experimental arm) or placebo plus ICE (control arm) for 6 cycles. Patients without disease progression continued either sintilimab or placebo monotherapy. Stratification factors were age (<50 vs ≥50), disease status (relapsed vs refractory), and international prognostic score (IPS, <3 vs ≥3). Primary endpoint was complete remission rate (CRR) assessed by investigators according to Lugano 2014 criteria. Secondary endpoints included progression-free survival (PFS), duration of complete remission (DoCR) and safety. **Results:** As of Nov 21, 2024, 81 pts (ITT set: 10 in safety run-in, 34 in experimental arm, 37 in control arm) were enrolled (age≥50: 12.3%, IPS≥3: 18.5%, relapsed: 56.8%, refractory: 43.2%) with a median follow-up of 38.4 months (range: 0-58). In mITT set (randomized pts, n=71), significant higher CRR was observed in the experimental arm than the control arm (61.8% vs 32.4%, p=0.0295). Consistent results were also observed in ITT set (CRR: 61.4% vs 32.4%, p=0.0105). In mITT and ITT sets, median DoCR was not reached in sintilimab plus ICE (events in 28.6% and 22.2% pts), and was 20.7 months in placebo plus ICE. There were 16 pts in control arm switching to sintilimab monotherapy after disease progression. In ITT set, median PFS was not reached in sintilimab plus ICE (events in 34.1% pts), and was 9.0 months in placebo plus ICE (HR: 0.48, 95% CI: 0.23-1.00). Favorable PFS was observed in CR pts than non-CR pts with either sintilimab plus ICE (HR: 0.22, 95% CI: 0.08-0.63) or placebo plus ICE (HR: 0.15, 95% CI: 0.04-0.52). In safety set (n=80), all pts had treatment-emergent adverse events (TEAEs) while ≥grade 3 TEAEs occurred in 81.4% pts with sintilimab plus ICE (n=43) and in 97.3% pts with placebo plus ICE (n=37). Most common ≥grade 3 TEAEs were neutrophil count decreased (62.8% vs 70.3%), white blood cell count decreased (53.5% vs 64.9%) and platelet count decreased (51.2% vs 67.6%). TEAEs led to treatment discontinuation in both arms (18.6% vs 13.5%). No TEAE led to death. **Conclusions:** Sintilimab plus ICE significantly improved CRR and showed a trend of favorable PFS compared with placebo plus ICE. The safety profiles were manageable and no new safety signal was observed. Clinical trial information: NCT04044222. Research Sponsor: Innovent Biologics (Suzhou) Co., Ltd.

7008 Oral Abstract Session

Results from the completed dose-finding part of phase 2 study of the innate cell engager acimtamig (AFM13) in combination with AlloNK (AB-101) in relapsed or refractory classical Hodgkin lymphoma (LuminICE-203). First Author: Joseph E. Maakaron, Division of Hematology, Oncology and Transplantation, Department of Medicine, Masonic Cancer Center, University of Minnesota, Minneapolis, MN

Background: There is an unmet need for new treatment approaches for patients (pts) with relapsed or refractory (R/R) classical Hodgkin lymphoma (HL) who progress following standard systemic therapies. Combining acimtamig (AFM13), a tetravalent bispecific CD30/CD16A innate cell engager (ICE), with AlloNK (AB-101), a cryopreserved, off-the-shelf, cord blood-derived NK cell product, induces antibody-dependent cellular cytotoxicity against CD30+ lymphoma cells. **Methods:** This Phase 2, open-label, multi-center, multi-cohort study (LuminICE-203; NCT05883449) is evaluating the efficacy and safety of acimtamig in combination with AlloNK in pts with R/R HL. An initial dose-finding part with 4 cohorts is investigating 2 doses of acimtamig (200 mg or 300 mg weekly flat dosing for 6 weeks) in combination with AlloNK (dose level 1 [DL1]: 3 doses of 2×10^9 cells on Days 1, 8 and 15; or dose level 2 [DL2]: 1 dose of 4×10^9 on Day 1, followed by 2 doses of 2×10^9 cells on Days 8 and 15), after a standard lymphodepletion up to 3 cycles, followed by a randomized part using a Simon's 2-stage design. The primary endpoint is objective response rate (ORR) assessed by an Independent Radiology Committee (IRC) based on PET-CT per Lugano classification criteria. **Results:** As of 16 December 2024, 24 pts with R/R HL were treated in the initial dose-finding part of the study and were assessed by the IRC for metabolic response. Median (range) age was 42.5 (23–80) years; 16 (67%) were male. All pts in the study were heavily pretreated with chemotherapy, brentuximab vedotin and PD-1 inhibitors; median (range) prior treatment lines was 4.5 (2–13), including previous stem cell transplant in 14 (58%) pts. An ORR of 88% was achieved with 14 (58%) complete responses (CR) (Table). The safety profile was in line with that previously reported, with mostly mild to moderate infusion related reactions as the most common reported treatment-related adverse event (TRAE) in 50% of patients; no fatal TRAEs and no stopping criteria have been observed. The study is ongoing and updated safety and efficacy results, including pharmacokinetic / pharmacodynamic analyses and preliminary results on duration of response will be presented. **Conclusions:** Acimtamig in combination with AlloNK shows promising efficacy with a well-managed safety profile with the potential to address an unmet need in pts with R/R HL who have exhausted standard-of-care treatment options. Clinical trial information: NCT05883449. Research Sponsor: Affimed GmbH and Artiva Biotherapeutics Inc.

Efficacy results of acimtamig plus AlloNK in pts with R/R HL.

Efficacy, n (%) (Best Response per Lugano Criteria)	AlloNK DL1 + 200 mg acimta-mig (N=6)	AlloNK DL1 + 300 mg acimta-mig (N=6)	AlloNK DL2 + 200 mg acimta-mig (N=6)	AlloNK DL2 + 300 mg acimta-mig (N=6)	Total dose-finding part (N=24)
CR	4 (67)	3 (50)	4 (67)	3 (50)	14 (58)
ORR	**5 (83)**	**5 (83)**	**6 (100)**	**5 (83)**	**21 (88)**

7009 Rapid Oral Abstract Session

Combination of zanubrutinib (zanu) + venetoclax (ven) for treatment-naive (TN) CLL/SLL: Results in SEQUOIA arm D. First Author: Mazyar Shadman, Fred Hutchinson Cancer Center and University of Washington, Seattle, WA

Background: Zanu monotherapy demonstrated superior progression-free survival (PFS) compared with bendamustine + rituximab in patients (pts) without del(17p) at 26.2-month follow-up and sustained PFS benefit at 5-year follow-up. In a single-arm cohort, zanu monotherapy was also shown to be effective in pts with del(17p). Several CLL studies have demonstrated promising efficacy with the combination of B-cell lymphoma 2 + Bruton tyrosine kinase inhibitors; however, pts with del(17p)/*TP53* mutation comprised a small percentage of or were excluded from study populations. Here, we present results in SEQUOIA (NCT03336333) arm D with zanu + ven in pts with or without del(17p) and/or *TP53* mutation. **Methods:** Arm D is a nonrandomized cohort of the SEQUOIA study in pts aged ≥65 years (or 18-64 years with comorbidities). Pts received zanu (160 mg twice daily) + ven (ramp-up to 400 mg once daily) from cycle 4 to cycle 28, followed by continuous zanu monotherapy until progressive disease (PD), unacceptable toxicity, or meeting undetectable minimal residual disease (uMRD)–guided early zanu or ven stopping rules (CR/CRi and uMRD [$<1\times10^{-4}$ by flow cytometry] in peripheral blood [PB] and bone marrow on 2 consecutive tests ≥12 weeks apart). Efficacy responses were assessed by investigator every 3 cycles until cycle 28, then every 6 cycles with PB MRD assessment. **Results:** Between Nov 2019 and Jul 2022, 114 pts were enrolled: 66 (58%) with del(17p) and/or *TP53* mutation, 47 (41%) without del(17p) and *TP53* mutation, and 1 with missing *TP53* results. In all pts, median age was 67 years (range, 26-87), 64 (56%) were male, 86 (75%) had unmutated IGHV, and 47 (41%) had complex karyotype (≥3 abnormalities). As of Sept 16, 2024, 85 (75%) remained on treatment. The most common reasons for early discontinuation were reaching the uMRD-guided early stopping rules (zanu: 7%; ven: 7%), adverse events (AEs) (zanu: 8%; ven: 6%), and PD (zanu: 5%; ven: 4%). Six pts died (5 due to non–treatment-related AEs; 1 due to PD). Pts with or without del(17p)/*TP53* mutation achieved similar efficacy responses and best PB uMRD (Table). The most common any-grade treatment-emergent AEs (TEAEs) were COVID-19 (54%), diarrhea (41%), contusion (32%), and nausea (30%). The most common grade ≥3 TEAEs were neutropenia (17%), hypertension (10%), diarrhea (6%), and neutrophil count decreased (6%). **Conclusions:** SEQUOIA arm D data demonstrate promising efficacy and tolerability of zanu + ven combination treatment in TN CLL/SLL, regardless of del(17p) and/or *TP53* mutation status. The safety profile of zanu + ven was consistent with results of prior zanu studies, and no new safety signals were identified. Clinical trial information: NCT03336333. Research Sponsor: BeiGene.

	del(17p)− and *TP53* wt n=47	del(17p)+ or *TP53* mut n=66	Total N=114
Median follow-up, mo	30	39	31
24-month PFS rate, %	89	94	92
ORR, n/N (%)	45/46 (98)	65/65 (100)	111/112 (99)
CR/CRi, n/N (%)	23/46 (50)	31/65 (48)	55/112 (49)
Best PB uMRD, %	60	59	59

7010 Rapid Oral Abstract Session

Phase 1/2 studies of DZD8586 in CLL/SLL patients after covalent or non-covalent BTK inhibitors and BTK degraders. First Author: Jianyong Li, Department of Hematology, the First Affiliated Hospital of Nanjing Medical University, Jiangsu Province Hospital, Nanjing, China

Background: New therapies are needed for patients with relapsed or refractory (r/r) CLL/SLL following covalent and/or non-covalent BTK inhibitors. While early clinical data showed encouraging anti-tumor activities from BTK degraders in these patients, resistance mutations to both BTK inhibitors and degraders have already been reported. In addition, concerns with emerging clinical safety signals from these degraders may limit their longer-term clinical use. DZD8586 is a rationally designed LYN/BTK dual inhibitor with high selectivity against other TEC family members. Here we report results from ongoing phase 1/2 clinical studies of DZD8586 in r/r CLL/SLL patients with prior treatment of covalent and/or non-covalent BTK inhibitors as well as BTK degraders. **Methods:** The data from two clinical studies, TAI-SHAN5 (NCT05824585) and TAI-SHAN8 (NCT06539182, CTR20240120), were pooled for the safety and efficacy analysis in patients with CLL/SLL. Modulation of PD biomarkers was evaluated at doses tested. Tumor response was assessed by investigators per iwCLL 2018 or Lugano 2014 criteria as appropriate. **Results:** As of January 3, 2025, a total of 40 patients with r/r CLL/SLL have been enrolled and received DZD8586 at doses ranging from 25 mg to 100 mg once daily (QD). The median age was 64.5 years, 62.5% were male, and 60% had ECOG score of 1 or 2. A total of 30 patients were evaluable for efficacy analysis. The median number of prior therapies was 2 (range 1-8). Most common prior CLL/SLL therapies included BTK inhibitor (76.7%), and Bcl-2 inhibitor (43.3%). Patients previously treated by non-covalent BTK inhibitor (13.3%) and BTK degrader (13.3%) were also reported. Across all dose levels, 15 out of 30 patients achieved tumor response, with objective response rate (ORR) of 50%. At the recommended phase 2 dose (RP2D) of 50 mg QD, 9 out of 14 patients achieved tumor response, with ORR of 64.3%. Efficacy was observed in patients with prior BTK inhibitor treatment (ORR 52.2%), and Bcl-2 inhibitor treatment (ORR 46.2%). Seventy five percent patients who received prior BTK degrader treatment achieved partial response. As of the data cut-off date, the longest responder was on therapy for 12.1 months. Deepening response was observed with longer treatment time. DZD8586 was well tolerated across the doses investigated. At the RP2D, the most common ≥grade 3 TEAEs were neutropenia (15%) and pneumonia (10%). No major bleeding or atrial fibrillation was reported. No grade 4/5 AEs reported. **Conclusions:** DZD8586 showed encouraging anti-tumor activity with a well tolerated and manageable safety profile in heavily pre-treated CLL/SLL patients, including patients with prior covalent BTKi, non-covalent BTKi, BTK degrader and Bcl-2 inhibitor treatment. PK/PD results confirmed dose/exposure-dependent pathway inhibition by DZD8586. The updated data will be presented at the meeting. Clinical trial information: NCT06539182, NCT05824585. Research Sponsor: None.

7011 Rapid Oral Abstract Session

SEQUOIA 5-year follow-up in arm C: Frontline zanubrutinib monotherapy in patients with del(17p) and treatment-naive chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL). First Author: Constantine Si Lun Tam, Alfred Hospital and Monash University, Melbourne, VIC, Australia

Background: Zanubrutinib (zanu) is a next-generation Bruton tyrosine kinase inhibitor that is approved for 5 indications, including CLL/SLL. Initial results from the SEQUOIA study (NCT03336333), at a median follow-up of 26.2 mo, demonstrated superior progression-free survival (PFS) by independent review with zanu vs bendamustine + rituximab (arms A and B) in patients (pts) with treatment-naive (TN) CLL/SLL without del(17p) as well as high overall response rate (ORR) and PFS benefit in pts with del(17p) (arm C). Additionally, the 5-y follow-up in arm A demonstrated durable PFS benefit, with estimated 54- and 60-mo PFS rates of 80% and 76%, respectively. Here we report updated results in SEQUOIA arm C, in pts with del(17p), after approximately 5 y of follow-up (data cutoff: Apr 30, 2024). **Methods:** Arm C is a nonrandomized cohort of SEQUOIA pts with del(17p) that received zanu monotherapy. Investigator-assessed PFS, overall survival (OS), ORR, and safety/tolerability were evaluated. Adverse events (AEs) were recorded until disease progression or start of next-line therapy. **Results:** Between Feb 2018 and Mar 2019, 111 TN ptswith del(17p) were enrolled to receive zanu. The median age was 71 y (range, 42-87 y), 79 (71%) were male, 67 (60%) were IGHV unmutated, and 47 (42%) had both del(17p) and *TP53* mutation. At a median follow-up of 65.8 mo (range, 5-75 mo), median PFS was not reached. The estimated 60-mo PFS rate was 72.2% (62.4%-79.8%), or 73.0% (63.3%-80.6%) when adjusted for COVID-19. Median OS was also not reached. The estimated 60-mo OS rate was 85.1% (76.9%-90.6%), or 87.0% (79.0%-92.1%) when adjusted for COVID-19. The ORR was 97.3%, and the complete response/complete response with incomplete hematologic recovery rate was 18.2%. Zanu treatment was ongoing in 62.2% of pts. The most common causes for treatment discontinuation were AEs and progressive disease (in 17.1% and 15.3%, respectively). Key AEs of interest (AEI) included any-grade infection (82%), bleeding (60%), neutropenia (19%), hypertension (18%), anemia (9%), thrombocytopenia (8%), and atrial fibrillation/flutter (7%). Grade ≥3 AEI included infection (33%), neutropenia (16%), hypertension (8%), bleeding (6%), atrial fibrillation/flutter (5%), and thrombocytopenia (2%). **Conclusions:** With this 5-y follow-up in SEQUOIA, the efficacy of zanu in TN higher-risk pts with del(17p) was maintained, and pts continue to demonstrate PFS benefits consistent with the randomized cohort of pts without del(17p) (arm A). Additionally, with longer-term follow-up, no new safety signals were identified. This update, in the largest cohort of uniformly treated pts with del(17p), suggests that zanu remains a valuable frontline treatment option for patients with or without del(17p) CLL/SLL. Clinical trial information: NCT03336333. Research Sponsor: BeiGene.

7012 Rapid Oral Abstract Session

A phase 1/2 study to evaluate the safety and efficacy of XNW5004, a selective EZH2 inhibitor, in subjects with relapsed/refractory non-Hodgkin lymphoma. First Author: Lugui Qiu, State Key Laboratory of Experimental Hematology, Institute of Hematology & Blood Diseases Hospital, Chinese Academy of Medical Science & Peking Union Medical College, Tianjin, China

Background: Prognosis of relapsed/refractory (R/R) non-Hodgkin Lymphoma (NHL) which has progressed on standard therapy remains poor. EZH2 is a methyltransferase playing crucial roles in gene regulation and epigenetic modifications. Gain-of-function mutations/overexpression of EZH2 has been found in NHL and correlates with disease progression. XNW5004 is a small molecule, highly selective inhibitor of EZH2. Here, we report the safety and efficacy of XNW5004 in subjects with R/R NHL from a phase 1/2 study. **Methods:** Subjects with histologically confirmed, R/R NHL who has received ≥ 2 lines of systemic therapies were eligible to enroll in this multicenter, open label, dose escalation and dose expansion study in China. Standard 3+3 design with accelerated titration was used for dose escalation in 6 doses of XNW5004 from 100mg to 2000mg, PO, BID. 800mg BID and 1200mg BID were selected for dose expansion in subjects with follicular lymphoma (FL) and peripheral T cell lymphoma (PTCL). **Results:** As of Dec 18, 2024, 120 subjects were enrolled (escalation:19, expansion: 101) including 51 FL and 58 PTCL. Median follow-up was 17.4 months (mos). 87.4% of the subjects had an Ann Arbor Stage of III-IV at baseline. The median lines of prior systemic therapy were 3. 93.8% of the FL subjects received anti-CD20 antibody, 68.8% were POD24 (progression of disease within 24 months of diagnosis). 91.7% of the PTCL subjects received HDAC inhibitor prior to enrollment. Any grade treatment-emergent adverse events (TEAEs) in ≥10% subjects included diarrhea, anemia, WBC count decreased, platelet count decreased, vomiting, nausea, and neutrophil count decreased. No DLT was observed. In dose escalation phase, ORR and DCR of the 16 evaluable subjects across doses was 56.3% and 87.5%, respectively. Median progression-free survival (mPFS) was 9.2 mos. Median duration of response (mDOR) and median overall survival (mOS) were not reached. In dose expansion phase, 1200mg BID was selected as RP2D. At 1200 mg BID, ORR in all FL, EZH2 wild type FL, and EZH2 mutant FL was 66.7%, 63.2%, and 70%, respectively. mPFS and mDOR in all FL was 10.8 mos and 7.4 mos, respectively. mOS was not reached. ORR in FL with POD24 was 56.5%. ORR in FL previously treated with CAR-T was 66.7%. ORR in FL previously received autologous stem cell transplantation was 100%. At 1200 mg BID, ORR in all PTCL, PTCL-NOS, and PTCL-AITL was 70.3%, 72%, and 68.2%, respectively. In all PTCL, mPFS was 15.7 mos and mDOR was 13.9 mos. mOS was not reached. **Conclusions:** XNW5004 has shown a well-tolerated safety profile and promising efficacy in different types of NHL. Pivotal studies of XNW5004 monotherapy in PTCL are ongoing. Clinical trial information: NCT06558513. Research Sponsor: Evopoint Biosciences, Co. Ltd.

7013 Rapid Oral Abstract Session

CD79b-targeted antibody-drug conjugate (ADC) SHR-A1912 in combination with rituximab, gemcitabine, and oxaliplatin (R-GemOx) in relapsed or refractory (r/r) diffuse large B-cell lymphoma (DLBCL): Data from a phase 1b/2 study. First Author: Yajun Li, Department of Lymphoma and Hematology, The Affiliated Cancer Hospital of Xiangya School of Medicine, Central South University/Hunan Cancer Hospital, Changsha, China

Background: Patients (pts) with transplant-ineligible r/r DLBCL have an unmet need, with an objective response rate (ORR) of around 40%. CD79b, a key component of the B-cell receptor and expressed in a majority of mature malignancies of B-cell origin, is an attractive therapeutic target for DLBCL. We initiated a phase 1b/2 study to assess the safety and efficacy of SHR-A1912, a novel CD79b-targeted ADC, in combination with chemotherapy in pts with r/r or treatment-naive DLBCL. Here, we report the findings of SHR-A1912 plus R-GemOx regimen in the r/r DLBCL cohort. **Methods:** The study comprised a dose-escalation (D-ESC) and dose-expansion (D-EXP) phase 1b part and an efficacy-expansion phase 2 part. For the r/r DLBCL cohort, pts who had failed to respond to or had progressed after ≥1 prior anti-cancer therapy were enrolled to receive SHR-A1912 plus R-GemOx (Q3W, IV) for up to 8 cycles, followed by maintenance therapy with SHR-A1912 until disease progression, intolerable toxicity, or investigator decision. The primary endpoints were safety and recommended phase 2 dose (RP2D) in the phase 1b part and ORR in the phase 2 part. **Results:** As of cutoff date on Nov 19, 2024, 41 pts were enrolled (n=7, 8, and 26 in D-ESC, D-EXP, and phase 2 parts). During D-ESC, DLTs were observed in 2 of the 4 pts receiving 2.7 mg/kg of SHR-A1912 plus R-GemOx (1 with grade 4 decreased platelet count and 1 with grade 3 asthenia and grade 3 decreased appetite); subsequently, 3 pts were given 1.8 mg/kg of SHR-A1912 plus R-GemOx, and no DLTs occurred. 1.8 mg/kg was determined to be the RP2D of SHR-A1912 when combined with R-GemOx. Totally, 37 r/r DLBCL pts received 1.8 mg/kg of SHR-A1912 plus R-GemOx in the study. Grade ≥3 treatment-emergent adverse events occurred in 21 (56.8%) out of the 37 pts, with the most common being hematological toxicities (decreased platelet count, 29.7%; decreased white blood cell count, 24.3%; decreased neutrophil count, 21.6%; anemia, 13.5%; decreased lymphocyte count, 10.8%). Among the 37 pts, 19 achieved a complete response (CR), and 8 achieved a partial response. The ORR was 73.0% (95% CI, 55.9–86.2), and the CR rate was 51.4% (95% CI, 34.4–68.1). 23 (85.2%) of the 27 responders showed an objective response at their first anti-tumor assessment, with a time to response of 1.4 mo (95% CI, 1.2–3.5). All responses were ongoing as of the cutoff date. **Conclusions:** Inpts with r/r DLBCL, SHR-A1912 at 1.8 mg/kg in combination with R-GemOx was tolerable and demonstrated a safety profile consistent with its individual components. This combination exhibited potent anti-tumor activity, as well as rapid and durable responses. Clinical trial information: NCT06104553. Research Sponsor: Jiangsu Hengrui Pharmaceuticals.

7014 Rapid Oral Abstract Session

Fixed duration subcutaneous (SC) mosunetuzumab (Mosun) in patients with previously untreated high-tumor burden follicular lymphoma (FL): Interim results from the phase II MorningSun study. First Author: Ian W. Flinn, Tennessee Oncology and OneOncology, Nashville, TN

Background: Mosun is a CD20xCD3 bispecific antibody that can be administered in the outpatient setting for a fixed duration. Intravenous Mosun is approved for the treatment of relapsed/refractory FL after ≥2 prior lines of therapy. Mosun SC achieved high response rates with manageable safety in patients with 3L+ FL in a pivotal Phase II study (Bartlett et al. ASH 2024). We report the efficacy and safety of Mosun SC in patients with previously untreated high-tumor burden FL in the Phase II MorningSun study (NCT05207670). **Methods:** Patients with previously untreated high-tumor burden FL, per GELF criteria, were enrolled into this cohort. Mosun SC was administered with step-up dosing in Cycle (C)1 (Day [D]1, 5mg; D8, 45mg; D15, 45mg) then 45mg on D1 for up to 17 cycles (1 year; 21-day cycles). Patients with a partial or complete metabolic response (CMR) after C17 could receive additional Mosun maintenance therapy (45mg every 8 weeks for up to 1 year). Corticosteroid prophylaxis to reduce the risk of cytokine release syndrome (CRS) was mandatory in C1–2 and optional thereafter. The primary endpoint was progression-free survival (PFS) rate at 24 months. Key secondary endpoints included objective response rate (ORR), time to response (TTR), and safety. **Results:** As of May 29, 2024, 102 patients were enrolled; 55 patients had completed initial treatment (17 cycles), 31 had discontinued (most commonly due to progressive disease [n=19] and adverse events [AEs; n=4]), and 16 were ongoing initial treatment. Forty-two patients received maintenance treatment, and this was ongoing in 38 patients. Median age was 65 years (range: 24–86); 52.0% of patients were female. Most patients had Ann Arbor stage III/IV (91.2%) and a FLIPI score ≥2 (78.4%). Median duration of follow-up was 13.9 months. The 12-month PFS rate was 82.8% (95% confidence interval [CI]: 73.0–89.3). ORR was 87.3%; 60.8% of patients had a CMR. Among the 89 patients with a response, the median TTR was 2.7 months (range: 1.2–5.8). The most common AEs (≥30%) were injection-site reaction (57.8%), fatigue (42.2%), CRS (34.3%), headache (31.4%), and nausea (30.4%). Grade ≥3 AEs and serious AEs (SAEs) were reported in 44.1% and 29.4% of patients, respectively. CRS events were all Grade 1/2 and SAE of CRS occurred in 10.8% of patients (Table); all events resolved. **Conclusions:** Mosun SC demonstrated promising efficacy in patients with previously untreated high-tumor burden FL. The manageable safety profile, including rate of CRS, supports the administration of fixed duration Mosun SC in an outpatient setting. Additional data, including cytokine profiling and T/B/NK dynamics, will be presented. Clinical trial information: NCT05207670. Research Sponsor: Genentech, Inc.

CRS events, n (%)	Patients N=102
Any grade	**35 (34.3)**
Grade	
1	30 (29.4)
2	5 (4.9)
SAE	**11 (10.8)**
Management	
Steroids	8 (7.8)
Tocilizumab	6 (5.9)
Steroids + tocilizumab	3 (2.9)
Fluids	3 (2.9)
ICU admission	2 (2.0)

7015 Rapid Oral Abstract Session

Glofitamab plus gemcitabine and oxaliplatin (Glofit-GemOx) in patients (pts) with relapsed/refractory (R/R) diffuse large B-cell lymphoma (DLBCL): 2-year (yr) follow-up of STARGLO. First Author: Jeremy S. Abramson, Massachusetts General Hospital Cancer Center, Boston, MA

Background: Glofitamab, a CD20:CD3 bispecific antibody, has shown durable responses as fixed duration monotherapy in R/R DLBCL after ≥2 prior lines of therapy (LOT; Dickinson et al. NEJM 2022). When combined with GemOx, glofitamab has shown overall survival (OS) and progression-free survival (PFS) benefits in autologous stem cell transplant (ASCT)-ineligible R/R DLBCL (Abramson et al. Lancet 2024). We present updated efficacy and safety of Glofit-GemOx vs rituximab (R)-GemOx in pts with R/R DLBCL after ≥1 LOT from the Phase 3 STARGLO trial (NCT04408638), including landmark analyses of pts in complete remission (CR). **Methods:** Pts were randomized 2:1 to Glofit-GemOx (8 cycles plus 4 cycles glofitamab monotherapy) or R-GemOx (8 cycles) and stratified by no. of prior LOT (1 vs ≥2) and refractoriness to last therapy. After obinutuzumab pretreatment, glofitamab was given in Cycle (C) 1 as weekly step-up doses (2.5/10mg) then 30mg target dose every 21 days from C2 Day 1. Pts with only 1 prior LOT must have been ASCT-ineligible. Primary endpoint was OS. Secondary endpoints included independent review committee (IRC)-assessed PFS and CR rate. A landmark analysis of pts in CR at end of treatment (EOT) was performed. **Results:** Of 274 pts (Glofit-GemOx, n=183; R-GemOx, n=91), 172 (62.8%) had 1 prior LOT, 102 (37.2%) had ≥2 prior LOT, 153 (55.8%) were primary refractory, and 166 (60.6%) were refractory to last therapy. Baseline characteristics were unchanged and balanced across arms. With 2 yrs follow-up (data cut off: June 17, 2024; median follow-up: 24.7 months [mo]), Glofit-GemOx continued to confer superior OS benefits (median: not evaluable [NE] vs 13.5 mo; HR 0.60, 95% CI: 0.42–0.85), median IRC-assessed PFS (13.8 vs 3.6 mo; HR 0.41, 95% CI: 0.29–0.58), and CR rate (58.5 vs 25.3%) vs R-GemOx. For Glofit-GemOx-treated pts in CR (n=107), median duration of CR was not reached (95% CI: 27.2–NE; median CR follow-up, 18.2 mo [range: 15.2–19.3]). In pts with a CR at EOT (n=82), the OS and PFS rates 1 yr after EOT were 89.3% and 82.4%, respectively. The Glofit-GemOx safety profile was unchanged. Cytokine release syndrome (CRS) was the most common adverse event in glofitamab-exposed pts (Grade [Gr] 1, 32.0%; Gr 2, 10.5%; Gr 3, 2.3%). Events consistent with immune effector cell-associated neurotoxicity syndrome occurred in 4 pts (all concurrent with CRS; most Gr 1–2 [n=3]). Exploratory biomarker and immune recovery data will be presented. **Conclusions:** With 2 yrs follow-up, Glofit-GemOx sustained a clinically meaningful benefit in OS and PFS vs R-GemOx in ASCT-ineligible pts with R/R DLBCL, with most (82%) pts in CR at EOT still in remission. The safety profile was consistent with known risks of each drug. The updated analyses support the long-lasting remissions and maintained OS benefit in pts with R/R DLBCL treated with fixed duration Glofit-GemOx. Clinical trial information: NCT04408638. Research Sponsor: F. Hoffmann-La Roche Ltd; N/A.

7016 **Rapid Oral Abstract Session**

Worldwide experience of chronic active EBV infection: Retrospective cohort study. First Author: Xinran Wang, Department of Hematology, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China

Background: Chronic active Epstein-Barr virus disease (CAEBV) is a rare, life-threatening disorder characterized by systemic inflammation and clonal proliferation of EBV-infected T or NK cells. The disease exhibits clinical variability, ranging from mild to rapidly progressive and fatal forms. Despite advances in understanding its features, most studies are based on small cohorts or case reports, with no standardized diagnostic or therapeutic guidelines. Regional differences in age distribution, clinical characteristics, and treatment strategies exist. This study analyzed 763 CAEBV cases to summarize global experiences and propose a new classification and risk stratification model. **Methods:** This retrospective cohort study analyzed 763 CAEBV cases from 57 centers across 9 countries, including data from a systematic review and institutional data from Tongji Hospital, Wuhan, China. A novel classification system and risk stratification model were developed based on clinical and pathological data. Treatment outcomes, including allo-HSCT, anti-PD-1 therapy, and chemotherapy, were evaluated using survival analysis and multivariate Cox regression. **Results:** Among the 763 cases, 98.1% were from East Asia (China 53%, Japan 41%, Korea 4%), with smaller contributions from America (2%) and other countries. The median age at diagnosis was 18 years, with 53.7% of cases in those under 20. EBV-infected T cells were seen in 52% of cases, NK cells in 38%, and mixed infections in 10%. A new classification system divided systemic CAEBV (sCAEBV) into four subtypes: cutaneous (10%), gastrointestinal (4.6%), vascular (3.2%), and not otherwise specified (82.2%). Gastrointestinal involvement was associated with the poorest prognosis, necessitating early intervention. Treatment data from 399 patients showed that allo-HSCT is the only curative option, significantly improving survival rates. For high-risk patients unable to undergo allo-HSCT, anti-PD-1 therapy showed potential as an adjunctive treatment. A risk stratification model categorized patients into low-risk, high-risk, and very high-risk groups. Low-risk patients were monitored and treated with anti-PD-1 therapy, high-risk patients received either anti-PD-1 therapy or allo-HSCT, and very high-risk patients were advised to undergo allo-HSCT. **Conclusions:** This study represents the largest global cohort of CAEBV cases, with 763 cases from 9 countries. A novel classification system for sCAEBV was proposed, highlighting gastrointestinal involvement as a poor prognostic factor. Based on clinical symptoms and laboratory findings, a new risk stratification model was developed, guiding personalized treatment. Allo-HSCT remains the only curative treatment, significantly improving survival, while anti-PD-1 therapy offers potential as an adjunctive treatment for high-risk patients who cannot undergo allo-HSCT. Research Sponsor: This study was supported by the National Natural Science Foundation of China, the Natural Science Foundation of Hubei Province.

7017 **Rapid Oral Abstract Session**

Efficacy and safety of first-line ibrutinib plus venetoclax in patients with mantle cell lymphoma (MCL) who were older or had *TP53* mutations in the SYMPATICO study. First Author: Michael Wang, Department of Lymphoma and Myeloma, The University of Texas MD Anderson Cancer Center, Houston, TX

Background: The phase 3 SYMPATICO study evaluated ibrutinib (Ibr) combined with venetoclax (Ven) in 3 cohorts of patients (pts) with MCL: an open-label safety run-in phase to evaluate concurrent initiation of Ibr+Ven in relapsed/refractory (R/R) MCL; a randomized phase to evaluate Ibr+Ven vs Ibr+placebo (Pbo) in R/R MCL; and an open-label cohort to evaluate first-line Ibr+Ven in treatment-naive (TN) MCL. Primary analysis of the randomized phase showed superior PFS with Ibr+Ven vs Ibr+Pbo in pts with R/R MCL (Wang M et al, *Lancet Oncol*, in press). Here, we report efficacy and safety of Ibr+Ven in pts with TN MCL in older pts (≥65 y) or younger pts with a *TP53* mutation (*TP53*mut) (≥18 y) who are in need of novel and better tolerated treatment options. **Methods:** Older pts (≥65 y) or pts with a *TP53*mut with TN MCL received oral Ibr 560 mg once daily and Ven (5-wk ramp-up to 400 mg once daily) for 2 y, then single-agent Ibr 560 mg until PD or unacceptable toxicity. Primary endpoint was complete response (CR) rate assessed by investigator per Lugano. Key secondary endpoints included overall response rate (ORR), duration of response (DOR), PFS, OS, and time to next treatment. Subgroup analyses were performed according to *TP53*mut status and age. **Results:** In total, 78 TN MCL pts were enrolled. At baseline, 83% of pts were ≥65 y, 97% had ECOG PS of 0–1, 45% had high-risk simplified MIPI score, 31% had bulky disease (≥5 cm), 78% had bone marrow involvement, 46% had splenomegaly, and 37% had *TP53*mut. Median time on study was 40.5 mo (range, 0.6+–46.9). CR rate was 69% (95% CI, 58–79), and ORR was 95% (95% CI, 87–99). Median DOR was 37.1 mo (95% CI, 30.3–NE). Median PFS was 40.2 mo, and 3-y OS was 79%. CR rate was 76% in pts ≥65 y without *TP53*mut, 44% in pts ≥65 y with *TP53*mut, and 73% in pts <65 y with *TP53*mut; median PFS was 40.2, 22.0, and 15.4 mo, and 3-y OS was 85%, 66%, and 73%, respectively (Table). Median duration of treatment was 24.0 mo (range, 0.3–46.9). Most common AEs were diarrhea (49%), fatigue (37%), neutropenia (35%), and COVID-19 (32%). Most common grade ≥3 AE was neutropenia (29%). **Conclusions:** First-line Ibr+Ven showed promising efficacy with high CR rates and durable remissions in pts with TN MCL with and without *TP53*mut. Safety was acceptable and trended better in younger pts. Ibr+Ven may be an option for older pts with TN MCL or pts of any age with *TP53*mut. Clinical trial information: NCT03112174. Research Sponsor: Pharmacyclics LLC, an AbbVie Company.

Outcomes (95% CI)	Without *TP53*mut n=44	With *TP53*mut n=29	≥65 y without *TP53*mut n=42	≥65 y with *TP53*mut n=18	<65 y without *TP53*mut n=2	<65 y with *TP53*mut n=11	Total N=78
CR rate, %	77 (62–89)	55 (36–74)	76 (61–88)	44 (22–69)	100 (16–100)	73 (39–94)	69 (58–79)
ORR, %	98 (88–100)	90 (73–98)	98 (87–100)	89 (65–99)	100 (16–100)	91 (59–100)	95 (87–99)
Median PFS, mo	40.2 (37.2–NE)	22.0 (9.2–NE)	40.2 (37.2–NE)	22.0 (11.3–NE)	NR (11.1–NE)	15.4 (8.2–NE)	40.2 (29.4–NE)
3-y OS, %	86 (71–93)	68 (47–82)	85 (70–93)	66 (39–83)	100 (100–100)	73 (37–90)	79 (68–86)

7018 **Poster Session**

Incidence of infections, cardiac events, neurological toxicity and cytokine response syndrome (CRS) in patients treated with chimeric antigen receptor (CAR) T cell therapy: A 3-year nationwide analysis. First Author: Himil Mahadevia, University of Missouri - Kansas City, Kansas City, MO

Background: CAR-T cell therapy represents a notable advancement in treating relapsed/refractory (R/R) hematological malignancies. Adverse events include CRS, infections, and neurological and cardiac complications. While there are reports from major academic institutions on the adverse effects of CAR-T therapy, we used data from the National Inpatient Sample (NIS) to gather national estimates of complications related to CAR-T therapy. **Methods:** A retrospective study was conducted to analyze patients who underwent CAR-T cell therapy by utilizing appropriate ICD-10-PCS procedure codes (XW033C3, XW043C3, XW23346, XW24346, XW23376, and XW24376) from NIS 2019 to 2021. Data regarding infections, toxic encephalopathy (a surrogate for neurological toxicity), and adverse cardiac events were extracted using relevant ICD-10-CM diagnostic codes. Patients experiencing various grades of CRS were identified through specific ICD-10 codes available in 2021 (Grades 1-5: D89.831-D89.835). **Results:** This study analyzed 6515 patients who underwent CAR-T cell therapy from January 2019 to December 2021. Among them, 60.7% were male. 74.6% were Caucasian, 11.7% were Asian and 6.7% were African American. 49.8% of patients had private insurance, 36.2% had Medicare, and 8.6% had Medicaid. 6.8% of patients were diagnosed with pneumonia, while sepsis occurred in 7.4% of patients and 3% experienced septic shock. 19.4% of patients experienced cardiac arrhythmias, and major cardiovascular events were recorded in 4.7% of the cohort. Acute myocardial infarction and stroke were documented in 0.6 and 1.2% of patients, respectively. Toxic encephalopathy was reported in 19.7% of patients. Among 2235 patients identified to have received CAR-T in 2021, 59.7% developed CRS. Grade 1 and grade 2 CRS were reported in 32% and 21% of patients, respectively, while grade 3 and grade 4 reactions were noted in 4.7% and 2% of patients, with no cases of grade 5 identified. The mean total cost of hospitalization was 308,364$, and the mean length of hospital stay was 19.5 days. The overall in-hospital mortality rate was 3.4%. **Conclusions:** Our study describes real-world outcomes from a large dataset of CAR-T patients. Infections pose a significant challenge with CAR-T therapy, highlighting the importance of early detection and timely antimicrobial treatment. CRS is common, with a 60% incidence, similar to previous clinical trials (55%). Immediate management is crucial for addressing CRS toxicity. Adverse neurological and cardiovascular incidents are often reported, emphasizing the need for meticulous monitoring and coordinating multidisciplinary care plans. The financial burdens also bear mentioning: CAR-T therapy costs significantly higher than autologous stem cell transplants. Further studies to address these issues are warranted. Research Sponsor: None.

7020 **Poster Session**

Association of enrichment of CD7$^+$CXCR3$^+$ CAR T cells in infusion products with remission in relapsed or refractory diffuse large B-cell lymphoma. First Author: Michel Obeid, CHUV, LCIT Center, Lausanne, Switzerland

Background: Chimeric antigen receptor (CAR) T-cell therapy is the standard of care for relapsed or refractory diffuse large B-cell lymphoma (R/R DLBCL), yet more than half of patients do not achieve durable remission. Identifying predictive biomarkers in CAR T-cell infusion products (IPs) could guide strategies to improve outcomes. **Methods:** This was a single-centre observational study conducted at Lausanne University Hospital (CHUV), Switzerland. IPs from 13 patients with R/R DLBCL who underwent CAR T-cell therapy were analyzed using a 39-marker mass cytometry panel. We compared phenotypic and functional markers between long-term responders (R) and non-responders (NR). Both unsupervised and supervised analyses were performed. Additionally, longitudinal blood samples collected over 30 days after infusion were examined to track CAR T-cell subpopulation dynamics. **Results:** At a median follow-up of 13.5 months, median progression-free survival (PFS) was 13.3 months (95% CI 9.7–24.3) in R (n=8) versus 3.5 months (95% CI 0.5–5.4) in NR (n=5) (hazard ratio 56.67 [95% CI 7.3–439.3]; p=0.0001). A subset of CD3$^+$CXCR3$^+$CD7$^+$ CAR T-cells—present within both CD4$^+$ and CD8$^+$ subsets—was significantly enriched in R. These cells showed increased expression of perforin, granzyme B, and NKG2D (restricted to CD8$^+$ cells). In contrast, NR had a higher frequency of CXCR3$^+$CD7$^+$LAG3$^+$ CAR T-cells. Surface expression levels of CD3, CD7, CXCR3, and NKG2D were higher in R, whereas LAG3, Ki67, and CD71 were elevated in NR. A predictive cut-off ratio of CD3$^+$CXCR3$^+$CD7$^+$LAG3$^+$CAR$^+$ T-cells <0.83 and CD3$^+$CXCR3$^+$CD7$^+$NKG2D$^+$CAR$^+$ T-cells >1.034 yielded a predictive accuracy of 0·92. Serum CXCL9 and CXCL10 concentrations did not differ between groups. **Conclusions:** The enrichment of CD7$^+$CXCR3$^+$ CAR T-cells and expression of NKG2D in R, as opposed to elevated LAG3 and CD71 in NR, emerged as robust correlates of therapeutic outcome. These findings could inform the development of biomarker-driven strategies to optimize CAR T-cell products and enhance the likelihood of sustained remission. Research Sponsor: CHUV pôle prioritaire.

7021 Poster Session

Clinical outcomes of cytomegalovirus infection among patients receiving chimeric antigen receptor T cell therapy. First Author: Muhammad Atif Khan, University of Kansas Medical Center, Collaborative Opportunities for Research, Training, And Excellence in Innovation (CORTEX), Kansas City, KS

Background: Chimeric antigen receptor T (CAR-T) cell therapy is a transformative treatment for hematologic malignancies, including multiple myeloma (MM), non-Hodgkin lymphoma (NHL), and acute leukemia (AL). Despite its success, CAR-T therapy is associated with significant toxicities and an increased risk of infections, particularly cytomegalovirus (CMV) infection. CMV infection in CAR-T recipients has been linked to increased non-relapse mortality (NRM) and prolonged hospital stays; however, comprehensive data on its clinical impact remains limited. This study aimed to evaluate the clinical impact of CMV infection on outcomes in CAR-T therapy recipients. **Methods:** This retrospective cohort study utilized the HCUP-National Readmission Database (NRD) 2021 database to analyze adult hospitalized patients (≥18 years) who underwent CAR-T cell therapy for MM, NHL, or AL in the USA. Patients with a prior CMV diagnosis or discharged in the last three months of 2021 were excluded. Propensity score matching (PSM) was applied to balance baseline characteristics, and weighted estimates were used for outcome analysis. The primary outcome was all-cause mortality within three months post-discharge. Secondary outcomes included length of hospital stay (LOS) and CAR-T-related complications. **Results:** A total of 1806 hospitalizations met the inclusion criteria. The mean age was 61.9 years, with a male majority of 64.4%. The underlying disorders were NHL (73.7%), MM (21.6%), and AL (4.7%). The incidence of CMV infection during the index hospitalization was 2.2%, increasing to 4.2% within three months post-CAR-T therapy. Matched analysis showed higher three-month mortality in CMV-infected patients (15.8%) compared to non-CMV patients (2.5%) (risk ratio 6.32, 95% CI: 1.46-27.30, p=0.004). CMV-infected patients had a significantly longer mean LOS (41.5 vs. 15.9 days, adjusted mean difference 15.5 days, 95% CI: 6.7-24.2, p=0.001). CMV infection was significantly associated with encephalopathy (risk ratio 13.21, 95% CI: 1.66-105.2, p=0.015), while other complications such as cytokine release syndrome (CRS), AKI, and transaminitis did not show a statistically significant association. **Conclusions:** CMV infection in CAR-T cell therapy recipients is associated with increased mortality, prolonged hospitalization, and risk of encephalopathy. These findings underscore the need for vigilant CMV surveillance and targeted management strategies to improve patient outcomes. Research Sponsor: None.

7022 Poster Session

Characterization of mechanisms driving CD20 loss in patients with relapsed or refractory large B-cell lymphoma treated with glofitamab. First Author: Linlin Cao, Roche Innovation Center Zurich, Schlieren, ZH, Switzerland

Background: Glofitamab is a CD20xCD3 T-cell engaging bispecific monoclonal antibody that redirects T cells to eliminate malignant B cells in patients (pts) with relapsed or refractory non-Hodgkin Lymphoma. We characterized mechanisms driving CD20 loss in pts from a Phase I/II trial (NP30179) receiving Glofitamab monotherapy for Relapsed/Refractory Large B-cell lymphoma (R/R LBCL). **Methods:** Pts with LBCL and ≥2 prior therapies received obinutuzumab pretreatment followed by fixed-duration Glofitamab at the approved dose in phase I/II trial NP30179 (NCT03075696) (Dickinson, et al. N Engl J Med 2022). Tumor biopsies were collected prior to treatment (Baseline, BL) in 128 pts, during treatment (tx) or at progression (PD) in 11 pts. The proportion of CD20+ tumor cells was determined by immunohistochemistry (IHC) using a dual CD20+ PAX5+ assay. Expression of *MS4A1*, the gene encoding CD20, was measured by RNA-sequencing (RNA-seq) in 105/139 biopsies. *MS4A1* mutation profiling was performed by next-generation sequencing on Cell-free circulating tumor DNA (ctDNA) from 133 pts. We subsequently characterized the functional consequences of identified mutations in vitro. **Results:** CD20 levels evaluated by IHC were high (>75% CD20+ tumor cells) in 110/128 BL biopsies. At BL, CD20 loss (<5% CD20+ tumor cells) was seen in 4/128 (3.1 %) biopsies. For 11 pts with BL and on-tx or at-PD biopsies, 7/11 (63.6%) pts presented CD20 loss on-tx/at-PD and 4/11 (36.4%) did not. Evaluation of gene expression profile showed a good correlation between CD20 gene and protein expression. Among the 7 pts with CD20 loss on-tx/at-PD biopsies, there were 4 biopsies with available gene expression data, and decreased CD20 expression was identified in 2/4. Evaluation of CD20 mutation revealed 11/134 (8.2%) pts harbored 16 *MS4A1* mutations at BL or on-tx/at-PD. IHC data were available for 8/11 pts at BL where 2/8 presented CD20 loss (<5% CD20+ tumor cells), and for 1 pt at-PD who presented CD20 loss. 12/16 mutations were not previously reported. We characterized 14 mutations in vitro and subsequently demonstrated that 8 frameshift or deletion mutations lead to truncation of the protein, and 4 missense mutations lead to disruption in the transmembrane domain of CD20. These 12 mutations lead to loss of intracellular and extracellular CD20 expression, and abrogation of Glofitamab-mediated cytotoxicity in vitro. **Conclusions:** In pts with R/R LBCL treated with Glofitamab, loss of tumor antigen CD20 expression is one resistance mechanism to Glofitamab. Genetic alterations (fs, del or missense mutations) and transcriptional downregulation can contribute to loss of CD20 expression and they were both observed in pts treated with Glofitamab. Acknowledgments: The NCT03075696 study is sponsored by F. Hoffmann-La Roche Ltd. Research Sponsor: Roche.

7023 Poster Session

Trends and outcomes by inpatient and outpatient infusion of axicabtagene ciloleucel (axi-cel) in the US for patients (pts) with relapsed/refractory large B-cell lymphoma (R/R LBCL). First Author: Fateeha Furqan, The University of Texas MD Anderson Cancer Center, Houston, TX

Background: Axi-cel is an autologous chimeric antigen receptor (CAR) T-cell therapy approved for adults with R/R LBCL after ≥ 1 prior line of therapy (LoT). Adverse events, such as cytokine release syndrome (CRS) and neurologic events (NEs), may deter centers from using axi-cel in an outpatient (OPT) setting, though individual centers have observed comparable safety and effectiveness in OPT and inpatient (IPT) care (Furqan et al. *Blood Adv*. 2024). Here, we present safety and effectiveness outcomes of axi-cel by intention to treat in OPT and IPT settings in a multicenter real-world dataset. **Methods:** Pts receiving axi-cel for R/R LBCL in the US from 01/2021-07/2023 with data in the Center for International Blood and Marrow Transplant Research (CIBMTR) registry were eligible for analysis. Pts with prior allogeneic transplant or unknown intended care setting were excluded. Of potential pts, 119 OPT pts were identified from 29 centers where an increasing trend was seen (9.6% of pts in 2021 were OPT, 13.5% in 2022, 22.8% in 2023). Pts were matched to 119 IPT pts by propensity score matching on age, sex, comorbidities, lactate dehydrogenase (LDH), bulky disease, prior LoT, chemosensitivity, and infusion year (see table). **Results:** OPT pts had median age of 63 y (25% ≥ 70), 66% were male, and 67% had ≥ 1 comorbidity. Half (50%) had elevated LDH and 73% had 1 prior LoT. Bulky disease was reported in 3%, and 60% had chemo-resistant disease. Outcomes were analyzed at median follow-up of 12 mo. Safety and effectiveness outcomes were similar between OPT and IPT pts (see table). In multivariate analyses, no differences were found between intended care setting and CRS (odds ratio [OR] 1.09 [95% CI 0.51-2.35]), CRS Gr ≥ 3 (OR 0.57 [0.12-2.60]), NEs (OR 1.14 [0.65-2.00]), or NEs Gr ≥ 3 (OR 0.98 [0.48-2.00]). Among OPT pts, 24% and 50% did not require hospital admission within 30 d and 3 d, respectively. In pts aged ≥ 70 y, only any Gr NEs were higher in the OPT group. **Conclusions:** After matching on key factors that may be used to select pts for OPT infusion, outcomes were comparable between intended care settings. These findings corroborate prior results and support the consideration of axi-cel in appropriate OPT care settings. Research Sponsor: Kite, a Gilead Company.

Outcomes between matched pts with R/R LBCL receiving axi-cel intended for OPT or IPT.

	OPT (n=119)[a]	IPT (n=119)[a]
CRS any Gr / Gr ≥ 3	83 (75–89) / 3 (<1–7)	83 (74–89) / 4 (1–10)
NE any Gr / Gr ≥ 3	47 (38–57) / 19 (12–27)	46 (37–56) / 21 (14–30)
Overall / complete response rates	78 (69–85) / 68 (59–76)	76 (67–83) / 62 (52-70)
Duration of response @ 12 mo	64 (52–74)	69 (58–78)
Progression-free survival @ 12 mo	53 (43–62)	53 (43–61)
Overall survival @ 12 mo	71 (61–78)	72 (62–79)
Non-relapse mortality @ 12 mo	6 (2–11)	4 (1–8)
Hospital admission within 30 days of infusion / median duration (range), d	76 (67–83) / 9 (2–53)	Not Applicable

[a]Percent (95% CI) unless otherwise specified.

7024 Poster Session

Real-world outcomes of axicabtagene ciloleucel (axi-cel) for the treatment of relapsed/refractory (R/R) secondary central nervous system lymphoma (SCNSL). First Author: Narendranath Epperla, Huntsman Cancer Institute, University of Utah, Salt Lake City, UT

Background: Axi-cel is an autologous anti-CD19 CAR T-cell therapy that demonstrated durable, long-term efficacy and manageable safety in R/R LBCL. However, there is paucity of data using axi-cel in SCNSL, a subset associated with poor clinical outcomes. Here, we describe effectiveness and safety outcomes of axi-cel in R/R SCNSL. **Methods:** Patients (pts) receiving commercial axi-cel for R/R active SCNSL from 2018-2023 were selected from the CIBMTR database. Pts with primary CNS lymphoma and diseases other than LBCL were excluded. Outcomes included overall response rate (ORR), complete response (CR) rate, cumulative incidence of relapse (CIR), duration of response (DOR), progression-free and overall survival (PFS and OS), cytokine release syndrome (CRS) and immune effector cell-associated neurotoxicity syndrome (ICANS) per ASTCT consensus grading, other adverse events, and non-relapse mortality (NRM). Outcomes were analyzed descriptively. **Results:** At May 2024 data cutoff, 65 pts from 28 centers were identified. Median age at infusion was 63 y (range, 21-79) with 66% male and 81% white. Few pts (9/58, 16%) had ECOG PS ≥2; 52/65 (80%) had clinically significant comorbidities. Double-/triple-hit lymphoma was seen in 12/50 pts (24%), and 51/58 (88%) had Stage III/IV disease. CNS sites involved preinfusion were brain (51%), cerebrospinal fluid (12%), epidural space (15%), leptomeninges (11%), eyes (9%), and spinal cord (5%). Median number of prior lines of therapy was 4 (IQR, 3-5); 12/65 pts (18%) had prior autologous stem cell transplantation. Median time from leukapheresis to infusion was 28 days (IQR, 26-34). Bridging therapy was given to 47/65 pts (75%; systemic, 40 [63%]; intrathecal, 12 [19%]; radiation, 17 [27%]). At 48.2-mo median follow-up, ORR was 72% (95% CI, 60-83); CR rate was 51% (95% CI, 38-63). Median (95% CI) DOR, PFS, and OS were 4.0 (2.3-NE), 3.6 (2.2-4.9), and 8.4 mo (6.6-18.2), respectively. CIR was 66% (95% CI, 51-77) at 1 and 2 y. At 2 y and 3 y, PFS (95% CI) was 26% (16-38) and 23% (13-35), respectively, and OS (95% CI) was 36% (24-49) and 32% (20-44). Among pts without progression at 1 y, PFS was 100% and 90% (47-99) at 2 y and 3 y, respectively; OS was 82% (59-93) and 72% (48-86). Grade ≥3 CRS and ICANS occurred in 14% and 37% of pts, respectively (any grade, 81% and 62%). Of 56 pts with CRS and/or ICANS, tocilizumab, corticosteroids, and anakinra were used in 68%, 73%, and 7% of pts, respectively. Prolonged cytopenia (by Day 30) was reported in 25/63 pts (40%; thrombocytopenia, 37%; neutropenia, 11%), and 39/65 (60%) had clinically significant infections. Subsequent cancers were found in 3/39 pts (8%); 2 were myeloid. NRM at 3 y was 12%. **Conclusions:** With 4-y median follow-up, this real-world study highlights the potential use of axi-cel as an option to treat this challenging group of pts. Further studies are needed to improve response durability. Research Sponsor: U.S. National Institutes of Health; Kite, a Gilead Company.

7025 Poster Session

Social vulnerability by neighborhood of association correlates with CAR T referrals. First Author: Clare E. Anderson, Durham VA Health Care System and Duke University, Durham, NC

Background: Chimeric antigen receptor T (CAR T) cell therapies are effective for relapsed/refractory (R/R) diffuse large B-cell lymphoma (DLBCL) and multiple myeloma (MM). However, factors influencing referrals remain unclear, particularly among the denominator of all eligible candidates. This study examines patterns of CAR T referral in the VA health system. **Methods:** A retrospective review identified veterans with R/R DLBCL or MM eligible for CAR T per FDA label during approval periods. Multivariable logistic regression assessed associations of CAR T referral with demographics, comorbidities, and social deprivation index (SDI). SDI is a composite social determinants of health measure at the zip code level, with higher SDI (range: 0-100) indicating greater social disadvantage. **Results:** Of 1,474 eligible patients across 112 VA hospitals, 25% (153/606) of DLBCL and 7.5% (65/868) of MM patients were referred for CAR T. Multivariable analysis showed that higher SDI (OR 0.90 per 10 points, 95% CI 0.84-0.96, p = 0.001) and older age (OR 0.58 per 10 years, 95% CI 0.49-0.69, p $<$ 0.0001) were associated with a lower chance of referral, while DLBCL diagnosis (OR 3.22, 95% CI 2.28-4.59, p $<$ 0.0001) and Hispanic ethnicity (OR 1.964, 95% 1.09-3.45, p = 0.02) were more likely to have referrals. Marital status, sex, race, psychiatric history, substance abuse, heart disease, kidney disease, cirrhosis, and rural/urban residence were not significant. Among referred patients, older age (OR 0.98, 95% CI 0.95-0.99) and substance abuse (OR 0.42, 95% CI 0.19-0.88) were linked to lower CAR T administration. Median lines of therapy for CAR T were 4 (range: 2-6) for DLBCL and 7 (range: 5-10) for MM. Common reasons for not receiving CAR T included death (23%), age/performance status (21%), alternative therapies (18%), adequate disease control (13%), comorbidities (8%), and patient preference (5%). **Conclusions:** Social vulnerability by neighborhood of association is associated with fewer CAR T referrals. Once referred, most variables minimally impacted CAR T administration. Efforts should focus on improving referral rates and addressing access barriers across all patients. Research Sponsor: None.

Baseline characteristics of DLBCL and multiple myeloma cohorts.

	DLBCL (n = 606)	Multiple Myeloma (n = 868)
Median Age (range)	70 (30 – 96)	73 (36 – 97)
Male Sex (%)	585 (97%)	829 (96%)
Race/Ethnicity (%)		
Non-Hispanic White	402 (66%)	458 (53%)
Non-Hispanic Black	94 (16%)	320 (37%)
Hispanic	56 (9%)	53 (6%)
Other	17 (3%)	14 (2%)
Rural-Urban Residence (%)		
Urban	410 (68%)	645 (74%)
Rural	188 (31%)	219 (25%)
Marital Status (%)		
Married	361 (60%)	495 (57%)
Never Married	64 (11%)	83 (10%)
Divorced/Separated/ Widowed	178 (29%)	287 (33%)
> 3 FACT-Accredited Centers in State (%)	342 (56%)	493 (57%)
Median SDI (range)	52 (1-99)	55 (1-100)
Comorbidities (%)		
Heart Disease	226 (37%)	315 (36%)
Severe CKD	55 (9%)	171 (20%)
Hepatic Cirrhosis	36 (6%)	39 (4%)
Psychiatric Diagnosis	336 (55%)	442 (51%)
Substance Abuse	100 (17%)	135 (16%)

7026 Poster Session

Optimizing post–chimeric antigen receptor (CAR) T cell monitoring: Evidence across lisocabtagene maraleucel (liso-cel) pivotal clinical trials and real-world experience. First Author: Manali Kirtikumar Kamdar, University of Colorado Cancer Center, Aurora, CO

Background: CAR T cell therapies have shown remarkable efficacy in B-cell NHL. Here, we report CRS and ICANS timing in 1579 patients (pt) treated with liso-cel in clinical trials across indications or in the standard of care (SOC) setting to inform safety monitoring requirements. **Methods:** Data from pivotal trials (TRANSCEND NHL 001, TRANSCEND CLL 004, TRANSFORM, PILOT, TRANSCEND FL) included pts treated with liso-cel for R/R LBCL, CLL/SLL, MCL, and FL; data from the Center for International Blood and Marrow Transplant Research (CIBMTR) Registry included pts who received commercial liso-cel for R/R LBCL and had $\geq$ 1 assessment after infusion. Outcomes were incidence, onset, grade (gr), and duration of CRS and ICANS from pivotal trials and the CIBMTR Registry. **Results:** Of 702 pts treated with liso-cel in 5 clinical trials, 46% had no CRS, 54% had any-gr CRS (gr $\geq$ 3 at onset, 1%); 98% of events had onset $\leq$ 2 wk after infusion and median duration was 5 d (Table). Of 7 pts with CRS onset $>$ Day 15 (gr 1, n = 5; gr 2, n = 2), all resolved. Most (69%) pts had no ICANS, 31% had any-gr ICANS (gr $\geq$ 3 at onset, 5%); 88% of events had onset $\leq$ 2 wk after infusion and median duration was 7 d (Table). Of 27 pts with ICANS onset $>$ Day 15 (gr 1, n = 20; gr 2, n = 6; gr 3, n = 1), all resolved except 1 pt with gr 2 leukoencephalopathy. Of 877 liso-cel–treated pts from the CIBMTR Registry, 51% had no CRS, 49% had any-gr CRS (gr $\geq$ 3, 3%); 97% of events had onset $\leq$ 2 wk after infusion and median duration was 4 d (Table). Of 15 pts with CRS onset $>$ Day 15 (gr 1, n = 9; gr 2, n = 2; gr 3, n = 1; unknown, n = 3), 13 resolved (missing, n = 2). Most (73%) pts had no ICANS, 27% had any-gr ICANS (gr $\geq$ 3, 7%). Of 150 pts with reported onset date, 95% had onset $\leq$ 2 wk after infusion and median duration was 5.5 d. Of 8 pts with ICANS onset $>$ Day 15 (gr 1, n = 5; gr 2, n = 1; gr 4, n = 2), 5 resolved (missing, n = 3). Further characterization/management of CRS/ICANS events will be presented. **Conclusions:** Data from the liso-cel pivotal clinical trials and SOC setting from the CIBMTR Registry demonstrated that most CRS/ICANS events occurred $\leq$ 2 wk after infusion and were not severe. For the few pts who experienced onset of CRS/ICANS after Day 15, most events were low grade and resolved. Clinical trial information: NCT02631044, NCT03331198, NCT03483103, NCT03575351, NCT04245839. Research Sponsor: This study was funded by Bristol Myers Squibb. Writing and editorial assistance were provided by Amy Agbonbhase, PhD, CMPP, of The Lockwood Group (Stamford, CT, USA), funded by Bristol Myers Squibb.

CRS and ICANS in liso-cel–treated pts.

	Pivotal clinical trials (N = 702)		CIBMTR Registry (N = 877)	
	CRS	ICANS	CRS	ICANS
Any gr, n (%)	381 (54)	220 (31)	430 (49)[a]	234[a,b] (27)
Gr 3/4/5,[c] n (%)	4 (0.6)/3 (0.4)/0	29 (4)/3 (0.4)/0	4 (0.5)/13 (1)/7[d] (0.8)	43 (5)/17 (2)/5 (0.6)
Median (range) time to onset, d	5 (1–63)	8 (1–63)	4 (IQR, 3–6)	6 (IQR, 4–9)
Median (range) duration from onset, d	5 (1–37)	7 (1–119)	4 (IQR, 2–6)	5.5 (IQR, 2–11)
Onset > Day 15, n/N (%)	7/381 (2)	27/220 (12)	15/430 (3)	8/150 (5)

[a]Gr was to be determined for 3 pts; [b]A total of 150/234 had a reported onset date; [c]Gr at onset for clinical trials; maximum gr during reporting period for CIBMTR; [d]Three pts had PD and 1 had ICANS reported as primary cause of death.

7027 Poster Session

Comprehensive precise CAR-T bridging therapy for diffuse large B-cell lymphoma: A multicenter study from the Chinese Southwest Study Group. First Author: Tongyu Lin, Sichuan Cancer Hospital and Institute, Sichuan Cancer Center, School of Medicine, University of Electronic Science and Technology of China, Chengdu, China

Background: Chimeric antigen receptor T-cell (CAR-T) therapy has showed substantial efficacy in relapsed/refractory diffuse large B-cell lymphoma (r/r DLBCL). However, over 50-60% of patients fail to respond or relapse following CAR T-cell treatment, underscoring the need for strategies to enhance its efficacy. **Methods:** We prospectively evaluated the efficacy of the Chinese Southwest Oncology Group (CSWOG) regimen, a precise bridging strategy, in patients with r/r DLBCL who received commercial CAR-T therapy. All patients underwent re-biopsy to assess the expression of biomarkers including CD19, CD20, CD22, CD30, CD38, CD79b, ALK, BCL2, PD-L1, and Ki-67 to identify potential treatment targets. Only patients with positive CD19 expression were eligible for inclusion. Patients received a precise salvage therapy consisting of non-cross-resistant chemotherapy and targeted immunotherapy guided by the re-biopsy results. Only those who responded to salvage therapy proceeded to leukapheresis and received an additional cycle of salvage immunochemotherapy. Non-responders were switched to an alternative precise regimen. Based on our previous findings that low-dose radiation enhances CAR-T cell recruitment and increases antigen exposure, all patients received involved-field low-dose radiation prior to CAR-T cell infusion. Patients treated with axicabtagene ciloleucel (axi-cel) in a real-world setting served as the control group. **Results:** Seventy-one patients with r/r DLBCL received the CSWOG bridging regimen, while 101 Chinese patients treated with axi-cel in a real-world setting served as the control group. In the CSWOG group, 63 patients (88.7%) responded to salvage precise immunochemotherapy, while 8 patients (11.3%) who did not respond were switched to alternative immunochemotherapy regimen. All patients in the CSWOG group received a median dose of 24.0 Gy involved-field radiation. After CAR-T infusion, the best overall response (BOR) rate was 84.5% in CSWOG group, with 74.6% achieving complete response (CR) and 9.9% partial response (PR). The BOR rate in control group was 83.2%, with 58.4% achieving CR and 24.8% achieving PR. After a median follow-up of 15.3 months, the 2 - year overall survival (OS) and progression-free survival (PFS) rates were 84.1% and 75.2%, respectively, in the CSWOG group, compared to 70.0% and 49.8% in the control group. Grade 3 or higher cytokine release syndrome occurred in 9.8% of the CSWOG group and 15.2% of the control group. Neurologic events of any grade were observed in 12.8% of the CSWOG group and 16.2% of the control group. Among the 4 CSWOG patients with neurologic events, all were managed with steroids and resolved; however, all 4 relapsed. **Conclusions:** Our results show that combining precise immunochemotherapy with low-dose radiation optimizes CAR-T therapy, supporting its global implementation. Clinical trial information: ChiCTR2100043613. Research Sponsor: National Natural Science Foundation of China; 82470237.

7028 Poster Session

Postmarketing safety profile of chimeric antigen receptor (CAR) T cell therapies in diffuse large B-cell lymphoma (DLBCL): Analysis of real-world (RW) AE reporting from the FDA Adverse Event Reporting System (FAERS). First Author: Matthew Alexander Lunning, University of Nebraska Medical Center, Omaha, NE

Background: CAR T cell therapies have emerged as effective treatment options with deep and durable responses in patients (pt) with DLBCL. Although efficacy and safety data from clinical trials are usually used for drug approval, potentially relevant AEs may not be captured due to limited study follow-up and population. Surveillance databases like FAERS can further characterize safety of therapeutic biologics by capturing RW AEs. We aimed to characterize the safety profile of CAR T cell therapies in the DLBCL population using FAERS. **Methods:** FAERS was used to identify AEs in pt with DLBCL treated with 2 commercially available CAR T cell therapies, lisocabtagene maraleucel (liso-cel) or axicabtagene ciloleucel (axi-cel). AEs of interest were cytokine release syndrome (CRS), neurological events (NE), hemophagocytic lymphohistiocytosis (HLH), cytopenia, and infections. The primary analysis examined all case reports from Q4 2017 to Q3 2024, the latest available quarterly release. Two sensitivity analyses adjusting for differences in follow-up after FDA approvals were performed: (1) AEs reported any time after liso-cel FDA approval (02/05/2021), which is later, and (2) AEs reported within 2 years of FDA approval for each CAR T cell therapy. Disproportionality analysis compared relative frequency of AEs. Reporting odds ratios (ROR) and 95% CIs were used to identify significant differences in AEs between treatments (ie, 95% CI did not cross 1). An ROR $>$ 1 indicated higher event frequency for axi-cel vs liso-cel. **Results:** From Q4 2017 to Q3 2024, 3251 AE reports in pt with DLBCL were associated with liso-cel (n = 232) or axi-cel (n = 3019). In disproportionality analysis, axi-cel had significantly higher ROR for CRS (1.48; 95% CI, 1.13–1.93), NE (1.61; 1.23–2.11), and cytopenia (2.45; 1.41–4.24) than liso-cel. Considering limitations of underreporting and incomplete information inherent in FAERS, no statistically significant difference can be inferred for infections (1.36; 95% CI, 0.75–2.48), seizures (1.36; 0.42–4.40), and HLH (1.18; 0.36–3.83). Observed trends were consistent in both sensitivity analyses, where reporting frequencies remained significantly higher with axi-cel vs liso-cel for CRS (1.60; 95% CI, 1.17–2.17 and 2.02; 1.37–2.98), NE (1.59; 1.18–2.15 and 2.04; 1.39–3.00), and cytopenia (2.00; 1.11–3.60 and 2.60; 1.24–5.46), after adjusting for differences in follow-up durations. **Conclusions:** This retrospective analysis of FAERS, using spontaneous safety reporting data after approval and broader population beyond clinical trials, demonstrated a favorable RW safety profile for liso-cel vs axi-cel for CRS, NE, and cytopenia. These findings provide valuable insights into the safety profile of CAR T cell therapies in DLBCL to inform clinical decision-making and pt management. Research Sponsor: This study was funded by Bristol Myers Squibb. Writing and editorial assistance were provided by Emily Burke, PhD, CMPP, of The Lockwood Group (Stamford, CT, USA), funded by Bristol Myers Squibb.

7029 Poster Session

Pregnancy and infant outcomes post–CD19-directed CAR-T therapy: Tisagenlecleucel (tisa-cel) and/or huCAR19 (CTL119). First Author: Stephan A. Grupp, Division of Oncology, Children's Hospital of Philadelphia, Philadelphia, PA

Background: Data on pregnancy post–CD19-directed CAR-T therapy for B-cell malignancies are limited (Ligon et al). There is a theoretical risk of cross-placental transmission of CAR-T cells in female patients (pts) during pregnancy. The impact of CAR-T on fertility, conception or pregnancy in pts is uncertain. High-dose chemotherapy/radiation has a high infertility risk (Lowe et al). Early use of CAR-T may increase the chance of fertility preservation. **Methods:** In this retrospective cohort analysis, a cumulative search in the Novartis Global Safety database for all CAR-T products, up to Jan 2025 was conducted using the Standard MedDRA Query: Pregnancy and neonatal topics (narrow). Transgene levels were monitored in clinical trial pts for all indications. Ongoing B-cell aplasia (BCA)/deficiency or intravenous immunoglobulin (IVIG) utilization was used as a surrogate marker for persistence of tisa-cel in pts with acute lymphoblastic leukemia (ALL). Pregnancy outcomes were collected via pregnancy and infant forms at birth and 3 and 12 month (mo), subject to reporter and/or patient consent. **Results:** Sixteen events of tisa-cel or CTL119 exposure during pregnancy were reported. Elective termination of pregnancy was noted in 2 cases. Pathology review of placental/fetal parts in one of these cases was unremarkable. One case did not have consent for follow-up (FU) and another one did not have newborn status. One pregnancy was ongoing with normal pregnancy to date and delivery expected in Q2 2025 (commercial tisa-cel). Eleven pregnancies resulted in live birth of 12 healthy infants (1 pregnancy with twins). Further details on these 11 pregnancies are provided in Table 1. Persistent CAR transgene levels in the clinical trial pts with ALL have shown concordance with the use of IVIG/ongoing BCA/deficiency (data not shown). One infant was enrolled to long-term FU and tested negative for huCAR19 transgene on day 7, though the number of B cells (80 cells/μL) and IgG levels were slightly low at birth. Among 3 commercial tisa-cel pts with reported pregnancies, 2 had ongoing IVIG during pregnancy and 1 at the time of delivery. **Conclusions:** Pregnancy and delivery of a healthy infant after CAR-T therapy is possible. The use of CAR-T therapy may improve chances of healthy pregnancy by avoiding the risks for infertility associated with high-dose chemotherapy and/or radiation. Capturing data on all pregnancies post CAR-T remains an important goal. Research Sponsor: Novartis Pharma AG.

Pregnancy and infant status post CAR-T.

Pts	1 *	2*	3	4	5	6	7	8	9	10	11
Indication	ALL					ALL				B-NHL	FL
Product	Tisa-cel*		CTL119					CTL019			
Approx. age at conception (y), sex	22F	25M	20F	30M	29F	39M	25M	35M	28F	31F	M
Approx. time from CAR-T to conception	1y	3y	3y	6.5y	8y	1.5y	7mo	2.5y	6y 9mo	1y 7mo	1y 3mo
Latest FU of healthy infant(s)	2y	4mo	22mo	18mo	Birth	1y	21mo	Birth (twins)	Birth	Birth	1y

*Commercial tisa-cel.
B-NHL, B-cell non-Hodgkin's lymphoma; FL, follicular lymphoma; y, years.

7030 Poster Session

Effect of prophylactic corticosteroids on toxicities and outcomes in CAR T-cell therapy: A cohort study. First Author: Anuja Vidyadhar Abhyankar, Roswell Park Comprehensive Cancer Center, Buffalo, NY

Background: Common toxicities associated with infusion of Chimeric antigen receptor T-Cell (CAR T-cell) therapy include cytokine release syndrome (CRS) and immune-effector-cell-associated neurotoxicity syndrome (ICANS). While early steroid use has correlated with a reduced risk of high-grade CRS and ICANS, there is conflicting data regarding its impact on CAR-T efficacy. We aim to study the impact of prophylactic steroid use on toxicities and outcomes at our institution. **Methods:** We performed a single-center comparative analysis between two patient cohorts at higher risk of CRS and ICANS based on elevated inflammatory markers, (ferritin $\geq$400 ng/mL and CRP $\geq$4 mg/dL). One cohort received prophylactic dexamethasone 10 mg on days 0,1, and 2. Univariate statistics were calculated using X2, Fisher's exact tests, and ANOVAs, where appropriate. Kaplan Meier was used to estimate overall survival (OS) and progression-free survival (PFS) and compared using the log-rank test. **Results:** Out of 63 patients with high ferritin and CRP, 10 patients received prophylactic steroids (Group PS) and 53 patients did not (Group NPS). In the NPS group, 46 patients had a primary diagnosis of non-Hodgkin lymphoma and 7 had a diagnosis of multiple myeloma. In the PS group, 9 had non-Hodgkin lymphoma and 1 had multiple myeloma. The median age at CAR-T was 58 years in PS and 64 years in NPS group (p=0.48). The rate of CRS grade $\geq$3 was higher in the NPS group compared to the PS group, (47.2 vs 20%, p=0.26) whereas ICANS grade $\geq$3 was similar (32% in NPS and 30% in PS group). More patients achieved a complete response in the PS group (60%) compared to the NPS group (30.2%). The1-year PFS was higher in PS group compared to NPS (60% vs 28%,p=0.08) which was also reflected in the 1-year OS (70% vs 38%, p=0.10). At a median follow-up of 22 months, 70% patients were alive in the PS group compared to 28.3% patients in the NPS group. **Conclusions:** Our study shows lower rates of CRS and a pattern towards higher rates of complete remission and survival benefit in patients undergoing CAR T-cell therapy receiving prophylactic steroids. The data must be interpreted with caution given the small sample size, but it warrants the need for future studies. Research Sponsor: None.

Outcomes of patients by prophylactic steroid status (n=63).

Parameter	NPS (n=53)	%	PS (n=10)	%	p-value*
Best Response					0.42
Complete Response	16	30.2	6	60.0	
Partial Response	4	7.5	1	10.0	
Stable Disease	2	3.8	0	0.0	
Progressive Disease	24	45.3	3	30.0	
NE*	7	13.2	0	0.0	
Disease progression					0.30
No	25	47.2	7	70.0	
Yes	28	52.8	3	30.0	
Time to disease progression, days, median (range)	66.5	5-996	96	92-158	0.75
Median follow-up among survivors (n=22), months (range)	46.5	9-73.8	11.4	8.3-24.2	<0.01
Alive	15	28.3	7	70.0	
Dead	38	71.7	3	30.0	
2nd Cancer	1	2.6	1	33.3	
CNS failure	2	5.3	0	0.0	
COVID	1	2.6	0	0.0	
Disease	23	60.5	2	66.7	
Hemorrhage	1	2.6	0	0.0	
Infections	9	23.7	0	0.0	
Unknown	1	2.6	0	0.0	

NE*= not included in analysis.

7031 Poster Session

Phase I study to evaluate the safety and efficacy of switchable CAR-T cell therapy with FY001 and CART001 in patients with refractory CD20-positive B-cell non-Hodgkin lymphoma (EPOC1803). First Author: Junichiro Yuda, Department of Hematology and Experimental Therapeutics, National Cancer Center Hospital East, Kashiwa, Japan

Background: CD19-targeted CAR-T cell therapy has shown remarkable efficacy against relapsed/refractory B-cell non-Hodgkin lymphoma (r/r B-NHL). However, clinical challenges persist, including relapse due to CD19 antigen loss and severe immune-related adverse events such as cytokine release syndrome (CRS) and immune effector cell-associated neurotoxicity syndrome (ICANS). We developed a combination therapy using FITC-labeled rituximab (FY001) with FITC-recognizing CAR-T cells (CART001). FY001 binds to CD20 on lymphoma cells, and CART001 activation occurs exclusively through FY001, enabling fine-tuning of anti-tumor activity while minimizing adverse events. This switchable CAR-T can be applied to broader r/r B-NHL cases, including elderly or frail patients. In addition, for patients with target antigen loss, FITC-labeled antibodies targeting different antigens can activate residual CART001 to combat relapsed lymphoma cells. We conducted a phase I trial to assess the safety and efficacy of the switchable CAR-T. **Methods:** This investigator-initiated phase I trial enrolled patients with r/r B-NHL, to evaluate adverse event, including dose-limiting toxicities (DLTs), as the primary endpoint. The trial design specified evaluating DLTs in 3 initial participants; zero DLTs prompted the addition of 3 expansion cohort participants; one DLT necessitated 3 additional participants for DLT evaluation; two or more DLTs led to enrollment discontinuation. Participants underwent lymphocyte-depleting chemotherapy (LDC) until the day before FY001 administration. Following LDC, participants received intravenous FY001 administration at 2 mg/kg, and CART001 infusion at 1×10^6 cells/kg on the subsequent day. **Results:** Between March 2020 and March 2022, 6 participants received FY001 and CART001 treatment, in DLT evaluation (n=3) and expansion (n=3) cohorts. Participant ages ranged from 68-79 years, with 2-8 prior therapy lines; five had diffuse large B-cell lymphoma and one had follicular lymphoma. In all cases, no DLTs occurred. Observed adverse events, none of which were determined to be causally related to FY001 or CART001, included 1 case of Grade 4 blood creatine phosphokinase elevation (16.7%) and 1 case of Grade 3 anemia (16.7%). Notably, no CRS or ICANS cases were reported. The best overall response rate reached 100% (95% CI: 54.1%-100%), comprising 4 complete responses (CR) and 2 partial responses (PR). As of January 2025, 2 patients continue maintaining CR (57 and 47 months). **Conclusions:** The switchable CAR-T demonstrated excellent tolerability and 100% response rate with long-term remission in r/r B-NHL patients. These promising results warrant further clinical development of this therapy. Clinical trial information: jRCT1080224690. Research Sponsor: Advanced Research and Development Programs for Medical Innovation.

7032 Poster Session

Impact of pre-lymphodepletion (pre LD) and day 30 (M1) immune cell counts on outcomes of CAR T therapy in patients with relapsed/refractory (R/R) large B-cell lymphoma (LBCL). First Author: Suheil Albert Atallah-Yunes, Division of Hematology, Mayo Clinic, Rochester, MN

Background: The impact of immune cell counts pre LD and during immune reconstitution on CAR T therapy outcomes is poorly understood. We investigated the association between CD4, CD8 and NK cell counts and CAR T therapy outcomes in patients with LBCL. **Methods:** Retrospective study of R/R LBCL patients who received CAR T cells between 2016-24 at Mayo Clinic, Rochester, were included in this analysis. Peripheral blood CD4, CD8 and NK counts were measured pre LD and at M1 post CAR T infusion. The receiver operating characteristic (ROC) curve was used to determine the optimal cutoff for pre LD and M1 immune cells to predict patients who were alive and in remission at 6 months (M6) post CAR T infusion. Patients who progressed or were lost to follow up prior to day 30 were excluded from M1 ROC analysis. **Results:** Of 140 patients, 81 were alive and in remission at M6 (Group A), while 59 had relapse or death (Group B). Axicabtagene ciloleucel was the CAR T product given in 81% of patients (114/140). Median pre LD CD4 counts were significantly lower in Group B compared to group A (143 vs 280 cells/μL, p = 0.001). No significant difference was observed in median pre LD CD8 counts (205 vs 221 cells/μL, p = 0.8). ROC analysis identified an optimal pre LD CD4 count of 124.5 cells/μL for M6 alive+remission. Lower pre LD CD4 counts ($<$124.5) predicted worse progression free survival (PFS) in univariate (HR = 3.02, 95% confidence interval [CI]: 1.73–5.27, p$<$ 0.01) and multivariable analysis (MVA) adjusted for IPI and the number of prior lines (aHR = 2.54, 95% CI: 1.39–4.62, p$<$ 0.01).Lower pre LD CD4 counts also predicted inferior overall survival (OS) in MVA (aHR = 2.27, 95% CI: 1.08–4.77, p = 0.03). (Table 1) On day 30 landmark analysis, ROC identified M1 optimal CD4 count of $\geq$ 99.5 cells/μL to be associated with a trend toward superior PFS (P=0.09), but not OS (p=0.90) in MVA. Median pre LD NK cell counts were significantly lower in Group B (73 vs 98 cells/μL, p = 0.04). ROC analysis identified an optimal pre LD NK count of 151 cells/μL for M6 alive + remission. Lower pre LD NK counts ($<$151) predicted worse PFS, both on univariate (HR = 4.17, 95% CI: 1.29–13.47, p = 0.02) and MVA (aHR = 4.64, p$<$ 0.01). The lower pre LD NK cell count group had worse OS in MVA (aHR = 5.69, 95% CI: 1.16–28.1, p = 0.01). (Table 1) On D30 landmark analysis, M1 NK cell count of $\geq$ 128.5 cells/μL was associated with a trend toward superior PFS (P=0.08), but not OS (p=0.30) in MVA. **Conclusions:** Pre LD CD4 and NK cell counts are significantly associated with PFS and OS post CAR T therapy in patients with R/R LBCL. Pre-treatment immune subset levels may identify patients at higher risk of relapse or death after CAR-T therapy. Research Sponsor: None.

Groups	Median PFS	2 Year PFS	Median OS	2 Year OS
CD4 $\geq$124.5 cells/μL (N=75)	NR	58%	3.31 years	67%
CD4 <124.5 cells/μL (N=30)	2.2 months	22%	1.59 years	45%
NK $\geq$151 cells/μL (N=17)	NR	77%	NR	84%
NK <151 cells/μL (N=82)	10.6 months	44%	3.31 years	62%

7033 **Poster Session**

Influence of pre-existing autoimmune disease on outcomes in patients treated with CD-19 targeting CAR-t cell therapy for lymphoma: A retrospective propensity score matched study utilizing TriNetX. First Author: Shanawar Ali Waris, West Virginia University, Department of Internal Medicine, Morgantown, WV

Background: There is a lack of studies in the literature about the impact of baseline autoimmune diseases (AD) on outcomes in patients with lymphoma treated with CD-19 targeting-chimeric antigen receptor T-cell (CAR-T) therapy. This retrospective propensity score matched study aims to provide real-world evidence to understand the impact of pre-existing AD on outcomes in this population. **Methods:** This multicenter retrospective study included 504 patients with pre-existing AD diagnoses prior to receiving treatment with CD-19 targeting CAR-T therapy for lymphoma and 504, 1:1 propensity-score matched controls, without pre-existing AD, in the TriNetX Network. The outcomes analyzed were 5-year mortality, development of cytokine release syndrome (CRS), development of immune effector cell-associated neurotoxicity syndrome (ICANS), all cause hospitalization, ICU level care, risk of infection, and steroid use. Kaplan-Meier analysis, hazard ratios (HR), risk ratios (RR), and 95% confidence intervals (CI) were used to assess the primary outcomes. **Results:** Patients with pre-existing AD diagnosis were not at a statistically significant increased risk of mortality when compared to non-AD patients (HR = 1.10 [95% CI, 0.90-1.36]; P= 0.081). Both all-cause hospitalization (RR, 1.07 [95% CI, 1.03-1.10]) and ICU level of care (RR, 1.49 [95% CI, 1.19-1.84]) were higher in the pre-existing AD group when compared to non-AD patients. There was an increased risk for development of CRS in the AD group when compared to the non-AD group (RR, 1.17 [95% CI, 1.06-1.28]). There was no significant difference in the development of ICANs between the AD and non-AD group (RR, 1.10 [95% CI, 0.88-1.37]). There was an increased risk of infection amongst the AD group when compared to the non-AD group (RR, 1.48 [95% CI, 1.32-1.66]). Steroid use was higher in the pre-existing AD group (RR, 1.22 [95% CI, 1.09-1.38]). There was no statistically significant difference in rates of subsequent bone marrow transplant in patients with the pre-existing AD compared to the non-AD group (RR, 1.17 [95% CI, 0.93 -1.47]). **Conclusions:** CD19 CAR T- therapy has emerged as a promising therapeutic option for patients with AD, given its capacity to target and eliminate B-cells, which are vital in the pathogenesis of many AD. To our knowledge, this study represents the largest examination of the real-world impact of a baseline AD on clinical outcomes in patients undergoing CD19-targeted CAR T-cell therapy for lymphoma. Our findings indicate that pre-existing AD is associated with an increased risk of hospitalization, ICU level of care, CRS, and infections, without significantly affecting survival probability. Clinical trials are ongoing to evaluate the efficacy and safety of CAR T therapy in patients with AD. Research Sponsor: None.

7034 **Poster Session**

Comparing outcomes of lymphoma-directed CAR T-cell therapy in patients with and without HIV: A retrospective cohort study from a global health research network. First Author: Cassandra Reimonn, UMass Chan Medical School, Department of Internal Medicine, Worcester, MA

Background: Since its introduction into the world of oncology, chimeric antigen receptor (CAR) T-cell therapy has revolutionized the treatment of relapsed and refractory lymphomas. However, patients with HIV (PWH) have historically been excluded from CAR T-cell studies. This is likely due to assumed decreased efficacy and increased infection-related morbidity and mortality due to their immunocompromised status. This lack of understanding contributes to healthcare disparities, resulting in fewer individuals from this vulnerable population receiving this innovative treatment. Thus, this study aims to compare the 1-year survival and safety outcomes of CAR T-cell therapy for Hodgkin and Non-Hodgkin lymphomas in adult patients with and without HIV. **Methods:** Using TriNetX global health research network, we identified 35 PWH who received lymphoma-directed CAR T-cell therapy. For the control group, we identified 2,575 patients without HIV who received lymphoma-directed CAR T-cell therapy. We then conducted a log-rank test and calculated relative risks (RR) to compare outcomes in 1-year overall survival (OS) and incidence of cytokine release syndrome (CRS), immune effector cell-associated neurotoxicity syndrome (ICANS), bacteremia and sepsis. **Results:** In our group of PWH, we observed a mean age of 56.1+/-12.6 years at time of CAR T-cell therapy, compared to a mean age of 63.0+/-13.0 years in our group of patients without HIV. RR analysis demonstrated significantly increased 1-year risk for development of sepsis (RR=1.75, 95%CI 1.03, 2.97) and bacteremia (RR=2.41, 95%CI 1.41, 4.12) in our group of PWH. However, it showed no statistically significant differences in risk for development of CRS (RR=1.11, 95%CI 0.788, 1.57), ICANS (RR=1.23, 95%CI 0.723, 2.08), or death from any cause (RR=1.43, 95%CI 0.873, 2.35). Log rank test revealed no significant differences in 1-year OS (p=0.208) or incidence of CRS (p=0.567), ICANS (p=0.223), bacteremia (p=0.561) or sepsis (p=0.225). Median OS was not reached in either group. **Conclusions:** This data supports that PWH may be at increased risk of infectious complications, but not increased mortality, following lymphoma-directed CAR T-cell therapy. While this study is limited by a small cohort size, its results support the need to include PWH in future clinical trials to better understand the effect of HIV infection on CAR T-cell treatment outcomes. Research Sponsor: None.

7035 **Poster Session**

Risk of invasive fungal infections in patients with chronic lymphocytic leukemia treated with Bruton tyrosine kinase inhibitors: A TriNetX-based retrospective cohort study from 2000-2025. First Author: Raza Aslam, Nishtar Medical University, Multan, Pakistan

Background: Chronic lymphocytic leukemia (CLL) is associated with immunosuppression, and Bruton tyrosine kinase inhibitors (BTKis) may further increase the risk of invasive fungal infections (IFIs). This retrospective study evaluates the trends in BTKi use and the associated risk of IFIs among CLL patients in a real-world setting. **Methods:** We conducted a retrospective cohort study using the TriNetX database, analyzing U.S. CLL patients diagnosed between January 2000 and January 2025. Propensity score matching (1:1) by age, comorbidities, and immunosuppressive therapy was performed. Outcomes included invasive fungal infections (candidiasis, aspergillosis, cryptococcosis, and pneumocystis jirovecii pneumonia), assessed using Kaplan-Meier survival analysis and risk measures. **Results:** Among 10,736 patients treated with BTK inhibitors and 80,446 controls, the median follow-up was 881 and 868 days, respectively. Patients in the BTK cohort had a mean age of 75 ± 10 years, predominantly male (62.21%) and primarily White (76.24%). In contrast, the control cohort had a mean age of 76 ± 12 years, with 55.87% male patients and 73.12% identified as White. On the other hand, the risk of invasive candidiasis was significantly lower in the BTK cohort (RR: 0.364, 95% CI: 0.193–0.686), as was the risk of invasive aspergillosis (RR: 0.532, 95% CI: 0.289–0.98). Pneumocystis jirovecii pneumonia (PJP) rates were comparable between the cohorts (RR: 0.961, 95% CI: 0.497–1.855). Cryptococcosis was detected in 0.001% of the BTKi group but did not occur in the control cohort; this variation, however, did not reach statistical significance (P = 0.823). **Conclusions:** This retrospective study reveals the complex infection profile associated with BTK inhibitor use in CLL patients. Treatment with BTK inhibitors was linked to a significant decrease in the occurrence of invasive candidiasis and aspergillosis in the BTK cohort, and rates of Pneumocystis jirovecii pneumonia (PJP) and Cryptococcus were similar between groups. Although the absolute rates of fungal infections remain low, these findings underscore the importance of identifying at-risk patients to guide preventive and cost-effective interventions. Further research is needed to differentiate infection risks across specific BTK inhibitors and develop tailored management strategies to optimize patient outcomes. Research Sponsor: None.

7036 **Poster Session**

Final analysis of fixed-duration ibrutinib + venetoclax for chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma (SLL) in the phase 2 CAPTIVATE study. First Author: Paolo Ghia, Università Vita-Salute San Raffaele and IRCCS Ospedale San Raffaele, Milano, Italy

Background: First-line ibrutinib (Ibr) + venetoclax (Ven) treatment for CLL/SLL was tested in the phase 2 CAPTIVATE study, including minimal residual disease (MRD)–guided randomized discontinuation (MRD cohort) and Fixed Duration (FD) cohorts. We report final analysis results for patients (pts) treated with FD Ibr+Ven in the FD cohort and MRD cohort placebo arm. **Methods:** Pts $\leq$70 y with previously untreated CLL/SLL received 3 cycles of Ibr, then 12 cycles of Ibr+Ven (Ibr, 420 mg/d orally; Ven, 5-wk ramp up to 400 mg/d orally), up to 13 cycles in the MRD cohort placebo arm. On-study retreatment included single-agent Ibr; FD cohort pts with progressive disease (PD) $>$2 y after end of treatment (EOT) could be retreated with FD Ibr+Ven. **Results:** 202 pts completed FD Ibr+Ven (FD cohort, n=159; MRD cohort placebo arm, n=43). With median follow-up of 68.9 mo (range, 0.8–83.9), 5.5-y PFS and OS rates (95% CI) were 66% (58–72) and 97% (93–99), respectively. 5.5-y PFS rates (95% CI) in pts without and with del(17p)/mutated *TP53* were 70% (62–76) and 36% (17–55), respectively. In pts with unmutated IGHV, 5.5-y PFS was 55% (45–64): 63% (49–74) in pts without, and 44% (28–60) in pts with, concomitant del(17p)/mutated *TP53*/complex karyotype. The corresponding rates for pts with mutated IGHV were 79% (68–87), 85% (71–93), and 62% (34–81). Undetectable MRD (uMRD4; $<10^{-4}$ by flow cytometry) was achieved in peripheral blood (PB) in 54% of pts at C7 and 69% at EOT, and in bone marrow in 69% of pts at EOT. 5.5-y PFS rates (95% CI) were higher in pts with uMRD4 in PB at EOT (75% [67–82]) vs those with MRD (47% [33–59]). 64 pts had PD after completion of FD Ibr+Ven. 5.5-y freedom from next-line treatment was 73% (95% CI 66–79). Of 40 pts with available samples at PD to date, 1 had an acquired subclonal mutation in *BCL2* of unclear significance (A113G, VAF 8.3%); none had acquired resistance-associated mutations in *BTK* or *PLCG2*. 36 pts initiated retreatment with Ibr (n=25) or Ibr+Ven (n=11). With 28.4 mo median follow-up on Ibr retreatment (range, 3.7–59.1), ORR was 76% (best response: 1 CR; 1 nodular PR; 17 PR; 4 SD; 1 PD [Richter transformation]; 1 no assessment); 2-y PFS and OS rates from the start of retreatment were 91% and 96%, respectively. With 15.2 mo median follow-up on Ibr+Ven retreatment (range, 7.4–29.3), ORR was 82% (best response: 1 CR; 8 PR; 2 SD); 1-y PFS and OS rates from the start of retreatment were both 100%. Second malignancies occurred in 24 pts across the entire study period, including 12 initial treatment and 4 retreatment TEAEs. **Conclusions:** Ibr+Ven is an all-oral, once-daily, chemotherapy-free FD regimen for first-line treatment of CLL/SLL that continues to provide durable PFS and OS with long-term follow-up, including in pts with high-risk genomic features. Ibr-based retreatment provided durable responses in pts needing subsequent therapy after completion of FD Ibr+Ven. Clinical trial information: NCT02910583. Research Sponsor: Pharmacyclics LLC, an AbbVie Company.

7037 Poster Session

Propensity score (PS) comparison between lisocabtagene maraleucel (liso-cel) plus ibrutinib combination therapy (combo) and liso-cel monotherapy (mono) cohorts from TRANSCEND CLL. First Author: William G. Wierda, The University of Texas MD Anderson Cancer Center, Houston, TX

Background: TRANSCEND CLL 004 (NCT03331198) is a phase 1/2, open-label, nonrandomized, multicohort study in adult patients (pt) with R/R chronic lymphocytic leukemia/small lymphocytic lymphoma with liso-cel mono and liso-cel + ibrutinib combo cohorts. Given the study design, we performed PS matching/weighting to adjust for differences in key covariates between cohorts to compare efficacy and safety. **Methods:** Here, PS is the probability of receiving combo given the covariates and estimated by logistic regression. Covariates were hemoglobin, LDH, number of prior therapies, platelets, prior BTKi + venetoclax exposure, R/R on prior BTKi, and bulky disease for efficacy; and ALC, bulky disease, CRP, ferritin, and number of prior therapies for safety. PS balancing methods were optimal 1:1 matching, average treatment effect for treated pts (ATT) full matching, and ATT inverse probability of treatment weighting (IPTW). Efficacy endpoints were response (CR rate, ORR) and time to event endpoints (DOR, PFS, OS). Safety endpoints were proportions of pts with any-grade (gr)/gr $\geq$ 3 cytokine release syndrome (CRS) and investigator-identified neurological events (NE). **Results:** Fifty-one and 88 efficacy-evaluable pts were treated at dose level 2 (100×10^6 CAR$^+$ T cells) in the combo and mono cohorts, respectively. Before matching/weighting on PS, odds of achieving CR and overall response were statistically significantly higher for combo (Table). DOR did not differ between cohorts. For PFS and OS, HRs were lower with combo vs mono (not statistically significant [NS]). Odds of gr $\geq$ 3 CRS/NE were lower with combo vs mono (NS). After matching/weighting, odds of CR (except IPTW ATT) and overall response remained statistically significantly higher in combo. HRs for PFS and OS and ORs for gr $\geq$ 3 CRS/NE were numerically lower with combo vs mono (NS, except IPTW ATT for PFS). HRs for DOR were less but close to HR of 1. **Conclusions:** The liso-cel + ibrutinib combo demonstrated a trend for better efficacy and safety vs liso-cel mono, with statistically significant differences for CR rate and ORR. Clinical trial information: NCT03331198. Research Sponsor: This study was funded by Bristol Myers Squibb. Writing and editorial assistance were provided by Nikola Vojtov, PhD, of The Lockwood Group (Stamford, CT, USA), funded by Bristol Myers Squibb.

Efficacy and safety outcomes: combo vs mono.

	No adjustment	ATT optimal 1:1	IPTW - ATT
CR rate, OR (95% CI)	2.07* (1.01–4.28)	2.40* (1.05–5.66)	2.00 (0.89–4.61)
ORR, OR (95% CI)	3.96* (1.68–10.51)	3.43* (1.33–9.71)	4.18* (1.63–11.78)
DOR, HR (95% CI)	0.98 (0.51–1.87)	0.88 (0.43–1.78)	0.96 (0.50–1.85)
PFS, HR (95% CI)	0.62 (0.37–1.02)	0.61 (0.35–1.05)	0.59* (0.35–0.98)
OS, HR (95% CI)	0.70 (0.38–1.28)	0.73 (0.37–1.43)	0.66 (0.36–1.22)
CRS, OR (95% CI)	0.63 (0.26–1.56)	0.67 (0.24–1.84)	0.69 (0.24–1.88)
Gr ≥ 3 CRS, OR (95% CI)	0.23 (0.01–1.35)	0.49 (0.02–5.28)	0.26 (0.01–1.94)
NE, OR (95% CI)	0.84 (0.41–1.68)	0.92 (0.40–2.08)	1.10 (0.48–2.52)
Gr ≥ 3 NE, OR (95% CI)	0.56 (0.19–1.45)	0.58 (0.16–1.89)	0.68 (0.19–2.30)

*Statistically significant difference at 5% level.

7038 Poster Session

Preliminary safety and efficacy data of ICP-248, a novel BCL2 inhibitor, in patients with relapsed or refractory B-cell malignancies. First Author: Shuhua YI, Institute of Hematology and Blood Diseases Hospital, Chinese Academy of Medical Sciences, Tianjin, China

Background: BCL2, a critical protein regulator of the apoptotic pathway, highly expressed in various malignancies, including B-cell non-Hodgkin lymphomas (B-NHLs). The only approved BCL2 inhibitor, Venetoclax, has been approved for the treatment of chronic lymphocytic leukemia/small cell lymphoma (CLL/SLL) or acute myeloid leukemia (AML). However, hematologic toxicities and tumor lysis syndrome (TLS) remain as safety challenges in clinical practice. ICP-248 was developed as a potent and highly selective BCL2 inhibitor. Preclinical studies have demonstrated favorable pharmacokinetics profile and excellent safety profile. **Methods:** ICP-CL-01201 is an ongoing phase I study (NCT05728658) including dose escalation and dose expansion parts. Safety and tolerability of ICP-248 was evaluated from target doses of 50 mg to 200 mg. Patients receive oral treatment every day until disease progression or intolerable toxicities. Eligible patients include those aged 18-80 years, diagnosed with CLL/SLL and B-NHLs who are in relapsed or refractory disease. Key exclusion criteria include CNS involvement, resistance to BCL2 inhibitors and clinically significant cardiovascular disease. Efficacy was evaluated according to the Lugano 2014 or iwCLL 2018 criteria. **Results:** As of 12 Dec 2024, 55 patients were enrolled in the study: 18 in dose escalation and 37 in dose expansion. 24 patients were CLL/SLL, 26 patients were mantle cell lymphoma (MCL), 5 patients were other B-NHLs. The median age was 65 years, and 72.7% of patients were refractory disease and 56.4% of the patients were previously treated with BTK inhibitors. The median prior therapeutic line was 2 (1-8). ICP-248 was well tolerated through all dose levels, with no dose-limiting toxicities (DLTs) observed, and maximum tolerated dose (MTD) not reached. Toxicity leading to drug discontinuation and death was not observed. Most of TEAEs were in grade 1-2. The most frequent TEAEs were hematologic AEs including neutropenia, leukopenia, and thrombocytopenia. Serious adverse events (SAEs) were reported in 16.4% patients. As cutoff date, 20 CLL/SLL and 19 MCL patients treated with ICP-248 dose ≥100 mg had at least one response assessment: ORR was 80% and CRR was 15% in r/r CLL/SLL patients, while those for r/r MCL patients were 78.9% and 42.1% respectively. uMRD was reported in 10% CLL/SLL and 15.8% MCL patients. In 10 patients with previous BTK inhibitor refractory MCL patients (2 blastoid or pleomorphic subtype and median 3.5 prior treatment lines), the ORR was 80% and CRR was 30%; in 11 patients with previous BTK inhibitor failure CLL/SLL, the ORR was 81.8% and CRR was 18.2%. **Conclusions:** The preliminary results of ICP-248 monotherapy suggests a well-tolerated safety profile and an exciting efficacy with dose-dependent effect in BTK failed, heavily treated, relapsed or refractory B-cell malignancies. Clinical trial information: NCT05728658. Research Sponsor: None.

7039 Poster Session

Comparison of outcomes for patients (pts) with R/R chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma (SLL) previously treated with Bruton tyrosine kinase inhibitor (BTKi) and venetoclax from the TRANSCEND CLL 004 study versus a matched cohort of real-world (RW) pts. First Author: William G. Wierda, The University of Texas MD Anderson Cancer Center, Houston, TX

Background: Pts with R/R CLL/SLL who failed BTKi and venetoclax have limited treatment (tx) options and poor prognoses. FDA approval of lisocabtagene maraleucel (liso-cel) for R/R CLL/SLL was based on positive results from TRANSCEND CLL 004 (NCT03331198), a single-arm trial. We assessed relative efficacy of liso-cel vs standard of care (SOC) by identifying (or assembling) an external comparator cohort of pts treated in a RW setting. **Methods:** Pts from TRANSCEND CLL 004 and a matched RW cohort were analyzed. Eligible pts were ≥ 18 y with CLL/SLL, had ≥ 2 prior lines of therapy (pLoT), including a BTKi and venetoclax, and started subsequent tx for CLL/SLL. SOC pts were selected from de-identified datasets (Flatiron [1993–2023], COTA [2000–2023], and ConcertAI [1997–2022]). TRANSCEND CLL 004 eligibility criteria were applied as applicable. Liso-cel pts were eligible trial participants treated with liso-cel and efficacy-evaluable. Endpoints were ORR, PFS, and OS. Inverse probability of tx weighting (IPTW) and regression model were used to balance pt characteristics between cohorts, including age, sex, race, time from initial diagnosis, Rai stage, bulky disease, ECOG PS, high-risk cytogenetics, pLOT, prior chemoimmunotherapy and phosphatidylinositol 3-kinase inhibitor (PI3Ki), and refractoriness to BTKi and venetoclax. **Results:** Analysis included 278 pts (SOC, n = 212; liso-cel, n = 66). SOC regimens included chemotherapy, immunotherapy (excluding CAR T cell therapy), BTKi, venetoclax, PI3Ki, and combinations. Median follow-up was 17.2 mo for SOC and 35.4 mo for liso-cel. Most pt characteristics were balanced after IPTW (Table) with imbalance adjusted by regression. After adjustment, ORR (95% CI) was 19.2% (14.1–26.1) for SOC vs 52.5% (34.8–79.2) for liso-cel. Median (95% CI) PFS was 4.4 mo (3.2–5.5) for SOC vs 12.0 mo (10.8–13.2) for liso-cel (HR, 0.40; 95% CI, 0.24–0.68). PFS probabilities at 24 and 36 mo were 11.5% and 5.1% for SOC vs 46.3% and 30.3% for liso-cel. Median (95% CI) OS was 14.8 mo (9.4–20.1) for SOC vs 33.6 mo (31.7–35.5) for liso-cel (HR, 0.47; 95% CI, 0.28–0.79). OS probabilities at 24 and 36 mo were 35.1% and 29.7% for SOC vs 73.4% and 42.6% for liso-cel. **Conclusions:** Liso-cel was associated with significantly improved response, delayed progression, and prolonged survival vs SOC in pts with R/R CLL/SLL after ≥ 2 pLOTs, including a BTKi and venetoclax. Clinical trial information: NCT03331198. Research Sponsor: This analysis was funded by Bristol Myers Squibb. Writing and editorial assistance were provided by Nikola Vojtov, PhD, of The Lockwood Group (Stamford, CT, USA), funded by Bristol Myers Squibb.

Characteristics before/after IPTW.

	SOC (before)	Liso-cel (before)	SOC (after)	Liso-cel (after)
Mean age, y	70.5	65.4	68.7	69.3
Rai stage III/IV, %	56	57	55	52
Bulky disease, %	86	62	77	69
High-risk cytogenetics, %	83	83	84	76
Mean pLOTs	3.9	6.1	4.5	4.6
Prior chemoimmunotherapy, %	58	88	67	72
Prior PI3Ki, %	18	30	22	23
BTKi refractory, %	69	88	74	77
Venetoclax refractory, %	54	92	64	84

7040 Poster Session

Circulating tumor DNA assessment in patients with early-stage classical Hodgkin lymphoma treated with combination of brentuximab vedotin and nivolumab. First Author: Ryan C. Lynch, Fred Hutchinson Cancer Center, University of Washington, Seattle, WA

Background: Recent data suggest circulating tumor DNA (ctDNA) can be detected in patients with classical Hodgkin lymphoma (cHL), with molecular response potentially complementing imaging assessments. We report on the use of an ultra-sensitive assay for ctDNA detection in patients with early-stage cHL to explore its utility in this population. **Methods:** In SGN35-027 (NCT03646123) Part C study, patients with stage I or II cHL without bulky disease (N=154) received brentuximab vedotin, nivolumab, doxorubicin, and dacarbazine (AN+AD) intravenously on days 1 and 15 of each 28-day cycle. Responses were assessed by PET/CT according to Lugano Classification with LYRIC at cycle (C) 2 day (D) 25-28 and end of treatment (EOT). 36 of 154 patients (23%) had plasma samples (collected at baseline, prior to C2D1 and C4D1, and EOT) analyzed for ctDNA using the PhasEDseq MRD assay. PET/CT results were compared with ctDNA dynamic changes in those with detectable baseline ctDNA. A genAI tool (12/19/24; Pfizer; GPT-4o) developed the 1st draft; authors assume content responsibility. **Results:** Baseline ctDNA was detectable in 34 of 36 patients (94%) and was higher in patients with greater disease burden (indicated by baseline stage/risk status [P=0.015] and International Prognostic Score [P=0.014]). At C2D1, ctDNA was undetectable in 27 of 33 patients (82%). ctDNA levels decreased in all patients after 1 cycle of treatment. At C2 interim PET/CT, 18 of 34 patients (53%) achieved complete metabolic response (CMR); of these, 17 patients had ctDNA samples evaluable with 16 patients having undetectable ctDNA. The remaining 16 patients achieved partial metabolic response (PMR); of these, 5 patients had detectable ctDNA and 11 had undetectable ctDNA (all 11 patients with undetectable ctDNA achieved CMR at later time points). At C4D1, only 1 patient continued to have detectable ctDNA. At EOT, PET/CT showed that 26 of 34 patients (76%) achieved CMR, 5 achieved PMR, and 3 achieved indeterminate response (IR); none had detectable ctDNA at EOT. In long-term follow up (LTFU), 4 of the 5 PMRs eventually converted to CMR; 1 patient developed a second primary malignancy (mantle cell lymphoma). Follow up assessments during LTFU confirmed that 2 IRs converted to CMR and 1 converted to PMR. **Conclusions:** ctDNA was detectable in majority of patients with early-stage cHL at baseline, and higher levels are associated with increased disease burden. Treatment with AN+AD reduced ctDNA levels, with ctDNA becoming undetectable by EOT in all patients. In some patients, decline in ctDNA levels was observed earlier than responses observed through imaging, suggesting that ctDNA clearance may be an early indicator of treatment response. The potential value of ctDNA as a biomarker for early detection and monitoring of treatment response in early-stage cHL should be further investigated. Clinical trial information: NCT03646123. Research Sponsor: Pfizer Inc.

7041 **Poster Session**

Updated efficacy and safety results from the phase 2 study of timdarpacept in combination with tislelizumab in patients with classical Hodgkin lymphoma for whom prior anti–PD-1 therapy failed. First Author: Ke-Shu Zhou, Department of Hematology, Henan Cancer Hospital, Zhengzhou, China

Background: Timdarpacept (IMM01), a recombinant SIRPa-Fc fusion protein, can activate macrophages to enhance anti-tumor activity by blocking CD47-SIRPa interaction. Timdarpacept showed unique property of weak human erythrocyte binding in preclinical studies, and low incidence of anemia in early clinical trials with no need for a priming dose. **Methods:** Eligible patients (pts) with R/R classical Hodgkin lymphoma (cHL) who had failed prior anti-PD-1 treatment were enrolled in this study (NCT05833984). Timdarpacept (2.0mg/kg, QW) and tislelizumab (200mg, Q3W) were intravenously administered in 3-week treatment cycle until disease progression or intolerable toxicity. Objective response rate (ORR) by Lugano 2014 was the primary endpoint and secondary endpoints include tolerability, disease control rate (DCR), duration of response (DoR), progression free survival (PFS) and time to response (TTR). **Results:** As of 18 Oct 2024, 33 cHL pts were enrolled with 19 refractory to anti PD-(L) 1 therapy (best objective response was SD/PD or CR/PR and progressed within 12 weeks of last dose). The median age was 35 years with 23 (69.7%) male pts. The median prior lines of therapy were 4. In all 33 efficacy-evaluable pts with median follow up of 13.83 months, the ORR, complete response (CR) rate and DCR were 69.7%, 24.2% and 93.9%, respectively. For PD-(L) 1 refractory pts, the ORR was 68.4%, and 1 pt achieved CR. The median TTR was 1.6 months. The median DoR was not reached. Further analysis indicated that pts could benefit from timdarpacept combined with tislelizumab treatment regardless of being relapsed or refractory to anti-PD-1 treatment, or having had prior CD30-ADC treatment or not. All pts experienced treatment-related adverse events (TRAEs), 17 (48.5%) of whom experienced grade 3/4 TRAE. The most common TRAEs were WBC decreased (57.6%), PLT decreased (42.4%), anemia (39.4%), ANC decreased (39.4%), lymphocyte decreased (30.3%). Six (18.2%) pts had treatment related SAE. Three pts (9.1%) had an IMM01 dose reduction. One pt (3.0%) experienced permanent discontinuation of IMM01. No TRAEs led to death. **Conclusions:** Timdarpacept in combination with tislelizumab showed promising therapeutic efficacy and a well-tolerated safety profile in cHL patients for whom anti-PD-1 failed, providing evidence for future investigation. Clinical trial information: NCT05833984. Research Sponsor: None.

7042 **Poster Session**

Longitudinal assessment from liquid biopsy of mutations in CD20: A pilot study using a PETE enrichment strategy. First Author: Tyler Landrith, Roche Molecular Systems, Pleasanton, CA

Background: In recent years, bispecific T cell Engagers (BsTCE) targeting CD3 and CD20 have emerged as a potent new class of therapeutics for NHL; however, a subset of patients still experience relapsed or refractory disease. Patients undergoing treatment with BsTCEs could benefit from longitudinal screening via liquid biopsy to identify baseline (primary) and treatment-induced (acquired) resistance mutations and tailor treatment accordingly. Here we present the results from a pilot study screening patients treated with Glofitamab (CD20xCD3) using a single gene Primer Extension Target Enrichment (PETE) strategy for *MS4A1* (CD20 gene) in liquid biopsies. **Methods:** Our pilot study was conducted using libraries from the plasma of 134/155 patients with relapsed or refractory large B cell lymphoma (r/r LBCL) who underwent Glofitamab treatment at approved dose in the phase I/II trial NP30179 (NCT03075696) (Dickinson, et al. N Engl J Med 2022), and paired PBMC/PDB available in 91 cases. Primers were designed against the coding regions of the *MS4A1* gene. Enrichment was performed using a workflow optimized for the detection of somatic variants in cell-free DNA isolated from plasma. Results were analyzed using a modified AVENIO circulating tumor (ct) DNA (Roche; For Research Use Only) analysis workflow. Variants detected by the analysis pipeline were further filtered based on inclusion criteria: allele fraction $>$ 0.1%, rarity in the cohort, impact on protein function *in silico*, and if sample was available, absence in germline. Tumor burden as assessed by ctDNA was obtained from retrospective sequencing data. Response to treatment was assessed by PET/CT using the Lugano Criteria. **Results:** Using inclusion criteria a total of 11/134 (8.2%) patients were identified with a total of 16 unique *MS4A1* candidate mutations at baseline or during treatment. The Best Overall Investigator Response (BOR) was progressive disease (PD) for 7 patients and partial metabolic response (PR) for 4 patients. All patients with BOR PR experienced disease progression before treatment completion. Sufficient samples were available to demonstrate expansion of the candidate mutation by the end of treatment (EOT) timepoint for 5 patients. Four of the identified mutations were previously reported in the literature, the remaining mutations were novel, and *in vitro* characterization demonstrated their functional impact. **Conclusions:** This work identifies known and novel mutations in CD20 in plasma samples as a potential contributing mechanism to relapsed or refractory cases of NHL. Although the prevalence appears to be low, this is consistent with previous reports and supports investigation of the clinical utility, including utility as a potential predictive biomarker, of sequencing this gene during treatment with CD20xCD3 BsTCE. Future and ongoing work will screen additional cohorts and therapy combinations. Research Sponsor: The NCT03075696 study was sponsored by F. Hoffman LaRoche Ltd.

7043 **Poster Session**

Novel analysis of 3-y results from the pivotal EPCORE NHL-1 study: Outcomes in patients (pts) with relapsed/refractory large B-cell lymphoma (R/R LBCL) and complete response (CR) at 2 y with epcoritamab (epcor) monotherapy. First Author: Yasmin Karimi, University of Michigan Division of Hematology/Oncology, Ann Arbor, MI

Background: Depth and duration of CR correlate with long-term outcomes in LBCL. Epcor is a subcutaneous (SC) CD3xCD20 bispecific antibody approved for the treatment (tx) of pts with DLBCL or high-grade BCL after $\geq$2 lines of tx (LOT). In the 3-y follow-up from the NHL-1 trial, epcor monotherapy led to durable CRs, with a 36-mo median CR duration (mDOCR), 37-mo median progression-free survival (mPFS), and not reached (NR) median overall survival (mOS) in pts with R/R LBCL who had CR. We report long-term outcomes from a post-hoc analysis of the NHL-1 trial in pts who were in CR 2 y after starting tx, referred to herein as pts in CR at 2 y. **Methods:** Pts with R/R CD20$^+$ LBCL and $\geq$2 prior LOT received epcor SC in 28-d cycles (C; 0.16- and 0.8-mg step-up doses in C1; 48-mg full dose thereafter; once weekly [QW], C1–3; Q2W, C4–9; Q4W, C$\geq$10) until progressive disease (PD) or unacceptable toxicity. The primary endpoint was overall response rate. **Results:** As of the May 3, 2024 data cutoff, 41% (65/157) of pts had CR, of whom 49% (n=32) remained in CR at 2 y. Among the 32 pts in CR at 2 y, median age was 63 y, 47% were male, and 66% were refractory to $\geq$2 consecutive prior LOT. Pts in CR at 2 y vs pts without CR at 2 y had lower tumor burden at baseline (bulky disease $>$7 cm 19% vs 34%; LDH 294 vs 501 U/L); pts in CR at 2 y had lower baseline ferritin levels (383 vs 856 μg/L) and similar CAR T exposure (38% vs 39%). At data cutoff, median follow-up for pts in CR at 2 y was 37 mo (range 32−46). All but 1 had a response (CR or partial response) by the 2nd assessment at wk 12. mDOCR was NR, and ~96% of pts remained in CR at 3 y. At the data cutoff, the longest ongoing CR was $>$43 mo. mPFS and mOS were NR. The overall epcor safety profile in pts in CR at 2 y was consistent with that of the intention-to-treat population. Median tx duration was 35 mo (range 8–43); 81% (26/32) of pts remained on tx at 2 y. 19% (5/26) pts still on tx at 2 y had $\geq$1 serious infection after 2 y, most commonly pneumonia (n=4). Two pts had a fatal infection (COVID-19 pneumonia, pneumonia) after 2 y. At data cutoff, 19/32 (59%) pts with CR at 2 y were still on tx. One pt discontinued (D/C) due to PD; 12 D/C for reasons other than PD, most commonly adverse events (n=6, including the 2 pts with fatal infections above). In 12 pts who D/C due to reasons other than PD, CR was maintained for a median of 14 mo (range 2−28) after tx D/C. **Conclusions:** This novel subgroup analysis of pts with R/R LBCL in CR at 2 y after starting epcor highlights long-term disease remission, overall survival, and potential for cure with epcor in some pts. Long-term safety remained manageable. These results underscore the benefits of epcor in the 3L+ setting and may inform personalized tx strategies. Additional data to further characterize pts with R/R LBCL and a prolonged CR with epcor monotherapy will be presented. Clinical trial information: NCT03625037. Research Sponsor: Genmab.

7044 **Poster Session**

Ibrutinib, venetoclax plus CD20 monoclonal Ab: Initial results of OASIS II, a prospective randomized phase 2 trial in previously untreated mantle cell lymphoma patients. First Author: Steven Le Gouill, Institut Curie, Paris, France

Background: Ibrutinib is approved in R/R MCL. Enrich trial (Lewis, ASH 2024, abst 235) showed that Ibrutnib/CD20mAb outperforms chemotherapy front-line. We demonstrated that Ibrutnib/CD20mAb plus Venetoclax has a good safety profile in R/R and untreated MCL (Le Gouill, Blood 2021). Whether or not Ibrutnib/CD20mAb is superior to Ibrutnib/CD20/Venetoclax front-line is a key question. OASIS 2 (NCT04802590) is a phase 2 prospective randomized international trial that investigates Ibrutinib/CD20mAb (Arm A) plus Venetoclax (Arm B) in untreated MCL. **Methods:** Patients were stratified by country, age ($<$ / $>$=66 years) and MIPI. All patients (18-80y) with untreated MCL, stage II-IV and nodal disease were eligible. Treatment consisted of Ibrutinib (560 mg/d, C1-24) and anti-CD20mAb (C1-6), then 2 monthly (C7-42). In Arm B, Venetoclax was added for a fixed duration of 2y (400 mg/d). The study uses a two-stage Simon's design. A preplanned interim futility analysis occurred after 39 pts with informative MRD were randomized in each arm. The primary endpoint of the futility analysis is the measurable residual disease (MRD) negativity rate assessed by digital-droplet PCR technique at the end of C6. Each treatment arm was to be considered effective if the 80% upper CI MRD negativity percentage was $\geq$ 64%. The interim analysis result was mandatory to re-open the trial (only for effective arms) for the second phase of recruitment. Herein, we present the results of the futility pre-planed interim analysis. **Results:** 102 pts were randomized (51 in each arm, 78 were MRD informative). Pts' characteristics were comparable between the two arms. One patient in arm B withdrew consent before any treatment. 46 in arm A and 45 in arm B completed the first 6 cycles. The median dose intensity for CD20mAb was 100%, 96% for Ibrutinib in arm A and 90% in Arm B, 91% for Venetoclax. At least one dose adjustment of Ibrutinib was more frequent in Arm B (28% vs 15.7%). At least one Venetoclax dose reduction was needed in 24% of patients in Arm B. AE, AESI, AE grade $\geq$ 3 were more frequent in Arm B (92% vs 82.4%; 82% vs 52.9%; 64% vs 47.1%) but not for SAE grade $\geq$ 3 (32% vs 31.4%). The most frequent grade 3 AE was neutropenia (11.8% vs 34%). MRD negativity was obtained in 53.8% (CI 80% 42.4% - 65%) in Arm A and 82.1% (CI 80% 71.7% - 89.7%) in Arm B. According to Lugano criteria at the end of C6, 21 out of 39 (54%) pts were in a complete metabolic remission in Arm A vs 27 out of 39 (69%) in Arm B. The export in Oct 2024 showed that the 2-y PFS and OS were 87.9% (95%CI, 79.7-92.9) and 91.9% (95% CI, 84.5-95.9). **Conclusions:** Ibrutinib/CD20mAb /Venetoclax frontline provides very high MRD negativity rate. According to the statistical analysis plan, both arms were thus re-opened for inclusion on 02APR24 and 102 new patients have been included (end of inclusion DEC 2024). Clinical trial information: NCT04802590. Research Sponsor: None.

7045 **Poster Session**

Survival outcomes of Epstein-Barr virus-positive diffuse large B-cell lymphoma, not otherwise specified: Results from Latin American and United States cohorts. First Author: Jose Concepcion-Holguin, The University of Texas MD Anderson Cancer Center, Houston, TX

Background: Epstein-Barr virus-positive diffuse large B-cell lymphoma (EBV+ DLBCL), not otherwise specified, is rare in North America and Europe (2–4%) but prevalent in Latin America (LATAM, 7–14%). Most studies are limited by single-center designs, small cohorts, short follow-up, and infrequent rituximab use. Prognostic systems like the International Prognostic Index (IPI) are widely used, yet their predictive power in EBV+ DLBCL remains unclear. Additionally, the optimal threshold for EBV-encoded RNA (EBER) positivity remains controversial, with cutoffs ranging from ≥20% to ≥80%. This study aimed to characterize clinical outcomes and evaluate prognostic scores and EBER thresholds in LATAM patients treated with chemoimmunotherapy, contrasted with a U.S.-based cohort. **Methods:** This multicenter retrospective cohort study included patients diagnosed with EBV+ DLBCL from 2002–2020 in five LATAM countries (GELL registry) and a two U.S. centers (2008–2023). EBV positivity was defined per institutional EBER standards. Patients managed without anti-CD20 antibodies were excluded. Outcomes (overall survival [OS] and progression-free survival [PFS]) were assessed using Kaplan-Meier analysis, log-rank tests, and Cox regression. Prognostic systems (IPI, NCCN-IPI, R-IPI, Oyama score) were evaluated using C-indices. **Results:** In the LATAM cohort (n=139), median age was 58 years, 71% had advanced-stage (stage III-IV) disease, and 90% received R-CHOP. In the U.S. cohort (n=136), median age was 67 years, 74% had advanced-stage disease, and 74% received R-CHOP. In the LATAM cohort, with a median follow-up of 61 months (95% CI=53-68), 43 deaths were observed. The 5-year OS and PFS rates were 63% (95% CI=54-73%) and 50% (95% CI=41-60%), respectively. In the US cohort, with a median follow-up of 54 months (95% CI=45-66), 52 deaths were observed. The 5-year OS and PFS rates was 54% (95% CI=45-65%), and 41% (95% CI=32-52%), respectively. All evaluated prognostic scores had a similar performance in the LATAM (OS: C-index range 0.595-0.674; PFS: C-index range 0.553-0.633) and US (OS: C-index range 0.679-0.744; PFS: C-index range 0.701-0.782) cohorts. EBER test ≥80% was associated with mortality in the US cohort (adjusted HR=2.76, 95% CI=1.53-5.00). **Conclusions:** To the best of our knowledge this is one of the largest studies on EBV+ DLBCL. This study highlights comparable survival outcomes for EBV+ DLBCL in LATAM and the U.S. with chemoimmunotherapy, supporting its use in the management of this rare entity. Prognostic systems show variable performance across regions, emphasizing the need for further validation in EBV+ DLBCL populations. Variability in EBER thresholds underscores the need for standardized diagnostic criteria to optimize prognostication and treatment. Research Sponsor: None.

7046 **Poster Session**

Safety and efficacy of AZD0486, a CD19xCD3 T-cell engager, in relapsed or refractory diffuse large B-cell lymphoma. First Author: Tae Min Kim, Seoul National University Hospital, Seoul, South Korea

Background: Treating relapsed/refractory (R/R) diffuse large B-cell lymphoma (DLBCL) is challenging despite advances. AZD0486, a novel IgG4 fully human CD19xCD3 bispecific T-cell engager, showed promising safety and efficacy in patients (pts) with heavily pretreated follicular lymphoma with an overall response rate (ORR) and complete response (CR) rate of 95% and 85%, respectively, at target doses (TD) ≥2.4 mg (Hou JZ, et al. *Blood.* 2024). We present results from an ongoing phase 1 trial in pts with R/R DLBCL (NCT04594642). **Methods:** Eligible pts with R/R CD19+ B-cell lymphoma and ≥2 prior lines of therapy (pLOT) received fixed-duration AZD0486 intravenously for 2 years. Initially, pts received either no or 1 step-up dose (SUD). Subsequently, 2SUD on D1/D8 was implemented with TD on D15. TDs were given every 2 weeks in 28-day cycles. After 2 consecutive CRs, pts could receive dosing every 4 weeks. Primary objectives are safety, tolerability, pharmacokinetics, and determining the maximum tolerated dose (MTD). RECIL-based response assessment is performed by central imaging review. Measurable residual disease (MRD) in plasma ctDNA is assessed by PhasED-seq CLARITY assay. CTCAE v5.0 and ASTCT criteria are used to grade adverse events (AEs). **Results:** As of Sept 29, 2024, 70 pts with R/R DLBCL received AZD0486 at TDs ≤0.8 mg (n=2), 2.4 mg (n=18), 7.2 mg (n=22), 15 mg (n=25), and 25 mg (n=3). Median pLOT was 3 (range, 1–12) and 34 (49%) pts received prior CD19-directed CAR-T therapy. In 61 evaluable pts who received TDs ≥2.4 mg, ORR and CR rate were 46% and 33%, respectively. ORR/CR rates tended to be higher with higher doses (39%/22% at 2.4 mg, 43%/33% at 7.2 mg, and 55%/41% at 15 mg, respectively). ORR/CR rates were higher in pts without prior CAR-T vs CAR-T–exposed pts (57%/39% vs 36%/27%). For pts who received 7.2 mg or 15 mg (median follow-up 8.8 months and 5.3 months, respectively), median duration of response (DOR) was not reached; 12-mo estimated DOR was 64%. One pt who achieved CR progressed. Of the 15 pts who achieved CR and were evaluable for MRD in the 7.2-mg and 15-mg cohorts, 87% (13/15) achieved undetectable MRD. In the overall population (N=70), infections occurred in 37% of pts, with 9% grade [G] ≥3; COVID-19 occurred in 13% of pts. Febrile neutropenia occurred in 3% of pts. Neutropenia ≥G3 occurred in 23% of pts, while anemia ≥G3 occurred in 14%. In pts who received 2SUD (n=54), CRS occurred in 44% of pts, all low grade (G1/G2, 41%/4%), and 20% received tocilizumab; ICANS occurred in 17% of pts (G3, 3%). All CRS and ICANS events in the 2SUD cohort occurred in C1 (except for 1 CRS event on C2D1), were transient, and did not require treatment discontinuation. No AZD0486-related deaths or AEs leading to discontinuation occurred. **Conclusions:** AZD0486 at TDs ≥2.4 mg showed promising efficacy and manageable safety in pts with R/R DLBCL. Target doses up to 25 mg have been tested without exceeding MTD. Dose escalation is ongoing. Clinical trial information: NCT04594642. Research Sponsor: AstraZeneca.

7047 **Poster Session**

High HDAC I/IIb selective inhibitor purinostat mesylate in relapsed and refractory diffuse large B-cell lymphoma: A single agent phase IIb study. First Author: Lijuan Chen, Department of Hematology, State Key Laboratory of Biotherapy and Cancer Center, West China Hospital, Sichuan University, Chengdu, China

Background: Relapsed/refractory diffuse large B-cell lymphoma (r/r DLBCL) has a poor prognosis. Purinostat Mesylate (PM) is a high selective HDAC I/IIb inhibitor. PM has demonstrated its safety and efficacy in r/r DLBCL in previous studies. Based on results of phase IIa, 11.2mg/m^2 was chosen to be the RP2D. The efficacy and safety of PM monotherapy in r/r DLBCL patients are evaluated in phase IIb study (NCT05563844). **Methods:** This multicenter, single-arm, phase IIb study is conducted in 37 sites in China. Key eligibilities include r/r DLBCL 2~5 lines; prior therapies include anti-CD20 monoclonal antibody and anthracycline-based chemotherapy; ECOG≤2. The IIb study plans to enroll 90 patients to receive IV of PM at 11.2mg/m^2 on day 1, 4, 8, 11 of 21-day cycle. Patients continue to receive PM until disease progression or unacceptable toxicity. Primary outcome is ORR. Secondary outcomes include PFS, OS and safety. **Results:** As of2025.1.18, 44 r/r DLBCL patients had been enrolled (median age 62.5 years, 45.5% female) with a median of 2 lines of prior therapy. 43 patients have at least one response evaluation. After a median follow-up of 6.0 months, the ORR is 60.5% (26/43) with 9 complete response (CR) and 17 partial response (PR). Most response (19/26) occurred at early cycle with median TTR of 1.3 months (95% CI, 1.25-2.00), and the mDOR is 8.6 months (95% CI, 4.24- NR). Among 26 patients with response, 16 patients remain on treatment and the longest treatment has lasted for 22 cycles (still CR at cycle 21). The mPFS is 6.2 months (95% CI, 3.22-NR) and the mOS is immature. In subgroup analysis, 16 double-expressor DLBCL patients obtained 56.3% (9/16) ORR and 32 patients with TP53 mutation by NGS/FISH test achieved 62.5% (20/32) ORR. The most common grade ≥3 treatment emergent adverse events include thrombocytopenia (81.8%), neutropenia (79.5%), leukocytopenia (47.7%), lymphocytopenia (27.3%), hypokalemia (11.4%), anemia (9.1%) and hypertriglyceridemia (9.1%). No PM-related death was reported. **Conclusion:** This ongoing study showed 11.2mg/m^2 PM in 21-day-cycle achieved remarkable efficacy in r/r DLBCL and acceptable safety profile. The strategy for pivotal study of PM in r/r DLBCL is discussed with NMPA. Clinical trial information: NCT05563844. Research Sponsor: Chengdu Zenitar Biomedical Technology Co., Ltd, Chengdu, Sichuan, China; Sichuan Province "14th Five-Year Plan" Life and Health Major Science and Technology Project (2022ZDZX0027).

7048 **Poster Session**

Combination of mitoxantrone hydrochloride liposome with cyclophosphamide, vincristine, and prednisone (CMOP) for patients with treatment-naïve peripheral T-cell lymphomas (PTCLs): Extended follow-up analysis of a multicenter, open-label, single-arm, phase Ib study. First Author: Huiqiang Huang, Sun Yat-sen University Cancer Center, Guangdong, China

Background: PTCLs represent a heterogeneous group of lymphomas generally majority of patients (pts) associated with a poor prognosis when treated with CHOP based therapy. Mitoxantrone hydrochloride liposome (Lipo-MIT) has demonstrated efficacy in relapsed/refractory PTCLs in our previous study. This study previously reported that CMOP regimen exhibits encouraging efficacy in treatment-naïve (TN) PTCLs. Here we present extended follow-up data of the final dose (NCT04548700). **Methods:** Eligible pts were aged 18-70 years with histologically confirmed TN PTCLs. Pts received Lipo-MIT combined with standard doses of COP regimen every four weeks for six cycles. The study consisted of a 3+3 dose-escalation phase (Lipo-MIT at 12, 15, 18, and 21 mg/m^2) and a specific dose-expansion phase (Lipo-MIT at the recommended phase 2 dose [RP2D]). The primary endpoints were dose-limiting toxicity (DLT) and safety. Secondary endpoints included objective response rate (ORR) assessed by an independent review committee (IRC), duration of CR (DoCR), DoR, PFS, OS, and pharmacokinetics (PK). **Results:** As of November 17, 2022,38 pts were enrolled (26 in the dose-escalation) from 7 centers in China, including 21 (55.3%) AITL, 6 (15.8%) PTCL-NOS, 4 (10.5%) ALK- ALCL, 3 (7.9%) ALK+ PTCL, and 4 (10.5%) other types,16 (42.1%) pts had stage IV disease. No DLTs were observed and a Lipo-MIT dose of 18 mg/m^2 was recommended as the RP2D. The most common treatment-related grade 3/4 adverse events were hematologic toxicities, including neutropenia (76.3%), leukopenia (73.7%), lymphopenia (44.7%), thrombocytopenia (15.8%) and anemia (13.2%). After a median follow-up of 23.8 (range 1.0-42.4) months, among the 35 response-evaluable pts, the IRC-assessed CR rate was 54.3% (95% CI, 36.6-71.2%), and the ORR was 88.6% (95% CI, 73.3-96.8%). According to the investigator assessment, the CR and ORR rate were 51.4% (95% CI, 34.0-68.6%) and 85.7% (95% CI, 69.7-95.2%), respectively. The median DoCR was not reached, while the median DoR were 20.1 (95% CI, 5.2-35.1) months. The median PFS was 20.8 (95% CI, 6.1-35.5) months, and the median OS was not reached with a 2-year OS rate of 93.3% (95% CI, 75.9-98.3%). Moreover, Lipo-MIT exhibited a favorable PK profile, with linear PK characteristics in the 12-18 mg/m^2 dose range. **Conclusions:** The CMOP regimen demonstrates a favorable PK profile, manageable safety profile, and encouraging preliminary anti-tumor activity. These results support further phase 2 and 3 trials clinical studies to confirm activity and assess efficacy in this population. Clinical trial information: NCT04548700. Research Sponsor: CSPC Zhongqi Pharmaceutical Technology Co., Ltd.

7049 **Poster Session**

Long-term follow-up of the phase 2 ELM-2 study: Odronextamab for patients (pts) with relapsed/refractory (R/R) follicular lymphoma (FL). First Author: Deepa Jagadeesh, Cleveland Clinic, Cleveland, OH

Background: Odronextamab, an investigational off-the-shelf CD20×CD3 bispecific antibody, demonstrated compelling efficacy and a generally manageable safety profile in heavily pretreated pts with R/R FL in the primary analysis of the Phase 2 ELM-2 study (NCT03888105; Kim TM, et al. *Ann Oncol* 2024). We present updated efficacy and safety data for odronextamab in pts with R/R FL from ELM-2 after >2 yrs follow-up. **Methods:** Odronextamab was administered intravenously until disease progression/unacceptable toxicity, with Cycle (C) 1 step-up dosing to help mitigate cytokine release syndrome (CRS) risk, as reported previously. Pts with a complete response (CR) for ≥9 months (mo) switched from maintenance dosing Q2W to Q4W. Primary endpoint: objective response rate (ORR) per Lugano criteria by independent central review (ICR); secondary endpoints: CR rate, duration of response (DOR), progression-free survival (PFS), overall survival (OS). **Results:** At the updated data cutoff (Aug 15, 2024), 157 pts with centrally confirmed R/R FL Grade (Gr) 1–3a were enrolled. Median no. of treatment cycles: 19.0 (range 0.1–117.3); 96.2% (n = 151) and 82.8% (n = 130) of pts completed C1 and C4, respectively. The global cohort comprised 128 pts evaluable for efficacy. At a median efficacy follow-up of 28.3 mo, ORR was 80.5% (n = 103) by ICR and CR rate was 74.2% (n = 95); 92.2% of responders achieved CR. Responses were durable (median DOR, 26.0 mo; median duration of CR, 32.2 mo). ORR was consistent across high-risk subgroups (Follicular Lymphoma International Prognostic Index score 3–5, 78.4%; progression of disease within 2 yrs of frontline therapy, 81.0%). Median PFS was 23.0 mo (estimated 36-mo PFS rate, 37.5%), and median OS was 54.2 mo (estimated 36-mo OS rate, 62.6%). Median PFS was longer in pts who were minimal residual disease (MRD) negative (42.4 mo) versus MRD positive (21.6 mo) at Week 12. Of 47/128 pts who switched to Q4W dosing, 32 remained in CR. The odronextamab long-term safety profile was consistent with the primary analysis. All 157 pts had TEAEs (Gr ≥3, 86.0%), and 15.3% discontinued treatment due to TEAEs (most common: COVID-19 infection, 2.5%). With 0.7/4/20 mg step-up dosing (n = 89), CRS events were mostly low grade (Gr 1, 46.1%; Gr 2, 13.5%; Gr 3, n = 1; Gr ≥4, n = 0), occurred mostly in C1, and resolved in a median of 8.4 hrs. Immune effector cell-associated neurotoxicity syndrome was reported in one pt (Gr 2). Infections were reported in 79.0% of pts (124/157; Gr ≥3, 42.0%). COVID-19-related infections were reported in 38.2% of pts (Gr 5, 5.7%). **Conclusions:** With longer follow-up, odronextamab demonstrated durable responses in heavily pretreated pts with R/R FL from ELM-2, with robust efficacy in those with high-risk features, and a generally manageable safety profile. Overall, these compelling results support odronextamab as a potential off-the-shelf treatment option for pts with R/R FL. Clinical trial information: NCT03888105. Research Sponsor: Regeneron Pharmaceuticals, Inc.

7050 **Poster Session**

Efficacy and safety of ifupinostat (BEBT-908) in combination with rituximab for relapsed/refractory diffuse large B-cell lymphoma: Results from an exploratory phase Ib study. First Author: Peng Liu, National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences & Peking Union Medical College, Beijing Key Laboratory of Clinical Study on Anticancer Molecular Targeted Drugs, Beijing, China

Background: Ifupinostat is a dual HDAC/PI3Kα inhibitor designed to target tumor cell signaling networks by simultaneously inhibiting HDAC and PI3Kα, thereby disrupting tumor cell proliferation and inducing apoptosis. A single-arm pivotal trial of Ifupinostat in patients who received at least two lines of systemic therapy for relapsed/refractory diffuse large B-cell lymphoma (r/r DLBCL) has been completed, with data currently under NDA review by the NMPA. This exploratory trial evaluates Ifupinostat in combination with rituximab as part of a confirmatory phase 3 trial to further assess its efficacy and safety as a second-line treatment for r/r DLBCL (NCT06164327). **Methods:** This multicenter Phase 1b trial was designed to evaluate the efficacy and safety of Ifupinostat in combination with rituximab (R) with or without standard second-line regimens (R-GemOx or R-ICE). Cohort 3 included 24 r/r DLBCL patients with prior exposure to at least one systemic therapy, all involving anti-CD20 antibody. Among these, 16 patients (66.6%) were primary refractory, 4 patients (16.7%) were refractory to their most recent line of therapy, and 4 patients (16.7%) were relapsed cases. Treatment consisted of Ifupinostat administered intravenously at a dose of 22.5 mg/m² on days 1, 3, 5, 8, 10, and 12 of each 21-day cycle. Rituximab was administered intravenously at a dose of 375 mg/m² on day 1 of each cycle. Tumor assessments were conducted following treatment, and efficacy was evaluated according to the Lugano 2014 criteria. Key endpoints included the objective response rate (ORR) and safety. **Results:** Of the 24 enrolled patients, 21 completed at least one treatment dose and underwent tumor assessment. The ORR was 76.2%, with 10 patients (47.6%) achieving a complete response (CR) and 6 (28.6%) achieving a partial response (PR). The disease control rate (DCR) was 85.7%. Median progression-free survival (PFS) has not yet been reached (>7.7 months). Common grade 3-4 hematological toxicities observed during treatment included thrombocytopenia (34.8%), leukopenia (17.4%), and lymphopenia (13.0%). No unexpected toxicities were observed, and the safety profile was deemed manageable. **Conclusions:** The study results demonstrate promising efficacy and a manageable safety profile for Ifupinostat in combination with rituximab as a second-line treatment for r/r DLBCL. These findings support further investigation in confirmatory phase 3 trials, which are currently underway. Clinical trial information: NCT06164327. Research Sponsor: None.

7051 **Poster Session**

Phase II safety and preliminary efficacy of amulirafusp alfa (IMM0306) in combination with lenalidomide in patients with relapsed or refractory CD20-positive follicular lymphoma. First Author: Yan Huang, Department of Hematology and Oncology, Jiangxi Cancer Hospital, Nanchang, China

Background: Amulirafusp alfa (IMM0306) consists of anti-CD20 monoclonal antibody fused with the CD47 binding domain of SIRPα. It exerts potent anti-cancer efficacy by activating both macrophages and NK cells via blockading of CD47-SIRPα interaction and FcγR engagement. Lenalidomide was approved for relapsed or refractory (R/R) indolent non-Hodgkin's lymphoma (iNHL). Here, we report results from a Phase II study of 34 patients with R/R CD20-positive follicular lymphoma (FL) (NCT05771883). **Methods:** Eligible patients with grade 1-3a FL received amulirafusp alfa 1.6 mg/kg intravenously once a week with lenalidomide 20 mg orally once a day on Days 1 to 21 in each 28-day cycle until disease progression or intolerable toxicity. Safety was evaluated by CTCAE 5.0, tumor assessments performed every 8 weeks by Lugano 2014. **Results:** Until Dec 26, 2024, 34 patients with R/R FL were enrolled. Median age was 54, 20 (58.8%) were males, and 32 (94.1%) had stage III-IV disease. The median number of prior line therapy was 2. All patients received previous anti-CD20 therapy. Among 22 efficacy-evaluable patients, 10 CR, 8 PR, 2 SD and 2 PD were observed. The CRR and ORR were 45.5% and 81.8%, respectively. Of the 4 efficacy-evaluable patients who did not achieve response, 2 SD patients were both CD20 therapy refractory, 1 PD patient had histologic transformation and 1 PD patient were lenalidomide-resistant (had taken lenalidomide continuously for about 4 years). The most common treatment related adverse events (TRAEs) (≥ 20%) were PLT decreased (70.6%), WBC decreased (58.8%), anemia (52.9%), ANC decreased (52.9%), lymphocyte decreased (52.9%), infusion-related reactions (35.3%) and hypoalbuminaemia (23.5%). Grade ≥3 TRAEs occurred in 22 (64.7%) patients, the most common ≥ grade 3 TRAEs (≥ 10%) were ANC decreased (29.4%), lymphocyte decreased (26.5%), PLT decreased (23.5%) and WBC decreased (11.8%). 5 (14.7%) patients experienced serious TRAE. 1 (2.9%) patient had a dose reduction of amulirafusp alfa, 5 (14.7%) patients had dose reductions of lenalidomide due to TRAEs. 1 (2.9%) patient experienced TRAE leading to the study drug discontinuation (Grade 4 Type I hypersensitivity, recovered with sequelae within 1 month). No patient experienced TRAE leading to death. There were no significant differences between amulirafusp alfa monotherapy and combination with lenalidomide in terms of PK exposure and ADA incidence rate. Pharmacodynamics analysis demonstrated amulirafusp alfa combine lenalidomide effectively depleted $CD19^{+}$B cell in peripheral blood and achieved sustained long-term B cell depletion. **Conclusions:** Amulirafusp alfa in combination with lenalidomide showed a preliminary anti-tumor activity and a well-tolerated safety profile in patients with R/R FL. This phase Ib/II study is still ongoing. Clinical trial information: NCT05771883. Research Sponsor: None.

7052 **Poster Session**

Impact of cell of origin, gene rearrangements, and frontline treatment on incidence of secondary central nervous system lymphoma in newly diagnosed diffuse large B-cell lymphoma. First Author: Ayo Samuel Falade, Department of Medicine, Mayo Clinic, Rochester, MN

Background: Secondary central nervous system lymphoma (SCNSL) is a rare but serious complication that occurs in 2-10% of patients (pts) with diffuse large B-cell lymphoma (DLBCL). The CNS-International Prognostic Index (CNS-IPI) is a validated tool used to assess the risk of CNS relapse. However, with advancements in molecular profiling and treatments, the predictors of SCNSL, including the predictive ability of CNS-IPI combined with other molecular markers and treatment regimens, have become uncertain. This study evaluates new prognostic markers for CNS relapse in DLBCL, focusing on cell-of-origin (COO), gene rearrangements, and treatment types. **Methods:** DLBCL pts enrolled from 2002-2015 in the Mayo Clinic and University of Iowa Lymphoma Molecular Epidemiology Resource were prospectively followed for incidence of CNS relapse. Pts with primary CNS lymphoma or CNS involvement at diagnosis, and pts treated with high-dose methotrexate containing regimens were excluded. COO classification (GCB vs non-GCB) was determined using Hans algorithm and/or NanoString data. Multivariate Cox regression models estimated hazard ratios (HRs) and 95% confidence intervals (CIs) for predictors of SCNSL. Survival analysis was performed from time of DLBCL diagnosis using Cox proportional hazards model. **Results:** Among 1278 newly diagnosed DLBCL pts included (median age: 63 years; 43.6% female), SCNSL occurred in 46 (3.6%) pts. Pts with SCNSL were more likely to have intermediate/high CNS-IPI scores (80.4%) than pts without SCNSL (63.9%, p=0.02). The 3 yr SCNSL incidence was 0.016 (0.008-0.0033) in low CNS-IPI vs 0.043 (0.031-0.0060) in high CNS-IPI. Those with SCNSL were significantly more likely at baseline to have non-GCB COO (56.3% vs. 36.5%, p=0.02), and advanced stage (76.1% vs. 59.9%, p=0.03) compared to those without SCNSL. The incidence of SCNSL was not influenced by MYC, BCL2, or BCL6 rearrangements, nor by treatment with R-CHOP, R-EPOCH, or other immunochemotherapy regimens. MVA showed that intermediate CNS-IPI (HR 2.32, 95% CI 1.09-4.92, p=0.029), high CNS-IPI (HR 3.59, 95% CI 1.49-8.62, p=0.004), and non-GCB COO (HR 2.19, 95% CI 1.08-4.42, p=0.0029) were independently associated with increased SCNSL risk. After a median follow-up of 12 years (IQR 9–15), overall survival (OS) was 52.1% for the cohort, with OS significantly worse for SCNSL pts (17.4% vs. 53.4%, p<0.001). **Conclusions:** This large cohort with extensive follow-up highlights the role of COO as an additional prognostic factor for SCNSL while reinforcing CNS-IPI's prognostic value. Non-GCB COO pts had a higher risk of SCNSL even when adjusted by CNS-IPI risk. Despite advancements in management, SCNSL pts continue to have poor outcomes. Strategies to reduce the incidence of CNS relapse in high-risk pts require further investigation. Research Sponsor: None.

MER CNS relapse hazard ratios (95% CI).

Characteristics	Hazard Ratio	95% CI	P-Value
CNS-IPI Group			
0-1 Low	Ref	Ref	Ref
2-3 Intermediate	2.32	1.09 - 4.92	0.029
4+ High	3.59	1.49 - 8.62	0.004
Cell of Origin*			
GCB	Ref	Ref	Ref
non-GCB	2.19	1.08 - 4.42	0.029
Double Hit*			
non-DHL	Ref	Ref	Ref
DHL	1.08	0.14 - 8.3	0.941
Not Done/Missing	1.38	0.76 - 2.51	0.297
Double Expressor*			
Negative	Ref	Ref	Ref
Positive	2.36	0.71 - 7.85	0.162
Not Done/Missing	1.91	0.89 - 4.08	0.097
IC Group*			
R-CHOP	Ref	Ref	Ref
R-EPOCH	1.63	0.71 - 3.74	0.249
Other IC	1.18	0.57 - 2.46	0.660
Any EN Involvement*			
No	Ref	Ref	Ref
Yes	0.98	0.51 - 1.88	0.946
Albumin Group*			
>=Normal	Ref	Ref	Ref
<Normal	1.70	0.75 - 3.85	0.201
Head & Neck Involvement*			
No	Ref	Ref	Ref
Yes	0.35	0.048 - 2.63	0.310

*Adjusted by CNS-IPI risk group.

7053 **Poster Session**

A phase I study of the EZH2 inhibitor TR115 in patients with relapsed/refractory non-Hodgkin's lymphomas and advanced solid tumors. First Author: Jie Jin, The First Affiliated Hospital, Zhejiang University School of Medicine, Hangzhou, China

Background: EZH2 gain-of-function mutations and overexpression lead to aberrant H3K27me3 levels and result in tumorigenesis and metastasis, including several categories of B cell and T cell lymphoid malignancies, and it is associated with poor clinical prognosis and outcomes. TR115, a novel, highly selective, orally administered EZH2 inhibitor, has demonstrated potent anti-tumor activity in preclinical models. This Phase I study aims to evaluate the safety, tolerability, and preliminary efficacy of TR115 in patients with relapsed/refractory non-Hodgkin's lymphomas (NHL) and advanced solid tumors. **Methods:** Dose escalation started at 200mg bid and progressed up to 1600mg bid. Patients received TR115 orally twice daily in 28-day cycles until disease progression, unacceptable toxicity, or patient withdrawal. Adverse events (AEs) were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 5.0. Efficacy was evaluated using Lugano 2014 criteria for lymphomas and RECIST v1.1 for solid tumors. **Results:** By January 10, 2025, a total of 20 patients were enrolled, including those with angioimmunoblastic T-cell lymphoma (AITL, n=4), diffuse large B-cell lymphoma (DLBCL, n=4), ovarian cancer (n=4), ALK-negative anaplastic large cell lymphoma (ALCL, n-2), peripheral T-cell lymphoma not otherwise specified (PTCL-NOS, n=2), mycosis fungoides (n=1), follicular lymphoma (FL, n=1), extranodal marginal zone mucosa-associated lymphoid tissue lymphoma (MALT, n=1) and breast cancer (n=1). Median age was 61 (range 37-77) with 10 (50%) males. Most were heavily pretreated with a median of 2 previous lines of therapy. the most common TRAEs (all grades/Grade $\geq$3) included thrombocytopenia (50%/15%), leukopenia (45%/10%) , anemia (40%/15%), neutropenia (35%/10%), hypertriglyceridemia (35%/5%), elevated blood creatinine (35%/0%), elevated lactate dehydrogenase (25%/0%), hypokalemia (25%/5%), hyperbilirubinemia (20%/0%), adynamia (20%/5%), Hypoproteinemia (20%/0%), and upper respiratory tract infection (10%/5%). Of the 11 patients with non-Hodgkin's lymphomas evaluable for response, the overall response rate (ORR) was 63.6%, and the disease control rate (DCR) was 81.8%. 6 patients with PTCL had an ORR of 100%, and 4 continue to receive treatment with the investigational drug. One PTCL-NOS patient achieved a complete response (CR) remaining on treatment at Cycle 16. PK parameters $AUC_{0\text{-}24h}$ and C_{max} were dose proportional with median T_{max} 2 hours. **Conclusions:** In this study, TR115 exhibited a favorable safety profile and promising efficacy in patients with relapsed/refractory non-Hodgkin's lymphoma, especially in relapsed/refractory PTCL patients. Further investigation of TR115 alone or in key therapeutic combinations is warranted. (NCT05650580). Clinical trial information: NCT05650580. Research Sponsor: Tarapeutics Pharmaceutical Science Inc.

7054 **Poster Session**

Lorlatinib therapy in relapsed/refractory ALK+ lymphomas previously treated with tyrosine kinase inhibitors. First Author: Federica Colombo, Università degli studi Milano Bicocca, Milano, Italy

Background: ALK+ Lymphomas are aggressive diseases with poor prognosis when chemoimmunotherapy (CIT) and Crizotinib fail. Lorlatinib is a 3rd-generation tyrosine kinase inhibitor (TKI), that inhibits all reported ALK kinase domain mutations responsible for resistance to Crizotinib. **Methods:** From 2019 to 2024, we enrolled 8 patients (pts) in a phase 2 open label monocentric study with Lorlatinib in relapse/refractory (r/r) ALK+ lymphomas previously treated with other TKI (EudraCT2016-003970-41). Overall response rate (ORR), the primary endpoint, was evaluated using 18F-FDG PET/CT scans and ALK RT-PCR on peripheral blood and bone marrow samples. Secondary endpoints were progression-free survival (PFS) and overall survival (OS) from the start of Lorlatinib to relapse and/or death. Side effects were classified according to CTCAEv4.03. Our cohort included 4 ALK+ Large B Cell Lymphoma (LBCL) with Clathrin-ALK (CLTC::ALK) rearrangement, 2 ALK+ Anaplastic Large Cell Lymphoma (ALCL) with ATIC::ALK fusion, 1 ALK+ ALCL Lymphoma with NPM::ALK translocation and 1 ALK+ histiocytosis with EML4::ALK rearrangement. **Results:** The median follow-up (fup) was 23 months (1,3- 62), the median age at diagnosis was 23 years (19-57); all pts were in stage IV Ann Arbor and treated with CIT and Crizotinib. 2 pts also received other TKIs (Alectinib and Ceritinib). Lorlatinib was administered daily at a dose of 100 mg. The ORR at one month (M1) was 100% (95% CI: 72-100%): 5 CR and 3 PR. 3 pts (2 ALCL [ATIC::ALK], 1 ALCL [NPM::ALK]), underwent Allogeneic Stem Cell Transplant (ASCT) while in CR and resumed Lorlatinib post-transplant. Due to hepatic GVHD and memory impairment, their Lorlatinib dosage was reduced from 100 mg to 75-50 mg/day. All of them are in CR. 2 pts (LBCL with CLTC::ALK) refused ASCT, maintained CR from M1 through their last fup at 15 and 65 months respectively, continuing with Lorlatinib at 100 mg/day. 2 ALK+ LBCL pts (CLTC::ALK) achieved PR at M1 but relapsed within 3 months and did not benefit from ASCT or salvage treatments. The pt with ALK+ histiocytosis was in PR at M1 and then obtained CR at M3 with Lorlatinib; surgical resection of a residual necrotic lung mass was performed. She has been in CR for $>$40 months. PFS rate at 3 months was 75%, with no additional events reported. OS was 87% at 3 and 12 months, and 72% at 24 months and stabilized thereafter. All ALK+ lymphoma pts in CR at M1 maintained a durable response, whereas those in PR died of disease progression. The type of lymphoma or of ALK translocation did not correlate with outcome. Main adverse effects (all grade I/II) included hyperlipidaemia, weight gain, muscle cramps, gastrointestinal symptoms, thrombocytopenia and memory difficulty. **Conclusions:** Our analysis confirms Lorlatinib's efficacy and safety as salvage therapy. Achieving a CR at M1 was found to be the most important prognostic factor for survival. Adverse events are manageable with dose adjustments. Clinical trial information: EudraCT2016-003970-41. Research Sponsor: None.

7055 **Poster Session**

Combination of mitoxantrone hydrochloride liposome with tislelizumab in patients with relapsed or refractory NK/T cell lymphoma: A phase Ib/II study. First Author: Qingqing Cai, Department of Medical Oncology, Sun Yat-Sen University Cancer Center, Guangzhou, China

Background: Natural killer/T-cell lymphoma (NKTCL) is a unique subtype of non-Hodgkin lymphoma with aggressive disease course. Mitoxantrone hydrochloride liposome (Lipo-MIT) is a nano-drug that has been approved for relapsed/refractory (r/r) PTCL, and has shown certain efficacy and safety in a pivotal phase II study (Cancer. 2025, e35672). Tislelizumab is a humanized immunoglobulin G4 variant monoclonal antibody against PD-1. This study aims to investigate the safety and efficacy of combining Lipo-MIT with tislelizumab in patients (pts) with r/r NKTCL. **Methods:** Pts with r/r NKTCL and failed asparaginase-based therapy were recruited in this single-arm, multicenter phase Ib/II study (NCT05464433). Phase Ib was 3+3 dose escalation design with two dose levels of Lipo-MIT (16 mg/m^2 and 20 mg/m^2, d1) plus tislelizumab 200 mg (d1, Q4W) induction therapy for up to 6 cycles, then tislelizumab 200 mg (Q3W) maintenance therapy for up to 1 year. Phase II was conducted at the recommended phase II dose (RP2D). The primary endpoints were safety and tolerability, and determination of the maximum tolerated dose (or RP2D) of Lipo-MIT in phase Ib, and the overall response rate (ORR) of phase II. **Results:** As of the data cut-off on January 24, 2025, a total of 40 eligible pts were enrolled (phase Ib, n=6 and phase II, n=34). The median age was 46.5 (range 22-73) years. Among the pts, 62.5% had stage III or IV and 87.5% had nasal type NKTCL. No dose-limiting toxicities (DLT) were observed in the phase Ib study, and the RP2D of Lipo-MIT was determined to be 20 mg/m^2. The ORR and DCR were all of 100.0% (6/6, 95% CI 60.7%-100.0%) and the CR rate was 66.7% (4/6, 95% CI 27.1%-93.7%) in phase Ib. In the ongoing phase II stage, 30 pts were evaluable for efficacy. The ORR, DCR and CR rate were 70.0% (21/30, 95% CI 50.6%-85.3%), 76.7% (23/30, 95% CI 57.7%-90.1%) and 46.7% (14/30, 95% CI 28.3%-65.7%), respectively. Overall, combining data from phase Ib and phase II, the ORR was 75.0% (27/36, 95% CI 57.8%-87.9%) and the CR rate was 50.0 (18/36, 95% CI 32.9%-67.1%). Among the 15 pts who had not used PD-1 before, CR rate was 66.7% and ORR reached 80.0%. The median PFS and OS will be reported with longer follow-up. The most common grade 3/4 treatment-related adverse events (TRAEs) included leucopenia (37.5%), neutropenia (30.0%) and decreased lymphocyte count (27.5%). Notably, no cardiac events occurred during the study. **Conclusions:** Lipo-MIT in combination with tislelizumab demonstrated an encouraging efficacy in r/r NKTCL pts with a manageable safety profile. Clinical trial information: NCT05464433. Research Sponsor: None.

7056 **Poster Session**

Comparative analysis of survival outcomes in infused versus not-infused patients with aggressive B-cell lymphoma referred for CART. First Author: John Seng Wang, Northwestern University Feinberg School of Medicine, Chicago, IL

Background: Chimeric antigen receptor T-cell therapy (CART) has changed the treatment paradigm for patients (pts) with relapsed/refractory (R/R) aggressive B-Cell Non-Hodgkin's Lymphoma (B-NHL). Yet, not all referrals complete the full process from harvest to re-infusion. This study evaluated a large cohort of pts "referred yet not infused" with CART to identify barriers to care and compare outcomes between pts infused vs non-infused. **Methods:** This is a retrospective analysis of adult pts with R/R B-NHL referred to Northwestern University from 2016-2024 for consideration for CART. Demographics, disease characteristics, and lines of therapy were evaluated. Survival analysis assessed median progression free survival (mPFS) and overall survival (mOS) in months (mo) from 2 starting timepoints (1) date of relapse with last line therapy prior to CART referral, denoted as PFS1 and OS1, and (2) date of treatment with CART or alternative to CART after referral, denoted as PFS2 and OS2. **Results:** Of 196 pts, 157 (80%) received CART (infused) whereas 39 (20%) were referred, but did not proceed to CART (non-infused). Comparison of demographics/disease characteristics demonstrated differences in age and ethnicity (Table 1). For infused pts, median time from apheresis to infusion was 33 days (range 9-86) and 94 pts (60%) received bridging therapy. For non-infused pts, median time from CART referral to alternative treatment was 14.5 days (range 1-80), most commonly rituximab-lenalidomide, rituximab-gemcitabine-based therapy (n=6 for each, 15%), or polatuzumab-based therapy (n=3, 8%). Death from disease progression was the most common reason for non-infusion (n=25, 64.1%). Median follow-up was 19 mo in surviving pts. Infused pts had higher mPFS1 than non-infused pts (5.6 [95% CI 3.7-7.5] vs 1.8 mo [95% CI 1.3-2.3]; p=0.05). Median PFS2 showed no significant difference. Infused pts had a markedly higher mOS1 (45.9 [95% CI 20-72] vs 2.5 mo [95% CI 1.8-3.2]; p=0.001), and mOS2 (32.3 [95% CI 0.1-64.5] vs 2.4 mo [95% CI 1.9-2.9]; p=0.001). **Conclusions:** CART infused vs non-infused pts differed with respect to age and ethnicity. The most common reason for failure to infuse was death due to disease progression. Infused pts demonstrated similar PFS to non-infused pts treated with alternative therapy. However, infused pts had a markedly improved OS. Collectively, our results suggest that survival in R/R B-NHL may be optimized by adopting measures that ensure success of proceeding to CART. Research Sponsor: None.

Baseline demographics and disease characteristics.

	Infused; N=157	Non-infused; N=39	P-value
Median Age (range)	58.5 (22-85)	67 (35-85)	0.04
Sex: Female	55 (35%)	17 (44%)	0.98
Race: Caucasian	134 (85%)	36 (92%)	0.57
Ethnicity: Hispanic	11 (7%)	8 (21%)	0.04
IPI > 3	21 (15%)	7 (20%)	0.49
Cell of Origin: GCB	64 (53%)	23 (61%)	0.46
Primary Refractory	91 (60%)	26 (68%)	0.46

7057 **Poster Session**

CD58 alterations and their role in regulating antitumor immune responses in diffuse large B-cell lymphoma. First Author: Yidan Zhang, Tianjin Medical University Cancer Institute and Hospital, Tianjin, China

Background: Recurrent abnormalities of immune surveillance-related genes play a crucial role in DLBCL progression. Prior studies have shown that CD58, a key adhesion molecule that acts as a ligand for the T-cell costimulatory molecule CD2, is frequently mutated or deleted in certain hematological malignancies. Downregulation or loss of CD58 is linked to resistance to ICB therapy in melanoma and CAR-T therapy in B-cell malignancies. Nevertheless, the role of CD58 in cancer is not yet well understood. **Methods:** Comprehensive analysis of the genetic characteristics of *CD58* were performed through targeted deep sequencing (n=176), whole exome sequencing (n=38), and RNA-sequencing (n=162) in patients with de novo DLBCL. To investigate the mechanistic impacts of CD58 alterations on co-inhibitory molecules expression and immune cell function, we performed bulk and single-cell RNA-sequencing analysis of tumor samples and conducted co-IP, flow cytometry and co-culture assays in vitro. **Results:** We identified that *CD58* mutation rate was 9.1%, and the copy number loss rate was 44.7% among all enrolled DLBCL patients. Notably, *CD58* genetic alterations, along with low CD58 expression, significantly correlated with reduced rates of response to R-CHOP therapy and inferior progression-free and overall survival. Single-cell RNA sequencing revealed that CD58 expression in tumor cells was negatively correlated with $CD8^+$ T cell exhaustion/dysfunction status. CD58 inhibited the activity of the JAK2/STAT1 pathway by activating the Lyn/CD22/SHP1 axis, thereby limiting PD-L1 and IDO expression. Elevated PD-L1 and IDO expression in CD58 deficient DLBCL cells led to immune evasion and tumor-intrinsic resistance to CAR T-cell therapy. Direct activation of CD58-CD2 costimulatory signaling in combination with anti-PD-L1 blockade or IDO inhibitor sensitized CD58-deficient DLBCL to CAR T-cell therapy. **Conclusions:** Our study comprehensively characterized *CD58* genetic alterations in DLBCL. We demonstrated that CD58 downregulation or mutation led to upregulation of PD-L1 and IDO expression mainly by regulating the LYN/CD22/SHP1 axis. Our findings provide novel insights for individualized therapy for DLBCL patients with CD58 mutation or deletion. Research Sponsor: None.

7058 **Poster Session**

Assessing the role of cytarabine-based regimens in mantle cell lymphoma: A real world study. First Author: Yanal Mufeed Alnimer, University of Kentucky, Lexington, KY

Background: Mantle cell lymphoma (MCL) is an aggressive subtype of non-Hodgkin lymphoma. For decades, cytarabine-based regimens have been the cornerstone of MCL treatment, offering substantial efficacy but often at the cost of significant toxicity. More recently, non-cytarabine-based regimens, such as bendamustine combined with rituximab, have emerged as a promising alternative, demonstrating comparable efficacy with more favorable toxicity profile. This study aims to compare the clinical efficacy of cytarabine-based (Ara-C) versus non-cytarabine-based (non-Ara-C) regimens. **Methods:** We conducted a retrospective cohort study for patients diagnosed with MCL between 2010 and 2023 at Allegheny Health Network and Markey Cancer Center. Data pertaining to demographics, MIPIc, Lugano stage and treatments at induction were collected. Patients were divided into two groups based on whether they received cytarabine based regimen during induction (Ara-c) or not (non-Ara-c). Primary outcomes were overall survival (OS) measured from the time of diagnosis to the time of last follow up or death, and relapse free survival (RFS), calculated from the time of diagnosis to the time of relapse, persistent or progressive disease at the last day of follow up. Sensitivity analysis, with censoring on the time of autologous bone marrow transplant (ASCT) was done. RFS and OS were compared between the two groups after weighted propensity score matching (PSM). **Results:** We identified 223 patients diagnosed with MCL. The median age was 67.7 (IQ 60-74.5), Majority of patients were males (71%). The median MIPIc score was 8.1(IQR 7-9.5). 72 patients (31%) were in the Ara-c group while 151 patients (69%) were in the non-Ara-c group. The median follow-up of 5.6 years (0.95CI 4.91-6.32). Median OS was 13 years (0.95 CI 7.24-NR) and median RFS was 4.1 years (0.95 CI 3-4.96) for the entire cohort. Baseline comparison between the two groups is shown in table_1. After PSM, Median RFS for Ara-c group was 4.8 (IQR=1.8-16.2) yrs VS 3.6 (IQR=1.52-7) yrs for non-Ara-c group (P value 0.03). However, after censoring on ASCT, median RFS for Ara-c group was 4.7 (IQR 1.5-16.2) yrs VS 3.3 (IQR 1.5-6.9) yrs (P value 0.16). Median OS for Ara-c group was 16.2 yrs (IQR=4.3-16.2) vs 12.95 yrs (IQR=3.7-17.8) for non-Ara-c group (P value 0.5), which was the same after censoring on ASCT. **Conclusions:** In our cohort, cytarabine use in induction chemotherapy for MCL was associated with longer RFS and OS but it did not reach statistical significance. Larger scale studies are warranted to confirm these results. Of note, older and less fit patients received less cytarabine. Research Sponsor: None.

	Cytarabine	Other	P value
Age	64 (57-69)	69 (63-77)	0.013
Eastern Cooperative group 0,1	96%	84%	0.05
MIPIc	7.56 (6.89-7.92)	8.28 (6.97-9.66)	0.01
Consolidation with ASCT	42%	13%	<0.01

7059 **Poster Session**

Total metabolic tumor volume for predicting cytokine release syndrome and treatment response in patients receiving bispecific antibodies for B-cell lymphoma. First Author: Xi Yang, Division of Hematology/Oncology, University of Michigan, Ann Arbor, MI

Background: CD20xCD3 bispecific antibodies (BsAb) show high response rates with manageable cytokine release syndrome (CRS) in B-cell non-Hodgkin lymphomas (B-NHLs). While emerging data suggest that total metabolic tumor volume (TMTV) may predict treatment response and CRS, these findings have not yet been validated in real-world settings or across diverse histologic subtypes. **Methods:** We conducted a single center retrospective study evaluating B-NHL patients treated with BsAb. Baseline characteristics, efficacy, and safety outcomes were analyzed. TMTV was calculated from baseline PET scans using a semi-automated method with a threshold of 2x liver SUV_{mean}. Median TMTV separated high/low groups. **Results:** A total of81 patients are included. The baseline characteristics, efficacy outcomes, and CRS outcomes of each histological subtype are summarized in Table 1. There were no Grade 4 CRS events observed. The median TMTV for DLBCL, FL and MCL was 107.1ml, 61.7ml, and 92.2ml, respectively. In DLBCL, patients with high TMTV were more likely to have bulky disease (>7.5cm) and elevated LDH. Other baseline characteristics as outlined in Table 1 were comparable to low TMTV group. High TMTV was associated with increased risk of CRS of any grade (OR 5.0, 95% CI 1.4-18.1, p=0.017) but was not associated with ORR, CR, PFS or OS. While bulky disease and elevated LDH levels were associated with TMTV, these clinical factors were not predictive of CRS. In contrast, TMTV retained its prognostic significance in multivariate analysis. In FL, high TMTV was associated with a higher rate of bulky disease while LDH level and other baseline characteristics did not differ from the low TMTV group. High TMTV correlated with a lower CR rate (OR 0.1, 95% CI 0.0-0.6, p=0.020) but did not influence CRS risk, PFS or OS. In the small cohort of MCL patients, no significant associations between TMTV and CRS or treatment efficacy were observed. TMTV has no correlation with neurotoxicity in all cohorts. **Conclusions:** High TMTV predicts for a higher rate of CRS on multivariate analysis in DLBCL, independent of clinical factors. High TMTV was associated with a lower CR rate in FL and further evaluation in MCL is needed with larger sample sizes. Research Sponsor: None.

Baseline characteristics, efficacy outcomes, and CRS outcomes.

	DLBCL N=47	FL N=20	MCL N=14
Age, median (yr)	70	66	67
Male, n(%)	27 (57.4)	15 (75.0)	13 (92.9)
BsAb regimen, n(%)			
Epcoritamab	39 (83.0)	6 (30.0)	2 (14.3)
Glofitamab	4 (8.5)	3 (15.0)	8 (57.1)
Mosunetuzumab	4 (8.5)	11 (55.0)	4 (28.6)
Single agent BsAb treatment, n(%)	32 (68.1)	9 (45.0)	8 (57.1)
Prior lines of therapy, median (range)	3 (0-10)	3 (1-7)	3 (2-5)
Overall response rate (ORR), n(%)	25 (53.2)	16 (80.0)	9 (64.3)
Complete response (CR), n(%)	10 (21.3)	8 (40.0)	7 (50.0)
CRS, n(%)	19 (40.4)	11 (55.0)	10 (71.4)
Grade 1	13 (68.4)	4 (36.4)	5 (50.0)
Grade 2	5 (26.3)	7 (63.6)	4 (40.0)
Grade 3	1 (5.3)	0 (0.0)	1 (10.0)

7060 **Poster Session**

DLBCL-associated PIM1 mutation and its impact on ANXA2 localization and lymphomagenesis. First Author: Yaxiao Lu, Tianjin Medical University Cancer Institute and Hospital, Tianjin, China

Background: Diffuse large B-cell lymphoma (DLBCL) is the most common subtype of non-Hodgkin lymphoma and has an overall cure rate of approximately 60%. Previously, we observed high PIM1 mutation rates in DLBCL patients with poor outcome. However, the mechanism whether they lead to enhanced PIM1 kinase activity and contribute to lymphomagenesis is currently unknown. **Methods:** In this study, a multifaceted approach was employed to elucidate the functional consequences of PIM1 gene mutations and their implications in DLBCL. Recurrent PIM1 gene mutations that exhibited high frequencies across various lymphoma cohorts from public databases were screened and patient outcomes were stratified by PIM1 genen mutational sites. Liquid chromatography-mass spectrometry (LC-MS/MS) analysis combined with Co-IP was used to identify proteins interacting with PIM1. Transcriptomics analysis was utilized to identify proteins involved in critical cellular pathways relevant to PIM1 mutation. A high-throughput drug screening platform was leveraged to find potential therapeutic vulnerabilities unique to PIM1 mutant cells. The antiproliferative effects of PIM1 and PI3K inhibitor were evaluated in DLBCL cell lines and further validated in NSG mouse xenograft models. **Results:** We have identified PIM1 mutations, specifically P81S, E135K, L184F, and S97N, as frequently occurring variants, with the former three significantly associated with poor outcome. In particular, the $PIM1^{L184F}$ mutation promoted cell proliferation and inhibited cell apoptosis in vitro and showed faster tumor growth in vivo. Mechanistically, the $PIM1^{L184F}$ mutation was found to interact with the annexin A2 (ANXA2) gene, activating it through phosphorylation of serine 26. The activated ANXA2 gene then translocated from the cytoplasm to the cell membrane, binding with the Toll-like receptor 4 (TLR4) gene and recruiting BCAP to the cell membrane to interact with p85α further activating the PI3K/AKT/mTOR signaling pathway. Additionally, the high-throughput drug screening demonstrated that the $PIM1^{L184F}$ mutated cells were more sensitive to the PI3K inhibitor YY20394. PIM1 inhibitor SMI-4a combined with YY20394 showed synergistic antitumor effects both in vitro and in vivo. **Conclusions:** Taken together, these findings not only shed light on an innovative regulatory mechanism for how $PIM1^{L184F}$ mutation contributes to the pathogenesis of DLBCL but also provide a potential therapeutic strategy for effectively managing DLBCL patients harboring $PIM1^{L184F}$ mutation. Research Sponsor: None.

7061 **Poster Session**

Efficacy and safety of polatuzumab vedotin plus rituximab, cyclophosphamide, doxorubicin and prednisone for previously untreated diffuse large B-cell lymphoma: A real-world, multi-center, retrospective cohort study. First Author: Peiqi Zhao, Department of Lymphoma, Tianjin's Clinical Research Center for Cancer, Key Laboratory of Cancer Prevention and Therapy, National Clinical Research Center for Cancer, Tianjin Medical University Cancer Institute and Hospital, Tianjin Medical University, Tianjin, China

Background: In the POLARIX study, Pola-R-CHP showed significant improvement in progression free survival (PFS) in previously untreated DLBCL compared to R-CHOP. However, there are still few reports about the efficacy and safety of Pola-R-CHP in real-world setting in China, leaving some questions about the optimal patient population for Pola-R-CHP. Therefore, we conducted this retrospective observational study to compare the efficacy and safety of Pola-R-CHP with R-CHOP in clinical practice. **Methods:** The Pola-R-CHP group included previously untreated DLBCL patients who received Pola-R-CHP therapy across 6 medical centers in China. The control group included previously untreated DLBCL patients treated with R-CHOP. Patients treated with Pola-R-CHP were matched by propensity scores with those treated with R-CHOP. The primary endpoint was 12-month PFS based on Lugano 2014 criteria. **Results:** A total of 650 eligible patients from 6 centers were identified, 155 receiving Pola-R-CHP and 495 R-CHOP. After 1:2 propensity score matching, 150 pairs were obtained for further survival and prognosis analysis. With a median follow-up of 14.3 months, 12-month progression-free survival (PFS) was numerically higher with Pola-R-CHP versus R-CHOP (90.5% vs 84.8%, P=0.19). Benefits were consistently observed across molecular subgroups, especially advanced stage, ECOG≥2, extranodal involvement ≥2 and non-GCB group. The complete response rate of the Pola-R-CHP group was higher than that of the RCHOP group (87.2% vs 80.1%; P=0.11), but there was no statistical difference. Among 150 patients treated with Pola-R-CHP, 110 underwent gene sequencing analysis: MCD (25.5%), combined subtype (14.5%), ST2 (10.9%), and other/unclassifiable subtype (31.8%). The most common mutations (>25% of cases) were PIM1, TP53, BCL-6, KMT2D, SOCS1, BCL-2. Genetic testing results show the correlation between genotyping, gene mutations in PIM1/TP53 and therapeutic efficacy. Safety was comparable between Pola-R-CHP and R-CHOP, including rates of grade 3 to 4 AE. Prophylactic PEG-G-CSF administration was given in most of the cases. No deaths due to AE were observed. Unexpected adverse events were not observed. **Conclusions:** This large real-world study supports Pola-R-CHP as an effective frontline option for DLBCL, with sustained efficacy versus R-CHOP observed in unselected populations. While 12-month PFS failed to reach statistical significance, subgroup analyses favor Pola-R-CHP. Further research with a wider population, longer follow-up, and screening of advantageous groups are warranted. Research Sponsor: None.

7062 **Poster Session**

Association between progression-free survival and overall survival in relapsed/refractory diffuse large B-cell lymphoma in the CAR T-cell era: A surrogate endpoint analysis. First Author: Charles J. Milrod, Brown University Health, Providence, RI

Background: In lymphoid malignancies, the strength of association between progression-free survival (PFS) and overall survival (OS) varies by disease aggressiveness. More-indolent malignancies such as multiple myeloma and follicular lymphoma have a weak correlation between PFS and OS, while more aggressive diseases like Hodgkin lymphoma have a stronger association. PFS has been validated as a surrogate for OS in first-line DLBCL, but its utility in R/R DLBCL in the era of CAR T-cell therapy has not been explored. This analysis is the first assessment of PFS as a surrogate endpoint for OS in DLBCL after the introduction of CAR T-cell therapy. **Methods:** A systematic review of ClinicalTrials.gov was conducted to identify phase 3 trials in DLBCL that reported hazard ratios (HR) for both PFS and OS. Trials initiated after 2015 were included to reflect the post-CAR T-cell therapy era, acknowledging that CAR T-cell therapy was approved in 2017 and most patients experience disease progression within two years. First-line trials were excluded from final analysis, resulting in an analysis focused exclusively on R/R DLBCL. Weighted linear regression analysis was performed, with the number of participants as the weighting factor. The strength of the association was evaluated using the coefficient of determination (R^2), with predefined thresholds: $R^2 > 0.80$ indicating a strong association, 0.60–0.80 indicating a moderate association, and $R^2 < 0.60$ indicating a weak association. **Results:** A total of 101 randomized clinical trials were identified. Upon screening, 20 trials reported rates for both PFS and OS. Of these, 4 trials, encompassing 1,139 patients, reported HRs and were included in the final analysis. The weighted regression analysis demonstrated a strong correlation between PFS and OS, with a correlation coefficient (r) of 0.98 and a coefficient of determination (R^2) of 0.98, indicating that 98% of the variance in OS could be explained by PFS (p = 0.012). **Conclusions:** This study provides the first surrogate endpoint analysis of PFS in R/R DLBCL in the post-CAR T-cell therapy era, excluding first-line trials. The findings suggest that PFS remains a strong surrogate for OS in this population. While the analysis is limited by the small number of available trials, the results highlight the need for ongoing surrogate validation as treatment landscapes evolve. Research Sponsor: None.

Trial Name	Participants	PFS* HR (95% CI)	OS HR (95% CI)
STARGLO	274	0.40 (0.28 - 0.57)	0.62 (0.43 - 0.88)
ZUMA-7	359	0.51 (0.38 - 0.67)	0.73 (0.54 - 0.98)
TRANSFORM	184	0.41 (0.25 - 0.66)	0.51 (0.26 - 1.00)
BELINDA	322	1.07* (0.82 - 1.40)	1.24 (0.83 - 1.85)
Total	1,139	-	-
Correlation Coefficient (r)	-	0.98 (p < 0.001)	-
Coefficient of Determination (R^2)	-	0.98	-

7063 **Poster Session**

Immune biomarkers as predictors of response to mosunetuzumab in previously untreated follicular (FL) and marginal zone lymphoma (MZL). First Author: Charles J. Milrod, Brown University Health, Providence, RI

Background: CD3xCD20 bispecific antibodies (BsAbs), including mosunetuzumab, induce high rates of complete response (CR) in indolent B-cell lymphomas. However, predicting the response and understanding systemic immune changes induced by the treatment (Tx) remain unmet needs. We hypothesized that changes in circulating immune biomarkers could predict Tx response in patients (pts) receiving first-line mosunetuzumab for FL and MZL. **Methods:** Immune biomarkers were measured in peripheral blood samples from pts enrolled in BrUOG-401 (NCT04792502), an investigator-initiated phase 2 trial of time-limited (8 cycles [C]) mosunetuzumab Tx for untreated, high-burden FL and MZL. Disease assessments by PET/CT occurred after C4 (MidTx) and C8 (end of Tx, EOTx). Pts without MidTx CR received additional lenalidomide in C4-8 with optional Tx extension up to C12. Samples were collected at baseline (PreTx), C1 day 8 (C1D8), C2 day 1 (C2), at MidTx, and at EOTx. We measured 25 plasma cytokines related to T-cell activation and regulation using a multiplex Luminex assay, and immune cell subsets using flow cytometry. Markers were compared by rank-sum tests or mixed-effects generalized linear models. P values were not corrected for multiplicity in this exploratory study. **Results:** Among 34 pts evaluable for EOTx response, 29 (85%) attained EOTx CR, and 22 (65%) achieved MidTx CR. Baseline cytokine levels were available for 22 pts, of whom 19 had EOTx CR, and 15 MidTx CR. No significant association was found between PreTx cytokine levels and CR at MidTx or EOTx. At C1D8, markers of T cell activation (IL2, IL7, IFNg, GZMA/B) increased overall (all P< 0.05), but only lower CTLA-4 levels significantly predicted MidTx CR (P=0.0031). Persistently lower CTLA-4 at MidTx also correlated with MidTx CR (P=0.008). No cytokine was significantly associated with EOTx CR. Flow cytometry (n=26) showed an overall increase in circulating NK cells on Tx (P<0.05 at all timepoints). Higher PreTx NK cell abundance significantly correlated with MidTx CR (P=0.043), while higher PreTx CD4+CD45RA+ (naïve helper T) cells (P=0.0035) and lower CD4+CD45RO+CD25- (memory helper) T cells (P=0.0061) were associated with EOTx CR. Increased NK (P=0.011) and HLA-DR+ NK cells (P=0.0042) at C2 also correlated with MidTx CR. Although the CD8+CD45RO+CCR7-CD27- effector memory T cell subset increased overall at MidTx (P=0.025), no CD8+ subset was predictive of CR at any timepoint. **Conclusions:** Although CD8+ T cells are the main effector cells engaged by mosunetuzumab, our observations in previously untreated FL/MZL suggest that increased naïve CD4+ helper T cells and NK cells PreTx, along with lower CTLA-4 levels during Tx may better predict CR. These findings suggest that cytokine-driven immune priming could influence response to BsAbs, providing a basis for future investigations of combinations therapies to enhance their efficacy. Research Sponsor: Conquer Cancer, The ASCO Foundation.

7064 **Poster Session**

Descriptive epidemiology of Waldenström macroglobulinemia (WM): Demographics, outcomes, and predictors of survival in the US community oncology setting. First Author: Alisha Monnette Kimble, Ontada, Boston, MA

Background: WM is a rare, indolent subtype of non-Hodgkin lymphoma (NHL), comprising <2% of annual U.S. NHL cases. Natural history studies and registries often lack sufficient patient-level data about treatment patterns and outcomes. This study describes demographics, clinical characteristics, and outcomes of patients with WM treated in the community oncology setting. **Methods:** This retrospective cohort study included adults diagnosed with WM in the U.S. Oncology Network from 2014 to 2022, with follow-up through 2023. Data were sourced from the iKnowMed electronic health record system. Structured data were used to assess patient characteristics and overall survival (OS). Chart abstraction was performed on a random subset (n=200) to evaluate treatment characteristics and outcomes (i.e. OS, time to next treatment (TTNT), and real-world progression-free survival (rwPFS)). Multivariable Cox proportional hazard models evaluated factors associated with these outcomes. **Results:** Among 2,554 patients with WM (mean age: 72.7 years, SD: 10.1), majority were male (58.9%), and White (77.3%), consistent with SEER data reflecting the indolent nature of WM, with 82.1% alive at study conclusion and median OS was not reached. At 5-years, OS probabilities stratified by Modified Staging System for WM (MSS-WM) were 96.4% (low risk, N=135), 87.3% (low-intermediate risk, N=237), 69.2% (intermediate risk, N=267), and 50.9% (high risk, N=278; $p < 0.0001$), aligning with the externally validated MSS-WM model, demonstrating its utility in risk stratification. In the subset of 200 patients, 8.5% (N=17) had smoldering WM, and 23% (N=46) experienced disease progression. MYD88 L265P and CXCR4 mutations were present in 85.4% and 29% of patients, respectively, consistent with reported case series. Most (78%) patients initiated LOT 1 therapy. Treatment patterns aligned with NCCN guidelines, with BTK inhibitors and Rituximab-based regimens comprising 98% of LOT 1 therapies. In the multivariable model, area deprivation index was significantly linked to poorer OS (HR: 12.8, CI: 2.6–63.4), shorter TTNT (HR: 2.2, CI: 1.1–6.3) and worse rwPFS (HR: 4.1, CI: 1.2–14.3). Patients with a Charlson Comorbidity Index score ≥2, were more likely to discontinue treatment (HR: 2.2, CI: 1.3–3.5) and progress to next therapy (HR: 2.2, CI: 1.2–4.0). **Conclusions:** This natural history study of patients with WM treated in the community oncology setting confirms WM's indolent nature, with long survival and effective risk stratification using the MSS-WM. Real-world treatment patterns aligned to guidelines, while area-level socioeconomic factors and comorbidities highlighted disparities impacting outcomes. These findings emphasize the need for tailored, equitable care strategies and provide insights to enhance treatment approaches and address unmet needs in patients with WM. Research Sponsor: Oncology Center of Excellence, Food and Drug Administration of the U.S. Department of Health and Human Services; 75F40123C00199.

7065 **Poster Session**

PET metabolic response in Lugano: Comparison of qualitative and quantitative outcome by independent central review. First Author: Danielle Phillippi, Clario, Philadelphia, PA

Background: The 2014 Lugano Criteria is the standard for radiographic assessment in lymphoma clinical trials, emphasizing qualitative evaluation of 18F-FDG PET-CT (PET) metabolic response (MR). In 2017, Van Heertum et al. introduced a quantitative approach defining strict percent change of standard uptake values (SUV) determination of MR, primarily for partial metabolic response (PMR) and progressive metabolic disease (PMD). Both Lugano and Van Heertum compared to baseline for determination of PMD, though industry practice frequently compare PMD to nadir. While both qualitative and quantitative approaches have been utilized in pivotal trials, few studies have compared qualitative and quantitative Lugano radiographic metabolic assessments to date. Thus, this study aims to investigate PET MR timepoint responses (TPRs) from blinded independent central review (BICR) radiologists using qualitative Lugano approach vs quantitatively derived TPRs. **Methods:** 3416 radiologist qualitatively assessed designated (desPET) responses consisting of PET TPR, 5PS, most-FDG avid lesion SUV, and liver SUV were analyzed. For desPET TPRs, radiologists compared MRs to baseline and nadir. We quantitatively derived PET (derPET) TPRs using the Van Heertum et al.,2017 %Δ utilizing SUV and 5PS, comparing to baseline and nadir, defining PMR as ≥25% decrease with a 5-point score (5PS) of 4 or 5; PMD as ≥50% increase with 5PS of 4 or 5; complete metabolic response (CMR) as 5PS of 1–3 without residual disease; and no metabolic response (NMR) as 5PS of 4 or 5, not meeting PMR or PMD criteria. To understand the merit of qualitative PET assessments, the desPET were compared to the derPET TPRs. Then, the desPET TPRs were compared among radiologists who reviewed the same case to determine concordance. **Results:** Results showed desPET differed from the derPET for 1198 TPRs (35.1%). When PMD was the derPET TPR, the desPET TPRs were: 270 PMD (53.9%), 134 NMR (26.8%) and 89 PMR (17.8%). When CMR was the derPET TPR, the desPET TPRs were: 830 CMR (51.7%), 634 PMR (39.5%), and 122 PMD (7.6%). When PMR was derPET TPR, desPET TPRs were: 177 PMR (61.9%), 55 NMR (19.2%), 51 PMD (17.8%). In the instances where desPET TPRs differed from the derPET, radiologists reviewing the same cases had concordance in desPET TPRs for 79.5% of cases. **Conclusions:** Our data show notable differences in PET MR when comparing derPET and desPET TPRs. Almost 20% BICR radiologists assessed a PMR, when our derived values were PMD and in over half the cases BICR radiologists assessed CMR when the derPET was PMR, thus suggesting that the quantitative approach results in more PD and fewer CR cases. When determining reader concordance, nearly 80% of readers aligned in desPET TPR when their TPRs differed from the derPET, suggesting that a qualitative assessment supports medical judgment in determining patient metabolic disease and consistency between readers assessments. Research Sponsor: None.

7066 **Poster Session**

Secondary primary malignancies (SPMs) with CAR-T cell therapy in RR-DLBCL from real-world data. First Author: Deevyashali Parekh, SUNY Upstate Medical University, Syracuse, NY

Background: Three CAR-T cell therapies i.e. axicabtagene ciloleucel, tisagenlecleucel and lisocabtagene maraleucel are currently approved for relapsed refractory DLBCL after 2 or more prior lines of treatment. Landmark trials have shown promising efficacy however, a notable concern with CAR-T therapy is the potential development of secondary primary malignancies. **Methods:** A retrospective study was performed using TriNetX, a global research de-identified database with data from 145 health care organisations as of January 2025. ICD-10 codes were used for associated diagnosis and medications. The database was queried to identify RR-DLBCL patients who had received any of axi-cel, tisa-cel or liso-cel. These treatments were set as the index event for outcome analysis. Demographics and prevalence of comorbidities were extracted. Outcome analysis queried for several hematological and solid tumor malignancies. The Measure of Association Analysis was used to calculate Odds Ratio. **Results:** 1842 adult patients with RR-DLBCL received one of the 3 CAR-T cell treatments as listed above and 12,431 patients with RR-DLBCL did not receive any of the 3 treatments. There were 1:1 propensity score matched adjusting for age, race, sex and tobacco use. Final number for both groups was 1842. For both cohorts, 1367 (73.8%) were white, 1055 were male (57%). The cohort had a mean follow up of 497 days, median follow up of 331.5 days. The CAR-T group had higher rates of MDS (3.9% vs 0.8%, p=<0.001) and AML (3.2% vs 1.2%, p=<0.001) in our database review of the US population. It did not show higher rates of other reported SPMs like Mature T/NK cell lymphoma, Hodgkin's lymphoma, multiple myeloma or solid tumours like lung, breast, prostate primary or malignant melanoma. Data on other SPMs is shown in Table 1. **Conclusions:** In our retrospective study of real-world population, RR-DLBCL patients who received CAR-T cell therapy with any of axi-cel, tisa-cel or liso-cel showed higher rates of MDS and AML compared to propensity matched patients with RR-DLBCL who did not receive CAR-T cell therapy while rates of other reported SPMs were not significantly different. Research Sponsor: None.

Frequency of SPMs in CAR-T receiving and no CAR-T receiving patients with RR-DLBCL.

SPM	Received CAR-T cohort (%)	Did not receive CAR-T cohort (%)	Odds Ratio	p-value
MDS	3.9	0.8	4.852 (2.767-8.507)	<0.001
AML	3.2	1.2	2.668 (1.624-4.382)	<0.001
Mature T/NK cell lymphoma	0.7	1.5	0.466 (0.238-0.909)	0.022
Hodgkin's lymphoma	0.9	1.9	0.469 (0.257-0.854)	0.011
Follicular lymphoma	3.8	3.6	1.055 (0.721-1.545)	0.781
Mantle cell lymphoma	1.0	0.5	1.792 (0.825-3.893)	0.135
Multiple Myeloma	1.4	2.4	0.566 (0.341-0.938)	0.025
Primary Lung site	0.7	0.5	1.292 (0.565-2.954)	0.543
Primary Breast site	0.5	0.7	0.815 (0.351-1.892)	0.634
Prostate cancer	0.5	0.6	0.902 (0.382-2.129)	0.814

7067 **Poster Session**

Distinct outcomes with the detection of endemic Burkitt lymphoma, T-cell receptor (TCR) complementarity determining region-3s (CDR3s) matching known anti-HIV TCR CDR3s. First Author: Taha Huda, HCA Healthcare/USF Morsani College of Medicine GME: Bayonet Point Hospital, Hudson, FL

Background: The adaptive immune response is represented by diverse complementary determining region 3's (CDR3s), which frequently represent antigen contact points and can be obtained from sequencing data. In particular, T-cell receptor (TCR) CDR3s in tumors have added an additional dimension to investigating the role of viruses in tumor development. Further, identifying TCR V- and J-gene segment usage, HLA allele combinations has been shown to represent outcome distinctions in various cancers. Given that endemic Burkitt lymphoma (BL) is well-known to be caused by Epstein-Barr virus (EBV), we aimed to characterize endemic BL adaptive immune features using TCR recombination reads, focusing on anti-HIV CDR3s and the presence of specific TCR V/J, HLA allele combinations. **Methods:** The Cancer Genome Characterization Initiative – Burkitt Lymphoma Genome Sequencing Project provided data available at the Genomic Data Commons website: 160 RNA-seq files from primary tumor that represented 105 cases. Phenotypic data representing these cases included gender, race, age at diagnosis, days to last follow-up, vital status, and Ann Arbor pathologic stage. The RNA-seq files were mined for TCR recombination reads using a high-stringency search algorithm (Chobrutskiy et al. 2020) and for HLA alleles utilizing xHLA (Xie et al. 2017). Anti-HIV CDR3s and specific TCR V/J, HLA allele combinations were then correlated with the progression of endemic BL as measured by overall survival (OS) and staging. **Results:** 47,302 productive TCR CDR3 recombination reads were recovered across all samples. We identified that the 22 cases with anti-HIV *TRA* CDR3s had improved OS as compared to those without an anti-HIV *TRA* recovery (median OS not reached vs. 215 days; log-rank p = 0.0013). Similarly, the 74 cases with anti-EBV *TRA* CDR3s were associated with an improved OS as compared to remaining cases (median OS 437 vs. 164 days; log-rank p = 0.005). Decreased disease progression as measured by lower pathologic stage was also noted in patients with anti-HIV *TRA* and *TRB*s compared to remaining cases (Mann-Whitney U p-value: 0.05, 0.01 respectively). Lastly, we identified five TCR V/J, HLA allele combinations which were associated with survival where the individual V or J gene segment and HLA allele was not associated with survival. An example of this were 33 cases with TRAV12-3 and DQB1*05:01, whose OS did not reach the median compared to the 199-day median OS of all other cases (log-rank p = 0.01). **Conclusions:** Early control of tumor progression via the T-cell response, whether by increased anti-viral T-cell receptors or via effective combination of antigen presentation and TCR antigen binding, appears to impact the progression of BL. Specifically, the success of anti-HIV TCRs indicates that treating co-infection with HIV may be a key factor in slowing disease progression. Research Sponsor: None.

7068 **Poster Session**

Effect of CD73 on immune escape via tryptophan metabolic reprogramming in diffuse large B-cell lymphoma. First Author: Yingfang Feng, Tianjin Medical University Cancer Institute and Hospital, Tianjin, China

Background: Immunotherapy is playing an increasingly important role in patients with relapsed or refractory DLBCL. Our previous studies have shown that high CD73 expression in DLBCL tumor cells correlates with poor prognosis and mediates immune escape. However, the underlying mechanism of CD73-mediated immune escape in DLBCL remains unclear. **Methods:** We analyzed RNA-Seq data from TCGA and de novo DLBCL patients at our center, comparing CD73 expression levels to identify enriched pathways related to tumor immune escape. These findings were validated in an syngeneic mouse model. To explore the mechanism by which CD73 regulates immune escape in DLBCL, we performed RNA sequencing and targeted tryptophan metabolism sequencing in cell lines. We further conducted co-culture, flow cytometry, Co-IP, ChIP-qPCR in vitro, and generated a mouse subcutaneous xenograft model for in vivo validation. **Results:** The syngeneic mouse model showed that CD73 knockdown significantly reduced tumor size compared to the control group, while increasing the infiltration of $CD8^+$ T cells and effector $CD8^+$ T cells in tumor tissue, and reducing $CD8^+$ T cell depletion. After systemic $CD8^+$ T cell depletion, the anti-tumor effect of CD73 monoclonal antibody was significantly weakened. RNA-seq and targeted tryptophan metabolism sequencing revealed a positive correlation between CD73 expression and tryptophan metabolism. In vitro, CD73 overexpression reduced ERK/c-Jun dephosphorylation by decreasing binding to INPPL1, leading to upregulation of IDO1 and TDO2 expression. Co-culture experiments showed weakened $CD8^+$ T cell proliferation in the CD73OE group compared to controls, while inhibition of IDO1/TDO2 significantly enhanced $CD8^+$ T cell proliferation, a result reversed in the knockdown group. The therapeutic effect of an IDO1/TDO2 inhibitor was assessed in an A20 mouse model, where both the AT-0174-treated vector and CD73 OE groups showed decreased tumor growth and increased $CD8^+$ T cell and effector $CD8^+$ T cell infiltration compared to the untreated group. Finally, we investigated whether combining CD73 monoclonal antibody with IDO1/TDO2 inhibitors could enhance immune cell infiltration in tumor tissues, and found that the combination treatment increased $CD8^+$ T cell infiltration. **Conclusions:** Our study uncovers a novel mechanism by which CD73 regulates immune escape in DLBCL through an adenosine-independent pathway. CD73 overexpression upregulates IDO1 and TDO2 levels by inhibiting ERK/c-Jun dephosphorylation via reduced binding to INPPL1. These findings offer new insights for combination therapies targeting CD73 in DLBCL patients with high CD73 expression. Research Sponsor: None.

7069 **Poster Session**

Outcomes of patients treated for monomorphic B-cell post-transplant lymphoproliferative disorder: A single-center experience. First Author: Imran Nizamuddin, Washington University School of Medicine, St. Louis, MO

Background: Patients (pts) with monomorphic B-cell post-transplant lymphoproliferative disorder (B-PTLD) have poor outcomes and high treatment-related mortality (TRM). With risk-stratified sequential treatment (RSST), some can be treated with rituximab alone. We sought to evaluate predictors of outcome in newly diagnosed B-PTLD, including involvement of extranodal (EN) sites and allograft. **Methods:** Adults diagnosed at Siteman Cancer Center with confirmed B-PTLD from 1/1/2006–12/31/2024 were identified via electronic health records. Kaplan-Meier and log-rank tests were used to evaluate progression-free survival (PFS) and overall survival (OS). Univariate analyses were done using Fisher's exact and $\chi 2$ tests with a=0.05. **Results:** 106 pts with monomorphic B-PTLD were identified (Table). The most common graft types were kidney (33%), liver (26%), and lung (15%). After diagnosis, immunosuppression was reduced in 93 (88%) pts and 105 pts received systemic therapy. 56 (53%) pts received frontline chemotherapy (chemo), most commonly R-CHOP (68%, n=38) and DA-EPOCH-R (21%, n=12), and overall response rate (ORR) was 66% (complete response [CR] 57%). 49 (46%) pts initially received rituximab monotherapy, including 39 on RSST, with ORR 36% (CR 23%). 28 (72%) were escalated to chemo, including 7 (18%) pts who progressed prior to reimaging. Treatments used were R-CHOP (71%, n=20), Pola-R-CHP (21%, n=6), and DA-EPOCH-R (7%, n=2), with ORR 59% (CR 56%). With median follow up of 58 months (mo), median PFS and OS were 33 and 64 mo, respectively. Pts who did not have CR to rituximab had worse PFS vs responders (12 mo vs 86 mo, p=0.037) and OS (27 mo vs 86 mo, p=0.04). Factors predicting CR to rituximab included early stage (p=0.001) and absence of EN disease (p=0.005). Graft type, involvement of allograft, tumor EBV status, and gene rearrangements were not predictive. Following frontline therapy, 33 (31%) pts developed relapsed/refractory disease. Elevated LDH (p=0.021) and extranodal disease (p=0.032) at diagnosis predicted relapse. 13 (12%) pts experienced graft failure, and 6 (6%) required repeat transplant. Discontinuation of antimetabolites was associated with higher rates of graft failure (p=0.020). 51 (48%) pts died, 8 (16%) due to TRM. **Conclusions:** In a large cohort of B-PTLD, ORR to rituximab on RSST and chemo confirm prior data. Pts with lack of response to rituximab monotherapy, EN disease, and elevated LDH have worse outcomes. Despite advances, TRM remains high in PTLD. Research Sponsor: None.

Demographics and predictors of response to rituximab.

Variable	Median (range)	Variable	n (%)	OR (response to rituximab)	p-value
Age	60 (22-86)	Male	66 (63)	1.7	0.65
Years since transplant	8 (0-34)	White	92 (87)	1.7	0.66
		Non-GCB	47/85 (55)	1.4	0.68
		EBV-neg	77/101 (76)	3.7	0.087
		Allograft involved	19 (18)	1.0	0.98
		FISH: MYC	20 (19)	2.4	0.46
		MYC + BCL2	1 (1)	NA	NA
		Early stage	15 (14)	0.04	0.001
		EN disease	85 (80)	0.14	0.005

7070 **Poster Session**

Clinical and biological subtypes of follicular lymphoma revealed by tumor and immune cell states. First Author: Hengqi Liu, Department of Lymphoma, Tianjin Medical University Cancer Institute and Hospital, Tianjin, China

Background: Follicular lymphoma (FL) exhibits considerable variability in biological features and clinical trajectories, compounded by a complex tumor microenvironment (TME) populated with nonmalignant immune cells. In this study, we comprehensively characterized FL by integrating multi-omics data that considered both tumor cells and microenvironmental components. This analysis revealed four subtypes of FL, each exhibiting distinct biological characteristics and differing clinical behaviors. **Methods:** Our study included 1,203 samples, 53 bulk transcriptomic samples from our center, 1,150 samples from public databases, and five single-cell RNA sequencing (scRNA-seq) cohorts. The Ecotyper algorithm was employed to identify immune cell states. Unsupervised clustering analysis using non-negative matrix factorization (NMF) was performed to identify distinct FL subtypes based on cellular infiltration. **Results:** A total of 30 unique cell states were identified from nine annotated cell populations (B cells, plasma cells, CD4 T cells, CD8 T cells, Tregs, NK cells, Tfh, monocytes/macrophages, and dendritic cells). Validation was performed across three independent scRNA-seq and bulk transcriptomic cohorts to ensure robustness. Four distinct B cell states were identified, each exhibiting unique gene expression profiles and varying prognostic implications. B cell S2 and S3 were associated with adverse outcomes. Notably, PRDM15 in B cell S2 had the most significant prognostic impact, remaining an independent adverse prognostic factor even after adjustment for m7-FLIPI. Mutational profile analysis demonstrated distinct mutation patterns across B cell states: mutations in CCND3, SPEN, and ARID1A were enriched in B cell S1; CREBBP and STAT6 mutations were prominent in B cell S2; and IRF8 and BCL2 mutations were observed in B cell S4, while no significant mutation enrichment was detected in B cell S3. Similarly, immune cells of the same type yet in different states exhibited functional and clinical heterogeneity. Four subtypes of follicular lymphoma characterized by distinct tumor cell states and varying immune infiltration were identified through unsupervised clustering analysis. FLE1 exhibits characteristics of a "cold tumor" with a high abundance of B cell S2. In contrast, FLE2 and FLE3 show moderate immune infiltration, while FLE4 is marked by abundant immune infiltration and elevated expression of immunosuppressive checkpoint molecules, resembling an "inflammatory" tumor phenotype. Prognostic analysis indicates that FLE1 has the most unfavorable prognosis, followed by FLE4. **Conclusions:** Our study stratifies FL patients based on the heterogeneity of tumor cells and the immune microenvironment, proposing an immune-based classification for FL. Targeting CREBBP and PRDM15 may offer promising new strategies for the clinical management of patients exhibiting a "cold tumor" phenotype. Research Sponsor: None.

7071 **Poster Session**

Clinical outcomes of hemophagocytic lymphohistiocytosis in patients with HIV-related lymphomas: A multicentre observational study. First Author: Alessia Dalla Pria, Department of Oncology and National Centre for HIV Malignancy, Chelsea and Westminster Hospital, London, United Kingdom

Background: Secondary Hemophagocytic Lymphohistiocytosis (HLH) is a rare and potentially fatal inflammatory disorder triggered by infections, malignancies, autoimmune diseases or drug reactions. A very limited body of evidence is available regarding HLH in people living with HIV (PLWH). The aim of this report is to evaluate the frequency, clinical characteristics and outcomes of HLH in a multicentre cohort of patients with HIV-related lymphomas (HRL). **Methods:** We retrospectively reviewed prospectively collected data of HRL patients treated at the National Centre for HIV Malignancy, Chelsea and Westminster Hospital, London (2013- 2024) and at the Department of Infectious Diseases at St. Joseph Hospital Berlin-Tempelhof, Germany (2020-2024). The diagnosis of HLH was based on both the HLH-2004 diagnostic criteria and the H-Score Saint Antoine. Statistical analyses were performed using IBM SPSS software. **Results:** We enrolled 253 patients in this study (17.4% female at birth; median age = 48.6 years, range 21.3 – 82.9). Median CD4 count was 206 cells /μL (range, 3-1.610) with 124 patients (49.2%) having a CD4 cell count $<$200/μL. Mean HIV viral load (VL) was 182.458 cop/mL (range, 0-26.000 .000), with 140 (55.3%) being undetectable at the time of lymphoma diagnosis. 206 (81.4%) had advanced stage disease, III (14.4%) or IV (67%). Median follow-up was 31 months and the 5-year overall survival was 51.3%. At the time of lymphoma diagnosis, 35 patients (13.5%) were diagnosed with HLH with an H-Score $\geq$169 points and/or $\geq$ 5/8 HLH criteria with a median age of 45.7 years (range 22.8-64.2), whereas 24 patients (9.5%) had an H-Score $\geq$ 200 points. HLH was present in 25% of patients with Primary Effusion Lymphoma, followed by 24.2% in Burkitt Lymphoma, 18.7% in Hodgkin´s Lymphoma, 9.5% in Plasmablastic Lymphoma, and 6.6% in Diffuse-large-B-cell Lymphoma. HLH patients were more likely to be diagnosed with HIV and lymphoma simultaneously (*p=0.001*), less likely to have a suppressed HIV-VL (31.4% vs 61%; $p < 0.01$) and had a lower median CD4 count (102 vs. 239 cells/μL; $p < 0.01$). A significant correlation was identified between a lower CD4 count and a higher H-Score in the bivariate analysis. Patients with HLH demonstrated a significantly poorer outcome with 1-, 2-, and 5-year overall survival of 41.2%, 32.4% and 11.8% compared to patients without HLH ($p < 0.01$). **Conclusions:** HLH is considerably more frequent in HRL in comparison to lymphomas affecting the general population. Outcome is poor and comparable to published data in HIV-negative cohorts. The acquired immune disfunction and the complex interplay of HIV and oncogenic viruses such as EBV and HHV8 in this population creates multiple potential triggers for this fatal inflammatory disorder of which the immunopathological basis is yet to be understood. Research Sponsor: None.

7072 **Poster Session**

Effect of pre-biopsy steroids on diagnostic yield in diffuse large B-cell lymphoma (DLBCL). First Author: Sathwik Madireddy, Brown University Health, Providence, RI

Background: DLBCL is an aggressive lymphoma, and patients (pts) often require urgent steroid administration for symptom relief or organ compromise prevention. Steroids before biopsy are avoided due to concerns about diagnostic accuracy. This supposition remains underexplored, with limited evidence supporting this practice. **Methods:** A retrospective chart review of pts with a diagnosis of DLBCL at Brown University Health between 2015 and 2024 was conducted for baseline demographics, steroid administration within 30 days of first biopsy, type and dose of steroids, markers of disease severity, type of biopsy, and biopsy results. Exclusion criteria included relapsed/refractory DLBCL. Statistical analysis was conducted using Chi-square test, T-test, and logistic regression. **Results:** 365 pts met inclusion criteria, of whom 65 received steroids prior to their first biopsy. Both steroid-treated and steroid-naive pts had similar baseline demographics (age) and markers of disease severity (LDH, "Double HIT" status, IPI score, and Stage), ($p > 0.05$). Both groups had similar rates of diagnostic first biopsies ($p > 0.05$). After initial negative biopsies, similar rates of diagnostic repeat biopsies were observed. Neither group had a significant difference in treatment delay from initial negative biopsy to start of chemotherapy ($p > 0.05$). Logistic regression analysis showed no statistical significance in the relationship between total dose of steroids and the likelihood of a diagnostic biopsy result (p = 0.07). Type of biopsy influenced diagnostic yield: fine needle aspiration (n = 32) was inferior with 28% diagnostic biopsies compared with core needle, excisional or incisional biopsies (n = 284) at 88% ($p < 0.001$). **Conclusions:** No significant differences were observed in biopsy success rates or treatment delays between steroid-treated and steroid-naive patients. These results support the safe use of corticosteroids when clinically indicated. Notably, biopsy type, rather than steroid exposure, was the primary determinant of diagnostic success, with fine needle aspiration yielding significantly lower diagnostic rates. These findings reinforce the importance of biopsy selection and support corticosteroid use without compromising diagnostic accuracy. Research Sponsor: None.

Characteristics	Steroids-treated (n=65)	Steroid-naive (n=283)	P value
Age (years), mean (95% CI)	67 (64 - 70)	67 (65 - 69)	0.805
Advanced Stage, proportion (95% CI)	64.15%	71.48%	0.286
LDH (U/L), mean (95% CI)	392 (297 - 487)	364 (315 - 413)	0.637
Percent "Double Hit"	13.85%	9.54%	0.304
Percent first biopsy diagnostic	86.67%	81.79%	0.219
Percent repeat biopsy diagnostic	87.50%	97.92%	0.116
Days from first negative biopsy to treatment, mean (95% CI)	39.5 (12.6 - 66.4)	50.7 (42.9 - 58.5)	0.327
Total steroid dose in prednisone equivalents (mg), mean (95% CI)	261 (193 - 329)	0	N/A
Total days on steroids, mean (95% CI)	6.8 (4.5 - 9.1)	0	N/A

7073 Poster Session

The optimized HLH inflammatory index: A novel prognostic tool for newly diagnosed patients with diffuse large B-cell lymphoma—Discovery and validation. First Author: Adi Zoref Lorenz, Meir Medical Center, Faculty of Medicine and Health Sciences, Tel Aviv University, Kfar Sava, Israel

Background: The Optimized HLH Inflammatory (OHI) index (Zoref-Lorenz et al., *Blood*, 2022), based on serum soluble CD25 (sCD25) and ferritin, is a prognostic tool identifying inflammation in the hemophagocytic lymphohistiocytosis (HLH) spectrum and early mortality risk. Prior studies were retrospective and enriched with HLH-suspected cases. We hypothesized that the OHI index would predict outcomes in unselected diffuse large B-cell lymphoma (DLBCL). **Methods:** 670 newly diagnosed DLBCL patients from a prospective cohort (2002–2015) were analyzed: 335 for discovery and 335 for validation. Pre-treatment serum sCD25 and ferritin levels were quantified via ELISA, and we evaluated original thresholds (sCD25 $\geq$ 3,900 U/mL; ferritin $\geq$ 1,000 ng/mL) and developed DLBCL-optimized thresholds (using receiver operator curves) for predicting 500-day mortality. We also evaluated event-free survival (EFS), EFS at 24 months (EFS24), and overall survival (OS). **Results:** The median age was 64, and 51% were male. Using original thresholds, 4.2% (n=14) of patients were OHI+, with a 5.6-fold higher risk of 500-day mortality (95% CI 1.6–17; p$<$0.001). Optimized thresholds identified 23.6% (n=78) as OHI+ with a 9.2-fold higher 500-day mortality risk (95% CI 4.0–24; p$<$0.001). Optimized OHI+ also had a higher risk of EFS24 failure and inferior EFS and OS (Table). OHI+ patients had higher rates of B symptoms (35% vs. 20%; p=0.027), elevated LDH (76% vs. 34%; p$<$0.001), worse performance status (ECOG $\geq$2: 38% vs. 12%; p$<$0.001), and advanced-stage disease (Stage IV: 57% vs 38%; p$<$0.001), though IPI scores (3–5) were not significantly different (44% vs 36%; p=0.28). Adjusting for age and IPI, OHI+ independently predicted 500-day mortality (OR=5.0; CI 1.9–13; p=0.001), EFS24 failure (OR=3.2; CI 1.5–6.5; p=0.0018), and inferior long-term EFS (HR=2.2; CI 1.1–4.3; p=0.030) and OS (HR=2.0; CI 1.0–4.0; p=0.040) at a median follow up of 9.8 years in living patients. In validation, optimized OHI predicted 500-day mortality, EFS24 failure, and long-term OS and EFS (Table). Cytokine profiling revealed elevated inflammatory markers in OHI+ patients, including IL1a (p=0.008), CCL2 (p=0.03), CXCL10 (p$<$0.001), and CXCL9 (p$<$0.001), reflecting systemic hyperinflammation. **Conclusions:** The OHI index is a powerful predictor of early and long-term outcomes in DLBCL patients. Optimized thresholds identify a larger OHI+ group, highlighting hyperinflammation's critical role in poor outcomes. These findings support its use in routine management and clinical trial design for novel therapies. Research Sponsor: ASCO-ICRF; Conquer Cancer, the ASCO Foundation; The Varda and Boaz Dotan Research Center for Hemato-Oncology Research.

Odds ratios or hazard ratios and p-values for optimized OHI+ and DLBCL prognosis.

Outcome	Discovery	Validation
OR for 500-day mortality	9.2; p$<$0.001	4.0; p=0.002
OR for EFS24 failure	5.2; p $<$0.001	6.3; p$<$0.001
HR for OS	2.3; p$<$0.001	1.8; p=0.006
HR for EFS	2.4; p$<$0.001	2.5; p$<$0.001

7074 Poster Session

The effect of patient self-reported confidence on psychosocial outcomes in the context of lymphoma and chronic lymphocytic leukaemia. First Author: Steve Kalloger, Lymphoma Coalition, Las Vegas, NV

Background: Adverse psycho-social outcomes (APSO's) are common side effects often underreported which have great impact on the wellbeing of patients with lymphoma or chronic lymphocytic leukemia (CLL). As patient's traverse through their unique cancer journey, relationships with their care team yield varying degrees of confidence. We explored how confidence in both the management of their care and in the doctor coordinating their care was associated with various APSO's. **Methods:** A cross-sectional, anonymous online global survey directed at patients with lymphoma or CLL was deployed in 2024. Two questions asked how confident the patient feels about 1) the management of their care (MOC) and 2) the doctor coordinating their care (DCC). Patients were split into dichotomous groups who were and were not confident. Nominal logistic regression was used to explore how answers to these two questions influenced the prevalence of 19 different APSO's controlling for age and biological sex. Results were expressed in odds ratios with 95% confidence intervals. **Results:** Responses were received from 5,186 patients with 64% female and a median age of 61 [20-96]. Significantly increased incidence of APSO's associated with a lack of confidence in the MOC included: conflicts between beliefs and cancer treatment OR = 2.3 [1.4 – 3.6]; loss of meaning/purpose OR = 1.9 [1.5 – 2.4]; depression OR = 1.7 [1.4 – 1.99]; grief/loss OR = 1.6 [1.3 – 1.96]; loss of interest in usual activities OR = 1.6 [1.3 – 1.9]; post-traumatic stress disorder OR = 1.5 [1.2 – 1.98]; isolation/loneliness OR = 1.5 [1.3 – 1.9]; feelings of worthlessness/being a burden OR = 1.5 [1.2 – 1.9]; loss of self-esteem OR 1.5 [1.2 – 1.8]; anxiety OR = 1.5 [1.2 – 1.7]; fear of incapacitation OR = 1.4 [1.1 – 1.7]; changes in relationships OR = 1.3 [1.1 – 1.6]; worry OR = 1.3 [1.1 – 1.5]. APSO's that significantly increased due to a lack of confidence in DCC included: anger OR = 1.6 [1.2 – 2.0]; isolation/loneliness OR = 1.5 [1.2 – 1.9]; fear of incapacitation OR = 1.5 [1.1 - 1.9]. The remaining APSO's examined failed to produce significant differences regarding patient confidence levels. This analysis illustrates that approximately 73% of the APSO's reviewed in our survey had significant odds of being associated with patients who reported a lack of confidence in their MOC or the DCC. **Conclusions:** These results suggest that patients with low confidence in the management of their care plan and in the doctor coordinating their care may disproportionately experience APSO's. It is important that care teams take time to build relationships with their patients to help reinforce confidence in their care. In doing so the patient might experience fewer APSO's. Going forward, we plan to explore the effect of general practitioner involvement on patient confidence and the effect confidence has on physical side effects experienced by patients with lymphoma and CLL. Research Sponsor: Astra Zeneca; Swedish Orphan Biovitrum; Takeda Pharmaceuticals; Eli Lilly; Incyte; Kite a Gilead Company; Johnson & Johnson Innovative Medicine; Novartis; Regeneron; F. Hoffmann-La Roche Ltd; SERB Pharmaceuticals.

7075 Poster Session

Clinical characteristics and treatment outcomes of hepatosplenic T-cell lymphoma: Mayo Clinic experience. First Author: Syeda A. Mina, Mayo Clinic, Rochester, MN

Background: Hepatosplenic T-cell lymphoma (HSTCL) is a rare, aggressive peripheral T-cell lymphoma arising primarily from $\gamma\delta$ T-cells. It carries a poor prognosis and resists conventional chemotherapy. Most reports on HSTCL are case-based. This study comprehensively analyzes a large cohort, evaluating treatment strategies and survival outcomes. **Methods:** This retrospective study included patients (pts) with pathologically confirmed HSTCL diagnosed between 2000-2024, consecutively seen at Mayo Clinic MN. Clinical, pathological, genomic, and treatment-related data were extracted when available. Descriptive statistics were used to summarize baseline characteristics. Time-to-event analyses, including Kaplan-Meier estimates, median overall survival (OS), and survival time estimates were conducted from the date of diagnosis. **Results:** A total of 20 patients with newly diagnosed HSTCL were included, with a median age of 57 years (range: 35-71). The cohort was predominantly male (70%) and non-Hispanic (93%). Molecular data was available for five patients, revealing abnormalities in *STAT5B, MLL3 deletion, TP53, EZH2, TERT*, and *NF1 E291D*. The median follow-up was 27.6 months (m) with a median OS of 17.6 m (95% CI: 11.2 - NA). First-line treatment was anthracycline-based in 68% of pts and non-anthracycline-based in 32%, with higher response rates in the latter group (50% vs.83%). Although non-anthracycline regimens showed a trend toward improved 3-year OS (100% vs. 29%) the difference was not statistically significant (p = 0.16). Achieving a complete response to first-line therapy was also associated with a trend towards a better 3-year OS compared to refractory disease (80% vs. 50%, p = 0.17). Most pts (79%) underwent hematopoietic stem cell transplant (HSCT), primarily allogeneic, with only one receiving autologous HSCT. First-line therapy before HSCT was evenly distributed between anthracycline (55%) and non-anthracycline (45%) regimens. HSCT recipients had significantly higher 3-year OS than non-recipients (83% vs. 33%, p = 0.017). Notably, the patient with a TP53 mutation has remained in remission for over a year post-allogeneic HSCT. **Conclusions:** HSTCL predominantly affects younger pts, with nearly half dying within a year. Allogeneic HSCT, rarely used in other NHL subtypes, improved survival. Non-anthracycline regimens and achieving CR trended toward better outcomes. Our study, leveraging a sizable cohort, highlights the need for targeted research and novel therapies to improve HSTCL management. Research Sponsor: None.

Summary of survival outcomes in HSTCL.

Characteristics	Median OS (y)	3-Year OS (95% CI)
	1.48 [0.93- NA]	46% [0.26 - 0.81]
Transplant		
Transplant	NA [NA - NA]	83% [0.58 - 1.00]
No Transplant	1.02 [0.93 - NA]	33% [0.07 - 1.00]
Treatment		
Anthracycline Based	1.02 [0.36 - NA]	29% [0.11 - 0.73]
Non-Anthracycline Based	4.61 [NA- NA]	100% [1.00 - 1.00]

7076 Poster Session

Influence of HIV on outcomes in patients with diffuse large B cell lymphoma treated with CD19 targeting CAR-T cell therapy. First Author: Shanawar Ali Waris, West Virginia University, Department of Internal Medicine, Morgantown, WV

Background: HIV+ patients have an 18-fold increased risk of developing diffuse large B Cell Lymphoma (DLBCL). There is uncertainty in the literature regarding the safety and efficacy of chimeric antigen receptor T-cell (CAR-T) therapy in HIV+ patients. This study aims to evaluate the influence of HIV infection on outcomes in patients treated with CD19 targeting CAR-T therapy. **Methods:** This is a multicenter retrospective cohort study that included patients with co-diagnosis of DLBCL and HIV who received a CD19 targeting CAR-T in the TriNetX Network, a database of deidentified electronic medical records with over 130 million patient records. Outcomes comprised of 5-year mortality, development of cytokine release syndrome (CRS), development of immune effector cell-associated neurotoxicity syndrome (ICANS), risk of infection, hypogammaglobinemia, and treatment with Tocilizumab, G-CSF, or IVIG. **Results:** Eighty-one patients met inclusion criteria. The mean current age was 62 years old, 75.6% were White, 16.3% were Black, 11.6% were Asian, and 73.3% were male. Approximately 72% of patients received Fludarabine/Cyclophosphamide, while 19% received Bendamustine as lymphodepletion chemotherapy. Within the cohort, 42% died within 5 years; 58% developed infection following treatment with CD19 targeting CAR-T therapy. The risks for CRS and ICANS were 65% and 14%, respectively; 53% treated with tocilizumab. Approximately 46% of patients developed hypogammaglobinemia; 31% were treated with IVIG, and 44% were treated with G-CSF. Further analysis to assess effect of development of CRS on outcomes showed no significant difference in survival probability among patients with or without CRS. **Conclusions:** CD19 CAR-T therapies have emerged for patients with refractory or relapsed DLBCL; however, HIV+ patients have been excluded from all registration CAR-T Cell clinical trials. Compared to the general population, our study demonstrates HIV+ patients with DLBCL have a similar mortality and morbidity rates when treated with CD19 targeted CAR-T therapy, indicating that in the future perhaps these patients should not be excluded from clinical trials. Research Sponsor: None.

Outcomes	Patients in Cohort	Patients with Outcome	Risk (%)
Mortality	81	34	42%
CRS	81	53	65.4%
CRS Grade 1 or 2	81	21	25.9%
CRS 3, 4, or 5	81	20	24.7%
ICANS	81	11	13.6%
Overall Infection	81	47	58%
Bacterial Infection	81	24	29.6%
Viral Infections	81	23	28.4%
Treatment with Tocilizumab	81	43	53.1%
Hypogammaglobulinemia	81	37	45.7%
Treatment with IVIG	81	25	30.9%
Treatment with G-CSF	81	36	44.4%

7077 **Poster Session**

Frontline brentuximab vedotin (BV) and CHP in patients (pts) with peripheral T-cell lymphoma (PTCL) with <10% CD30 expression: Primary analysis results from the phase 2 SGN35-032 study. First Author: Swaminathan P. Iyer, The University of Texas MD Anderson Cancer Center, Houston, TX

Background: BV, an antibody-drug conjugate targeting CD30, has shown single-agent activity in lymphomas with low CD30 expression. The combination of BV plus cyclophosphamide, doxorubicin, and prednisone (A+CHP) was effective in pts with PTCL with CD30 ≥10%. We report primary analysis results of frontline A+CHP in pts with non-systemic anaplastic large cell lymphoma (non-sALCL) PTCL with CD30 <10%. **Methods:** SGN35-032 (NCT04569032) is an open-label, multicenter, phase 2 study. Pts received 21-day cycles of A+CHP (BV 1.8 mg/kg, cyclophosphamide 750 mg/m^2, and doxorubicin 50 mg/m^2 by IV infusion on day 1 of each cycle and prednisone 100 mg by mouth daily [days 1-5]) up to 6-8 cycles. The primary endpoint, objective response rate (ORR), was assessed by blinded independent central review per Cheson 2007. Secondary endpoints included safety and complete response (CR) rate, PFS, OS, and duration of response (DOR). Efficacy endpoints are reported per central CD30 assessment unless otherwise noted. A genAI tool (12/13/24; Pfizer; GPT-4o) developed the 1st draft; authors assume content responsibility. **Results:** As of Jul 22, 2024, 82 pts received ≥1 dose of A+CHP, including 34 in the CD30 <1% cohort and 48 in the CD30 1% to <10% cohort per local CD30 assessment. At data cutoff, all pts were off study treatment. Overall median age was 63.5 y; most pts were male (56%), were White (77%), had an IPI score of 2-3 (66%), and had an ECOG PS ≤1 (90%). The most common (≥10%) disease subtypes were PTCL-not otherwise specified (45%), angioimmunoblastic T-cell lymphoma (32%), and nodal PTCL with T-follicular helper phenotype (10%). Overall median duration of treatment was 18.0 w (range, 3-24). The ORR at treatment completion was 77% (95% CI, 66.2-85.4) with a CR rate of 63% (95% CI, 52.0-73.8). Median (95% CI) PFS and OS were 12.7 mo (9.0-not estimable [NE]) and not reached (NR; 24.4-NE). Median (95% CI) DOR was 15.9 mo (8.3-NE), but NR in either cohort. Other efficacy parameters per cohort are listed in the table. Most pts (95%) had a treatment-emergent adverse event (TEAE), with 59% having a grade ≥3 TEAE. The most common (≥10%) overall grade ≥3 TEAEs were neutropenia (18%), febrile neutropenia (17%), and anemia (10%). Treatment-related grade 5 TEAEs were reported in 2 pts (2%); 19 pts (23%) reported a BV-related serious TEAE. **Conclusions:** As a frontline therapy, A+CHP demonstrated clinically meaningful efficacy in pts with non-sALCL PTCL regardless of CD30 expression, with a safety profile consistent with the label. Clinical trial information: NCT04569032. Research Sponsor: Pfizer.

	CD30 <1%	CD30 1% to <10%
Per local CD30	**n=34**	**n=48**
ORR (95% CI), %	74 (55.6-87.1)	79 (65.0-89.5)
CR rate (95% CI), %	56 (37.9-72.8)	69 (53.7-81.3)
Per central CD30	**n=23**	**n=31**
ORR (95% CI), %	61 (38.5-80.3)	81 (62.5-92.5)
CR rate (95% CI), %	52 (30.6-73.2)	71 (52.0-85.8)
PFS, median (95% CI), mo	10.9 (5.0-NE)	NR (8.5-NE)
OS, median (95% CI), mo	NR (11.1-NE)	NR (21.3-NE)

7078 **Poster Session**

ALK-positive anaplastic large cell lymphoma: Statistics and survival trends. First Author: Hassan Ali, Mercy Catholic Medical Center, Darby, PA

Background: Anaplastic lymphoma kinase positive anaplastic large cell lymphoma (ALK+ ALCL) is a rare subtype of peripheral T-cell lymphoma, characterized by CD 30+ large pleomorphic lymphoid cells with horseshoe nuclei and abundant cytoplasm. It frequently involves t(2;5) combining ALK with nucleophosmin (NPM1) gene. ALK+ ALCL is chemotherapy responsive, and CHOP, CHOEP (CHOP+etoposide) or BV-CHP (brentuximab instead of vincristine) are the popular drug combinations used. **Methods:** We extracted ALK+ ALCL cases using the ICD Code 9714/3, from Surveillance, Epidemiology and End Result (SEER) database Research Plus Data, 17 Registries, Nov 2023 Sub (2000-2021). The analysis was stratified based on age, sex, race, primary site labelled, laterality, stage, median household income inflation adjusted to 2022, and treatment options utilized. Survival curves were compared using the Log-Rank test (GraphPad Prism). **Results:** Total 3916 cases of ALK+ ALCL were identified, with median age at diagnosis of 53.5 years. Of the cases, 61% were males. Racial distribution was noted as: Caucasians 63.2%, Hispanics 16.1%, Blacks 12.4%, Asian/Pacific Islanders 6.7%, American Indians/Alaskan and unknown race were <1%, each. Overall median of survival (MoS) was 118 months, with 1-year OS of 0.696 (CI 95%, 0.68-0.71), 3-year OS of 0.61 (CI 95%, 0.596-0.63), and 5-year OS of 0.57 (CI 95%, 0.56-0.59). MoS were significant for Age: 0-30 yrs (undefined), 31-60 (233), 60+ yrs (17) (p <0.0001); Gender: males (94) and females (153) (p 0.0011); Race: White (119), Black (49), Hispanics (118), Asian/Pacific Islanders (180), Alaskan/Native Americans (87), and unknown race (undefined) (p <0.0001); Laterality: right (162), left (173), bilateral (144), and unknown side (66) (p <0.0001). Survival based on stage was undefined for loco-regional disease, 67 for distant and 65 months for unknown stage (p <0.0001). Anatomically, analysis revealed higher MoS with connective tissue (179), head/face/neck (72), and lymphoid origin (119); while lower survival with GI (21), thorax (13), and unknown site (7) (p <0.0001). MoS improved with increasing income, <70,000$ (73), 70K-100K (129), and >100K (135) (p <0.0001). Treatment based analysis showed: surgery (151) vs no surgery (100) (p <0.0001), chemotherapy (182) vs no chemo (27) (p <0.0001), radiotherapy (XRT) (173) vs no XRT (108) (p <0.0001). Undefined MoS were likely observed due to insignificant numbers of death in those age categories to calculate 50% survival probability. **Conclusions:** ALK+ ALCL is a rare malignancy that favors male gender, and Caucasian race. Our analysis revealed superior survival outcomes associated with younger age, female sex, Asian/Pacific Islander origin, connective tissue involvement, unilateral and loco-regional disease, and treatment involving either surgery or non-surgical options, specifically chemotherapy. This is the first study to our knowledge to establish association of ALK+ ALCL to income, showing higher survival with increasing income bracket. Research Sponsor: None.

7079 **Poster Session**

Safety and efficacy of chimeric antigen receptor (CAR)—T cell therapy (BRG01) targeting the Epstein-Barr virus (EBV) envelope protein in EBV+ lymphoproliferative disease patients. First Author: Xinfeng Chen, The First Affiliated Hospital of Zhengzhou University, Zhengzhou, Henan, China

Background: Epstein-Barr virus (EBV) is a type I carcinogen which has infected more than 95% of population. EBV infection is closely associated with infectious mononucleosis and various malignancies. The envelope glycoprotein gp350 is present on EBV-infected host cells and serves as a potential tumor-specific antigen for the treatment of EBV$^+$ solid tumors like nasopharyngeal cancer as reported previously (NCT05864924)[1,2]. Anti-gp350 CAR-T also demonstrated robust inhibition for EBV replication and lymphoproliferation in a humanized mouse EBV infection model[3]. Here we explored the safety and efficacy of anti-gp350 CAR-T (BRG01) against EBV$^+$ T cell lymphoproliferative disease (LPD) in an exploratory pilot trial study. **Methods:** Patients with EBV$^+$ T cell LPD failing at least two lines of standard therapies were enrolled. Other criteria include EBER$^+$ and Gp350$^+$ expression on tumor biopsies. A single dose of EBV CAR-T cells (BRG01) were infused after a lymphodepletion regimen (cyclophosphamide 250-350 mg/m^2/day, fludarabine 25-30 mg/m^2/day for three days). Safety profile, pharmacokinetics (PK), EBV DNA copy number in the peripheral blood and tumor burden were monitored after BRG01 treatment. **Results:** From September 2021 to June 2023, a total of three patients with EBV$^+$ T cell LPD, subject 01, 02 and 03 were treated with 3*10^6/kg, 9*10^6/kg and 1.5*10^7/kg BRG01 respectively. The cells expanded and proliferated well in the patients. The EBV DNA copies in the peripheral blood of subject 01 and 03 decreased significantly post BRG01 infusion and remained at less than 500 copies/ml for subject 02. The disease control rate for the three patients is 100% (3/3) and the overall response rate is 66.7% (2/3) based on Lugano 2014 criteria. One patient showed complete metabolic remission 28 days post 9*10^6/kg BRG01 infusion and remained disease free for over three years. **Conclusions:** BRG01 is well tolerated and expanded in all treated patients. The durabler efficacy in all treated patients supports its further clinical investigation in various subtypes of EBV$^+$ lymphomas and LPD. 1. Zhang X, Wang T, Zhu X, et al: GMP development and preclinical validation of CAR-T cells targeting a lytic EBV antigen for therapy of EBV-associated malignancies. Frontiers in Immunology 14: 1103695, 2023. 2. Zhang L, Zhao H, Ma Y, et al: 899P Safety and efficacy of a novel CAR-T cell therapy (BRG01) targeting the Epstein-Barr Virus envelope glycoprotein in advanced metastatic nasopharyngeal cancer patients. Annals of Oncology 35:S636, 2024. 3. Slabik C, Kalbarczyk M, Danisch S, et al: CAR-T cells targeting Epstein-Barr virus gp350 validated in a humanized mouse model of EBV infection and lymphoproliferative disease. Molecular Therapy-Oncolytics 18:504-524, 2020. Clinical trial information: ChiCTR2100044497. Research Sponsor: None.

7080 **Poster Session**

Second primary malignancy in patients with diffuse large B-cell lymphoma (DLBCL) receiving chimeric antigen receptor T-cell (CAR T) therapy and other systemic anti-cancer therapy: A real-world data analysis. First Author: Matthew Alexander Lunning, University of Nebraska Medical Center, Omaha, NE

Background: CAR T therapy is a recent class of treatment for DLBCL and has been linked to the development of second primary malignancy (SPM), specifically T-cell malignancies. This study compared the risk of SPM in patients (pts) with DLBCL receiving CAR T therapy vs other systemic anti-cancer therapy (SACT). **Methods:** Adult pts with a diagnosis of DLBCL who received CAR T therapy or other SACT as second or higher line of therapy (LoT) were identified from Komodo Health claims data (10/18/2017–1/31/2024). Incident SPM (first diagnosis in pts with no history of that malignancy) was assessed from index treatment initiation through earliest report of death, disenrollment from medical coverage, or data cutoff (4/30/2024). Cumulative incidence of SPM was calculated using the Aalen–Johansen estimator with baseline risk factors, including previous treatments and number of prior LoTs (pts may contribute to multiple LoTs), demographic and lifestyle factors, and comorbidity history balanced between the treatment groups using inverse probability of treatment weighting. **Results:** The study assessed a total of 1079 (CAR T therapy) and 5836 (SACT) LoTs over a median follow-up of 10.6 months (IQR 4.3–24.3). The risk of SPM (95% CI) at 3 years post-index tended to be nominally lower in the CAR T therapy group vs the SACT group for any (37.2% [33.4, 40.7] vs 41.6% [35.5, 48.7]), hematologic (27.4% [23.8, 30.7] vs 28.5% [22.8, 35.0]; excluding DLBCL relapse), solid (14.7% [12.3, 17.1] vs 18.4% [14.8, 23.0]) (Table) and T-cell (2.6% [1.7, 3.8] vs 4.3% [2.8, 5.9]) SPM. A sensitivity analysis identifying SPM using ≥2 ICD-10 codes showed similar associations. In another sensitivity analysis excluding SPMs occurring in the first 3 months of follow-up, the risk in the CAR T therapy group remained nominally lower for any, solid, and T-cell SPMs, and higher for hematologic SPM, compared with the SACT group (Table). **Conclusions:** A large proportion of pts with DLBCL experienced SPMs with current treatment options. At 3 years post-index, there was no evidence of an increased risk of SPM in pts treated with CAR T therapy compared with those receiving SACT. Longer term studies are needed to confirm this observation. Research Sponsor: Regeneron Pharmaceuticals, Inc.

Cumulative incidence (%) and 95% CI of SPM at 3 years post-index.

SPM	Analysis	SACT	CAR T therapy	p-value
Any	Main	41.6 (35.5, 48.7)	37.2 (33.4, 40.7)	0.20
	S1	32.4 (26.0, 40.3)	23.1 (20.0, 26.3)	0.08
	S2	34.4 (27.7, 41.2)	32.5 (28.6, 36.2)	0.81
Hematologic	Main	28.5 (22.8, 35.0)	27.4 (23.8, 30.7)	0.28
	S1	20.1 (14.4, 26.2)	16.9 (14.2, 20.3)	0.35
	S2	20.7 (15.3, 26.8)	22.9 (19.3, 25.9)	0.55
Solid	Main	18.4 (14.8, 23.0)	14.7 (12.3, 17.1)	0.34
	S1	13.8 (9.6, 18.6)	8.3 (6.4, 10.2)	0.11
	S2	17.7 (12.8, 23.5)	13.6 (11.5, 16.2)	0.41

S1: ≥2 ICD-10 codes for SPM identification; S2: excludes SPM diagnosed in the first 3 months.
S1/2, sensitivity analysis 1/2.

7081 **Poster Session**

A phase I/II trial of high-dose methotrexate (HDMTX) followed by prophylactic glucarpidase in patients with impaired renal function and central nervous system lymphoma (CNSL). First Author: Sven Liebig, Department of Hematology, Oncology and Cancer Immunology (Campus Benjamin Franklin), Charité – Universitätsmedizin Berlin, Corporate Member of Freie Universität and Humboldt-Universität Zu Berlin, Berlin, Germany

Background: HDMTX is a key component of treatment protocols for CNSL patients (pts), but impaired renal function in elderly or comorbid pts limits its use. The recombinant enzyme glucarpidase rapidly hydrolyzes MTX into non-toxic metabolites and is approved for therapeutic use in pts with delayed MTX elimination following HDMTX. We conducted a phase I/II study (NCT04841434) to assess the efficacy of prophylactic glucarpidase in HDMTX-treated pts with renal impairment or a history of delayed MTX elimination. **Methods:** A total of 18 pts with CNSL and pre-existing renal insufficiency (glomerular filtration rate [GFR] 40–80 mL/min) or a history of renal failure post-HDMTX were treated with up to six HDMTX cycles. HDMTX was given as a 4-hour infusion at three dose-escalation levels (3.0, 3.5, and 4.0 g/m²; 6 pts each). Glucarpidase (2000 U IV) was administered in each cycle 24 hours after start of HDMTX. The coprimary endpoints were safety and pharmacological efficacy of glucarpidase. Plasma concentrations of MTX and its metabolites were monitored using combined liquid chromatography-tandem mass spectrometry. **Results:** Overall, 18 pts (63-86 years, median 78) were enrolled with a median baseline GFR of 69.5 mL/min. A median of 3.5 HDMTX treatment cycles was given, with 6 pts completing the maximum allowed 6 cycles. Reasons for protocol-predefined early termination included clinical non-response or radiological disease progression (n=8), investigator decision due to adverse event (AE; n=2), and termination criteria (n=2). Administration of glucarpidase resulted in a median reduction of MTX plasma levels within 15 minutes by 99.2% (95% CI: 98.4-99.1%). Results from serum samples analyses for anti-glucarpidase antibodies were performed and will be available by the meeting, but in pts with more than two HDMTX cycles, there was no statistically significant difference in the reduction of MTX plasma levels between the first and last cycles (p=0.47). Glucarpidase treatment reduced MTX plasma levels to a median of 0.05 μmol/L (range 0.00-0.84) within 15 minutes. MTX plasma levels remained consistently below 0.6 μmol/L across all cycles at 42 hours or later after start of the HDMTX infusion. A single grade III AE potentially related to glucarpidase was recorded: a transient facial flushing with a brief loss of consciousness and rapid and spontaneous full recovery. This event prompted implementation of a premedication (prednisolone, antihistaminic) in all subsequent treatment cycles. No further glucarpidase-related AE's grade >II occurred. **Conclusions:** The repeated prophylactic application of glucarpidase was feasible and safe and facilitated HDMTX treatment in pts at risk for delayed MTX elimination. This approach may enable adequate HDMTX dosing in pts with renal insufficiency and limiting comorbidities, and should be further evaluated. Clinical trial information: NCT04841434. Research Sponsor: Protherics Medicines Development Limited.

7082 **Poster Session**

Variable response rates across chemotherapy regimens for severe idiopathic multicentric Castleman disease. First Author: Saishravan Shyamsundar, Center for Cytokine Storm Treatment & Laboratory, Department of Medicine, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA

Background: Idiopathic multicentric Castleman disease (iMCD) is a hematologic disorder treated by oncologists and characterized by diffuse lymphadenopathy and systemic inflammation that can cause multi-organ failure. iMCD subtypes include thrombocytopenia, anasarca, fever, renal dysfunction, and organomegaly (TAFRO) and not otherwise specified. Siltuximab, an interleukin 6 (IL6) antagonist, is the only FDA-approved treatment. For patients with severe disease worsening after siltuximab, consensus guidelines recommend combination chemotherapy though data is limited in guiding chemotherapy selection. **Methods:** The ACCELERATE registry leverages an expert panel who reviewed medical history and lymph node biopsy slides to rigorously confirm the diagnosis for each patient. To achieve a clinical response, the proportion of abnormal clinical and laboratory criteria assessed prior to regimen initiation has to decrease by at least 50% after regimen initiation. Regimens were grouped based on inclusion of cyclophosphamide, etoposide, doxorubicin, and bortezomib. We quantified response rates and times to next treatment for regimens containing these chemotherapies but statistical comparisons were not possible due to overlapping treatments used across these groups. Response rates for chemotherapy ± IL6 inhibition were compared. **Results:** We identified 34 (31%) chemotherapy recipients among 111 diagnosis-confirmed iMCD patients: 71% were male, 91% had iMCD-TAFRO; 35 years median age at diagnosis. All iMCD-TAFRO patients met the criteria for severe disease. We found 52 chemotherapy regimens administered to 34 patients. We observed 33 (64%) of the 52 regimens included cyclophosphamide; 23 (44%) etoposide; 21 (40%) doxorubicin; 15 (29%) bortezomib. Regimens were typically given with more than one agent. Twenty-two (42%) were co-administered with anti-IL6. Nineteen (68%) patients had a response if the regimen included cyclophosphamide; 14 (64%) etoposide, 10 (56%) doxorubicin; and 9 (69%) bortezomib. Response rates for all regimens were 60% with IL6 inhibition compared to 64% without. For cyclophosphamide, etoposide, doxorubicin, and bortezomib regimens, median time to next treatment was 9, 4, 4, 6 months, respectively. **Conclusions:** We found that almost all iMCD patients who received chemotherapy had TAFRO with severe disease. We observed relatively similar response rates across different chemotherapy containing regimens and for patients who received chemotherapy with and without IL6 inhibition. Time to next treatment was longer in the cyclophosphamide group, but this could not be statistically tested. Altogether, we provide the first study of the comparative effectiveness of chemotherapies against iMCD. Research Sponsor: U.S. Food & Drug Administration; R01FD007632.

TPS7083 **Poster Session**

SOUNDTRACK-E: A phase 1/2, open-label, multicenter study to evaluate the safety and efficacy of AZD0486 monotherapy or combination therapy in patients with mature B-cell malignancies. First Author: Toby Andrew Eyre, Cancer and Haematology Centre, Oxford University Hospitals NHS Foundation Trust, Oxford, United Kingdom

Background: AZD0486 is an IgG4 fully human CD19xCD3 bispecific T-cell engager that binds CD3 with low affinity to potentially reduce cytokine release upon T-cell activation while preserving effective T-cell cytotoxicity against malignant B cells. In a first-in-human phase 1 trial (NCT04594642), AZD0486 was active and well tolerated in patients (pts) with relapsed/refractory (R/R) follicular lymphoma or R/R diffuse large B-cell lymphoma (Gaballa S, et al. *Blood*. 2024;144:868; Hou JZ, et al. *Blood*. 2024;144:341). This study assesses fixed-duration subcutaneous (SC) AZD0486 monotherapy in B-cell malignancies and fixed-duration SC or intravenous AZD0486 in combination with other anticancer agents. This study is the first to evaluate SC AZD0486, and the first to evaluate AZD0486 in chronic lymphocytic leukemia (CLL). **Methods:** SOUNDTRACK-E (NCT06564038) is a phase 1/2 dose-escalation, global, multicenter trial of AZD0486 with 3 substudies. The study is recruiting pts aged ≥18 years with Eastern Cooperative Oncology Group performance status 0–2 and a histologically confirmed diagnosis. Pts with clinically significant central nervous system events (eg, seizure, stroke) or cardiovascular disease are excluded. Substudy 1 evaluates SC AZD0486 in R/R CLL/small lymphocytic lymphoma and includes a monotherapy cohort (1A; ≥2 prior lines of therapy [pLOT] with Bruton tyrosine kinase inhibitor exposure) and a cohort that receives combination with acalabrutinib (1B; ≥1 pLOT). Substudy 2 evaluates SC AZD0486 in R/R mantle cell lymphoma and includes a monotherapy cohort (2A; ≥2 pLOT) and a cohort that receives combination with acalabrutinib (2B; ≥1 pLOT). Substudy 3 evaluates AZD0486 in combination with R-CHOP in pts with untreated large B-cell lymphoma with International Prognostic Index ≥2, or R/R B-cell non-Hodgkin lymphoma with ≥1 pLOT. In each cohort, AZD0486 is administered via a double step-up dosing schedule in cycle 1; the target dose is given every 2 weeks. Treatment is administered for 24 (28-day) cycles in substudy 1, 12 (28-day) cycles in substudy 2, and 17 (21-day) cycles in substudy 3. Pts in cohorts 1B and 2B receive acalabrutinib 100 mg orally BID beginning at cycle 2. In substudy 3, R-CHOP is administered once every 3 weeks for 6 cycles. Dose escalation decisions will be based on a modified probability interval (mTPI-2) design. Approximately 46 pts for each cohort in substudies 1 and 2 and 36 pts in substudy 3 (~200 total pts) will be recruited. Primary objectives are to assess safety and tolerability, and to determine the recommended phase 2 dose for AZD0486 as monotherapy and combination therapy in mature B-cell malignancies. Secondary objectives include efficacy endpoints, pharmacokinetics, and immunogenicity. Enrollment opened in October 2024. Clinical trial information: NCT06564038. Research Sponsor: AstraZeneca.

TPS7084 **Poster Session**

A phase 2 trial to evaluate the efficacy and safety of WZTL-002, a third-generation anti-CD19 CAR T-cell therapy, in patients with relapsed or refractory large B-cell lymphoma (ENABLE-2). First Author: Aine Hurley, Malaghan Institute of Medical Research, Wellington, New Zealand

Background: Autologous chimeric antigen receptor (CAR) T-cells directed against CD19 are a standard of care for relapsed or refractory (r/r) large B-cell lymphoma (LBCL). CAR T-cells incorporating a CD28 costimulatory domain are among the most effective CAR T-cell therapies for LBCL, but are associated with high rates of cytokine release syndrome (CRS) and immune effector cell-associated neurotoxicity syndrome (ICANS). In a phase I dose escalation and expansion study (ENABLE-1, NCT04049513), a new 'third-generation' CAR T-cell incorporating a TLR2 co-stimulatory domain alongside CD28 (WZTL-002) demonstrated low rates of CRS and ICANS and promising efficacy. a recommended phase 2 dose (RP2D) of 0.5 – 1.0×10^6 CAR^+ cells/kg was selected following dose escalation, and outpatient management and automated closed-system WZTL-002 manufacture were implemented within a dose expansion cohort. ENABLE-2 (ClinicalTrials.gov NCT06486051) is a multicentre phase 2 that aims to assess the efficacy and safety of WZTL-002 in patients with r/r LBCL. **Methods:** Eligible participants are age 18 – 75 years with relapsed or refractory LBCL (either de novo or transformed from follicular or marginal zone lymphoma) following 1 or 2 prior lines of therapy, have assessable disease and satisfactory organ function. Leukapheresis is conducted to obtain autologous T-cells, which are transduced *ex vivo* to express a third-generation CD19-directed CAR incorporating CD28, TLR2 and CD3zeta stimulatory domains (1928T2z). Bridging therapy is permitted pending WZTL-002 manufacture and product release. Lymphodepletion comprises intravenous fludarabine (30mg/m^2) and cyclophosphamide (500mg/m^2) daily for 3 days. Two days later a single dose of WZTL-002 is administered at 0.5 – 1.0×10^6 CAR^+ cells/kg (capped at 10^8 CAR^+ cells). Participants undergo daily outpatient assessments for toxicities including CRS and ICANS for the first 11 days after WZTL-002 administration, and at days 14 and 28. Disease response is assessed by PET/CT scans at day 28, 3 months and 6 months, and duration of response by CT scan at months 12 and 24. The co-primary endpoints are complete response rate (Lugano criteria) and ICANS rate (any grade) 3 months after WZTL-002 administration. Secondary outcomes include safety (with CRS, ICANS and cytopenias as adverse events of special interest), and progression-free, event-free and overall survival. The first participant was enrolled on 13 August 2024. Clinical trial information: NCT06486051. Research Sponsor: None.

TPS7085 **Poster Session**

ALPHA3: A pivotal phase 2 study of first-line (1L) consolidation with cemacabtagene ansegedleucel (cema-cel) in patients (pts) with large B-cell lymphoma (LBCL) and minimal residual disease (MRD) after response to standard therapy. First Author: Jason Westin, The University of Texas MD Anderson Cancer Center, Houston, TX

Background: R-CHOP as 1L therapy for LBCL has a cure rate of ~60%. However, ~10% of pts are refractory (Coiffier, *NEJM* 2002) and ~30% of responders relapse within 2 years (Maurer, *J Clin Oncol* 2014). Autologous CAR T cell therapies have revolutionized treatment of relapsed/refractory (R/R) LBCL and are considered standard 2L treatment due to improved overall survival (OS; Westin, *NEJM* 2023) but may not be an option due to aggressive disease, pt comorbidities, access barriers, and/or manufacturing issues/delays. Identifying responders to 1L therapy at high risk of relapse and rapidly administering an off-the-shelf CAR T cell therapy for remission consolidation may improve outcomes. Presence of circulating tumor DNA–based MRD, measured by PhasED-Seq, at the end of 1L therapy is highly prognostic for relapse (Roschewski, *Hematol Oncol* 2023). Cema-cel is an immediately available, off-the-shelf, HLA-unmatched allogeneic CD19 CAR T cell product made using Cellectis technologies. A phase 1 study of cema-cel in pts with R/R LBCL showed safety and efficacy comparable to that of autologous CAR T cell therapies (Locke, *J Clin Oncol* 2023). We describe the design of the pivotal ALPHA3 phase 2 study of cema-cel, the first randomized, open-label study to assess a CAR T cell therapy as a consolidation strategy in pts with detectable MRD measured by PhasED-Seq after standard 1L immunochemotherapy. **Methods:** ALPHA3 (NCT06500273) will evaluate efficacy and safety of cema-cel with 1 of 2 lymphodepletion (LD) regimens compared to standard-of-care (SOC) observation in pts with LBCL who are in response at the end of 1L therapy but test MRD+. Key eligibility criteria include histologically confirmed LBCL, completion of a full course of standard 1L therapy, ECOG PS 0/1, and adequate organ function. The study will consist of a 2-part seamless design. In Part A (currently enrolling), pts will be randomized to SOC observation or to 1 of 2 treatment arms (cema-cel [120×10^6 CAR T cells] following 3-day LD with fludarabine [30 mg/m^2/day] and cyclophosphamide [300 mg/m^2/day] with/without the anti-CD52 monoclonal antibody, ALLO-647 [30 mg/day]). Part A will conclude with an interim analysis to select the optimal LD regimen. Part B will assess efficacy of the selected regimen vs observation. The primary endpoint is event-free survival per independent review committee (IRC), with hierarchical testing of key secondary endpoints of progression-free survival per IRC and OS. Other secondary endpoints include MRD clearance, safety of cema-cel and ALLO-647, and disease outcomes after subsequent therapy. The study will enroll ~240 pts across ~50 sites at academic- and community-based centers. Site activation is ongoing; sites outside the US are being considered. The study was initiated in June 2024 with accrual into 2026. Clinical trial information: NCT06500273. Research Sponsor: Allogene Therapeutics, Inc.

TPS7086 **Poster Session**

A phase 2 study to confirm safety and efficacy of MB-105, an autologous CD5-directed CAR T-cell therapy, in relapsed/refractory T-cell lymphoma (R/R TCL). First Author: Swaminathan P. Iyer, The University of Texas MD Anderson Cancer Center, Houston, TX

Background: R/R TCL presents an unmet clinical need with limited treatment options and 3-year survival $<$ 20%. MB-105 is an autologous CD5-targeting CAR T-cell therapy developed at Baylor College of Medicine that has been designed to address the unique challenge of treating T-cell malignancies by overcoming CAR T-cell fratricide without additional engineering. In the phase 1 trial, 44% (4/9) patients experienced objective responses, including 2/3 complete responses with survival $>$5 years. Mid-trial manufacturing refinements enhanced MB-105 potency and persistence without compromising safety. We have developed an industrialized, 6-day process of manufacturing MB-105 and are conducting a phase 2, multicenter study in the USA to evaluate MB-105 in patients with R/R peripheral and cutaneous TCL (PTCL, CTCL). Durable responses and safety observed across all dose levels in phase 1 guided the dose selection for this trial. **Methods:** The study follows a Simon two-stage design with a safety run-in to confirm tolerability of the recommended phase 2 dose (RP2D) of 50 million cells in 6 patients. This is followed by an efficacy evaluation first in 15 patients then 46 total. Adaptive elements allow the independent data monitoring committee to adjust doses, monitoring schedules, or lymphodepletion regimens without formal protocol amendments Primary objectives are first to confirm tolerability of the recommended dose by CTCAE v5 and ASTCT for cytokine release syndrome and immune effector cell-associated neurotoxicity syndrome (CRS/ICANS) and then evaluate efficacy through central review. Secondary/other objectives include assessing response durability, overall survival, persistence, immune correlates and manufacturing success. Adults with R/R TCL who have failed $\geq$ 1 prior systemic therapy for PTCL or $\geq$ 2 for high-volume CTCL are eligible. Local pathology for CD5 expression is required, later confirmed by central lab. Patients must have adequate organ function, Karnofsky PS $\geq$70%, and no prior cell therapy/transplant within 60 days of leukapheresis. Key exclusions are Sezary syndrome (potential for high circulating tumor cells to affect manufacturing), active CNS involvement, infections, graft-versus-host disease $>$ grade 2, or comorbidities that may interfere with study participation or endpoints. Patients are closely monitored for CRS/ICANS. Safety and efficacy are assessed intensively for the first 3 months and gradually less frequently over the subsequent 21 months. Imaging and post-infusion testing, including CAR-T persistence, immune profiling and biomarkers are conducted throughout. Patients are encouraged to participate in a separate long-term follow-up study. Recruitment is ongoing. Clinical trial information: NCT06534060. Research Sponsor: None.

TPS7087 **Poster Session**

CD5-deleted chimeric antigen receptor cells (Senza5 CART5) to enhance immunotherapy against T-cell non-Hodgkin lymphoma: A first-in-human phase I clinical trial (NCT06420089). First Author: Stefan K. Barta, Lymphoma Program, Abramson Cancer Center, University of Pennsylvania, Philadelphia, PA

Background: Autologous CART options for patients with relapsed or refractory (R/R) T-cell lymphomas (TCL) have faced challenges such as T-cell fratricide during CART manufacture and safety concerns regarding depletion of normal T cells. To overcome these obstacles, we proposed a dual cell population CART product, which contained both autologous 4-1BB costimulated CART cells against CD5 and healthy T-cells, with both populations knocked out for CD5 (CRISPR-Cas9 CD5 short-guide RNA to delete CD5 - Senza5). In vivo experiments using the dual population product of (Senza5 CART5) demonstrated increased CART5 expansion and enhanced antitumor efficacy in TCL xenograft models compared to wild-type (WT) CART5. For clinical use, a novel 5-day manufacturing process was designed to obtain a less differentiated and less exhausted product, with enhanced in vivo expansion and fitness. **Methods:** A human phase I trial was designed to determine the safety, effectiveness and recommended phase 2 dose (RP2D) of Senza5 CART5 cells in participants with R/R TCL with $\geq$50% expression of CD5 on malignant cells, and no circulating CD5+ cells. Participants must have a suitable backup stem cell product or donor identified in the unlikely event of T-cell aplasia. Patients with prior allo HCT are currently excluded. Cohorts of patients are treated with escalating doses of Senza5 CART5 cells ($3x10^6$ to $1.25x10^8$) using a Bayesian Optimal Interval design following lymphodepletion. The study will enroll and treat participants until a maximum of 9 participants are infused and evaluable for dose limiting toxicity (DLT) assessments at a given dose level, or a maximum of 30 DLT-evaluable participants from all dose levels are infused. The RP2D will be determined based on both safety and biological evidence of efficacy. Study objectives include frequency and severity of treatment-related adverse events, as well as efficacy by assessing overall and complete response rates, duration of response, progression-free and overall survival. Manufacturing feasibility will be determined by the frequency of product release failures and occurrence of dose failures (inability to meet targeted dose). Exploratory objectives will evaluate the persistence and trafficking of Senza5 CART5 cells in blood and tumor by characterizing the kinetics of the infused cells by flow cytometry and qPCR gene expression. We will perform profiling of the tumor microenvironment and measure systemic soluble cytokines before and after treatment. We will also assess the impact of CART5 on normal T cells, and the persistence of CD5KO untransduced T cells that are infused as part of the Senza5 CART5 product by multicolor flow cytometry and qPCR. The trial is sponsored by Vittoria Biotherapeutics and is registered at clinicaltrials.gov as NCT06420089. Enrollment in this trial has begun. Clinical trial information: NCT06420089. Research Sponsor: Vittoria Biotherapeutics.

TPS7088 **Poster Session**

Efficacy and safety of nemtabrutinib in relapsed or refractory chronic lymphocytic leukemia/small lymphocytic lymphoma: Cohort J of the phase 2 BELLWAVE-003 study. First Author: Thomas Kipps, UC San Diego, San Diego, CA

Background: Treatment options for patients with relapsed or refractory (R/R) chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL) can be limited if patients do not respond to both Bruton tyrosine kinase inhibitors (BTKis) and B-cell lymphoma 2 inhibitors (BCL2is). Nemtabrutinib is a once-daily, potent, noncovalent, reversible BTKi with a distinct kinase profile that inhibits BTK and other B-cell receptor relevant kinases. The multicenter, open-label, single-arm, phase 2 BELLWAVE-003 study (NCT04728893) is designed to evaluate nemtabrutinib at the recommended phase 2 dose (RP2D) in participants with R/R CLL/SLL, Richter transformation, mantle cell lymphoma, marginal zone lymphoma, follicular lymphoma, and Waldenström macroglobulinemia. Cohort J will evaluate nemtabrutinib in participants with R/R CLL/SLL who are relapsed/refractory to both a BTKi and BCL2i. **Methods:** Key eligibility criteria for cohort J include participants aged $\geq$18 years with CLL/SLL whose disease is R/R to prior therapy with both a BTKi (covalent or irreversible) and a BCL2i, and an ECOG PS of 0 to 2. Additional use of noncovalent or reversible BTKis is permitted if disease is R/R to such therapy. Participants must have received and not responded to, been intolerant to, or determined by their treating physician to be a poor PI3Ki candidate or ineligible for PI3Ki per local (institution) guidelines. Exclusion criteria include prior exposure to nemtabrutinib, active CNS disease, and prior systemic therapy with a monoclonal antibody within 5 half-lives or 4 weeks before allocation. Overall, the BELLWAVE-003 study comprises a dose escalation and confirmation phase (part 1) to establish the RP2D, and a cohort expansion phase (part 2). Part 1 evaluated nemtabrutinib in $\geq$6 to $\leq$20 participants with R/R CLL/SLL after $\geq$2 prior lines of therapy. The RP2D has been established as nemtabrutinib 65 mg QD. In part 2, ~460 participants will be enrolled across 9 expansion cohorts. Approximately 40 participants will be enrolled in cohort J. Treatment will continue until unacceptable toxicity, disease progression, or withdrawal. Adverse events will be monitored throughout and graded using NCI CTCAE version 5.0. Hematologic toxicities in participants with CLL will be assessed using iwCLL 2018 criteria. CT/MRI and/or PET will be performed every 12 weeks unless needed more frequently. The primary end point for cohort J is ORR per iwCLL 2018 criteria by independent central review (ICR). Additional end points include DOR and PFS per iwCLL 2018 criteria by ICR, OS, and safety and tolerability. Recruitment is ongoing. This is the first clinical trial with a dedicated cohort to assess noncovalent BTKis in patients whose disease has failed to respond to both BTKi and BCL2i. Clinical trial information: NCT04728893. Research Sponsor: Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA.

TPS7090 **Poster Session**

Phase 2 study of MK-3475A in relapsed or refractory classic Hodgkin lymphoma or primary mediastinal large B-cell lymphoma. First Author: Alejandro Berkovits, Immunocel Chile, Providencia, Chile

Background: The PD-1 inhibitor pembrolizumab is approved globally for the treatment of multiple cancers, including relapsed or refractory (R/R) classic Hodgkin lymphoma (cHL) and R/R primary mediastinal large B-cell lymphoma (PMBCL). Pembrolizumab is currently administered as an intravenous infusion. Subcutaneous administration of pembrolizumab offer advantages to patients, providers, and the healthcare system. MK-3475A is pembrolizumab with berahyaluronidase alfa for subcutaneous administration (subcutaneous pembrolizumab). Berahyaluronidase alfa, a human hyaluronidase variant developed and manufactured by Alteogen Inc., is a permeation enhancer that increases dispersion and allows for subcutaneous administration of pembrolizumab in 1 injection for both Q3W and Q6W dosing. Here, we describe the methodology of a single-arm, open-label, phase 2 study (NCT06504394) designed to evaluate subcutaneous pembrolizumab in participants with R/R cHL or R/R PMBCL. **Methods:** Key eligibility criteria include participants aged ≥18 years with a histologically confirmed diagnosis of cHL or PMBCL that is FDG-avid per WHO classification criteria, radiographically measurable disease, and an ECOG performance status of 0 or 1. Participants with cHL must be anti–PD-1 naive and have not responded to or relapsed after ≥1 line of multiagent therapy, did not achieve a complete response (CR) or relapsed after autologous stem cell transplant (auto-SCT), or are ineligible for auto-SCT. Participants with PMBCL must be anti–PD-1 naive and have not responded to or relapsed after ≥2 prior lines of therapy (≥1 rituximab based), or did not achieve a CR or relapsed after auto-SCT or are ineligible for auto-SCT. Key exclusion criteria include clinically significant cardiovascular disease, pericardial effusion or clinically significant pleural effusion, or an additional malignancy that is progressing or has required active treatment within the past 2 years. Approximately 60 participants will be enrolled. All participants will receive subcutaneous pembrolizumab 790 mg every 6 weeks for up to 18 cycles (~2 years), or until disease progression or other discontinuation criteria are met. Primary end points are pharmacokinetics during cycle 1 and objective response rate per Lugano classification criteria by investigator review. Secondary end points are pharmacokinetics at steady state (cycle 3), antidrug antibody levels, safety and tolerability, and duration of response per Lugano classification criteria by investigator review. CT scans will be performed every 12 weeks; PET scans will be performed at week 12, week 24, and to confirm CR. Adverse events (AEs) will be monitored throughout the study and for ≤30 days after treatment end (90 days for serious AEs; or 30 days if new anticancer therapy is initiated) and will be graded per NCI CTCAE v5.0. Recruitment is ongoing. Clinical trial information: NCT06504394. Research Sponsor: Merck Sharp & Dohme LLC., a subsidiary of Merck & Co., Inc., Rahway, NJ, USA.

TPS7091 **Poster Session**

TITANium: An open-label, global multicenter phase 1/2 study of AZD5492, a first-in-class subcutaneous CD8-guided tri-specific T-cell engager (TCE), in patients (pts) with relapsed or refractory (r/r) B-cell malignancies. First Author: Mazyar Shadman, Medical Oncology Division, University of Washington School of Medicine, Seattle, WA

Background: Bispecific CD20 x CD3 TCEs are changing the treatment landscape for pts with r/r non-Hodgkin lymphomas (NHL); however, they are associated with immune-related toxicities, namely cytokine release syndrome (CRS) and immune effector cell-associated neurotoxicity syndrome (ICANS), which limit their use. AZD5492 is a first-in-class, humanized, asymmetric, subcutaneously-administered, trispecific monoclonal IgG1 antibody that harbors two Fab binding domains to CD20, one VHH binding domain to T-cell receptor and one VHH binding domain to a CD8 co-receptor. Preclinical data have shown that AZD5492 drives B-cell killing through preferential engagement of CD8+ T cells, with reduced CD4+ T-cell activation and associated cytokine production. Thus, AZD5492 may have a wider therapeutic index and safety advantage compared with first generation CD20 x CD3 TCEs which equally engage and activate CD4+ and CD8+ T cells. In an in vivo NHL model, AZD5492 showed potent antitumor activity with reduced cytokine release compared with a CD20 x CD3 comparator. TITANium is a global Phase 1/2 multicenter dose escalation (Part A) and expansion (Part B) study (NCT06542250) of AZD5492 in pts with r/r B-cell malignancies. **Methods:** We present the study design of Part A. Eligible pts are aged ≥18 years with histologically documented CD20+ mature B-cell neoplasm, specifically large B-cell lymphoma (LBCL), follicular lymphoma (FL), mantle cell lymphoma (MCL), chronic lymphocytic leukemia (CLL), and small lymphocytic lymphoma (SLL), with ≥1 measurable lesion (except for CLL) and r/r disease after ≥2 prior lines of therapy. Pts with history of Grade ≥3 CRS or ICANS, post-transplant lymphoproliferative disease, Ritcher's transformation, Burkitt's lymphoma or Burkitt-like lymphoma are excluded. Part A will consist of two independent dose escalation groups: Part A1 will enroll pts with MCL or CLL/SLL; Part A2 will enroll pts with LBCL or FL. Dose escalation will start with pts receiving AZD5492 subcutaneously at a fixed dose per dose-level. An immune-related toxicity during Part A will trigger a double step-up strategy. Thereafter, treatment will continue for a limited duration. Each part will continue dose escalation independently, using fixed or step-up dosing. Part A will initially follow an accelerated titration design and will switch to a modified toxicity probability interval-2 design when triggered by emerging data. The primary objective is to assess safety and tolerability of AZD5492. Key secondary objectives are to evaluate preliminary efficacy, pharmacokinetics and immunogenicity of AZD5492. Enrollment began in September 2024 and is currently ongoing. Clinical trial information: NCT06542250. Research Sponsor: AstraZeneca.

TPS7092 **Poster Session**

waveLINE-010: Zilovertamab vedotin plus R-CHP versus R-CHOP in untreated diffuse large B-cell lymphoma. First Author: Russell Patrick Trapletti Gollard, Optum Care Cancer Care, Las Vegas, NV

Background: Despite recent advances in the treatment of diffuse large B-cell lymphoma (DLBCL), 5-year survival rates range between 60% and 80%. Modest improvements have been made over standard-of-care with rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) immunochemotherapy being used in the first-line setting. Zilovertamab vedotin, an ROR1-targeting antibody-drug conjugate with a monomethyl auristatin E payload, has demonstrated promising efficacy in patients with DLBCL. The randomized, open-label, phase III waveLINE-010 (NCT06717347) study will evaluate the efficacy and safety of zilovertamab vedotin in combination with rituximab plus cyclophosphamide, vincristine, and prednisone (R-CHP) versus R-CHOP in patients with untreated DLBCL. **Methods:** Eligible participants are aged ≥18 years and have histologically confirmed DLBCL per World Health Organization classification of neoplasms of the hematopoietic and lymphoid tissues (including but not limited to: DLBCL, not otherwise specified [NOS] germinal center B-cell type, or activated B-cell type; DLBCL leg-type; Epstein-Barr virus–positive DLBCL, NOS; and T-cell histiocytic-rich DLBCL), positron emission tomography–positive disease at screening (4-5 on the Lugano 5-point scale), no prior treatment for DLBCL, an International Prognostic Index (IPI) score of 2-5, and an ECOG performance status score of 0-2. Approximately 1046 patients will be randomly assigned (1:1) to receive zilovertamab vedotin 1.75 mg/kg plus R-CHP on day 1 of every 3-week cycle for 6 cycles, or R-CHOP on day 1 of every 3-week cycle for 6 cycles. Patients with high-risk DLBCL in both treatment arms will receive rituximab (or biosimilar) for an additional 2 cycles. Randomization will be stratified by 3 geographic regions (Western Europe, the United States, Canada, and Australia vs Asia vs rest of world), IPI score (2 vs 3-5), and bulk (<7.5 cm vs ≥7.5 cm). The primary end point is PFS per Lugano criteria by blinded independent central review (BICR). Secondary end points include complete response rate at end of treatment (EOT) per Lugano criteria by BICR, overall survival, event-free survival per Lugano criteria by BICR, duration of complete response, safety and tolerability, and changes from baseline in health-related quality-of-life assessments. Response assessments will be performed after day 1 of cycle 4 but before day 1 of cycle 5, and then at 12 weeks after cycle 4 scan (EOT assessment). Efficacy follow-up assessments will be completed every 24 weeks for 2 years from EOT assessment, then every year for 3 years (total of 5 years). Adverse events will be graded per NCI CTCAE v5.0. Recruitment is ongoing. Clinical trial information: NCT06717347. Research Sponsor: Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA.

TPS7093 **Poster Session**

A phase 1 first-in-human study evaluating safety, pharmacokinetics, and efficacy of ABBV-291, a CD79b-targeting antibody-drug conjugate, in patients with relapsed/refractory B-cell non-Hodgkin lymphoma. First Author: Dai Maruyama, Department of Hematology Oncology, Cancer Institute Hospital, Japanese Foundation for Cancer Research, Tokyo, Japan

Background: Chemoimmunotherapy successfully treats ~60% of patients (pts) with diffuse large B-cell lymphoma (DLBCL), the most common form of B-cell non-Hodgkin lymphoma (B-NHL). However, pts who are not cured often die from relapsed/refractory (R/R) disease, highlighting the need for new therapies. CD79b is expressed on most major subtypes of B-NHL and is a validated target in DLBCL. ABBV-291 is an antibody-drug conjugate (ADC) comprising the anti-CD79b antibody conjugated to a potent topoisomerase 1 inhibitor payload, and offers potential as a best-in-class treatment in DLBCL. Preclinical data indicate that ABBV-291 has robust antitumor activity, with superior responses compared with other anti-CD79b ADCs. There is also the possibility for lower rates of key adverse events (AEs) such as neuropathy compared with monomethyl auristatin E-payload ADCs. Herein, we describe a first-in-human study evaluating the safety, pharmacokinetics (PK), and efficacy of ABBV-291 monotherapy in pts with R/R B-NHL. **Methods:** This phase 1, open-label, multicenter, dose-expansion study (NCT06667687) is enrolling pts (≥18 years) who have a documented diagnosis of B-NHL (except chronic lymphocytic leukemia), measurable disease, ECOG 0–1, and are R/R to or intolerant of ≥2 prior lines of therapy, with no other available therapies of clinical benefit. Primary objectives are to assess safety/tolerability of ABBV-291 and determine its recommended phase 1 expansion dose (RP1ED). Secondary objectives are to evaluate preliminary efficacy of ABBV-291 in specified subsets of R/R B-NHL (eg DLBCL, follicular lymphoma [FL], mantle cell lymphoma [MCL]) and to characterize its PK. Exploratory objectives include investigating the association between biomarkers, safety, efficacy, and PK. The study consists of 2 parts: dose escalation (up to ~45 pts), and dose expansion and optimization (~120 pts). ABBV-291 is administered intravenously. In the BOIN-guided dose-escalation, ABBV-291 administration for the first 2 pts is staggered by ≥24 hours at the first 2 dose levels (DLs); dose-limiting toxicities (DLTs) are assessed for 35 days from the initial dose. In dose expansion, ABBV-291 is evaluated at the RP1ED in DLBCL and FL; for dose optimization, ABBV-291 is evaluated in ≥2 DLs in MCL. Pts continue treatment until disease progression, intolerable toxicity, or other study discontinuation criteria are met. Safety evaluations include AE monitoring, DLTs, vital signs, ECG, and clinical laboratory parameters. Response evaluations are performed per disease-specific response criteria and include objective response rate, duration of response, and progression-free survival. PK parameters are determined using noncompartmental methods. The study is actively enrolling globally. Clinical trial information: NCT06667687. Research Sponsor: AbbVie, Inc.; n/a.

TPS7094 **Poster Session**

Optimizing frontline therapy for diffuse large B cell lymphoma (DLBCL) in older adults: A glofitamab-based, response-adapted, window-style study (GLORY). First Author: Pallawi Torka, Memorial Sloan Kettering Cancer Center, New York, NY

Background: Older adults (OA) with DLBCL classified as unfit or frail based on simplified geriatric assessment (sGA) do poorly with standard doses of anthracycline based chemotherapy. Bispecific antibodies have a preserved risk-benefit profile in OA and their combination with chemotherapy represents a promising strategy to increase cure rates in DLBCL. Interim PET scans have a high negative predictive value and can be harnessed to guide response adapted therapy in this setting to minimize exposure to chemotherapy for responsive patients. GLORY is a window-style, glofitamab-based, response-adapted study with polatuzumab-rituximab-miniCHP (pola-R-miniCHP) backbone specifically designed for unfit and frail older adults with DLBCL who are being treated with curative intent. The dual goals of this personalized strategy are: 1. To improve cure rates in patients with iPET2 positivity, 2. To reduce chemotherapy dosage and ensuing toxicities in patients with iPET2 negativity while maintaining/improving cure rate. **Methods:** In this Phase II, prospective, open label, single arm, single institution study, OA $\geq$ 65 years of age with newly diagnosed DLBCL, high grade or transformed B-cell lymphoma, classified as unfit or frail by simplified geriatric assessment (sGA) will be included. All patients will receive 2 cycles of glofitamab and polatuzumab followed by an interim PET scan (iPET2). If iPET2 is negative (Deauville 1-3), patients will receive 4 cycles of glofitamab-pola-R-miniCHP. If iPET2 is positive without progression, patients receive 6 cycles of glofitamab-pola-R-miniCHP. All patients undergo end of treatment (EOT) PET and are followed for 5 years. ctDNA and dynamic changes in aging biomarkers [epigenetic aging clock, senescence associated secretory phenotype (SASP)] will be measured at baseline, after cycle 1 (C1), after C2 and at the EOT and correlated with outcomes. On therapy tumor biopsy after cycle 1 of glofitamab+polatuzumab is optional. The trial has been thoughtfully designed to be OA-friendly with pragmatic eligibility criteria and stepwise strategies (eg. prephase) to mitigate the risk of toxicities. The primary endpoints are complete response rate (CRR) after 2 cycles of glofit-pola and CRR after completion of therapy. Key secondary end points include other measures of efficacy such as overall response rate (ORR), progression free survival (PFS) and overall survival (OS) and safety. The target CRR at the end of therapy is 60% with an unacceptably low rate of 40%. Based on these assumptions, a sample size of 42 patients provides a 5% one sided type 1 error and 80% power. This is a single stage design, and the study will be considered positive if 23 of 42 patients achieve a CR at the end of therapy. Additionally, the coprimary endpoint of CR rate after 2 cycles of glofitamab+polatuzumab will be used to stop for futility. Clinical trial information: NCT06765317. Research Sponsor: Genentech; Memorial Sloan Kettering Cancer Center.

TPS7095 **Poster Session**

Sequencing-guided chemotherapy optimization using real-time evaluation in newly diagnosed DLBCL with circulating tumor DNA: SHORTEN-ctDNA (NCT06693830). First Author: Hua-Jay Jeffery Cherng, Columbia University Irving Medical Center, New York, NY

Background: Circulating tumor DNA (ctDNA) is a clinically valid tool for detection of measurable residual disease (MRD) in patients with diffuse large B-cell lymphoma (DLBCL). Phased variant enrichment and detection sequencing (PhasED-seq), which uses multiple somatic mutations on individual DNA fragments, improves upon first-generation single nucleotide variant-based MRD tests with improved sensitivity (Kurtz et al. *Nat Biotech* 2021). To utilize ctDNA-MRD testing in a clinical setting to guide treatment decisions, the ability to test and report in a real-time manner is required. However, the feasibility of real-time MRD testing using the PhasED-seq-based Foresight CLARITY platform to inform treatment decisions has yet to be established. Therapy de-escalation after 4 cycles of standard R-CHOP therapy was non-inferior and less toxic than 6 cycles for patients with DLBCL with no baseline risk factors (Poeschel et al. *Lancet* 2019). Identification of patients who are ideal candidates for de-escalation based on treatment response remains a challenge as radiographic imaging has a high false-negative rate (Le Gouill & Casanovas, *Blood* 2017). ctDNA-MRD has a higher sensitivity and may be a better test to guide dose de-escalation decisions in patients with DLBCL. This feasibility study will have two co-primary objectives: (1) to evaluate the feasibility of ctDNA sequencing for real-time guidance of clinical decision making during frontline therapy for DLBCL; and (2) to determine the outcomes of patients with newly diagnosed DLBCL who become undetectable for ctDNA and demonstrate a radiographic complete response (CR) during standard frontline therapy and discontinue chemotherapy early. **Methods:** This single-center investigator-initiated study began enrolling in November 2024 and is enrolling patients (N=32) with newly diagnosed stage II-IV, CD20+ DLBCL with measurable disease. Patients will receive 4 cycles of standard-of-care therapy (R-CHOP or R-pola-CHP). Positron emission tomography/computed tomography (PET/CT) scans will be performed after cycle four (C4) and at the end of therapy. Additionally, whole blood samples will be drawn on C4 day 1 (C4D1) and shipped to Foresight Diagnostics, Inc. (Boulder, CO) for real-time MRD testing. Patients who experience a CR on iPET4 and have undetectable ctDNA on C4D1 will de-escalate therapy and receive rituximab alone for C5-6. Patients not meeting these response criteria or with unsuccessful real-time MRD testing for any reason will continue standard therapy for the remaining cycles. MRD will also be evaluated in a batched manner at the end of the study at other timepoints to evaluate the kinetics of ctDNA as well as correlation with clinical outcomes. The primary efficacy endpoint is the EOT CR rate on PET/CT performed 10-14 weeks after C6D1 in the patients who receive de-escalated treatment. Clinical trial information: NCT06693830. Research Sponsor: Foresight Diagnostics, Inc.; National Cancer Institute; Conquer Cancer, the ASCO Foundation.

TPS7096 **Poster Session**

A phase 1a/1b trial in relapsed/refractory T-cell non-Hodgkin lymphoma to determine the safety profile, pharmacology, and maximum tolerated dose of ST-001, an intravenous fenretinide phospholipid suspension (12.5 mg/mL). First Author: Oleg Akilov, University of Pittsburgh, Pittsburgh, PA

Background: N-(4-hydroxyphenyl)retinamide (4-HPR; fenretinide) is a synthetic amide derivative of all-trans retinoic acid. Clinical data from trials of earlier fenretinide formulations indicate that higher plasma levels of fenretinide correlate with improved patient responses. Although fenretinide intravenous emulsion (4-HPR-ILE) increased plasma concentration and yielded complete and partial responses in peripheral T-cell lymphomas, its dose-limiting hypertriglyceridemia mainly related to triglyceride from the soy oil vehicle posed a significant impediment to clinical development (Maurer BJ et al. *Clin Cancer Res.* 2017). **Methods:** A new formulation of intravenous fenretinide, designated ST-001 nanoFenretinide, is an innovative dosage form composed of phospholipid nanoparticles in a free-flowing solution (Patent number US 8709379 B2). ST-001 effectively eliminates the risk of vehicle-related hypertriglyceridemia, because it is free of triglycerides. It is also free of adjuvants, non-ionic surfactants, polyoxylated compounds, alkoxylated oils, and animal-derived substances known to cause allergy or hypersensitivity. ST-001 potentially provides a safer form of intravenous fenretinide for achieving therapeutic plasma concentrations. In this Phase 1a/1b clinical trial (NCT04234048), ST-001 is administered via intravenous infusion (IV) to patients with relapsed/refractory T-cell non-Hodgkin's lymphoma (NHL) following at least one prior treatment, including cutaneous (CTCL) and non-cutaneous T-cell lymphoma subtypes (angioimmunoblastic T-cell lymphoma, peripheral T-cell lymphoma not otherwise specified, and follicular T-cell lymphoma). The U.S.-based trial will enroll up to 54 patients across three stages: up to 9 patients (single patient cohorts) for Phase 1a accelerated dose escalation, up to 15 patients (3 patient cohorts) for Phase 1a standard dose escalation and determination of maximum tolerated dose (MTD), and 30 patients for Phase 1b to determine the optimal dose. The primary objectives are to determine the MTD, toxicity profile, adverse events and dose-limiting toxicities (DLTs) based on NCI Common Toxicity Criteria, and anti-tumor activity, when administered over 4 hours daily for 5 consecutive days every 3 weeks, for a maximum of 8 cycles. Secondary objectives include pharmacokinetic profiling and investigating potential mechanisms of action using pharmacodynamic biomarkers. The accelerated stage has completed enrollment, and the standard stage is open for enrollment as of January 2025. This study investigates a novel fenretinide formulation aiming to address treatment challenges in T-cell NHL, with a focus on safety, tolerability, clinical activity, and pharmacology. Clinical trial information: NCT04234048. Research Sponsor: None.

TPS7097 **Poster Session**

A phase 1 trial of BTM-3566 in relapsed/refractory mature B cell lymphomas. First Author: Michael Wang, The University of Texas MD Anderson Cancer Center, Houston, TX

Background: Relapsed/refractory (R/R) aggressive B-cell lymphomas, including diffuse large B-cell lymphoma (DLBCL) and mantle cell lymphoma (MCL), remain challenging to treat, particularly in patients who have exhausted approved therapies. BTM-3566, a novel compound demonstrated efficacy against diverse B-cell malignancies, with the most pronounced impact observed in DLBCL and MCL. BTM-3566 initiates the mitochondrial ATF-4-mediated integrated stress response (ISR) pathway via a unique mechanism governed by the mitochondrial protein FAM210B. In vitro, BTM-3566 induces apoptosis across multiple hematological and solid tumor cell lines with several in vivo models demonstrating tumor regression or significant tumor growth inhibition. This includes complete tumor regressions in DLBCL and MCL patient-derived xenograft (PDX) mouse models carrying genetic alterations linked to unfavorable prognosis such as double hit (DH) and triple hit lymphoma (TH) and MCL PDX models from patients previously treated with CAR T, rituximab, venetoclax and/or BTK inhibitors. **Methods:** This ongoing Phase 1, single-arm, open-label, multi-center trial is evaluating the safety, tolerability, and preliminary efficacy of BTM-3566 in adult patients with mature B-cell lymphomas. Eligible participants must have histologically confirmed mature B cell lymphoma that has progressed after at least two prior lines of systemic therapy. BTM-3566 is administered orally in two weeks cycles (7 days on, 7 days off). Primary endpoints include incidence of dose-limiting toxicities (DLTs) and treatment-emergent adverse events (TEAEs). Secondary and exploratory endpoints include objective response rate (ORR), duration of response (DoR), progression-free survival (PFS) pharmacokinetics and pharmacodynamic assessments. Enrollment is scheduled to start in Q1 2025 in US and Canada. Clinical trial information: NCT06792734. Research Sponsor: None.

7500 Oral Abstract Session

MRD-driven strategy following IsaKRD induction in transplant-eligible NDMM: Primary endpoints of the phase 3 MIDAS trial. First Author: Aurore Perrot, Toulouse University, CHU Oncopole, Toulouse, France

Background: The phase III IFM2020-02-MIDAS study (NCT04934475) evaluated a minimal residual disease (MRD)-driven consolidation and maintenance strategy following induction with isatuximab, carfilzomib, lenalidomide, and dexamethasone (IsaKRD) in transplant-eligible patients with newly diagnosed multiple myeloma (NDMM). Results from the IsaKRD induction phase have been previously published (Perrot et al., Blood, 2025). Here, we present the results from the MRD-driven consolidation phase of the trial. **Methods:** MIDAS is a multicenter, open-label, randomized phase 3 trial involving transplant-eligible patients aged 18-65 with NDMM. Patients achieving post-induction MRD negativity at a threshold of 10^{-5} by next-generation sequencing (NGS) were randomized to either 6 additional cycles of IsaKRD (Arm A) or autologous stem cell transplantation (ASCT) followed by 2 cycles of IsaKRD (Arm B), followed by lenalidomide maintenance. MRD-positive patients after induction (MRD $\geq 10^{-5}$) were randomized to either single ASCT plus 2 cycles of IsaKRD (Arm C) or tandem ASCT (Arm D) followed by isatuximab plus iberdomide maintenance. Randomization was stratified by cytogenetic risk and center for both comparisons, and by MRD negativity at 10^{-6} post-induction for the Arm A vs. Arm B comparison. The primary endpoint was MRD negativity at 10^{-6} (by NGS) prior to maintenance for both comparisons. **Results:** A total of 485 patients with post-induction MRD negativity were randomized to Arm A (n=243) or Arm B (n=242). The pre-maintenance MRD negativity rates at 10^{-6} were 84% in Arm A and 86% in Arm B (Odds Ratio [OR] 1.17, 95% confidence interval [CI] 0.64–2.76, p=0.64). Additionally, 233 MRD-positive patients (10^{-5}) were randomized to Arm C (n=109) or Arm D (n=124), with 19 patients (15%) not receiving the planned tandem ASCT. Pre-maintenance MRD negativity rates at 10^{-6} were 40% in Arm C and 32% in Arm D (OR 0.73, 95% CI 0.42–1.25, p=0.31). During the consolidation phase, 5 patients experienced disease progression (2 in Arm A, 0 in Arm B, 0 in Arm C, 3 in Arm D), and 2 patients died without progression in Arm A. No new safety signals were identified compared to the induction phase. The study is ongoing. With a median follow-up of 16.8 months in Arms A/B and 16.3 months in Arms C/D, sustained MRD negativity and progression-free survival (PFS) data are not yet available. **Conclusions:** After 6 induction cycles with IsaKRD, in patients who achieved MRD negativity at 10^{-5}, MRD negativity rates at 10^{-6} before maintenance were not significantly different between the transplant-based approach and IsaKRD consolidation alone, whereas in patients who do not achieve MRD negativity at 10^{-5}, tandem ASCT did not significantly improve MRD negativity rates at 10^{-6} before maintenance. Further follow-up, including sustained MRD negativity and PFS data, is needed to evaluate the long-term outcomes of this MRD-adapted strategy. Clinical trial information: NCT04934475. Research Sponsor: None.

7501 Oral Abstract Session

Subcutaneous daratumumab (Dara) + bortezomib/lenalidomide/dexamethasone (VRd) with Dara + lenalidomide (DR) maintenance in transplant-eligible (TE) patients with newly diagnosed multiple myeloma (NDMM): Analysis of sustained minimal residual disease negativity in the phase 3 PERSEUS trial. First Author: Philippe Moreau, University Hospital Hôtel-Dieu, Nantes, France

Background: Minimal residual disease (MRD) negativity (neg) and sustained MRD neg are associated with longer survival and are strong prognostic clinical endpoints. PERSEUS (NCT03710603) evaluated subcutaneous Dara + VRd induction/consolidation (ind/consol) + DR maintenance (maint) vs VRd ind/consol + R maint in TE NDMM. DVRd significantly improved PFS, complete response or better rate (≥CR), and MRD neg rate. Nearly two-thirds of patients (pts) on DR maint could stop treatment (tx) after achieving sustained remission, leading to DVRd being recommended by NCCN as a preferred TE NDMM regimen. Here, we report the impact of sustained MRD neg status on PFS inPERSEUS. **Methods:** TE pts with NDMM age 18–70 years (y) were randomized 1:1 to DVRd (DVRd ind/consol + DR maint) or VRd (VRd ind/consol + R maint). The primary endpoint was PFS; MRD neg rate (MRD neg 10^{-5} and ≥CR) was a key secondary endpoint. Sustained MRD neg, assessed in the intent-to-treat population, was defined as confirmed MRD neg ≥12 months (mo) apart and without MRD positivity in between. Functionally high risk (FHR) was defined as disease progression ≤18 mo from tx initiation, excluding pre-progression deaths. **Results:** A total of 709 pts were assigned to DVRd (n=355) or VRd (n=354). At 47.5-mo median follow-up, ≥12-mo sustained MRD neg rates were higher overall with DVRd (64.8%; n=230) vs VRd (29.7%; n=105), and across clinically relevant subgroups, including age ≥65 y and high-risk cytogenetics. Similarly, ≥24-mo sustained MRD neg rates were higher with DVRd (55.8%; n=198) vs VRd (22.6%; n=80). Pts with ≥12-mo sustained MRD neg vs those without had improved 48-mo PFS rates regardless of tx arm (Table). DVRd vs VRd reduced FHR rates (3.1% vs 6.8%), and rates of FHR or pre-progression deaths were lower with DVRd vs VRd (5.4% vs 11.0%) in the first 18 mo. **Conclusions:** In TE NDMM, nearly two-thirds of pts treated with DVRd induction and DR maint achieved ≥12-mo sustained MRD neg, associated with >95% 48-mo PFS rate. Moreover, ≥24-mo sustained MRD neg rates with DVRd were 2.5 times as high as VRd, and FHR incidence was halved with DVRd vs VRd. Collectively, these data further support the PERSEUS regimen as standard of care for TE NDMM. Clinical trial information: NCT03710603. Research Sponsor: Johnson & Johnson.

	Achieved sustained (≥12 mo) MRD neg (10^{-5})			Without achieving sustained (≥12 mo) MRD neg (10^{-5})		
	DVRd (n=230)	VRd (n=105)		DVRd (n=125)	VRd (n=249)	
Median PFS, mo (95% CI)	NE (NE–NE)	NE (NE–NE)	HR=0.83 (95% CI 0.3–2.3) *P*=0.7149	NE (47.9–NE)	NE (45.3–NE)	HR=0.80 (95% CI 0.6–1.2) *P*=0.2489
48-mo PFS rate, % (95% CI)	95.3 (91.4–97.5)	94.2 (87.6–97.4)		60.3 (48.0–70.5)	54.9 (47.7–61.4)	

Hazard ratio, HR; NE, not estimable.
Median PFS and 95% CI are from Kaplan-Meier estimates.
P-value is from unstratified log-rank test.

7502 Oral Abstract Session

Sustained MRD negativity in patients with newly diagnosed multiple myeloma treated with carfilzomib-lenalidomide-dexamethasone with or without isatuximab (phase III IsKia trial). First Author: Francesca Gay, Division of Hematology, AOU Città della Salute e della Scienza di Torino, University of Torino and Department of Molecular Biotechnology and Health Sciences, University of Torino, Torino, Italy

Background: The phase III IsKia trial assessed the efficacy and safety of isatuximab-carfilzomib-lenalidomide-dexamethasone (IsaKRd) as pre-ASCT induction and post-ASCT consolidation vs KRd. The rate of measurable residual disease (MRD) negativity was significantly higher in IsaKRd vs KRd patients (pts) after both induction and consolidation (Gay et al. ASH 2023). Here we report the rates of 1-year sustained (sust)MRD negativity and findings about the light consolidation phase. **Methods:** Transplant-eligible NDMM pts aged <70 years were enrolled. IsaKRd pts received 4 full-dose IsaKRd induction cycles, MEL200-ASCT, 4 full-dose IsaKRd consolidation cycles and, thereafter, 12 28-day light consolidation cycles [Isa 10 mg/kg IV on days (dd) 1, 15; K 56 mg/m^2 IV dd 1; R 10 mg PO daily dd 1–21; d 20 mg PO dd 1, 15]. Pts in the KRd arm received the same KRd schedule used in the other arm. MRD was tested by NGS in all pts who achieved ≥VGPR. 1-year sustMRD was defined as 2 sequential MRD-negative evaluations at least 1 year apart. Analyses were based on the ITT principle (pts with missing MRD data or who did not achieve VGPR were considered as MRD positive). The data cut-off was Jul 22, 2024. **Results:** 151 vs 151 pts were randomly assigned to the IsaKRd vs KRd arms. Pt characteristics were well balanced: 43% vs 41% had R2-ISS stage III/IV disease; 9% vs 11% had ≥2 high-risk cytogenetic abnormalities [CA; including del(17p), t(4;14), t(14;16), 1q+]. The median follow-up was 35 months (IQR 32–38). In the ITT analysis, the MRD negativity rates at the 10^{-5} cut-off after full-dose consolidation were 77% vs 67% (OR 1.67; p=0.049) with IsaKRd vs KRd; the rates of 10^{-5} 1-year sustMRD after light consolidation were 66% vs 59% (OR 1.36; p=0.21). The MRD negativity rates at the 10^{-6} cut-off after full-dose consolidation were 67% vs 48% (OR 2.29; p<0.001) with IsaKRd vs KRd; the rates of 10^{-6} 1-year sustMRD after light consolidation were 52% vs 38% (OR 1.82; p=0.012). The 10^{-6} 1-year sustMRD negativity advantage with IsaKRd was retained in all subgroups. In particular, the 10^{-6} 1-year sust MRD negativity rates were: 62% vs 20% in pts with ≥2 high-risk CA (OR 6.3, 95% CI 1.11–35.66) and 47% vs 35% in pts with R2-ISS III/IV (OR 1.62, 95% CI 0.77–3.41). During light consolidation, in the IsaKRd vs KRd arms, the main grade 3–4 hematologic AEs were neutropenia (17% vs 18%) and thrombocytopenia (2% vs 3%); the main grade 3–4 non-hematologic AEs included infections (8% vs 5%), gastrointestinal (4% vs 4%) and vascular AEs (3% vs 1%); discontinuation for toxicity occurred in 3% vs 2%; treatment-related deaths were 2 (1 cerebral ischemia, 1 pulmonary embolism) vs 0. **Conclusions:** The addition of isatuximab to KRd induction-consolidation and the prolonged light consolidation significantly increased the rates of 10^{-6} sustMRD negativity in NDMM pts, including those with high-risk disease. Clinical trial information: NCT04483739. Research Sponsor: Sanofi; Amgen.

7503 Oral Abstract Session

Randomized, multi-center study of carfilzomib, lenalidomide, and dexamethasone (KRd) with or without daratumumab (D) in patients with newly diagnosed multiple myeloma (NDMM): The ADVANCE clinical trial. First Author: Carl Ola Landgren, Myeloma Program and Experimental Therapeutics Program, University of Miami, Miami, FL

Background: The use of modern combination therapy in NDMM patients delivers deep and durable treatment responses independent of transplant status. In the current ADVANCE study (NCT04268498), patients were randomly assigned to receive 8 cycles of carfilzomib-lenalidomide-dexamethasone with or without daratumumab (DKRd vs KRd). Transplants were offered to patients who were minimal residual disease (MRD) positive after 8 cycles. All patients transitioned to lenalidomide maintenance. Primary endpoint was MRD negativity 10^-5 by NGS after up to 8 cycles of combination therapy. **Methods:** 306 NDMM patients were randomly assigned 1:1 to receive 8 cycles (28-day cycles) of either DKRd or KRd (D: 1800 mg SC, days 1, 8, 15, and 22 (C1-2), days 1 and 15 (C3-6), day 1 (C7-8); K: 20/56 mg/m2 IV, days 1, 8, and 15; R: 25 mg days 1-21; d: 40/20 mg). Stem cell collection was encouraged after 4 cycles for eligible patients. After completion of cycle 8, patients were evaluated for MRD (ClonoSEQ). Transplant was reserved for MRD-positive patients (post C8). MRD-negative patients transitioned to lenalidomide 10 mg maintenance (D1-21/28). Sustained MRD status was monitored annually. Key eligibility included NDMM with ECOG PS 0-2 and adequate organ function, independent of transplant status. The study was monitored and approved by an independent data safety monitoring committee. **Results:** At 2nd prespecified analysis (data cutoff 01/15/25) demographics and disease characteristics were well balanced and included: median age 62 y/o (range: 35-76), Hispanic: 23%, Black: 11%, ISS 2-3: 39%, ECOG PS 2: 6%, and high-risk cytogenetics: 35%. The primary endpoint of MRD negativity at 10^-5 by NGS was significantly higher in the DKRd arm compared to the KRd arm (59% vs 36%, adjusted OR=2.5, 95% CI: 1.5-4.2; P<0.0007). EFS, PFS and OS data are currently immature, however, at 32.7 months median follow-up, PFS events included one death in each arm, PD 4 vs 5%, and 86 vs 79% were progression-free and censored in the DKRd vs KRd arms, respectively. Overall, 98% had an adverse event (AE) with hematologic AEs occurring in 15 vs 24%; cardiac AEs: 13 vs 16%; gastrointestinal AEs: 68 vs 72%; infections: 61 vs 53%; acute kidney injury: 1 vs 4%; vascular disorders: 6 vs 2% with DKRd vs KRd, respectively. Serious AEs occurring in >1% included: febrile neutropenia: 2 vs 2%; pyrexia: 5 vs 2%; chest pain: 0 vs 3%; non-cardiac chest pain: 2 vs 0%; pneumonia: 3 vs 10%; sepsis: 2 vs 0%; COVID-19: 2 vs 0%; wound infection: 2 vs 0%; hip fracture: 2 vs 0%; infusion reaction: 2 vs 0%; back pain: 2 vs 0%; syncope: 2 vs 0%; acute kidney injury: 0 vs 3%; and dyspnea: 2 vs 0%, with DKRd vs KRd, respectively. **Conclusions:** In this large randomized, multicenter investigator-initiated trial for NDMM, treatment with DKRd (59%) compared to KRd (36%) showed a significant, 2.5-fold higher MRD negativity rate with no new safety concerns. Updated EFS, PFS and OS results will be presented at the meeting. Based on these results, DKRd should be a new standard for most NDMM patients receiving initial KRd-backbone therapy. Clinical trial information: NCT04268498. Research Sponsor: U.S. National Institutes of Health; P30CA240139; Janssen; Amgen.

7504 Oral Abstract Session

Elranatamab in combination with daratumumab and lenalidomide (EDR) in patients with newly diagnosed multiple myeloma (NDMM) not eligible for transplant: Initial results from MagnetisMM-6 part 1. First Author: Hang Quach, St Vincent's Hospital Melbourne, University of Melbourne, Melbourne, Vic, Australia

Background: Elranatamab (ELRA), a BCMA-CD3 bispecific antibody, induced deep and durable responses with a manageable safety profile in patients (pts) with relapsed/refractory multiple myeloma (RRMM). MagnetisMM-6 (NCT05623020) is a phase 3, open-label, randomized study evaluating the efficacy and safety of ELRA in combination with lenalidomide (R) ± daratumumab (DARA) (EDR or ER) vs DARA + R + dexamethasone (DRd) in pts with transplant-ineligible (TI) NDMM. Part 1 of the study evaluates the optimal dose of EDR or ER in pts with RRMM or NDMM to determine the recommended phase 3 dose for part 2. Initial results from part 1 dose level G (DLG) are presented. **Methods:** In DLG, eligible pts had TI (age ≥65 or age <65 years with comorbidities impacting the possibility of transplant) NDMM, measurable disease, ECOG ≤2, and adequate liver, renal and bone marrow function. Pts received subcutaneous (SC) ELRA with a priming regimen followed by ELRA 76 mg SC every 4 weeks (Q4W) on cycle (C) 1 day (D) 1; DARA 1800 mg SC weekly (D1, D8, D15, D22 in C1-C2), every 2 weeks (D1, D15 in C3-C6), and Q4W (D1 in C7+); and oral R 25 mg daily on D1-D21 in 28-day cycles. Endpoints assessed in DLG include safety and preliminary efficacy. **Results:** A total of 37 pts were enrolled in DLG; 34 received EDR. The median age was 75.0 years (range, 67-83); 37.8% were male; 86.5% were White, 13.5% Asian. Four patients (10.8%) had R-ISS stage III disease, 9 (24.3%) had ≥50% baseline bone marrow plasma cells, 1 (2.7%) had ECOG=2, none had EMD, and 9 (24.3%) were frail according to the simplified IMWG frailty score. At data cutoff (Dec 23, 2024), the median follow-up was 4.6 months (range, 1.2-6.2); treatment was ongoing in 33 pts. TEAEs were reported in 97.3% (G3/4 94.6%) of pts, hematological TEAEs in 78.4% (G3/4 70.3%), and infections in 64.9% (G3/4 18.9%). The most frequent TEAEs (any grade ≥25% or G3/4 ≥10%) are shown in the Table. CRS occurred in 62.2%, all ≤G2; 1 case of G2 ICANS was reported. There was one G5 candida pneumonia. Overall, 36 out of 37 pts are responders with 2 pending confirmation as of DCO. The confirmed ORR (95% CI) by investigator was 91.9% (78.1-98.3), 81.1% with VGPR or better. In pts enrolled ≥4 months before the DCO (n=23), confirmed ORR was 95.7% (78.1-99.9), all with VGPR or better. **Conclusions:** In pts with TI NDMM, EDR demonstrated a manageable safety profile consistent with the known toxicities of components. High response rate and early responses were observed. Enrollment in dose level H evaluating the ER combination is ongoing. Updated safety and efficacy data with a longer follow-up will be presented. Clinical trial information: NCT05623020. Research Sponsor: Pfizer.

TEAEs, %	Any grade	G3/4
Neutropenia, incl. neutrophil count decreased	70.3	67.6
CRS	62.2	0
Pyrexia	35.1	0
Anemia, incl. hemoglobin decreased	32.4	16.2
Injection site reaction	29.7	0
Nausea	27.0	0
Thrombocytopenia, incl. platelet count decreased	13.5	10.8
Asthenia	16.2	10.8

7505 Oral Abstract Session

First-in-human study of JNJ-79635322 (JNJ-5322), a novel, next-generation trispecific antibody (TsAb), in patients (pts) with relapsed/refractory multiple myeloma (RRMM): Initial phase 1 results. First Author: Niels W.C.J. van de Donk, Amsterdam University Medical Center, Vrije Universiteit Amsterdam, Department of Hematology, Amsterdam, Netherlands

Background: Bispecific antibodies (BsAbs) have begun to transform outcomes in MM. Emerging data suggest that targeting two MM antigens with T-cell redirection may overcome tumor heterogeneity and acquired resistance to further improve clinical outcomes. JNJ-5322 is a next-generation TsAb dually targeting BCMA and GPRC5D via T-cell redirection, comprising novel binding domains, including low affinity CD3, selected in vitro to enhance on-tumor effects and reduce off-tumor impact. We report first results from an ongoing phase 1 study of JNJ-5322 (NCT05652335). **Methods:** Dose escalation/expansion cohorts enrolled measurable RRMM pts previously exposed to a proteasome inhibitor, immunomodulatory drug, and anti-CD38 monoclonal antibody. Escalating fixed Q2W or Q4W SC doses (0.4–300 mg) were explored, including 100 mg Q4W, the putative recommended phase 2 dose (RP2D). Pts received 1 step-up dose (SUD) (5 mg) prior to receiving the 100 mg Q4W dose, allowing faster full dose initiation and attenuation of cytokine release syndrome (CRS) risk. Adverse events (AEs) were graded by CTCAE v5.0; CRS and immune effector cell-associated neurotoxicity syndrome (ICANS) were graded per ASTCT guidelines. Overall response rate (ORR) was assessed by IMWG criteria. **Results:** As of Jan 15, 2025, 126 pts received JNJ-5322 (36 at 100 mg Q4W); median follow-up (mFU) 8.2 mo. Median age 64 yrs; median 4 prior lines of therapy; 100% triple-class exposed (56% refractory); 31% high-risk cytogenetics; 23% had prior anti-BCMA/-GPRC5D therapy (77% naïve). The putative RP2D was identified as 100 mg Q4W. Overall, 99% of pts had ≥1 AE, most commonly CRS (59%; all grade [gr] 1 [45%]/2 [14%]; no gr ≥3), nail AEs (gr 1/2 56%), taste AEs (gr 1/2 56%), neutropenia (48%; gr 3/4 41%), and non-rash skin AEs (47%; gr 3/4 1%). Overall, 16% had weight decreases (no gr ≥3), 16% had rashes (no gr ≥3), 2% had ICANS (all gr 1), and 75% had infections (gr 3/4 28%). 5 pts had dose-limiting toxicities. 4 pts died due to AEs. In response-evaluable pts, ORR was 86% (75% ≥VGPR) at the RP2D (n=36), and 73% (66% ≥VGPR) overall (n=124). ORR was 100% (89% ≥VGPR) at the RP2D among pts naïve to anti-BCMA/-GPRC5D therapies (n=27), and all patients remain in response (mFU 8.5 mo). Median time to first response was 1.2 mo. **Conclusions:** In the largest data set for a next-generation dual antigen T-cell redirecting TsAb, the first clinical data for JNJ-5322 showed a 100% ORR at the putative RP2D in anti-BCMA/-GPRC5D naïve patients, with convenient Q4W dosing. Tolerability appeared improved, including lower incidence and severity of GPRC5D-associated AEs vs anti-GPRC5D BsAbs and manageable gr 3/4 infection rates. CRS was mostly gr 1 (no gr ≥3 CRS) using 1 SUD. First data with JNJ-5322 suggest a paradigm shift, offering ORRs similar to CAR-Ts but as an off-the-shelf therapy intended for outpatient dosing. Clinical trial information: NCT05652335. Research Sponsor: None.

7506 Oral Abstract Session

Isatuximab (Isa) subcutaneous (SC) via an on-body delivery system (OBDS) vs Isa intravenous (IV), plus pomalidomide and dexamethasone (Pd) in relapsed/refractory multiple myeloma (RRMM): Results of the randomized, non-inferiority, phase 3 IRAKLIA study. First Author: Sikander Ailawadhi, Mayo Clinic, Jacksonville, FL

Background: IV Isa-Pd is approved to treat RRMM patients (pts) based on the ICARIA-MM study. A Phase 1b study showed safety and efficacy of Isa SC via an OBDS, an investigational wearable bolus injector, plus Pd, in RRMM pts. Isa SC offers shorter duration, fixed dose and smaller administration volume. Here, we report results of the IRAKLIA trial (NCT05405166); Isa SC vs IV + Pd in RRMM pts, the first Phase 3 myeloma trial reporting the use of an OBDS. **Methods:** This multicenter, open-label study enrolled pts aged ≥18 years with ≥1 prior line of therapy (LOT). Pts were randomized 1:1 to Isa SC (1400 mg) or Isa IV (10 mg/kg) weekly in Cycle (C)1, then every 2 weeks + P (4 mg/day, Day [D]1–21) + d (40 mg [20 mg if age ≥75 years] weekly). Pts had 4-week cycles until progression, unacceptable toxicity or patient request. Co-primary endpoints were overall response rate (ORR; non-inferiority [NI] margin of 0.839) and Isa trough level (C_{trough}) at steady state (predose at C6D1; NI if lower limit of 90% CI of geometric mean ratio ≥0.8). **Results:** 531 pts (SC n=263; IV n=268 [4 not treated]) were randomized. Baseline characteristics were balanced (median age 66 years; median 2 prior LOT). After median 12 months follow-up, ORR was 71% (SC arm) and 71% (IV arm; relative risk [95% CI] = 1.008 [0.903–1.126]; lower CI > NI margin). Mean (SD) C_{trough} at C6D1 was 499 (259) μg/mL for SC and 340 (169) μg/mL for IV. C_{trough} geometric mean ratio (90% CI) was 1.532 (1.316–1.784); lower CI > NI margin. Co-primary and all 4 key secondary endpoints including pt experience are in the Table. Grade ≥3 treatment-emergent adverse events occurred in 82% (SC) and 76% (IV) of pts; with treatment discontinuation rates of 8% and 9%. Injection site reactions (ISRs) occurred in 4% (11/263) of the SC arm and in 19 (0.4%) of 5145 SC injections (all Grade 1–2). 99.9% of OBDS injections were completed without interruption. **Conclusions:** IRAKLIA met its co-primary endpoints, showing efficacy and pharmacokinetic NI between Isa SC vs IV + Pd. No new safety signal besides a low ISR incidence was observed, showing excellent Isa SC tolerability. Far fewer infusion reactions and higher pt satisfaction were also noted for SC vs IV. Efficacy and safety are comparable to Isa IV in ICARIA-MM. These results support potential use of Isa SC delivered via the OBDS, designed to improve pt experience and practice efficiency. Clinical trial information: NCT05405166. Research Sponsor: Sanofi.

	Isa SC + Pd	Isa IV + Pd
Efficacy, %	**N=263**	**N=268**
ORR	71	71
≥VGPR	46	46
PK*, μg/mL	**N=131/121**	**N=126/121**
Geometric mean Isa C_{trough} at C2D1 / C6D1	360/426	277/278
Safety, %	**N=263**	**N=264**
All grade IR	2	25
Pt satisfaction with injection method at C5D15, %	70	53

*PK was analyzed at C6D1 with PP PK population and at C2D1 with PP CT4W population.
CT4W, C_{trough} at 4 weeks; IR, infusion reaction; PK, pharmacokinetics; PP, per protocol; VGPR, very good partial response.

7507 Oral Abstract Session

Long-term (≥5 year) remission and survival after treatment with ciltacabtagene autoleucel (cilta-cel) in CARTITUDE-1 patients (pts) with relapsed/refractory multiple myeloma (RRMM). First Author: Peter M. Voorhees, Atrium Health / Levine Cancer Institute, Wake Forest University School of Medicine, Charlotte, NC

Background: CARTITUDE-1 evaluated cilta-cel in pts with heavily pretreated RRMM who historically have an expected median progression-free survival (PFS) of <6 months (mo) and median overall survival (OS) of ~1 year (y). At 33.4 mo median follow-up, median PFS was 34.9 mo, and median OS was not reached (36-mo OS rate, 62.9%; Lin et al, ASCO 2023). We report OS, ≥5 y progression-free outcomes, and safety with a median study follow-up of 60.3 mo. **Methods:** Pts in CARTITUDE-1 received a single cilta-cel infusion. Correlative analyses were performed utilizing drug product, baseline, and postinfusion samples. Pts are followed for progression, survival, and safety in a 15-y follow-up study, CARTinue (NCT05201781), with pt evaluations per local standard of care (reported annually at a minimum). **Results:** Of 97 pts treated, 32 (33.0%) remain alive and progression free for ≥5 y after cilta-cel, without further MM treatment. For these 32 pts, prior to enrollment in CARTITUDE-1, median time from start of last line of therapy (LOT) to progression was 4.0 mo (range, 0.7–48.6). Among the 32, median age was 60 y (range, 43–78), median number of prior LOT was 6.5 (range, 3–14), 23.3% had high risk cytogenetics, 12.5% had extramedullary disease (EMD), 90.6% were triple-class refractory, and 46.9% were penta-drug refractory. Baseline characteristics of pts who were progression free for ≥5 y, including those with high-risk cytogenetics and EMD, were comparable to pts with progressive disease (PD) within 5 y. Compared with pts who had PD within 5 y, biomarkers significantly associated with ≥5 y progression free status included a higher fraction of naïve T cells in the drug product, lower neutrophil to T cell ratio, higher hemoglobin and platelets at baseline, and higher effector-to-target ratio (Cmax to sBCMA at baseline). At Cmax, these pts also had significantly higher CD4 central memory CAR+ T cell subsets and CAR+ T cells that were positive for the activation markers CD38, CD25, and PD-1. Data were collected on a subset of pts from a single center where local serial MRD assessments were performed. All 12 pts at this center who were progression free for ≥5 y were MRD negative at 10^{-6} and imaging negative by PET/CT yearly for 5 y. Overall, at 60.3 mo median follow-up in CARTITUDE-1 (N=97), median OS was 60.6 mo (95% CI, 41.9–NE). With continued follow-up, 3 additional pts reported a second primary malignancy (1 of which was acute myeloid leukemia; onset, 2.8 y after infusion). No new cases of movement and neurocognitive disorders were reported. **Conclusions:** The median OS for pts enrolled in CARTITUDE-1 was 5 y, and 33% of pts remain progression free for ≥5 y following a single cilta-cel infusion. These data provide the first evidence that cilta-cel is potentially curative in pts with RRMM. Clinical trial information: NCT03548207, NCT05201781. Research Sponsor: None.

7508 Oral Abstract Session

Safety and efficacy data from Nexicart-2, the first US trial of CAR-T in R/R light chain (AL) amyloidosis, Nxc-201. First Author: Heather Jolie Landau, Memorial Sloan Kettering Cancer Center, New York, NY

Background: No FDA approved treatments exist for relapsed/refractory (RR) AL Amyloidosis. Chimeric antigen receptor T-cell (CAR-T) is a novel approach to treating RR AL Amyloidosis. In this study, we report safety and efficacy data from NEXICART-2, the first U.S. clinical trial of any CAR-T in RR AL Amyloidosis. **Methods:** NEXICART-2 (NCT06097832) is a single-arm, multi-site U.S. Phase 1b/2 dose escalation and expansion trial of autologous BCMA-targeted CAR-T NXC-201 in RR AL Amyloidosis. It will enroll 40 patients (pts) with a 6 patient safety run-in, that has now completed. Pts must have been exposed to bortezomib and anti-CD-38 antibody with persistent or relapsed disease. Lymphodepletion was with fludarabine and cyclophosphamide. The primary endpoint is complete hematologic response (CR) rate (Palladini. 2012). **Results:** 7 pt (4 F, 3 M), median age 66 years (range: 56-82) were included. Median follow-up 97 days (range 7-209). Median prior lines 4 (range: 2-9); including 4(57%) with prior autologous stem cell transplant; 6/7 had gain 1q. Median dFLC at enrollment were 5.4 mg/dL (range: 2.4-12.1). 57% (4/7) had cardiac involvement (Mayo stage I (N =2), II (N=4) and IIIa (N=1) with median NT-proBNP 909 pg/mL (range: 146 – 2,532)); 2/7 had New York Heart Association (NYHA) class II heart failure, 5/7 class I. 2 pts had kidney involvement, with 4.5 and 10.0gm of proteinuria in 24h. 3 pts received 150 million and four 450 million CAR+T cells. CRS was observed in 5 pts (grade 1 (N=4), grade 2 (N=1)); onset day 1 (N=3) or 3 (N=2), lasting $<$24 hours following 1 dose of tocilizumab in all pts. No pt had neurotoxicity. Adverse events included neutropenia (grade 3 (N=3), grade 4 (N=2). 1 pt with pre-existing stage 4 chronic kidney disease prior to enrollment had Grade 4 acute on chronic kidney injury. There was no febrile neutropenia, treatment-related infections, cardiac toxicity, and no deaths. All pts (7/7, 100%) normalized pathological disease markers after NXC-201. Pts 1, 2, 4, 5, 6, 7 normalized FLCs at median 7 days (range 7-14) following NXC-201, all with reduction of dFLC to $<$1 mg/dL. Pts 1, 2, 4, 5, 6 had MRD negativity in bone marrow by flow cytometry (10^{-6} sensitivity) at day 25 or 26 (Pt 7 was not MRD evaluable as of the cut-off date). Pt 3 had a renal organ response per AL criteria (reduction in albuminuria) and resolution of the m-spike 15 days following NXC-201 (0.79g/dl at enrollment). As of the data cutoff, all pts are in VGPR/CR, with no relapses recorded. Improvement in NYHA class from II to I occurred in 1 pt 14 days following NXC-201 treatment. 15 pts are expected to have been treated at presentation time. **Conclusions:** In this first reported U.S. CAR-T clinical trial experience in RR AL Amyloidosis, we demonstrate that NXC-201 can be given safely and resulted in rapid and deep hematologic responses in all pts treated. Our data suggests that the novel anti-BCMA CAR-T NXC-201 may become a valuable treatment option for RR AL pts. Clinical trial information: NCT06097832. Research Sponsor: Immix Biopharma; MSK Cancer Center Support Grant/Core Grant (P30 CA008748).

7509 Rapid Oral Abstract Session

Isatuximab, carfilzomib, lenalidomide, and dexamethasone (Isa-KRd) for high-risk (HR) newly diagnosed multiple myeloma (NDMM): First-time report of the full cohort of transplant-eligible (TE) patients in the GMMG-CONCEPT trial. First Author: Lisa B. Leypoldt, University Medical Center Hamburg-Eppendorf, Hamburg, Germany

Background: Patients (pts) with HR NDMM have shown impaired survival outcomes even in the era of modern combination therapies. Establishing Isa-KRd in an intensified first-line regimen, the Phase II CONCEPT trial (NCT03104842) aimed at improving outcomes for HR NDMM pts for whom clinical trials had long been missing. **Methods:** The prospective, multicenter, academic Phase II CONCEPT trial has 2 parallel treatment arms according to transplant-eligibility. Adult NDMM pts with HR disease, defined as $\geq$1 HR cytogenetic aberration (CA) (del(17p), t(4;14), t(14;16), $\geq$3 copies 1q21) in combination with ISS stage II/III were included. All pts received Isa-KRd induction (6 cycles), intensification (HD-MEL+ASCT [TE pts; arm A] or 2 cycles Isa-KRd [non-TE pts; arm B]), 4 cycles Isa-KRd consolidation and 2 years Isa-KR maintenance. Primary endpoint is minimal residual disease (MRD) negativity (NGF, 10^{-5}) at the end of consolidation, tested against the null hypothesis MRD-neg rate $\leq$50% (TE pts); key secondary endpoints include survival times (PFS, OS). The trial recruited in 2 phases: 2017-2020 (TE+TNE; 1st cohort) and 2021-2022 (TE only; 2nd cohort), with a switch in carfilzomib application implemented in 2021 (1x weekly instead of 2x weekly). Interim results of the 1st cohort have been shown before. Here, we report for the first time the final analysis on the primary endpoint from the full cohort of TE pts. **Results:** 219 TE pts (and 26 TNE pts) were included and dosed. At data cut-off (9 Jan 2025), 66 pts were still on treatment. Median age of TE pts was 60 years (range, 31-73) with 119 and 100 showing ISS II and III. Del(17p) and gain1q were the most common HRCA (40.6% and 46.6%) and 35.6% had $\geq$2 HRCA. The trial met its primary endpoint with an MRD-neg rate after consolidation of 73.2% in the MRD-analysis population (153/209; 10 not assessable). Further analyses confirmed the benefit across different CA subgroups. Overall, 58.4% reached MRD-neg $\geq$CR, 86.8% reached MRD-neg at any time. 64.8% and 40.6% retained $\geq$1-year- and $\geq$2-year-sustained MRD-neg. With a median follow-up (mFU) of 42 mo (0-85.5 mo), mPFS for TE pts was 69.7 mo, while mOS has not been reached. For TNE pts (mFU 60 mo), mPFS and mOS have not been reached. Reaching and remaining in MRD-neg state led to a significant PFS benefit (*hr* 0.16 [0.08;0.32], time-dependent Cox regression). Carfilzomib 1x weekly resulted in fewer K discontinuations than 2x weekly dosing (0.6% and 4.8%, TE pts), with more dose reductions in the 1x weekly dosing (9.5% and 5.5%, TE pts). **Conclusions:** The full CONCEPT cohort represents the largest prospective trial cohort of purely HR NDMM pts reported so far. Isa-KRd resulted in unprecedented rates of MRD-neg., sustained MRD-neg. and survival supporting the use of Isa-KRd as a standard-of-care regime in this hard-to-treat population. Clinical trial information: NCT03104842. Research Sponsor: University Medical Center Hamburg-Eppendorf; Sanofi; Amgen; BMS/Celgene.

7510 Rapid Oral Abstract Session

Linvoseltamab (LINVO) + bortezomib (BTZ) in patients (pts) with relapsed/refractory multiple myeloma (RRMM): First results from the LINKER-MM2 trial. First Author: Paula Rodríguez-Otero, Department of Hematology, Clínica Universidad de Navarra, Pamplona, Spain

Background: LINVO, a BCMA$\times$CD3 bispecific antibody, has shown high efficacy and generally manageable safety in triple-class exposed (TCE: anti-CD38 Ab + immunomodulatory drug [IMiD] + proteasome inhibitor [PI]) pts with RRMM. PIs such as BTZ have direct anti-MM activity and may enhance LINVO activity by improving immune function. We report safety and preliminary efficacy data from dose escalation and expansion in the LINVO + BTZ cohort of the phase 1b, open-label LINKER-MM2 trial (NCT05137054). **Methods:** Eligible pts were $\geq$18 yrs with RRMM that progressed after $\geq$3 lines of therapy (LoT), or $\geq$2 LoT if either TCE or double-class refractory (IMiD + PI). Prior BTZ was allowed if previously tolerated and $\geq$6 months (mos) had elapsed since last exposure. BTZ-refractory pts were allowed during dose escalation. Treatment (tx) began with LINVO alone (Cycle [C] 0: 2 step-up doses [5 and 25 mg] and $\geq$1 full dose [dose level [DL] 1 = 100 mg or DL2 = 200 mg]) before initiating standard dose BTZ (1.3 mg/m^2 twice weekly over 21-day cycles) at C1. LINVO was given once weekly (QW) in C1–4, then Q3W thereafter. BTZ dosing could be switched to QW after C3 and ended after a total of 8 cycles. Dexamethasone premedication was limited to C0–1. Primary endpoints were dose-limiting toxicities (DLTs; dose-finding portion) and incidence/severity of tx-emergent AEs (TEAEs). Secondary endpoints included objective response rate (ORR), duration of response (DOR), and progression-free survival (PFS). **Results:** As of Sept 30, 2024, 22 pts had received tx (DL1: n=6; DL2: n=16). Median follow-up duration was 6.3 mos (range 1–21), with 55% of pts still receiving tx. Median age was 68.5 yrs (range 45–77), 68% were male, 23% had ISS stage III, and 55% had extramedullary or paraskeletal disease. Median prior LoT was 3 (range 2–9), including 86% of pts with TCE and 41% with triple-class refractory disease; 59% were refractory to $\geq$1 PI (9% BTZ-refractory). Among evaluable pts, ORR was 79% (11/14; DL1 80% [4/5]; DL2 78% [7/9]). The 6-month DOR rate was 90% (95% CI 47–99) and 6-month PFS rate was 79% (95% CI 47–93). PK analysis found LINVO concentrations were not affected by addition of BTZ. The most common TEAEs were neutropenia (any Grade [Gr] 59%; Gr 3–4 45%), thrombocytopenia (50%; 36%), and cytokine release syndrome (55%; 0%). ICANS was reported in 4 pts (all Gr 1–2 with onset during step-up dosing). Infections were reported in 82% of pts (Gr 3–4 36%); 1 pt died of pneumonia $\leq$30 days after last dose before start of combination tx. One DLT occurred at DL2 (Gr 3 CMV colitis on day 48; resolved with tx delay and ganciclovir). **Conclusions:** LINVO + BTZ induced high response rates, with encouraging early DOR and PFS, in a population that was mostly PI-refractory. Safety was consistent with the known profile of each drug, and risk of Gr 3–5 infection was similar to LINVO monotherapy. These data will inform LINVO combination strategies for earlier LoT. Clinical trial information: NCT05137054. Research Sponsor: Regeneron Pharmaceuticals, Inc.

7511 Rapid Oral Abstract Session

Heterogeneity in the expression of GPRC5D between patients with multiple myeloma. First Author: Harsh Parmar, John Theurer Cancer Center, Hackensack University Medical Center, Hackensack, NJ

Background: G-protein-coupled receptor class C group 5 member D (GPRC5D) is a protein inducible by all-trans retinoic acid with expression levels that vary depending on cellular differentiation. This protein receptor is targeted by several therapeutic modalities including chimeric-antigen receptor T-cell therapy (CAR-T), T-cell engagers (TCEs) and antibody-drug conjugates (ADCs). However, our understanding of GPRC5D expression levels in multiple myeloma cells and patient-to-patient heterogeneity remains limited. We investigated the expression levels of GPRC5D in the plasma cells of patients with multiple myeloma and compared its level of expression with those of CD38, CD138 and BCMA (TNFRSF17). **Methods:** Plasma cells from the bone marrow aspirates of 290 patients with multiple myeloma were enriched using CD138 column. RNA was extracted from the CD138 enriched population and sequenced by next generation sequencing (NGS) using a targeted RNA panel of 1600 genes. The RNA expression levels of various genes were quantified and expressed as transcript per million (TPM). **Results:** There was significant variation in the expression of GPRC5D between myeloma samples. The median and standard deviations for CD38, CD138, BCMA, and GPRC5D were 89 and 113, 69 and 134, 58 and 132, and 10 and 166, respectively. There was significant correlation ($P <$ 0.00001) between CD38, CD138 and BCMA. However, there was no correlation between the levels of GPRC5D and CD38 (R=-0.05, P= 0.4), CD138 (R=0.3, P= 0.6) or BCMA (R=0.1, P=0.02). Ten samples (3%) had zero TPM expression of GPRC5D despite relatively high CD138 (between 33 TPM and 487 TPM). The ratio of GPRC5D: BCMA varied from 0 to 39 with one sample with an exceptionally high ratio of 459 due to very low BCMA with high CD138 due to anti-BCMA therapy. **Conclusions:** Analysis of these data suggests that unlike BCMA, there is a significant patient-to-patient heterogeneity in GPRC5D expression. GPRC5D expression levels show a wide variation with approximately 3% of patients showing an absence of GPRC5D expression. Clinical trials exploring anti-GPRC5D therapy should consider measuring GPRC5D expression levels and potentially explore other therapies that may induce its increased expression given our findings. Research Sponsor: None.

RNA Expression Levels (TPM)

Variable	Median	Lower Quartile	Upper Quartile
CD38	89	63	135
CD138	69	44	134
BCMA	58	35	106
GPRC5D	10	2	50

Spearman Correlations

Pair of Variables	R	t(N-2)	p-value
CD38 & CD138	0.362809	6.60727	0.0000000
CD38 & BCMA	0.383742	7.05224	0.0000000
CD138 & BCMA	0.63282	13.86974	0.0000000
CD138 & GPRC5D	0.028007	0.47548	0.6348020
CD38 & GPRC5D	-0.045081	-0.76583	0.4444070
BCMA & GPRC5D	0.138314	2.37004	0.0184450

7512 Rapid Oral Abstract Session

Belantamab mafodotin plus lenalidomide/dexamethasone in newly diagnosed intermediate-fit & frail multiple myeloma patients: Long-term efficacy and safety from the phase 1/2 BELARD clinical trial. First Author: Evangelos Terpos, Department of Clinical Therapeutics, National and Kapodistrian University of Athens, School of Medicine, Athens, Greece

Background: We report the long-term safety & efficacy results of a novel, extended dosing schedule of belantamab mafodotin (belamaf) combined with Lenalidomide & Dexamethasone (Rd), in transplant-ineligible newly diagnosed Multiple Myeloma patients (pts). **Methods:** Phase 1/2 BelaRd trial (NCT04808037) Part 1 evaluated the safety/tolerability of belamaf 2.5/1.9/1.4 mg/kg plus Rd & established a recommended phase 2 dose (RP2D) of 1.9 mg/kg Q8W, extended to Q12W for Ocular Adverse Events (OAEs, Best Corrected Visual Acuity [BCVA] change from baseline & keratopathy). Dosing was led by ophthalmologist-assessed OAEs. In Part 2 RP2D is assessed in 2 groups: Dosing in Group A is guided as in Part 1 & in Group B by Vision-Related Anamnestic (a 9-question tool on pt-reported ocular symptoms & their impact on daily functioning) & ≥Gr3 OAEs. Safety/efficacy results from both Parts of the trial are presented. **Results:** Of Part 1 pts (n=36; median age: 72.5; male: 53%), 25 (69%) are ongoing & 11 (31%) discontinued (8 [22%] due to fatal events; 1 [3%] progressive disease; 2 [6%] withdrew consent). 17%/75% of pts had stage I/II disease per R-ISS & 8% high-risk cytogenetics (HRC). At a median follow-up (FU) of 36.2 months, Overall Response Rate (ORR) was 100%. Meaningful BCVA decline (Snellen <20/50) was recorded in 12% & Gr2/≥Gr3 keratopathy in 12%/3% of ocular exams. Median time to resolution was 1.9/1.1 months for ≥Gr2 BCVA/keratopathy OAEs, respectively. The most common (≥10%) Gr≥3 non-ocular AEs were fatigue, diarrhea, rash, COVID-19, pneumonia & insomnia. Of Part 2 pts (n=30; median age: 75; male: 67%), 22 (73%) are ongoing & 8 (27%) discontinued (6 [20%] due to fatal events; 1 [3%] progressive disease; 1 [3%] withdrew consent). 27%/63% of pts had stage I/II disease per R-ISS & 17% had HRC. At a median FU of 19.7 months, ORR was 96.7%. Meaningful BCVA decline was recorded in 27% & Gr2/≥Gr3 keratopathy in 9%/<1% of ocular exams. Median time to resolution of ≥Gr2 OAEs was 1.75 months. The most common Gr≥3 non-ocular AEs were fatigue & rash. The 12/24/36-months Time to Progression rates for all 66 pts were 98.2%/98.2%/94.4% (table 1). **Conclusions:** As has also been shown in the DREAMM-7/-8 studies,belamaf exhibits substantial clinical activity, with rapid, deep & durable responses in an unfit pt population, with only 2 PDs observed after a median of ~2 years FU. Only a few high-grade OAEs were recorded, that resolved quickly & no new safety signals were observed. Moving forward, the BelaRd combination, with the extended belamaf dosing schedule, warrants further investigation in larger pt numbers. Clinical trial information: NCT04808037. Research Sponsor: None.

Time to progression (TTP) rates in the overall population (66 pts).

	TTP rate in % (95% CI)
12 months	98.21 (87.99-99.75)
24 months	98.21 (87.99-99.75)
36 months	94.44 (77.81-98.70)

CI: Confidence Interval.

7513 Rapid Oral Abstract Session

Linvoseltamab (LINVO) + carfilzomib (CFZ) in patients (pts) with relapsed/refractory multiple myeloma (RRMM): Initial results from the LINKER-MM2 trial. First Author: Salomon Manier, Hematology Department, Lille University Hospital, Lille, France

Background: LINVO, a T-cell redirecting BCMA×CD3 bispecific antibody, has demonstrated high efficacy and generally manageable safety in triple-class exposed (TCE: anti-CD38 Ab + immunomodulatory drug [IMiD] + proteasome inhibitor [PI]) pts with RRMM. Combination treatment (tx) with CFZ, a potent second-generation PI, may enhance clinical activity via rapid cytoreduction and complementary immunostimulatory mechanisms like immunogenic cell death and antigen spreading. We report safety and preliminary efficacy from dose escalation in the LINVO + CFZ cohort of the phase 1b, open-label LINKER-MM2 trial (NCT05137054). **Methods:** Eligible pts were ≥18 years with RRMM that progressed after ≥3 lines of therapy (LoT), or ≥2 LoT if either TCE or double-class refractory (IMiD + PI). Prior CFZ was allowed if previously tolerated and ≥6 months had elapsed since last exposure. CFZ-refractory pts were allowed during dose escalation. Tx began with LINVO alone (Cycle [C] 0) consisting of 2 step-up doses (5 mg and 25 mg) and 2 full doses (dose level [DL] 1 = 100 mg or DL1b = 150 mg) before initiation of CFZ (20/56 mg/m^2 on days 1, 2, 8, 9, 15, 16) at C1. LINVO was given once weekly (QW) in C1–4, and Q2W thereafter. CFZ dosing could be switched to QW after C2. Dexamethasone premedication was limited to C0–1. Primary endpoints were dose limiting toxicities (DLTs) and tx-emergent adverse events (TEAEs). Secondary endpoints included objective response rate (ORR), duration of response (DOR), and progression-free survival (PFS). **Results:** As of Sep 30, 2024, 18 pts were treated at DL1 (n = 12) or DL1b (n = 6). Median duration of follow-up was 16.9 (DL1) and 7.7 months (DL1b), with 67% and 83% of pts still receiving tx, respectively. Median age was 68 years (range 53–79), 50% were male, 6% had ISS stage III, 50% had extramedullary or paraskeletal disease, and 17% had high-risk cytogenetics. Median prior LoT was 3 (2–6), including 83% of pts with TCE and 33% with triple-class refractory disease. Among evaluable pts, ORR was 91% at DL1 (10/11; ≥VGPR 91%) and 100% at DL1b (6/6; ≥VGPR 80%). Median DOR was not reached at either DL. For DL1, the PFS rate was 91% (95% CI 51–99) at 6 months and 73% (95% CI 37–90) at 12 months. No PFS events had occurred at DL1b. PK analysis found LINVO concentrations were not affected by addition of CFZ. The most common TEAEs were neutropenia (any Grade [Gr] 78%; Gr 3–4 61%), thrombocytopenia (61%; 39%), and cytokine release syndrome (61%; Gr ≥3 0%). One pt experienced ICANS (Gr 1). Infections were reported in 89% of pts (Gr ≥3 44%). One DLT was observed at DL1, Gr 4 thrombocytopenia in the setting of tumor lysis syndrome, from which the pt recovered and afterward resumed tx. **Conclusions:** LINVO + CFZ induced a high rate of deep and durable responses with a safety profile consistent with the individual drugs, supporting further development. Enrollment at 200 mg LINVO in combination with CFZ is ongoing. Clinical trial information: NCT05137054. Research Sponsor: Regeneron Pharmaceuticals, Inc.

7514 Rapid Oral Abstract Session

Phase 1, first-in-human study of ISB 2001: A BCMAxCD38xCD3-targeting trispecific antibody for patients with relapsed/refractory multiple myeloma (RRMM)—Dose escalation (DE) results. First Author: Eben I. Lichtman, UNC Lineberger Comprehensive Cancer Center, Chapel Hill, NC

Background: MM remains an incurable disease and resistance mechanisms are emerging. ISB 2001, a first-in-class trispecific T cell engager, redirects cytotoxic T cells to BCMA and/or CD38-expressing myeloma cells. By simultaneously targeting two TAA, ISB 2001 enhances avidity binding to tumor cells in vitro, hence potency, while the distal positioning of the CD38 vs CD3 binders minimizes CD38-related off-tumor adverse events. **Methods:** We report data from the DE portion of a Phase 1 study of ISB 2001, assessing safety, tolerability, efficacy, pharmacokinetics (PK), and pharmacodynamics (PD) in RRMM patients (pts) exposed to immunomodulatory drugs, proteasome inhibitors, and anti-CD38 therapies and refractory or intolerant to established therapies. Prior BCMA-targeted and/or T-cell directed therapies were allowed. ISB 2001 was administered weekly subcutaneously (SC) in 28-day cycles, with initial step-up doses on Days 1 (15μg/kg) and 4 (variable). DE utilized an accelerated titration design (initial 3 cohorts with single-patient dosing) followed by a standard 3+3 design. DLTs were evaluated in the first 28 days. After DE, the study will proceed with Part 2 (dose expansion) to confirm safety and select the recommended Ph2 dose under FDA Project Optimus. **Results:** As of January 13, 2025, 24 pts were treated with ISB 2001 across 8 dose levels (5–1800 μg/kg) with a median follow-up of 6 months (range: 2–12). DL9 (2700 μg/kg) is last dose level and currently enrolling. Among 24 pts, median age was 66 years; 58% male, 83% white with a median of 6 prior lines of therapy (range: 3-11). All pts were triple-exposed, 17/24 (71%) penta-exposed, and 3/17 penta-refractory (18 %). No DLT, adverse events (AE) leading to treatment discontinuation or deaths occurred. Serious AEs were reported in 8 (33%) patients. Drug related Grade (Gr) 3-4 AEs were seen in 13 (54%) pts. CRS was reported in 17 (70.8%) patients, primarily Grade 1–2, with a median onset of 3 days and a median duration of 2 days. No neurologic AEs or ICANs. The Overall Response Rate (ORR) was 75% across all 8 doses, including stringent CR (sCR) 13%, CR 13%, VGPR 38%, PR 13%. Responses were observed from dose level as low as 50 μg/kg (MRD-neg, sCR) with an ORR of 82% at doses ≥50 μg/kg. Median time to response was 36 days. ISB 2001 showed near dose-proportional PK, a half-life >10 days, and consistent T-cell activation, supporting its mechanism of action. **Conclusions:** ISB 2001 was well tolerated with manageable CRS, no ICANS and demonstrated robust anti-myeloma activity in heavily pretreated RRMM pts (NCT05862012). Full clinical data, including PK and PD results from the dose-escalation portion of the study, will be presented at the conference. Clinical trial information: NCT05862012. Research Sponsor: IGI.

7515 Rapid Oral Abstract Session

Minimal residual disease (MRD) negativity (neg) in patients (pts) with relapsed or refractory multiple myeloma (RRMM) treated with belantamab mafodotin plus pomalidomide and dexamethasone (BPd) vs pomalidomide, bortezomib, and dexamethasone (PVd): Analysis from the DREAMM-8 trial. First Author: Suzanne Trudel, Department of Medical Oncology and Hematology, Princess Margaret Cancer Centre, Toronto, ON, Canada

Background: In DREAMM-8 (NCT04484623), BPd demonstrated a statistically significant, clinically meaningful benefit to progression-free survival (PFS) vs PVd in pts with RRMM who received ≥1 prior line of treatment including lenalidomide. MRD neg has been shown to be a predictor of PFS and overall survival (OS) in MM. We assessed efficacy outcomes by MRD status. **Methods:** Ptswere randomized (1:1) to BPd or PVd. The primary endpoint was independent review committee (IRC)–assessed PFS; OS, duration of response, and MRD status determined by next-generation sequencing with 10^{-5} sensitivity threshold was assessed in pts with complete response or better (≥CR) every 6 mo until progressive disease. Post hoc subgroup analyses of PFS and OS were conducted based on IRC-assessed response (≥CR or ≥VGPR) and MRD-neg status using Kaplan-Meier method; CIs were estimated using Brookmeyer-Crowley method. **Results:** 302 pts were randomized to BPd (n=155) or PVd (n=147). As previously reported (median follow-up, 21.8 mo), more pts with BPd had CR-based MRD neg vs PVd (37/155 [24%] vs 7/147 [5%]). A similar trend was seen in pts with ≥VGPR; 50/155 pts (32%) had VGPR-based MRD neg with BPd vs 8/147 (5%) with PVd. In the DREAMM-8 trial, MRD neg was associated with improved efficacy outcomes (Table). Pts with CR-based MRD neg had a lower risk of disease progression or death compared with pts without MRD neg (PFS HR, 0.14; 95% CI, 0.06-0.32; Table); median was NR overall and in each treatment arm (HR [BPd vs PVd], 0.90; 95% CI, 0.10-7.76). MRD neg pts had a lower risk of death (OS HR, 0.18; 95% CI, 0.07-0.49). In all pts who did not have CR-based MRD neg, pooled median PFS was 14.0 mo (95% CI, 11.1-18.6 mo; BPd, 19.6 mo; PVd, 10.2 mo; HR [BPd vs PVd], 0.67; 95% CI, 0.47-0.94), and the pooled 18-mo PFS rate was 46% (95% CI, 39%-52%; BPd, 52%; PVd, 39%). Median OS was NR overall, 33.0 mo (95% CI, 23.7-NR) with BPd and NR with PVd; 18-mo OS rate was 69% (95% CI, 63%-75%; BPd, 72%; PVd, 67%). **Conclusions:** Consistent with previous reports, MRD neg was associated with a robust benefit in PFS and OS, highlighting the significance of a greater response depth. Pts with BPd achieved a 5-fold improvement in CR-based MRD neg vs PVd (24% vs 5%). Pts who did not achieve CR-based MRD neg had a clinically meaningful benefit in PFS with BPd vs PVd. Clinical trial information: NCT04484623. Research Sponsor: Funding statement: This study sponsored by GSK. Editorial support provided by Nucleus Global and funded by GSK. Drug linker technology licensed from Seagen Inc.; monoclonal antibody produced using POTELLIGENT Technology licensed from BioWa.

	MRD neg			Non-MRD neg		
MRD status (≥CR), n	**Pooled (44)**	**BPd (37)**	**PVd (7)**	**Pooled (258)**	**BPd (118)**	**PVd (140)**
Median PFS (95% CI), mo	NR (NR-NR)	NR (NR-NR)	NR (NR-NR)	14.0 (11.1-18.6)	19.6 (13.5-NR)	10.2 (8.4-17.1)
18-mo PFS rate (95% CI), %	93 (79-98)	91 (75-97)	100 (100-100)	46 (39-52)	52 (42-62)	39 (30-48)
18-mo OS rate (95% CI), %	93 (80-98)	92 (76-97)	100 (100-100)	69 (63-75)	72 (62-79)	67 (59-74)

7516 Rapid Oral Abstract Session

Daratumumab plus bortezomib, lenalidomide, and dexamethasone (DVRd) in patients with newly diagnosed multiple myeloma (NDMM): Subgroup analysis of transplant-ineligible (TIE) patients in the phase 3 CEPHEUS study. First Author: Thierry Facon, University of Lille, CHU Lille, Lille, France

Background: After readout of the PERSEUS and CEPHEUS trials, daratumumab-based therapy + VRd is emerging as the standard of care in NDMM treatment. In CEPHEUS (NCT03652064), DVRd improved minimal residual disease negativity (MRD neg) and progression-free survival (PFS) vs VRd in patients (pts) with TIE or transplant-deferred (TD) NDMM. As transplant deferral is not a common clinical pathway in many regions, here we report a post hoc analysis of DVRd efficacy in TIE pts. **Methods:** CEPHEUS enrolled pts with TIE or TD NDMM, ECOG performance status (PS) 0–2, and an International Myeloma Working Group (IMWG) frailty score of 0 or 1. Pts were randomized (1:1) to DVRd or VRd. In this analysis, the primary endpoint of overall MRD neg rate (MRD neg at 10^{-5} and complete response or better [≥CR]), and key secondary endpoints, including PFS and sustained MRD neg (confirmed MRD neg ≥12 months [mo] apart without MRD positivity in between) were assessed in the CEPHEUS TIE population. **Results:** Of 395 pts, 289 were TIE (DVRd, n=144; VRd, n=145). TIE population baseline (BL) characteristics were generally well balanced between DVRd vs VRd. In the TIE vs intent-to-treat (ITT) population, median age was older (72 vs 70 years [y]), and a higher percentage of pts were intermediate fit per IMWG criteria (41.2% vs 35.2%). In TIE pts, overall MRD neg rate at 10^{-5} was 60.4% for DVRd and 39.3% for VRd (odds ratio [OR] 2.37; 95% CI 1.47–3.80; $P<0.0001$); at 10^{-6}, it was 45.8% vs 26.9% (OR 2.28; 95% CI 1.40–3.73; $P=0.001$). Sustained MRD neg rate (10^{-5}) was 46.5% vs 27.6% (OR 2.27; 95% CI 1.39–3.70; $P=0.0010$). Overall ≥CR rate was 80.6% vs 61.4% (OR 2.73; 95% CI 1.71–4.34; $P<0.0001$). At 58.7-mo median follow-up, median PFS was NR for DVRd and 49.6 mo for VRd, and the 54-mo PFS rate was 69.0% vs 48.0% (HR 0.51; 95% CI 0.35–0.74; $P=0.0003$); OS favored DVRd vs VRd (HR 0.66; 95% CI 0.42–1.03; after censored for deaths due to COVID-19, HR 0.55; 95% CI 0.34–0.90). Treatment effect was generally consistent across subgroups (Table). Safety profile was consistent with ITT and the known profile for daratumumab subcutaneous and VRd. **Conclusions:** In CEPHEUS TIE pts, the ≥CR rate was 80.6% and overall MRD neg rate (10^{-5}) was 60.4%, with ~50% of pts sustaining MRD neg for ≥1 y. Nearly 70% of pts were alive and progression free at 4.5 y. These subgroup data reinforce the strong efficacy of DVRd in the TIE population. Clinical trial information: NCT03652064. Research Sponsor: Johnson & Johnson.

	MRD neg (10^{-5}) rate, %				Median PFS, mo			
BL characteristic	DVRd	VRd	OR	95% CI	DVRd	VRd	OR	95% CI
ISS stage I	66.0	41.7	2.72	1.20–6.17	All not estimable	60.6	0.58	0.30–1.12
II	59.3	43.9	1.86	0.88–3.96		49.4	0.41	0.21–0.77
III	55.0	30.0	2.85	1.14–7.15		33.6	0.61	0.31–1.19
Cytogenetic risk High	50.0	50.0	1.00	0.28–3.57		31.7	0.82	0.33–2.03
Standard	62.9	38.7	2.68	1.54–4.64		60.6	0.54	0.33–0.86
ECOG PS 0	57.7	43.9	1.75	0.82–3.73		60.6	0.33	0.16–0.69
≥1	62.0	36.4	2.85	1.56–5.22		47.2	0.63	0.40–0.99

7517 Rapid Oral Abstract Session

Isatuximab, bortezomib, lenalidomide, and dexamethasone (Isa-VRd) in newly diagnosed multiple myeloma (NDMM): Outcomes in patients with 1q21+ status in the phase 3 IMROZ study. First Author: Meletios Athanasios Dimopoulos, Department of Clinical Therapeutics, School of Medicine, National and Kapodistrian University of Athens, Athens, Greece

Background: Gain or amplification of 1q21 (1q21+, ≥3 copies) is a chromosomal abnormality often detected in MM that can negatively affect prognosis by its involvement in resistance to therapy and MM progression. Results from the global, randomized Phase 3 IMROZ study (NCT03319667) demonstrated significant progression-free survival (PFS) benefit with Isa-VRd followed by Isa-Rd compared with VRd followed by Rd, along with deep and sustained responses, in transplant-ineligible patients (pts) with NDMM. To evaluate efficacy of combination treatment with Isa-VRd/Isa-Rd vs VRd/Rd in NDMM pts with 1q21+ status, we analyzed clinical outcomes (PFS, overall response, minimal residual disease negativity [MRD−]) for 1q21+ pts in the IMROZ study. **Methods:** In IMROZ, 446 pts were randomized 3:2 to receive Isa-VRd (n=265) in the initiation phase followed by maintenance with Isa-Rd vs VRd (n=181) followed by Rd. 1q21+ status was assessed by FISH (30% cutoff) and prespecified as ≥3 copies (gain=3, amplification >3). Isolated 1q21+ was defined as presence of 1q21+ and absence of high-risk chromosomal abnormalities [HRCAs; del(17p), t(4;14), t(14;16)]. MRD data by NGS were reported at 10^{-5} sensitivity threshold. **Results:** Overall, 35.9% and 38.7% of pts had 1q21+ status in the Isa-VRd and VRd arms, respectively (23.8% and 26.0% with gain(1q21), 12.1% and 12.7% with amp(1q21); 7.2% and 8.3% also had ≥1 HRCA). Treatment with Isa-VRd significantly prolonged PFS vs VRd in 1q21+ pts (with or without HRCA) and in pts with isolated 1q21+ (see Table) and led to higher rates of complete response (CR) and MRD−. A substantially greater proportion of pts with 1q21+ or isolated 1q21+ achieved MRD− CR and sustained MRD− for ≥12 months with Isa-VRd than with VRd. Data for gain(1q21) and amp(1q21) will be presented. **Conclusions:** Results from our analysis of outcomes in 1q21+ pts in the IMROZ trial demonstrate consistent PFS benefit with Isa-VRd vs VRd, as reported in the overall study population. Benefit was observed regardless of 1q21+ or isolated 1q21+ status.These findings are in line with similar analyses done with Isa-pomalidomide-dexamethasone and Isa-carfilzomib-dexamethasone in Phase 3 studies. Clinical trial information: NCT03319667. Research Sponsor: Sanofi.

	1q21+		Isolated 1q21+[a]		Standard risk[a]	
	Isa-VRd	VRd	Isa-VRd	VRd	Isa-VRd	VRd
n (%)	95 (35.9)	70 (38.7)	75 (28.3)	55 (30.9)	207 (78.1)	140 (77.4)
mPFS, mo (95% CI)	NR (NR–NR)	39.13 (22.93–48.95)	NR (NR–NR)	43.01 (20.60–59.70)	NR (NR–NR)	53.91 (43.01–NR)
PFS HR (95% CI)	0.407 (0.253–0.653) $p=0.0002$		0.369 (0.213–0.642) $p=0.0004$		0.517 (0.363–0.737) $p=0.0003$	
ORR %	95.8	85.7	96.0	81.8	97.5	100
≥CR %	76.9	60.0	78.7	52.7	72.5	79.4
MRD− %	63.2	41.4	65.3	40.0	58.9	40.7
MRD− CR %	62.1	38.6	64.0	36.4	55.6	37.9
Sustained MRD− ≥12 mo %	51.6	22.9	50.7	23.6	45.4	22.9

[a]Absence of del(17p), t(4;14) and t(14;16). NR, not reached.

7518 Poster Session

Disease response at apheresis and association with long-term outcomes following CAR-T cells for relapsed/refractory multiple myeloma (RRMM). First Author: Thomas Luo, Abramson Cancer Center, Hospital of the University of Pennsylvania, Philadelphia, PA

Background: The two approved BCMA-targeted CAR-T products, cilta-cel and ide-cel, have significant efficacy in RRMM, but are not considered curative. Initial studies in ≥4th line RRMM required progressive disease (PD) at time of enrollment and T cell apheresis. We hypothesized that using CAR-T cells as a planned consolidation strategy (i.e. in patients (pts) with stable or responsive disease on their current therapy) may lead to lower toxicity and better long-term disease control. **Methods:** We conducted a retrospective review of all RRMM pts receiving commercial CAR-T cells at the University of Pennsylvania from 6/1/21 to 4/30/24, with at least 6 months of follow-up. Intent for consolidation was retroactively assigned by chart review. Kaplan-Meier methodology was used to determine PFS and OS. **Results:** We identified 149 pts for analysis, with a median follow-up of 14.4 months (mos). Median prior lines was 6 and 81% of pts were triple class-refractory; 46% had high-risk cytogenetics, 26% had extramedullary disease, and 17% had prior BCMA-directed therapy. Pts received either cilta-cel (54%) or ide-cel (46%), and 95% received bridging therapy. CAR-T cells were intended as planned consolidation in 51 pts (34%); of these, 36 (71%) had ≥PR at time of apheresis. For consolidation vs non-consolidation groups, this translated into greater depth of response post-CAR-T cells (≥VGPR, 86% vs. 66%, p=0.01), lower rates of ≥grade 3 CRS (1.9% vs. 9.1%, p=0.16), and longer PFS (median not reached vs. 10 mos, p=0.001), respectively. The PFS improvement was seen for both cilta-cel (p=0.01) and ide-cel (p=0.04). No differences in neurotoxicity were noted. We also performed analyses based on response at apheresis, regardless of intent (8% ≥VGPR, 23% PR, 27% stable disease (SD), and 42% PD). PFS at 20 mos was 88%, 47%, 55%, and 31% for ≥VGPR, PR, SD, and PD at apheresis, respectively (p=0.015). Median PFS of pts with at least SD (≥SD) at apheresis was not reached vs. 9.4 mos in those with PD (p= 0.003), with 20-month OS of 87% in the ≥SD group and 68% in the PD group (p=0.015). Subgroup analysis confirmed this PFS difference for both cilta-cel and ide-cel, while the OS impact was only seen for cilta-cel. On multivariate analysis, having ≥SD at apheresis was an independent predictor for PFS. No statistically significant differences in CRS and ICANS were observed based on response at apheresis. Pts with ≥SD at apheresis had higher absolute lymphocyte counts at days 7 and 14 post-CAR-T infusion than those with PD, indicating disease status at apheresis may be associated with CAR-T product quality. **Conclusions:** Our data suggest that disease control (≥SD) at time of T-cell collection is associated with more durable responses, supporting use of CAR-T cells as a consolidation strategy in RRMM. We cannot conclude these associations are causal. Further analyses of apheresed T cell characteristics are planned. Research Sponsor: None.

7519 Poster Session

Second primary malignancy (SPM) in patients (pts) with multiple myeloma (MM) receiving chimeric antigen receptor T-cell (CAR T) therapy or other systemic anticancer therapy (SACT): A comparative study using a real-world database. First Author: Attaya Suvannasankha, Department of Medicine, Indianna University, Indianapolis, IN

Background: Cases of SPM have been reported following CAR T therapy, but comparative studies are scarce. We compared the risk of SPM following CAR T therapy vs other SACT in pts with MM. **Methods:** Pts aged ≥18 years with MM who initiated CAR T therapy or other SACT, except stem cell transplant, in second-line or beyond were identified from Komodo Health claims data (3/26/2021–1/31/2024). Incident SPM was identified by ≥1 diagnostic code through death, disenrollment, or data cutoff (4/30/2024), whichever was earliest. Cumulative incidence of SPM following CAR T therapy or other SACT was estimated through 24 months, weighted by baseline factors including prior MM treatments; p-values were calculated for differences in the area under the curves through 24 months. **Results:** Pts who received CAR T therapy (n=436) or other SACT (n=18,603) were followed for a median of 11.8 months (IQR 5.7–22.8). Compared to pts who received other SACT, pts who received CAR T therapy had nominally higher risk (cumulative incidence [95% CI]) of any SPM (p = 0.05; 24.1% [18.4%, 29.8%] vs. 18.1% [13.5%, 22.8%] at 24 months), driven by significantly higher heme SPM risk (p=0.01; 8.7% [6.1%, 11.4%] vs. 5.6% [3.0%, 8.8%] at 6 months, 12.1% [8.7%, 15.3%] vs. 7.2% [4.3%, 10.4%] at 12 months, and 17.9% [12.8%, 23.5%] vs. 8.7% [5.4%, 11.7%] at 24 months; respectively), including higher risks of myelodysplastic syndrome and leukemias. The risk of solid SPM was nominally lower following CAR T vs other SACT (p=0.28; 9.1% [6.2–12.3] vs 13.9% [9.6–18.4] at 24 months). In the sensitivity analysis requiring ≥2 diagnostic codes to identify an SPM, the absolute risk was reduced and the difference in heme SPM risk was attenuated (p=0.39; Table). Notably, pts were more likely to receive bone marrow examination following CAR T therapy vs other SACT (47% vs 10% at 0–3 months, respectively). **Conclusions:** Pts with MM appeared to have a higher risk of heme SPM through 24 months following CAR T therapy compared with other SACT. However, the difference was attenuated in a sensitivity analysis that required ≥2 diagnostic codes, assumed to represent a confirmed diagnosis. Potential detection bias may exist, suggested by a higher rate of bone marrow examination following CAR T therapy. Longer term studies are needed to further evaluate this association. Research Sponsor: Regeneron Pharmaceuticals, Inc.

Cumulative incidence (%) and 95% CI of SPM at 24 months.

SPM	Analysis	CAR T therapy	Other SACT	p-value
Any	Main	24.1 (18.4–29.8)	18.1 (13.5–22.8)	0.05
	Sensitivity	11.5 (8.1–15.1)	9.5 (6.3–13.2)	0.10
Heme	Main	17.9 (12.8–23.5)	8.7 (5.4–11.7)	0.01
	Sensitivity	5.5 (3.4–7.6)	4.7 (2.3–7.6)	0.39
Solid	Main	9.1 (6.2–12.3)	13.9 (9.6–18.4)	0.28
	Sensitivity	6.4 (3.8–9.7)	5.1 (3.0–8.4)	0.14

Sensitivity analysis requires 2+ diagnostic codes to identify an SPM.

7520 Poster Session

Utilization and cost implications for collection and storage of excess autologous hematopoietic stem cells in patients with multiple myeloma. First Author: Liz Thaliath, Marshfield Clinic, Marshfield, WI

Background: Treatment for transplant-eligible patients with multiple myeloma (MM) is typically induction therapy followed by autologous hematopoietic cell transplantation (autoHCT). Guidelines recommend leukapheresis to collect sufficient hematopoietic progenitor cells (HPCs) for initial and potential second autoHCT. But with novel immune effector therapies, the need for salvage autoHCT has decreased. HPC mobilization and collection are resource-intensive, both in time and costs. We aimed to assess the utilization and costs of cryopreserved HPCs stored for potential second autoHCTs at our center to evaluate the impact for adopting a single-transplant collection strategy for all MM patients. **Methods:** We conducted a retrospective study using clinical and laboratory databases at a small transplant center in upper Midwest. A total of 97 patients (age ≥18 years) with confirmed diagnosis of MM who underwent HPC mobilization and collection between 2013 and 2023 were included. We extracted demographical patient information as well as clinical data including disease characteristics, previous lines of therapies, number of mobilization and apheresis sessions, and number of CD34 cells/kg collected, used, and stored. As part of our quality improvement, we proposed a target collection goal of ≥3.5x10^6 CD34 cells/kg versus current 5-10 x10^6/kg and used this to assess excess HPC apheresis collections. Based on our current institution-specific charges, estimate cost of 1 session of HPC collection was 7625, processing and cryopreservation per product 7792, and storage of excess cells after 1st transplant 3943 per year. **Results:** Of the 97 patients who underwent HPC collection for two autoHCTs (mean age at collection 64.5 ±8.7), only 4 (4.1%) underwent a salvage autoHCT. Based on the proposed reduced collection target, 29 (29.9%) patients had ≥1 excess collection sessions. Among the patients who underwent excess collections, median cost of these collections was 7625 per patient and median cost for processing and cryopreservation of those products was 23,308 per patient. Total cost for the excess collection sessions plus cryopreservation of the cells collected was 871,768. Median number of years of excess HPC cells stored beyond the 1st transplant but not used was 4 (0.2-11.8), with an estimated median cost of 23,576 per patient. Total storage cost for unnecessary excess HPCs for all patients was 2,471,775. **Conclusions:** This study demonstrates even for our small center excess HPCs collected during the first autoHCT are rarely used for 2nd or salvage transplant, incurring substantial costs for the institution and patient. Similar to prior HPC utilization studies, our results support changing collection practices for MM patients to improve resource allocation and reduce unnecessary expenditures. Research Sponsor: None.

7521 Poster Session

Impact of venous thromboembolism on survival in multiple myeloma patients receiving bispecific antibody therapy: Insights from real-world data. First Author: Vladimir Otasevic, Parexel International, Durham, NC

Background: Patients with multiple myeloma (MM) have a significantly higher risk of venous thromboembolism (VTE), up to 20 times greater than the general population. This risk is influenced by the disease, anti-myeloma treatments, and patient-related factors. However, there is limited information regarding the rates of VTE and survival outcomes with FDA-approved bispecific antibodies (BsAbs) such as teclistamab, elranatamab, and talquetamab. This study aims to assess these endpoints using real-world data (RWD). **Methods:** A retrospective, multicenter RWD analysis was conducted using the TriNetX database on Jan 17, 2025. Two cohorts were analyzed: 1) MM patients who have been treated with one of the FDA-approved BsAbs (teclistamab, elranatamab, or talquetamab) and who developed VTE (deep vein thrombosis or pulmonary embolism) within 18 months from initiation of BsAb treatment, 2) MM patients treated with the same BsAbs who did not develop VTE in the same time frame. Kaplan-Meier analysis, log-rank test, hazard ratios (HR), risk ratios (RR), and 95% confidence intervals (CI) were used to assess the primary outcomes, which were overall survival and risk of VTE development. Propensity score matching was used to control the impact of specific known confounders. **Results:** We identified 1530 MM patients treated with the aforementioned BsAbs and had data available regarding VTE development within 18 months of treatment initiation. The patients' mean age at the index event (treatment initiation and VTE) was 69±9.9 years, and 52.2% were males. The rate of VTE was 8.5% (n=130). The MM patients treated with BsAbs and developed VTE had a statistically significant higher risk of death compared to the patients without VTE (RR 1.475, 95% CI 1.117-1.946). The MM patients with VTE had statistically significantly shorter overall survival and higher risk of death (526 days vs. not reached median survival, 49.83% vs. 65.61% survival probability at 18 months, log-rank test p=0.003; HR 1.667, 95% CI 1.193-2.329). After propensity score matching for covariates [accounting for age, sex, ECOG, BMI, COVID-19, pneumonia types, certain infectious diseases, hypertensive diseases, surgery, and medications (dexamethasone, epoetin alfa, darbepoetin alfa)] although RR lost statistical significance (RR 1.333, 95% CI 0.888-2.001), the MM patients with VTE still had statistically significantly shorter overall survival and higher risk of death (50.07% vs. 72.27% survival probability at 18 months, log-rank test p=0.007; HR 1.989, 95% CI 1.190-3.325). **Conclusions:** RWD demonstrated that MM patients treated with BsAbs who developed VTE had a higher risk of death and shorter overall survival. Further analysis, possibly evaluating patient-level data on a larger cohort of patients with more sophisticated confounding controls, is needed to further clarify this finding. Research Sponsor: None.

7522 Poster Session

Investigating the association between peak post-infusion absolute lymphocyte count (ALC) and delayed toxicity in myeloma (MM) patients (pts) receiving cilta-cel. First Author: Kenneth J.C. Lim, Mayo Clinic, Rochester, MN

Background: Movement and neurocognitive treatment emergent adverse events (MNTs), cranial nerve palsies (CNPs) and immune-effector cell enterocolitis (IEC-EC) are late onset toxicities associated with cilta-cel and are associated with significant morbidity and mortality. We aimed to identify predisposing risk factors to allow for formulating risk-reduction strategies. **Methods:** Retrospective study of MM pts who received FDA approved cilta-cel at Mayo Clinic between Feb 2022-Dec 2024. Interrogated factors included demographics, disease and treatment characteristics, and selected lab values at different time points. In odds ratio (OR) analyses, pts were divided by toxicity type (1) No delayed toxicity (2) MNT (3) IEC-EC without MNT (4) isolated CNP. Differences between pts in the MNT, IEC-EC and CNP groups were compared separately in a pairwise manner vs. those with no delayed toxicity. **Results:** Of 235 pts, 26 (11%) had delayed toxicity [MNT = 8 (3%), IEC-EC = 9 (4%), CNP = 14 (6%)]; 3 pts had both MNT/IEC-EC and 2 had both CNP/IEC-EC. Median onset from CAR-T infusion for MNT, IEC-EC and CNP was 19 (range 8-96), 106 (35-169) and 21 (7-43) days respectively. Of 164 evaluable pts, those who had ICANS had increased odds for any delayed toxicity (OR 4.7; 95% CI 1.6-13.8). Pts who had ICANS (OR 7.7; 1.6-36.9), HLH/MAS (OR 6.2; 1.1-6.7) and Ferritin >400mcg/L at time of lymphodepletion (OR 6.3; 1.5-32) had increased odds for MNTs. Pts who received alkylator-based bridging therapy had increased odds (OR 6.1; 1.1-35) for IEC-EC. Analysis of serial post-CAR infusion lab values showed that peak ALC was the most significant variable with differences between groups shown in table. Median time to peak ALC was 12 days (IQR 11-13). ROC analysis determined peak ALC >3 x 10^9/L as a meaningful cut point. Pts with peak ALC >3.0 x 10^9/L had increased odds of developing any delayed toxicity (OR 9.3; 3.5-29.3), MNT and CNP (table). Absolute risk of any delayed toxicity was 33% in pts with peak ALC >3 x 10^9/L vs 5% without. At this threshold, number needed to treat was 3.6. **Conclusions:** Real-world data shows that cilta-cel associated delayed toxicity is seen in ~10% of patients, with specific toxicity rates between 4-8%. Factors associated with these toxicities predominantly occur in the post CAR-T infusion period. Given that ALC expansion in the first 2 weeks correlate with CAR-T expansion, peak ALC is potentially predictive of toxicity and 3 x 10^9/L may be an interventional threshold for primary prophylaxis. Research Sponsor: None.

Peak ALC by toxicity groups.

	No Tox N=138	MNT N=8	CNP N=12	IEC-EC N=6	p value
Peak ALC (10^9/L), median (IQR)	1.8 (1.0-4.1)	6.2 (4.8-14.4)	4.3 (3.2-6.7)	3.6 (1.9-5.2)	<0.001[1]
ALC >3 x 10^9/L, n (%)	43 (31%)	7 (88%)	10 (83%)	4 (67%)	<0.001[2]
Odd Ratios vs no Tox[3], 95% CI		15.5 (2.6-293.7)	11.0 (2.8-73.9)	4.4 (0.8-25.0)	

[1]Wilcoxon/Kruskal-Wallis Tests, [2]Chi square test, [3]Logistic regression analysis.

7523 Poster Session

Risk of second primary hematological malignancy post CAR-T cell therapy in relapsed/refractory multiple myeloma: Propensity-matched analysis using TriNetX database. First Author: Rushi Shah, Trinity Health Oakland/ Wayne State University School of Medicine, Pontiac, MI

Background: The Food and Drug Administration (FDA) issued a black box warning regarding the risk of T-cell lymphoma post CAR-T cell therapy has drawn global attention yet comprehensive profiling of Second Primary Malignancies is lacking in this group of patients. To address this knowledge gap, we aimed to comprehensively elucidate the current landscape of SPMs post CAR-T therapy in patients with multiple myeloma using real-world, large-scale data from TrinetX. Such efforts will be instrumental in guiding the lifelong safety monitoring of CAR-T products in the future. **Methods:** We conducted a retrospective study that included adult patients with RRMM who received CART cell therapy versus those who did not receive CART cell therapy using the TrinetX database network, a federated EMR network of more than 117 million de-identified patients. The outcomes of interest were assessing Second Primary Hematological Malignancies. Propensity matching analysis was done to assess the risk of SPM post-CART cell therapy. **Results:** A total of 803 RRMM patients received CAR-T cell therapy and 62038 RRMM patients without CART cell therapy were identified. Before matching the median follow-up was 12 months in the CART group versus 33.2 months in the non-CART group. After propensity matching analysis at a median follow-up of 12 months in the CART group and 34.4 months in the non-CART group, it was found that there was no significant increase in the risk of SPM in the CART group. (Table 1) The most common SPM remains to be AML (5%) followed by MDS (3.5%). No cases of Adult T-cell leukemia/lymphoma were detected. **Conclusions:** This real-world study shows no increased risk of second primary malignancies (SPM) following CAR T-cell therapy. Although we may have underestimated the cases if they were not admitted, and also due to limited follow-up which might not capture the late-onset SPMs. The group's next step is to re-evaluate the risk of SPM in this subgroup at five years of follow-up. Research Sponsor: None.

Hematological SPM post CART cell therapy after propensity matching analysis.

Type of SPM	RRMM post CART (n=800)	RRMM without CART (n=796)
Follicular lymphoma	0%	10 (1.25%)
Mantle cell lymphoma	0%	0 %
DLBCL	10 (1.25%)	10 (1.25%)
Hairy cell leukemia	0 %	0%
CLL	10 (1.25%)	10 (1.25%)
Hodgkin lymphoma	0 %	10 (1.25%)
Adult T cell leukemia/lymphoma	0%	0%
Mature T/NK cell lymphoma	0%	10 (1.25%)
AML	40 (5%)	32 (4.0%)
MDS	28 (3.5%)	21 (2.6%)
ALL	13 (1.62%)	20 (2.5%)

MDS: Myelodysplastic syndrome; AML: Acute myelogenous leukemia; ALL: Acute lymphoblastic leukemia; DLBCL: Diffuse Large B Cell Lymphoma; CLL: Chronic Lymphocytic Leukemia; NK: Natural Killer cells; RRMM: Relapse/Refractory Multiple Myeloma; CART: Chimeric Antigen Receptor T cell therapy; SPM: Second primary malignancy.

7524 Poster Session

Investigating metabolic connectivity in patients with multiple myeloma receiving BCMA CAR T cell therapy. First Author: Mehrnaz Jenabi, Memorial Sloan Kettering Cancer Center, New York, NY

Background: BCMA-targeted CAR T cell therapy is a highly effective treatment for patients with relapsed/refractory multiple myeloma (MM) with side effects such as CRS, ICANS, and movement and neurocognitive toxicities (MNTs). Regional changes on [^{18}F] fluoro-deoxy-2-D-glucose PET (PET) can be used to derive metabolic connectivity, an emerging technique that models brain function from the uptake on a PET, allowing us to investigate alterations of regional metabolism (SUV) and changes in metabolic brain networks (connectivity) peri-CAR T. **Methods:** Patients were included in this retrospective study if they were treated with commercially available BCMA-directed CAR T cells and had pre-and post-CAR therapy PET imaging. We analyzed the connectivity of the whole brain and parcellated the brain to generate global and regional connectivity matrices and investigated the association of regional metabolic differences and differences in metabolic connectivity with clinical parameters. **Results:** Of the 108 consecutive patients (65 Cilta-cel, 43 Ide-cel), there were 61 men and 47 women (median age 65), with PET a median of 12 days prior to infusion 28 days post infusion. Toxicities included CRS alone (n=66), CRS + ICANS (n=8), CRS+facial palsy (n=3), and CRS + Parkinsonism + facial palsy (n=2). Within the entire cohort, a significantly higher SUV-mean was noted in putamen ($p<0.0004$) post-CAR T compared to pre-CAR T, with other brain regions not showing a difference. These regional differences were significantly and inversely associated with the grade of ICANS (Post-Pre: Left: t=-1.76, p=0.08; Right t=-2.1 p=0.04). When comparing patients with (n = 79) and without (n=29) any post-CAR T cell CRS/ICANS/MNT, the post SUV-mean was significantly higher in the bilateral basal ganglia (BG) of patients who experienced toxicity ($p<0.05$). The SUV-mean was significantly lower in the bilateral inferior frontal opercularis, triangularis, and bilateral Rolandic operculum of those who developed ICANS (Grade 1-2, all with CRS, n=8) vs with CRS alone (all grade 1, n=46) ($p<0.05$). Globally, the metabolic connectivity network had less efficiency (post<pre: 0.69<0.75), and density (post<pre: 63<74). In local measurements, post-CAR T cell PET showed significantly lower local efficiency ($p=10^{-30}$), degree ($p=10^{-15}$), strengths (p=0.001), clustering coefficient ($p=10^{-12}$), and higher edge betweenness centrality (p=0.02) compared to the pre-CAR T timepoint. The decreases in network measurement were more severe in the frontal lobe and basal ganglia ($p=10^{-6}$ and p=0.004, respectively). **Conclusions:** Patients with neurotoxicity after BCMA CAR T had an increased SUV in the putamen, but decreased in the frontal regions and basal ganglia at Day 28. Metabolic networks were globally less efficient and less dense and have changes that signify injury or attempts at compensation. Research Sponsor: U.S. National Institutes of Health; R01CA293922.

7525 Poster Session

Machine learning–based sequential analysis for optimal selection between IRD and KRD regimen in multiple myeloma patients. First Author: Taemin Park, Kyung Hee Corp., Seoul, South Korea

Background: Multiple myeloma (MM) is hematologic malignancy where personalized treatment strategies are essential to improve outcomes. Proteasome inhibitor-based therapy, including ixazomib (IRD) or carfilzomib with lenalidomide and dexamethasone (KRD), is one of the most commonly used regimens for treatment of MM. Early treatment response (ETR) and progression-free survival (PFS) are critically important, as these factors are among the most significant considerations in clinical decision-making for selecting optimal drug regimens in MM treatment. This study aimed to develop a machine learning (ML) model using real-world data (RWD) to predict ETR and PFS in MM patients treated with these two regimens. **Methods:** This was a retrospective analysis using real-world data (RWD) from 535 MM patients treated with either IRD or KRD regimens. We developed separate ML models for IRD and KRD treatment group to stratify the risk for inadequate treatment response for predicting ETR or PFS outcomes. ETR was assessed based on myeloma protein and the extent of plasma cell proliferation. Patients with complete response (CR), very good partial response (VGPR) were classified as the low-risk (LR) group, indicating optimal treatment response. The other patients were categorized as the high-risk (HR) group, reflecting a suboptimal treatment response. PFS was defined by the standard definition for MM treatment: LR group as at least 2 years of survival without disease progression and otherwise, HR group. ML models were trained using demographic, clinical and genetic data obtained at the initial diagnosis or prescription for IRD or KRD. Additionally, each patient's predicted ETR risk was incorporated as a feature in training the PFS model to enhance its predictive accuracy. **Results:** The area under the receiver-operating characteristic curve (AUROC) of of the PFS models improved significantly from 0.72 and 0.62 without predicted ETR as feature to 0.81 and 0.85 with ETR incorporated. ML models classified patients as 6 subgroups to suggest optimal drug selection for each group to improve ETR and PFS outcomes. Notably, IRD or KRD given to all patients without considering patient subgroups resulted in a PFS hazard ratio of 5.94 (95% CI: 1.59 – 10.31). Implementation of our ML models might inform drug drug selection in 369 patients (69.0%) among a total of 535 patients. **Conclusion:** In this study, ML models were developed to predict ETR and PFS in MM patients, facilitating personalized therapy in clinical practice. PFS models demonstrated improved performance by incorporating predicted ETR risk as an additional feature. The ETR-incorporated models with clinical and genetic data stratified patients into low-and high-risk groups proposing optimal treatment strategies to potentially improve PFS in 185 patients (35%). Our findings implicate the potential of RWD and ML to advance precision medicine and improve outcomes through ML-informed treatment decisions. Research Sponsor: None.

7526 Poster Session

Efficacy and safety of isatuximab subcutaneous (SC) plus carfilzomib and dexamethasone (Isa-Kd) in patients with relapsed/refractory multiple myeloma (RRMM): Results of the phase 2 study IZALCO. First Author: Gurdeep Parmar, Illawarra Cancer Care Centre, Wollongong, NSW, Australia

Background: IV isatuximab (Isa) can provide benefit to patients (pts) in multiple combinations across the therapeutic spectrum for MM. SC administration would offer a more convenient treatment option for pts and caregivers.Results of a Phase 1b study demonstrated safety and efficacy of Isa SC administration via an on-body delivery system (OBDS; an investigational wearable injector), plus pomalidomide and dexamethasone in RRMM pts. In the Phase 2 IZALCO study, we evaluated efficacy (primary objective), safety, pharmacokinetics (PK), and pt preference for Isa SC administration by manual injection or OBDS, in combination with carfilzomib and dexamethasone (Kd), in RRMM pts. **Methods:** Isa SC 1400 mg was given weekly in cycle [C]1 then biweekly. In Part 1 of the study, pts received Isa injected SC manually. In Part 2, pts were randomized to Isa administered SC via OBDS (C1-C3) followed by manual injection (C4-C6), or to manual injection (C1-C3) followed by OBDS administration (C4-C6); from C7, pts could choose either treatment modality.All pts received treatment with carfilzomib (20 mg/m^2 on D1-2 then 56 mg/m^2 biweekly) and dexamethasone (20 mg). Primary study endpoint (EP) was overall response rate (ORR); pt preference for Isa SC administration modality was the key secondary EP. **Results:** Overall, 74 RRMM pts were enrolled: 8 in Part 1 and 66 in the randomized cohort (Part 2). At study entry, pts had a median age of 65 (44-85) yrs and a median of 1 prior therapy line (1-5); 56.8%, 32.4% and 10.8% had ISS stage I, II or III, respectively. The ORR rate was 79.7% (median follow-up 10.1 mo). After treatment with both modalities for Isa SC delivery, 74.5% of pts expressed a preference for the OBDS rather than manual injection (p=0.0004); 8.5% had no preference. Other key efficacy and safety results are shown in table. Treatment with Isa SC plus Kd was well tolerated. A single infusion reaction event (1 of Grade [G]1, 1 of G2) occurred in 2 pts (2.7%, both with manual injection at 1st dose). Six (8.1%) pts had 18 injection site reactions (17 of G1, 1 of G2) in 1297 (1.1%) manual or OBDS injections. Comparable PK exposure was observed between OBDS and manual administration. **Conclusions:** The study met its primary endpoint, demonstrating efficacy and safety of Isa SC administration in combination with Kd, either by manual injection or OBDS. Our study findings are comparable to those reported in the Phase 3 study IKEMA with Isa IV. Pts expressed a clear preference for receiving Isa SC by an OBDS. Clinical trial information: NCT05704049. Research Sponsor: Sanofi.

Isatuximab SC + Kd	All N=74
Efficacy, %	
ORR	79.7
≥VGPR	62.2
≥CR	21.6
Safety, %	
≥G3 TEAE	54.1
Serious TEAE	40.5
G5 TEAE	5.4
Treatment-related ≥G3 TEAE	35.1

G, grade; TEAE, treatment-emergent adverse event; VGPR, very good partial response.

7527 Poster Session

Long-term efficacy and safety of etentamig, a B-cell maturation antigen (BCMA) bispecific antibody in patients with relapsed/refractory multiple myeloma (RRMM). First Author: Muhamed Baljevic, Vanderbilt University Medical Center, Nashville, TN

Background: Etentamig (etenta) is a differentiated BCMA x CD3 bispecific T-cell engager composed of high avidity bivalent BCMA-binding domains, low-affinity CD3-binding domain designed to reduce cytokine release syndrome (CRS), and silenced Fc tail for extended half-life enabling convenient dosing. We present long term results from 2 ongoing Ph 1 studies evaluating efficacy and safety of etenta in patients (pts) with RRMM. **Methods:** Data were from a Ph 1 multicenter, open-label, dose escalation/expansion (NCT03933735) trial and Arm A of a Ph 1b, open label (NCT05650632) trial of etenta; both enrolled pts ≥18 years with RRMM, ≥3 prior lines of therapy (LoT), and triple-class exposed. Pts received 60 mg Q4W or 40 mg Q3W, both regimens with similar dose intensity, in the Ph 1 trial; pts from Arm A of the Ph 1b trial received a step-up dose (SUD) on day 1 and full dose of 60 mg Q4W on day 4. This pooled analysis assessed long-term efficacy, safety, and tolerability. Tumor response was assessed per IMWG 2016 criteria. **Results:** Of 146 pts with RRMM who received etenta, 87 (60%) were male, median age (range) was 68 (40–87) years, median prior LoT were 4 (3–23), and median duration of follow-up was 13 (1–48) months (mo). ORR was achieved in 96 (66%) pts and ≥VGPR in 79 (54%) pts. Response rates across subgroups are reported in the Table. Median duration of response was not reached (NR) (NR–NR) among responders; Kaplan-Meier (KM) estimate at 12 mo was 71% (58.5%–80.5%). Median PFS (mPFS) was NR (8.7–NR) mo; KM estimate at 12 mo was 55% (44.9%–63.1%). Any grade and G3/4 treatment emergent adverse events (TEAEs) occurred in 145 (99%) pts and 116 (79%) pts. Most common G3/4 TEAEs (≥15%) were neutropenia (38%), anemia (23%), lymphopenia (25%), and thrombocytopenia (16%). Infections G3/G4 were reported in 32 (22%) pts; most common infections G3/G4 (≥5%) were pneumonia (12%) and sepsis (5%). TEAEs leading to etenta discontinuation were reported in 13 (9%) pts. Deaths from TEAEs were reported in 13 (9%) pts; 10 were not attributed to etenta treatment. In Arm A of Ph 1 study where 60mg Q4W was administered with SUD and modified dex as premedication, CRS incidence was 30% (4% G2; No ≥G3 events) with median time to CRS onset of 22.3 (5.5–29.6) hours; and median time to CRS resolution of 20.7 (1.8–131.7) hours. **Conclusions:** Etenta with SUD demonstrated a low CRS incidence, durable response, and tolerability in pts with heavily pretreated RRMM. Efficacy across all subgroups was comparable and maintained, suggesting therapeutic benefits among a broad population and supporting further exploration in the ongoing Ph 3 Cervino study. Research Sponsor: AbbVie.

Subgroup	ORR, n (%)	≥VGPR, n (%)	mPFS, months (range)
Age ≥75years	26 (72)	23 (63.9)	NR (7.5–NR)
Race: Black	15 (63)	13 (54.2)	13.7 (5.0–NR)
High cytogenetic risk	21 (55)	18 (47.4)	7.4 (2.8–NR)
3 prior LoT	29 (64.4)	23 (51.1)	13.5 (5.6–NR)
≥4 prior LoT	67 (67)	56 (56)	NR (8.3–NR)

7528 Poster Session

Efficacy and safety from the phase 1/2 MonumenTAL-1 study of talquetamab, a GPRC5D×CD3 bispecific antibody, in patients with relapsed/refractory multiple myeloma: Analyses at an extended median follow-up. First Author: Leo Rasche, University Hospital of Würzburg, Würzburg, Germany

Background: Talquetamab (Tal) is the first and only approved anti-GPRC5D bispecific antibody (BsAb) for relapsed/refractory multiple myeloma (RRMM). In previous results from the phase 1/2 MonumenTAL-1 study (CCO Jan 2024; median follow-up [mFU] 20–30 mo), Tal elicited deep, durable responses with low discontinuation rates. We report efficacy and ongoing safety from MonumenTAL-1 at an extended mFU of 30–38 mo, the longest mFU for any anti-GPRC5D agent. **Methods:** Patients (pts) were intolerant to or progressed on established therapies (phase 1, NCT03399799) or had ≥3 prior lines of therapy (LOT), including ≥1 PI, ≥1 IMiD, and ≥1 anti-CD38 mAb (phase 2, NCT04634552). Pts received recommended phase 2 doses (RP2D) of SC Tal 0.4 mg/kg weekly (QW) or 0.8 mg/kg every other week (Q2W), with step-up doses. **Results:** As of Sept 2024, mFU was 38.2, 31.2, and 30.3 mo in the QW (n=143), Q2W (n=154), and prior T-cell redirection (TCR; n=78, received either RP2D) cohorts, respectively. Across cohorts, overall response rate (ORR; 67–74%) was unchanged vs previous results. Median duration of response (mDOR) and median progression-free survival (mPFS) continued to demonstrate superior outcomes in the Q2W vs QW cohort (mDOR 17.5 vs 9.5 mo; mPFS 11.2 vs 7.5 mo). In the prior TCR cohort, mDOR was reached with longer mFU (19.2 mo), and mPFS was 7.7 mo. In the QW, Q2W, and prior TCR cohorts, median overall survival (OS) was 34.0 mo, not reached, and 28.3 mo (36-mo OS rates: 49%, 61%, and 45%), respectively (Q2W data not mature). In pts with <4 vs ≥4 prior LOT, ORR was higher (85% vs 72%), but responses were less durable (mDOR 6.8 vs 10.8 mo) in the QW cohort, whereas ORR was similar (71% vs 69%), but responses were more durable (mDOR 20.7 vs 16.8 mo) in the Q2W cohort. As previously reported, most common adverse events (AE) were CRS and GPRC5D-associated (oral and dermatologic) AEs, and most common grade 3/4 AEs were cytopenias. No new discontinuations occurred due to oral or dermatologic GPRC5D-associated AEs and no new discontinuations occurred due to weight loss. In QW, Q2W, and prior TCR cohorts, respectively, any-grade infections occurred in 61%, 71%, and 78% of pts; grade 3/4 infections (23%, 21%, 26%) were mostly limited to early treatment cycles. A new safety signal, ataxia/balance disorders, was recently identified in association with Tal and had low prevalence in MonumenTAL-1. Dose reduction and discontinuation rates due to AEs remained low. No pts died due to Tal-related AEs. **Conclusions:** At an extended mFU, high ORRs elicited by Tal were durable and led to promising 36-mo OS rates (45–61%). The safety profile was consistent with previous results and continued to show lower risk of high-grade infections relative to approved anti-BCMA BsAbs, potentially contributing to the OS benefit seen in pts receiving Tal. Clinical trial information: NCT03399799/NCT04634552. Research Sponsor: None.

7529 Poster Session

Daratumumab + bortezomib, lenalidomide, and dexamethasone (DVRd) vs VRd in transplant-ineligible (TIE)/transplant-deferred (TD) newly diagnosed multiple myeloma (NDMM): Phase 3 CEPHEUS trial cytogenetic subgroup analysis. First Author: Nizar J. Bahlis, Arnie Charbonneau Cancer Research Institute, University of Calgary, Calgary, AB, Canada

Background: In CEPHEUS, DVRd significantly improved overall MRD negativity (MRD neg + ≥CR) and sustained MRD neg rates and PFS in patients (pts) with TIE/TD NDMM. In this post hoc analysis, we report outcomes in cytogenetic risk subgroups. **Methods:** Pts with TIE/TD NDMM were randomized 1:1 to DVRd or VRd. High-risk (HiR) cytogenetic abnormalities (HRCAs) were assessed by FISH. HiR was ≥1 of: del(17p); t(4;14); t(14;16). Revised HiR (R-HiR) was ≥1 of above or gain (3 copies) or amp(1q) (≥4 copies). Standard risk (SR) was 0 HRCAs; revised SR (R-SR) was 0 revised HRCAs. Additional risk groups included: gain or amp(1q) + other HRCAs; 1 and ≥2 revised HRCAs. We assessed overall MRD neg rate, sustained MRD neg, ≥CR rate, and PFS. We reported all MRD neg rates at 10^{-5} unless noted. **Results:** Of 395 randomized pts (DVRd, n=197; VRd, n=198), 298 had SR (DVRd, n=149; VRd, n=149) and 52 HiR (DVRd, n=25; VRd, n=27). 184 pts had R-SR (DVRd, n=94; VRd, n=90) and 167 R-HiR (DVRd, n=83; VRd, n=84). At median 58.7-month (mo) follow-up, overall MRD neg rate was higher with DVRd vs VRd in SR (64% vs 38%; $P<0.0001$) and R-SR pts (68% vs 38%; $P<0.0001$). Rates by treatment (tx) arm in HiR (48% vs 56%; $P=0.7816$) and R-HiR pts (55% vs 45%; $P=0.2169$) were comparable. DVRd improved ≥1-year (y) sustained MRD neg rate vs VRd in SR (51% vs 26%; $P<0.0001$) and R-SR pts (54% vs 24%; $P<0.0001$). Sustained MRD neg rates by tx arm were comparable in HiR (40% vs 37%; $P=1.0000$) and R-HiR pts (43% vs 30%; $P=0.0782$). PFS was improved with DVRd vs VRd in SR and R-SR pts and was comparable by tx arm in HiR and R-HiR pts (Table), including in MRD neg pts (R-SR: hazard ratio [HR]=0.63 [95% CI, 0.26–1.52]; $P=0.3003$; R-HiR: HR=0.71 [95% CI, 0.32–1.58]; $P=0.3995$). Remaining outcomes, including rates of ≥CR, ≥2-y sustained MRD neg, and overall and ≥1-y sustained MRD neg at 10^{-6}, were improved with DVRd in SR and R-SR pts and comparable by tx arm in HiR and R-HiR pts. **Conclusions:** In CEPHEUS, DVRd consistently improved the key response outcomes of MRD neg and PFS in (R-)SR pts. In HiR pts, MRD and PFS outcomes trended lower in both tx arms vs those in SR pts. Here, DVRd mostly improved PFS outcomes vs VRd; however, pt numbers were small, with the study underpowered for HiR pts. These data support use of DVRd for TIE/TD NDMM regardless of cytogenetic risk status. Clinical trial information: NCT03652064. Research Sponsor: Johnson & Johnson.

	DVRd		VRd		
	n	mPFS, mo	n	mPFS, mo	HR (95% CI); *P*-value
HiR[a]	25	39.8	27	31.7	0.88 (0.42–1.84); 0.7387
R-HiR	83	NE	84	45.6	0.73 (0.46–1.15); 0.1739
SR[a]	149	NE	149	60.6	0.61 (0.41–0.91); 0.0136
R-SR	94	NE	90	60.6	0.54 (0.32–0.91); 0.0189
Gain(1q) + other HRCAs	43	60.3	48	42.2	0.80 (0.45–1.43); 0.4496
Amp(1q) + other HRCAs	31	NE	20	NE	0.97 (0.38–2.47); 0.9525
1 revised HRCA	66	NE	72	47.2	0.63 (0.37–1.09); 0.0938
≥2 revised HRCA	17	22.7	12	29.7	1.01 (0.42–2.44); 0.9868

[a]Unknown cytogenetic risk: DVRd, n=23; VRd, n=22.
mPFS, median PFS; NE, not estimable.

7530 Poster Session

Assessment of normal plasma cell biomarkers after arlocabtagene autoleucel (arlo-cel) treatment in patients with ≥3L relapsed refractory multiple myeloma (MM). First Author: Kristina Jordahl, Bristol Myers Squibb, Princeton, NJ

Background: B-cell maturation antigen (BCMA) and G protein-coupled receptor class C group 5 member D (GPRC5D) are validated targets in MM. GPRC5D is expressed most strongly on MM cells with minimal expression on normal plasma cells (nPC), while BCMA is highly expressed on MM cells and nPCs. Anti-BCMA chimeric antigen receptor T cell therapy (CAR T) and T cell engagers (TCE), but not anti-GPRC5D TCE, are associated with B cell aplasia and worsened hypogammaglobulinemia. Uninvolved free light chain (uiFLC) and immunoglobulin G (IgG) were used as biomarkers of nPCs following treatment with arlo-cel, a GPRC5D-targeting CAR T therapy with promising efficacy and 19% grade 3/4 infection rate (Bal, et al. ASH 2024 Abstract 922), and treatment with a BCMA CAR T therapy. **Methods:** Clinical endpoints included treatment-emergent adverse events for patients treated with arlo-cel (NCT04674813; n = 84) and idecabtagene vicleucel (ide-cel, NCT03361748; n = 137). Biomarker analysis included complete responders (CR) treated with arlo-cel (n = 42) and ide-cel (n = 38). For uiFLC, Kaplan-Meier curves of time to clearance below the limit of detection (LOD; 1.3 mg/L for κ and 1.7 mg/L for λ) and time to first return above the LOD were used to calculate median time to event and compared using log-rank test. Logistic regression models adjusted for pre-treatment levels were used to test for differences in biomarker levels at specific time points. Hypogammaglobulinemia was defined as IgG levels < 500 mg/dL. Fisher's exact test was used to compare infection rates. All analyses were restricted to the first 6 months after infusion. P-values less than 0.1 were considered statistically significant. **Results:** Arlo-cel cleared uiFLC below the LOD in 67% of CR compared to 100% of ide-cel CR ($p < 0.0001$). When cleared, time to uiFLC clearance was the same (median = 29 days; p = 0.82), but time to return above the LOD was significantly faster for arlo-cel (median = 101 days) than for ide-cel (median = 264 days; p = 0.001), indicating faster nPC recovery for arlo-cel. Post-infusion uiFLC concentrations were lower in ide-cel CR at 2 (p = 0.09), 4 (p = 0.05), 5 (p = 0.02), and 6 months (p = 0.09) compared to arlo-cel. Despite more post-infusion intravenous immunoglobulin usage for ide-cel vs arlo-cel CR (89% vs 26%), IgG levels were lower for ide-cel CR at 2 (p = 0.09) and 3 months (p = 0.01). Among treated patients, the proportion with hypogammaglobulinemia at 3 months (p = 0.05) and the 6-month infection rate (p = 0.03) were lower for arlo-cel. **Conclusions:** Arlo-cel patients had higher levels of uiFLC from months 2–6, demonstrating greater anti-tumor specificity and preservation of humoral immunity. As a result, arlo-cel has the potential to achieve lower rates of hypogammaglobulinemia and infections compared to BCMA-targeting therapies, with fewer interventions. Clinical trial information: NCT04674813. Research Sponsor: Juno Therapeutics, Inc., a Bristol-Myers Squibb Company.

7531 Poster Session

Indirect comparison of linvoseltamab versus elranatamab for triple-class exposed (TCE) relapsed/refractory multiple myeloma (RRMM). First Author: Sundar Jagannath, Icahn School of Medicine at Mount Sinai, New York, NY

Background: In the absence of head-to-head trials comparing anti-BCMA×CD3 bispecific antibodies in TCE RRMM, this study used an unanchored matching-adjusted indirect comparison (MAIC) to compare the efficacy of linvoseltamab and elranatamab. **Methods:** Patient (pt)-level data from LINKER-MM1 (117 pts receiving linvoseltamab 200 mg, data cut-off [DCO] 7/2024, median follow-up [mFU] 21.3 months [mos]) and published data from MagnetisMM-3 Cohort A (123 elranatamab pts, DCO 9/2024, mFU 33.9 mos) were analyzed. Ten LINKER-MM1 pts with prior BCMA antibody–drug conjugate exposure were excluded to align with MagnetisMM-3. LINKER-MM1 pts were weighted to match MagnetisMM-3 pts on prespecified prognostic factors deemed most important by an international expert panel: cytogenetic risk, age, refractory status, R-ISS stage, ECOG PS, extramedullary and/or paramedullary disease. Objective response rate (ORR), very good partial response or better (≥VGPR) and complete response or better (≥CR) rates, duration of response (DOR), progression-free survival (PFS), and overall survival (OS) were compared. DOR and PFS in LINKER-MM1 were recalculated to match MagnetisMM-3 censoring rules. Additional MAICs matched all available prespecified prognostic factors, included all 117 LINKER-MM1 pts, or matched to a MagnetisMM-3 subgroup with ECOG PS 0/1. **Results:** After matching, linvoseltamab effective sample size (ESS) was 71.3 (range of patient weights: 0.04–2.90). Linvoseltamab demonstrated statistically significant higher ORR and ≥CR rate, a numerically higher ≥VGPR rate, and longer DOR, PFS, and OS vs elranatamab (Table). The additional MAICs yielded directionally consistent findings. **Conclusions:** Linvoseltamab demonstrated significantly higher ORR and ≥CR rate, numerically better ≥ VGPR rate, DOR, PFS, and OS compared with elranatamab, though the follow-up was shorter. These results highlight the potential of linvoseltamab as a highly effective treatment option for TCE RRMM. Research Sponsor: Regeneron Pharmaceuticals, Inc.

	Elranatamab	Linvoseltamab	Linvoseltamab	Linvoseltamab vs elranatamab	Linvoseltamab vs elranatamab
	N=123	Unadjusted N=107	Adjusted ESS= 71.3	Unadjusted	Adjusted
	%	%	%	*OR (CI)*	*OR (CI)*
ORR	61	71	71	1.57 (1.04–2.37)*	1.60 (1.00–2.57)*
≥VGPR	56	64	65	1.36 (0.93–2.00)	1.45 (0.94–2.24)
≥CR	37	52	50	1.84 (1.26–2.68)*	1.71 (1.12–2.61)*
	Median, mos (CI); 12-mo landmark %	*Median, mos (CI); 12-mo landmark %*	*Median, mos (CI); 12-mo landmark %*	*HR (CI)*	*HR (CI)*
DOR	NR (29.4–NE); 73.9	NR (NE–NE); 82.8	NR (NE–NE); 84.4	0.93 (0.53–1.66)	0.82 (0.43–1.55)
PFS	17.2 (9.8–NE); 56.4	NR (15.7–NE); 65.5	NR (16.2–NE); 64.7	0.86 (0.59–1.27)	0.86 (0.55–1.34)
OS	24.6 (13.4–NE); 62.3	31.4 (27.8–NE); 75.5	NR (27.8–NE); 74.6	0.70 (0.47–1.04)	0.67 (0.42–1.05)

OR >1 or HR <1 favor linvoseltamab.
*Statistically significant at $p<0.05$.
CI: 95% confidence interval, HR: hazard ratio, NE: not estimable, NR: not reached, OR: odds ratio.

7532 Poster Session

Iberdomide, bortezomib, and dexamethasone (IberVd) in transplant-ineligible (TNE) newly diagnosed multiple myeloma (NDMM): Updated results from the CC-220-MM-001 trial. First Author: Darrell White, Dalhousie University and Queen Elizabeth II Health Sciences Centre, Halifax, NS, Canada

Background: Lenalidomide (LEN), bortezomib (BORT), and dexamethasone (DEX) are recommended for NDMM. Iberdomide (IBER), an oral CELMoD agent, has stronger tumoricidal and immune-stimulatory effects than LEN and shows synergy with DEX and BORT in preclinical models. IberVd has shown meaningful efficacy and safety in patients (pts) with TNE NDMM in the ongoing phase 1/2 CC-220-MM-001 trial (NCT02773030). Here we report updated results with longer follow-up from the IberVd dose-expansion cohort. **Methods:** Eligible pts had untreated NDMM and were TNE or deferred. Oral IBER was given on days (D) 1–14 of each 21-d cycle (C) in C1–8 and on D1–21 of each 28-d cycle in C $\geq$ 9, with subcutaneous BORT (starting at 1.3 mg/m^2) on D1, 4, 8, and 11 in C1–8, plus oral DEX on D1, 2, 4, 5, 8, 9, 11, and 12 in C1–8 and weekly in C $\geq$ 9 (20 or 10 mg if $>$ 75 y of age in C1–8; 40 or 20 mg if $>$ 75 y in C $\geq$ 9). Endpoints included efficacy, safety, pharmacokinetics, and minimal residual disease (MRD) assessment by next-generation flow cytometry. **Results:** As of May 29, 2024, 18 pts had received IberVd (1 pt 1.0 mg; 17 pts 1.6 mg). Median age was 77.5 (57–84) y, 12 (66.7%) pts were male, 17 (94.4%) White, 1 (5.6%) Hispanic/Latino, and 11 (61.1%) had high-risk cytogenetics. Median follow-up was 25 (0.7–29.5) mo. Median treatment duration was 24.9 (0.7–29.5) mo, median number of cycles received was 25 (1–34), and 11 (61.1%) pts remain on treatment; 3 pts discontinued due to withdrawal, 2 to adverse events (AEs), 1 to progressive disease, and 1 to physician decision. One death was reported during follow-up. In the safety population (n = 17), 14 (82.4%) pts had grade (Gr) 3/4 treatment-emergent AEs (TEAEs); primarily infections (47.1%), including pneumonia (17.6%) and COVID-19 (11.8%). The most common hematologic Gr 3/4 TEAE was neutropenia (29.4%); 2 (11.8%) pts had Gr 3–4 peripheral neuropathy. Other Gr 3/4 non-hematologic TEAEs like fatigue and diarrhea were rare. IBER dose interruptions and reductions due to TEAEs occurred in 14 (82.2%) and 10 (58.8%) pts, respectively. Dose reductions were mainly due to peripheral neuropathy (23.5%), neutropenia (11.8%), and thrombocytopenia (11.8%). TEAEs were manageable with dose modifications/interruptions and G-CSF use. In the evaluable pts (n = 16), the overall response rate was 100% with 8 stringent complete responses, 4 complete responses (CRs), 3 very good partial responses, and 1 partial response. Median time to response was 0.7 (0.7–3.9) mo, median duration of response was not reached, and 4 pts deepened response post 1 y treatment. MRD negativity at 10^{-5} was reported in 8 (50.0%) pts, and all had $\geq$ CR. **Conclusions:** With longer follow-up (13–25 mo), IberVd confirmed durable deep responses, with $\geq$ CR % rising from 56.3% to 75.0%, and an encouraging safety profile with no new signals in pts with TNE NDMM. These data support IberVd evaluation in the frontline setting. Clinical trial information: NCT02773030. Research Sponsor: Bristol Myers Squibb.

7533 Poster Session

DREAMM-8 study of belantamab mafodotin plus pomalidomide and dexamethasone (BPd) vs pomalidomide plus bortezomib and dexamethasone (PVd) in relapsed/refractory multiple myeloma (RRMM): A subgroup analysis in patients with high-risk cytogenetic features. First Author: Suzanne Trudel, Department of Medical Oncology and Hematology, Princess Margaret Cancer Centre, Toronto, ON, Canada

Background: In DREAMM-8 (NCT04484623), BPd demonstrated a significant improvement in the risk of progression or death vs PVd in patients (pts) with RRMM who received $\geq$1 prior line of therapy, including lenalidomide. Pts with high-risk cytogenetic abnormalities (HRCAs) have a poor prognosis and need more efficacious treatments. Here we present a subgroup analysis in pts with HRCAs. **Methods:** Pts were randomized 1:1 to BPd (28-day cycles) or PVd (21-day cycles). Pts were treated until progressive disease, unacceptable toxicity, or death. Efficacy assessments occurred every 4 weeks. Pts with HRCAs were defined as having $\geq$1 of the following: t(4;14), t(14;16), amp1q, and del(17p13). Descriptive statistics were used to summarize the results, along with 95% exact CIs. Hazard ratios (HRs) for progression-free survival (PFS) were estimated using the Cox model, with 95% CIs based on the Brookmeyer-Crowley method. **Results:** The intention-to-treat population included 302 pts: 155 in the BPd arm and 147 in the PVd arm. In the BPd arm, 68 of 155 (44%) pts had HRCAs; of them, 23 (15%) had t(4;14), 7 (5%) had t(14;16), 32 (21%) had del(17p13), and 40 (26%) had amp1q. In the PVd arm, 60 of 147 (41%) had HRCAs; of them, 20 (14%) had t(4;14), 11 (7%) had t(14;16), 26 (18%) had del(17p13), and 33 (22%) had amp1q. Median PFS in pts with $\geq$1 HRCA was 21.1 mo (95% CI, 13.5 mo-NR) with BPd vs 9.2 mo (95% CI, 6.5-14.8 mo) with PVd (HR, 0.58; 95% CI, 0.36-0.95); 18-mo PFS rates were 53% and 33%, respectively. PFS benefit favored BPd across HRCA subgroups (HR [95% CI]: t(14;14), 0.74 [0.31-1.76]; del(17p13), 0.45 [0.22-0.92]; and amp1q, 0.49 [0.24-1.03]). In pts with $\geq$1 HRCA, overall response rate (ORR) was higher with BPd (n=52; 76%; 95% CI, 64.6%-85.9%) than PVd (n=39; 65%; 95% CI, 51.6%-76.9%), and more pts achieved $\geq$ complete response with BPd (Table). Benefit was maintained across HRCA subgroups. **Conclusions:** In pts with RRMM with HRC features, BPd demonstrated clinically meaningful PFS benefit, higher ORR, and a higher rate of deep responses vs PVd. These data support the potential use of BPd as a standard-of-care regimen in this key pt population with a high unmet need. Clinical trial information: NCT04484623. Research Sponsor: This study was sponsored by GSK. Editorial support was provided by Nucleus Global, an Inizio Company, and funded by GSK. Drug-linker technology licensed from Seagen Inc; monoclonal antibody produced using POTELLIGENT Technology licensed from BioWa.

Patients achieving ≥CR in HRC groups n/N (%); 95% CI	BPd	PVd
t(4;14)	9/23 (39); 19.7-61.5	5/20 (25); 8.7-49.1
t(14;16)	3/7 (43); 9.9-81.6	2/11 (18); 2.3-51.8
del(17p13)	11/32 (34); 18.6-53.2	0/26; 0-13.2
amp1q	17/40 (43); 27.0-59.1	3/33 (9); 1.9-24.3
≥1 HRCA	29/68 (43); 30.7-55.2	9/60 (15); 7.1-26.6

7534 Poster Session

Immune profiling to identify a functionally high-risk smoldering multiple myeloma patient population. First Author: Ross Firestone, Memorial Sloan Kettering Cancer Center, New York, NY

Background: Smoldering multiple myeloma (SMM), a precursor to active multiple myeloma (MM), is characterized by a high plasma cell burden but no evidence of the end-organ damage that defines MM. The Mayo 2/20/20 model, and others, relies on tumor-burden estimates to assign risk scores. We hypothesized that algorithm-assisted and explainable artificial intelligence (xAI) tools could ingest peripheral blood (PB) T cell profiles to identify immune signatures predictive of progression to active MM. **Methods:** We analyzed a cohort of Mayo risk-matched SMM patients with and without early progression to active MM. This included 9 patients with early progression from SMM to MM (median PFS 2.1 years) and a 9 patient "mayo risk matched" cohort without clinical progression (median follow-up 8.6 years). Using high-dimensional spectral cytometry with a 37-color T cell focused panel, we captured 1.4 million PB T cells from 18 SMM patients banked at the time of SMM diagnosis. Algorithm-assisted analysis was performed using dimensionality reduction analysis with UMAP and cell clustering using PhenoGraph. xAI analysis was performed by training a random forest (RF) classifier to predict clinical outcomes using single-cell data followed by feature importance analysis using Shapley Additive Explanations (SHAP) scores. **Results:** Analysis identified 21 unique T cell characteristic clusters across all patients. Among these, SMM patients with early progression had enrichment for CD8$^+$CD45RA$^+$CD62L$^-$CCR7$^-$ T effector cells re-expressing CD45RA when compared to non-progressing SMM patients (4.3-fold increase, p = 0.018). This cluster had the highest mean expression level of CD57 and TOX among all algorithm-defined clusters, demonstrating similar phenotypic characteristics to terminally exhausted effector T cells. The RF model to predict progression had an overall accuracy of 75% (stratified five-fold cross validated, repeated ten times). A UMAP analysis of c misclassified cells did not reveal any obvious patterns. SHAP analysis identified high expression of Granzyme B, CD272, Granzyme K, and CD45RA as the four most influential features for predicting progression. **Conclusions:** Our results show that patient-specific immune phenotypes could offer a method of prognosticating SMM outcomes separate from traditional tumor burden quantification. Both the clustering-based and feature importance analyses demonstrated that a more differentiated T cell phenotype is associated with early progression in SMM. Recent reports have found more differentiated T cell biology in MM patients compared to SMM patients. Our results support the hypothesis that SMM patients displaying an "MM-like" T cell phenotype are at increased risk of early progression to active MM. These results support work to identify a clinically usable patient-specific immune signature to identify SMM patients at increased risk of progression to overt MM. Research Sponsor: ASCO / CCF Young Investigator Award.

7535 Poster Session

Carfilzomib, lenalidomide, and dexamethasone (KRd) as maintenance therapy after autologous stem-cell transplantation (ASCT) in patients with newly diagnosed multiple myeloma (NDMM). First Author: Andrzej J. Jakubowiak, University of Chicago, Chicago, IL

Background: In patients with NDMM, therapy after ASCT aims to deepen remission and prolong survival. Although lenalidomide (R) monotherapy after ASCT is well established, the impact of combination therapy on survival remains to be established. Interim results of the ATLAS study suggested that extended KRd after ASCT treatment prolongs progression-free survival (PFS) compared with R alone in patients with NDMM (Dytfeld et al, Lancet Oncol. 2023; 24:139–150). Here we provide the results from the primary analysis of the ATLAS study. **Methods:** This international, open-label phase 3 study randomly assigned adults with NDMM who completed induction and had stable disease or better after ASCT 1:1 to KRd or R alone as maintenance therapy. Randomization was stratified by post-transplant response, presence or absence of $\geq$1 high-risk cytogenetic abnormality, and by country. For the KRd group, patients with standard-risk cytogenetics and measurable residual disease (MRD) negativity at 10^{-5} after cycle 6 were switched to R maintenance after cycle 8; remaining patients continued KRd up to 36 cycles and then switched to R. The preplanned primary endpoint was PFS. Secondary endpoints included overall survival (OS), MRD negativity, response rate, and safety. **Results:** At data cutoff (21 Oct 2024), median follow up was 5.7 years. The median number of treatment cycles initiated was 35 and 31 for KRd and R, respectively. After cycle 8, 40 of 81 patients on KRd switched to R. The 4-year PFS rate with KRd was superior to R (67.5% vs 36.8%; HR 0.46 [95% CI: 0.30, 0.70]; p=0.0002). The PFS benefit was consistent across subgroups, including high-risk cytogenetics (HR 0.52 [95% CI: 0.24, 1.1]) and MRD-positive status at randomization (HR 0.52 [95% CI: 0.29, 0.93]). Median PFS was 72.8 months and 37.3 months in the KRd and R groups, respectively. The 4-year OS rate also was increased with KRd vs R (84.3% vs 79.2%; HR 0.49 [95% CI: 0.26, 0.90]; p=0.02). The depth of response improved across all response categories; the rate of MRD $<10^{-5}$ and at least a complete response as best response was 74% and 51% (OR 2.7 [95% CI: 1.5, 5.1]; (p=0.002), and 12-month sustained MRD-negativity was 48% and 24% (OR 2.9 [95% CI 1.5, 5.5]; p=0.001) for KRd and R, respectively. No new safety signals were observed (Table). **Conclusions:** The ATLAS phase 3 study demonstrated superior PFS as well as longer OS with MRD-directed, risk-stratified KRd treatment compared with R alone in patients with NDMM after ASCT. Extended KRd maintenance treatment may represent a new standard of care. Clinical trial information: NCT02659293. Research Sponsor: Amgen Inc.; Celgene [Bristol Myers Squibb].

Treatment emergent adverse events.

Patients, n (%)	KRd (n=91)	R (n=87)
Any grade	89 (98)	83 (95)
Grade ≥3	72 (79)	64 (74)
Grade 5	2 (2.2)[a]	2 (2.3)[b]
Any serious adverse event	29 (32)	20 (23)

[a]Lung infection (n=2).
[b]Lung/Covid infection (n=1); heart failure (n=1).

7536 Poster Session

Belantamab mafodotin + pomalidomide + dexamethasone (BPd) vs daratumumab + bortezomib + dexamethasone (DVd) in relapsed/refractory multiple myeloma: An indirect comparison using patient-level data. First Author: Meral Beksac, Department of Hematology, Ankara Liv Hospital, Istinye University, Ankara, Turkey

Background: Belantamab mafodotin (belamaf) is being studied in combination with bortezomib + dexamethasone (BVd) or pomalidomide + dexamethasone (BPd) in the phase 3 DREAMM-7 (D7; NCT04246047) and DREAMM-8 (D8; NCT04484623) trials, respectively; both enrolled patients (pts) with relapsed/refractory multiple myeloma (RRMM) who had received ≥1 prior line of therapy. D7 compared BVd vs daratumumab + bortezomib + dexamethasone (DVd); D8 compared BPd vs bortezomib + pomalidomide + dexamethasone (PVd). In both trials, belamaf combinations showed significant progression-free survival (PFS) benefits vs comparators. In D7, median PFS (95% CI) was 36.6 mo (28.4-not reached [NR]) with BVd vs 13.4 mo (11.1-17.5) with DVd (HR, 0.41; 95% CI, 0.31-0.53; $P<.001$). In D8, median PFS (95% CI) was NR with BPd vs 12.7 mo (9.1-18.5) with PVd (HR, 0.52; 95% CI, 0.37-0.73; $P<.001$). This study compared the efficacy of BPd (D8 active arm) vs DVd (D7 comparator). **Methods:** The overlapping D7 and D8 RRMM population was analyzed. To align cohorts, D8 BPd pts refractory to any anti-CD38 were excluded, as were D7 DVd pts without prior lenalidomide exposure or pomalidomide-refractory disease. The primary endpoint was PFS. Secondary endpoints included overall survival (OS), minimal residual disease (MRD)−negativity rate, duration of response (DOR), overall response rate (ORR), and time to treatment discontinuation (TTD) with all treatments. This indirect comparison used inverse probability of treatment weighting to match baseline characteristics between DVd and BPd arms, estimating the average treatment effect in the treated population (IPTW-ATT). In the matched population, time-to-event analyses used the Kaplan-Meier method and Cox proportional hazards models. **Results:** Of 155 pts in the D8 BPd arm and 251 in the D7 DVd arm, 120 and 111, respectively, met inclusion criteria for this analysis. Baseline characteristics were generally balanced after IPTW-ATT. After adjustment, BPd significantly improved PFS vs DVd (median [95% CI], NR [21.1-NR] vs 11.1 mo [6.4-19.1]; HR, 0.41; 95% CI, 0.25-0.65; $P=.0002$). Median (95% CI) DOR was NR (24.9-NR) with BPd vs 10.5 mo (5.0-17.7) with DVd; adjusted MRD-negativity (CR+) rates (95% CI) were 30.2% (21-39.4) vs 5.3% (0.9-9.8), respectively (OR, 7.67; 95% CI, 3.10-22.72; $P<.0001$). ORR and TTD favored BPd vs DVd (ORR not significant). **Conclusions:** This post hoc indirect comparison analysis showed that BPd significantly improved PFS vs DVd (similar HR to BVd vs DVd in D7). Median PFS for the adjusted DVd population was similar to that reported with PVd in D8. These findings suggest that BPd may be a more effective treatment option vs DVd, warranting further studies of belamaf combinations in this population. Research Sponsor: GSK.

7538 Poster Session

GPRC5D and BCMA bi-specific CAR-T: Ex vivo study to simulate early to late-line multiple myeloma (MM) with elevated soluble BCMA. First Author: Jincai Zhou, Oricell Therapeutics Co., Ltd., Shanghai, China

Background: GPRC5D and BCMA are near-universally expressed on MM cells, with independent target expression and double-negative cells relatively rare. This profile supports the rationale for developing a bi-specific CAR-T therapy to enhance patient coverage, improve efficacy, and reduce the risk of relapse due to antigen loss. Dual-targeting GPRC5D and BCMA represents a novel advancement in the developed antibody therapies. The clinical outcomes of combination of GPRC5DxCD3 and BCMAxCD3 were highly promising. Tri-specific antibodies (GPRC5DxBCMAxCD3) have exhibited superior preliminary efficacy compared to bsAbs or their combinations, However, these approaches require weekly administrations and may pose potential risk. A recent publication (Freeman et al., Blood, 2024) reported that elevated pre-lymphodepletion soluble BCMA (sBCMA) levels were significantly associated with high-risk characteristics as well as high incidence and severity of CRS & ICANS, and metabolic tumor volume (MTV) were correlated with poor clinical outcomes. To address these challenges, we have developed bi-specific CAR-Ts incorporating novel armors to effectively eliminate heavy MM burdens and enhance efficacy, even in the presence of sBCMA. **Methods:** Aiming to broadly eradicate MM subsets and reduce heavy tumor burden or extramedullary disease (EMD), we have developed a bi-specific CAR-T with two novel humanized VHH binders specifically targeting either BCMA or GPRC5D. Our design incorporates novel secreted and/or membrane-bound armors. Pre-clinical studies were conducted to evaluate the features and drugability of these armored and non-armored bispecific-CAR-Ts. **Results:** Targeting dual-Ag, the bi-specific CAR-T showed increased T cell activation, superior functionality, and enhanced expansion under re-stress. Notably, the bi-CAR-T retained its functionality against single-Ag expressing cells and displayed robust potency against MM cells with very low BCMA expression, even in the presence of high concentrations of sBCMA. Compared to industry benchmarks, Oricell's bi-CAR-T showed superior efficacy in a xenograft mouse model with heterogeneous MM cells. Armored bi-CAR-Ts were potent in eliminating heavy tumor burdens and enhancing T cell infiltration and expansion. **Conclusions:** The pre-clinical data demonstrated that the bi-specific CAR-T not only outperformed in targeting MM cells mimicking early or middle lines but also reduced the incidence of antigen-negative escape. By enhancing sensitivity and leveraging unique epitopes, the bi-CAR-T maintained robust efficacy in late-line MM models. Future clinical studies will be conducted to validate the safety and efficacy in treating high-risk MM patients. Research Sponsor: None.

7539 Poster Session

Ciltacabtagene autoleucel (cilta-cel) vs standard of care (SOC) in patients (pts) with relapsed/refractory multiple myeloma (MM): CARTITUDE-4 survival subgroup analyses. First Author: Surbhi Sidana, Stanford University School of Medicine, Stanford, CA

Background: In CARTITUDE-4, a single cilta-cel infusion significantly improved progression-free survival (PFS; hazard ratio [HR] weighted, 0.29 [95% CI, 0.22–0.39]) and overall survival (OS; HR, 0.55 [0.39–0.79]; $P=0.0009$) vs SOC in pts with relapsed and lenalidomide-refractory MM after 1–3 prior lines of treatment (pLOT) at 33.6 mo median follow-up (Mateos et al, IMS 2024). PFS and OS from subgroups in the intent-to-treat (ITT) population are reported. **Methods:** Pts randomized to cilta-cel underwent apheresis, received pomalidomide, bortezomib, and dexamethasone (PVd), or daratumumab, pomalidomide, and dexamethasone (DPd) bridging treatment, lymphodepletion, and then cilta-cel infusion. Pts randomized to SOC received physician's choice of PVd or DPd until progression. HR for PFS was analyzed using unweighted Cox proportional hazards model for the ITT set. **Results:** As of May 1, 2024, median follow-up was 33.6 mo. PFS and OS benefit of cilta-cel over SOC in the ITT analysis was consistent across pts with standard-risk cytogenetics and high-risk cytogenetics, defined as del(17p), t(4;14), t(14;16), or gain/amp(1q) (Table). Comparing cilta-cel (n=21) vs SOC (n=18) in pts with extramedullary disease (EMD), median PFS was 13 mo vs 4 mo (HR, 0.71 [95% CI, 0.34–1.49]), respectively, and median OS was not reached (NR) vs 16 mo (HR, 0.61 [95% CI, 0.26–1.47]). In pts with 1, 2, or 3 pLOT (cilta-cel, n=68, 83, 57; SOC, n=68, 87, 56), median PFS was NR with cilta-cel across all pLOT vs 17 mo (HR, 0.41 [95% CI, 0.25–0.67]), 12 mo (HR, 0.30 [95% CI, 0.19–0.49]), and 8 mo (HR, 0.20 [95% CI, 0.11–0.34]) with SOC, respectively; median OS was NR with cilta-cel across all pLOT vs NR (HR, 0.56 [95% CI, 0.28–1.11]), NR (HR, 0.63 [95% CI, 0.36–1.09]), and 34 mo (HR, 0.49 [95% CI, 0.26–0.91]) with SOC. **Conclusions:** ITT analysis showed that cilta-cel improved PFS and OS vs SOC in all subgroups, including pts with EMD and 1 pLOT and beyond. Compared with SOC, cilta-cel improved PFS and OS in pts with high-risk cytogenetics, suggesting it may overcome the poor prognosis associated with these high-risk features. These data continue to support a positive benefit-risk ratio for cilta-cel in pts with lenalidomide-refractory MM as early as after first relapse. Clinical trial information: NCT04181827. Research Sponsor: Johnson & Johnson; Legend Biotech USA Inc.

	Cilta-cel, n	SOC, n	Median PFS cilta-cel, mo	Median PFS SOC, mo	HR (95% CI)	Median OS cilta-cel, mo	Median OS SOC, mo	HR (95% CI)
Standard-risk cytogenetics	69	70	NR	21	0.43 (0.26–0.72)	NR	NR	0.62 (0.33–1.19)
High-risk cytogenetics[a]	123	132	37	10	0.38 (0.27–0.52)	NR	38	0.54 (0.35–0.85)
del(17p)	49	43	30	9	0.40 (0.24–0.68)	NR	NR	0.52 (0.26–1.04)
t(4;14)	30	30	37	7	0.34 (0.17–0.68)	NR	27	0.46 (0.20–1.08)
gain/amp(1q)	89	107	37	10	0.39 (0.27–0.57)	NR	38	0.58 (0.35–0.96)
≥2 cytogenetic abnormalities[a]	43	49	30	7	0.43 (0.25–0.73)	NR	23	0.57 (0.30–1.07)

[a]Cytogenetic abnormalities: del(17p), t(4:14), t(14;16), or gain/amp(1q).

7540 Poster Session

Carfilzomib or bortezomib with lenalidomide, and dexamethasone (VRd) for initial therapy of newly diagnosed multiple myeloma (NDMM): Long-term follow-up of the ECOG-ACRIN ENDURANCE phase 3 trial. First Author: Shaji Kumar, Mayo Clinic Rochester, Rochester, MN

Background: The combination of a proteasome inhibitor (PI) with lenalidomide (R) and dex (d) has been a common initial therapy for newly diagnosed myeloma (NDMM). We designed a randomized phase 3 trial to examine if carfilzomib (K), a next generation PI, improved progression free survival (PFS) compared with bortezomib (V) when either is combined with Rd for initial treatment of NDMM. Initial analysis at a median follow up of 15.3 months (mos) showed comparable PFS for both triplets. We present the long-term results of the trial with ~70 months median follow up. **Methods:** Patients (Pts) with NDMM, were randomized 1:1 to receive VRd or KRd for 36 weeks followed by a 2nd randomization (1:1) to indefinite versus 2 yrs of R maintenance. Pts without del17p, t(14;16), t(14;20), plasma cell leukemia or high-risk GEP70 profile, were enrolled. VRd arm included V 1.3 mg/m^2 on days(d) 1, 4, 8, and 11 (d1, 8 for cycles 9-12), R 25 mg d1-14, and d 20 mg d1, 2, 4, 5, 8, 9, 11, 12 of a 3-week (wk) cycle for 12 cycles, while pts in the KRd arm received K 36 mg/m^2 d1, 2, 8, 9, 15, 16 with R 25 mg daily on d1-21 and d 40 mg wkly, in 4 wk cycles for 9 cycles. Maintenance used 15 mg R d1-21 q4 wks. **Results:** The study accrued 1087 pts (VRd=542, KRd=545). Median age was 65y; baseline characteristics including intent to transplant were similar across the arms. Median induction duration (mos; IQR) was 7.2 (3.4-8.9) and 8.4 (5.1-9.1) for VRd and KRd, respectively; 59.8% in VRd and 45.3% in KRd did not proceed to Step 2. Median PFS (mos) was VRd=41.9 and KRd=44.6; HR = 0.89 (0.76-1.04). Toxicity data, PFS sensitivity analyses and OS probabilities are as in the table. **Conclusions:** In this randomized trial, with median follow up of nearly 6 years, KRd and VRd had comparable PFS and OS in an intent to treat analysis. While similar numbers proceeded to SCT in the 2 arms, more did so during induction in the VRd arm while more patients in the KRd arm went to SCT later. VRd remains a standard triplet induction regimen in standard and intermediate risk NDMM, and a suitable backbone for 4 drug combinations. Clinical trial information: NCT01863550. Research Sponsor: None.

N (%)		VRd (n=527)	KRd (n=526)
SCT anytime		186 (34.3)	183 (33.6)
SCT without Step 2 registration		146	112
Median Time to SCT (mos; range)		7.7 (3.5-83.9)	10.6 (3.7-70.6)
Grade 3-4 Treatment-Related Toxicity		315 (59.8)	344 (65.4)
Grade 5 Treatment-Related Toxicity		2 (0.4)	9 (1.7)
Grade 5 All Events		11 (2.1)	20 (3.8)
Survival outcomes			
	HR	Median (95% CI)	Median (95% CI)
PFS Primary: PD or death within 3 months of last evaluation as events	0.89 (0.76-1.04)	41.9 (35.7, 50.3)	44.6 (38.2, 51.9)
PFS Sensitivity: All deaths as events,	0.87 (0.75-1.02)	39.5 (34.9, 46.0)	42.8 (37.4, 49.7)
PFS Sensitivity: Censor at alternate Rx	0.83 (0.69-0.99)	35.0 (31.3, 42.6)	38.7 (34.7, 49.0)
PFS Sensitivity: Event at alternate Rx	0.84 (0.73-0.97)	18.0 (14.2, 23.0)	24.4 (20.9, 27.9)
Overall survival	0.92 (0.75-1.12)	119 (100, NE)	118 (103-NE)

7541 Poster Session

Clinical characteristics, cytogenetic associations, and outcomes in multiple myeloma with chromosome 1q abnormalities. First Author: Abdullah Ramzan, Mayo Clinic, Rochester, MN

Background: Multiple myeloma (MM) is characterized by recurrent cytogenetic abnormalities, including translocations involving the immunoglobulin heavy chain locus on chromosome 14 and trisomies, which are considered primary and clonal. Throughout disease progression, MM cells may acquire additional abnormalities, which include chromosome 1 abnormalities (gain or amplification of 1q or deletion of 1p) and chromosome 17 abnormalities (del 17p or monosomy 17p). All these factors are considered high-risk markers that predict below-average outcomes. While outcomes related to 1q have been documented, their relationship with other abnormalities and clinical characteristics is less clearly defined. **Methods:** We created a cohort of newly diagnosed MM (NDMM) patients from April 1996 to December 2023 for whom FISH testing was performed using a panel that included 1q findings. Data on clinical and laboratory characteristics, other FISH abnormalities, and survival outcomes were collected from existing databases and the electronic medical record (EMR). **Results:** The cohort included 875 patients, with a median age of 65. Of these patients, 60% were male and 91% identified as white. A 1q abnormality was observed in 443 patients (51%); 87% exhibited a gain of 1q, while 13% showed amplification of 1q. Among those tested, other abnormalities included del13 (58%), t(11;14) (25%), t(4;14) (17%), t(14;16) (6%), del 17p (13%), and trisomies (51%). The distribution of abnormalities concerning the presence of 1q is presented in the table. Patients with 1q abnormalities were more likely to present with additional high-risk cytogenetic abnormalities. The median overall survival (OS) for those with a 1q abnormality was 73 months, compared to 105 months for those without it. Among these, patients with 1q amplification tended to have worse outcomes than those with a 1q gain, though this observation did not reach statistical significance. **Conclusions:** Abnormalities of chromosome 1, including 1q gain and amplification, can be seen in nearly 50% of patients with NDMM who are tested. 1q abnormalities are associated with other high-risk cytogenetic abnormalities. Measures of disease burden are higher among those with a 1q abnormality. Interestingly, we observed a higher proportion of patients with lambda light chain and those with IgA among those with a 1q abnormality. The presence of a 1q abnormality was associated with inferior survival, with a trend towards worse outcomes among those with 1q amplification compared to 1q gain. Research Sponsor: None.

Clinical characteristics and cytogenetic associations of multiple myeloma patients with and without 1q abnormalities.

	1q abnormality present	1q abnormality absent	P
del13	78%	39%	<0.01
t(4;14)	25%	8%	<0.01
t(11;14)	22%	27%	NS
t(14;16)	15%	3%	<0.01
Trisomies	48%	53%	NS
17p del	24%	12%	<0.01
Lambda light chain	45%	26%	<0.01
IgA	32%	16%	<0.01
Hemoglobin	10.3 g/dL	11.2 g/dL	<0.01

7542 Poster Session

Real-world comparison of anti-BCMA vs anti-GPRC5D BiTE therapy in relapsed/refractory multiple myeloma without prior CAR-T cell exposure. First Author: Ali Younas Khan, West Virginia University, Morgantown, WV

Background: In recent years, three bispecific T-cell engager (BiTE) agents have been approved for Refractory/Relapsed Multiple Myeloma (rrMM). These have shown remarkable efficacy, particularly in patients who have failed multiple lines of prior therapy. However, there is a paucity of data to guide choice between available agents. **Methods:** We performed a multicenter, retrospective, propensity score matched (PSM), safety and efficacy comparison between anti-BCMA (Cohort 1: Teclistamab and Elranatamab) and anti-GPRC5D (Cohort 2: Talquetamab) therapy in rrMM, using TriNetX database. Patients with prior CAR-T therapy were excluded. Outcomes assessed included survival, remission rates, subsequent CAR-T therapy, subsequent alternate BiTE therapy, risk of infections, cytokine release syndrome (CRS), immune effector cell-associated neurotoxicity syndrome (ICANS), hypogammaglobulinemia and IVIG use with a follow up of 2 years following treatment. **Results:** A total of 888 and 296 patients were identified in cohort 1 (C1) and cohort 2 (C2), respectively. The two cohorts were matched for 25 characteristics yielding 266 patients in the PSM analysis. No differences in survival probability (HR 0.95; 95% CI 0.65-1.39, p=0.83) or remission rates (C1 vs C2: 37.2 vs 35.0 %, p=0.588) were observed. Subsequent CAR-T therapy was used in 3.8% in C1 and 15% of patients in C2. Any grade CRS (C1 vs C2: 34.6 vs 48.1%, p=0.002) was more common in the Talquetamab cohort, with majority being grade<3 CRS (C1 vs C2: 16.2 vs 27.8%, p=0.001). There was no difference observed for any grade ICANS (C1 vs C2: 14.7 vs 9.8%, p=0.08). No significant differences were found between rates of overall infection (C1 vs C2: 45.5 vs 43.6 %, p=0.63), bacterial (C1 vs C2: 23.3 vs 21.1%, p=0.53), viral (C1 vs C2: 28.6 vs 28.2 %, p=0.92), or fungal (C1 vs C2: 5.8 vs 8.9 %, p=0.29) infections rates. The incidence of hypogammaglobulinemia (C1 vs C2: 74.4 vs 77.8%, p=0.36) and treatment with IVIG (C1 vs C2: 52.3 vs 44.4 %, p=0.06) were similar across both groups. **Conclusions:** Our analysis of real-world patients with relapsed/refractory multiple myeloma (rrMM) showed similar efficacy and tolerability between anti-BCMA and GPRC5D BiTE therapies. However, the Talquetamab group had a higher rate of CRS, consistent with the high incidence observed in the phase 2 MonumenTAL-1 trial. The extent of comorbidities, safety profile of individual agents and plan for subsequent CAR-T cell therapy can guide the choice between available BiTE therapies. Research Sponsor: None.

BiTE therapy: Demographics and outcomes.

Outcome	Cohort 1	Cohort 2	p-value
Total # of pts	266	266	
Mean Age (years)	67.2	67.4	0.82
Male/Female (%)	52.6 / 43.6	50.4 / 43.2	0.60/0.93
Mean duration of treatment (Days)	246 (Teclist) 163 (Elra)	182	
2-yr Survival	55 (54.5%)	53 (50.6%)	0.76
Complete Remission	99 (37.2%)	93 (35.0 %)	0.59
CRS	92 (34.6%)	128 (48.1%)	0.002

7543 Poster Session

Correlation of a senescence-associated gene signature with prognosis in multiple myeloma. First Author: Andras Lanczky, Semmelweis University Department of Bionformatics, Budapest, Hungary

Background: Multiple myeloma (MM), an incurable malignancy of plasma cells, is predominantly a disease of aging. Cellular senescence, a fundamental biological process associated with aging, has been implicated in developing age-related malignancies, including MM. This study investigated the prognostic significance of senescence-associated genes within a large cohort of MM patients. **Methods:** Gene expression and clinical data from 1,416 MM patients were obtained from four GEO datasets (GSE24080, GSE4204, GSE57317, and GSE9782) and integrated into a unified database. Rigorous preprocessing of raw data ensured cross-platform comparability. We employed the SenMayo gene signature, a curated set of senescence-associated genes, computed as a weighted mean expression of the genes. Cox proportional hazards regression, Kaplan-Meier survival analysis, and multivariate models were used to evaluate the prognostic value of the SenMayo signature. Univaraite visualizations were plotted using the Kaplan-Meier plotter (www.kmplot.com). Clinical parameters, including gender, isotype, and molecular subtypes, were incorporated into multivariate analyses, and False Discovery Rate (FDR) correction was applied to correct for multiple hypothesis testing. **Results:** The SenMayo gene signature strongly correlated with overall survival (OS) in MM patients (HR = 0.6, 95% CI = 0.47–0.76, p = 1.7e-05). Patients in the low-expression group had an upper quartile survival duration of 36.1 months, compared to 57 months for those in the high-expression group. Independent validation across three datasets confirmed its prognostic value (GSE4204: HR = 0.58, 95% CI = 0.39–0.88, p = 0.0089; GSE24080: HR = 0.61, 95% CI = 0.45–0.83, p = 0.0012; GSE57317: HR = 0.25, 95% CI = 0.08–0.77, p = 0.0095). Multivariate analyses underscored the SenMayo signature as a prognostic factor, even after adjusting for established clinical parameters such as gender and isotype. **Conclusions:** These findings underscore the pivotal role of cellular senescence in the progression of MM. The senescence gene signature warrants further investigation to support its integration into clinical practice for improved risk stratification and informed therapeutic decision-making. Research Sponsor: None.

7544 Poster Session

Baseline ocular conditions and risk of ocular events in patients (pts) with relapsed/refractory multiple myeloma (RRMM) from the DREAMM-7 and DREAMM-8 trials of belantamab mafodotin (belamaf). First Author: Meral Beksac, Department of Hematology, Ankara Liv Hospital, Istinye University, Ankara, Turkey

Background: Belamaf combinations were evaluated for RRMM in the phase 3 DREAMM-7 (belamaf + bortezomib + dexamethasone [BVd]; NCT04246047) and DREAMM-8 (belamaf + pomalidomide + dexamethasone [BPd]; NCT04484623) trials, and significant progression-free survival benefits were reported over standard of care, with significant overall survival benefit reported for BVd. Ocular events (e.g., ocular adverse events [oAEs], blurred vision, dry eye) occurred with belamaf and most resolved with dose holds and modifications. We examined the baseline eye health of pts with RRMM receiving BVd or BPd, and whether baseline ocular conditions affected rates of treatment-emergent (TE) oAEs. **Methods:** Pts with ≥1 prior therapy were eligible for DREAMM-7/8; pts with ocular conditions were eligible except for corneal epithelial disease (mild punctate keratopathy was allowed). Mandatory ophthalmic examinations (best corrected visual acuity [BCVA], slit lamp, and funduscopic exams) were performed in both arms of the trials at baseline and routinely during treatment. oAEs were graded by Common Terminology Criteria for Adverse Events. Regardless of presence/absence of baseline ocular conditions, the same protocol-defined strategies were used for ocular event management during the studies. **Results:** In 392 pts treated with belamaf (n=242 DREAMM-7 and n=150 DREAMM-8), baseline ocular conditions were reported in 62% of pts (n=135 and 106); baseline conditions included cataract 50% (n=101 and 96), keratopathy 14% (n=33 and 23), dry eye 14% (n=31 and 24), visual acuity of 20/50 or worse 6% (n=18 and 7), glaucoma 6% (n=11 and 13), blepharitis 2% (n=4 and 3), age-related macular degeneration 1% (n=3 and 2), and diabetic retinopathy <1% (n=0 and 2). Any TE oAE was reported in 74% (n=100/135) and 87% (n=92/106) of pts with baseline ocular conditions in DREAMM-7 and DREAMM-8, respectively, compared with 79% (n=85/107) and 91% (n=40/44) of pts without baseline ocular conditions (Table). **Conclusions:** The safety profiles of belamaf combinations for oAEs were similar between patients with vs without baseline ocular conditions, suggesting that these baseline ocular conditions did not increase the risk of TE oAEs. The effect of each baseline ocular condition on TE oAEs, as well as TE corneal exam findings and visual acuity changes, will be presented. Clinical trial information: NCT04246047, NCT04484623. Research Sponsor: GSK (207499/207503); drug linker technology licensed from Seagen; monoclonal antibody produced using POTELLIGENT Technology licensed from BioWa.

TE ocular events in patients receiving a belamaf combination in DREAMM-7/8.

	DREAMM-7		DREAMM-8	
	With any baseline ocular condition, n=135	No baseline ocular condition, n=107	With any baseline ocular condition, n=106	No baseline ocular condition, n=44
Any oAE, n (%)	100 (74)	85 (79)	92 (87)	40 (91)

7546 Poster Session

DREAMM-7 study of belantamab mafodotin plus bortezomib and dexamethasone (BVd) vs daratumumab plus bortezomib and dexamethasone (DVd) in relapsed/refractory multiple myeloma (RRMM): A subgroup analysis in patients (pts) with high-risk cytogenetic (HRC) features. First Author: Maria-Victoria Mateos, Hospital Universitario de Salamanca/IBSAL/CIC/Ciberonc, Salamanca, Spain

Background: In DREAMM-7 (NCT04246047), BVd exhibited a significant improvement in the risk of progression or death vs DVd in pts with RRMM who had ≥1 prior line of treatment. In a post hoc analysis (Mateos et al; ASCO 2024) of pts with ≥1 HRC abnormality (HRCA), including t(4;14), t(14;16), and 17p13del, more pts had deep responses (defined as complete response [CR] or better) with BVd (45%; 95% CI, 32.6%-57.4%) than with DVd (13%; 95% CI, 6.1%-23.3%). Up to 70% of pts at early relapse have amp1q, which confers an increased risk of disease progression. Here we present an updated post hoc efficacy analysis in pts with HRCA, including amp1q. **Methods:** Pts were randomized 1:1 to BVd or DVd as previously reported. For this analysis, pts with HRC were defined as those having ≥1 HRCA, including t(4;14), t(14;16), t(14;20), 17p13del, and amp1q (defined as ≥4 copies of chromosome 1q21). Descriptive statistics were used to summarize results, with 95% exact CI. Hazard ratios (HRs) for progression-free survival (PFS) were estimated using the Cox model, with 95% CI based on the Brookmeyer-Crowley method. **Results:** The ITT population included 494 pts: BVd, n=243; DVd, n=251. In the BVd arm, 122/243 pts (50%) had HRC, of which 41 (17%) had t(4;14), 8 (3%) had t(14;16), 1 (0.4%) had t(14;20), 30 (12%) had 17p13del, and 94 (39%) had amp1q. In the DVd arm, 115/251 (46%) had HRC, of which 42 (17%) had t(4;14), 6 (2%) had t(14;16), 1 (0.4%) had t(14;20), 35 (14%) had 17p13del, and 79 (31%) had amp1q. Median PFS in pts with ≥1 HRCA was 33.2 mo (95% CI, 20.1 mo-not reached) with BVd vs 11.1 mo (95% CI, 9.0-15.1 mo) with DVd (HR, 0.40; 95% CI, 0.27-0.59), and 18-mo PFS rates were 61% and 38%, respectively. PFS benefit favored BVd across subgroups (HR [95% CI]): t(4;14), 0.36 [0.19-0.67]; 17p13del, 0.25 [0.11-0.61]; amp1q, 0.48 [0.31-0.73]; t (14;16) and t(14;20) were not analyzed due to low numbers. In pts with ≥1 HRCA, overall response rate was 81% (n=99; 95% CI, 73.1%-87.7%) with BVd and 69% (n=79; 95% CI, 59.4%-77.0%) with DVd; more pts achieved ≥CR with BVd than with DVd (Table). The benefit was maintained across subgroups. **Conclusions:** In pts with RRMM and ≥1 HRCA, PFS benefit favored BVd vs DVd, and BVd demonstrated a higher rate of deep response. Current outcomes in pts with HRC features are suboptimal, and these data support BVd as a potential standard-of-care regimen in these pts with high unmet need. Clinical trial information: NCT04246047. Research Sponsor: This study was sponsored by GSK. Editorial support was provided by Nucleus Global, an Inizio Company, and funded by GSK. Drug linker technology licensed from Seagen Inc.; monoclonal antibody produced using POTELLIGENT Technology licensed from BioWa.

Patients achieving ≥CR in HRC Groups n/N (%); 95% CI	BVd	DVd
t (4;14)	20/41 (49); 32.9-64.9	6/42 (14); 5.4-28.5
t (14;16)	1/8 (13); 0.3-52.7	0/6; 0-45.9
17p13del	11/30 (37); 19.9-56.1	4/35 (11); 3.2-26.7
amp1q	31/94 (33); 23.6-43.4	16/79 (20); 12.0-30.8
≥1 HRCA	48/122 (39); 30.6-48.6	20/115 (17); 11.0-25.6

7547 Poster Session

Leveraging AI for validating the association between minimal residual disease (MRD) and survival outcomes in multiple myeloma. First Author: Zexin Ren, The George Washington University, Washington, DC

Background: Minimal residual disease (MRD) has been recently accepted by the Food and Drug Administration (FDA) as an endpoint for accelerated approval in Multiple Myeloma. However, emerging data from recent trials were not included in previous analyses. While literature-based meta-analyses on the correlation between MRD and approved clinical outcomes typically require extensive manual review, leveraging AI with expert-in-the-loop validation can efficiently generate reliable evidence from comprehensive clinical studies with up-to-date outcomes. **Methods:** An AI-assisted framework was developed to identify relevant studies and extract critical information via two independent objectives. The first objective examined trial-level associations, modeling treatment effects on MRD and clinical endpoints across patient populations using weighted least squares, with association strength measured by coefficients of determination (R^2) and 95% confidence intervals (CIs). The second objective analyzed individual-level associations using synthetic individual patient data (SynthIPD) generated from the published Kaplan-Meier plots and summary statistics of patient subgroups. **Results:** AI-assisted screening identified eligible studies (>50 patients per treatment arm) reporting progression-free survival (PFS), overall survival (OS), and MRD-negative complete response rates (MRD-CR rate) using multi-parameter next-generation flow cytometry or sequencing methods (sensitivity threshold $\geq 10^{-5}$), expanding previous analyses from 15 to 20 two-arm studies. Trial-level analysis demonstrated an R^2 of 0.69 (95% CI 0.50–0.89) for PFS log hazard ratio versus MRD-CR rate log odds ratio. Analysis of synthetic individual data from Kaplan-Meier curves using a novel digitization method yielded a global odds ratio of 7.28 (95% CI 5.60–8.95) for individual-level correlation between MRD-CR rates and PFS outcomes. **Conclusions:** This study validates MRD-CR rate as an endpoint for accelerated approval in MM through rapid AI-assisted literature review and synthetic individual patient data. The findings demonstrate moderate correlation between MRD-CR rate and median PFS at both trial and individual levels, consistent with previous literature but incorporating additional eligible studies. The novel SynthIPD approach presents an efficient alternative to traditional data-sharing methods while maintaining analytical robustness. These results align with current Oncologic Drugs Advisory Committee (ODAC) surrogacy analysis methods and support the utility of MRD assessment in MM clinical trials. Research Sponsor: None.

7548 Poster Session

Efficacy and safety outcomes in patients (pts) with renal impairment in the phase 3 DREAMM-7 and DREAMM-8 trials. First Author: Marcelo Pitombeira de Lacerda, Universidade da Região de Joinville and Centro de Hematologia e Oncologia, Joinville, Santa Catarina, Brazil

Background: Renal impairment is a frequent complication in relapsed/refractory multiple myeloma (RRMM). Results from DREAMM-7 (NCT04246047) showed significant PFS and OS benefit favoring belantamab mafodotin (belamaf), bortezomib, and dexamethasone (BVd) vs daratumumab-Vd (DVd). DREAMM-8 (NCT04484623) showed significant PFS benefit with belamaf, pomalidomide, and dexamethasone (BPd) vs pomalidomide, bortezomib, and dexamethasone (PVd). In an ongoing phase 1 study (NCT04398745), renal impairment did not impact belamaf pharmacokinetics. We report outcomes in pts with mild/moderate renal impairment from DREAMM-7 and DREAMM-8. **Methods:** Renal function of eligible pts with RRMM was defined based on estimated glomerular filtration rate (eGFR) derived by local labs at screening: normal (≥90 mL/min/1.73 m^2), mild (≥60 to <90 mL/min/1.73 m^2), or moderate (≥30 to <60 mL/min/1.73 m^2) impairment. Pts with eGFR <30 mL/min/1.73 m^2 were ineligible for these trials. **Results:** Results included pts with mild/moderate renal impairment in DREAMM-7 (BVd, n=175; DVd, n=183) as of October 2, 2023, and DREAMM-8 (BPd, n=117; PVd, n=109) as of January 29, 2024. Median PFS was NR with BVd vs 12.6 mo with DVd (HR, 0.39; 95% CI, 0.29-0.53) in DREAMM-7 and 24.0 mo with BPd vs 9.7 mo with PVd (HR, 0.52; 95% CI, 0.35-0.76) in DREAMM-8. Belamaf-containing regimens in both trials had numerically higher 18-mo PFS rates, overall response rates (ORRs), and complete response or better (≥CR) rates (Table). OS benefit favored BVd vs DVd (HR, 0.58; 95% CI, 0.39-0.86) and BPd vs PVd (HR, 0.71; 95% CI, 0.46-1.09). Median OS was NR in either arm of both trials. In pts with mild/moderate renal impairment in DREAMM-7, 95% with BVd and 79% with DVd had a grade 3/4 AE. AEs leading to discontinuation of any study drug occurred in 33% and 18%, respectively. Fatal serious AEs occurred in 10% with BVd and 8% with DVd. In DREAMM-8, 90% with BPd and 73% with PVd had a grade 3/4 AE. AEs leading to discontinuation of any study drug occurred in 13% with BPd and 15% with PVd. Fatal serious AEs were observed in 13% and 12%, respectively. **Conclusions:** In pts with mild/moderate renal impairment, belamaf-containing regimens (BVd and BPd) showed improved efficacy vs standard triplets, indicating they are an efficacious alternative SOC in a broad range of pts with RRMM. Safety results in this pt population were consistent with the ITT populations. Research Sponsor: This study was sponsored by GSK. Editorial support was provided by Nucleus Global, an Inizio company, and funded by GSK. Drug linker technology licensed from Seagen Inc.; monoclonal antibody produced using POTELLIGENT Technology licensed from BioWa.

ITT population with mild/moderate renal impairment	BVd n=175	DVd n=183	BPd n=117	PVd n=109
18-mo PFS rate (95% CI)	0.69 (0.61-0.75)	0.41 (0.33-0.48)	0.61 (0.51-0.70)	0.40 (0.29-0.50)
ORR (95% CI), %	86 (79.6-90.5)	74 (67.4-80.5)	76 (67.3-83.5)	72 (62.1-79.8)
≥CR (95%CI), %	34 (26.8-41.2)	15 (10.4-21.3)	38 (29.6-47.9)	13 (7.2-20.6)

Safety population with mild/moderate renal impairment	BVd n=175	DVd n=183	BPd n=112	PVd n=107
Grade 3/4 AE, %	95	79	90	73
AEs leading to discontinuation of any study drug, %	33	18	13	15
Serious fatal AEs, %	10	8	13	12

7549 Poster Session

Efficacy and safety of less frequent dosing with elranatamab (ELRA) in patients with relapsed or refractory multiple myeloma (RRMM): A US subgroup analysis from MagnetisMM-3. First Author: Ajay K. Nooka, Winship Cancer Institute, Emory University, Atlanta, GA

Background: The ongoing phase 2 MagnetisMM-3 (NCT04649359) study demonstrated the efficacy and safety of ELRA in patients (pts) with RRMM and no prior BCMA-directed therapy (Cohort A). With a median follow-up of 33.9 mo, ORR was 61.0%, mPFS was 17.2 mo, and mOS was 24.6 mo. Here we report results for the subgroup of pts enrolled in MagnetisMM-3 in the US. **Methods:** Eligible pts had RRMM with disease refractory to ≥1 immunomodulatory drug, ≥1 proteasome inhibitor, and ≥1 anti-CD38 antibody. Pts were given subcutaneous ELRA as step-up priming doses followed by 76 mg QW for 6 cycles. Pts given QW dosing for ≥6 cycles who achieved partial response or better lasting ≥2 mo were transitioned to Q2W dosing and to Q4W after ≥6 cycles of Q2W dosing. The subgroup of pts within Cohort A enrolled in the US (n=47) was analyzed. As of the data cutoff date (September 10, 2024), the median follow-up was 33.8 mo (95% CI, 32.9-35.7; estimated by reverse Kaplan–Meier), approximately 32 mo after the last pt first dose. **Results:** Pts in the US subgroup received a median of 5 prior lines of therapy (range, 2-22); 93.6% were triple-class refractory, and 46.8% were penta-drug refractory. Eight (17.0%) pts were Black or African American. ORR (95% CI) by Blinded Independent Central Review was 66.0% (50.7-79.1); 42.6% of pts achieved complete response (CR + stringent CR). Median (range) time to response was 1.08 mo (0.95-7.36), and median time to CR or better was 4.76 mo (1.22-12.75). Median duration of response (95% CI) was not reached (NR) (24.0 mo-not estimable [NE]); the probability of maintaining response at 30 mo (95% CI) was 65.7% (43.3-81.0). Median (95% CI) PFS was 27.3 mo (4.3–NE). Median (95% CI) OS was NR (14.9–NE); the probability of survival at 30 mo (95% CI) was 55.8% (40.1-68.9). Any grade [G] and G3/4 treatment-emergent adverse events were reported in 100% and 78.7% pts, respectively. Infections (any G, G3/4, G5) were reported in 70.2%, 40.4%, and 0.0%, respectively; 51.1% received Ig replacement. Anti-viral, anti-pneumocystis jirovecii pneumonia, anti-bacterial, and anti-fungal prophylaxis were received by 80.9%, 21.3%, 14.9%, and 8.5% of pts, respectively. The rate of cytokine release syndrome (CRS) was 61.7% (G1, 34.0%; G2, 27.7%; G≥3, 0.0%). Immune effector cell-associated neurotoxicity syndrome was reported in 8.5% of pts (G1, 4.3%; G2, 4.3%; G≥3, 0.0%). 22 pts switched from QW to Q2W, and 8 pts further switched from Q2W to Q4W dosing. **Conclusions:** The pts with RRMM enrolled in MagnetisMM-3 Cohort A, including the US subgroup, were heavily pretreated. Consistent with overall Cohort A data, ELRA was associated with deep, durable responses in the US subgroup, with a mPFS of 27.3 mo. CRS was G1 and G2 only. Infections were consistent with what was observed in the overall study population; infection prophylaxis including Ig replacement are recommended. Clinical trial information: NCT04649359. Research Sponsor: Pfizer.

7550 Poster Session

Belantamab treatment of multiple myeloma: Results from part 1 of the first-in-human phase 1/2 DREAMM-20 trial. First Author: Hang Quach, University of Melbourne, St Vincent's Hospital, Melbourne, VIC, Australia

Background: Belantamab mafodotin (belamaf) is a B-cell maturation antigen (BCMA)–targeted monoclonal antibody (mAb) conjugated with a monomethyl auristatin-F (MMAF) payload. In DREAMM-7 and DREAMM-8 phase 3 trials in relapsed/refractory multiple myeloma (RRMM), belamaf combinations significantly improved progression-free survival vs standard care, and DREAMM-7 showed significant overall survival benefit. Belantamab (GSK2857914) is the naked BCMA mAb without MMAF; therefore MMAF-related toxicities are not expected. DREAMM-20 is a phase 1/2 trial to evaluate safety, tolerability, and clinical activity of belantamab in patients (pts) with MM. We present the planned analysis of part 1 of belantamab dose escalation. **Methods:** Part 1 of DREAMM-20 (NCT05714839) is a phase 1, open-label, multicenter, dose-escalation study in pts with RRMM with ≥3 prior lines of therapy. Dose escalation was conducted using a modified toxicity probability interval method. The primary endpoint was incidence of adverse events (AEs), including dose-limiting toxicities (DLTs). Secondary endpoints included overall response rate (ORR). **Results:** Across 3 cohorts, 18 pts enrolled and received belantamab 300, 900 or 2000 mg IV Q2W (n=6 each). Data cutoff (DCO) was Aug 23, 2024. Median age was 76 y (range, 42-86 y), 17 of 18 pts were triple-class exposed, and 2 of 18 pts had prior BCMA-targeted therapy. The overall median duration of exposure was 63.5 days. No DLTs or treatment-related AEs (TRAEs) leading to permanent discontinuation were reported. The most common TRAEs were infusion-related reactions and hematologic AEs (Table). Two pts had grade ≥2 corneal events per the Keratopathy and Visual Acuity (KVA) scale that were considered unrelated to belantamab. The ORR was 28% (5/18 pts; very good partial response, n=2 [900 mg]; partial response, n=3 [1 in 300 mg and 2 in 2000 mg]) with responses across all cohorts. Median duration of exposure in the 5 responders was 253 days; none of the responders had progressed as of DCO. No pts had minimal response and 28% (5/18 pts) had stable disease. Follow-up is ongoing. **Conclusions:** Belantamab showed an encouraging safety profile with no DLTs, AEs leading to discontinuation, or belantamab-related grade ≥2 corneal events. Durable responses were observed across dose levels in this triple-class–exposed population. Results support the hypothesis that belantamab provides clinical antimyeloma activity with an acceptable safety profile. Clinical trial information: NCT05714839. Research Sponsor: This study was sponsored by GSK (study 218670). Editorial support was provided by Nucleus Global, an Inizio Company, and funded by GSK. Monoclonal antibody produced using POTELLIGENT Technology licensed from BioWa.

n (%)	Belantamab 300, 900, or 2000 mg (N=18)
Any-grade AEs	17 (94)
TRAEs	12 (67)
Most common TRAEs (≥2 patients)	
Infusion-related reactions	4 (22)
Neutrophil count decreased	4 (22)
Anemia	2 (11)
Vision blurred	2 (11)
Platelet count decreased	2 (11)
Grade ≥3 AEs	12 (67)
Most common grade ≥3 AEs (≥2 patients)	
Neutrophil count decreased	4 (22)
Anemia	3 (17)
Serious AEs	6 (33)
Treatment related	1 (6)
Fatal AEs	0

7551 Poster Session

Positron emission tomography with computed tomography (PET/CT) and minimal residual disease (MRD) for efficacy assessment in transplant-ineligible newly diagnosed myeloma (Ti NDMM) patients (pts): IMROZ analysis. First Author: Elena Zamagni, Seragnoli Institute of Hematology, Bologna University School of Medicine, Bologna, Italy

Background: MRD is a measure of response in the bone marrow (BM) but is limited by patchy infiltration of BM plasma cells and lack of plasmacytoma assessment. Imaging-based MRD assessment, which is non-invasive, such as PET/CT, may overcome these limitations, and distinguish metabolically active MM from non-active. Isatuximab (Isa) is an anti-CD38 monoclonal antibody approved in combination with bortezomib, lenalidomide and dexamethasone (VRd) in Ti NDMM pts based on the Phase 3 IMROZ study. Here, we present an analysis of IMROZ (NCT03319667), investigating PET/CT negativity (−) with MRD− in front line efficacy assessment. **Methods:** In IMROZ, pts were randomized 3:2 to receive Isa-VRd or VRd as initiation, then Isa-Rd or Rd as maintenance. BM MRD was assessed by next generation sequencing at 10^{-5} sensitivity at baseline (BL), then in case of complete response (CR) or very good partial response at end of initiation, and every 6 months for 2 years, then once a year until disease progression (PD). PET/CT scans were assessed by central review and performed at BL, then yearly until PD; if positive for soft tissue plasmacytoma, repeated at time of CR and/or end of induction, then following time points for MRD assessment. PET/CT positivity (+) was defined as FDG 5PS Score ≥4, and PET/CT− as FDG 5PS ≤3. **Results:** Across the global and China populations, 244 Isa-VRd and 162 VRd pts had PET/CT at BL, of which 153 (62.7%) and 101 (62.3%) were PET/CT+, respectively. Of these, 121 (41.6%) and 83 (43.0%) had a post-BL PET/CT assessment. 155 pts presented with plasmacytoma at BL (95 Isa-VRd, 60 VRd), with comparable BL characteristics to the global population. Among PET+ pts at BL, the double negativity rate (PET/CT FDG 5PS score ≤3 + MRD−) was significantly higher in Isa-VRd pts than VRd (odds ratio [OR] 1.54; 95% CI 1.04-2.29; p=0.0155), and similarly for double negativity + ≥CR (OR 1.60; 95% CI 1.07-2.38; p=0.0108). As shown in Table, more Isa-VRd than VRd pts with plasmacytoma reached PET/CT 5PS ≤3 and MRD−, and PET/CT 5PS ≤3 with MRD− + ≥CR. Progression-free survival (PFS) in pts PET/CT+ at BL was in favor of the Isa-VRd arm (median PFS [mPFS] not reached [NR; 95% CI 59.4-NR]) vs VRd (mPFS 49.1 [95% CI 39.1 -NR]) (hazard ratio [HR] 0.58; 95% CI 0.39-0.88; p=0.6303), and HR was comparable to the intent to treat population. PFS in pts with plasmacytoma at BL was similar to the global population (HR 0.685; 95% CI 0.40-1.18; p=0.5332). **Conclusions:** This analysis of IMROZ shows the prognostic value of BL PET/CT findings. More Isa-VRd pts reached double negativity than VRd, including pts with plasmacytomas. This translated to a better PFS in pts treated with Isa-VRd. Clinical trial information: NCT03319667. Research Sponsor: Sanofi.

	Isa-VRd (n=77)	VRd (n=52)
PET/CT 5PS score ≤3 and MRD−, %	45.5	34.6
OR (95% CI), p	1.57 (0.76-3.26), 0.1107	
PET/CT 5PS score ≤3 and MRD− + ≥CR, %	44.2	32.7
OR (95% CI), p	1.63 (0.78-3.39), 0.0966	

7552 Poster Session

Impact of autoimmune disease on toxicity and outcomes after idecabtagene vicleucel in patients with multiple myeloma. First Author: Rebecca Albuquerque, USF Health Morsani College of Medicine, Tampa, FL

Background: Idecabtagene vicleucel (ide-cel), an autologous BCMA-directed chimeric antigen receptor (CAR) T-cell therapy, has the potential to cure patients with relapsed/refractory multiple myeloma (RRMM). However, cytokine release syndrome (CRS) and immune effector cell-associated neurotoxicity syndrome (ICANS) are common treatment-related adverse events. Historically, patients with autoimmune disease (AD) have been excluded from CAR-T trials due to uncertain outcomes. This study evaluates differences in ICANS, relapse, and survival in RRMM patients with and without AD treated with ide-cel. **Methods:** A retrospective study of RRMM patients with AD treated with ide-cel at Moffitt Cancer Center in Tampa, FL between 2021-2024 was conducted. Clinically significant AD requiring medical management prior to apheresis included AIHA, autoimmune thyroiditis, ITP, RA, AIDP, CIDP, UC, SLE and PMR. T-tests and Kaplan-Meier estimates analyzed associations between AD, toxicities, and survival. **Results:** Of 179 patients with RRMM who received ide-cel, 13 (7%) had clinical AD with a median age of 72 years (range: 58 - 81 years, 54% female [n=7]). The incidence of ICANS was 23.1%, versus 23.6% for patients without AD (n = 166). The incidence (p = 1) and duration (p = 0.822) of ICANS was not significantly different in those with or without AD. Two patients (with AIHA and ITP) were tapered off of prednisone prior to ide-cel. Per medical records, the remaining patients were not on immunosuppressive medications for AD at treatment. All AD patients experienced CRS versus 85% of patients without AD (p = 0.225). For AD patients who experienced ICANS, median LDH (202 U/L vs 189 U/L, p = 0.061) and ferritin (528 ng/mL vs 284 ng/mL, p = 0.866) 5 days prior to infusion (day -5) was not significantly higher versus AD patients with no ICANS. However, median CRP at day -5 was significantly higher (1.2 mg/L vs 0.365 mg/L, p = 0.05). In AD patients who experienced ICANS, median LDH (872 U/L vs 268U/L, p = 0.01) and ferritin (10200 ng/ml vs 3000 ng/ml, p = 0.05) were significantly higher at the day of maximum grade ICANS versus patients without AD. However, there was no difference in median CRP (7.46 mg/L vs 7.72 mg/L, p = 0.9). Among patients who experienced ICANS, AD patients did not have significantly lower progression free survival (PFS) versus patients without AD at 30 days, 12 months, and 18 months (p = 0.07). There was no difference in overall survival between patients with or without AD. **Conclusions:** This retrospective study shows that pre-existing AD does not increase the risk of ICANS in patients with RRMM who were treated with ide-cel. Although LDH and ferritin levels were similar, levels of CRP were significantly higher in AD patients who experienced ICANS versus those that did not. Given notable differences in levels of inflammation and relapse rates among patients with AD, these patients may benefit from close monitoring. Research Sponsor: None.

7553 Poster Session

Carfilzomib, iberdomide, and dexamethasone (KID) in patients with transplant-eligible newly diagnosed multiple myeloma (NDMM): Updated results from phase 1/2 study. First Author: Noa Biran, John Theurer Cancer Center, Hackensack University Medical Center, Hackensack, NJ

Background: SOC regimens for patients (pts) with transplant-eligible NDMM include VRd, D-VRd, and KRd. Iberdomide, a cereblon modulator, enhances immune stimulatory activity *in vitro* compared to thalidomide analogs. A phase 1 study reported the MTD of iberdomide 1.6 mg plus carfilzomib (CFZ) and dexamethasone (DEX), KID regimen, in NDMM pts (Biran 2023). Herein we report longer term safety and efficacy data from a phase 2 dose expansion study of KID in NDMM pts (NCT05199311). **Methods:** Adults with NDMM eligible for ASCT were enrolled in this multicenter, investigator-initiated phase 1/2 study. In the phase 2 portion, pts received CFZ (IV; 20 mg/m^2 on C1D1; then 56 mg/m^2 C1 D8, 15; then 56 mg/m^2 C2-4 D1, 8, 15), iberdomide (1.6 mg; D1-21), and DEX (40 mg if ≤75 years; 20 mg if >75 years; D1, 8, 15) in 28-day cycles for 2-3 cycles followed by ASCT. The primary objective is to evaluate the rate of CR + sCR. **Results:** As of 1/10/25, 38 pts signed consent, including 20 in follow-up, 7 off study (5 screen failures/1 consented/1 withdrew due to rash), and 4 on treatment (tx). Of 31 pts who received tx, median age was 66 years (range 41-78), 52% male, 77% White, 16% Black, 3% Asian, 58%/16%/6% ISS stage 1/2/3, respectively. Thirteen pts (42%) had high-risk cytogenetics: t(4;14) (n=3), t(4;16) (n=1), del(17p)/monosomy 17/*TP53* (n=2), 1q21 (n=9), and *MYC* (n=1). Two pts had double- and 1 was triple-hit MM. Thirty-one pts completed a median of 3 cycles (range 1-4) of KID. At end of induction, ORR was 96% (23/24, CR 4%, VGPR 42%, PR 50%). Twenty-three pts proceeded to ASCT; 8 did not (4 on tx/1 collecting cells/1 withdrawal/1 death). Median number of stem cells mobilized was 11.3 x 10^6 cells/kg (range 4.74-29.8). At 3 months post-ASCT, ORR was 100% (19/19, sCR 5%, CR 21%, VGPR 53%, PR 21%), CR + sCR is 26%, and of those, 100% are MRD-negative. Median tx duration was 84 days (IQR, 63-91). At median follow-up of 12.4 months, median PFS and OS were NR (95% CI, NA-NA). Most common hematologic TEAEs were anemia (19%), neutropenia (39%), and thrombocytopenia (23%). Most common non-hematologic TEAEs were pruritus (23%) and rash (23%). Grade 3 TEAEs occurred in 26% of pts; most common were neutropenia (26%), thrombocytopenia (6%), and rash (6%). Six pts developed grade 1-2 SAEs unrelated to tx. One patient experienced grade 3 SAE of fever and colonic hemorrhage that required hospitalization and supportive care. No tx-related deaths occurred; 1 patient died on study due to a possible thrombotic event in the setting of medication non-compliance. **Conclusions:** Induction therapy with KID appears safe and effective leading to deep responses and adequate stem cell collection despite short tx duration and 42% harboring high-risk cytogenetics. Long-term follow-up is needed to determine durability of response. Correlative studies are underway to evaluate immune phenotype and microbiome changes pre/post-tx. Clinical trial information: NCT05199311. Research Sponsor: Amgen; Bristol Myers Squibb.

7554 **Poster Session**

Updated results from phase 2b study of selinexor in combination with carfilzomib, daratumumab, or pomalidomide in patients with multiple myeloma (MM) relapsing on current therapy. First Author: Noa Biran, John Theurer Cancer Center, Hackensack University Medical Center, Hackensack, NJ

Background: Selinexor is a potent selective inhibitor of nuclear export and exhibits synergistic effects when combined with other myeloma therapies. Preliminary results on the combination of selinexor with carfilzomib (CFZ), daratumumab (DARA), or pomalidomide (POM)-based regimens in patients relapsing on therapy were reported (Biran 2023); overall response rate (ORR) Arm 1 (33%), Arm 2 (29%), and Arm 3 (44%). Herein we present the updated results with longer follow-up of selinexor plus CFZ, POM or DARA in MM patients relapsing on current treatment (NCT04661137). **Methods:** Patients were enrolled to each arm if their disease was refractory to the specific drug. Patients on Arm 1 were treated with selinexor 80 mg on D1, 8, 15; CFZ 20 mg/m^2 IV on D1, 8, 15; and dexamethasone (DEX) on D1, 8, 15, 22. Arm 2 patients received selinexor 60 mg on D1, 8, 15; POM 4 mg on D1-21; and DEX on D1, 8, 15, 22. Arm 3 patients were treated with selinexor 100 mg on D1, 8, 15, 22; DARA 16 mg/kg IV or 1,800 mg SQ on D1, 8, 15, 22 for C1-2; then D1 and 15 for C3-6; then D1 for ≥C7; and DEX on D1, 8, 15, 22. The primary objective was to investigate the ORR of selinexor plus CFZ, POM, or DARA-based regimens. **Results:** As of Jan 10, 2025, 28 patients were enrolled. Twenty-four were evaluable for response; 7 withdrew consent in which 5 were due to disease progression. Median age was 68 years (range 52-82), 50% male, 54% White, 96% had prior autologous transplant and 21% had extramedullary disease. Nineteen (79%) patients had high-risk cytogenetics, including 1q21 duplication (n=11), t(4;14) (n=8) and *TP53* mutation (n=6). The ORR was 38% (95% CI, 19-59%) (PR, 8 [33%]) and clinical benefit rate (CBR) was 83% (95% CI, 63-95%) (PR, 8 [33%]; MR, 1 [4%]; SD, 11 [46%]). With a median follow-up of 11.0 months, the median PFS was 5.7 months (95% CI, 4.7-NR), and median OS was NR months (95% CI, 15-NR). Median DOR was 3.6 months (IQR, 2.5-5.1) with a median treatment duration of 4.0 months (range 0.3-10.8 mos). Most commonly reported Grade 1-2 TEAEs were electrolyte abnormalities (50%) and fatigue (38%). Most commonly reported grade ≥3 TEAEs were neutropenia (25%) and pneumonia (8%).Three patients experienced treatment-related grade 3 SAEs and recovered. One developed chest pain that required hospitalization. One had parainfluenza A-1 pneumonia requiring a treatment delay. One experienced sepsis and pneumonia which led to hospitalization and interruption of treatment. **Conclusions:** Selinexor as an add-on to CFZ, POM, or DARA-based regimens, in patients actively progressing on these regimens, is well tolerated and safe. This trial demonstrates that selinexor can restore sensitivity to regimens to which MM patients are actively refractory. Future studies can evaluate these combinations in the setting of chimeric antigen receptor T-cell bridging or in the post-bi-specific T-cell engager setting. Clinical trial information: NCT04661137. Research Sponsor: Karyopharm Therapeutics.

7555 **Poster Session**

Clinical activity of novel targeting of S100A9 with tasquinimod for relapsed and refractory multiple myeloma (RRMM). First Author: Dan T. Vogl, Abramson Cancer Center, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA

Background: S100A9, a protein produced by myeloid-derived suppressor cells in the bone marrow microenvironment, promotes multiple myeloma (MM) progression and confers therapeutic resistance. Tasquinimod (tasq), an oral S100A9 inhibitor, has pre-clinical anti-myeloma effects alone and combined with proteasome inhibitor (PI) and immunomodulator (Imid) therapy (Cancer Res Commun 2023;3(3):420) and improved progression-free survival in prostate cancer patients (pts) (JCO 2016;34(22):2636-43). We previously reported preliminary results of a phase 1 trial of tasq alone and in combination with ixazomib (ixa), lenalidomide (len), and dexamethasone (dex) (IRd) in pts with RRMM (JCO 2023;41(16) suppl:8042; NCT04405167). For single-agent tasq, the recommended phase 2 dose (RP2D) was 1 mg daily (qd) after a 1 week (wk) run-in at 0.5 mg qd. We now report updated results of tasq in combination with IRd. **Methods:** In dose escalation, pts were refractory, intolerant, or contraindicated to len, pomalidomide, bortezomib, carfilzomib, and an anti-CD38 monoclonal antibody. In dose expansion, pts were refractory to the most recent Imid/PI combination or triple-class refractory. Tasq was given in 28-day cycles at 1 mg daily with either a 2 wk run-in (dose level 1: 0.25 mg qd x1 wk then 0.5 mg qd x1 wk) or a 1 wk run-in (dose level 2: 0.5 mg qd x1 wk). In dose escalation, pts received full doses of ixa (4 mg days 1/8/15), len (25 mg days 1-21, adjusted for renal dysfunction), and dex (40 mg qwk), but in dose expansion, doses of ixa, len, and dex were reduced per investigator discretion. **Results:** 16 pts received tasq with IRd at dose levels 1 (3 pts) and 2 (13 pts: 3 in escalation, 10 in expansion). Median age was 67 y (range 52-81); 75% were male; 19% were African American and 81% Caucasian. Pts had received median 7 prior lines of therapy (range 3-19), and all were triple-class refractory, with 81% (13 pts) refractory to their most recent Imid/PI combination. In dose escalation, no dose limiting toxicities were observed, and dose level 2 was the RP2D of tasq with IRd. The most common treatment-emergent adverse events were fatigue (10 pts: grade [gr] 3 in 1 pt), pain (9 pts: 0 gr ≥3), respiratory infection (9 pts: 4 gr 3, 2 gr 5), nausea/vomiting (8 pts: 0 gr ≥3), dyspepsia/gastritis (5 pts: 1 gr 3), and thrombocytopenia (5 pts: 1 gr 3, 3 gr 4). Among all 16 pts, there was 1 partial response (PR) and 7 minimal responses (MR). Among the 13 pts who were previously refractory to their most recent Imid/PI combination and would therefore not be expected to respond to the IRd backbone, there was 1 PR (lasting 20 months) and 5 MRs (lasting 1, 1, 2, 2, and 7 months). **Conclusions:** Tasquinimod, an S100A9 inhibitor, is well tolerated in combination with IRd and has anti-myeloma activity, as evidenced by responses in patients previously refractory to Imid/PI combination therapy. Further study is warranted of tasquinimod in combination with standard myeloma therapies. Clinical trial information: NCT04405167. Research Sponsor: Leukemia and Lymphoma Society; 6609; Active Biotech, AB.

7557 **Poster Session**

ASCOmind: Is instant ASCO abstract analysis possible with AI agents? First Author: Kyeryoung Lee, IMO Health, Rosemont, IL

Background: The ASCO Annual Meeting receives thousands of abstracts annually on ongoing therapies. Extracting actionable insights from this large volume of data through manual review is time-consuming. To reduce manual workload and accelerate evidence synthesis, we implemented an AI-Agent system to assess the feasibility of deploying AI agents for efficient, large-scale data analysis and insight generation. **Methods:** GPT4o-based ASCOmind was designed with a robust framework of six autonomous and collaborative AI agents: Pre-processor, Categorizer, MetadataExtractor, Analyzer, Visualizer, and ProtocolMaker to systematically generate and visualize insights from ASCO abstracts. We demonstrate and evaluate ASCOmind by applying it to 2024 multiple myeloma (MM) studies. Using human reviewers as the gold standard, we assessed the quality and efficiency of the system focusing on outcome data accuracy, visualized charts, and workflow recipes documentations. **Results:** ASCOmind processed abstracts in the plasma cell dyscrasia section, categorizing 60 MM abstracts into 26 clinical trials and 34 as real-world studies. Manual abstraction of 51 predefined data elements required >60 mins/abstract, whereas ASCOmind completed the same task in <5min/article. The ASCOmind not only significantly reduced the processing time but also instantly analyzed and visualized the extracted data within 10 min. For instance, 27 included high-risk populations with cytogenetic abnormalities (n=20), extramedullary disease (n=7), or elderly patients (n=4). Across 51 interventional studies, 33 targeted relapsed/refractory MM (RRMM) and 18 focused on newly diagnosed MM (NDMM). ASCOmind generated a treatment distribution table for RRMM and NDMM (Table 1), with one misclassification corrected by humans-Mezigdomide reclassified from ADC to the correct category. Additionally, granular efficacy/safety outcome values and summarized study findings were also successfully extracted and visualized. **Conclusions:** Our preliminary analysis of ASCOmind demonstrated high accuracy and efficiency in automating abstract analysis, enabling rapid analysis of trends and outcomes. This feasibility study highlights the scalability of AI systems across all cancer types, supporting decision-making. Research Sponsor: None.

Treatment distribution in RRMM and NDMM studies.

Total (N=51)	Therapy Category	Examples	No. of Studies	%
RRMM (N=33)	BCMA-CAR-T Therapies	Cilta-cel, Ide-cel, ARI0002h	8	24.3%
	BCMA-Bispecific Ab Therapies	Teclistamab, Talquetamab, Elranatamab, Linvoseltamab, ABBV-383	16	48.5%
	ADC	Belantamab mafodotin, Elotuzumab,	5	15.2%
	Cereblon E3 Ligase Modulator	Mezigdomide, Iberdomide,	2	6.0%
	Others	OriCAR017, Venetoclax	2	6.0%
	Triplet/Quadruplet SOC	VRd, Isa-VRd	8	44.5%
NDMM (N=18)	Transplantation	ASCT, Tandem Transplantation	6	33.3%
	ADC	Belantamab mafodotin,	2	11.1%
	BCMA-Directed Therapies	Cilta-cel + Lenalidomide, Teclistamab	2	11.1%

7558 **Poster Session**

Gene-expression-profiling plus integrated multidisciplinary approach to detect new-generation risk-adapted prognostic index in smoldering myeloma and multiple myeloma (GIMPI). First Author: Claudio Cerchione, Hematology Unit, Istituto Romagnolo per lo Studio dei Tumori "Dino Amadori" - IRST IRCCS, Meldola, Italy

Background: In our Institution, a prospective study to test the combination of gene-expression-profiling (SKY92 gene signature) and new generation imaging (PET/CT + Whole body MRI) was applied to all consecutive patients affected by smoldering (SMM), newly diagnosed (NDMM) and relapsed/refractory (RRMM) MM and evaluated its potential to predict or correlate with established HR markers of this disease and potentially defining new basis for a personalized treatment. **Methods:** Patients' bone marrow aspirate, plasma, imaging and clinical data were collected in our Institute under approved protocol and according to the Declaration of Helsinki guidelines. **Results:** In this study a cohort of 139 patients referring to our Institute was enrolled (SMM n=47, NDMM n=54 and RRMM n=38): here we present only the molecular part of the study, combination with imaging analysis is currently ongoing. Proportion of patients with SKY92 HR increased from SMM (8.4%) to NDMM (36.7%) and RRMM (53.3%, p=0.0162). Virtual FISH in NDMM patients showed 100% accuracy (95% CI) (100.0-100.0) for both t(4;14) and gain(1q) and of 90.0 (71.4-100.0) for del(17p), and this could be really useful for the daily clinical practice. The concentration of sBCMA was measured in our patients' cohort and in healthy subjects (n=12, control) with a statistically significant increase of sBCMA in the blood of NDMM and RRMM with respect to SMM (p=0.0009, p=0.0222) and control (p<0.0001, p=0.0010). Consistently with the literature, no statistically significant differences were observed among NDMM and RRMM. Thus, we hypothesize that SKY92 HR could capture patients with high levels of sBCMA. We compared the concentration of this disease biomarker among SR and HR including SMM, NDMM and RRMM patients and we observed increased levels of sBCMA in HR patients with respect to SR (p=0.0049). A risk-based intragroup comparison showed a similar trend in SMM and RRMM and, importantly, this result was confirmed in NDMM patients (p=0.0445). However, in this category of MM patients ISS could partially recapitulate differences in sBCMA among risk classes with the only statistically significant difference between Class I and III (p=0.0381). Therefore, we combined ISS with SKY92 and we observed that n=11 patients considered as LR by ISS (Class I), were relocated to the IR from this analysis with an overall improvement in the distribution of sBCMA levels according to risk categories (SR vs HR p=0.0011, IR vs HR p=0.0036). **Conclusion:** The results of this first pilot Italian study, that in the next future will be framed in a national network contest, strengthen the prognostic relevance of SKY92 based on its potential to (i) predict HR cytogenetic markers of disease; (ii) capture MM patients with high levels of sBCMA supporting the introduction of this GEP-based tool in the clinical diagnostic practice. Research Sponsor: None.

7559 Poster Session

The impact of glucagon-like peptide-1 agonists on MGUS progression in patients with type 2 diabetes. First Author: Tajana Juranovic, Charleston Area Medical Center, Charleston, WV

Background: Monoclonal gammopathy of undetermined significance (MGUS) is a pre-malignant condition with limited interventions to reduce progression to multiple myeloma (MM). Glucagon-like peptide-1 (GLP-1) agonists, widely used for glycemic control and weight loss in type 2 diabetes mellitus (T2DM), have demonstrated cardiovascular, renal, and anti-cancer benefits, including reduced risks of obesity-associated cancers. This study assesses the association between GLP-1 agonists and MGUS progression in T2DM patients. **Methods:** We queried TriNetX – a Research Network - of 141 healthcare organizations from 30 countries between 2011 and 2024.MGUS patients with T2DM were divided into two cohorts: those on GLP-1 agonists and those not on GLP-1. Two sub-analyses were conducted: one in MGUS T2DM patients with a normal body mass index (BMI), and another in patients with BMI $\geq$25. Patients aged 18–80 years with monoclonal protein $<$3 g/dL, and GLP-1 use or other diabetic medications $\geq$2 years prior to MGUS diagnosis were included. Patients with prior diagnosis of MM, progression to MM within 1 year, kappa/lambda light chain $>$100 mg/dL, osteolytic lesions, creatinine $>$2 mg/dL, hemoglobin $<$10 g/dL, calcium $>$10.2 mg/dL, or prior treatment with bortezomib, lenalidomide, or daratumumab, were excluded. A 1:1 propensity score matching was performed to match the covariates (age, sex, race [white or African American], M protein, kappa/lambda ratio, and BMI). MM rates were compared at 2, 3, 5, 7, and 10 years. **Results:** The study included 5,901 MGUS patients with T2DM in the main analysis (22.45% on GLP-1 [n=1,325]; 77.55% not on GLP-1 [n=4,576]). The sub-analysis involved 818 normal-BMI patients (22.37% on GLP-1 [n=183]; 77.63% not on GLP-1 [n=635]). Matched cohorts (main analysis: n=1,319 each, sub-analysis n=181each) revealed significantly lower MM rates in GLP-1 users at 2- (1.21% vs 2.50, p=0.014), 3- (1.36% vs 2.50%, p=0.33), 5- (1.36% vs 2.57%, p=0.025), 7- (1.36% vs 2.57%, p=0.025) and 10-years (1.51% vs 2.65%, p=0.041). Similar findings were observed in the sub-analysis among patients with MGUS and T2DM with BMI $\geq$ 25 at 2- (1.08% vs 3.05%, p=0.001), 3- (1.18% vs 3.15%, p=0.002), 5- (1.08% vs 3.05%, p=0.001), 7- (1.18% vs 2.85%, p= 0.07, and 10-years (1.37% vs 3.05%, p=0.01). However, in the sub-analysis, normal-BMI GLP-1 users showed no difference in MM rates compared to non-users at 10-years (5.52% vs 5.52%, p=1.00). **Conclusions:** The use of GLP-1 agonists was significantly associated with reduced rates of MM among patients with T2DM and MGUS over a 10-year period, particularly in those with a body mass index $\geq$ 25. The lack of significant effects in normal-BMI patients suggests weight loss or related metabolic changes may mediate these protective effects. These results underscore GLP-1 agonists as a promising therapeutic strategy for managing MGUS in T2DM patients, especially those with elevated BMI. Research Sponsor: None.

7560 Poster Session

Role of the combination of 3 T whole-body MRI and 18F-FDG PET/CT in the management of multiple myeloma and smoldering myeloma: The new era of imaging. First Author: Claudio Cerchione, Hematology Unit, Istituto Romagnolo per lo Studio dei Tumori "Dino Amadori" - IRST IRCCS, Meldola, Italy

Background: FDG-PET/TC and MRI are both imaging diagnostic tools adopted in diagnosis and/or response assessment in multiple myeloma (MM) which can be useful in smoldering, newly diagnosed as well in relapsed myeloma. **Methods:** From January 2021 to January 2025, we enrolled into a prospective trial 139 consecutive patients (54 Male; mean age, 67 years $\pm$ 10 [SD]) divided into 3 groups; 34 had a newly diagnosed MM according to the IMWG (group 1); 20 were in follow-up after autologous stem cell transplantation with clinical or laboratory data suspicious for relapse or progression (group 2) and 38 were affected by relapsed/refractory MM during treatment (group 3). In addition we enrolled 47 patients newly diagnosed high risk SMM, according to IMWG (19 Male, mean age 59 years+-10 [SD]). **Results:** On a per-patient basis, 126/139 (90%) had concordant PET/CT and WB-MRI scans, while 13/139 (10%) had discordant scans in terms of positivity/negativity. Among concordant studies, 47/139 (34%) were negative with both imaging methods while 93/139 (67%) were positive at both (including FLs and/or BMI). Among discordant studies, 8/9 had a positive WB-MRI scan and a negative PET-CT scan (6 cases with BMI or micronodular involvement alone), whereas 1/9 had a positive PET-CT and a negative WB-MRI. PET/CT detected FLs pattern in 83/139 patients, WB-MRI alone identified FLs pattern in 6 patients. PET-CT led to a change of treatment approach in 72/139 patients (52%), WB-MRI in 84/139 patients (60%), the combination of the two methods led to a change of management in 86/139 (62%), highlighted in the case of suspected post-transplant relapse. Furthermore, WB-MRI led to a change of management for incidental findings in additional 9 patients (8 suspected malignancies and 1 spinal cord compression). Interim analysis in HR- SMM showed discordance between the results of the two imaging modalities in 32/139 (23%). WB-MRI detected BMI pattern without any overt focal lesion in 11 patients (only 1 correlated with PET/CT) and FLs pattern in 7 patients (4 confirmed also in PET/CT), while PET/CT detected an additional FLs pattern in 1 patient, without bone lytic lesion evidence at the CT images. Both methods led to 6 changes of management, whereas MRI alone led to a change of treatment approach in 14 patients (10%), 13 diagnoses and 1 accessory finding of suspected cholangiocarcinoma. **Conclusions:** Our preliminary data underlines the fundamental role of functional imaging in the evaluation of FLs and BMI in MM with a superior detection rate of WB-MRI related to the ability to identify diffuse and micronodular pattern. A potential complementary role of the two methods in clinical management could be suggested in suspicion of relapsed or progressing MM. Furthermore our prospective trial supports the utmost role of WB-MRI (performed according to MY-RADS) in the assessment of high risk Smoldering Myeloma. Research Sponsor: None.

7561 Poster Session

Real-world analysis of thromboembolism in SAVED/IMPEDE risk-stratified newly diagnosed multiple myeloma (NDMM). First Author: Kian University Medical Rahbari, Vanderbilt University Medical Center, Nashville, TN

Background: The rate of thromboembolic (TE) events in NDMM patients (pts) treated with IMiD-containing regimens ranges from 11-19%, with venous events (VTE) being more common than arterial events (ATE). The SAVED and IMPEDE scores have been developed to risk-stratify thrombotic risk in NDMM. However, data on risk of VTE based on SAVED and IMPEDE VTE scores is largely unavailable for adequate contextual understanding of the problem. **Methods:** We queried the electronic medical record at Vanderbilt University Medical Center for pts with NDMM treated between January 2017 and May 2022, with a follow up for $\geq$ 2 years or until death. Information on incidence of TE, SAVED and IMPEDE scores at diagnosis, and the type of thromboprophylaxis (ppx) [any dose anticoagulation (AC) vs any dose aspirin (ASA) vs no ppx] present at induction therapy was analyzed. Pts were categorized as having elevated VTE risk if they had either SAVED $\geq$ 2 or IMPEDE $\geq$ 4 (patients with ATE were excluded). VTE rates were compared by χ^2 tests, and time to event was compared by Wilcoxon rank-sum test. **Results:** Among 178 pts with NDMM, the median (range) age was 65 (39-88) years. Upfront transplant was done in 76 (42.7%) of pts and IMiD containing therapy was used in 113 (63.5%) pts. The median (range) SAVED score was 1 (-2 to 7), and the median IMPEDE score was 2 (-3 to 12). Overall, 39 pts (21.9%) were diagnosed with TE [35 (19.7%) VTE, 4 (2.2%) with ATE]. Median (range) time to VTE was 7.7 months (mo) (0-42.3). Overall, 132 (74.1%) pts were on ASA, 26 (14.6%) were on AC, and 20 (11.2%) on no ppx. Among VTE pts, 25 (71.4%) were on ASA, 5 (14.3%) were on AC, and 5 (14.3%) on no ppx. Among VTE pts vs those without an event, a total of 20 (57.1%) vs 67 (48.2%) (p = 0.3) pts were categorized as having elevated risk, respectively. Among all pts with elevated VTE risk (n=84) vs not (n=90): VTE incidence was 23.8% (n=20) vs 16.7% (n=15) (p=0.24), and median (range) time to VTE was 5.5 (0-24.1) mos vs 9.1 (0-42.3) mos (p=0.12). Among those with elevated VTE risk, 18 (21.4%) received AC, 53 (63.1%) received ASA, and 13 (15.5%) were on no ppx. Among pts with elevated risk on AC versus ASA, VTE incidence was 11% (n=2) vs 26.9% (n=14) (p=0.3). Lastly, VTE rate was 19.1% (deep vein thrombosis (DVT) 12.2%, pulmonary embolism (PE) 6.9%), 19.2% (15.4% DVT, 3.8% PE), and 30% (10% DVT, 20% PE) among all pts on ASA, AC, and no ppx, respectively. **Conclusions:** Despite most patients harboring low predicted VTE risk at diagnosis by SAVED/IMPEDE, VTE rate was unacceptably high, and primarily occurred beyond 6 mos in our real-world NDMM cohort. Furthermore, VTE risk was not adequately mitigated in this ASA-ppx-enriched cohort. Though limited by small sample size, VTE events were numerically higher and had faster onset among patients with elevated SAVED/IMPEDE risk compared to those with low risk, while AC ppx in elevated-risk pts showed a trend towards reduced VTE incidence compared to ASA. Research Sponsor: None.

7562 Poster Session

Teclistamab in relapsed/refractory systemic AL amyloidosis. First Author: Vasil Mico, Tufts Medical Center, Boston, MA

Background: Systemic light chain amyloidosis (AL) is clonal plasma cell disorder characterized by the deposition of fibrils derived from immunoglobulin light chains. Treatment paradigms have been based on therapies for multiple myeloma. Teclistamab is a bispecific antibody approved for use in relapsed refractory multiple myeloma. We report on its impact in patients with AL. **Methods:** We analyzed data on hematologic and organ responses and treatment-related side effects in patients receiving Teclistamab for relapsed refractory AL. Mayo systems were used to characterize the disease stages. Adverse events were graded with the NCI CTCAE v5.0; CRS was graded according to ASTCT criteria. **Results:** Eight patients were identified (Table 1). All had relapsed refractory disease. Six had AL-λ and 2 AL-κ type. Five had cardiac involvement, 3 with stage III and 2 with stage II. Median prior lines of therapy was 4 (3-10). All were previously treated with Daratumumab and 5/8 had previously undergone autologous stem cell transplant. Median bone marrow plasmacytosis was 8.5% and median involved free light chain (iFLC) was 64.3mg/L (23.1 - 331). CD138-selected marrow findings included t(11;14), gain 1q and del 17p, each in 2 patients. Patients received escalating doses of Teclistamab. Two patients had grade 3 toxicities; one, a woman in her 80's, experienced a hepatic aminotransferase spike greater than 1000 the day after receiving the first 0.6mg/kg dose and subsequently after only that dose achieved an unmaintained CR that has continued for over 7 months; the other, a woman in her 70's, had grade 3 thrombocytopenia that has slowly resolved after Teclistamab was stopped. Two patients experienced grade 1 CRS. The hematologic response rate was 100% with 7 CR and 1 VGPR. The cardiac response rate was 29% (2/7; 1 CR, 1 PR) and the renal response rate was 20% (1/5). No patients have relapsed or died. **Conclusions:** In patients with relapsed refractory AL Teclistamab showed impressive hematologic activity and manageable side effects. A strong case exists for investigating Teclistamab prospectively in this population. Research Sponsor: None.

Baseline characteristics and response.

Patient	iFLC	Cytogenetics	BM Plasma cells	Cardiac stage	Renal stage	Organs involved	Prior lines of therapies	Best Hematological response	Organ response
1 (78M)	313 (λ)	gain 1q, trisomy 9, 15, 19, 21	3-5%	1	1	Tongue Soft Tissue	3	CR	Not Evaluable
2 (81F)	23.1 (λ)	t(11:14)	12.4%	3a	2	Heart Kidney	4	CR	No Response
3 (72F)	59.6 (λ)	Low risk	10%	2	1	GI Heart	7	CR	Cardiac Response
4 (78M	114 (κ)	Normal	3-5%	3a	2	Heart Kidney	10	CR	No Response
5 (68)	35.1 (λ)	Normal	30-40%	3a	2	Heart Kidney	3	VGPR	No Response
6 (65F)	69 (κ)	t(11:14), del(17p)	3-5%	3b	2	Peripheral Nervous System Heart Kidney	4	CR	No Response
7 (69M)	228 (λ)	Normal	7%	3a	1	Heart	4	CR	No Response
8 (69f)	42.4 (λ)	gain 1q, trisomy 9, del17p	10%	2	2	Heart Kidney	4	CR	Renal Response

TPS7563 **Poster Session**

QUINTESSENTIAL: A multicenter phase 2 study evaluating the efficacy and safety of arlocabtagene autoleucel (arlo-cel) in triple- and quad-class exposed patients with relapsed or refractory multiple myeloma (RRMM). First Author: Krina K. Patel, Department of Lymphoma and Myeloma, The University of Texas MD Anderson Cancer Center, Houston, TX

Background: There are limited treatment options for patients (pts) with RRMM who are triple-class exposed (TCEx: immunomodulatory drugs [IMiD], anti-CD38 antibodies [aCD38], and proteasome inhibitors [PI]) and quad-class exposed (QCEx: IMiD, aCD38, PI, and B-cell maturation antigen [BCMA]-targeted therapy). To address this unmet need, new treatment options are needed for late-line populations, which will continue to grow with more QCEx pts due to the approval of BCMA-targeted therapies in earlier lines. G protein-coupled receptor class C group 5 member D (GPRC5D) is an orphan receptor expressed on plasma cells, with limited expression elsewhere, making it a promising therapeutic target for MM. Data from a phase 1 first-in-human study (NCT04674813) suggested that arlo-cel, a GPRC5D-directed autologous chimeric antigen receptor (CAR) T-cell therapy, is safe and efficacious in pts with TCEx RRMM, including pts who received prior BCMA-targeted therapy. At the recommended phase 2 dose (RP2D) of 150×10^6 CAR T cells, overall response rate (ORR) was 91% (21/23), median progression-free survival (PFS) was 18.3 months, and median overall survival (OS) was not reached in those with ≥3 prior lines of therapy (LOT) (Bal S et al. ASH 2024. Abstract 922). Here, we present the study design of QUINTESSENTIAL, an open-label, multicenter, phase 2 study (NCT06297226) evaluating arlo-cel in pts with TCEx and QCEx RRMM. **Methods:** For analyses, enrollment is planned at ~138 pts with ~125 pts receiving therapy. Key inclusion criteria include age ≥18 years, confirmed diagnosis of MM as per IMWG criteria, ≥3 classes of MM treatment (including IMiD, PI, and anti-CD38), and ≥3 prior LOT. Pts must also have documented disease progression (PD) during or after the most recent regimen as per IMWG, measurable disease, and an ECOG performance status of 0 or 1. Pts who previously received a GPRC5D-targeted therapy are excluded. After screening, pts will undergo leukapheresis followed by bridging therapy. Pts will then receive lymphodepleting chemotherapy followed by a single infusion of arlo-cel at the RP2D of 150×10^6 CAR T cells (range: $120–180 \times 10^6$). The primary endpoint is ORR by IMWG response criteria per an independent review committee in pts who are QCEx and received ≥4 prior LOT. Key secondary endpoints are ORR and complete response rate in all pts. Other secondary and exploratory endpoints include time to response, duration of response, PFS, OS, minimal residual disease-negative status, and safety. Pts will be followed for ≤5 years after the last pt receives arlo-cel, with a subsequent long-term follow-up study continuing for ≤15 years. This study will recruit at 47 centers across the USA, Canada, and Japan. The first pt first visit was achieved on March 21, 2024. Clinical trial information: NCT06297226. Research Sponsor: Juno Therapeutics, Inc., a Bristol-Myers Squibb Company.

TPS7564 **Poster Session**

QUINTESSENTIAL-2: A phase 3 study comparing efficacy and safety of arlocabtagene autoleucel (arlo-cel) versus standard regimens in adult patients with relapsed or refractory multiple myeloma (RRMM) refractory to lenalidomide. First Author: Rakesh Popat, University College London Hospitals NHS Foundation Trust, London, United Kingdom

Background: Despite advances in MM treatment, nearly all patients (pts) will relapse, highlighting the need for new drug classes to improve outcomes in RRMM. Further, MM refractory to lenalidomide, an immunomodulatory drug (IMiD) used in frontline and maintenance therapies, poses an additional challenge as the disease is less likely to respond to subsequent treatment. G protein-coupled receptor class C group 5 member D (GPRC5D) is a promising therapeutic target for MM as the receptor is highly expressed on malignant plasma cells; it has little to no expression on non-plasma immune cells and limited expression elsewhere. Arlo-cel is a GPRC5D-directed autologous CAR T-cell therapy that has demonstrated safety and efficacy in patients with RRMM in a first-in-human ph1 study. Following a single infusion of arlo-cel at the recommended ph2 dose (RP2D) of 150×10^6 CAR T cells, overall response rate (ORR) was 96% (23/24) and 91% (21/23) in those with 1-3 and ≥3 prior lines of therapy (pLOT), respectively (Bal S, et al. ASH 2024. Abstracts 2069 and 922). Here we present the design of the QUINTESSENTIAL-2 study. **Methods:** QUINTESSENTIAL-2 (NCT06615479) is a randomized, open-label, multicenter, ph3 confirmatory study comparing the efficacy and safety of arlo-cel versus standard of care (SOC) in adults with RRMM. Pts aged ≥18 y must have received 1-3 pLOT (may include a proteasome inhibitor, IMiD, and anti-CD38 monoclonal antibody) and be refractory to lenalidomide (progression on or within 60 days of completing therapy). Additional inclusion criteria include confirmed MM diagnosis per International Myeloma Working Group criteria, measurable disease during screening, and Eastern Cooperative Oncology Group performance status 0 or 1. Eligible pts will be randomized 1:1 to one of 2 treatment arms. Arm A: single infusion of arlo-cel (RP2D of 150×10^6 CAR T cells), including leukapheresis within 3 days of randomization, bridging therapy of DPd (daratumumab, pomalidomide, dexamethasone) or Kd (carfilzomib, dexamethasone) per Investigator within 3 days of leukapheresis, and lymphodepleting chemotherapy prior to arlo-cel infusion. Arm B: SOC of DPd or Kd per Investigator, dosed per labeling. Primary endpoints are progression-free survival and minimal residual disease (MRD) negativity in complete response. Secondary endpoints include overall survival, ORR, MRD negative status, complete response rate, time to response, duration of response, pharmacokinetics, patient-reported quality of life outcomes, and safety. Pts will be followed for ≤5 years after the last patient is randomized, with a subsequent long-term follow-up study (≤15 years post infusion) for pts receiving arlo-cel. The trial is expected to enroll 440 pts across 111 sites globally, with first patient enrollment planned for Feb 2025. Clinical trial information: NCT06615479. Research Sponsor: Juno Therapeutics, Inc., a Bristol-Myers Squibb Company.

TPS7565 **Poster Session**

Prophylactic interventions for oral toxicities with the GPRC5D×CD3 bispecific antibody talquetamab in relapsed/refractory multiple myeloma: An update on the open-label, phase 2, randomized TALISMAN study. First Author: Rakesh Popat, University College London Hospitals NHS Foundation Trust, London, United Kingdom

Background: Talquetamab (Tal) is the first GPRC5D×CD3 bispecific antibody approved for the treatment of relapsed/refractory multiple myeloma (RRMM). Early onset oral toxicities, including dysgeusia, have been reported with Tal and can impact patient (pt) quality of life. Current CTCAE grading limits detailed assessment of dysgeusia. We provide an update on the TALISMAN study (NCT06500884), which investigates prophylactic interventions for GPRC5D-related oral toxicities using objective and subjective assessment tools that may establish a standard to measure taste changes and mitigation strategies in future studies with MM pts. **Methods:** This phase 2, multicenter, open-label, randomized study is enrolling pts aged ≥18 years with RRMM and prior exposure to a proteasome inhibitor, immunomodulatory drug, and anti-CD38 antibody; prior anti-GPRC5D therapy is not permitted. Pts must have an ECOG PS of 0/1 (ECOG PS of 2/3 permitted once physical limitations are stable) and cannot have a "severe" score for dysgeusia per the Waterless Empirical Taste Test (WETT) scale. Pts are randomized to 1 of 4 cohorts: 1 control cohort (Tal only) and 3 experimental cohorts (Tal plus an experimental prophylaxis). The experimental prophylaxes are dexamethasone mouthwash (0.5 mg/5 mL twice daily [BID]), oral pregabalin (50 mg BID), or clonazepam orally dissolving tablets (0.25 mg BID). Pts take their prophylaxis 7 days before the first step-up dose (cycle 1 day 1) of Tal (3 step-up doses followed by 0.8 mg/kg every other week). A dose reduction to every 4 weeks is permitted if a ≥VGPR or ≥PR is achieved at cycle 5 or 7, respectively. Study assessments and procedures include taste assessment using WETT strips; smell assessment using the University of Pennsylvania Smell Identification Test and threshold testing; pt-reported outcomes (PROs, including PRO-CTCAE); optional tongue and/or salivary gland biopsies (at selected sites); microbiome analysis via tongue swab (control cohort only); and salivary flow and salivary-specific protein content assessments. The 4 co-primary endpoints are the rate of occurrence of dysgeusia, rate of occurrence of severe dysgeusia, time to first onset of severe dysgeusia, and rate of resolution/improvement of dysgeusia at 3 and 6 months, as defined by the WETT score. Key secondary endpoints include changes from baseline in WETT score, body weight, and smell identification and smell detection threshold test scores over time; characterization of the safety and efficacy of Tal; change from baseline in PRO (including impacts of oral toxicities) assessments; and frequency of dose modifications. Enrollment opened in August 2024 for these 4 cohorts and target enrollment is 70–130 pts across 6 countries, with the potential to open additional cohorts. Clinical trial information: NCT06500884. Research Sponsor: None.

TPS7566 **Poster Session**

MagnetisMM-30: A phase 1b, open-label study of elranatamab in combination with iberdomide in patients with relapsed or refractory multiple myeloma (RRMM). First Author: Alexander M. Lesokhin, Memorial Sloan Kettering Cancer Center, New York, NY

Background: Elranatamab (ELRA), a BCMA–CD3 bispecific antibody, induced deep and durable responses with a manageable safety profile as a single agent in patients (pts) with RRMM enrolled in the phase 2 registrational MagnetisMM-3 study (Lesokhin et al, *Nat Med* 2023). Iberdomide (IBER) is a novel CELMoD agent that enhances antimyeloma tumoricidal and immunomodulatory activity in pts with RRMM (Lonial et al, *Lancet Haematol* 2022). While IBER in combination with ELRA has not been evaluated clinically, it may provide additional benefit to pts with RRMM based on the mechanisms of action of this novel combination. **Methods:** MagnetisMM-30 (NCT06215118) is a phase 1b, open-label, prospective study evaluating the safety, efficacy, and pharmacokinetics of ELRA in combination with IBER in pts with RRMM. The study has 2 parts: Part 1 guided by BOIN for dose-escalation and Part 2, randomized for dose optimization. In Part 1, after 2 step-up priming doses of subcutaneous (SC) ELRA followed by 1 full dose, pts will receive SC ELRA at dose level (DL) 1 or DL2 in 28-day cycles. IBER will be given daily for 21 days of each cycle. In DL1, pts will receive ELRA weekly followed by every 2 weeks (Q2W) and finally Q4W. In DL2, pts will receive ELRA Q2W followed by Q4W, with a higher IBER dose. If DL1 or DL2 is not tolerated, IBER dosing will be lowered (DL-1 and DL-2). Once 2 combination dose levels are selected from Part 1 as the recommended doses for expansion for ELRA and IBER, pts in Part 2 will be randomized 1:1 (stratified by the number of prior lines of therapy [LOTs; 1 vs >1]) to dose levels A or B. Key inclusion criteria are pts aged ≥18 years with a MM diagnosis per IMWG criteria, Eastern Cooperative Oncology Group performance status of 0-1, adequate organ and bone marrow function, and disease relapsed or refractory to the last antimyeloma regimen per IMWG response criteria. Pts who received 2-4 or 1-3 prior LOTs, including ≥1 immunomodulatory drug (IMiD) and ≥1 proteasome inhibitor (PI), are eligible for Parts 1 and 2, respectively. All pts must have received ≥2 consecutive cycles of an IMiD-containing regimen and ≥2 consecutive cycles of a PI or PI-containing regimen. Key exclusion criteria are pts with stem cell transplant ≤12 weeks prior to enrollment; active, uncontrolled infection; prior treatment with BCMA-directed or CD3 redirecting therapy or prior CELMoD agents (ie, IBER or mezigdomide). Primary endpoints are dose-limiting toxicities during the first cycle of treatment (Part 1) and AEs and lab abnormalities (Part 2). Secondary endpoints include AEs and lab abnormalities (Part 1 only), ORR, CRR, time-to-event outcomes, pharmacokinetics, minimal residual disease negativity rate, and immunogenicity. This study is ongoing; Part 1 and Part 2 will enroll up to approximately 36 and 60 pts, respectively. Clinical trial information: NCT06215118. Research Sponsor: Pfizer.

TPS7567 **Poster Session**

Design of the phase 3 DREAMM-10 study: Belantamab mafodotin plus lenalidomide and dexamethasone (BRd) vs daratumumab plus lenalidomide and dexamethasone (DRd) in transplant-ineligible, newly diagnosed multiple myeloma (TI-NDMM). First Author: Sagar Lonial, Winship Cancer Institute, Emory University Hospital, Atlanta, GA

Background: Treatment options have advanced for patients (pts) with TI-NDMM, but outcomes remain worse compared to pts with transplant-eligible NDMM, indicating a need for novel therapies to improve the prognosis of TI-NDMM. Belantamab mafodotin is an antibody-drug conjugate targeting B-cell maturation antigen. Phase 3 studies have shown significant survival benefits with belantamab mafodotin in combination regimens vs standard of care combinations for relapsed/refractory MM [1–3], and preliminary data have shown promising clinical activity with belantamab mafodotin combination regimens, including BRd, for TI-NDMM [4,5]. The design of the DREAMM-10 study, investigating BRd vs DRd in pts with TI-NDMM, is presented here. **Methods:** DREAMM-10 (NCT06679101) is a randomized, phase 3, open-label, multicenter study. Pts aged ≥18 years with TI-NDMM, measurable disease, and Eastern Cooperative Oncology Group performance status 0–2 are eligible. Specific reasons for transplant ineligibility will be collected. Pts who were previously treated for MM or smoldering MM are excluded. Approximately 520 eligible pts will be randomized 1:1 to BRd or DRd, stratified by age (<75, ≥75 years), International Staging System (I, II, III), and region (North America, rest of world). Belantamab mafodotin will be administered intravenously at 1.9 mg/kg every 8 weeks for 24 weeks, then 1.9 mg/kg every 12 weeks thereafter. Daratumumab will be administered subcutaneously using the approved dose and schedule. In both treatment arms, lenalidomide will be administered orally at 25 mg on Days 1–21, and dexamethasone will be administered orally at 40 mg on Days 1, 8, 15, and 22 of every 28-day cycle. Pts will be treated until disease progression, death, unacceptable toxicity, consent withdrawal, or end of study. The dual primary endpoints are progression-free survival (PFS) and minimal residual disease negativity rate. Key secondary endpoints are overall survival and PFS2 (time from randomization to progression on first subsequent anti-myeloma therapy or death). The statistical plan includes multiplicity adjustment for primary endpoints and hierarchical testing for key secondary endpoints. Other efficacy endpoints, safety (adverse events [AEs]/serious AEs), and health-related quality of life will also be assessed. The study opened for enrollment on December 30, 2024. 1. Hungria V, et al. *N Engl J Med* 2024. 2. Dimopoulos MA, et al. *N Engl J Med* 2024. 3. https://us.gsk.com/media/11819/belamaf-dreamm-7-os-full-data-press-release_final_us-version-08dec24.pdf. 4. Terpos E, et al. *Haematologica* 2024. 5. Usmani SZ, et al. *Blood* 2024;144(Suppl 1):497. Clinical trial information: NCT06679101. Research Sponsor: GSK (214828); drug linker technology licensed from Seagen; monoclonal antibody produced using POTELLIGENT Technology licensed from BioWa.

TPS7568 **Poster Session**

MagnetisMM-32: A phase 3 randomized study of elranatamab vs EPd, PVd, or Kd in patients with relapsed or refractory multiple myeloma (RRMM) and prior anti-CD38–directed therapy. First Author: Steven Robert Schuster, UCHealth Cancer Care and Hematology, Fort Collins, CO

Background: Elranatamab (ELRA), a BCMA-CD3 bispecific antibody, has shown efficacy and manageable safety as a monotherapy in patients with RRMM. This study will evaluate ELRA monotherapy vs elotuzumab-pomalidomide-dexamethasone (EPd), pomalidomide-bortezomib-dexamethasone (PVd), or carfilzomib-dexamethasone (Kd) in patients with RRMM to determine whether ELRA can provide superior clinical benefit in early relapse (2L+). **Methods:** MagnetisMM-32 (NCT06152575), a phase 3, open-label, multicenter, randomized study, will enroll ≈492 patients. Patients will receive ELRA (Arm A) or investigator's choice of EPd, PVd or Kd (Arm B), until disease progression, unacceptable toxicity, withdrawal of consent, loss to follow-up, or study termination. Patients treated with ELRA will receive 2 step-up priming doses followed by weekly doses and subsequently less frequent doses in 28-day cycles. Patients will be randomized 1:1 (stratified by prior line of therapy [1 vs 2 vs 3/4] and International Staging System disease stage [1/2 vs 3]). Key inclusion criteria include age of ≥18 years, prior multiple myeloma diagnosis with measurable disease (per IMWG criteria), evidence of progressive disease or failure to achieve a response to last line of multiple myeloma therapy, 1 to 4 prior lines of therapy including an anti–CD38 antibody–containing regimen (for ≥2 consecutive cycles) and a lenalidomide-containing regimen (for ≥2 consecutive cycles), adequate bone marrow function, and an ECOG performance status of ≤2. Key exclusion criteria include stem cell transplant ≤12 weeks prior to enrollment or active graft vs host disease; active, uncontrolled infection; any other active malignancy <3 yrs prior to enrollment; ongoing grade ≥3 peripheral sensory or motor neuropathy; history of any grade ≥3 peripheral motor polyneuropathy, prior BCMA-directed or CD3-redirecting therapy; never achieved ≥PR with any treatment during disease course; and unable to receive any of the Arm B regimens (EPd, PVd, or Kd). The primary and key secondary endpoints are progression-free survival (PFS) by blinded independent central review (BICR) per IMWG criteria and overall survival (OS), respectively. Other secondary endpoints include PFS and PFS2 (PFS on next line of therapy) by investigator per IMWG, objective response rate, duration of response, very good partial response rate, complete response rate, duration of complete response, and time to response (all by BICR per IMWG), MRD negativity rate (including sustained for ≥12 months) and duration, safety and pharmacokinetics of ELRA, immunogenicity, and health-related quality of life outcomes. The primary endpoint and OS will be compared statistically between treatment arms by stratified log-rank tests. Study funding: Pfizer. Clinical trial information: NCT06152575. Research Sponsor: Pfizer.

LBA8000 Oral Abstract Session

Overall survival with neoadjuvant nivolumab (NIVO) + chemotherapy (chemo) in patients with resectable NSCLC in CheckMate 816. First Author: Patrick M. Forde, Trinity St. James's Cancer Institute, Trinity College Dublin, Dublin, Ireland

The full, final text of this abstract will be available at meetings.asco.org on the day of presentation and in the online supplement to the June 10, 2025, issue of the *Journal of Clinical Oncology*.

8001 Oral Abstract Session

Neoadjuvant (neoadj) osimertinib (osi) ± chemotherapy (CT) vs CT alone in resectable (R) epidermal growth factor receptor-mutated (EGFRm) NSCLC: NeoADAURA. First Author: Jamie E. Chaft, Thoracic Oncology Service, Memorial Sloan Kettering Cancer Center, New York, NY; Department of Medicine, Weill Cornell Medical College, New York, NY

Background: Based on the Ph 3 ADAURA study, adjuvant (adj) treatment (Tx) with osi, a 3rd-generation, EGFR-TKI, is SoC for resected EGFRm stage (stg) IB–IIIA NSCLC (AJCC 7th ed). Neoadj Tx may improve surgical and long-term outcomes. NeoADAURA (NCT04351555) is a global, Ph 3, randomized, controlled, 3-arm study assessing outcomes with neoadj osi ± CT vs CT alone, in EGFRm R-NSCLC. **Methods:** Eligible pts: aged ≥18 yrs; WHO PS ≤1; EGFRm (Ex19del/L858R) stg II–IIIB (AJCC 8th ed) R-NSCLC. Pts were stratified (stg II vs III; non-Asian vs Chinese vs other Asian; Ex19del vs L858R) and randomized 1:1:1 to neoadj osi 80 mg QD (≥9 wks) + CT (cis/carboplatin + pemetrexed; 3 cycles, Q3W), osi monotherapy (mono) 80 mg QD (≥9 wks) or placebo (PBO) QD + CT (3 cycles, Q3W). Osi/PBO + CT: double blind; osi mono: open label, sponsor blind. Adj osi was offered to all pts who completed surgery (Sx). Primary endpoint: major pathological response (MPR) by blinded central pathology review. Secondary endpoints included pathological complete response (pCR), event-free survival (EFS), and safety. Data cut-off: Oct 15, 2024. **Results:** Overall, 358 pts were randomized: osi + CT n=121/osi mono n=117/PBO + CT n=120; baseline characteristics were generally balanced across the respective arms (stg II: 49%/50%/51%; non-Asian: 27%/26%/25%; Ex19del: 50%/51%/51%). After neoadj Tx, 92%/97%/89% of pts underwent Sx in the osi + CT/osi mono/PBO + CT arms. Osi + CT (MPR rate 26%) and osi mono (25%) showed statistically significant improvement in MPR vs PBO + CT (2%): odds ratios were 19.8 ($p<0.0001$) and 19.3 ($p<0.0001$), respectively. Interim EFS (15% maturity) trended in favor of osi + CT and osi mono vs PBO + CT (Table); ≥80% of pts in each arm received adj osi. In the neoadj period, grade ≥3 all-cause AEs and AEs leading to discontinuation of any Tx occurred in 36%/13%/33% and 9%/3%/5% of pts, respectively, for osi + CT/osi mono/PBO + CT. No pts died within 30 days of Sx. **Conclusions:** Neoadj osi with or without CT showed statistically significant improvement in the MPR rate over CT alone. EFS data were immature and trended in favor of the osi containing arms. There were no new safety concerns. Neoadj osi ± CT should be considered when planning Tx for pts with EGFRm stg II–IIIB R-NSCLC. Clinical trial information: NCT04351555. Research Sponsor: AstraZeneca.

	Osi + CT (n=121)	Osi mono (n=117)	PBO + CT (n=120)
MPR rate, % (95% CI)	26 (18, 34)	25 (17, 34)	2 (<1, 6)
Difference vs PBO + CT, % (95% CI)	24 (15, 32)	23 (15, 32)	–
Odds ratio vs PBO + CT (adjusted 100×[1−alpha]% CI) p-value	19.8 (4.6, 85.3[a]) <0.0001	19.3 (1.7, 217.4[b]) <0.0001	– –
pCR rate, % (95% CI)	4 (1, 9)	9 (4, 15)	0 (0, 3)
12-mo EFS rate, % (95% CI)	93 (87, 97)	95 (89, 98)	83 (75, 89)
EFS hazard ratio vs PBO + CT (CI)	0.50 (0.17, 1.41[c])	0.73 (0.40, 1.35[d])	–
p-value	0.0382[e]	–	–
Median EFS follow-up, mos (range)[f]	16 (0–42)	18 (2–42)	19 (2–42)

[a]95.002% CI; [b]99.9% CI; [c]99.8% CI; [d]95% CI; [e]p-value ≤0.002 required for statistical significance at interim analysis; [f]censored pts.

8002 Oral Abstract Session

Lung cancer diagnosis rates (LCDR) in lung cancer screening (LCS) and incidental pulmonary nodule (IPN) cohorts in the Mississippi Delta. First Author: Wei Liao, Baptist Cancer Center, Multidisciplinary Thoracic Oncology Program, Memphis, TN

Background: The LCDR in the CT screened cohort in the National Lung Screening Trial (NLST) was 1.1% over a median of 6.5 years follow up. We evaluated the LCDR in a regional US community. **Methods:** Prospective cohort study of patients in LCS and IPN programs in 22 facilities across a 125 county service area population. We compared LCDR over 3 years in LCS stratified by Lung-RADS (L-R) score (1 to 4X), IPN by nodule size (≤6, >6-15, >15-20, >20-30 mm) on initial CT scans. Comparisons used Chi-square tests, Wilcoxon tests, and Cox regression models with Hazard Ratios (HR) for lung cancer diagnosis adjusted for age, sex, race, and insurance. **Results:** From 2015 to 2023, 7121 persons were enrolled in LCS – 5447 (76%) L-R 1/2, 823 (12%) L-R 3, 452 (6%) L-R 4A, 205(3%) L-R 4B, and 114(2%) L-R 4X; and 22,455 in IPN - 8141 (36%) ≤6mm, 11177 (50%) >6-15 mm, 1596 (7%) >15-20 mm, 1535 (7%) >20-30 mm. Over this period, 334 (4.7%) and 1016 (4.5%) were diagnosed with lung cancer in LCS and IPN cohorts, respectively, including 91 (2%), 40 (5%), 60 (13%), 68 (33%), and 66 (58%) L-R 1-4X and 69 (1%), 421 (4%), 224 (14%) and 302 (20%) of IPN cohort in ascending order of nodule size. The cumulative LCDR at 36 months were: 5% (95% CI 4.4 – 5.6) in LCS- 1.9% (1.5-2.4), 5.0% (3.4-7.0), 14%(10-18), 33%(27-40), and 60% (49-68) for L-R 1 to 4X, respectively; and 4.4% (4.1 – 4.7)- 0.66% (0.49-0.88), 3.5% (3.2-3.9), 14% (12-16) and 20% (18-22) for the respective IPN cohorts. With L-R 1/2 as reference, aHR for lung cancer diagnosis was 2.9 (2.0 - 4.1, $p<0.0001$), 7.6 (5.4 - 10.6, $p<0.0001$), 24.1 (17.4 - 33.4, $p<0.0001$), and 66.3 (47.7 - 92.3, $p<0.0001$) for L-R 3, 4A, 4B & 4X in LCS cohort. With nodule >6-15 as reference, aHR was 0.2 (0.2 - 0.3, $p<0.0001$), 4.2(3.6 - 4.9, $p<0.0001$) and 5.7 (4.9 - 6.7, $p<0.0001$) in IPN cohort. **Conclusions:** LCDR of this Mississippi Delta LCS and IPN cohort was greater than 4-fold the NLST. The NLST significantly underestimates the potential impact of LCS in this population. Research Sponsor: Baptist Memorial Health Care Foundation; 15BD03.

	LCS						IPN				
	1-2 N = 5447	3 N = 823	4A N = 452	4B N = 205	4X N = 114	P	0-6mm N = 8147	6-15 N = 11177	15-20 N = 1596	20-30 N = 1535	P
Lung Cancer*	91 (2)	40 (5)	60 (13)	68 (33)	66 (58)	<0.0001	69(1)	421(4)	224 (14)	302(20)	<0.0001
Age Median (Q1 - Q3)	65 (60-70)	65 (60-70)	67 (61-71)	67 (63-73)	67 (63-72)	<0.0001	62(51-72)	64 (52-74)	66 (53-75)	68 (57-77)	<0.0001
Female*	2795 (51)	400 (49)	218 (48)	107 (52)	57 (50)	0.4709	4777(59)	6191 (55)	884 (55)	788 (51)	0.0005
Black*	1005 (19)	157 (19)	87 (19)	37 (18)	25 (22)	0.972	2376(29)	3126 (28)	479 (30)	443 (29)	0.0713
Commercial insurance*	2168 (40)	297 (36)	142 (31)	58 (28)	30 (26)	0.0005	3612(44)	4544 (41)	596 (37)	515 (34)	0.0005
Never smoked*	13 (0.2)	3 (0.4)	0	0	0	0.4628	3662(45)	4537 (41)	549 (34)	474 (31)	0.0005
Adenocarcinoma**	31 (34)	15 (38)	29 (48)	31 (46)	44 (67)	0.075	24(35)	222 (53)	130 (58)	164 (54)	0.0235
Clinical stage I/II**	58 (64)	26 (65)	48 (80)	49 (72)	40 (61)	0.3168	29(42)	255 (61)	141 (63)	183 (61)	0.14

*N (%).
**Denominator is # of lung cancer patients.

8003 Oral Abstract Session

SWOG/NRG S1914: Randomized phase III trial of induction/consolidation atezolizumab + SBRT versus SBRT alone in high risk, early-stage NSCLC. First Author: Charles B. Simone II, New York Proton Center and Memorial Sloan Kettering Cancer Center, New York City, NY

Background: Stereotactic body radiation therapy (SBRT) is the standard of care (SoC) for early stage, medically inoperable non-small cell lung cancer (NSCLC). While rates of in-field control exceed 90%, regional and distant control after SBRT remain suboptimal. A prior phase II randomized trial suggested a benefit to adding immunotherapy (PMID 37478883). SWOG/NRG S1914 (NCT#04214262) is a randomized phase III trial evaluating neoadjuvant, concurrent and adjuvant atezolizumab plus SBRT for early-stage NSCLC vs SoC. **Methods:** Eligible patients (pts) had T1-3N0M0 NSCLC ≤7cm, were medically inoperable or declined surgery, and had ≥1 risk factor for increased recurrence: tumor diameter ≥2 cm, ≥6.2, moderately/poorly/undifferentiated histology. Randomization was to SoC SBRT (S [3-8 fractions, biologically effective dose ≥100 Gy]) or neoadjuvant, concurrent and adjuvant atezolizumab (AS [1200 mg IV Q3 week, 8 cycles]) with SBRT initiated with cycle 3, stratifying by tumor location (central vs peripheral), size (<4 cm vs ≥4cm) and ECOG performance status (PS, 0-1 vs 2). The primary objective was to compare overall survival (OS) between the arms. Secondary objectives included comparisons of progression free survival (PFS), failure patterns, toxicity and quality of life (QoL). OS and PFS were compared using a 1-sided stratified log-rank test at the 2.5% level, confidence intervals (CI) are 95%. The accrual goal was 432 eligible pts. **Results:** From 8/13/20 - 9/6/24, 417 pts were randomized, 403 met eligibility [201 to S, 202 to AS]. Accrual closed at the first interim analysis for futility based on OS and PFS per design. Median follow-up for pts still alive was 12 (range: 0.03-49) months. Median age was 73 (41-91) years and 89% had PS 0-1. Median tumor diameter was 2.3 cm. No protocol treatment was received for 6 pts on S and 8 on AS. With 49 deaths, OS was not different between the arms (HR (CI): 1.15(0.65-2.01), p=0.63; 2-year OS: 82% S vs 80% AS). With 88 events, PFS was not better with AS (HR (CI): 1.35(0.89-2.06), p=0.16); 2-year PFS was 71% on S vs 60% on AS. Regional (2% vs 3%) and distant (4% vs 5%) failures were not different; there were more local failures with AS (13% vs 7%). Among former (53%)/never (3%) smokers, AS had worse OS and PFS than S (HR(CI): 2.50 (1.11-5.59), p=0.03); HR(CI): 2.16(1.15-4.04), p=0.01), respectively. Grade (G) ≥3 adverse event (AE) rates were 12% on AS (N=21 G3, 1 G4, 1 G5 respiratory failure) vs 2% on S (N=3 G3, 1 G4). **Conclusions:** In the first reported phase III trial to assess immunotherapy (IO) added to SBRT in early-stage NSCLC, IO failed to improve survival. More G ≥3 adverse events were reported with AS. Central review of local recurrence events is ongoing. Additional investigation into subgroups, PD-L1 status, QoL and blood/tissue are pending to determine whether there are subsets who can benefit from this combination and shed further insights into these findings. Clinical trial information: NCT04214262. Research Sponsor: NIH/NCI grants U10CA180888, U10CA180819, U10CA180820, U10CA180821, U10CA180868; Genentech Pharmaceutical/Biotech Company.

LBA8004 **Oral Abstract Session**

R-ALPS: A randomized, double-blind, placebo-controlled, multicenter phase III clinical trial of TQB2450 with or without anlotinib as maintenance treatment in patients with locally advanced and unresectable (stage III) NSCLC without progression following concurrent or sequential chemoradiotherapy. First Author: Ming Chen, State Key Laboratory of Oncology in South China, Sun Yat-sen University Cancer Center, Guangzhou, China

LBA8005 **Oral Abstract Session**

Randomized phase II trial investigating whether atezolizumab after chemoradiotherapy (CRT) prolongs survival in limited stage (LS) small cell lung cancer (SCLC). First Author: Bjorn Henning Gronberg, Department of Clinical and Molecular Medicine, NTNU, Norwegian University of Science and Technology and Department of Oncology, St. Olavs Hospital, Trondheim, Norway

The full, final text of this abstract will be available at meetings.asco.org on the day of presentation and in the online supplement to the June 10, 2025, issue of the *Journal of Clinical Oncology*.

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8006 **Oral Abstract Session**

Lurbinectedin (lurbi) + atezolizumab (atezo) as first-line (1L) maintenance treatment (tx) in patients (pts) with extensive-stage small cell lung cancer (ES-SCLC): Primary results of the phase 3 IMforte trial. First Author: Luis G. Paz-Ares, Hospital Universitario 12 de Octubre, H12O-CNIO Lung Cancer Unit, Universidad Complutense and Ciberonc, Madrid, Spain

Background: Despite improved efficacy when adding 1L PD-(L)1 inhibitors to platinum-based chemotherapy for ES-SCLC, long-term survival remains limited. We report primary results from the global open-label, randomized, Phase 3 IMforte study (NCT05091567) of 1L maintenance tx with lurbi + atezo vs atezo in pts with ES-SCLC. **Methods:** Tx-naive pts with ES-SCLC received standard induction tx with atezo, carboplatin, and etoposide for four 21-day cycles (q3w). After induction, eligible pts without disease progression (PD) were randomized 1:1 to receive maintenance tx q3w with lurbi (3.2 mg/m^2 IV; with G-CSF prophylaxis) + atezo (1200 mg IV) or atezo alone until PD, unacceptable toxicity, or withdrawal. Pts were stratified by liver metastases at induction baseline (BL; yes/no), receipt of prophylactic cranial irradiation before randomization (yes/no), ECOG PS (0/1) and LDH ($\leq$ULN/ $>$ ULN) at maintenance BL. Crossover was not allowed. Primary endpoints were independent review facility (IRF)–assessed PFS per RECIST v1.1 and OS assessed from randomization into the maintenance phase. **Results:** Of 660 enrolled pts, 483 were randomized to receive lurbi + atezo (n = 242) or atezo (n = 241). BL characteristics were generally balanced between arms. With a median 15.0-mo follow-up (data cutoff: Jul 29, 2024), IRF-PFS was significantly improved with lurbi + atezo vs atezo (stratified HR, 0.54 [95% CI: 0.43, 0.67]; $P<$ 0.0001; Table). A significant OS benefit was seen with lurbi + atezo vs atezo (stratified HR, 0.73 [95% CI: 0.57, 0.95]; $P=$ 0.0174). Median maintenance tx duration was 4.1 mo with lurbi and 4.2 mo with atezo in the lurbi + atezo arm (n = 242) and 2.1 mo in the atezo arm (n = 240). In the lurbi + atezo and atezo arms, respectively, treatment-related AEs (TRAEs) occurred in 83.5% vs 40.0% of pts, G3/4 TRAEs in 25.6% vs 5.8% and G5 TRAEs in 0.8% (2 pts; sepsis, febrile neutropenia) vs 0.4% (1 pt; sepsis); AEs led to tx discontinuation in 6.2% vs 3.3%. **Conclusions:** IMforte met both primary endpoints of IRF-PFS and OS, demonstrating a clinically meaningful benefit with 1L maintenance tx with lurbi + atezo vs atezo in pts with ES-SCLC. Lurbi + atezo was generally well tolerated, with no new or unexpected safety signals. IMforte is the first global Phase 3 study to show PFS and OS improvement with 1L maintenance tx for ES-SCLC and supports maintenance lurbi + atezo as a new option for pts with this aggressive disease. Clinical trial information: NCT05091567. Research Sponsor: Genentech, Inc.

Efficacy from randomization into maintenance phase	Lurbi + atezo (n=242)	Atezo(n=241)
IRF-PFS		
Event, n (%)	174 (71.9)	202 (83.8)
Median (95% CI), mo	5.4 (4.2, 5.8)	2.1 (1.6, 2.7)
Stratified HR (95% CI)	0.54 (0.43, 0.67); $P<0.0001$[a]; $\alpha=0.001$[b]	
OS		
Event, n (%)	113 (46.7)	136 (56.4)
Median (95% CI), mo	13.2 (11.9, 16.4)	10.6 (9.5, 12.2)
Stratified HR (95% CI)	0.73 (0.57, 0.95); $P=0.0174$[a]; $\alpha=0.0313$[b]	

[a]Stratified log-rank.
[b]2-sided boundary.

8007 **Oral Abstract Session**

A phase 2 dose expansion study of ZG006, a trispecific T cell engager targeting CD3/DLL3/DLL3, as monotherapy in patients with advanced small cell lung cancer. First Author: Xinghao Ai, Shanghai Chest Hospital, Shanghai, China

Background: ZG006 is a trispecific T cell engager (Tri-TE) targeting Delta-like ligand 3 (DLL3) and CD3, designed to bridge tumor cells and T cells by binding to two distinct DLL3 epitopes on tumor cells and CD3 on T cells, thereby mediating T cell-specific killing of DLL3-expressing tumor cells such as small cell lung cancer (SCLC). Here, we report the results from the phase 2 dose expansion study of ZG006 for the treatment of patients (pts) with advanced SCLC. **Methods:** This is a randomization, multi-center, open-label phase 2 study of ZG006 as monotherapy in SCLC pts failed to at least 2 prior lines of standard systemic treatments. Based on ZG006 phase 1 study results, both 10 mg and 30 mg Q2W dose levels with a priming dose of 1 mg are being evaluated in this phase 2 dose optimization study, 60 pts are to be randomized at a ratio of 1:1 to receive ZG006. The primary endpoint was objective response rate (ORR) according to RECIST1.1. DLL3 expression was not required but retrospectively evaluated by IHC. **Results:** As of Dec. 31, 2024, a total of 40 SCLC pts were randomized (19 on 10 mg, 21 on 30 mg) and received$\geq$1 dose of ZG006. Median age was 57.5 (range: 48-73) years. Of the 40 pts, 31 (77.5%) were males and 27 (67.5%) had smoking history; all had received $\geq$2 prior line treatments and 45.0% $\geq$3 lines; majority (72.5%) had prior anti-PD-(L)1 treatments. Baseline metastatic sites of liver and brain accounted 52.5% (21/40) and 20.0% (8/40), respectively. Among 27 (13 at 10 mg, 14 at 30 mg) efficacy-evaluable SCLC pts who had at least one post-baseline tumor scan, 18 (5 confirmed, others pending confirmed) achieved partial response (7 at 10 mg, 11 at 30 mg). Overall, the ORR was 66.7% and the DCR was 92.6%. For the 10 mg group, ORR was 53.8% and DCR was 84.6%; for the 30 mg group, ORR was 78.6% and DCR was 100.0%. DoR and PFS, not yet matured and will be updated with additional follow-up time. Among the all combined 27 pts, 21 (77.8%) pts had low (N = 17) or medium (N = 4) DLL3 expression at baseline, and they demonstrated reasonably great anti-tumor efficacy with 15 PRs and 71.4% ORR. Treatment-related adverse events (TRAEs) occurred in 35 pts (87.5%); most commonly ($\geq$20%): pyrexia (57.5%), cytokine release syndrome (CRS, 47.5%), vomiting (27.5%), rash (25.0%), decreased appetite (25.0%), aspartate aminotransferase increased (22.5%), white blood cell count decreased (22.5%) and platelet count decreased (22.5%). Only five pts (12.5%) experienced grade 3/4 TRAEs including one grade 3 CRS, and no pts experienced TRAEs leading to treatment discontinuation or death. Five pts (12.5%) experienced serious TRAEs. No significant difference was observed in the safety profile between these two dose groups. **Conclusions:** ZG006 exhibited promising efficacy and acceptable safety in SCLC pts receiving $\geq$2 lines of prior treatment, even in pts with low DLL3 expression. The enrollment of ZG006-002 study is ongoing. Clinical trial information: NCT06283719. Research Sponsor: None.

LBA8008 **Oral Abstract Session**

Tarlatamab versus chemotherapy (CTx) as second-line (2L) treatment for small cell lung cancer (SCLC): Primary analysis of Ph3 DeLLphi-304. First Author: Charles M. Rudin, Fiona and Stanley Druckenmiller Center for Lung Cancer Research, Memorial Sloan Kettering Cancer Center, New York, NY

The full, final text of this abstract will be available at meetings.asco.org on the day of presentation and in the online supplement to the June 10, 2025, issue of the *Journal of Clinical Oncology*.

8009 **Rapid Oral Abstract Session**

Association of post-surgical MRD status with neoadjuvant ctDNA dynamics, genomic mutations, and clinical outcomes in patients with resectable NSCLC (R-NSCLC) from the phase 3 AEGEAN trial. First Author: Martin Reck, Lung Clinic Grosshansdorf, Airway Research Center North, German Center for Lung Research, Grosshansdorf, Germany

Background: In AEGEAN, perioperative durvalumab (D) + neoadj CT significantly improved the primary endpoints of event-free survival (EFS) and pathological complete response (pCR) vs neoadj CT alone in pts with R-NSCLC. Prior analyses of AEGEAN suggest that pts without ctDNA clearance during neoadj Tx or with molecular residual disease (MRD; i.e. ctDNA detected) at a landmark timepoint after Sx (adj C1D1) had worse outcomes. Using data from all biomarker-evaluable pts, we report exploratory analyses for associations of post-Sx MRD status with pt characteristics, neoadj ctDNA dynamics, pathological response, genomic mutations and outcomes. **Methods:** AEGEAN is a double-blind PBO-controlled study (NCT03800134). Adults with Tx-naïve R-NSCLC (stage II–IIIB[N2]) and ECOG PS 0/1 were randomized 1:1 to receive neoadj platinum-based CT + D or PBO IV (Q3W, 4 cycles) before Sx followed by D or PBO IV (Q4W, 12 cycles) after Sx. Efficacy was assessed in the mITT population, which excluded pts with known *EGFR*/*ALK* aberrations. ctDNA analysis was performed on plasma collected before each neoadj Tx cycle, Sx, and adj C1, C3/4 and C10/11 using pt-specific tumor-informed assays. Whole exome sequencing analysis of diagnostic tumor biopsies was performed to identify mutations associated with MRD status at the post-Sx landmark. **Results:** Among MRD-evaluable pts, 10% (17/168) were MRD-positive (D, n=10; PBO, n=7) and 90% (151/168) were MRD-negative (D, n=78; PBO, n=73) at the landmark timepoint (median 6.9 wk post-Sx). 88% [15/17] of MRD-positive pts were initially diagnosed with stage III disease. In the D arm, the majority of MRD-positive pts (9/10) also had ctDNA detected at the pre-Sx visit. No MRD-positive pts in the D arm had pCR or major pathological response. As expected, overall disease-free survival (DFS) rates at 12 mo were worse in MRD-positive (14.3%; 95% CI, 2.4–36.3) vs MRD-negative pts (89.3%; 95% CI, 82.6–93.5). In both arms, MRD-positive pts had worse DFS outcomes vs MRD-negative pts (D: HR, 21.28; 95% CI, 7.70–58.83; PBO: HR, 14.29; 95% CI, 4.94–41.36) with DFS trends favoring the D vs PBO arm, particularly in pts with no ctDNA detected (MRD-negative: HR, 0.56; 95% CI, 0.26–1.20; MRD-positive: HR, 0.78; 95% CI, 0.26–2.36). Mutated genes associated with MRD-positive status in the D arm included *KEAP1* and *KMT2C*; despite small pt numbers, EFS benefit in the D vs PBO arm was not evident in pts with the mutations (m) *(KEAP1*m: HR, 1.39; 95% CI, 0.29–6.77; *KMT2Cm:* HR, 2.03; 95% CI, 0.70–5.91). In contrast, EFS benefit was evident in pts with wild type (wt) (*KEAP1*wt: HR, 0.54; 95% CI, 0.36–0.79; *KMT2C*wt: HR, 0.52; 95% CI, 0.35–0.78). **Conclusions:** Exploratory analyses based on post-Sx MRD status and genomic analysis identified a small high-risk subgroup of pts with markedly worse prognosis with potentially reduced benefit from the AEGEAN regimen. Clinical trial information: NCT03800134. Research Sponsor: AstraZeneca.

LBA8010 **Rapid Oral Abstract Session**

Perioperative nivolumab (NIVO) vs placebo (PBO) in patients (pts) with resectable NSCLC: Updated survival and biomarker analyses from CheckMate 77T. First Author: Tina Cascone, The University of Texas MD Anderson Cancer Center, Houston, TX

The full, final text of this abstract will be available at meetings.asco.org on the day of presentation and in the online supplement to the June 10, 2025, issue of the *Journal of Clinical Oncology*.

8011 **Rapid Oral Abstract Session**

ctDNA-based MRD detection in unresectable NSCLC undergoing curatively intended chemoradiotherapy and durvalumab. First Author: Henrik Horndalsveen, Oslo University Hospital, Department of Oncology and Department of Cancer Genetics, Oslo, Norway

Background: Durvalumab consolidation after chemoradiotherapy (CRT) has improved clinical outcomes in patients with unresectable stage III non-small cell lung cancer (NSCLC). Despite durvalumab treatment, a substantial proportion of patients relapse, while up to 20% achieve long-term survival without durvalumab. Circulating tumor DNA (ctDNA)-based minimal residual disease (MRD) detection has shown promise as a tool for risk-adaptive and personalized treatment strategies in resectable NSCLC but is still underexplored as a biomarker in patients with stage III NSCLC treated with CRT and consolidative durvalumab. **Methods:** The DART study is a multicenter phase II clinical trial enrolling 86 patients with unresectable stage III NSCLC. All patients received two cycles of platinum-doublet chemotherapy concomitant with radiotherapy to a total dose of 60–66 Gy, followed by durvalumab. We prospectively collected serial plasma samples from all patients at baseline(before CRT), at the initiation of durvalumab (one month post-CRT), and at predefined timepoints during durvalumab treatment. Plasma samples were analyzed using a novel tumor-agnostic ctDNA MRD assay (MEDICOVER Genetics), tailored to each patient's cancer biomarker profile. This hybrid capture-based assay leverages genomic information in cell-free DNA from selected coding regions in 293 genes to classify plasma samples as positive ("ctDNA detected") or negative ("ctDNA not detected"). Here, we present results of the first MRD analysis conducted in the trial, involving a total of 138 plasma samples from 20 patients who completed all scheduled blood draws. **Results:** The baseline ctDNA detection rate was 91.8% in the entire study population and 73.7% in the 20 patients with completed longitudinal MRD analyses. Detectable ctDNA at baseline varied according to stage and histology and was not associated with PFS. Nine patients had detectable ctDNA in at least one plasma sample during the first four months after CRT, which was significantly associated with shorter progression-free survival (PFS) (HR: 4.7; 95% CI: 1.6–13.1; p = 0.004). When assessing specific timepoints, patients with detectable ctDNA four months post-CRT had shorter PFS compared to patients without detectable ctDNA at this timepoint (HR: 3.77; 95% CI: 1.32–10.74; p = 0.013). In contrast, detectable ctDNAone month post-CRT was not associated with shorter PFS (HR: 2.23; 95% CI: 0.78–6.36; p = 0.13). Preliminary overall survival data indicate that detectable ctDNA during the first four months post-CRT significantly increased the odds of death within 24 months (OR: 16.48; 95% CI: 1.29–1000.51; p = 0.017). **Conclusions:** Detection of ctDNA during consolidative durvalumab after CRT using a novel tumor-agnostic MRD assay was associated with inferior outcomes, demonstrating the potential of ctDNA as a biomarker to identify high-risk patients for tailored interventions. Clinical trial information: NCT04392505. Research Sponsor: Helse Sør-Øst RHF; AstraZeneca; Medicover Genetics.

8012 Rapid Oral Abstract Session

The preliminary results of a randomized phase II trial evaluating induction toripalimab plus chemotherapy followed by concurrent chemoradiotherapy and consolidation toripalimab in bulky unresectable stage III non-small-cell lung cancer (InTRist). First Author: Yu Wang, Department of Radiation Oncology, National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China

Background: Unresectable stage III NSCLC patients with large tumor volumes remain challenging. Our previous retrospective study has showed promising results of induction chemoimmunotherapy before definitive chemoradiotherapy (CRT) for these patients. Here we report preliminary results of the randomized phase II study on this regimen. **Methods:** This InTRist study is a randomized, single-center, phase 2 trial, enrolling patients with unresectable stage III NSCLC with bulky diseases, and without *EGFR/ALK* alterations. Bulky diseases were defined as primary tumor ≥5 cm in greatest dimension or metastatic lymph nodes ≥2 cm in shortest diameter. Eligible patients were 1:1 randomly assigned to receive induction toripalimab (240 mg every 3 weeks) plus platinum-based doublet chemotherapy for 2 cycles (toripalimab group) versus induction chemotherapy alone for 2 cycles (chemo group) followed by concurrent CRT (60 Gy radiotherapy plus concurrent platinum-based chemotherapy). All patients without disease progression or grade ≥2 pneumonitis after CRT received consolidation toripalimab (240 mg every 3 weeks) for up to 12 months. Randomization was stratified according to histologic type. The primary endpoint was progression-free survival (PFS) from randomization. This trial is registered with ClinicalTrials.gov, NCT05888402. **Results:** BetweenJanuary 20th, 2023 and October 8th, 2024, 52 patients were randomized to induction toripalimab (n = 27) or chemo (n = 25) groups. By the data cutoff date (January 15th, 2025), the median follow-up was 13.1 months. Induction toripalimab plus chemotherapy exhibited significantly longer PFS compared to chemotherapy alone (median not reached [NR] vs NR; hazard ratio 0.25 [95% CI, 0.07-0.90], *P*=0.034). The 12-month PFS rate was 89.4% (95% CI, 76.0%-100%) in the toripalimab group and 57.8% (95% CI, 40.7%-81.9%) in the chemo group. Objective response rate after induction therapy was 77.8% (21/27) for the toripalimab group and 40.0% (10/25) for the chemo group (median tumor reduction 32% vs 21%). Grade 2 pneumonitis occurred in 26.9% (14/52) of all patients, with 18.5% (5/27) in the toripalimab group and 36.0% (9/25) in the chemo group. Grade 3 pneumonitis occurred in 7.7% (4/52) of all patients, with 11.1% (3/27) in the toripalimab group compared to 4.0% (1/25) in the chemo group. No grade 4-5 pneumonitis. **Conclusions:** Induction toripalimab plus chemotherapy, followed by concurrent CRT and consolidation toripalimab, demonstrated potentially improved short-term efficacy and manageable toxicity for patients with bulky unresectable stage III NSCLC. Further follow-up is necessary to confirm these results. Clinical trial information: NCT05888402. Research Sponsor: Chinese Academy of Medical Sciences (CAMS) Innovation Fund for Medical Sciences; 2024-I2M-C&T-B-065.

8013 Rapid Oral Abstract Session

Safety and efficacy of lurbinectedin plus atezolizumab as second-line treatment for advanced small-cell lung cancer: Results of the 2SMALL phase 1/2 study (NCT04253145). First Author: Santiago Ponce Aix, Hospital Universitario 12 de Octubre and Oncosur Foundation, Madrid, Spain

Background: Small-cell lung cancer (SCLC) is an aggressive malignancy, accounting for 13% of all lung cancers, with a 5-year survival rate below 12%. Relapsed SCLC remains a major therapeutic challenge, underscoring the need for innovative second-line treatments. The combination of lurbinectedin (LUR) plus atezolizumab (ATZ) has shown synergy in immunocompetent models, and clinical feasibility in a phase I trial. Here we evaluate the efficacy and safety of the regimen as second line treatment for SCLC patients. **Methods:** This prospective, open-label, multicenter study enrolled patients with ECOG PS 0-1, measurable disease by RECIST 1.1, and progression after one prior platinum-based chemotherapy alone (cohort 1 - C1) or combined with PD-1/ PD-L1 blockade (cohort 2 - C2). Key inclusion criteria included a chemotherapy-free interval (CTFI) of ≥30 days, adequate organ function. Treated brain metastases previously managed with radiotherapy were permitted. Patients received LUR (3.2 mg/m² i.v. 1 hour infusion) following ATZ (1200 mg i.v. 30–60 minutes infusion) on day 1, every 3 weeks. Primary G-CSF prophylaxis was administered for 5 days. The primary endpoint was overall response rate (ORR) per RECIST v1.1. Secondary endpoints included progression-free survival (PFS), overall survival (OS), and safety. **Results:** Between June 2022 and March 2024, 218 patients were screened, and 151 were enrolled: 68 in C1 and 83 in C2. The median age was 64 years (range: 45–79), with 58% being male. Most patients (73%) had an ECOG 1, and 60.92% had a CTFI of ≥90 days. Efficacy results are summarized in Table 1. The combination was well-tolerated, with no unexpected safety signals. Treatment-emergent adverse events (TEAEs) were reported in 91% of patients. Grade ≥3 hematological toxicities included neutropenia (C1: 16.18%; C2: 7.23%), febrile neutropenia (C1: 2.94%; C2: 2.41%) and thrombocytopenia (C1: 8.82%; C2: 1.20%). Treatment- emergent deaths occurred in 7 patients (C1: 4; C2: 3). **Conclusions:** The combination of LUR and ATZ showed promising efficacy in patients with relapsed SCLC regardless of prior exposure to immunotherapy, including those with resistance to platinum. The associated safety profile is manageable. The regimen is being evaluated in a phase III trial in the maintenance setting (IMforte trial NCT05091567). Clinical trial information: NCT04253145. Research Sponsor: None.

	Cohort 1 (n=68)	Cohort 2 (n=83)	CTFI<90 (n=59)	CTFI≥90 (n=92)
Overall Response, % (95% CI)	44.12 (32.27-56.63)	37.35 (27.18-48.7)	35.59 (23.87-49.20)	43.48 (33.30-54.20)
CR, n (%)	3 (4.41%)	1 (1.20%)	0 (0.00%)	4 (4.35%)
PR, n (%)	27 (39.71%)	30 (36.14%)	21 (35.59%)	36 (39.13%)
SD, n (%)	21 (30.88%)	25 (30.12%)	20 (33.90%)	26 (28.26%)
Median PFS (months), n (95%CI)	4.90 (3.87-7.27)	4.43 (3.27-5.17)	4.77 (3.27-5.90)	4.63 (3.60-6.13)
Median OS (months), n (95%CI)	11 (9.37-15.07)	9.53 (7.90-12.87)	10.10 (8.17-11.97)	11 (8.67-15.07)

8014 Rapid Oral Abstract Session

Clinical and molecular characteristics of early progressors (EPs) and long-term progression-free survivors (LTPs) from the phase 3 ADRIATIC trial of consolidation durvalumab (D) vs placebo (P) after concurrent chemoradiotherapy (cCRT) in limited-stage small-cell lung cancer (LS-SCLC). First Author: David Allen Barbie, Lowe Center for Thoracic Oncology, Dana-Farber Cancer Institute, Boston, MA

Background: At the first planned interim analysis of ADRIATIC, consolidation D significantly improved the dual primary endpoints of overall and progression-free survival (PFS) vs P in patients (pts) with LS-SCLC and no progression after cCRT. We assess clinical characteristics, patterns of progression, and associated molecular biomarkers in EPs (pts with PFS <6 mos) and LTPs (PFS or censored after >12 mos) in the D and P arms. **Methods:** Pts with stage I–III LS-SCLC, WHO performance status (PS) 0/1, and no progression after cCRT were randomized to D (n=264), D + tremelimumab (n=200; arm still blinded), or P (n=266) for up to 24 months. Pre-cCRT tumor samples were collected at screening and immune-related biomarkers (CD8, MHC I, PD-L1, T-cell inflamed signature [TIS], *CD8A*, and STING pathway) were assessed by immunohistochemistry or RNA sequencing for their role in response to immunotherapy (IO). **Results:** At data cutoff (15 Jan 2024), 83 (31.4%) and 113 (42.8%) pts in the D arm and 97 (36.5%) and 100 (37.6%) in the P arm were EPs and LTPs, respectively. For EPs and LTPs, respectively: 67.5% and 61.1% in the D arm and 74.2% and 72.0% in the P arm were male; 44.6% and 54.9% in the D arm and 51.5% and 48.0% in the P arm had WHO PS 0; and 90.4% and 89.4% in the D arm and 91.8% and 89.0% in the P arm were current/former smokers. Among EPs, 47.0% vs 45.4% had extrathoracic (ET) only progression, 43.4% vs 43.3% had intrathoracic (IT) only progression, and 6.0% vs 1.0% died without progression in the D vs P arms, respectively. Among LTPs, 16.8% and 25.0% of pts in the D and P arms had progression events, which were mostly IT (D: 14.2%; P: 16.0%). Similar rates of PD-L1+ tumors were observed in EPs and LTPs in both arms (Table). Trends for higher TIS and STING pathway expression were seen in LTPs vs EPs in the D arm but not the P arm. CD8 density, and *CD8A* and MHC I expressions were lower in EPs vs LTPs in both arms, regardless of D vs P (Table). **Conclusions:** Exploratory analyses suggest similar rates of IT and ET progression with D and P in EPs, but mostly IT progression in LTPs. Compared with EPs, LTPs were generally characterized by a pre-cCRT tumor microenvironment more conducive to fostering an IO response, with higher antigen presentation and cytotoxic marker expression potentially enhancing D's mechanism of action. Clinical trial information: NCT03703297. Research Sponsor: AstraZeneca.

	D, EPs	P, EPs	D, LTPs	P, LTPs
PD-L1 TC or IC ≥1%, n (%)	25 (52.1)	32 (55.2)	40 (56.3)	42 (61.8)
MHC I n, median TC score* (%)	42, 65.0	46, 75.0	66, 77.5	56, 80.0
CD8 density n, median cells/mm²	39, 46.7	43, 50.7	57, 94.2	53, 78.7
RNASeq BEP, n	17	27	29	24
***CD8A* expression†**	1.1	1.1	1.3	1.7
TIS value†	2.3	3.1	3.2	3.4
STING signature value†	0.28	1.4	0.90	1.4

*% MHC I-positive TCs in the total tumor area.
†Median.
BEP, biomarker-evaluable population; TC, tumor cell; IC, immune cell.

8015 Rapid Oral Abstract Session

Alectinib as neoadjuvant treatment in potentially resectable stage III ALK-positive NSCLC: Final analysis of ALNEO phase II trial (GOIRC-01-2020-ML42316). First Author: Alessandro Leonetti, University Hospital of Parma, Parma, Italy

Background: Stage III Non-Small Cell Lung Cancer (NSCLC) is a heterogeneous group of tumors with a wide spectrum of clinical presentations and no single definitive therapeutic approach. The role of neoadjuvant alectinib in stage III ALK-positive NSCLC is still unclear. Here, we present the final analysis of the phase II, open-label, single-arm, multicenter study aimed at investigating the activity and safety of alectinib in potentially resectable locally advanced stage III ALK-positive NSCLC patients (ALNEO trial, EUDRACT number 2020-003432-25). **Methods:** Treatment-naïve patients with potentially resectable stage III ALK-positive NSCLC, ECOG PS≤1 were registered to receive neoadjuvant alectinib for 2 cycles (8 weeks) followed by surgery and adjuvant alectinib for 24 cycles (96 weeks). The primary endpoint was major pathological response (MPR) by Blinded Independent Central Review (BICR). Secondary endpoints included pathological complete response (pCR) by BICR, objective response (OR), event-free survival (EFS), disease-free survival (DFS), overall survival (OS) and adverse events (AEs). According to the Simon's design (P0=20%, P1=40%), 18 and 33 patients were required for the first and second stage, respectively. **Results:** A total of 33 patients were registered in 20 Italian Oncology Centers from May 2021 to July 2024. Median age was 62 years (Interquartile Range [IQR], 49–74 years), 23 (70%) patients were female and 17 (52%) were never smokers. Clinical stage according to the 8th AJCC TNM was IIIA in 21 (64%) and IIIB in 12 (36%) patients. The most represented stage was T3N2 (n=8, 24%), followed by T1aN2 (n=4, 12%), T2aN2 (n=4, 12%), T4N0 (n=4, 12%) and T4N2 (n=4, 12%). All the patients completed the neoadjuvant phase and 28 (85%) underwent surgery, which consisted of lobectomy in 21 (64%), pneumonectomy in 3 (9%) and other surgery in 4 (12%) patients. Among patients who completed surgery, R0 was achieved in 24 (86%) patients. According to the BICR, MPR was documented in 15 (46%, 90% Confidence Interval [CI]: 31%–61%) patients and pCR in 4 (12%, 95% CI: 3%–28%) patients. Overall, an OR was observed in 22 (67%) patients. Adjuvant treatment was started in 26 (79%) patients with a median interval from surgery of 5.1 weeks (IQR, 3.6–6.0 weeks). After a median follow-up of 15.2 months (IQR, 6.8–27.8 months), 31 (94%) patients were alive and 5 (19%) patients completed the adjuvant treatment. Median EFS and OS were not reached. A total of 6 (18%) patients experienced disease progression/recurrence. Grade≥3 AEs occurred in 3 (9%) and 2 (8%) patients during neoadjuvant and adjuvant phase, respectively. **Conclusions:** ALNEO study met its primary endpoint, suggesting alectinib as a feasible peri-operative option in resectable locally advanced stage III ALK-positive NSCLC patients. The study was partially supported by Roche S.p.A. Clinical trial information: NCT05015010. Research Sponsor: Roche S.p.A.

8016 Rapid Oral Abstract Session

Efficacy and safety of nivolumab plus ipilimumab for patients with pre-treated type B3 thymoma and thymic carcinoma: Results from the EORTC-ETOP NIVOTHYM phase II trial. First Author: Nicolas Girard, Institut du Thorax Curie Montsouris, Institut Curie, Paris, and UVSQ, Paris Saclay University, Versailles, France

Background: Thymic malignancies represent a therapeutic challenge in the advanced, metastatic setting, with limited options after the failure of platinum-based chemotherapy. **Methods:** NIVOTHYM is a multicenter phase II, 2-cohort, single-arm trial evaluating the use of nivolumab (N)+/-ipilimumab (I) in patients ≥18yo, with advanced/relapsed type B3 thymoma or thymic carcinoma (TC), after previous exposure to platinum-based chemotherapy.Primary endpoint wasProgression-Free Survival (PFS) rate at 6 months based on RECIST1.1 per independent radiological review. We report the results of cohort 2 with patients who received N 240 mg Q2W and I 1mg/kg Q6W. **Results:** From Feb 2021 to Jan 2023, 56 patients – 8 (14%) with type B3 thymoma, 48 (86%) with TC - were enrolled in 15 centers/5 countries, of which 37 (66%) men/19 (34%) women. Median age was 64 years. 23 (41%) patients had had surgery. After a median follow-up of 16.0 months, 50 patients had discontinued N+I for: progression in 36 (72%) pts, treatment-related adverse events (TRAEs) in 11 (22%) pts, completion in 2 (4%) pts, and pt decision for 1 pt (2%). Maximal grade of adverse events was 1/2 in 29 (52%) patients, and 3/4 in 27 (48%) patients. Grade ≥3 TRAEs occurred in 16 (29%) pts: myocarditis (2 pts), colitis (4 pts), infusion-related reaction/allergy (2 pts), skin rash (2 pts), heart failure, immune-related hepatitis, arthritis, myositis, hypophysitis, Gougerot Sjogren syndrome, pharyngitis, fatigue, fever, infusion-related reaction (1 pt each); there was no grade 5 TRAE. PFS rate at 6 months was 21.6%. Objective Response and Disease Control Rates were 17.7% and 60.8%, respectively. Median PFS and Overall Survival were 3.2 (95%CI 2.1-3.6) and 22.0 (95%CI 16.6-NR) months, respectively; median duration of response was 7.1 (95%CI 1.4-17.0) months, and 8 (14%) pts received treatment for ≥12 months. **Conclusions:** N+I demonstrated limited efficacy in advanced thymic tumors, as prespecified PFS rate at 6 months of 40% was not reached, compared to the previously reported cohort 1 of this trial with N as single-agent. Numerically more patients experienced grade ≥3 TRAEs, while efficacy endpoints were not numerically higher. Clinical trial information: NCT03134118. Research Sponsor: None.

8017 Rapid Oral Abstract Session

Integrin $\alpha_V\beta_3$-targeted imaging for identification of lung cancer and mapping of lymph-node metastases: A prospective, multicenter, self-controlled phase 3 trial (TRIIL study). First Author: Zhaohui Zhu, Peking Union Medical College Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China

Background: Integrin $\alpha_V\beta_3$ mediates tumor formation, invasion, metastasis and angiogenesis. ^{99m}Tc-3PRGD2, a first-in-class radiopharmaceutical targeting integrin $\alpha_V\beta_3$, was advanced into a phase 3 clinical trial for evaluation of lung cancer via single photon emission computed tomography (SPECT)/computed tomography (CT), with mapping the lymph-node metastases as the primary objective. **Methods:** A prospective, multicenter, phase 3 trial of ^{99m}Tc-3PRGD2 SPECT/CT enrolled 409 patients with solid lung lesions ≥ 1.5×1.0 cm in high suspicion of lung cancer (TRIIL; ClinicalTrials.gov identifier: NCT04233476; chinadrug-trials.org.cn identifier: CTR20191465). A self-controlled design was used for a head-to-head comparison with the conventional metabolic imaging via F-18 fluorodeoxyglucose (^{18}F-FDG) positron emission tomography (PET)/CT. The primary outcome was to define the superiority of diagnostic specificity of ^{99m}Tc-3PRGD2 SPECT/CT over that of ^{18}F-FDG PET/CT in assessment of lymph-node metastases of lung cancer. The secondary outcomes included the other diagnostic values and safety. **Results:** No severe adverse event was observed in 407 patients with complete safety data. In 268 patients with pathological diagnosis of the lung tumors, no significant difference was found between ^{99m}Tc-3PRGD2 SPECT/CT and ^{18}F-FDG PET/CT for detection of lung malignancies (sensitivity, 96% vs 98%, P = 0.083). In 259 patients with pathological diagnosis of 1601 lymph-node stations, ^{99m}Tc-3PRGD2 SPECT/CT demonstrated superiority over ^{18}F-FDG PET/CT in the diagnostic specificity (74% vs 50%, $P <$ 0.001) and accuracy (70% vs 55%, $P <$ 0.001) for mapping the lymph-node metastases station-by-station, with a relatively lower sensitivity (55% vs 75%, $P <$ 0.001) mainly due to spatial resolution limitation of the current SPECT systems. In a semi-quantitative analysis of the tumor-to-background ratios in each method, the areas under the receiver operating characteristic curves were 0.69 for ^{99m}Tc-3PRGD2 SPECT/CT and 0.63 for ^{18}F-FDG PET/CT (P = 0.13), respectively, for discriminating lymph-node stations with and without metastasis. In a case-by-case analysis, the integrin $\alpha_V\beta_3$-targeting ^{99m}Tc-3PRGD2 SPECT/CT corrected the false-positive diagnosis of ^{18}F-FDG PET/CT in 344 lymph-node stations from 152 (59%) of the 259 patients, providing more accurate evaluation of lymph-node metastasis in 116 (45%) patients, whereas ^{18}F-FDG PET/CT held better diagnosis of the lymph-node involvement only in 40 (15%) patients. **Conclusions:** This trial substantiates the advantages of the integrin imaging for mapping the lymph-node metastases of lung cancer, and paves the way for ^{99m}Tc-3PRGD2 SPECT/CT to be evolved into a universally accessible and cost-efficient technique for tumor diagnosis and staging, and further towards precise therapy. Clinical trial information: NCT04233476. Research Sponsor: None.

8018 Poster Session

Assessment of survival benefit with immunotherapy in combination with adjuvant chemoradiation in pathologic stage II-IIIB non-small cell lung cancer. First Author: Natasha Venugopal, Penn State Health Milton S. Hershey Medical Center, Hershey, PA

Background: Since the Food and Drug Administration (FDA) approvals in 2021 and 2023, atezolizumab and pembrolizumab, respectively, became standard management for curatively resected stage II-III non-small cell lung cancer (NSCLC) based on improved disease-free survival. Because these studies excluded the planned use of adjuvant radiation therapy, survival benefit of adding immune checkpoint inhibitor (ICI) in those who are treated with adjuvant chemoradiation (CT+RT) have never been assessed. **Methods:** Using National Cancer Database (NCDB), we identified 8,235 cases that were completely resected, pathologic stage II-IIIB NSCLC per AJCC 8th edition and survived for at least 1 month without neoadjuvant CT or RT. Due to the timing of FDA approval and availability, only cases diagnosed in 2021 were investigated. They have been assigned into groups based on types of adjuvant treatments. Kaplan-Meier methods and multivariable Cox regression models were used for survival analysis. Propensity Score Matching (PSM) was performed to compare groups (adjuvant CT+RT+ICI vs CT+RT). A p-value of <0.05 was considered statistically significant. **Results:** Consistent with previous clinical trials, addition of ICI to adjuvant CT improved overall survival (OS) (2-year OS 90.1% vs 86.0%, Univariate and Multivariate HRs 0.72 and 0.66, p=0.0024 and 0.0003, respectively). However, no OS benefit was seen in those who received adjuvant CT+RT (2-year OS 77.8% vs 76.1%, Univariate and Multivariate HRs 0.83 and 0.85, p=0.3677 and 0.4369, respectively). PSM analysis showed similar results (2-year OS 77.8% vs 79.6%, Univariate and Multivariate HRs 0.91 and 0.87, p=0.7143 and 0.5868, respectively). **Conclusions:** Our retrospective real-world analysis suggests that adjuvant ICI do not improve survival outcome when combined with adjuvant CT+RT. This result appears to mirror recent negative trials using concurrent use of ICI with CT+RT in unresectable stage III NSCLC (PACIFIC2) and limited-stage SCLC (NRG-LU005). Further investigations are warranted. Research Sponsor: None.

Overall survival of p-stage II-IIIB NSCLC treated with designated therapy regimens.

Groups	Adjuvant CT+ICI	Adjuvant CT	Adjuvant CT+RT+ICI	Adjuvant CT+RT
N	3,549	878	132	375
2-year OS (month)	90.1%	86.0%	77.8%	76.1%
Univariate HR (95%CI)	0.72 (0.57-0.89)		0.83 (0.55-1.23)	
p-value (Log-rank)	0.0034		0.3744	

8019 Poster Session

Real world characteristics of stages II-III NSCLC patients (pts) who initiate neoadjuvant chemo-immunotherapy (NACT-I) and do not undergo surgical resection. First Author: Jair Bar, Jusidman Cancer Center, Sheba Medical Center, Ramat Gan, Israel

Background: Neoadjuvant and perioperative chemo-immunotherapy studies report 15%-20% of pts initiating NACT-I do not undergo surgical resection. **Methods:** Real-world data of pts who initiated NACT-I was collected retrospectively for January 1st 2022 till September 30th 2024. Pts and treatment details, reason for not undergoing resection (as assessed by the clinicians) and later treatments and outcomes were recorded. Total number of pts who initiated NACT-I in this period was identified from each center's records. Missing data was not imputed. **Results:** Data was collected from 10 centers in 4 countries (USA, Israel, Switzerland, France). Out of 330 pts that started NACT-I 43 pts (13%; range 4-33% in different centers) did not undergo surgical resection. Of these 43 pts, 34.9% became unresectable due to disease progression (PD). 20.9% in retrospect were non-resectable and did not regress as expected. 11.6% in retrospect were non-operable. 11.6% suffered toxicity and became unfit for surgery. 7% of pts refused surgery, 14% were not resected for other reasons (Table). Of the non-resected pts, 9.3% died prior to any second-line treatment. As a second line, 44.2% of the non-resected pts were treated with chemo-radiation, 14% with radiation alone, 7% chemotherapy and immunotherapy, 4.7% immunotherapy alone and 2.3% chemotherapy alone. 7% received palliative radiation followed by chemo or immunotherapy, 7% had follow-up alone. **Conclusions:** The rate of no surgical resection in this real-world multi-national cohort was 13%, in line with the rate in reported studies. Most un-resected pts underwent appropriate staging. Most were male, with high rate of T3/T4. Survival rate at 12 months was 73.7%. The most common causes for no surgery were PD or being upfront unresectable. The patients with the worst outcome were those who experienced PD during NACT-I. Research Sponsor: None.

	N (% out of 43 non-resected)	Male (%)	Age (median)	PET Done prior to any therapy (%)	Brain MRI staging (%)	Documented MDT decision of NACT-I (%)	Documented surgeon evaluation prior to NACT-I decision (%)	T3-4 (%)	N2a/b (9th V TNM; %)	Survival rate at 12 month (95% CI)
	43 (100.0)	69.8	71	95.3	95.0*	96.6*	86.2*	69.8	40.5	73.7% (50.5-87.2%)
PD	15 (34.9)	80.0	67	93.3	100.0*	100.0*	92.3*	80.0	40.0	68.2% (14.2-89.7%)
In retrospect not resectable	9 (20.9)	55.6	69	100.0	100.0	100.0*	50.0*	77.8	33.3	76.2% (33.2-93.5%)
In retrospect not operable	5 (11.6)	80.0	71	100.0	60.0	100.0*	33.3*	40.0	20.0	100.0% (100.0-100.0%)
Toxicity	5 (11.6)	80.0	72	100.0	100.0	100.0*	100.0*	80.0	80.0	80.0% (20.4-96.9%)
Patient refusal	3 (7.0)	0.0	72	100.0	100.0	100.0	100.0	66.7	33.3	100% (100.0-100.0%)
Other **	6 (14.0)	83.3	75	83.3	100.0*	75.0*	100.0	50.0	40.0*	50.0% (11.1-80.4%)

Percentages relate to the total of each row, besides 1st column relating to total of 43.
*% of available data.
**Death (n=3), intra-operative decision (n=2), additional malignancy (n=1).

8021 **Poster Session**

Adjuvant icotinib of 12 months versus observation as adjuvant therapy for completely resected EGFR-mutated stage IB non-small-cell lung cancer: 5-year update from CORIN (GASTO1003). First Author: Si Yu Wang, Shenshan Medical Center, Sun Yat-sen Memorial Hospital, Shanwei, China

Background: In the phase II CORIN trial,adjuvant therapy of icotinib for 1-year shows prolonged disease-free survival (DFS) and acceptable toxicity in patients with completely resected epidermal growth factor receptor (EGFR)-mutated stage IB non-small-cell lung cancer (NSCLC). Here, we report the 5-year survival update from this study. **Methods:** In the phase II, open-label, randomized CORIN trial, patients with completely resected, EGFR-mutated, stage IB (7th TNM staging) NSCLC without adjuvant chemotherapy according to physician and patient choice were randomly assigned in a 1:1 ratio to receive icotinib (125mg, three times daily, 12 months) or undergo observation. Therapy continued until disease recurrence or intolerable toxicity. The primary endpoint was DFS. Secondary endpoints included overall survival (OS) and toxicity. **Results:** Of 128 enrolled patients, 63 received icotinib and 65 underwent observation. At the December 20 2024 database lock, the median follow-up was 65.0 (95% confidence interval [CI], 58.4-71.5) months. A total of 30 recurrence events had occurred, including 9 in the icotinib arm and 21 in the observation arm. Icotinib for 1 year continued to improve DFS versus observation, with the 5-year DFS of 88.5% and 67.7%, respectively (log-rank P=0.012, hazard ratio [HR], 0.38; 95%CI: 0.18-0.83). Icotinib showed a marginal OS improvement versus observation (log-rank P=0.045, HR, 0.15; 95%CI: 0.02-1.27). The 5-year OS was 98.3% in the icotinib group and 90.5% in the observation group. No new safety signals were observed at this update. Additional efficacy outcomes will be presented. **Conclusions:** In this 5-year update analysis from CORIN, adjuvant icotinib continues to demonstrate durable DFS benefit versus observation in resected EGFR-mutated stage IB NSCLC, with a manageable safety profile. Icotinib sustained OS separation versus observation over time and demonstrated a marginal OS benefit, which is limited by the small sample size and wide CIs. Adjuvant icotinib for 1 year provides a treatment option for these patients. Clinical trial information: NCT02264210. Research Sponsor: None.

8022 **Poster Session**

IMpower010: Genomic profiling and clinical outcomes with adjuvant atezolizumab in early-stage non-small cell lung cancer (eNSCLC). First Author: Heather A. Wakelee, Stanford University School of Medicine/Stanford Cancer Institute, Stanford, CA

Background: In metastatic NSCLC (mNSCLC), genomic alterations (MUT) are well studied and have led to the development of efficacious new drugs. However, the association of MUT in the adjuvant setting in eNSCLC is not as well understood. Here, we describe an exploratory, retrospective analysis of genomic profiling by whole exome sequencing and clinical association in IMpower010. **Methods:** Whole exome sequencing was done on baseline tumor samples and germline DNA from whole blood from the biomarker-evaluable population (n=623). Multiple MUT were identified in the full population, including by histology. Disease-free survival (DFS) and overall survival (OS) were assessed in the most common gene subgroups. **Results:** The distribution of MUT and co-occurrence patterns were similar to expected non-squamous and squamous patterns in mNSCLC, except for lower prevalence of *STK11* (17%) and *KEAP1* (12%) MUT. In non-squamous disease, *STK11*, *EGFR*, and *KEAP1* MUT were associated with increased prevalence in PD-L1−negative tumors, and *TP53* MUT with PD-L1−positive tumors (adjusted $P<0.1$). *KRAS* MUT were associated with Stage II; *STK11* MUT were associated with Stage I more than with Stages II and III (adjusted $P<0.1$). Increased enrichment of *KRAS*, *STK11*, *KEAP1*, and *TP53* MUT was seen in those with previous or current smoking status, and *EGFR* MUT were enriched in those who never smoked (adjusted $P<0.1$). In non-squamous disease, *STK11* MUT were a poor prognostic for OS but not DFS, whereas *KEAP1* MUT were not significantly associated with poor prognosis for DFS or OS (Table). Neither *STK11* or *KEAP1* MUT were significantly associated with differential atezolizumab vs best supportive care DFS or OS benefit (interaction $P>0.05$). **Conclusions:** This analysis represents the largest dataset evaluating the genomic profile of patients with eNSCLC who were treated with cancer immunotherapy. The prevalences of *STK11* and *KEAP1* MUT were lower than in mNSCLC and were enriched for PD-L1−negative non-squamous NSCLC. Unlike in mNSCLC, patients with tumors that harbored *KEAP1* MUT did not have poor prognosis in IMpower010. Data are hypothesis generating and require validation in independent eNSCLC datasets with larger numbers. Clinical trial information: NCT02486718. Research Sponsor: Genentech, Inc.; Medical writing assistance for this abstract was provided by Nimisha H. Bhoola, PhD, of Nucleus Global, an Inizio Company, and funded by F. Hoffmann-La Roche Ltd.

***STK11* and *KEAP1* associations with DFS and OS in combined arms (non-squamous).**

		STK11 MUT	*STK11* WT	*KEAP1* MUT	*KEAP1* WT
	n	71	342	49	364
DFS	Median, mo	43.1	41.8	45.3	41.8
	HR (95% CI)	1.03 (0.73, 1.46)		0.91 (0.60, 1.39)	
OS	Median, mo	NR	NR	NR	NR
	HR (95% CI)	1.66 (1.10, 2.52)		1.08 (0.63, 1.85)	

CI, confidence interval; mo, month; NR, not reached; WT, wild type.

8023 **Poster Session**

Evaluating the role of consolidative chest radiotherapy after chemoimmunotherapy in extensive-stage small cell lung cancer: A retrospective study. First Author: Jorge Raul Vazquez Urrutia, Penn State Health Milton S. Hershey Medical Center, Hershey, PA

Background: Consolidative chest radiotherapy (XRT) after chemoimmunotherapy may provide benefits in extensive-stage small cell lung cancer (ES-SCLC) due to the condition's high sensitivity to radiation. Current guidelines suggest chest XRT for ES-SCLC patients who respond to chemotherapy, given its association with improved 2-year overall survival (OS), and reduced progression and recurrence rates. However, its role in the era of chemo-immunotherapy in ES-SCLC remains unclear. **Methods:** Data from the National Cancer Database (NCDB) for ES-SCLC patients diagnosed between 2017 and 2020 were analyzed (n=24,676). Cases included those treated with multi-agent chemotherapy, with data for T, N, and M status, and chest XRT. Exclusion criteria included survival <30 days, limited-stage SCLC cases, and missing key data elements. The primary outcome was OS from diagnosis, analyzed using Kaplan-Meier and multivariate Cox regression models. Propensity Score Matching (PSM) was performed to compare outcomes in ES-SCLC patients receiving chest XRT after immunotherapy versus immunotherapy alone, adjusting for T, N, and M status, institution, sex, and CD score. A p-value of <0.05 was considered statistically significant. **Results:** The study stratified patients in two groups: 10,437 immunotherapy receivers and 14,239 not receiving immunotherapy. The proportion of chest XRT receivers was similar across both groups (13% vs. 14%, p=0.17). Receipt of XRT was significantly associated with younger age (<70), female sex, T3-4 stage, N2-N3, and M1a status; ($p<0.05$). Chest XRT was associated with a significant increase median OS in both groups: immunotherapy (13.1 months vs. 9.8 months; $p<0.001$) and non-immunotherapy (11.6 months vs. 8.4 months; $p<0.001$). XRT was an independent predictor of better OS in both groups after controlling for other covariates (HR 0.72 and 0.66; $p<0.001$). PSM analysis of 1,399 patients receiving XRT and 1,399 receiving immunotherapy alone confirmed the OS benefit of XRT after immunotherapy (13.1 months vs. 9.4 months; HR 0.63, $p<0.001$) with a 3-year survival of 16% (95%CI: 13.7-18.3%) vs 7% (95%CI: 5.3-8.7%), respectively. **Conclusions:** Our analysis shows that consolidative chest XRT is associated with improved overall survival in patients with ES-SCLC, especially when combined with chemoimmunotherapy. These findings are hypothesis-generating and support ongoing randomized studies evaluating consolidative radiotherapy in the chemoimmunotherapy era. Research Sponsor: None.

Multivariable Cox regression analyses for overall survival in ES-SCLC.

Factor	Immunotherapy +	Immunotherapy -
	HR (95% CI)	HR (95% CI)
Chest XRT (Yes/No)	0.72 (0.68-0.77)	0.67 (0.64-0.71)
p-value	P<0.0001	P<0.0001

ES, extensive stage; SCLC, small cell lung cancer; HR, hazard ratio; CI, confidence interval; Ref, reference; CD, Charlson-Deyo; XRT, radiation.

8024 **Poster Session**

Ensartinib as postoperative adjuvant therapy in patients with ALK-positive non-small cell lung cancer (NSCLC): A registered, retrospective, real-world study. First Author: Lin Wang, National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences & Peking Union Medical College, Beijing Key Laboratory of Clinical Study on Anticancer Molecular Targeted Drugs, Beijing, China

Background: Ensartinib has been approved as ALK-positive locally advanced/metastatic NSCLC, but its role in adjuvant therapy remains unknown. This real-world study aimed to evaluate the efficacy and safety of ensartinib as adjuvant therapy in ALK-positive NSCLC. **Methods:** Data were retrospectively collected from "Ensacove Patient Assistance Program" held by Betta pharmaceutical company. The patients who were ≥18 years-old and had completely resected, histologically confirmed stage I-III NSCLC as classified according to the eighth edition of AJCC/UICC, were documented ALK-positive, and had at least one post-baseline CT scan. The primary endpoint is 2-year disease-free survival (DFS) rate. Secondary endpoints include DFS, safety and OS. **Results:** From November 19, 2020, to May 31, 2024, a total of 296 patients were screened. 222 patients were enrolled. The median age was 55 years-old. 128 females. 98 (44.1%) were stage I, 42 (18.9%) were stage II, 82 (36.9%) were stage III. 98.2% were lung adenocarcinoma. Thirty-two patients (14.4%) received postoperative chemotherapy. The median duration of ensartinib treatment was 25.3 (95% confidence intervals [CI], 3.1-47.2) months. At the data-cutoff date of December 29, 2024, median follow-up time was 23.5 months (95% CI, 21.7-26.2). The median DFS was immature. The 2-year DFS rate was 92.1% (95% CI, 86.6%-95.5%) for all patients, and 89.3% (95% CI, 77.9%-95.0%), 100.0% (95% CI, NR-NR) and 91.0% (95% CI, 80.6%-95.9%) for patients with stage I, stage II, and stage III, respectively. 16 patients had disease recurrence or death, including 7 patients with local recurrence and 9 patients with distant metastasis. The OS data was immature with only 2 deaths occurred. The treatment-related adverse events (TRAEs) of any grade occurred in 169 patients (76.1%), and 11 patients (5.0%) experienced ≥grade 3 TRAEs. The most common TRAEs were rash (60.8%). Serious TRAEs were 8 (3.6%) patients. TRAEs led to dose reductions, dose interruptions and permanent discontinuation were 21.2%, 9.0% and 3.2% of the patients, respectively. No deaths due to TRAEs were reported. **Conclusions:** To our knowledge, this real-world study has the largest sample size on postoperative adjuvant therapy with ALK inhibitors. In this real-world setting, ensartinib demonstrated encouraging efficacy and well-tolerated safety profile among stage IA1-IIIB ALK-positive NSCLC, providing a potential adjuvant therapy option in this patient population. Research Sponsor: None.

8025 **Poster Session**

Molecular profiling of neoadjuvant immunochemotherapy and identification of residual cancer cells in pCR NSCLC: A single-cell analysis of CTONG 1804 clinical trial. First Author: SiYang Maggie Liu, Guangdong Lung Cancer Institute, Guangdong Provincial People's Hospital (Guangdong Academy of Medical Sciences), Southern Medical University, Guangzhou, China

Background: Previously, we reported the clinical findings of stage-one enrollment from a phase II trial of neoadjuvant immunochemotherapy (IO) in untreated patients with resectable non-small cell lung cancer (NSCLC) (CTONG1804, NCT04015778). Recently, two-stage enrollment has been completed. This trial provided an opportunity to investigate the correlation of pathological response and early immune microenvironment during neoadjuvant IO. **Methods:** We conducted single-cell RNA sequencing (scRNA-seq) on fresh tumor tissue of 21 patients at pre- and post-IO treatment. Multi-omics sequencing was also used in this exploratory study, that included bulk RNA sequencing and tumor-informed MRD sequencing. **Results:** The pathological complete response (pCR) rate was 42.9% (9/21). Unexpectedly, a total of 143 cancer cells with genome alterations were identified in six (6/9=66.7%) patients with pCR. Only one pCR patient presented MRD positive within one month after surgery, who had the highest number of cancer cells. These residual cancer cells exhibited reduced proliferative capacity and diminished stem cell-like features but retained epithelial-mesenchymal transition (EMT) markers, suggesting metastatic potential and drug resistance. Elevated antigen presentation pathways, particularly involving CD74-MHC class II, were observed in pCR cancer cells, alongside a significant reduction in tumor neoantigen burden. When comparing the immune cells of different pathological response, we found that conventional dendritic cell type 2 (cDC2) emerged as a critical antigen-presenting cell subtype in pCR patients, enhancing T-cell activation and promoting immune response. Reduced CD4-Treg3 populations correlated with improved treatment outcomes, while CD8-MAIT cells exhibited functional plasticity, transitioning from tumor-promoting to tumor-rejecting phenotypes post-therapy. **Conclusions:** Our study highlights the persistence of residual cancer cells even in pCR patients and identifies key immune cell subsets, such as cDC2 and CD8-MAIT cells, that play pivotal roles in modulating anti-tumor response. These findings provide valuable insights into the mechanisms of immune activation and suppression in NSCLC and suggest potential biomarkers and therapeutic targets for optimizing neoadjuvant immunochemotherapy. Clinical trial information: NCT04015778. Research Sponsor: None.

8026 **Poster Session**

Molecular profiling and survival in oncogene-addicted resected stage IIIAN2 non-small cell lung cancer (NSCLC): A study from the Lung ART IFCT 0503 trial. First Author: Victor Albarran-Artahona, Department of Cancer Medicine, Gustave Roussy, Villejuif, France

Background: Molecular profiling is standard-of-care in metastatic NSCLC and increasingly important in earlier stages as personalized approaches arise. The role of adjuvant radiotherapy (ART) in oncogene-addicted, fully-resected stage IIIAN2 NSCLC remains undefined. **Methods:** The LungART trial (NCT00410683) randomized 501 patients (pts) with resected stage IIIAN2 NSCLC (AJCC 7th ed.) to ART or observation. No disease-free survival (DFS) benefit was found for ART. For consenting pts, a tumor block was collected. A histological central review was performed in all cases. Molecular profiling was conducted by Whole transcriptome sequencing (WTS; mRNA capture with Agilent exome lit and Illumina NovaSeq 6000 S4 Reagent Kit v1.5-300 cycles paired sequencing) to identify relevant alterations, with findings treated as per standard procedures. **Results:** 282 pts had available samples, from which 50% received ART. 90% were current or former smokers. Baseline characteristics were well balanced (table 1). After review, 79% of pts were classified as non-squamous cell carcinoma. *TP53* was the most common mutation (mut) identified (46%). Targetable mutations included *KRAS* p.G12C (8.8%), *EGFR*-sensitizing -exon 19 in-frame deletion and L858R mut- (3.5%), and *BRAF* p.V600 (1.4%). Non p.G12C *KRAS* mut were found in 28 pts, while atypical *EGFR* mut including exon 20 insertion, and non V600 *BRAF* were identified in 3.1% and 2.8% of pts, respectively. A *ERBB2* exon 20 insertion mut was identified in one case. *STK11* and *KEAP1* mutation were identified in 5.3% and 3.5% of pts, respectively. No translocations were detected. In the *STK11* mut subgroup, a significant difference in DFS (p=0.032) and OS (p=0.0043) was observed. No differences in outcomes were observed for other major molecular alterations nor between treatment arms, including *TP53* (p=1.0 and 0.86 for DFS and OS, respectively). **Conclusions:** Our study did not found a significant outcomes difference among major oncogenic-driven alterations, probably due to population characteristics and small representation of oncogene addicted subgroups. Our findings confirm *STK11* as a poor prognostic factor in resected stage IIIAN2 NSCLC. Of note, *TP53* did not show any impact on survival. Further studies are needed to confirm these observations and explore its implications. Research Sponsor: None.

Baseline characteristics.

Characteristic	ART N=141	Observation N=139
Age	61 (54-68)	61 (55-66)
Gender		
Female	44 (31%)	42 (30%)
Male	97 (69%)	97 (70%)
Neoadj. ChT	22 (16%)	23 (17%)
Adj. ChT	120 (85%)	120 (86%)
Smoking		
Current	16 (11%)	14 (10%)
Former	110 (78%)	112 (81%)
Never	15 (11%)	13 (9.4%)
Major molecular alterations		
TP53	67 (47%)	65 (46%)
***KRAS* p.G12C**	16 (11%)	9 (6.4%)
***KRAS* non-p.G12C**	14 (9.9%)	14 (10%)
***EGFR* sensitizing**	4 (2.8%)	6 (4.3%)
***EGFR* (others)**	3 (2.1%)	6 (4.3%)
STK11	6 (4.3%)	9 (6.5%)
KEAP1	6 (4.3%)	4 (2.9%)
***BRAF* p.v600**	0 (0%)	3 (2.1%)
***BRAF* non-p.V600**	6 (4.2%)	3 (2.1%)

LBA8027 **Poster Session**

An international, multicenter, prospective randomized trial of adjuvant chemotherapy for stage Ia-IIa non-small cell lung cancer identified as high-risk by a 14-gene molecular assay. First Author: David R. Spigel, Sarah Cannon Research Institute Oncology Partners, Nashville, TN

The full, final text of this abstract will be available at meetings.asco.org on the day of presentation and in the online supplement to the June 10, 2025, issue of the *Journal of Clinical Oncology*.

8028 **Poster Session**

A panel of four protein tumor markers for effective and affordable lung cancer early detection by artificial intelligence. First Author: Mao Mao, Research & Development, SeekIn Inc, San Diego, CA

Background: Lung cancer is the most common and deadly malignancy worldwide. While low-dose computed tomography (LDCT) reduces mortality in high-risk populations, its high false-positive rate and the required specialized infrastructure and radiologists limit its application. This study assesses LungCanSeek, a novel blood-based protein test for lung cancer early detection. **Methods:** This study enrolled 1,814 participants (1,095 lung cancer, 719 non-cancer) from three independent cohorts. Blood samples were analyzed for four protein tumor markers (PTMs) using Roche cobas. Artificial intelligence (AI) algorithms were developed for lung cancer detection and subtype classification (lung adenocarcinoma (LUAD), lung squamous cell carcinoma (LUSC), and small cell lung cancer (SCLC)). A two-step lung cancer screening approach was modeled, using LungCanSeek for initial screening, followed by LDCT for LungCanSeek's positive cases. **Results:** LungCanSeek showed 83.5% sensitivity, 90.3% specificity, and 86.2% accuracy overall. Sensitivities of LUAD, LUSC, and SCLC were 83.3%, 81.4%, and 91.9%. Sensitivity increased with clinical stage in non-small cell lung cancer (NSCLC): 59.5% (I), 69.8% (II), 86.5% (III), and 91.3% (IV). Sensitivities of limited- and extensive-stage SCLC were 91.3% and 93.0%. The subtype classification accuracy was 77.4%. Compared with the other blood-based lung cancer early detection tests like OncImmune's EarlyCDT-Lung (41.0% sensitivity, 91.0% specificity) and DELFI's FirstLook-Lung (84.1% sensitivity, 50.9% specificity), LungCanSeek's performance was superior. LDCT had 93.1% sensitivity and 76.5% specificity in NLST study. A screening was modeled for 9 million high-risk adults, based on the number of 15 million eligible individuals in the USA in 2024 at a 60% rate, with a 1.2% lung cancer incidence. While LungCanSeek reduced false positives by 2.4-fold to 862,524 compared to 2,089,620 with LDCT, the two-step approach further lowered false positives by 10.3-fold to just 202,693. Additionally, LDCT's total cost was $2,493 million, exceeding LungCanSeek's $720 million by 3.5-fold and two-step's $978.5 million by 2.5-fold. **Conclusions:** LungCanSeek is a non-invasive, easy to perform, cost-effective (reagent cost $15) and robust test for lung cancer early detection. It also provides accurate subtype prediction that may guide patients' clinical management and monitor subtype switching during treatment. The two-step approach not only effectively reduces LDCT's high false positives but also yields substantial economic benefits, making it a cost-effective strategy for population-wide lung cancer screening. Research Sponsor: None.

8029 **Poster Session**

Genomic characterization of STAS in stage 1 EGFR-mutated NSCLC and prognostic implications. First Author: Stephanie Pei Li Saw, Division of Medical Oncology, National Cancer Centre Singapore, Singapore, Singapore

Background: Spread through air spaces (STAS) is a poor prognostic factor and was recently introduced as a histologic descriptor in the TNM edition 9 for stage 1 lung cancer. While STAS-positivity (STAS+) is known to be associated with adenocarcinoma, the molecular epidemiology and determinants of STAS+ specific to epidermal growth factor receptor-mutated lung cancer (EGFRm) and prognostic implications remain unknown. **Methods:** Consecutive patients from National Cancer Centre Singapore diagnosed with AJCC8 stage 1 lung adenocarcinoma with minimum 3 years follow up post-surgery and known EGFR and STAS status (+ or -) were included. Fresh frozen tumour and normal samples were subject to whole exome sequencing (WES) at 400X and 100X coverage respectively, with 50 million paired-end reads for RNA-seq per sample. PD-L1 expression by immunohistochemistry was scored using SP263. Wilcoxon and Fisher's exact tests were used for association analysis and Kaplan Meier method for survival. **Results:** Between 1/1/16-31/12/21, 300 patients were included (203 EGFRm; 97 EGFR-wildtype (EGFRwt)). While the incidence of STAS+ was similar between EGFRm and EGFRwt (49.8% versus (vs) 56.7%, p=0.316), 5-year disease-free survival (DFS) was significantly worse for STAS+ vs STAS- EGFRm (67.8% vs 93.2%, p=0.005) but not EGFRwt (78.9% vs 82.0%, p=0.6). Comparing STAS+ and STAS- EGFRm, there was no significant difference in the proportion of never-smokers (77.2% vs 76.4%, p=0.248) and females (52.5% vs 60.8%, p=0.292). Distribution of EGFR mutation subtype was also similar (ex19del 43.6% vs 41.2%; L858R 37.6% vs 44.1%; others 18.8% vs 14.7%, p=0.576). Lymphovascular invasion (LVI) (20.8% vs 3.9%, $p<0.001$) and high histological grade (32.7% vs 4.0%, $p<0.001$) were significantly more common in STAS+ vs STAS- EGFRm. Among EGFRm, 193 patients had available WES and RNA-seq. Incidence of TP53 co-mutations (60.7% vs 43.2%, p=0.020) and whole genome doubling (WGD) (34% vs 17%, p=0.013) was significantly more common among STAS+ than STAS- tumours. No other significant differences in co-mutations or copy number alterations were observed. The proportion of PD-L1 expression $\geq$1% (42.3% vs 21.2%, p=0.011) and non-TRU transcriptomic subtype (55.9% vs 22.2%, $p<0.001$) were also significantly higher in STAS+ compared to STAS- tumours. Controlling for stage (1A vs 1B), age, smoking status, gender, histological grade and LVI, STAS+ remained an independent predictor of inferior DFS in stage 1 EGFRm (hazard ratio: 4.0, 95% confidence interval: 1.1-15.2, p=0.04). **Conclusions:** Despite a similar incidence, STAS+ independently predicts for inferior DFS in patients with stage 1 EGFRm but not EGFRwt. STAS+ stage 1 EGFRm demonstrate a higher frequency of *TP53* co-mutations, WGD, non-TRU subtype and PD-L1$\geq$1% as compared to STAS- stage 1 EGFRm. Our findings highlight the molecular determinants of STAS+ and support STAS as a risk stratification factor for stage 1 EGFRm. Research Sponsor: National Medical Research Council of Singapore.

8030 **Poster Session**

Genomic and immunophenotypic landscape of early-stage pulmonary carcinoid tumors. First Author: Song Xu, Tianjin Medical University General Hospital, Tianjin, China

Background: Pulmonary carcinoids (PCs), which encompass atypical carcinoids (ACs) and typical carcinoids (TCs), represent a rare category of lung cancer characterized by low to moderate malignancy. However, there is a limited understanding of the genomic and immune characteristics associated with PCs on a global scale. **Methods:** This study included a cohort of 126 surgically resectable Chinese PC patients, comprising 44 ACs and 82 TCs. Next-generation sequencing utilizing a 578-gene panel was conducted on 90 of PC patients, followed by the calculation of tumor mutation burden (TMB). Additionally, immunohistochemical staining for PD-L1 (n=108) and CD8 (n=94) was carried out to investigate the characteristics of the tumor microenvironment in PCs. **Results:** The most frequently altered genes in early-stage PCs were identified as *EGFR* (n=16, 18%), *KMT2C* (n=11, 12%), *LRP1B* (n=10, 11%), *MEN1* (n=10, 11%), and *NOTCH2* (n=9, 10%). Dysregulation of the RTK/RAS, NOTCH, and PI3K pathways was commonly observed in these PCs. Notably, genetic alterations in TP53, ARID1A, and CUL3 were more prevalent in ACs compared to TCs. However, TMB, PD-L1 expression, and CD8+ T cell infiltration were found to be low in early-stage PCs, with no significant differences observed between ACs and TCs. We identified age, gender, TNM stage, tumor type, smoking status, TMB, and *LRP1B* mutation, as indicators of poor prognosis, and further established a molecular classification that categorizes early-stage PCs into three distinct subtypes, each associated with varying clinical outcomes. **Conclusions:** We depicted the genetic and immune landscape of early-stage PCs and subsequently proposed a molecular classification based on the status of *LRP1B* mutation and smoking history. Our research offers novel insights into the biological mechanisms of PCs which contributes to the individualized treatment for Chinese PC patients. Research Sponsor: None.

8031 **Poster Session**

Association of 8-gene signature with early recurrence in resected non-small cell lung cancer. First Author: Arsalan A Khan, Rush University Medical Center, Chicago, IL

Background: Limited evidence exists defining a genetic signature associated with early-recurrence in patients with non-small cell lung cancers (NSCLC). This study aims to identify a genomic panel associated with early recurrence, defined as recurrence within 12 months from surgery. **Methods:** Patients with resected pT1-2aN0 NSCLC that underwent tumor RNA sequencing at a single institution from 2010-2021 were included. Exclusion criteria included neoadjuvant therapy, unknown pN status, and no recurrence. Differential gene expression (DGE) analysis was performed using DESeq2 after count normalization, identifying 50 genes with a log2 fold change $>$ 1 or $<$ -1 and an adjusted p-value$<$0.05. Recursive feature elimination (RFE) with random forests was applied to evaluate subsets of genes, utilizing repeated 10-fold cross-validation to ensure robust performance estimation. Accuracy and model stability were compared across subsets to identify the gene panel most strongly associated with early recurrence. Cross-validation was performed using a secondary RFE random forest analysis optimized for AUC, to refine the gene selection process. A multivariable logistic regression analysis was conducted to examine the association between the gene panel and early recurrence, while controlling for potential confounders. **Results:** 118 patients met study criteria, of whom 54% (64/118) were female, 82% (97/118) had adenocarcinomas, and 59% (70/118) underwent lobectomy. The median tumor size was 1.8 cm (IQR 1.5–2.6). Early recurrence was observed in 25.4% (30/118). DGE analysis involved 61.4% (27,009/43,959) of genes. After filtering for low total counts, using an FDR $<$0.1, 2% (530/27,009) were upregulated and 1.3% (351/27,009) downregulated in patients with early recurrence. After RFE with random forests, an 8-gene panel was selected, including *ART3*, *SLC51A*, *SNAP25*, *CCNA1*, *GRK1*, *GPR63*, *CNTNAP2*, and *TNFRSF11B* achieving an accuracy of 71.7%. The panel had an area under the curve (AUC) of 79.1, sensitivity of 93.9%, and specificity of 33.3%. On multivariable logistic regression, after adjusting for tumor size, histology, surgical procedure, pack years, and number of nodes sampled, and performance status, patients with differential expression of four or more genes within the panel were associated with early recurrence (OR: 4.11, 95% CI:1.27–13.31, p=0.02). **Conclusions:** A unique tumoral 8-gene signature is associated with early recurrence in resected early-stage NSCLC patients. Research Sponsor: None.

Univariable and multivariable logistic regression analysis examining predictors of early recurrence.

Variable	Unadjusted OR (95% CI)	*p-value*	Adjusted OR (95% CI)	*p-value*
≥ 4 of the 8 Gene Panel	**4.17 (1.46–11.88)**	**0.01**	**4.11 (1.27–13.31)**	**0.02**
Tumor Size	1.39 (0.86–2.26)	0.18	**2.22 (1.10–4.46)**	**0.03**
Histology				
Adenocarcinoma	Ref		Ref	
Squamous Cell Carcinoma	1.22 (0.42–3.49)	0.72	0.58 (0.14–2.41)	0.46
Surgical Resection				
Anatomic	Ref		Ref	
Sub-anatomic	1.82 (0.78–4.29)	0.17	1.85 (0.48–7.09)	0.37
Pack-Years	1.00 (0.99–1.02)	0.61	1.01 (0.99–1.03)	0.22
Performance Status >0	1.21 (0.52–2.77)	0.66	0.91 (0.82–1.03)	0.13
Number of nodes sampled	**0.91 (0.83-0.99)**	**0.04**	1.27 (0.45–3.54)	0.65

8032 **Poster Session**

Study on optimizing serum-based lung cancer diagnosis using a multi-biomarker approach. First Author: Hyejin Sung, Beyonddx, Gwangmyeong, South Korea

Background: Lung cancer remains the leading cause of cancer-related mortality, largely due to the challenges in early diagnosis. Elevated levels of serum carcinoembryonic antigen (CEA), serum amyloid A (SAA), and osteopontin (OPN) have been reported in various cancers. However, the diagnostic efficiency of these biomarkers as a combined panel for lung cancer detection is not well understood. This study evaluates the diagnostic value of combining these three biomarkers for lung cancer screening. **Methods:** Serum samples from 1,429 lung cancer patients and 1,000 healthy donors were analyzed for CEA, SAA, and OPN levels to assess their diagnostic accuracy. The data were divided into three independent cohorts: a development set, a training set, and a validation set. The diagnostic performance of each individual biomarker and the combined multi-biomarker panel was evaluated. **Results:** In the discovery set, the most influential variables in the support vector machine model were OPN, SAA, CEA, in that order, while the least influential were NSE, SCC, CYFRA. The optimized multi-biomarker panel comprising SAA, CEA, and OPN, with a cut-off value of 0.61, demonstrated sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of 83.59%, 90.10%, 93.16%, and 77.29%, respectively, in the training set. Validation confirmed robust performance with sensitivity of 81.21%, specificity of 86.86%, PPV of 90.87%, and NPV of 74.15%. The multi-biomarker panel outperformed individual biomarkers across all stages of lung cancer, achieving AUC values of 0.9320 in the training set and 0.9230 in the validation set. **Conclusions:** The combined multi-biomarker panel of CEA, SAA, and OPN significantly improves diagnostic performance compared to single biomarkers. This panel represents a promising non-invasive tool for early and accurate lung cancer diagnosis. Research Sponsor: Ministry of SMEs and Startups(MSS, Korea); RS-2024-00437469.

8033 **Poster Session**

A novel aptamer-based non-invasive test for lung cancer: A proof-of-concept. First Author: Line Nederby, Department of Biochemistry and Immunology, Vejle Hospital, University Hospital of Southern Denmark, Vejle, Denmark

Background: Lung cancer (LC) is the leading cause of cancer-related mortality, primarily due to late-stage diagnoses. Low-dose computed tomography (LDCT) screening lowers mortality rates by detecting LC at earlier stages, but the program is limited by high costs, capacity constraints, and low compliance. We describe the early-phase development of a test based on the APTASHAPE technology, designed as a cost-effective, scalable tool to pre-qualify individuals for LDCT screening. This technique uses RNA aptamers to analyze protein composition in lung cancer patients, identifying cancer-specific protein fingerprints across all stages. Variations in aptamer ratios reflect plasma protein composition, profiled through next-generation sequencing and machine learning. **Methods:** A discovery cohort of 24 LC patients (stage I+II, n=12; stage III+IV, n=12) and 24 individuals initially referred on suspicion of LC but ultimately diagnosed as non-cancer cases were analyzed. Additionally, a test cohort of 48 LC patients (stage I+II, n=24; stage III+IV, n=24) and 48 non-LC cases were analyzed. In four rounds of Systematic Evolution of Ligands by EXponential Enrichment (SELEX), a library of 10^{15} 2'-fluoro-protected RNA aptamers was incubated with a pool of plasma prepared from the LC patients in the discovery cohort to facilitate binding to the plasma proteins. Non-binders were removed, and bound aptamers were amplified by PCR. Following SELEX, linear regression identified the aptamers capturing LC-specific protein signatures. The selected aptamers were then applied to the test cohort and their ability to differentiate between LC and non-LC cases was evaluated using principal component analysis and receiver operating characteristic (ROC) curve. **Results:** In the discovery cohort, statistical analysis identified 13 aptamers whose binding to plasma proteins formed a cancer-specific fingerprint, able to discriminate participants with lung cancer from those without. We used this profile to predict LC in the test cohort and obtained an area under the curve (AUC) of 0.74 (95% confidence interval (CI) 0.62-0.87). Importantly, the discriminatory ability was equally effective for stage I+II and stage III+IV (AUC=0.71 (95% CI 0.58-0.84) and AUC=0.74 (95% CI 0.61-0.86), respectively). **Conclusions:** We present a proof-of-concept for a promising, cost-effective, and scalable technique for pre-qualifying individuals for LDCT screening. While still in the earliest stage of development, we anticipate that expanding the study population will improve the machine learning algorithm and markedly increase the AUC value. Importantly, this approach holds significant promise in detecting early-stage lung cancer -an area where blood-based technologies usually face substantial limitations. Ongoing optimizations aim to enhance its performance. Research Sponsor: None.

8034 **Poster Session**

Diagnostic properties of a novel ctDNA assay for lung cancer detection. First Author: Peter Hjorth-Hansen, Department of Oncology, Vejle Hospital, Vejle, Denmark

Background: Lung cancer is a devastating disease, characterized by high mortality rates and limited treatment options once it progresses to advanced stages. Early detection is critical for improving survival outcomes, as curative treatments are only possible in the early stages of the disease. Developing a blood test for lung cancer detection would provide a minimally invasive, highly valuable tool for early diagnosis and could significantly enhance screening efforts. A novel digital droplet polymerase chain reaction multiplex assay was evaluated for its diagnostic accuracy in detecting hypermethylated circulating tumor DNA (ctDNA) in lung cancer in a high-risk population. **Methods:** The study enrolled 249 patients undergoing diagnostic evaluation for suspected lung cancer. Blood samples for ctDNA analysis were collected during the first hospital visit. Lung cancer diagnoses were subsequently determined through clinical workup and assessment by a multidisciplinary team (MDT). If the initial MDT assessment refuted the suspicion of lung cancer, participants were followed for at least 12 months to ensure they did not develop lung cancer in the follow up period. The assay targeted hypermethylated CpG-islands in five genes: *HOXA9, OTX1, MCIDAS, TFAP1B*, and *SP9*. ROC-analyses were performed for the five ctDNA markers alone and in combination. **Results:** The assay, using the combined model of the five markers, showed a sensitivity of 67% (95% Confidence Interval [CI]: 57–76) and a specificity of 77% (95% CI: 69–8) to discriminate cases from cancer-free controls. Positive and negative predictive values were 70% (95% CI: 60–78) and 75% (95% CI: 67–82), respectively. Sensitivity increased to 73% (95% CI: 62–83) in subgroup analysis of stages III and IV lung cancer and cancer-free controls. Notably, the assay successfully detected all 9 cases of small cell lung carcinoma (SCLC) within the cohort. Additional analysis revealed an association in stage IV participants between ctDNA and higher tumor burden, potentially explaining the improved assay performance in these advanced stages. Conversely, amongst the seven false negative stage IV cases, they all had lower tumor burden and were diagnosed with adenocarcinomas. **Conclusions:** The presence of aberrantly methylated ctDNA is a potential diagnostic biomarker for lung cancer. Further optimization of the multiplex assay might improve its overall performance making it a relevant tool for early detection of lung cancer. Importantly, this study was performed in a high-risk cohort, with a lung cancer prevalence of 43%, and hence, the assay would potentially perform better in a screening population. Research Sponsor: None.

8035 **Poster Session**

Actionable gene alterations in resected non-small cell lung cancer (AGA-R study). First Author: Ilaria Attili, Division of Thoracic Oncology, European Institute of Oncology IRCCS, Milano, Italy

Background: To date, molecular testing indication in resected non-small cell lung cancer (NSCLC) is limited to epidermal growth factor receptor (*EGFR*) mutations (mut) and anaplastic lymphoma kinase (*ALK*) rearrangements, because of demonstrated benefit and approval of adjuvant targeted therapies. The use of next generation sequencing (NGS), routinely adopted in the metastatic setting to guide treatment, is very limited in resected NSCLC. The prevalence of driver gene alterations other than *EGFR* and *ALK*, and their impact on adjuvant treatment outcomes, disease recurrence (DR) and survival remain unclear. **Methods:** We retrospectively analyzed molecular, clinical and survival data from consecutive Caucasian patients (pts) who underwent surgery for stage IA-IIIB NSCLC (AJCC 8th Edition) and had NGS performed on tumor tissue between January 2020 and December 2023 at our Institute. Primary endpoint was the prevalence of driver gene alterations in the overall cohort. Exploratory analyses were planned to evaluate DR, disease free survival (DFS) and overall survival (OS) and their relationship with the mutational status. **Results:** Overall, 216 resected NSCLC pts had NGS available. The prevalence of oncogenic driver alterations was 71%, the most common being *KRAS* (30%; 13% G12C and 17% non-G12C), followed by *EGFR* (26%; stage I: 29%), with exon 19 deletions (13%), exon 21 L858R substitution (6%), exon 20 insertion (2%), and uncommon mut (5%). Other detected alterations included *MET* exon 14 skip (6%; stage I: 8%), *BRAF* (4%; 2% V600), and *HER2* exon 20 mut (3%). Only 1% of cases had *ALK* or *RET* rearrangements. The overall prevalence of gene alterations was similar in men (69%) and women (70%), however *KRAS* and *MET* exon 14 skip were reported more frequently in men, *EGFR* in women. Among 181 pts with available follow up (median f up 14mo), n=52 DR events were observed. Median time to DR was 13.5 months (95% CI 11-16mo). Of note, among resected stage I pts with *EGFR* common mut who did not receive adjuvant TKI (n=10), 30% DR occurred. The overall highest DR rates (75%) were observed in the presence of gene fusions, exon 20 ins, and *BRAF* non-V600, followed by (50%) *KRAS* non-G12C and *HER2* mut. The lowest DR rate was observed in *MET* ex14 skip (8%) and BRAF V600 (0%). DR rate in other mut subtypes was similar to that observed in wild-type population. Median DFS was 32 months (24-NA), OS data are still not mature at data cut-off. **Conclusions:** Our study detected driver mutations in 70% of resected NSCLC, including stage I. The prevalence of *EGFR* and *MET* exon 14 skip mut in the early stage setting almost doubled the reported prevalence in the metastatic setting. Differential DR rates according to specific mut subtypes, are hypothesis-generating, and suggest the need of NGS testing to inform prognosis and personalize follow up in current clinical practice. Further investigation on tailored adjuvant treatments, also in stage I resected tumors, is supported by our results. Research Sponsor: None.

8036 **Poster Session**

Tumor type prediction via tissue- and liquid-based comprehensive genomic profiling: High-specificity tobacco signature detection to support lung cancer diagnosis. First Author: Soo-Ryum Yang, Memorial Sloan Kettering Cancer Center, New York, NY

Background: Cigarette smoking exposes the lungs to tobacco mutagens, producing a distinct mutational pattern with elevated tumor mutational burden and strand bias for C>A mutations, aiding identification of lung origin in cancer of unknown primary (CUP). We evaluated a tobacco signature (TSig) caller for diagnosing lung cancer on tissue (TBx) and liquid biopsies (LBx) tested via the FoundationOne CDx (F1CDx) and FoundationOne Liquid CDx (F1LCDx) comprehensive genomic profiling (CGP) assays. **Methods:** We analyzed 351,611 TBx and 68,888 LBx samples, assessing TSigs (COSMIC v2 signatures 4 and 29) in a research use only capacity in cases with $\geq$10 somatic non-driver variants. For LBx, ctDNA tumor fraction (TF) was estimated via aneuploidy, fragment length, and variant features. TSig caller performance and co-occurring genomic alterations were evaluated against submitted diagnoses. Concordance was assessed in paired TBx and LBx samples (TF $\geq$1%) collected within 90 days of one another. **Results:** In all, 20.3% (71,211/351,611) of TBx and 13.6% (9,385/68,888) of LBx specimens had sufficient somatic variants for TSig analysis, with TSigs detected in 13.1% (9,302/71,211) of TBx and 10.2% (954/9,385) of LBx cases. Of TSig+ TBx cases, 87.5% (8,140/9,302) were submitted with a primary lung cancer diagnosis, 6.2% (579/9,302) as CUP, and 6.3% (583/9,302) as non-lung cancer. For TSig+ LBx cases, 81.9% (781/954) were submitted as primary lung cancers, 6.4% (61/954) as CUP, and 11.7% (112/954) as non-lung cancer. TSig+ cases were enriched for *TP53*, *KRAS*, *STK11*, *KEAP1*, *SMARCA4*, and *MET* alterations ($P < 0.001$), consistent with their association with smoking-related lung cancer, regardless of submitted diagnosis, indicating that many cases submitted as CUP or non-lung cancer represented misdiagnosed lung cancers. Conversely, TSig− lung cancers were enriched for *EGFR*, *ALK*, *ROS1*, and *RET* alterations ($P < 0.001$), common in non-smokers. For cases with sufficient variants for TSig analysis, the TBx TSig caller had a high specificity of 97.1% but a lower sensitivity of 26.3%, with an accuracy of 66.3%, positive predictive value (PPV) of 87.5%, and negative predictive value (NPV) of 63.1%. LBx performance was comparable, with 96.7% specificity, 18.6% sensitivity, 61.8% accuracy, 81.9% PPV, and 59.5% NPV. In 272 paired TBx and LBx lung cancer samples, the positive percent agreement for TSig detection was 61.0%. **Conclusions:** TSig analysis identified misdiagnoses in 6.3% of TBx and 11.7% of LBx cases and supported lung origin in 6.3% of CUP cases. High specificity and PPV established TSig+ results as strong indicators of lung cancer, while lower sensitivity reflected the intrinsic limitation of the biomarker in detecting non-smoking-related cancers. These data highlight the utility of F1CDx and F1LCDx TSig analysis in refining lung cancer diagnosis and treatment. Research Sponsor: None.

8037 **Poster Session**

Racial and ethnic disparities in risk of second primary lung cancer among initial lung cancer survivors in the United States. First Author: Pragati Gole Advani, Roswell Park Cancer Institute, Buffalo, NY

Background: Previous studies have reported significant racial/ethnic disparities in incidence and mortality of lung cancer. However, with several studies reporting significantly increased risk of second primary lung cancer (SPLC) among these first primary lung cancer (FPLC) survivors, we sought to examine SPLC risk among FPLC survivors by race/ethnicity and age utilizing a large population-based database. **Methods:** From 17 United States population-based Surveillance, Epidemiology and End Results (SEER) program cancer registry areas, we identified 305,432≥12-month FPLC survivors diagnosed between 2000-2021. Standardized incidence ratios (SIRs) and accompanying 95% confidence intervals (CIs) quantified SPLC risk by race/ethnicity (non-Hispanic White, Black, Asian/Pacific Islander [API] and Hispanic), compared with the general population. Excess SPLC risks were calculated based on SIRs and excess absolute risks (EARs) per 10,000 person-years at risk (PYR). **Results:** Overall, we observed 13,005 SPLCs representing a 5.6-fold significantly increased risk (95% Confidence Interval [CI]=5.51-5.71) among FPLC survivors compared to the general population and an excess of 118 cases per 10,000 PYR. SPLC risk varied significantly by race/ethnicity with Hispanic FPLC survivors presenting highest risk ($SIR_{Hispanic}$=8.42; CI=7.73-9.16) followed by the API and Black patients (SIR_{API}=6.58; CI=6.11-7.07; SIR_{Black}=5.63; CI=5.32-5.96) ($P_{heterogeneity}<0.001$). Although 81% SPLC cases were reported among White FPLC survivors, the SIR compared to the other patients was relatively lower among the White (SIR_{White}=5.45; CI=5.35-5.56). Analysis by age at FPLC diagnosis reported a significantly increasing trend in SPLC risk with decreasing age ($P_{trend}<0.001$). Heterogeneity by race/ethnicity in SIRs was most pronounced in younger, particularly the adolescent and young adult (AYA) patients aged between 20 to 39 years at FPLC diagnosis. Strikingly elevated risk was observed among the Hispanic and API AYA FPLC survivors (SIRs of 49.62 and 87.17, respectively), followed by the corresponding Black and White patients (SIRs of 39.64 and 22.15, respectively) ($P_{heterogeneity}<0.001$). Similar pattern in racial/ethnic and age-related disparity was observed by latency, with higher SPLC risk among the young and minority patients within first 5 years since FPLC diagnosis. **Conclusions:** We observed substantial disparities in SPLC risk by race/ethnicity, with patients belonging to minority groups, particularly the Hispanic, and the AYA age group experiencing higher risks. Further research to understand drivers of these observed racial/ethnic and age-related heterogeneity is warranted. Similarly, tailored surveillance strategies are required to reduce disparities among FPLC survivors by accounting for these patient characteristics. Research Sponsor: None.

8038 **Poster Session**

Longitudinal *EGFR* assessment in plasma and tissue samples in early non–small cell lung cancer (NSCLC). First Author: Sara Torresan, Department of Medicine (DME), University of Udine, Italy and Medical Oncology Department, Vall d'Hebron University Hospital and Vall d'Hebron Institute of Oncology, Barcelona, Spain

Background: Osimertinib has become the standard adjuvant treatment for patients (pts) with surgically resected, early-stage, *EGFR*-mutated non-small cell lung cancer (NSCLC), after the results of the ADAURA trial. However, the temporal distribution of *EGFR* mutations (mut) and its relation with recurrence patterns in this population have not been established yet. Aim of the study is to describe the prevalence of circulating tumor DNA and *EGFR* mut at different timepoints in early-stage NSCLC and the correlation between their presence and prognosis. **Methods:** This is a single center study conducted at the Vall d'Hebron Institute of Oncology, including consecutive pts with surgically resected, stage I-III NSCLC harbouring *EGFR* mut from 2008 to 2024. Next Generation Sequencing (NGS) with ONCOMINE panel was performed on tissue samples, archival when surgery pre-dated the start of the study. NGS on plasma samples was performed using Guardant360 panel at timepoints: 1, 3 and 6 months after surgery and at recurrence. For pts receiving adjuvant osimertinib, additional plasma samples were collected before drug initiation and during treatment. Pts were referred for genetic consultation if NGS on tissue samples detected a *TP53* mut with a variant allele frequency (VAF) >30%, or if NGS on plasma identified *TP53* or *BRCA* mut with a VAF >20%, or a basal T790M mutation. **Results:** Currently, 70 pts were enrolled, of which 24.3% were male. Median age was 68 years, and 35.7% were former/current smokers. Pts with stage IA were 37.1%, IB 24.3%, IIA 2.9%, IIB 11.4%, IIIA 14.3%, IIIB 5.7%. All pts had an EGFR mut, 54.2% detected by NGS on surgical or pre-surgical specimens. *EGFR* mut of the other samples were detected using PCR Cobas, and NGS are ongoing. *EGFR* mut was not detected on plasma after surgery (except for 1). Most pts harboured common mut (47.1% ex19del and 45.7% exon21 L858R on COBAS, 65.6% ex19del and 34.4% exon21 L858R on ONCOMINE). Interestingly, of the 43 pts with post-surgery NGS on plasma, 41.9% had a pathogenic mutation (*TP53* 50%, *ARID1* and *BRCA1/2* 11.1% each, 5.6% each *SMAD4, MPL, TSC1, NOTCH1, JAK2, APC, FGFR1* and *KRAS*) with a median VAF of 0.25% (tissue confirmation is needed to exclude hematopoietic origin). Liquid biopsies were obtained from all pts, with at least one sample collected post-surgery at varying time points. Adjuvant/neoadjuvant chemotherapy was administered to 31.4% of pts, while 17.1% received adjuvant osimertinib (100% after adjuvant osimertinib approbation by local label if indicated) and 11.4% also received radiotherapy. Disease recurrence occurred in 22 patients (31.4%), with 8 being local recurrence. At data lock 83% of pts were alive. **Conclusions:** Evaluation of *EGFR* in early-stage NSCLC should be standard procedure. We aim to identify a pattern associated with higher risk of recurrence and worse prognosis. Dynamic monitoring of *EGFR* could aid in personalising adjuvant treatments and follow-up scheduling. Research Sponsor: None.

8039 **Poster Session**

Clinical utility of pathologist-directed comprehensive comparative molecular profiling for the classification of separate primary lung cancers vs. intrapulmonary metastasis. First Author: Douglas I Lin, Foundation Medicine, Inc., Cambridge, MA

Background: Lung cancers can present as multiple pulmonary tumors, representing either separate primary lung carcinomas (SPLCs) or intrapulmonary metastases (IPMs) arising from a single advanced cancer. Distinguishing SPLCs from IPMs is important for effective staging, prognosis, and treatment. Comparative molecular profiling (CMP) of paired tumors can elucidate their clonal relationship. We report real-world data on the use of CMP to distinguish SPLCs versus IPMs. **Methods:** Paired lung tumors from the same patients, submitted for FoundationOne CDx (F1CDx) comprehensive genomic profiling within a 12-month period from one another between 2014 and 2024, were centrally reviewed by a board-certified pathologist. After excluding clonal hematopoiesis and germline alterations, 1) tumors with different driver alterations were classified as SPLCs, 2) tumors with shared drivers and other alterations as IPMs, and 3) tumors with 1 common driver but different other alterations as SPLCs. The molecular landscapes of SPLCs and IMPs as defined by CMP were subsequently compared. **Results:** In all, 359 paired lung cancers were identified and analyzed using pathologist-directed CMP. Of these, 32.6% (117/359) were classified as SPLCs, 63.8% (229/359) as IPMs, and 1.1% (4/359) as misdiagnoses (i.e., not lung cancer). Among SPLC pairs, 89.7% (105/117) harbored actionable genomic alterations in one tumor but not the other. Classification of 2.5% (9/359) of pairs was inconclusive due to suboptimal sequencing quality control metrics. Misdiagnoses, based on the molecular results, included 2 metastatic HPV-associated carcinomas (supported by high-risk HPV reads), and 2 metastatic cutaneous squamous or basal cell carcinomas (supported by ultraviolet mutational signatures). Of 31 paired lung tumors with different histologies, 67.7% (21/31) were SPLCs, while 32.3% (10/31) were IPMs. Molecular landscape analysis showed that IPMs had significantly higher frequencies of *CDKN2B* (20.1% vs. 10.3%, P=0.03, OR=2.2) and *ERBB2* (6.3% vs. 0.9%, P=0.03, OR=7.8) alterations, while SPLCs were more likely to have elevated tumor mutational burden (i.e., TMB ≥10 Muts/Mb) (39.8% vs. 21.3%, P<0.0001). **Conclusions:** Pathologist-directed CMP using F1CDx facilitates the classification of multiple lung cancers as SPLCs or IMPs and may identify diagnostic errors associated with conventional histopathological examination. The higher prevalence of *ERBB2* alterations in IPMs suggests a role in their development and opportunities for targeted therapy, while the increased rate of elevated TMB in SPLCs indicates a field cancerization effect, driven by smoking or other exposures, and possible responsiveness to immunotherapy. Accurately classifying SPLCs and IPMs is important for proper staging and therapeutic planning in patients with lung cancer. Research Sponsor: None.

8040 **Poster Session**

A window of opportunity study for preoperative brigatinib in resectable anaplastic lymphoma kinase (ALK)-positive non-small-cell lung cancer (NSCLC): WILDERNESS trial. First Author: Chang Gon Kim, Division of Medical Oncology, Department of Internal Medicine, Yonsei Cancer Center, Yonsei University College of Medicine, Seoul, South Korea

Background: Although ALK inhibitors are approved for patients with *ALK*-positive recurrent and/or metastatic NSCLC or resected NSCLC, their role as neoadjuvant therapy in resectable NSCLC remains unclear. Here, we report the results of a window-of-opportunity study evaluating neoadjuvant brigatinib in resectable *ALK*-positive NSCLC, aiming to identify the molecular mechanisms underlying drug-tolerant persister cells in cancer (NCT05361564). **Methods:** We conducted a single-arm, open-label, phase 2 trial of neoadjuvant brigatinib in patients with resectable *ALK*-positive NSCLC. Patients received brigatinib at a dose of 180 mg once daily following a 7-day lead-in period at 90 mg. Radiologic objective response rate (ORR), major pathologic response (MPR) rate, disease-free survival (DFS), event-free survival (EFS), and overall survival (OS) were evaluated. Single-cell transcriptomic analyses were performed to characterize the tumor microenvironment according to the achievement of MPR. **Results:** All 12 enrolled patients underwent surgical resection following neoadjuvant treatment without delays or increased surgical complications. The median time interval between neoadjuvant treatment initiation and surgical resection was 45 days (range: 38-64 days). The ORR was 83.3% (10/12), and MPR (defined as ≤10% residual cancer cells in the surgical specimen) was achieved in 7 patients (58.3%). The most common adverse event was elevated creatine phosphokinase (50.0%), and one patient experienced a grade 3 adverse event (asymptomatic creatine phosphokinase elevation). Over a median follow-up period of 602 days (range: 300–826 days), three patients experienced recurrence, resulting in a 2-year EFS rate of 70.1%. Single-cell transcriptomic analysis revealed that ZNF683-positive CD8+ T cells expressing effector-related genes including Blimp-1, were significantly enriched in patients with MPR. In contrast, FOXP3-positive regulatory CD4+ T cells were enriched in patients without MPR. **Conclusions:** Neoadjuvant brigatinib was effective and safe in patients with resectable *ALK*-positive NSCLC. Single-cell transcriptomic analysis highlights the balance between effector and regulatory T cell programs as a critical determinant of pathologic response and the clearance of drug-tolerant and persister cancer cells. Clinical trial information: NCT05361564. Research Sponsor: None.

8041 **Poster Session**

Genomic landscape of NSCLC with no targetable driver mutation among different races: An exploratory analysis of the AACR Project GENIE Database. First Author: Yazan Hamadneh, University of Jordan, Amman, Jordan

Background: Non-small cell lung cancer (NSCLC) is the most prevalent subtype of lung cancer, and it has been historically associated with poor prognosis. Fortunately, recent advancements in targeted therapies have significantly improved the prognosis of this disease. However, around 40% of those diagnosed with NSCLC do not harbor a targetable oncogenic driver mutation. This percentage is not consistent among all races, as those who are eastern Asian or from eastern Asian descent have higher rates of targetable drivers and a unique genomic signature that makes them distinct to others. Even though Asians have higher rates of targetable NSCLC, about 20% of Asians diagnosed with NSCLC do not harbor targetable mutations. This raises the need to study the genomics of non-targetable NSCLC in different races to understand the nature of the disease and have a more precise understanding of its behavior in different populations. **Methods:** The Association for Cancer Research Project Genomics Evidence Neoplasia Information Exchange (AACR-GENIE) cohort v17.0-public registry was queried to study patients diagnosed with non-targetable NSCLC (n = 16,866). Non-targetable NSCLC was defined as NSCLC that does not harbor targetable driver mutation for the following genes (EGFR, NTRK1/2/3, KRAS, BRAF, MET, RET, NRG1, ERBB2) The patients were divided into three racial groups: White (85.2%), Black (9.5%), and Asian (5.3%). cBioportal was used to study the genetic mutations and clinical differences between the groups. Black & White groups were merged due to the patients' disease having similar genomic features and the group was named non-Asian (94.7%). Chi-squared test was used to measure the relationship between mutation frequencies between different groups. **Results:** A higher proportion of Asian patients with non-targetable mutations were males compared to the non-Asian group (61.96% vs 47.54%,$P < 0.001$). The most significant differences were found in 4 genes: *KRAS* (Asian 21.16%, non-Asian 30.22%, $P < 0.001$), *STK11* (Asian 9.88%, non-Asian 17.58%, $P < 0.001$), *KEAP1* (Asian 13.61%, non-Asian 20.50% ,$P < 0.001$), and *TERT* (Asian 12.22%, non-Asian 7.56%, $P < 0.001$). There was a significant difference in the prevalence of *TP53* mutations (Asian 52.13%, non-Asian 56.31%, P = 0.0232). **Conclusions:** Among non-targetable driver mutations, KRAS, KEAP1, STK11 and TP53 were less frequent in the Asian group vs non-Asian, while TERT was higher in the Asian group. These differences can be explained by variation in carcinogens exposure (smoking rates) and the unique genetic profile between ethnicities. It supports the significance of ethnicity and racial background even in the era of precision medicine. Research Sponsor: None.

8042 **Poster Session**

Trends in lung cancer epidemiology and mortality over 12 years: Socioeconomic and demographic disparities. First Author: Ali Shahbaz Baloch, John H. Stroger, Jr. Hospital of Cook County, Chicago, IL

Background: Lung cancer (LC), the most common cancer worldwide, remains a significant health burden with high rate of incidence and mortality in the United States and worldwide. Studies show that Black patients are 15% less likely to obtain an early diagnosis and have lower 5-year survival compared to White patients. **Methods:** The National Inpatient Sample database (2010–2021) was analyzed to identify adult hospitalizations with LC as a primary or secondary diagnosis. Multivariate logistic regression assessed epidemiologic and mortality trends and their association with demographic factors. **Results:** A total of 1,462,998 hospitalizations were identified with LC between 2020 and 2021. Of these, 196,225 patients (13.4%, 95% CI: 13.2–13.6) received palliative care. For metastatic LC admissions (n = 574,935), 21.5% (123,577) received palliative treatment. In 2010, the mean patient age was 67.6 years, which went up to 69.1 years in 2021. The percentage of LC patients with age over 65 years increased from 62.7% to 68.3%, whereas for patients under 45 and those between 45 and 65 years old, the percentage decreased from 2.0% to 1.4%, and 35.3% to 30.3%, respectively. The percentage of women diagnosed with lung cancer increased from 47.1% to 52.3% in 12 years. From 2010-2021, overall mortality from LC decreased (OR 0.96, 95% CI: 0.95–0.96). However, mortality was found to be lower in females (OR 0.80, 95% CI: 0.78–0.82, $p < 0.001$), and higher in Blacks than Whites (OR 1.07, 95% CI: 1.02–1.17, p = 0.003), and higher in those over 65 than in those between the ages of 18 and 45 (OR 1.11, 95% CI: 0.99–1.24, p = 0.063). Mortality rates were greater among Black people across all genders. While age-related differences were not significant among females, older age was linked to higher mortality among males (OR 1.15, 95% CI: 0.99–1.34, p = 0.066). Across all ethnicities, the death rate was consistently lower for females. Only White people showed substantial variations in age-related mortality, with older patients having higher mortality. Mortality rates within the lowest income bracket were the same for any age and ethnic group. Conversely, Black people had a higher mortality rate than White people in the highest income category (OR 1.24, 95% CI: 1.08–1.41, p = 0.002). **Conclusions:** Over the years, while LC mortality has decreased overall, disparities persisted with Black patients showing higher mortality compared to Whites, even in the higher income brackets. Increased mortality was associated with older age and male gender. These findings highlight the need for targeted interventions to address racial, gender, and socioeconomic disparities and to improve the survival of the identified high-risk population, especially minorities. Research Sponsor: None.

8043 **Poster Session**

Safety and efficacy of radiotherapy combined with anlotinib in locally advanced non-small cell lung cancer patients intolerant to concurrent chemoradiotherapy: Preliminary result of a phase II clinical trial. First Author: Yupei Yuan, Cancer Hospital Chinese Academy of Medical Sciences, Beijing, China

Background: Concurrent chemoradiotherapy (cCRT) is the standard treatment for patients with unresectable locally advanced non-small cell lung cancer (LA-NSCLC). However, parts of patients only receive sequential chemoradiotherapy (sCRT) due to various reasons. This phase II study aimed to improve the outcomes of patients receiving sCRT by combining anti-angiogenesis therapy (anlotinib) during radiotherapy course. **Methods:** Patients with unresectable LA-NSCLC intolerable to cCRT were prospectively enrolled. Induction chemotherapy with or without immunotherapy were given for 4-6 cycles. Then patients were prescribed oral 12 mg anlotinib up for 3 cycles during radiotherapy. The primary endpoint is 2-year overall survival (OS). Acute adverse events (AEs) were defined as any treatment related events from the start of radiotherapy until 3 months post-radiotherapy. The trial has been registered in ChiCTR.org as ChiCTR2200060712. **Results:** From October 2020 to January 2024, 41 patients with stage II-III NSCLC were enrolled. 11 (26.8%) patients received induction chemotherapy and 30 (73.2%) patients received induction chemotherapy combined with immunotherapy. The rate of grade 3–4 acute hematological AEs was 29.3% (12 cases). The rates of grade 3 hemoptysis were 2.4% (1 case), with no grade 4 hemoptysis reported. The incidence of grade 3–4 radiation pneumonitis was 9.8% (4/41). No grade 5 AEs occurred in all patients. The median follow-up was 16.8 (range: 7.0–50.7) months. 22 (53.7%) patients experienced recurrence, including 5 patients (12.2%) with primary-site recurrence and 7 patients (17.1%) with regional-node recurrence, 12 patients (29.3%) had distant metastases. The median progression-free survival (PFS) was 18.9 months (95% CI 14.6-23.2 months) and 1-year PFS was 77.2%. 9 patients (22.0%) died, including 3 patients who died of covid-19 pneumonia during the follow-up period, 1 patient who died of hydatid pneumonia due to long-term bed rest after cerebral infarction, and 4 patients who died of tumor-related diseases. The 1-year overall survival was 89.9%. **Conclusions:** Our data first showed the combination of thoracic radiotherapy and anti-angiogenesis therapy (anlotinib) is of safety, well controlled toxicity, and efficacy for inoperable LA-NSCNC patients who cannot tolerate cCRT. Clinical trial information: ChiCTR2200060712. Research Sponsor: Beijing Hope Run Special Fund of Cancer Foundation of China (LC2020A14); Chinese Academy of Medical Sciences (CAMS) Innovation Fund for Medical Sciences (2024-I2M-C&T-B-065).

8044 **Poster Session**

Clinical characteristics and prognosis of pulmonary lymphoepithelioma-like carcinoma: A multicentre retrospective study. First Author: Zan Hou, Department of Radiation Oncology, Sichuan Clinical Research Center for Cancer, Sichuan Cancer Hospital & Institute, Sichuan Cancer Center, Affiliated Cancer Hospital of University of Electronic Science and Technology of China, Chengdu, Sichuan, China

Background: Pulmonary lymphoepithelioma-like carcinoma (PLELC) is a rare form of squamous lung cancer, and large-scale clinical studies on its clinical features, prognosis at different stages, and outcomes following treatments are limited. **Methods:** Patients with PLELC diagnosed by pathology from January 2009 to December 2023 at Sichuan Cancer Hospital and Sun Yat-sen University Cancer Centre were retrospectively analysed. Survival curves were estimated using the Kaplan-Meier method, Log-rank tests were used to compare differences between groups, and the Bonferroni method was used to correct the p-value when two-by-two comparisons between multiple groups were involved. **Results:** A total of 1,106 PLELC patients were included in the study. Most patients were non-smokers (73.4%), and brain metastasis was rare (0.3%). Tumor-specific characteristics showed a low incidence of EGFR mutation (0.6%) but a high prevalence of PD-L1 positivity (71.6%). The median follow-up duration was 31.6 months. The two-year overall survival (OS) rates for stage I, II, III, and IV patients were 99.4%, 97.7%, 92.7%, and 70.4%, respectively, while the five-year OS rates were 94.8%, 88.7%, 70.6%, and 37.8%, respectively. No statistically significant differences in progression-free survival (PFS) or OS were observed between surgery alone and surgery combined with adjuvant therapy in stage I and II patients, or between radiochemotherapy and combined surgery-radiochemotherapy in stage IIIA and IIIB patients. However, in stage IV patients, chemotherapy combined with immunotherapy resulted in significantly better PFS and OS compared to chemotherapy alone. **Conclusions:** PLELC patients, mostly non-smokers with rare brain metastasis and high PD-L1 positivity, show favorable prognosis, but further research is needed to refine its optimal treatment strategies. Research Sponsor: None.

PFS and OS in patients with different stages.

Stage	Number of cases	Median PFS (months)	2-year PFS	95% CI	5-year PFS	95% CI	Median OS (months)	2-year OS	95% CI	5-year OS	95% CI
IA	145	108.3	94.0%	88.9%-99.1%	75.6%	63.2%-88%	Incalcu	99.1%	97.3%-100%	95.7%	90.7%-100%
IB	56	119.2	78.0%	65.3%-90.7%	65.2%	49.5%-80.9%	Incalcu	100.0%	100%-100%	93.5%	84.8%-100%
IIA	37	Incalcu	85.4%	70.1%-100%	62.9%	40.9%-85%	Incalcu	100.0%	100%-100%	96.2%	88.8%-100%
IIB	104	87.9	78.0%	68.6%-87.4%	60.0%	47.2%-72.8%	Incalcu	96.9%	93.6%-100%	85.6%	77.1%-94.1%
IIIA	213	47.9	70.6%	63.5%-77.7%	42.8%	33.9%-51.7%	161.5	97.9%	95.9%-99.9%	79.7%	72.4%-87%
IIIB	132	24.6	51.1%	41.3%-60.9%	21.3%	11.7%-30.9%	83.7	87.9%	81.6%-94.2%	65.3%	54.8%-75.8%
IIIC	73	22.0	44.0%	29.5%-58.5%	24.7%	8.4%-41%	53.5	84.9%	75.3%-94.5%	49.4%	31.8%-67%
IVA	123	12.0	29.8%	20.4%-39.2%	0.0%	0%-4.5%	50.0	79.3%	70.9%-87.7%	44.1%	30.9%-57.3%
IVB	223	9.0	16.0%	10.3%-21.7%	2.7%	0%-6%	33.6	65.4%	58.1%-72.7%	34.1%	24.3%-43.9%

Incalcu: Incalculable; CI: confidence interval.

8045 **Poster Session**

Neoadjuvant immunotherapy and surgery in patients with stage IIIB-IIIC (N3) non-small cell lung cancer. First Author: Wen-Yu Zhai, Sun Yat-sen University Cancer Center, Guangzhou, Guangdong, China

Background: Stage IIIB-IIIC (N3) non-small cell lung cancer (NSCLC) is generally seen as unresectable, and Durvalumab following concurrent chemoradiotherapy (CCRT) is the standard of care for these patients. The use of immune checkpoint inhibitor (ICI) in neoadjuvant therapy has resulted in unprecedented rates of pathological response and lymph node downstaging, which has made resecting previous unresectable disease possible. However, it remains uncertain whether certain N3 patients may derive survival benefit from surgery after neoadjuvant immunotherapy. **Methods:** This multicenter retrospective study included patients with cN3 NSCLC who received inducing immunochemotherapy and completed surgery. As a comparison, patients with cN3 NSCLC who received ICI following CCRT, ICI plus CCRT, and CCRT following inducing immunochemotherapy were also included. 1:1 Propensity score matching (PSM) was implemented to balance important baseline characteristics included gender, age, smoking history, histologic type, differentiated degree, cT stage between patients with surgery and radiotherapy. Log-rank test was used to compared progression-free survival (PFS). **Results:** The median follow-up time of 82 patients with surgery and 114 patients with radiotherapy was 28.1 months and 21.8 months, respectively. In patients with surgery, 29 patients reach complete pathological response (pCR) and 53 patients reached node clearance. After PSM, 74 patients with surgery and 74 patients with radiotherapy showed balanced baseline characteristics. Before PSM, patients with surgery displayed a significant advantage in median PFS (24.6 months vs 21.3 months, p=0.040) but this advantage disappeared after PSM (31.3 months vs 30.8 months, p=0.132). In post-treatment subgroup analyses, patients reached pCR had better PFS than patients with radiotherapy (median PFS not reach vs 30.8 months, p=0.001). In addition, patients reached node clearance also had better PFS than patients with radiotherapy (median PFS not reach vs 30.8 months, p=0.010). In pre-treatment subgroup analyses, surgery did not outperform radiotherapy in male or female patients, smokers or nonsmokers, squamous or non-squamous carcinoma and poorly differentiated carcinoma. In patients with high or moderately differentiated tumors, patients with surgery had better PFS than patients with radiotherapy (median PFS not reach vs 13.2 months, p=0.001). **Conclusions:** In patients with cN3 NSCLC, surgery after neoadjuvant immunochemotherapy do not transcend ICI with CCRT in PFS. Only patients with high or moderately differentiated tumors, or reached pCR, node clearance after surgery have better PFS than patients with radiotherapy. Prospective clinical is needed to evaluate the benefit of surgery after neoadjuvant immunotherapy for cN3 NSCLC. Research Sponsor: None.

8046 **Poster Session**

Neoadjuvant durvalumab (D) + chemotherapy (CT) + novel anticancer agents and adjuvant D ± novel agents in resectable non-small-cell lung cancer (NSCLC): Updated outcomes from NeoCOAST-2. First Author: Tina Cascone, Department of Thoracic/Head and Neck Medical Oncology, The University of Texas MD Anderson Cancer Center, Houston, TX

Background: Perioperative CT + immune checkpoint inhibitor therapy has improved outcomes in resectable NSCLC but most patients (pts) still do not experience pathological complete response (pCR) and long-term benefit. We report final pCR rates, ongoing circulating tumor DNA (ctDNA) findings, and updated safety data from Arms 1/2/4 of NeoCOAST-2 (NCT05061550), a phase 2 platform study evaluating neoadjuvant and adjuvant D ± novel agent-based combinations in pts with untreated Stage IIA–IIIB resectable NSCLC. **Methods:** Pts were stratified by PD-L1 expression (<1% vs ≥1%) and randomized to neoadjuvant D + platinum-doublet CT + oleclumab (anti-CD73 monoclonal antibody [mAb]) then adjuvant D + oleclumab (Arm 1), neoadjuvant D + platinum-doublet CT + monalizumab (anti-NKG2A mAb) then adjuvant D + monalizumab (Arm 2), or neoadjuvant D + single-agent platinum CT + Dato-DXd (TROP2-directed antibody-drug conjugate [ADC]) then adjuvant D (Arm 4). Neoadjuvant therapy was given Q3W for 4 cycles. Adjuvant therapy was given for up to 1 year or until disease progression. Primary endpoints were pCR rate by blinded independent pathology review and safety and tolerability. Key secondary endpoints included major pathological response (mPR) rate, ctDNA clearance, and feasibility of surgery. **Results:** As of Dec 19 2024, 202 pts were randomized (Arms 1/2/4, N=76/72/54). Among dosed pts with confirmed NSCLC, pCR and mPR rates were numerically higher in Arm 4 vs Arms 1/2 overall and in pts with a PD-L1 TPS <1% or ≥1% (Table). Rates of ctDNA clearance in the neoadjuvant period were higher in Arm 4 vs Arms 1/2, and higher in pts with pCR vs non-pCR and with mPR vs non-mPR across arms. Among dosed pts, 69/74 (93.2%) pts in Arm 1, 66/71 (93.0%) pts in Arm 2, and 51/54 (94.4%) pts in Arm 4 underwent surgery; overall, grade ≥3 treatment-related adverse events occurred in 36.5%, 40.8%, and 20.4% of pts, respectively. **Conclusions:** All arms show that novel perioperative combinations may improve pCR rates and maintain tolerability and feasibility of surgery in resectable NSCLC. The final analysis of pCR and mPR rates in Arm 4 is the first for an ADC in this setting and confirms the encouraging efficacy and manageable safety profile of D + CT + Dato-DXd. Presurgical ctDNA clearance is associated with pathological responses. Clinical trial information: NCT05061550. Research Sponsor: AstraZeneca.

	Arm 1	Arm 2	Arm 4
Overall, n (%) [95% CI]	n=74	n=70	n=54
pCR	**15 (20.3) [11.8–31.2]**	**18 (25.7) [16.0–37.6]**	**19 (35.2) [22.7–49.4]**
mPR	31 (41.9) [30.5–53.9]	35 (50.0) [37.8–62.2]	34 (63.0) [48.7–75.7]
PD-L1 TPS <1%, n (%)	n=25	n=28	n=16
pCR	**4 (16.0)**	**5 (17.9)**	**5 (31.3)**
mPR	10 (40.0)	10 (35.7)	10 (62.5)
PD-L1 TPS ≥1%, n (%)	n=49	n=42	n=38
pCR	**11 (22.4)**	**13 (31.0)**	**14 (36.8)**
mPR	21 (42.9)	25 (59.5)	24 (63.2)

8047 **Poster Session**

Initial treatment and survival outcomes for early-stage NSCLC in Veterans: Insights from cancer cube data. First Author: Madison Panell, Albany Medical Center Hospital, Albany, NY

Background: Non-small cell lung cancer (NSCLC) accounts for 85% of lung cancer cases and remains the leading cause of cancer-related deaths in the United States. Early-stage NSCLC (Stage I) is potentially curable, with surgical resection as the standard of care. However, for patients who are medically inoperable or decline surgery, stereotactic ablative radiotherapy (SABR) is an alternative. Prior studies suggest that demographic factors, including age, race, and sex, may influence treatment decisions and outcomes, particularly among veterans with a high burden of comorbidities. This study examines treatment patterns and survival outcomes for veterans with Stage I NSCLC using data from the Veterans Affairs Cancer Care Cube. **Methods:** This retrospective study included veterans diagnosed with Stage I NSCLC between 2000 and 2023. Patients were categorized by initial treatment (surgery or radiation therapy) and stratified by demographics (age, race/ethnicity, gender, and ECOG status). Survival outcomes were analyzed using Kaplan-Meier curves, log-rank tests, and Cox proportional hazards models to control for confounding variables. Logistic regression identified predictors of treatment choice. Patients with incomplete data or advanced-stage disease were excluded. Statistical analyses were conducted using R and Python. **Results:** Surgery demonstrated superior survival outcomes across all demographics. ▪ Age: Surgery offered significantly higher 5-year survival rates in younger (40–59 years, 41.77–54.32%) and older (>70 years, 42.32%) patients compared to radiation (0–24.68%). ▪ Race: Surgery utilization was consistent across racial groups, with the highest 5-year survival in Asian patients (60.87%). Native Hawaiian/Pacific Islander (NHPI) patients had the lowest survival for both treatments, highlighting disparities in care. ▪ Sex: Women were more likely to undergo surgery (71.79%) and had better survival outcomes than men, similar to trends seen in non-veteran populations. ▪ ECOG Status: Surgery remained the preferred treatment across all ECOG scores, though long-term survival declined with higher ECOG scores. ▪ Exposure Type: Agent Orange and asbestos exposure were associated with the best survival outcomes following surgery, while radiation offered limited long-term benefits regardless of exposure. **Conclusions:** Surgery consistently yields better survival outcomes than radiation therapy for veterans with early-stage NSCLC, even among subgroups with higher comorbidity burdens. Demographic and exposure-related disparities highlight the need for tailored interventions to optimize care. These findings inform clinical decision-making and emphasize the importance of equitable access to curative treatments in this vulnerable population. Research Sponsor: None.

8048 **Poster Session**

Survival of induction aumolertinib followed by aumolertinib and concurrent radiotherapy (RT) in unresectable *EGFR*-mutated stage III NSCLC: Final analysis of the phase III ADVANCE trial and real-world data. First Author: Nan Bi, National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital & Shenzhen Hospital, Beijing, China

Background: The LAURA trial established concurrent chemoradiotherapy (cCRT) followed by consolidation targeted therapy as the standard for unresectable stage III EGFR-mutated non-small cell lung cancer (NSCLC). The phase III ADVANCE trial (ChiCTR2000040590) evaluated induction aumolertinib followed by aumolertinib and concurrent RT versus cCRT. **Methods:** Eligible patients (pts) aged 18-75 with unresectable stage III non-squamous NSCLC and centrally confirmed *EGFR* exon 19 deletion or L858R mutation were randomized 1:1 to receive aumolertinib+RT (experimental) or cCRT (control). The primary endpoint was progression-free survival (PFS), assessed by investigator. The accrual target was 98 pts, aiming for a hazard ratio (HR) of 0.5 (80% power, one-sided α =0.025). A real-world database (RWD; NCT04304638) from 6 trial sites was developed to validate long-term survival outcomes for pts treated with RT and third-generation EGFR TKIs. **Results:** Between March 2021 and March 2024, 43 eligible pts were randomized (24 to experimental, 19 to control) following early termination due to feasibility issues. At a median follow-up of 25.5 months (mo), the experimental group showed significantly longer PFS (34.0 vs. 7.8 mo; HR 0.15, 95% CI 0.06–0.24). Median overall survival (OS) was not reached in the experimental group but was 30.5 mo in the control (p = 0.17). The control group reported more neutropenia (52.6% vs. 16.7%, p = 0.01) and nausea (26.3% vs. 0.0%, p = 0.03), while quality of life was better in the experimental group. Among 18 experimental and 16 control pts completing RT without progression, the experimental group had significantly longer PFS (not reached vs. 12.8 mo; HR 0.05, 95% CI 0.01–0.16) and OS (HR 0.09, 95% CI 0.01–0.68). From 2012 to 2024, 125 consecutive pts were included in the RWD cohort: 31 in RT + TKI, 33 in CRT + TKI, and 61 in CRT. At a median follow-up of 32.7 mo, PFS and OS were significantly longer in RT + TKI and CRT + TKI compared to CRT (PFS: not reached vs. 36.7 vs. 9.8 mo; OS: not reached vs. not reached vs. 48.9 mo; p < 0.001). No significant differences in PFS and OS were observed between RT + TKI and CRT + TKI (p=0.59 and 0.80, respectively). **Conclusions:** The ADVANCE trial and RWD demonstrate that induction EGRF TKI followed by TKIs and RT delays progression and improves survival in unresectable stage III EGFR-mutated NSCLC. Clinical trial information: ChiCTR2000040590. Research Sponsor: None.

8049 **Poster Session**

A prospective, single-arm, phase II study to evaluate the efficacy and safety of perioperative tislelizumab in resectable non-small-cell lung cancer (NSCLC). First Author: Daqiang Sun, Department of Thoracic Surgery, Tianjin Chest Hospital, Tianjin, China

Background: Perioperative immunotherapy has emerged as a promising strategy for the treatment of resectable non-small cell lung cancer (NSCLC). This study was designed to evaluate the efficacy and safety of a comprehensive perioperative regimen, comprising neoadjuvant tislelizumab in combination with chemotherapy, followed by surgical resection and adjuvant tislelizumab, in patients with resectable stage II-IIIB NSCLC. **Methods:** This open-label, single-arm, phase 2 trial was designed to enroll patients (pts) with resectable stage II-IIIB (N2) NSCLC (AJCC 8th edition). Participants received neoadjuvant therapy consisting of intravenous tislelizumab in combination with chemotherapy administered every 3 weeks for 2 to 4 cycles prior to surgery, and 0 to 2 cycles following surgery (totaling up to 4 cycles of perioperative therapy). This was followed by adjuvant tislelizumab monotherapy administered Q3W for 1 year. The primary endpoint of the study was the major pathological response (MPR) rate. Secondary endpoints included the pathological complete response (pCR) rate, objective response rate (ORR), event-free survival (EFS), overall survival (OS), and safety. **Results:** Between February 2023 and June 2024, a total of 30 patients were enrolled. The median age was 64 years (range: 43-77 years), with 25 males (83.3%). Twenty-eight patients (93.3%) had squamous cell carcinoma, while 2 patients (6.7%) had adenocarcinoma. In terms of disease stage, 12 patients (40%) were at stage II, and 18 patients (60%) were at stage III. For treatment, 23 patients (76.7%) received three cycles of neoadjuvant immunotherapy, and 7 patients (23.3%) received four cycles. The objective response rate (ORR) was 53.3% and surgical resection was performed in 27 patients (90%), with a complete (R0) resection rate of 96.3% (26/27). A major pathological response (MPR) was observed in 53.3% (16/30) of patients, and the pathological complete response (pCR) rate was 33.3%(10/30). With a median follow-up of 12.1 months, the median event-free survival (EFS) and overall survival (OS) data were not yet mature. In the intention-to-treat (ITT) population, the 1-year EFS rate and OS rate were 92.3% and 96.7%, respectively. During the neoadjuvant phase, the incidence of treatment-related adverse events (TRAEs) of any grade was 70%, with grade 3-4 adverse reactions occurring in 13% of patients. **Conclusions:** Perioperative tislelizumab achieved notable major pathological response (MPR) and pathological complete response (pCR) rates, while also demonstrating feasible surgical resection and manageable toxicity in patients with stage II-IIIB non-small cell lung cancer (NSCLC). The current data align with the initial findings and underscore the need for continued follow-up to further validate these outcomes. Clinical trial information: ChiCTR2300068140. Research Sponsor: None.

8050 **Poster Session**

Characteristics, treatment patterns, and outcomes of HIV-associated lung cancer. First Author: Tina Roy, Georgetown Lombardi Comprehensive Cancer Center, Washington, DC

Background: Lung cancer is a leading cause of cancer-related mortality in people with HIV (PWH). Prior studies have shown worse survival in PWH with lung cancer compared to people without HIV (PWoH) with lung cancer. However, it is unclear whether this difference in survival is due to differences in tumor biology, socioeconomic factors, and/or treatment disparities. **Methods:** This is a retrospective study of PWH and lung cancer identified from 2005 - 2024 within MedStar Health serving a major urban area with a high burden of HIV. Age and race matched PWoH and lung cancer were used as a control group. Clinical, pathological, and molecular characteristics, along with social determinants of health, treatment patterns, and outcomes were collected. Factors associated with survival and receipt of stage-appropriate treatment were determined using multivariable analysis. **Results:** We analyzed 148 PWH with lung cancer and 127 PWoH with lung cancer. The median age at lung cancer diagnosis among PWH was 61.8 years, with a statistically significant trend of increasing age over the study period. PWH were disproportionately male (65%), unmarried (62%), had government provided health insurance (79%), and had more comorbidities compared to the control group. The stage at diagnosis was similar between both groups, with 68% of PWH and 66% of PWoH diagnosed at stage III and IV, and no evidence of stage migration to earlier stage observed over the study period. Similar rates of KRAS/EGFR/ALK/BRAF alterations were observed. Stage-appropriate treatment was received by 70% of PWH and 82% of PWoH (p=0.057). Median OS (mOS) in stages I and II was 5.8 years in PWH and 8.8 years in PWoH (p=0.22). Across all stages, mOS was 1.5 years in PWH and 1.9 years in PWoH (p=0.23); the difference in mOS was attenuated when comparing patients who received stage-appropriate treatment (p=0.52). Among PWH with lung cancer, factors associated with improved survival included receipt of chemotherapy (HR 0.35, p$<$0.001) and immunotherapy (HR 0.53, p=0.042), and higher CD4 count ($>$400 cells/mm3) at diagnosis (p=0.013). Factors that contributed to whether PWH received stage appropriate treatment were based on performance status, with an ECOG $\geq$3 significantly associated with lower likelihood of receiving treatment (OR 0.01, p=0.003). Among PWH, 96 were eligible for lung cancer screening per the USPSTF criteria, but only 7 patients (7.3%) were diagnosed through a screening CT scan. **Conclusions:** Decreased CD4 count, poor performance status at presentation, and advanced disease stage at diagnosis may contribute to worse outcomes in PWH with lung cancer. The lower rate of diagnosis through lung cancer screening and the potential number of eligible patients at the time of lung cancer diagnosis highlight missed opportunities for early detection in PWH. Targeted interventions to address barriers to timely diagnosis and stage-appropriate treatment could improve survival outcomes in PWH. Research Sponsor: U.S. National Institutes of Health.

8051 **Poster Session**

Impact of lymph node characteristics on clinical outcomes in clinical N2 non-small cell lung cancer patients treated with chemoradiotherapy: Single- vs. multiple-stations, bulky vs. non-bulky and discrete vs. infiltrative. First Author: Yuki Kato, National Cancer Center Hospital East, Kashiwa, Japan

Background: Stage III, N2 non-small cell lung cancer (NSCLC) is a heterogeneous disease with various patterns of lymph node metastasis. Recently, chemoradiotherapy followed by immune-checkpoint inhibitors (ICIs) and neoadjuvant chemotherapy with ICIs followed by surgery have been developed as treatment strategies for clinical N2 (cN2) NSCLC. However, the difference of clinical outcomes according to cN2 subclassification, such as single- vs. multiple-stations, non-bulky vs. bulky and discrete vs. infiltrative, in NSCLC patients treated with chemoradiotherapy are still unclear. **Methods:** The clinical outcomes in cN2 NSCLC patients who received chemoradiotherapy at our institution were retrospectively investigated and compared according to cN2 subclassification; single- vs. multiple-stations, non-bulky vs. bulky (short-axis diameter$\geqq$2cm) and discrete vs. infiltrative. **Results:** A total of 146 cN2M0 NSCLC patients received chemoradiotherapy from May 2018 to December 2023, and 98 (67%) patients received durvalumab after chemoradiotherapy. As of January 2025, the median follow-up was 20.9 months. The characteristics of the patients were showed that the median age was 71 (range 40-88) year-old, 77% were male, 89% had smoking history, 99% were ECOG PS 0-1, 44% had histology of adenocarcinoma and 23% were PD-L1 (22C3) $\geq$50%. Among them, 69 patients (47%) had single-station N2, 90 patients (62%) had non-bulky N2, and 81 patients (55%) had discrete N2. There was no significant difference of the progression-free survival (PFS) in the patients who received chemoradiotherapy between single- vs. multiple-stations (median: 17.5 vs. 12.5 months, HR [95%CI]: 0.90 [0.60–1.37], *P* = 0.63), non-bulky vs. bulky (median: 15.6 vs. 12.3 months, HR [95%CI]: 0.98 [0.64–1.50], *P* = 0.92), and discrete vs. infiltrative (median: 18.2 vs. 12.0 months, HR [95%CI]: 0.72 [0.47–1.08], *P* = 0.11). Similarly, there was no significant difference in the overall survival (OS) in the patients who received chemoradiotherapy between single- vs. multiple-stations (median: NR vs. NR months, HR [95%CI]: 1.01 [0.59–1.72], *P* = 0.97), non-bulky vs. bulky (median: 51.4 vs. NR months, HR [95%CI]: 1.06 [0.61–1.84], *P* = 0.84), and discrete vs. infiltrative (median: 51.4 vs. NR months, HR [95%CI]: 0.89 [0.52–1.52], *P* = 0.67). In the patients who received durvalumab after chemoradiotherapy, there was no significant difference in the PFS and OS according to cN2 subclassification. The time to recurrence in the radiated field showed no significant difference between single- vs. multiple-stations, non-bulky vs. bulky and discrete vs. infiltrative. **Conclusions:** Lymph node characteristics have no impact on clinical outcomes in cN2M0 NSCLC patients treated with chemoradiotherapy. Research Sponsor: None.

8052 **Poster Session**

Outcomes with neoadjuvant chemotherapy and/or osimertinib in patients with *EGFR*-mutant resectable non-small cell lung cancers. First Author: Prashasti Agrawal, Memorial Sloan Kettering Cancer Center, New York, NY

Background: There are currently no *EGFR*-tyrosine kinase inhibitors approved for neoadjuvant treatment of resectable *EGFR*-mutant non-small cell lung cancers (NSCLC). The phase III multi-center trial NeoADAURA aims to evaluate neoadjuvant osimertinib with or without chemotherapy versus chemotherapy alone in patients with resectable *EGFR*-mutant NSCLC. The primary endpoint of NeoADAURA is major pathologic response (MPR) rate. The statistical assumptions for the chemotherapy control arm were derived from the literature in NSCLC but not specific to an *EGFR*-mutant population. The true rates of pathologic response to neoadjuvant chemotherapy in patients with *EGFR*-mutant NSCLC are unknown. We report a multi-institutional analysis of surgical and pathologic outcomes in patients with resectable *EGFR*-mutant NSCLC treated with neoadjuvant therapies. **Methods:** This retrospective study evaluated patients at Memorial Sloan Kettering Cancer Center and Dana Farber Cancer Institute with stage II-IIIB N2 (AJCC v8) NSCLC with *EGFR* exon 19 deletions, exon 21 L858R mutations, or exon 18 G719X mutations who received neoadjuvant platinum-based doublet chemotherapy and/or neoadjuvant off-label osimertinib and underwent surgical resection with curative intent. Clinical characteristics, tumor next-generation sequencing results, R0 resection rate, pathologic complete response (pCR) rate, MPR rate, and downstaging rate were evaluated. **Results:** 51 patients with *EGFR*-mutant NSCLC met eligibility criteria and were treated with neoadjuvant osimertinib alone (N=23, 45.1%), platinum-based doublet chemotherapy alone (N=18, 35.3%), or osimertinib and platinum-based doublet chemotherapy (N=10, 19.6%). R0 resection rates were 91.3% with osimertinib, 72.2% with chemotherapy, and 90% with osimertinib and chemotherapy. Rates of pCR were 17.4% with osimertinib, 0% with chemotherapy, and 0% with osimertinib and chemotherapy. Rates of MPR were 43.5% with osimertinib, 0% with chemotherapy, and 10% with osimertinib and chemotherapy. Pathologic tumor downstaging occurred in 47.8% with osimertinib, 44.4% with chemotherapy, and 40% with osimertinib and chemotherapy; pathologic lymph node downstaging occurred in 34.8% with osimertinib, 27.8% with chemotherapy, and 40% with osimertinib and chemotherapy. Among the 4 patients with pCR, 3 had stage IIIA and 1 had stage IIIB adenocarcinomas at diagnosis; three had ex.19 deletions and 1 had an ex.21 L858R mutation. The most common co-occurring tumor genomic alterations were in *TP53* (49%), *CDKN2A/B* (14%), and *RB1* (10%). **Conclusions:** In this real-world multi-institution series, we did not observe pCR or MPR in patients with *EGFR*-mutant NSCLC treated with neoadjuvant chemotherapy. EGFR inhibitors may play an important role in the preoperative management of *EGFR*-mutant lung cancer. Research Sponsor: National Cancer Institute; P30 CA008748.

8053 **Poster Session**

Leveraging electronic medical records for early lung cancer diagnosis: An evaluation of the C the Signs AI cancer prediction platform using the Mayo data platform. First Author: Seema Dadhania, Imperial College, London, London, United Kingdom

Background: In the US, only 27.4% of lung cancer cases are diagnosed early, with 5-year survival rates of 63% for localized and 27% for late-stage cancers. Despite recommendations since 2012 for screening high-risk individuals with low-dose CT, uptake has been limited, and most lung cancer diagnoses occur after symptoms appear. Similarly, chest x-rays, while commonly used as an initial test to investigate patients with symptomatic suspected lung cancer, have demonstrated limited sensitivities between 50-70% and specificities over 80%. Symptoms often overlap with common conditions, making detection challenging, and studies have identified median delays of 187 days from symptom onset to diagnosis. This prolonged interval presents an opportunity for improvement. This study examines the use of the AI cancer prediction platform, C the Signs, to passively screen for lung cancer by leveraging electronic medical records (EMRs) for early lung cancer detection. **Methods:** Utilizing the Mayo data platform, we conducted a retrospective analysis of EMR data from 894,409 patients, including 7,395 individuals diagnosed with lung cancer. We assessed the sensitivity and specificity of the AI cancer prediction platform, in identifying patients at risk of lung cancer. Additionally, we compared the timing of lung cancer risk identification by the AI cancer prediction platform with the timing of diagnoses made by physicians to determine whether the platform enabled earlier detection. **Results:** The AI cancer prediction platform detected 6,749 cases of lung cancer among the 7,395 individuals diagnosed, resulting in an early detection sensitivity of 91.5%. The platform identified 423,249 false positives among the 887,014 patients who did not have lung cancer, leading to a specificity of 52.3%. Additionally, it identified the risk of a lung cancer diagnosis in 26.6% of patients up to five years earlier than the diagnoses made by physicians. **Conclusions:** This study highlights the potential of leveraging EMR data and AI platforms like C the Signs to enhance early lung cancer detection. Chest X-rays, with their reduced sensitivity for early-stage lesions and reliance on symptom-driven use, remain limited as a screening tool. In contrast, the AI platform achieved a sensitivity of 91.5% and identified 26.6% of cases up to five years earlier than traditional diagnoses. These findings underscore the promise of AI-based platforms as supplementary tools for improving early detection and facilitating timely intervention to enhance patient outcomes. Research Sponsor: None.

8054 **Poster Session**

Survival impact of lymphocytopenia during chemoradiation in locally advanced NSCLC patients treated with adjuvant durvalumab. First Author: Monika Satoskar, The Ohio State University, Columbus, OH

Background: Adjuvant durvalumab has transformed the treatment landscape for patients with locally advanced non-small cell lung cancer (NSCLC) following concurrent chemoradiotherapy (CRT). However, in the landmark PACIFIC trial, only one-third of patients achieved long-term disease-free survival, underscoring the need for additional biomarkers to guide patient selection. Lymphocytopenia, a common side effect of CRT, has been associated with poor responses to immunotherapy. In this study, we investigate the incidence, degree, and timing of CRT-induced lymphocytopenia and association with survival among patients receiving durvalumab adjuvant therapy. **Methods:** This retrospective study included patients with unresectable Stage III NSCLC who underwent CRT followed by at least one dose of durvalumab at The Ohio State University. Clinical data was extracted through review of electronic medical records. Absolute lymphocyte count (ALC) was collected at baseline prior to CRT initiation, the lowest ALC during CRT, and 30 days post-CRT. Lymphocytopenia was classified using the Common Terminology Criteria for Adverse Events V5. Overall survival (OS) was calculated from CRT initiation to date of death or loss to follow-up. Cox proportional hazards model was used to evaluate the associations of baseline, lowest, post-CRT ALC, as well as the percentage change in ALC from baseline to lowest (relative ALC change) with OS. **Results:** This study included 118 patients with a mean age of 63.9 years (SD: 9.7), who received durvalumab within 12 weeks of completing CRT. Baseline characteristics were obtained (Table 1). Median baseline ALC was 1645 cells/μL (IQR: 1340–2190), dropping to 300 cells/μL (IQR: 200–450) during CRT and 755 cells/μL (IQR: 510–1040) post-CRT. Grade $\geq$3 lymphocytopenia occurred in 97 patients (82.2%) during CRT. Baseline, lowest, and post-CRT ALC were not associated with OS, but the relative decline in ALC from baseline was strongly associated. A 10% decrease in ALC from baseline was associated with a 48% increased risk of death (HR = 1.48; 95% CI: 1.14–1.91; $p < 0.01$) after adjusting for age, ECOG performance status (PS), histology, PD-L1 expression, chemotherapy regimen, and RT duration. **Conclusions:** Dynamic change in ALC from pre-treatment baseline to nadir during CRT is a strong prognostic indicator for OS in patients with advanced NSCLC receiving adjuvant durvalumab. Studies are warranted to elucidate the underlying mechanisms. Additionally, this highlights lymphocytopenia as a potentially modifiable side effect, which could be addressed with myeloprotective treatment. Research Sponsor: None.

Baseline characteristics.

Characteristic	No. of Patients (%)
ECOG PS = 0	18 (15.4)
ECOG PS = 1	80 (68.4)
Positive PD-L1 expression	80 (76.9)
Squamous cell vs. other	51 (43.2); 67 (56.8)
Weekly carboplatin/paclitaxel vs. other	88 (74.6); 30 (25.4)

8055 **Poster Session**

Lung cancer screening in high-risk never-smokers with artificial intelligence (LC-SHIELD study). First Author: Molly SC Li, The Chinese University of Hong Kong, Hong Kong, China

Background: Approximately 50% of Asian lung cancer patients are never smokers. Screening with low-dose computed tomography (LDCT) of thorax in high-risk never-smokers with family history may reduce mortality. However, implementation of LDCT screening in Asia faces barriers including high cost and shortage of radiologists. Artificial intelligence (AI) programmes designed for automated detection of lung nodules may serve as first-readers, facilitating cost reduction and improving efficiency. LC-SHIELD is a prospective study designed to evaluate the feasibility and clinical utilization of AI-based lung cancer screening in a high-risk never smoker population. **Methods:** This study enrolled never smokers, defined as individuals with a lifetime exposure to fewer than 100 cigarettes, aged between 50 and 75 years, with at least one first-degree relative diagnosed with lung cancer. Participants underwent LDCT of thorax, and the scans were analyzed using LungSIGHT, an AI-assisted software fine-tuned with local data for lung nodule detection. Nodules with a maximum diameter of $\geq$5mm are classified as AI-positive and referred to radiologists for formal reporting and workup. As a gold standard all scans are retrospectively reviewed by radiologists who are blinded to the LungSIGHT results. Primary endpoint is baseline detection rate of early stage lung cancer and secondary endpoints include sensitivity and specificity of LungSIGHT in nodule detection compared to radiologist assessment. The target sample size is 1000 and here we report the interim analysis. **Results:** Between July and December 2024, total of 405 subjects were enrolled. Median age was 61 (range 50-75) and 266 (66%) were female. Three patients were diagnosed with invasive adenocarcinoma (lung cancer detection rate 0.7%, all EGFR mutation positive) and 12 individuals (3.0%) had suspicious lung nodules requiring further diagnostic workup. Testing of AI algorithm was based on the first 181 subjects. At the testing phase, 78 (43%) were AI-positive with sensitivity and specificity at 81% and 85%, respectively. In the validation cohort (n=224), 86 (39%) were AI-positive with sensitivity and specificity at 73% and 77%, respectively. **Conclusions:** AI assisted first-reader of screening LDCT in high-risk never smokers is feasible. LungSIGHT showed high sensitivity and specificity in lung nodule detection using standard radiologist assessment as gold standard comparator. Recruitment for the study is ongoing. Clinical trial information: NCT06295497. Research Sponsor: AstraZeneca.

8057 **Poster Session**

Enhancing early detection of lung cancer: Methylation anchor probe for low-signal enrichment (MAPLE). First Author: Wenzhao Zhong, Guangdong Lung Cancer Institute, Guangdong Provincial People's Hospital (Guangdong Academy of Medical Sciences), Southern Medical University, Guangzhou, China

Background: Non-Small Cell Lung Cancer (NSCLC) is among the most lethal cancers worldwide. Lung adenocarcinoma (LUAD) and lung squamous cell carcinoma (LUSC) represent approximately 80% of NSCLC cases in China. While low-dose computed tomography (LDCT) is widely used for annual screening, its high false-positive rate highlights the need for more accurate early detection methods. Circulating tumor DNA (ctDNA) analysis provides a promising non-invasive alternative for early cancer detection. However, conventional hybrid capture methods lack the sensitivity to detect low-abundance ctDNA in early-stage cancers. Previously, we developed ultra-sensitive Methylation Anchor Probes for Low signal Enrichment (MAPLE) that significantly improved the detection of colorectal cancer (Xie et al., 2024). Here, we have advanced this technology to develop a novel assay to enhance early detection of NSCLC and distinguish LUAD from LUSC, paving the way for more personalized treatment strategies. **Methods:** NSCLC-related methylation haplotypes were identified using in-house whole-genome bisulfite sequencing data from lung cancer tumor tissues and paired normal adjacent tissues (NATs). Haplotype selection was performed by filtering for those with a frequency difference greater than 0.1 between tumor and NATs and a frequency below 0.001 in healthy cfDNA, resulting in a panel targeting 12,904 methylation haplotypes. The panel was evaluated on 234 clinical samples, including 44 LUSC patients, 43 LUAD patients, 19 individuals with chronic obstructive pulmonary disease (COPD), and 128 healthy controls. All cfDNA samples underwent bisulfite conversion, library preparation, hybrid capture using the custom panel, and next-generation sequencing (NGS). The dataset was split into a 75% training set and a 25% validation set. A primary classifier was developed to identify cancer samples, and true positives were further analyzed with a subtype classifier to differentiate between LUAD and LUSC. Model performance was assessed for robustness using 40 resampling processes. **Results:** The methylation panel combined with a machine-learning classifier achieved an AUC of 0.93 (0.93–0.93) in the training set and 0.91 (0.91–0.92) in the validation set in the detection of NSCLC. Furthermore, the assay effectively distinguished COPD patients from cancer cases, with a specificity of 92.5% (90.0%–95.9%). Additionally, the subtype classifier accurately differentiated LUAD from LUSC with 100% accuracy. **Conclusions:** We developed a technique to specifically enrich NSCLC-related methylation haplotypes, improving sensitivity for early-stage NSCLC detection. The assay demonstrated strong performance in accurately distinguishing LUAD from LUSC, highlighting its potential to guide treatment decisions. The MAPLE platform is versatile and shows promise for broader applications in cancer early detection. Research Sponsor: Shanghai Xiaohe Medical Laboratory Co., Ltd.

8058 Poster Session

Hypofraction radiotherapy followed by immune checkpoint inhibitors for locally advanced non-small cell lung cancer: A phase I/II trial. First Author: Xiao-yang Li, Anhui Provincial Hospital, Hefei, China

Background: To explore the safety and primary efficacy of hypofraction radiotherapy followed by immune checkpoint inhibitors (ICI) for stage III locally advanced non-small cell lung cancer patients. **Methods:** Patients with stage III non-small cell lung cancer were enrolled to receive hypofraction radiotherapy (48-64Gy/12-16f) followed by ICI maintenance treatment. After the completion of radiotherapy, one-year maintenance ICI treatment was encouraged. The primary objective was to explore the toxicity of hypofractionated radiotherapy with immunotherapy. The secondary objective was survival outcome. We also performed multicolor immunohistochemistry (mIHC) of tumor tissues, peripheral blood single-cell RNA sequencing (scRNA-seq) and flow cytometry to characterize the immune microenvironment of enrolled patients. **Results:** According to the inclusion criteria, totally 51 patients were enrolled from June 2021 to January 2024. The median follow-up time was 28 months (8-22 months). After the completion of hypofractionated radiotherapy, 13 patients received no or less than 5 cycles of immunotherapy. All kinds of radiation-induced toxicity (≥ grade 3) occurred in 17 patients (33.3%). The rate of over grade 3 PBT injury and over grade 3 radiation-induced pneumonitis was 3.9% and 17.6% respectively, resulting in 11.8% of over grade 3 cough and 9.8% of over grade 3 dyspnea. No over grade 3 radiation-induced esophagitis occurred. The median progression-free survival (PFS) was 28 months with 1-year PFS rate of 72.1% and 2-year PFS rate of 54.7%. The median overall survival (OS) was not reached with 1-year OS rate of 84.0% and 2-year OS rate of 61.6%. In subgroup analysis, high-dose (60-64Gy/15-16f) group did not demonstrate survival benefit to low-dose group (48-52Gy/12-13f), but more grade III and higher toxicity (41.2% vs. 17.6%, p=0.002). In addition, mIHC, scRNA-seq and flow cytometry showed an increase in the number of anti-tumor immune cells in the treated tumor tissues, as well as an expansion of T-cell clones with cytotoxic T-cell phenotype and enhanced anti-tumor activity of neutrophils in the peripheral blood. **Conclusions:** Hypofraction radiotherapy (48-64 Gy/12-16f) with ICI treatment was safe and efficient. But the use of high dose (over 60Gy/15f) should be alerted due to its toxicity. Further, hypofraction radiotherapy can provide patients with an immune-activated tumor microenvironment that makes them respond better to immunotherapy. Clinical trial information: NCT05269485. Research Sponsor: NSFC 82102821.

Clinical characteristic of total patients.

	Total patients n=51	High-dose Subgroup (≥60 Gy) n=34	Low-dose Subgroup (<60 Gy) n=17	Statistical Method and p value
Gender				
Male	48 (94.1%)	33 (97.1%)	15 (88.2%)	χ^2 test
Female	3 (5.9%)	1 (2.9%)	2 (11.8%)	p=0.255
Age				
Median (Range)	69 (41-84)	65 (51-83)	70 (41-84)	Independent sample t-test p=0.916
Clinical Stage				
II	4 (7.8%)	2 (5.9%)	2 (11.8%)	Mann-Whitney p=0.304
IIIA	11 (21.6%)	8 (23.5%)	3 (17.6%)	
IIIB	23 (45.1%)	13 (38.2)	10 (58.8%)	
IIIC	13(25.5%)	11 (32.4)	2 (11.8%)	
Pathology				
Squamous Cell Carcinoma	41 (80.4%)	29 (85.3%)	12 (70.6%)	χ^2 test
Adenocarcinoma	10 (19.6%)	5 (14.7%)	5 (29.4%)	p=0.190
Tumor Location				
Centrally Located	38 (74.5%)	30 (88.2%)	8 (47.1%)	χ^2 test
Peripherally Located	13 (25.5%)	4 (11.8%)	7 (52.9%)	p=0.003
Treatment Modality				
No Inductive ICI Therapy	24 (47.1%)	19 (55.9%)	5 (29.4%)	χ^2 test
Inductive ICI Therapy	14 (27.5%)	6 (17.6%)	8 (47.1))	p=0.071
CRT only	13 (25.5%)	9 (26.5%)	4 (23.5%)	
Cycles of ICI Treatment				
Median (Range)	3 (0-24)	2 (0-24)	4 (0-24)	Independent sample t-test p=0.776
Type of ICI				
PD-1 Inhibitors	21 (41.2%)	11 (32.4%)	10 (58.8%)	χ^2 test
PD-L1 Inhibitors	16 (31.4%)	13 (38.2%)	3 (17.6%)	p=0.220
PD-L1 level				
<1%				
1-50%				
>50%				
ITV Volume				
Median (Range)	69.44 (17.05-297.10)	73.24 (21.96-297.10)	69.44 (17.05-144.92)	Independent sample t-test p=0.198
PTV Volume				
Median (Range)	169.19 (64.75-548.64)	174.78 (78.11-548.64)	155.27 (64.75-323.03)	Independent sample t-test p=0.370

8059 Poster Session

Clinical outcomes with definitive surgery or radiotherapy after neoadjuvant immunochemotherapy in stage II-III NSCLC: Full cohort pragmatic analysis. First Author: Jie He, National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China

Background: Recently, several landmark randomized controlled trials on neoadjuvant immunochemotherapy (NIC) have significantly changed the treatment paradigm for locally advanced NSCLC. However, 8.8-19.0% of patients (pts) receiving NIC did not undergo surgery due to various reasons. The treatment strategies and clinical outcomes following NIC for stage II-III NSCLC, encompassing both surgical and non-surgical approaches, remain unclear. **Methods:** We conducted a multicenter, retrospective cohort study involving stage II-III (T1-4N0-2) pts who underwent radical surgery or radiotherapy after NIC in routine clinical practice across 12 medical centers in China between January 2018 and December 2023. For pts receiving radical radiotherapy, we documented the reasons for non-surgical management, and planned surgical procedures. Propensity score matching (PSM) was performed based on age, gender, smoking history, clinical stage, and histology to balance the clinicopathologic characteristics. The primary outcomes were progression free survival (PFS) and overall survival (OS). **Results:** 967 pts were included: 683 (70.6%) underwent surgery and 284 (29.4%) received radiotherapy. Reasons for radiotherapy after NIC included potentially resectable but declined surgery after shared decision-making (65.5%, 186/284), functionally unresectable (14.4%, 41/284), and technically unresectable (20.1%, 57/284), respectively. At the database lock (November 24, 2024; median follow-up: 23.3 months), PFS (HR: 0.32, 95% CI: 0.23-0.44, p<0.001) and OS (HR: 0.41, 95% CI: 0.26-0.66, p<0.001) were significantly improved in pts undergoing surgery after PSM. PFS across most key subgroups favored surgery: stage IIIA (HR: 0.34, 95% CI: 0.21-0.55, p <0.001), stage IIIB (HR: 0.39, 95% CI: 0.24-0.63, p <0.001), (planned) pneumonectomy (HR: 0.47, 95% CI: 0.26-0.85, p=0.013) and (planned) lobectomy (HR: 0.24, 95% CI: 0.13-0.45, p<0.001). However, the pts planned for pneumonectomy in radiotherapy group exhibited similar OS compared to those undergoing pneumonectomy. **Conclusions:** Among pts with locally advanced NSCLC treated with NIC, radical surgery demonstrated long-term clinical benefit. Research Sponsor: None.

	Subgroups	N (S)	N (R)	HR (95% CI)	p-value
PFS	All patients	365	183	0.32 (0.23, 0.44)	<0.001
	Disease stage				
	II	34	17	0.05 (0.01, 0.24)	<0.001
	IIIA	175	89	0.34 (0.21, 0.55)	<0.001
	IIIB	142	76	0.39 (0.24, 0.63)	<0.001
	(Planned) Surgery				
	Pneumonectomy	66	66	0.47 (0.26, 0.85)	0.013
	Left pneumonectomy	46	46	0.52 (0.26, 1.04)	0.066
	Lobectomy	106	54	0.24 (0.13, 0.45)	<0.001
OS	All patients	365	183	0.41 (0.26, 0.66)	<0.001
	Disease stage				
	II	34	17	0.08 (0.01, 0.44)	0.004
	IIIA	175	89	0.60 (0.28, 1.25)	0.17
	IIIB	142	76	0.45 (0.23, 0.87)	0.018
	(Planned) Sugery				
	Pneumonectomy	66	66	0.87 (0.37, 2.06)	0.76
	Left pneumonectomy	46	46	0.59 (0.23, 1.49)	0.26
	Lobectomy	106	54	0.33 (0.14, 0.76)	0.009

8060 Poster Session

ImmunoDriver-1: Driver alterations (dAlts) and their immunological implications in early and metastatic non-small cell lung cancer (NSCLC). First Author: Jay M. Lee, Division of Thoracic Surgery, University of California, Los Angeles (UCLA), Los Angeles, CA

Background: NSCLC treatments and clinical trials include targeted agents and immunotherapy (IO) across stages, yet dAlts and how they relate to the tumor immune microenvironment (TIME) are incompletely characterized in early NSCLC (eNSCLC; stage I-III) and metastatic NSCLC (mNSCLC; stage IV). Here, we evaluated the NSCLC TIME by dAlt status to inform IO biomarker strategies. **Methods:** From the Tempus Database, we selected de-identified lung adenocarcinoma samples sequenced by xT DNA assay (eNSCLC n=5,535; mNSCLC n=10,299), a subset with whole transcriptome analysis. Targetable dAlts were defined as classic (c) (L858R and exon 19 del) or non-classic (nc) *EGFR*, *KRAS* G12C, other non-G12C variants, other guideline defined dAlts (ALK, ROS1, RET, NTRK1-3 fusions, ERBB2 alt, METex14), or no dAlt. Immune cell proportions were estimated by quanTIseq. Additional markers, PD-L1 TPS (IHC) and TMB (mt/mB; DNAseq) were analyzed. Significance ($p<0.05$) was assessed using χ^2 or Wilcoxon/Kruskal-Wallis rank sum tests. **Results:** The dAlt prevalence was similar ($|\Delta| < 2\%$) across early and late stage (Overall %: cEGFR=13, ncEGFR=2.9, KRAS G12C=15 and KRASother=22). The prevalence of other dAlt were less than 4% across stages. The CD8 proportion was higher in eNSCLC than mNSCLC ($p<0.001$). Across stages, CD4 Treg and CD8 proportions in the *KRAS* G12C cohort were nearly identical to the non-dAlt cohort, while c/nc*EGFR* tumors exhibited the lowest percentage of CD8 cells and higher Tregs cells compared to non-dAlt tumors (Table). PD-L1 and TMB were similar between *KRAS* G12C and non-dAlt tumors and lowest among c/nc*EGFR* (Table). **Conclusions:** This real-world analysis demonstrated similar dAlt prevalence across eNSCLC and mNSCLC, while the TIME was distinct across stage and dAlts. The TIME of *KRAS* G12C tumors was similar to non-dAlt tumors, and was least immunogenic in the c/nc*EGFR* cohort. These findings highlight immunological differences across stages and dAlts that should be considered when developing IO strategies. Research Sponsor: Tempus AI, Inc.

Group	IO marker	Overall	No dAlt	cEGFR	ncEGFR	KRAS G12C	KRAS other	Other dAlt
eNSCLC		1.3 (0.5, 2.4)	1.4 (0.6, 2.8)	0.9 (0.4, 1.7)	1.0 (0.5, 1.9)	1.4 (0.6, 2.6)	1.3 (0.5, 2.4)	1.1 (0.5, 2.1)
	% CD8 cells[1]*							
	% Tregs[1]*	6.9 (4.8, 9.2)	6.3 (4.2, 8.8)	7.4 (5.6, 9.4)	8.2 (5.8, 10.3)	7.0 (5.1, 9.3)	7.1 (5.2, 9.3)	6.7 (4.6, 8.6)
	% PDL1[2]*	22	20	9.3	7.9	31	25	24
	TMB*	5.8 (3.2, 9.5)	7.9 (3.7, 13.2)	3.2 (2.1, 4.7	4.2 (2.3, 6.3)	6.8 (4.2, 10.0)	5.8 (3.7, 8.9)	3.2 (1.6, 5.3)
mNSCLC		0.6 (0.04, 1.6)	0.8 (0.1, 1.9)	0.4 (0.0, 1.3)	0.5 (0.0, 1.5)	0.7 (0.1, 1.7)	0.5 (0.01, 1.5)	0.5 (0.0, 1.4)
	% CD8 cells[1]*							
	%Tregs[1]*	4.0 (2.6, 5.9)	3.8 (2.4, 5.6)	4.2 (2.9, 6.1)	4.7 (3.0, 6.8)	4.2 (2.7, 6.0)	4.0 (2.6, 6.0)	3.9 (2.6, 5.6)
	% PDL1[2]*	28	24	15	17	37	34	34
	TMB*	5.8 (3.2, 10.0)	7.9 (4.2, 13.1)	3.7 (2.1, 5.8)	4.2 (2.6, 6.8)	7.4 (5.2, 11.1)	6.3 (4.2, 10.0)	3.2 (1.6, 5.8)

[1]Median (IQR); [2]PDL1 >50; *p<0.001, excluding "Overall."

8061 Poster Session

Unique mutational landscape and therapeutic implications in non-small cell lung cancer with comorbid fibrotic interstitial lung disease. First Author: Jacob Michalski, Stanford Health Care, Stanford, CA

Background: Patients with established interstitial lung disease (ILD) have both increased risk of developing non-small cell lung cancer (NSCLC) and higher mortality than patients without a history of ILD. We hypothesized the mutational landscape of NSCLC arising in the setting of ILD would be different than sporadic or smoking-associated cancers, potentially leading to different treatment options given the question of safety of immune checkpoint inhibitors (ICIs) in this population. **Methods:** We retrospectively identified 330 patients with NSCLC, of which 77 patients had pre-existing diagnoses of ILD with probable or definite usual-interstitial pattern made by radiographic or biopsy findings for comparison to randomly selected patients with NSCLC without clinically apparent ILD. Clinical characteristics, histologic information, mutational data, and treatment regimens were collected using the Stanford Research Repository and compared between patients with NSCLC and established ILD (LC-ILD) and NSCLC without ILD (LC). Statistical comparisons between groups were done with Mann-Whitney testing with significance set at $p<0.05$. **Results:** Baseline characteristics including age, sex, race, ethnicity, smoking status, NSCLC type, and NSCLC stage at diagnosis did not differ between the LC-IPF and LC groups. There was significantly lower prevalence of *EGFR* mutations in the LC-IPF group (33.0% vs 3.0%, $p<0.0001$) and significantly higher prevalence of *KRAS G12D* mutations (19.0% vs 41.7%, p=0.05). Baseline tumor proportion score (TPS) between LC and LC-ILD groups was not significantly different (28.2% vs 16.3%, p=0.063) however there were significantly fewer patients with high PD-L1 expression (TPS ≥ 50%) in the LC-ILD group (32.0% vs 16.7%, p=0.036). Occurrence of clinically significant treatment-related pneumonitis occurred in 15 patients in the LC-ILD group with etiologies identified as radiation (n=8, N=20, 40.0%), surgery (n=1, N=40, 2.5%), osimertinib (n=1, N=1, 100%), pembrolizumab (n=2, N=5, 40.0%), docetaxel (n=2, N=4, 50.0%, and pemetrexed (n=1, N=19, 5.7%). **Conclusions:** These retrospective data highlight the differences in driver mutations in NSCLC in patients with preceding fibrotic lung disease, suggesting potentially divergent biologic underpinnings for tumorigenesis. These results, particularly the under-representation of *EGFR*-mutations, over-representation of KRAS G12D mutations, and scarcity of therapeutically actionable mutations in the LC-ILD population, lead to limited therapeutic options. Surgically-associated pneumonitis was rare, but radiation, docetaxel, and pembrolizumab appeared high risk for pneumonitis in treated patients, suggesting need careful consideration of risks when treating this unique population. Research Sponsor: None.

8062 **Poster Session**

Differential prognostic significance of distant and locoregional recurrence on survival in surgically resected non-small cell lung cancer post-chemotherapy: Multicenter dynamic prediction with landmark model. First Author: Zeliang Ma, National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China

Background: Recurrence remains a significant challenge in patients with surgically resected non-small cell lung cancer (NSCLC) following adjuvant chemotherapy. Recurrence status evolves over the course of follow-up, dynamically influencing survival outcomes. This study aimed to investigate the differential impact of distant metastasis (DM) and locoregional recurrence (LR) on survival, and to develop prognostic models to guide treatment strategies and individualize follow-up protocols. **Methods:** From four institutions, patients with pN2 NSCLC who underwent complete resection followed by four cycles of platinum-based doublet chemotherapy were included. A dynamic prediction landmark model was constructed to assess the impact of LR and DM on survival. The primary endpoint was overall survival (OS). Baseline factors included age, sex, smoking history, histology, tumor laterality, pT stage, and the number of positive lymph nodes, while DM and LR status were treated as time-dependent covariates. **Results:** A total of 2,120 patients were included in the study, with a median follow-up time of 55.80 months (IQR: 39.47–85.12). The landmark model identified older age, smoking history, advanced T stage, DM, and LR as significant factors associated with worse OS. DM had the most substantial impact on OS (odds ratio [OR], 3.85; 95% CI, 3.32–4.48; $P < 0.01$), while LR also significantly decreased OS (OR, 2.07; 95% CI, 1.73–2.47; $P < 0.01$). Multivariate Cox analysis revealed that the pT stage, number of positive lymph nodes, and histology were independently associated with DM. A nomogram was developed to predict the risk of DM for individual patients, categorizing them into three distinct risk subgroups. Postoperative radiotherapy did not significantly improve OS in the low- or high-risk subgroups but demonstrated a survival benefit in the medium-risk subgroup (hazard ratio [HR], 0.73; 95% CI, 0.63–0.87; $P < 0.01$). Intensified systemic therapy and closer monitoring would be required for patients in the high-risk subgroup. **Conclusions:** The dynamic prediction model estimated future survival probabilities based on individual recurrence status throughout follow-up in patients with surgically resected NSCLC post-chemotherapy. Both DM and LR significantly affected OS, with DM being more detrimental. The DM risk nomogram aids in assessing the benefits of additional treatments and guiding personalized follow-up strategies. Research Sponsor: None.

8063 **Poster Session**

Neoadjuvant hypofractionated radiotherapy plus tislelizumab with anlotinib followed by adjuvant tislelizumab with anlotinib in patients with resectable non-small cell lung cancer (NSCLC): Preliminary analysis of a phase II trial (NEO-PIONEER). First Author: Min Fang, Zhejiang Cancer Hospital (Zhejiang Cancer Center), Hangzhou, China

Background: Although neoadjuvant immune checkpoint inhibitors (ICIs) combined with chemotherapy is the current standard of care for resectable NSCLC, the optimal combination strategy to improve efficacy with low toxicity remains to be explored. Preclinical and clinical studies have shown that anti-angiogenic therapy can enhance the efficacy of immunotherapy and sensitize radiotherapy through a variety of mechanisms. We designed a trial to test the activity of triple therapy of radiotherapy, angiogenesis inhibitors and ICIs for resectable NSCLC. **Methods:** This is a prospective, single-arm, phase II (NCT06379087) to explore the efficacy and safety of hypofractionated radiotherapy followed by sequential tislelizumab and anlotinib in the perioperative treatment of resectable NSCLC. A total of 20 eligible patients aged 18 years or older, with histologically confirmed stage II/IIIA resectable NSCLC, and without prior systemic anticancer treatment or known EGFR mutations, ALK rearrangements or ROS1 fusions are enrolled. The treatment regimen involved hypofractionated radiotherapy on d1-3 (24 Gy/3 fractions), followed by tislelizumab plus anlotinib within 1 week for 2 cycles after radiotherapy. Patients without disease progression after two cycles were followed by surgical resection within 4-6 weeks after the last dose of neoadjuvant treatment, and receive adjuvant treatment with tislelizumab plus anlotinib after surgery up to 1 year. The primary endpoint was pCR rate. And the secondary endpoint was MPR rate, 1-year EFS rate and the incidence of treatment-related AE. **Results:** Between May 1, 2024, and December 31, 2024, a total of 10 patients were enrolled. 6 (60%) of them had pathological stage IIIA. All patients enrolled have completed radiotherapy and 2 cycles of neoadjuvant treatment with tislelizumab plus anlotinib. 1 patient experienced disease progression following neoadjuvant and did not receive surgery. 7 patients have underwent surgery. While 2 patients were waiting surgery. Among the 7 patients who underwent surgery, 5 (71.4%) of 7 patients achieved pCR, all 7 patients demonstrated a MPR. In terms of safety, 1 patient experienced grade 3-4 treatment related adverse events, which was alanine aminotransferase and aspartate aminotransferase. There were no treatment-related deaths reported during the study period. **Conclusions:** Preoperative hypofractionated radiotherapy followed by immunotherapy and anti-angiogenesis therapy is tolerable, leads to a clinically significant pCR. Clinical trial information: NCT06379087. Research Sponsor: None.

8064 **Poster Session**

Five-year survival outcomes from CRES^{3}T: S-1 plus cisplatin with concurrent radical-dose radiotherapy followed by surgery for superior sulcus tumor. First Author: Kazuya Takamochi, Department of General Thoracic Surgery, Juntendo University School of Medicine, Tokyo, Japan

Background: CRES^{3}T is a multicenter, single-arm, confirmatory trial of S-1 plus cisplatin and concurrent radical-dose thoracic radiotherapy (TRT) followed by surgery in patients with superior sulcus tumor (SST). The 3-year overall survival (OS) and progression-free survival (PFS) rates were 73% (95% confidence interval [CI]; 60–83%) and 53% (95% CI; 40–65%), respectively. The primary endpoint, 3-year OS rate, was met. We report the exploratory analyses of survival outcomes approximately 5 years after the last patient was enrolled. **Methods:** Patients with SST (pathologically proven non-small cell lung cancer that directly invades the chest wall, including the first rib or further cephalad, subclavian artery, or subclavian vein according to computed tomography or magnetic resonance imaging) received induction therapy comprising three cycles of S-1 plus cisplatin with concurrent TRT (66 Gy in 33 fractions) followed by surgery. S-1 was administered orally at 40 mg/m^2 twice daily for 14 days along with an intravenous infusion of cisplatin (60 mg/m^2) on day 1. The treatment cycles were repeated every four weeks. The 5-year OS, 5-year PFS, and patterns of postoperative recurrence were analyzed. Prognostic factors of OS were analyzed in patients who underwent surgical resection using Cox proportional hazard model. **Results:** The median follow-up duration for 60 eligible patients was 67.1 months. The 5-year OS and PFS rates were 66.3% (95% CI; 52.8–76.8) and 48.1% (95% CI: 35.0–60.0), respectively. The median follow-up duration for 49 patients with surgical resection was 71.0 months. The 5-year OS and PFS rates were 71.0% (95% CI; 56.0–81.7) and 52.8% (95% CI: 37.9–65.6), respectively. Age was the only significant prognostic factor for OS (P = 0.01, HR 1.1, 95% CI; 1.02–1.20). Sex, smoking status, clinical T stage, clinical N stage (cN0 versus cN1/ipsilateral supraclavicular cN3), symptoms associated with brachial plexus involvement, histology, preoperative serum CEA and CYFRA levels, pathological complete response, and major pathological response had no significant prognostic impacts on OS. Twenty (41%) patients developed postoperative relapse. The patterns of postoperative relapse were locoregional only in one (2%), distant metastasis only in 16 (33%), and both in three (6%) patients. **Conclusions:** Better 5-year survival outcomes of CRES^{3}T compared to those in the pivotal studies (5-year OS: 56% in JCOG9806 and 44% in SWOG9416/INT0160) indicated that induction therapy using S-1 plus cisplatin and concurrent radical-dose TRT followed by surgery could be a new standard treatment for patients with SST. Clinical trial information: s031180401. Research Sponsor: None.

8065 **Poster Session**

Initial results of a screening trial for evaluating oncogenic drivers in Japanese patients with surgically resected early-stage non-small cell lung cancer: LC-SCRUM-Advantage. First Author: Yuki Matsumura, National Cancer Center Hospital East, Kashiwa, Japan

Background: The LC-SCRUM-Advantage is a screening trial to evaluate oncogenic drivers in patients with surgically resected early-stage non-small cell lung cancer (NSCLC). Recent clinical trials, such as the ADAURA and ALINA trials, have demonstrated the efficacy of molecular targeted therapy as adjuvant therapy following surgery for patients with early-stage NSCLC harboring oncogenic drivers. Our study aims to determine the proportion of early-stage NSCLC with any actionable oncogenic drivers that are candidates for adjuvant targeted therapy. This abstract presents the initial data collected until Dec 2024. **Methods:** Patients with operable clinical stage I to III NSCLC were eligible for this study. Surgical tumor samples were collected post-surgery, and genomic analysis of oncogenic drivers was centrally evaluated using a next-generation sequencing system, the Oncomine Precision Assay, which targets 50 gene alterations. PD-L1 immunohistochemistry using the 22C3 antibody was also performed on the submitted tumor samples. If possible, preoperative biopsy tumor samples were also collected and evaluated using the AmoyDx Pan Lung Cancer PCR Panel. An actionable oncogene was defined as EGFR, ALK, ROS1, KRAS, BRAF, HER2, RET, MET, NRG1, or NTRK genes. **Results:** Between August 2022 and December 2024, 646 patients were enrolled in the LC-SCRUM-Advantage. Among them, 57% had stage I, 27% had stage II, 16% had stage III, and 71% had adenocarcinoma histology. Of the 591 evaluable patients in this analysis, an actionable oncogenic driver was found in 46% of cases (274/591). Identified oncogenic drivers included 190 (24%) EGFR mutations (89 L858R, 77 ex19del, 10 ex20ins, 14 uncommon), 26 (4%) MET ex14 skipping, 20 (3%) KRAS G12C, 18 (3%) HER2 mutations (including ex20ins), 7 (1%) ALK fusion, 5 (1%) NRG1 fusion, 4 (1%) BRAFV600E, 2 (<1%) RET fusions, 1 (<1%) ROS1 fusion, and 1 (<1%) NTRK fusion. PD-L1 expression was observed in 19% for >50%, 40% for 1-49%, and 41% for <1%. Among patients with paired tumor samples from surgery and preoperative biopsy, the concordance rate of detected actionable oncogenic drivers was 95%. **Conclusions:** Our study found actionable oncogenic drivers in 46% of Japanese patients with surgically resected early-stage NSCLC. Based on historical control, the proportion of any oncogenic drivers in early-stage NSCLC is similar to that in advanced NSCLC. Comprehensive genomic screening of patients with early-stage NSCLC will accelerate the development of clinical trials for adjuvant-targeted therapy. Research Sponsor: CHUGAI PHARMACEUTICAL CO., LTD., Eli Lilly Japan K.K.

8066 **Poster Session**

Are we casting the net wide enough? Applying the proposed lung cancer screening criteria in single centre lung cancer resections. First Author: Clement Lim, St John of God Subiaco Hospital, Perth, Australia

Background: The Australian National Lung Cancer Screening Program (NLCSP) commences in July 2025. Thoracic surgery is a key treatment option in screen-detected early-stage lung cancers. St. John of God Subiaco Hospital is a private hospital in Western Australia (WA) and is part of the Australian and New Zealand Thoracic Clinical Quality Registry (ANZTHOR) collaborative database as one of the inaugural sites. We examined the resected primary lung cancers at our centre to assess if our cohort aligned with the characteristics of the targeted at-risk patient population as defined by the NLCSP proposed screening criteria. **Methods:** Demographic patient data was retrieved from ANZTHOR at our centre who underwent surgical resection for primary lung cancer between March 2023 to November 2024. Retrospective data analysis was then conducted on the mode and symptoms at time of diagnosis, age and smoking history. The NLCSP criteria for screening (aged 50-70 years, history of $\geq$30 pack-years smoking in current smokers or ex-smokers who quit within the last 10 years) was then applied to this cohort of privately insured primary lung cancer patients to evaluate the proportion of patients that would have been eligible/ineligible for screening. **Results:** Of the 107 patients, median age was 71 (range 42-87) and 67 (63%) were females. 96 (90%) patients were asymptomatic and 98 (92%) were early-stage cancers (Stage 2 and below). 58 (54%) patients were $>$70 years old and 34 (32%) were never-smokers. **Conclusions:** A substantial proportion (86%) of this cohort of asymptomatic resected lung cancer patients would not have been identified via lung cancer screening by NLCSP screening criteria. This is likely in part related to the different demographics of patients attending private hospitals but nonetheless raises the possibility that the current screening criteria is overly stringent and will miss many primary lung cancer presentations. Supplementary methods (i.e. blood biomarker testing) may improve screen detection rates of lung cancer and enable better identification of at-risk groups. Research Sponsor: Bendat Family Research and Development Fund.

	Total patients (n=107)	Asymptomatic patients (n=96)
Ineligibility based on age	61 (57%)	56 (58%)
Ineligibility based on smoking history	73 (68%)	67 (70%)
Ineligibility based on full NLCSP criteria	91 (85%)	83 (86%)

8067 **Poster Session**

Commission on Cancer lung cancer surgery quality metric and overall survival in a population-based cohort. First Author: Sora Ely, George Washington University, Washington, DC

Background: The American College of Surgeons Commission on Cancer (CoC) quality metric for curative-intent lung cancer surgery, Operative Standard 5.8 (OS 5.8), requires lymph node sampling from $\geq$3 mediastinal and $\geq$1 hilar ("3+1") stations. We assessed association between adherence to this standard and overall survival in a population-based lung cancer resection cohort. **Methods:** We evaluated the Mid-South Quality of Surgical Resection cohort, which includes data from all 14 hospitals performing $\geq$5 annual lung cancer resections across five Hospital Referral Regions in MS, AR, and TN. We compared clinical stage I-III curative-intent resections from 2009 to 2020, examining demographics, tumor characteristics, and outcomes between CoC OS 5.8-concordant and non-concordant groups using chi-squared tests. We calculated adjusted odds ratios (aORs) to quantify concordance association with binary outcomes using logistic regression and adjusted hazard ratios (aHRs) for overall survival with proportional hazards models, adjusting all models for age, race, sex, Charlson comorbidity index, insurance, rurality, institutional volume, smoking status, clinical stage, histology, surgical technique, extent of resection, margin status, and neoadjuvant therapy. **Results:** Of 5,536 patients, 1,859 (41%) were concordant and 2,677 (59%) were non-concordant. Concordant cases included more White patients (80% v 76%, p$<$0.0001), metropolitan residents (61% v 47%, p$<$0.0001), clinical stage II/III cases (25% v 22%, p=0.0055), and anatomic resections (99% v 87%, p$<$0.0001). Surgical complications were more common in concordant cases (48% v 42%, p=0.0001). After adjustment for key variables, concordance with OS 5.8 was associated with more frequent nodal upstaging (aOR 1.34, 95% CI: 1.11–1.60), adjuvant chemotherapy use (aOR 1.58, 95% CI: 1.33–1.88), and more complications (aOR 1.21, 95% CI: 1.06–1.38). Patients with OS 5.8 concordant resections had significantly lower hazard of death (aHR 0.85, 95% CI: 0.77–0.93, Table). **Conclusions:** Adherence to CoC OS 5.8 lymph node sampling standards for lung cancer resections was associated with greater nodal upstaging, adjuvant therapy use, and likelihood of postoperative morbidity. Overall survival was significantly better among OS 5.8-concordant cases, supporting the use of this quality metric for curative-intent lung cancer surgery. Research Sponsor: U.S. National Institutes of Health; R01CA172253.

Oncologic characteristics and outcomes in CoC OS 5.8-concordant v non-concordant resections.

	Concordant n=1859	Non-concordant n=2677	P-value
Clinical stage I	74%	78%	0.0055
Clinical stage II	17%	14%	
Clinical stage III	8%	8%	
Nodal upstaging	16%	14%	0.0209
Adjuvant therapy	22%	14%	$<$0.0001
Median overall survival, years (95% CI)	7.8 (7.1-8.6)	6.2 (5.7-6.7)	0.0001
5-year overall survival (95% CI)	60% (58-62)	55% (53-57)	0.0001
aHR (95% CI)	0.85 (0.77-0.93)	Ref	0.0004

8068 **Poster Session**

Racial and ethnic disparities in receipt of guideline concordant treatment for early-stage non-small cell lung cancer in Los Angeles County. First Author: Miriam L Gorbatov, Department of Population and Public Health Sciences, Keck School of Medicine of USC, Los Angeles, CA

Background: Non-small cell lung cancer (NSCLC) is the leading cause of cancer mortality in California. Black patients experience the highest mortality rates (39 per 100,000) compared to Non-Hispanic White (NHW) (34 per 100,000), Asian/Pacific Islanders (A/PI) (23 per 100,000), and Hispanic patients (17 per 100,000). The most modifiable factor contributing to these differences is the receipt of guideline-concordant treatment (GCT), with surgical resection or radiation therapy recommended for all medically operable patients with stage I-II NSCLC. Despite rigorous clinical evidence supporting these guidelines, a higher proportion of Non-Hispanic Black (NHB) and Hispanic patients do not receive GCT compared to NHW patients. This study analyzed differences in receipt of GCT across racial and ethnic groups, leveraging data from a robust, population-based cohort of all early-stage NSCLC cases diagnosed in Los Angeles County. **Methods:** Patients diagnosed with early-stage NSCLC (tumors $<$4cm, no lymph node involvement, and no metastases) between 2012-2022 were identified from the Los Angeles County Cancer Surveillance Program. Using a logistic regression model, we evaluated the association between race and ethnicity and receipt of guideline concordant treatment, adjusting for confounders including age, sex, socioeconomic status, insurance type, marital status, and tumor size. Outcomes were defined as receipt of GCT (surgery or radiation only), while non-GCT included no treatment or any combination of multiple treatments. **Results:** A total of 2,033 patients with early-stage NSCLC were identified of which 57.2% were NHW, 8.9% were NHB, 14.8% were Hispanic, and 18.2% were A/PI. Patients with early-stage NSCLC were on average 70.3 years of age, majority female (63.7%), and had an average tumor size of 1.9 cm. While most patients (85.6%) received GCT, NHB patients had the highest proportion of non-GCT treatment (21.1%) followed by Hispanic patients (16.9%). NHB patients had significantly higher oddsof not receiving GCT compared to NHW patients (OR: 1.62, 95% CI: 1.05-2.46; p$<$0.05). No statistically significant differences in GCT receipt were observed for A/PI or Hispanic patients compared to NHW patients. **Conclusions:** Addressing disparities in GCT for patients diagnosed with early-stage NSCLC is critical to improving survival outcomes. Future studies identifying factors influencing a patient's decision to receive GCT and a physician's decision to recommend and adhere to GCT guidelines is needed to understand the complexity of treatment decision-making. Research Sponsor: American Cancer Society.

8069 **Poster Session**

Impact of time to neoadjuvant treatment initiation (TTI) for resectable non-small cell lung cancer (NSCLC) on clinical outcomes. First Author: Srinidhi Radhakrishnan, University of Maryland, Baltimore, MD

Background: There has been significant progress in the management of resectable NSCLC, now utilizing biomarker selected criteria. However, in the era of these new perioperative treatments, the impact of treatment initiation and surgical timing on clinical outcomes have yet to be explored. **Methods:** Using the NCDB, we compiled an analytic data set of patients with stage IB-IIIB (per AJCC 8th staging edition) who underwent definitive resection after receiving neoadjuvant systemic therapy between 2010-2021. These patients received neoadjuvant chemotherapy (CT), chemoradiotherapy (CRT) or chemoimmunotherapy (CIO). The following clinically relevant time intervals were estimated: time from diagnosis to systemic therapy initiation, from diagnosis to definitive surgery and from systemic therapy initiation to surgery. The association between these time intervals and overall survival (OS) were assessed using multivariable Cox proportional hazards model, stratified by clinical T-stage. Cox model was adjusted for year of diagnosis and age, treatment modalities, sex, race, Charlson score, income, and hospital affiliation. Data were analyzed using R studio and statistical significance was set at α = 0.05. **Results:** The analytic data set included 13,372 eligible patients. 40.5% of patients had stage I/II disease and 59.5% were diagnosed with stage III disease. Treatment included 45.2% CT, 48.3% CRT, 6.4% CIO, with median TTI being 108, 97 and 107 days, respectively. Compared to neoadjuvant CT, CIO combination conferred a positive impact on OS (HR=0.62, 95%CI: 0.52-0.74). Both time from diagnosis to treatment initiation and time from systemic therapy start to surgery increased by 7 days between 2010-2018 and 2019-2021. Time to neoadjuvant treatment initiation did not impact OS. However, surgical resection done later than 150 days from diagnosis was associated with lower OS (HR=1.12, 95%CI:1.04-1.19). Based on the multivariable Cox regression model, patients' survival was longer if they were diagnosed between 2019-2021, treated at an academic hospital, age $<$ 63 years at diagnosis, female, non-white, had lower Charlson score, income $>$ 40K, private-payer insurance, and if surgical resection was performed $\leq$ 150 days from diagnosis. **Conclusions:** Exploring the NCDB, neoadjuvant CIO showed significantly favorable impact on OS compared to CT. Despite increased TTI between the years of 2019-2021, there was no appreciable impact on timing of systemic therapy initiation on OS across our cohort. Time to surgical resection within 150 days, adjusted for other clinical and demographic parameters, was associated with improved OS. Pertinent demographic variables, including race, insurance status, and income level, significantly impacted OS and warrant further investigation in this clinical setting. Research Sponsor: None.

8070 Poster Session

Driving precision oncology in lung cancer: Patient stratification through comprehensive genomic profiling. First Author: Vidya H Veldore, 4baseCare Precision Health Pvt Ltd., Bangalore, India

Background: Next Generation Sequencing (NGS)-guided targeted therapy is a standard practice in lung cancer, as recommended by professional guidelines. Various gene panels, exome, and genome sequencing strategies are employed to detect therapeutic targets. Selecting the right test is critical for achieving favorable patient outcomes. This study compares the efficacy and clinical utility of gene panels and exome sequencing in stratifying patients for different therapeutic options. **Methods:** We retrospectively analyzed genomic profiles of 1,224 advanced lung cancer patients (Stage III and Stage IV) sequenced using small gene panel (SP; 72 genes, NCCN biomarker driven TarGT First) and broad gene panel (BP; 1,212 genes, NCCN and pathways driven TarGT IndieGene. Tumor FFPE samples were screened for SNVs/InDels, CNVs, gene fusions, and immunotherapy biomarkers, including TMB, MSI, and PD-L1 expression. **Results:** Among the 1,224 patients, 791 were screened with small panels, 552 with broad panels, and 42 with exome sequencing. Sequencing with BP identified at least one driver/pathogenic mutation in 89.7% patients, which was higher than that detected in SP (73.6%). BP detected a higher proportion of patients with therapeutically targetable variants than SP (80.6% vs. 73.3%). Both SP and BP detected equivalent proportion of patients as eligible for level 1 (FDA-approved) therapy (SP 38.7% vs. BP 37.5%) and level 2 therapy (3.2% vs. 4%) and while a significantly higher number of patients eligible for level 3 (clinical trials) therapies were detected in BP (SP 31.5% vs. BP 39.1%). In a subset of 172 patients screened with both SP and BP. BP identified driver/pathogenic mutations in all patients (100% diagnostic yield) while SP identified mutations in 62.8% of the patients. BP also detected targetable variants in 84.9% of cases, compared to 62.8% detected in SP. Patients eligible for FDA-approved therapy (48.3% vs. 41.9%), off-label therapy (5.2% vs. 3.5%), and clinical trial therapies (38.4% vs. 17.4%) were more frequently detected with BP than in SP. **Conclusions:** BP outperform SP in detecting clinically significant drivers and therapeutic biomarkers, demonstrating their utility in precision oncology. This study highlights the advantages of comprehensive genomic profiling (CGP) over small panels for guiding prognosis and therapy decisions in advanced lung cancer during disease progression. Research Sponsor: 4baseCare internal funding.

	Patients with targetable variants (No. of patients; %)	Level 1 therapy (No. of patients; %)	Level 2 therapy (No. of patients; %)	Level 3 therapy (No. of patients; %)	No therapy (No. of patients; %)
Small panel sequencing (SP) (n=791 patients)	580; 73.3%	306; 38.7%	25; 3.2%	249; 31.5%	211; 26.7%
Broad panel sequencing (BP) (n=552 patients)	445; 80.6%	207; 37.5%	22; 4%	216; 39.1%	107; 19.4%

8071 Poster Session

Real-world (rw) study to identify disparities in outcomes for patients (pts) with early-stage resected NSCLC who received biomarker-targeted adjuvant treatment (BTRx). First Author: Raymond U. Osarogiagbon, Baptist Cancer Center, Multidisciplinary Thoracic Oncology Program, Memphis, TN

Background: BTRx improves survival of pts with resected early-stage NSCLC, making thorough biomarker testing critical in this setting. Disparities in testing and receipt of guideline-supported BTRx may adversely impact outcomes. We evaluated rw biomarker testing patterns, outcomes, and receipt of BTRx in pts with resected NSCLC. **Methods:** This was a retrospective US cohort study of Flatiron Health data from pts with stage IB–IIIB (T3N2) NSCLC diagnosed during 2021–2023, who had surgical resection. Biomarker testing, BTRx rates, and clinical outcomes (rw recurrence-free survival [rwRFS]; overall survival [OS]) were evaluated and compared across clinical and sociodemographic groups. BTRx was defined as 1) osimertinib for EGFR+ (Ex19del/L858R) NSCLC; 2) atezolizumab or pembrolizumab (per PD-L1 status) for EGFR- and ALK-negative (-) NSCLC. **Results:** In this cohort (N=885), biomarker testing rates were lower among stage I (75%) vs III (93%), older (83%) vs younger (87%), non-Hispanic Black (74%) vs White (84%), and pts with smoking (83%) vs no smoking history (89%) (Table). 539 (61%) pts received adjuvant therapy; 231 (43%) had actionable biomarkers, of whom 137 (59%) received BTRx, with rates highest for pts with EGFR+ disease (85%) and lowest for pts with EGFR-/ALK- disease (49%). BTRx was received more often by pts who never smoked (76% vs 55% of pts who smoked) and pts of Asian ethnicity (100% vs 56% White) (all $p<0.05$). At 24 months, 90% of pts who had BTRx were alive vs 77% who did not ($p<0.05$). Median rwRFS was 35 months for BTRx vs 28 months for non-BTRx cohort ($p<0.05$). In multivariable analysis among pts who had BTRx, younger age was significantly associated with OS. **Conclusions:** In this large rw analysis, BTRx was significantly associated with OS in early-stage NSCLC, irrespective of age, stage and sex. Ensuring biomarker testing and BTRx for all pts may reduce outcomes disparities in NSCLC. Research Sponsor: AstraZeneca.

Table	Overall	Stage IB	Stage IIIB	<65 yrs	≥65 yrs	Male	Female	Non-Hispanic White	Non-Hispanic Black	Smoked	Never smoked	SES Quintile 1	SES Quintile 5
≥1 Biomarker test after diagnosis, %	84	75	93*	87	83	85	83	84	74	83	89	80	86
Received adjuvant Rx (n=539), %	61	31	90*	74	56*	59	63	62	60	60	64	63	65
BTRx rate in pts with actionable bioms (n=231), %	59	64	73	57	60	63	57	56	61	55	76*	51	68
24-mo OS, % (95% CI) (all pts)	84 (81–87)	87 (80–92)	72 (46–87) *+†	92 (86–96)	81 (77–85) *+†	81 (75–85)	87 (82–90) *+†	86 (82–89)	88 (70–96)	83 (80–87)	89 (79–94)	85 (74–92)	88 (80–93)
24-mo OS, % (95% CI) (pts with BTRx)	90 (80–95)	91 (51–99)	NR	100 (100–100)	86 (71–93)**	83 (58–94)	94 (82–98)	88 (73–95)	100 (100–100)	89 (76–95)	95 (68–99)	80 (41–95)	86* (53–96)

*χ2-test $p<0.05$.
**Log-rank $p<0.05$, for comparisons within stage and sociodemographic groups.
†Results significant in multivariable Cox regressions adjusted for age, sex, stage and practice type. NR, not reached.

8072 Poster Session

Definitive radiation as a nonsurgical option after chemoimmunotherapy for stage III lung cancer. First Author: Giorgio Caturegli, Yale School of Medicine, New Haven, CT

Background: The immunotherapy era has led to a resurgence of interest in surgical management of clinical Stage III non-small cell lung cancer (NSCLC). However, patient eligibility or interest in surgery may decline after neoadjuvant treatment, leaving many in need of a non-operative form of local therapy. Here we evaluate outcomes of definitive radiation after chemoimmunotherapy as a potential nonsurgical option for stage III NSCLC patients. **Methods:** Clinical Stage III lung adenocarcinoma and squamous cell carcinoma patients diagnosed in the National Cancer Database between 2017 and 2021 who received chemoimmunotherapy followed by thoracic radiation within 20 weeks were included. Patients receiving any palliative therapies were excluded. Three-year overall survival was assessed by Cox proportional hazards models and by the Kaplan-Meier method, after landmarking at 10 weeks (median time from immunotherapy to radiation). Propensity-matching was performed 2:1 on year, age, sex, race/ethnicity, Charlson-Deyo score, insurance, region, facility type, histology, and clinical T and N stage. **Results:** 873 patients were treated with radiation after chemoimmunotherapy. Over 90% received a total radiation dose of at least 50 Gy, and 90-day mortality after initiation of radiation was 4.9%. To evaluate radiation as a local therapy after chemoimmunotherapy, these patients were compared to those who received chemoimmunotherapy only (Table). Patients receiving radiation were less likely to have T4 tumors (37.7% vs. 44.2%, $p<0.0001$) but had a similar proportion of N3 tumors (28.2% vs. 29.9%, p=0.73) compared to chemoimmunotherapy alone. Three-year overall survival of propensity-matched patients was superior in the radiation group (50.8%) versus chemoimmunotherapy alone (35.9%, $p<0.001$). In a Cox model, the addition of radiation was associated with lower mortality risk (HR 0.66, 95% 0.58-0.84, $p<0.0001$) compared to chemoimmunotherapy alone. **Conclusions:** Radiation after chemoimmunotherapy appears to be a safe and effective regimen for Stage III NSCLC. Further study is indicated to evaluate radiation as a nonsurgical option for clinical stage III patients who begin with chemoimmunotherapy but do not progress to surgery. Research Sponsor: None.

Characteristics and survival of patients receiving chemoimmunotherapy with or without subsequent radiation.

	Chemoimmunotherapy followed by radiation (n=873)	Chemoimmunotherapy only (n=1408)	P (Chi-squared or Wilcoxon rank sum)
Age (median, IQR)	67 (60-73)	69 (62-75)	**<0.0001**
Female	369 (42.3%)	667 (47.4%)	**0.02**
Charlson-Deyo ≥ 2	131 (15.0%)	242 (17.2%)	0.34
Adenocarcinoma	463 (54.0%)	886 (62.9%)	**<0.0001**
Stage 3A	350 (40.1%)	579 (41.1%)	0.78
Stage T4	329 (37.7%)	622 (44.2%)	**0.0022**
Stage N3	255 (29.2%)	421 (29.9%)	0.73
3-Year Survival*	489 (56.0%)	630 (44.7%)	**<0.0001**

For reference: 3-year survival of immunotherapy after chemoradiation for Stage III NSCLC in the PACIFIC trial was 57%.

8073 Poster Session

Sequential versus concurrent strategy of immunotherapy and radiotherapy in advanced non-small-cell lung cancer: A territory-wide multicenter study (OCEANUS study). First Author: Han Zhou, The University of Hong Kong-Shenzhen Hospital, Shenzhen, China

Background: Combination of immunotherapy with radiotherapy (iRT) has been a hot topic of research during last 10+ years with controversial results. In advanced non-small cell lung cancer (NSCLC), the optimal combination of iRT is not clear in the PACIFIC series of study. Using a prospective territory-wide multicenter study, this OCEANUS study aimed to compare the survival between sequential and concurrent iRT in locally advanced NSCLC. **Methods:** This real-world evidence study evaluated NSCLC patients treated in Hong Kong between January 1, 2010, and December 31, 2021. Patients diagnosed with unresectable locally advanced, de novo metastatic, or progressive NSCLC who received at least one cycle of immunotherapy combined with radiotherapy were included. The primary endpoint was real-world overall survival (rwOS). Survival outcomes were compared across various iRT combinations, with a focus on the impact of iRT strategies (concurrent versus sequential), the iRT time interval, and immune checkpoint inhibitor (ICI) maintenance duration. **Results:** A total of 3,522 patients received immunotherapy, of whom 338 underwent iRT (151 with initial iRT and 187 with salvage iRT). Patients who received iRT had significantly better overall survival (OS) compared to those who did not. Sequential iRT demonstrated significantly superior survival compared to concurrent iRT, with a 5-year rwOS of 45.3% (95% CI, 35.6–57.7%) versus 15.7% (95% CI, 7.2–33.8%; HR, 0.587; 95% CI, 0.382–0.901; P = 0.014). For salvage iRT, radiotherapy combined with maintenance ICIs achieved a median rwOS of 11.7 months (95% CI, 7.4–15.5), outperforming RT administered after ICI discontinuation (HR, 0.679; 95% CI, 0.470–0.979; P = 0.014). Shorter iRT intervals (<1 week) and 1 year of ICI maintenance were associated with additional survival benefits. **Conclusions:** The OCEANUS study provides significant real-world evidence supporting sequential iRT as the preferred strategy for unresectable locally advanced and de novo metastatic NSCLC. Salvage RT combined with maintenance ICIs was associated with improved rwOS in patients with progressive NSCLC. These findings offer actionable insights for optimizing iRT strategies in advanced NSCLC. Research Sponsor: the Shenzhen Science and Technology Program; KQTD20180411185028798; National Natural Science Foundation of China; 82403787; Shenzhen Medical Research Fund; A2403002.

8074 **Poster Session**

Evaluating lung cancer clinical characteristics and tumor subtypes using cell-free DNA fragmentomes. First Author: Milou Schuurbiers, Radboud University Medical Center, Nijmegen, Netherlands

Background: Liquid biopsies provide an opportunity for non-invasive lung cancer detection and tumor subtyping when tumor tissue is not available. Here we evaluate a blood-based liquid biopsy approach and its relationship to clinical and tumor subtype characteristics of lung cancer cases using a cohort of 578 individuals from a prospective clinical trial (LEMA, NCT02894853). **Methods:** Pre-treatment plasma samples were processed using the DELFI assay, a cell-free DNA (cfDNA) approach using a genome-wide fragmentomics based machine learning classifier. Clinical data, including overall cancer stage (I=164, II=59, III=133, IV=184), tumor stage, histologic subtypes, lymph node invasion, comorbidities, medications, smoking history, treatment type, and overall-survival (OS) data were collected for all patients. Tissue molecular profiling was performed to identify actionable alterations in driver oncogenes (ALK, BRAF, EGFR, ERBB, KRAS, ROS1, RET, MET) and cancer-specific protein levels (CEA, CA153, CA125, CYFRA, HE4) were measured in the plasma collected from 445 cancer cases. **Results:** DELFI scores were significantly higher with increasing tumor stage. T2 cases had a 1.3-fold increase in mean scores compared to T1 ($p<0.001$, Wilcoxon rank-sum), while T4 cases had a 16.2-fold increase ($p<0.0001$). A similar trend was observed with node staging, with N2 cases having an 11.3-fold higher mean scores compared to N0 ($p<0.0001$, Wilcoxon rank-sum), while N3 stage cases had a 27-fold increase ($p<0.0001$). Lung adenocarcinoma (ADC) displayed lower DELFI scores compared to squamous cell carcinomas (SCC) ($p<0.01$, Wilcoxon rank-sum), while small-cell lung cancer cases had the highest scores among all subtypes ($p<0.0001$, Wilcoxon rank-sum). cfDNA fragmentome changes in patients with ADC and SCC reflected chromosomal alterations observed in TCGA cohorts (ADC n=518; SCC n=501). The combination of DELFI cfDNA fragmentome characteristics with plasma protein measurements were used to train and cross-validate a classifier that could differentiate ADC from SCC (AUC for stage I=0.71, II=0.85, III=0.85, IV=0.82). Patients with low DELFI scores (below the median) had longer overall-survival (OS) compared to patients with high DELFI score (low DELFI score=18.51 months; high DELFI score=6.58 months; $p<0.01$, log-rank). DELFI scores were unaffected by underlying patient comorbidities, tumor-specific mutations, or medication status. **Conclusions:** Overall, this study revealed that DELFI scores are related to tumor burden, predict survival outcomes, and that cfDNA fragmentome analyses can be used to identify lung cancer subtypes. These results suggest future opportunities for subtype-specific treatments in lung cancer based on non-invasive plasma-only analyses. Clinical trial information: NCT02894853. Research Sponsor: None.

8075 **Poster Session**

EMBER-Lung: Electronic medical record boosting molecular testing in early stage NSCLC. First Author: Willdragon Wang, University of Pennsylvania, Philadelphia, PA

Background: Actionable alterations are identified in 30-40% of patients with advanced non-squamous (NSq) non-small cell lung cancer (NSCLC). Although previous efforts focused on testing for actionable alterations in the metastatic setting, the emergence of adjuvant targeted therapies and perioperative chemoimmunotherapy has made it imperative to perform molecular testing in the early stage setting as well. We present a prospective clinical trial evaluating an electronic medical record (EMR)-based nudge intervention to promote timely completion of molecular testing in patients (pts) with early stage NSq NSCLC. **Methods:** The EMBER-Lung trial prospectively enrolled pts undergoing surgical resection in the University of Pennsylvania Health System. The intervention included an EMR-based nudge at the time of the 1st post-operative visit prompting the clinician to accept an order for comprehensive molecular testing based on NCCN guidelines. A reflex alert detailing therapeutic options was sent to the pt's care team provided that the pt had at least one actionable alteration detected and tissue was consistent with NSq NSCLC. The primary endpoint was the proportion of pts who underwent comprehensive molecular testing in the pre and post intervention cohorts. Secondary outcomes included the delivery of appropriate adjuvant targeted therapy if a targetable alteration was detected. Clinical characteristics of the pre- and post-intervention cohorts were compared using the Chi-square test or Z score. **Results:** Between July 2021 and November 2023, 460 pts were included: 243 pts in the post-, and 217 pts in the pre-intervention cohorts. Median age was 68.4 years, 64.3% female; 74.1% were former or current smokers, and mostly stage I (I/II/III; 75.9%, 14.1%, 10.0%, respectively). Pt demographics, smoking, tumor stage, and histology were similar in the pre- and post-intervention cohorts. The proportion of pts with any molecular testing improved after the intervention (101/217, 46.5% vs 208/243, 85.6%, $p<0.00001$). Moreover, the proportion of pts whose molecular testing was comprehensive also increased post-intervention (80/217, 36.9% vs 197/243, 81.1%, $p<0.00001$); and this increase was observed across all stages (I-III). A greater proportion of pts with classical *EGFR* mutations were detected in the post-intervention setting (14/217, 6.5% vs 41/243, 16.9%, $p<0.001$). No *ALK* fusions were detected in the pre-intervention cohort, while 5/243 (2.1%) were detected in the post-intervention cohort. Of note, a higher proportion of *KRAS* G12C mutations were also found post intervention (12/217, 5.5%, vs 33/243, 13.6%, $p<0.01$). **Conclusions:** An EMR-based nudge intervention during the post-operative visit after resection of early stage NSCLC improved the proportion of patients with molecular testing. The intervention was feasible, and future research will incorporate this strategy earlier to inform neoadjuvant therapy. Research Sponsor: None.

8076 **Poster Session**

A retrospective study of induction immunochemotherapy followed by definitive chemoradiotherapy and consolidation immunotherapy in unresectable locally advanced non-small cell lung cancer. First Author: Yuliang Meng, Shandong Cancer hospital and institute, Jinan, China

Background: The standard treatment for patients with unresectable stage III non-small cell lung cancer (NSCLC) involves concurrent chemoradiotherapy (cCRT) followed by one year of durvalumab consolidation therapy. Numerous clinical studies have sought to optimize this treatment paradigm to enhance clinical outcomes. In this retrospective real-world study, we evaluated the efficacy and safety of the addition of induction chemoimmunotherapy prior to the PACIFIC regimen compared with the standard PACIFIC regimen. The aim was to determine whether introducing immunotherapy earlier into the treatment strategy for unresectable stage III NSCLC could improve disease control rates. **Methods:** This study included patients with unresectable stage III NSCLC. Patients received either induction chemoimmunotherapy followed by cCRT or sequential chemoradiotherapy (sCRT) with consolidation immunotherapy, or cCRT/sCRT directly followed by consolidation immunotherapy. The primary endpoint was progression-free survival (PFS), defined as the time from the initiation of consolidation immunotherapy to disease progression or death. The incidence of radiation-induced immune pneumonitis was also assessed between the two groups. **Results:** A total of 210 patients with unresectable stage III NSCLC were included in this study, enrolled between July 2019 and April 2023. Among them, 76 patients received induction chemoimmunotherapy, and 134 patients were treated without induction chemoimmunotherapy. Baseline characteristics between the two groups showed no significant differences. The proportion of patients receiving cCRT in the induction chemoimmunotherapy group and the non-induction chemoimmunotherapy group was 29/76 (38.1%) and 110/134 (82.1%), respectively. Within each group, there was no statistically significant difference in progression-free survival (PFS) between patients treated with cCRT or sCRT. The induction chemoimmunotherapy group demonstrated superior median PFS (mPFS) compared to the non-induction chemoimmunotherapy group (not reached vs. 17.2 months, P=0.01). Overall survival (OS) data remain immature for analysis. The incidence of pneumonitis was observed in 52/76 (68.4%) patients in the induction chemoimmunotherapy group, with ≥Grade 2 pneumonitis occurring in 18/76 (23.7%) patients. In the non-induction chemoimmunotherapy group, pneumonitis occurred in 86/134 (64.2%) patients, with ≥Grade 2 pneumonitis in 30/134 (22.4%) patients. No significant differences in pneumonitis incidence or severity were observed between the two groups. **Conclusions:** The addition of induction chemoimmunotherapy prior to the PACIFIC regimen demonstrated improved disease control rates compared to the standard approach, with no increased risk of pneumonitis. Research Sponsor: None.

8077 **Poster Session**

Association of radiomic features with disease-free survival following neoadjuvant chemoimmunotherapy in resectable NSCLC. First Author: Bryan Berube, Cleveland Clinic, Cleveland, OH

Background: Neoadjuvant chemoimmunotherapy (chemo-IO) has emerged as a promising approach to improve disease-free survival (DFS) in patients with surgically resectable non-small cell lung cancer (NSCLC). While recent clinical trials have demonstrated the efficacy of combining chemotherapy with immune checkpoint inhibitors in this setting, DFS remains variable among patients. Currently, there is no reliable biomarker to predict the risk of recurrence in this population. Predictors such as PD-L1 expression have shown limited utility, underscoring an unmet clinical need to identify robust biomarkers for DFS. This study investigates whether radiomic texture features derived from pre-treatment CT scans are associated with DFS in patients with NSCLC undergoing neoadjuvant chemo-IO prior to surgery. **Methods:** The study included 101 patients with NSCLC (median age: 66 years, range: 34–85) treated at the Cleveland Clinic. All patients received neoadjuvant platinum-doublet chemotherapy combined with an anti-PD-1 inhibitor prior to surgery. Radiomic features characterizing tumor heterogeneity were extracted from pre-treatment CT images. Patients were divided into a training set (St=50) and a validation set (Sv=51). A least absolute shrinkage and selection operator (LASSO) Cox regression model was used to identify prognostic features for DFS in St. A radiomic risk score (RRS) was computed as a linear combination of the selected features and their corresponding coefficients. High- and low-risk groups were determined based on the median RRS in St. A Cox regression analysis was performed to assess the impact of each factor on DFS. Kaplan–Meier survival analysis, accompanied by log-rank tests, was conducted to evaluate the prognostic performance of the biomarkers. **Results:** In a univariable analysis, the RRS was significantly associated with DFS in both St (HR = 2.77, 95% CI: 1.84 – 4.1, $P < 0.0001$) and Sv (HR= 2.28, 95% CI: 1.48 – 3.5, P = 0.0002). Kaplan-Meier analyses revealed significantly shorter DFS in the high-risk group compared to the low-risk group in both St ($P < 0.0001$) and Sv ($P < 0.011$). In a multivariable analysis that included clinicopathologic factors (age, race, tumor stage, and PD-L1 expression) along with RRS, both RRS and PD-L1 expression were significantly associated with DFS in St (RRS: HR = 2.99, 95% CI: 1.89 – 4.7, $P < 0.0001$; PD-L1: HR = 1.57, 95% CI: 1.14 – 2.15, P = 0.005). However, in Sv, RRS was the only factor significantly associated with DFS (RRS: HR= 2.31, 95% CI: 1.49 – 3.6, P = 0.0001), while PD-L1 expression was not (HR = 1.27, 95% CI: 0.35 – 4.6, P = 0.71). **Conclusions:** Identifying patients with locoregional NSCLC at risk of recurrence after neoadjuvant chemo-IO is crucial for effective treatment planning. Preliminary findings suggest that radiomic features hold promise as a reliable, non-invasive biomarker for risk stratification and guiding treatment decisions. Research Sponsor: None.

8078 Poster Session

Real-world surgical and treatment patterns after neoadjuvant checkpoint inhibition in US patients with stage II/III non-small cell lung cancer. First Author: Jay M. Lee, Division of Thoracic Surgery, University of California, Los Angeles (UCLA), Los Angeles, CA

Background: Since 2021, several immuno-oncology (IO) agents were approved for use in patients with resectable non-small cell lung cancer. In the phase III neoadjuvant and perioperative IO trials, 16-26% of patients did not undergo surgery. The objectives of this study were to evaluate the real-world rate of surgery following neoadjuvant IO, reasons for preoperative attrition to resection, and subsequent treatment patterns for those who did not undergo surgery. **Methods:** This retrospective observational study used the nationwide Flatiron Health electronic health record-derived deidentified database. Included were patients diagnosed with stage II or III NSCLC between Jan 2022 and Oct 2023 who received nivolumab (nivo) and doublet chemotherapy (CT) as the first therapy within 90 days of diagnosis. We excluded patients with no documented neoadjuvant intent from the no surgery group. Per approved protocol, descriptive statistics were utilized for patient characteristics and treatment patterns. **Results:** A total of 484 patients received nivo. Among these, the average age was 67 years, 253/484 (52.3%) were male, 339/484 (70.0%) were white, and 403/484 (83.3%) were treated in a community setting. The rate of surgery was 317/484 (65.5%). Rates by stage and ECOG are found in Table 1. Among those most similar to the population in clinical trials (ECOG 0-1 and Stage IIA-IIIA) the rate was 238/334 (71.3%). The most common reasons for attrition were medical fitness (45/484; 9.2%), tumor resectability (30/484; 6.2%), and progression (28/484; 5.8%). Of those not receiving surgery, 131/167 (78.4%) received subsequent treatment, including 57 who received radiation (+/- chemo) during the follow-up period (median 10.5 months from diagnosis). **Conclusions:** In this real-world analysis, most patients were treated in community centers. The resection rate following neoadjuvant CT-IO in stage II and III NSCLC was high and comparable to the clinical trials. Medical operability, tumor resectability, and progression of disease as reasons for preoperative attrition to surgery occurred in a minority of patients that received neoadjuvant therapy. Many of the patients who did not undergo resection received subsequent therapy including consolidation radiation. Future research is needed to determine ways to improve surgical rates following neoadjuvant CT-IO. Research Sponsor: AstraZeneca.

Surgical rates by ECOG and stage at diagnosis.

	Stage IIA	Stage IIB	Stage II (unspecified)	Stage IIIA	Stage IIIB	Stage IIIC	Stage III (unspecified)
ECOG 0-1	28/35 (80.0%)	80/97 (82.5%)	7/10 (70.0%)	123/192 (64.1%)	11/24 (45.8%)	0/7 (0%)	5/5 (100.0%)
ECOG ≥2	1/4 (25.0%)	4/10 (40.0%)	0/0 (0%)	4/13 (30.8%)	1/5 (20.0%)	0/1 (0%)	0/0 (0%)
Unknown	5/6 (83.3%)	16/26 (61.5%)	1/1 (100.0%)	27/41 (65.9%)	2/4 (50.0%)	0/0 (0%)	2/3 (66.7%)
Overall	34/45 (75.6%)	100/133 (75.2%)	8/11 (72.7%)	154/246 (62.6%)	14/33 (42.4%)	0/8 (0%)	7/8 (87.5%)

8079 Poster Session

Pronounced gender-based and regional disparities in lung cancer mortality in the US: Insights from five decades of nationwide mortality data. First Author: Muhammad Ahmad, Khyber Medical University, Peshawar, Pakistan

Background: Lung cancer remains the leading cause of cancer-related mortality in the United States, necessitating an understanding of long-term mortality trends to evaluate public health interventions and identify disparities. This study examines lung cancer mortality trends from 1968 to 2016 using data from the CDC WONDER database, stratified by demographic and regional characteristics. **Methods:** The analysis included deaths attributed to lung cancer, identified using International Classification of Disease (ICD) codes across three periods: ICD-8 (1968–1978), ICD-9 (1979–1998), and ICD-10 (1999–2016). Crude and age-adjusted mortality rates (AAMRs) per 100,000 population were calculated. Temporal trends were assessed with Joinpoint regression analysis to estimate annual percentage changes (APC) and average annual percentage changes (AAPC) with 95% confidence intervals (CIs). Data were stratified by gender, race, and U.S. Census regions. **Results:** Between 1968 and 2016, there were 6,289,300 deaths attributed to lung cancer in the U.S. The overall AAMR rose from 53.53 to 59.28, with an AAPC of 0.22 (95% CI: 0.19 to 0.25). Notable trends included a sharp rise from 1968 to 1980 (APC: 3.02; 95% CI: 2.88 to 3.18), a slowdown from 1980 to 1991 (APC: 1.72; 95% CI: 1.60 to 1.83), a decline from 1991 to 2004 (APC: -0.84; 95% CI: -0.92 to -0.75), a steeper drop from 2004 to 2012 (APC: -2.17; 95% CI: -2.36 to -1.96), and an acceleration from 2012 to 2016 (APC: -3.83; 95% CI: -4.40 to -3.40). Of the total, 37.1% of deaths were females (2,333,863) and 62.9% were males (3,955,437). The male AAMR decreased from 97.85 to 72.2 (AAPC: -0.65; 95% CI: -0.69 to -0.62), while the female AAMR rose from 17.96 to 49.24 (AAPC: 2.14; 95% CI: 2.10 to 2.19). Racially, 656,875 deaths (10.4%) involved Black or African Americans, who had higher AAMRs than the 5,534,744 deaths (88%) among Whites. Whites saw a more marked increase in AAMR (AAPC: 0.29; 95% CI: 0.27 to 0.32) compared to Blacks (AAPC: 0.095; 95% CI: 0.055 to 0.14). Regionally, the South had the highest AAMR at 83.2, while the West, with the lowest at 68.58, was the only region to experience an overall decrease from 52.74 in 1968 to 45.64 in 2016. **Conclusions:** The decline in overall mortality rates since 2004 underscores the effectiveness of smoking cessation programs and treatment advancements; yet, rising female mortality and high rates in the South call for a reassessment of outreach efforts to ensure public health strategies. Research Sponsor: None.

8080 Poster Session

Radiomic signatures as predictors of pathological response to neoadjuvant chemoimmunotherapy in surgically resected NSCLC. First Author: Ryan Brown, Cleveland Clinic, Cleveland, OH

Background: Historically, pathological complete response (pCR), a potential early predictor of survival, was achieved by a small fraction of patients with non-small cell lung cancer (NSCLC) receiving neoadjuvant chemotherapy. Now with chemoimmunotherapy (chemo-IO) becoming the cornerstone of perioperative treatment, the rate of pCR has significantly increased to over 15%. Existing factors like PD-L1 expression and circulating tumor DNA clearance have shown limited efficacy in reliably predicting response to neoadjuvant chemo-IO, thus underscoring the need for novel biomarkers. In this study, we aim to investigate the potential of radiomic texture features derived from pre-treatment CT scans to predict pCR in patients with NSCLC undergoing neoadjuvant chemo-IO prior to surgery. **Methods:** The study included 101 patients with surgically resected NSCLC treated at Cleveland Clinic. All patients received neoadjuvant platinum-doublet chemotherapy combined with an anti-PD-1 inhibitor prior to surgery. Tumor stage, histology, PD-L1 expression levels, and treatment details (e.g., chemotherapy regimen, immunotherapy agent, number of treatment cycles) were collected for analysis. Pathological responses were assessed based on the percentage of residual viable tumor in the surgical specimen, with pathological complete response (pCR) defined as 0% viable tumor. Radiomic features were extracted from both intratumoral and peritumoral regions on pre-treatment CT images. Patients were randomly divided into training and validation cohorts, ensuring an equal distribution of pCR and non-pCR cases in the training set. The training cohort (St) comprised 50 patients, while the validation cohort (Sv) included 51 patients. A linear discriminant classifier (LDA) was trained using St and subsequently evaluated on Sv. The predictive performance was assessed using the area under the curve (AUC). **Results:** 37 of 101 patients (37%) achieved a pCR. Utilizing a combination of 5 peritumoral and intratumoral radiomic features extracted from pretreatment CT scans, the AUC for predicting pCR was 0.82 (95% CI: 0.79 − 0.86) in St and 0.78 (95% CI: 0.76 − 0.81) in Sv. In contrast, the predictive capability of PD-L1 expression alone yielded an AUC of 0.57 for pCR prediction. Moreover, no significant difference was observed in pCR rates between patients with low and high PD-L1 expression levels (P = 0.1). The integration of radiomic features with clinicopathologic factors, including age, race, tumor stage, and PD-L1 expression, resulted in a modest improvement in predictive performance (AUC = 0.8) but was not statistically significant (P > 0.5). **Conclusions:** This analysis suggests that radiomic features extracted from both intra- and peri-tumoral regions on pre-treatment CT images may be indicative of the probability of achieving a pCR in patients with NSCLC receiving neoadjuvant chemo-IO. Research Sponsor: None.

8081 Poster Session

Impact of *MTAP* deletion on immunotherapy outcomes in patients with mesothelioma. First Author: Jessica Ross, Memorial Sloan Kettering Cancer Center, New York, NY

Background: *MTAP* (*methylthioadenosine phosphorylase*) is located on chromosome 9p21 and often co-deleted with *CDKN2A* across a variety of cancers. *MTAP* deletions (del) are found in about 30% of diffuse pleural mesotheliomas (DPM). *MTAP*del has been associated with resistance to immunotherapy (IO) treatment (tx) in multiple tumor types. In patients (pts) with DPM, objective response rate (ORR) on ipilimumab/nivolumab is 40%, disease control rate (DCR) 77%, and median progression-free survival (PFS) 6.8 months (mos): the implications of *MTAP* status on IO outcomes is unclear but represents a potential predictive biomarker. With multiple targeted therapies underway for *MTAP*del tumors, such as PRMT5 inhibitors, this alteration is also of therapeutic importance. **Methods:** We prospectively identified pts with pathologically confirmed DPM whose tumors were sequenced with MSK-IMPACT version 7, a 505-gene next generation sequencing panel that includes *MTAP* and *CDKN2A*. IO regimens included anti-PD(L)1 monotherapy, dual checkpoint blockade with additional anti-CTLA4 tx, and anti-PD(L)1 + chemotherapy. *MTAP*del was defined as low read count and confirmed by FACETS copy number when able. Radiologists reviewed imaging to determine best response and PFS on IO using mRECIST or, when not applicable, RECIST. Overall survival (OS) was compared between *MTAP*del and *MTAP*wildtype (WT) cohorts using Kaplan-Meier curves and log-rank tests. Baseline demographics were compared using Fisher's exact test. **Results:** We examined 156 pts with DPM: 39 had *CDKN2A*del (25%) and 32 had *MTAP*del (21%). 18/32 were treated with IO and available for analysis. 79 pts with *MTAP*WT DPM treated with IO were analyzed as a control. There were more pts treated with dual checkpoint blockade in the *MTAP*del vs *MTAP*WT group (83% vs 56%, single-agent IO 6% vs 39%, single-agent IO + chemo 11% vs 5%, p=0.03) and more men (94% vs 70%, p=0.04); there was no statistically significant difference in age (median 72 vs 69, p=0.5), histology (72% epithelioid vs 79%, p=0.5), or smoking status (current/former 61% vs 57%, p=0.9). All tumors with *MTAP*del also harbored a *CDKN2A*del: 5/79 tumors in the *MTAP*WT cohort had a *CDKN2A*del (p<0.001). Among the *MTAP*del cohort, 13 patients had (m)RECIST-evaluable disease. ORR on IO was 15% (2/13), DCR 38% (5/13), and median PFS 2.5 mos. OS was similar between the *MTAP*del and *MTAP*WT cohorts: median 25.4 vs 27.6 mos (HR 0.84, 95% CI 0.36 − 1.94, p=0.98). **Conclusions:** *MTAP*del (co-occurring with *CDKN2A*del) was identified in both epithelioid and non-epithelioid DPM and was associated with a low ORR and short PFS on IO, but OS was similar compared to *MTAP*WT. Larger, multi-institution cohorts are needed to validate this finding. If confirmed, this could have implications for tx selection, particularly among pts with epithelioid DPM, in which the optimal choice between 3 FDA-approved first-line regimens is uncertain. Research Sponsor: None.

8082 **Poster Session**

Test performance of a DNA methylation–based liquid biopsy biomarker for detection and classification of pleural mesothelioma (PM). First Author: Sabine Schmid, Inselspital, Universitätsspital Bern, Bern, Switzerland

Background: Circulating tumor DNA (ctDNA) profiling in pleural mesothelioma (PM) is challenging due to its molecular heterogeneity and lack of mesothelioma-specific mutations. Diagnosis can be challenging and may require repeat biopsies. Cell-free methylated DNA immunoprecipitation sequencing (cfMeDIP-seq) of plasma cell-free DNA (cfDNA) offers a non-invasive approach to analyzing differentially methylated regions (DMRs), providing insights into epigenetic changes that could serve as potential biomarkers for diagnosis, histological differentiation, and prognosis in PM. **Methods:** cfMeDIP-seq was performed on plasma samples from 55 PM patients and 24 asbestos-exposed non-cancer controls (NCC). Libraries were sequenced to an average depth of 70 million reads, and chromosomes 1-22 were binned into 300 bp windows for read tallying. For NCCs, bins with a mean beta-value <0.3 and CG density >2 (n = 3,537,691 windows) were analyzed. DMR analysis and pathway enrichment were conducted using R packages (limma, clusterProfiler), and machine learning models were developed with Python modules (pandas, numpy, sklearn). **Results:** Among the 55 PM patients (72% epithelioid, 13% biphasic, 15% sarcomatoid), the median age was 70 years, 85% were male, and 78% had prior asbestos exposure. Using a stringent filter (mean beta-value <0.1; CG density >5), a random forest classifier was developed with 141 windows, distinguishing PM from NCC with 91% accuracy, 88% precision (or positive predictive value, PPV), and an area under the ROC curve (AUC) of 0.94 across 5-fold cross-validation cohorts. DMR analysis of epithelioid vs. sarcomatoid PM revealed 1,585 significantly different windows (adjusted $p < 0.05$), achieving 83% accuracy, 74% precision, and an AUC of 0.98. Gene ontology analysis indicated significant enrichment in RNA processing pathways. Among epithelioid PM patients, distinct DMRs were identified between those with overall survival (OS) $\leq$ 6 months and $>$6 months (n = 1,824 windows, adjusted $p < 0.05$). Patients with OS $\geq$ 36 months and $<$36 months showed 37 significantly differential windows (adjusted $p < 0.05$), though test performance assessment was limited by the small sample size. **Conclusions:** If validated, global methylome profiling of ctDNA via cfMeDIP-seq offers a novel, non-invasive method that may enhance accurate diagnosis and histological differentiation. Additionally, identifying epigenetic biomarkers could provide deeper insights into PM biology, paving the way for personalized medicine and improved patient outcomes. Research Sponsor: von Tobel Foundation; Dr. Hans Altschuler Foundation.

8083 **Poster Session**

Prognostic significance of VISTA expression in patients with malignant pleural mesothelioma treated with nivolumab: Results of a retrospective multi-institutional analysis (HOT1901). First Author: Hiroshi Yokouchi, Department of Respiratory Medicine, NHO Hokkaido Cancer Center, Sapporo, Japan

Background: Nivolumab as a second-line treatment for pleural mesothelioma (PM) has demonstrated efficacy in the MERIT phase 2 trial in Japan and the CONFIRM phase 3 trial in the UK. However, the response rate and survival outcomes were modest. Therefore, the exploration of biomarkers that can determine its efficacy and prognosis is crucial. Recently, V-domain immunoglobulin suppressor of T cell activation (VISTA), and other coinhibitory or costimulatory molecules which are expressed on T cells and tumor cells, have attracted attention as novel therapeutic targets and predictors of clinical outcomes beyond PD-L1 for immunotherapy against various solid tumors. However, few studies have explored the efficacy of nivolumab by examining these molecules, as well as specific gene mutation profiles, in patients with PM. Thus, we aimed to identify biomarkers associated with survival in our cohort. **Methods:** This retrospective, multi-institutional cohort study included patients with PM who received nivolumab monotherapy as a second-line or later treatment at 18 hospitals in Japan between August 2018 and October 2019. We investigated the association of progression-free survival (PFS) and overall survival (OS) with clinical variables, expression of CD4, CD8, OX40, PD-L1, Tim-3, LAG-3, and VISTA in tumor tissues via immunohistochemistry (IHC), and gene expression profiles using next-generation sequencing (NGS). **Results:** Fifty-five patients were enrolled in this study. IHC and NGS were performed in 42 and 33 patients, respectively. The median survival follow-up time for all patients was 12.3 months (range, 0.2–47.0 months). The median PFS was 4.8 months (95% confidence interval [CI], 3.6–6.0), and the median OS was 12.3 months (95% CI, 10.3–14.4). No differences in OS or PFS were observed based on histological type. The IHC analysis revealed that high VISTA expression in tumor cells was significantly associated with improved PFS and OS compared with low VISTA expression (PFS, median: 5.1 months [95% CI, 3.5–6.7] vs. 2.4 months [95% CI, 0.0–5.1], p = 0.001; OS, median: 12.8 months [95% CI, 11.0–14.6] vs. 4.3 months [95% CI, 1.2–7.3], p = 0.007). Multivariate analysis confirmed that high VISTA expression in tumor cells was an independent predictor of prolonged PFS and OS (PFS: hazard ratio [HR], 0.14; $p < 0.001$; OS: HR, 0.38; p = 0.044). NGS data showed that gene alterations commonly reported in PM, such as mutations in *CDKN2A*, *BAP1*, and *NF2*, were not associated with PFS or OS. **Conclusions:** For PM patients with low VISTA expression in tumor cells, nivolumab may not be the optimal treatment choice, and alternative therapies should be considered. These findings provide a basis for further biomarker exploration in combination therapies, such as nivolumab-ipilimumab or chemoimmunotherapy, for patients with PM. Research Sponsor: Research funding from the Department of Respiratory Medicine, Hokkaido Cancer Center.

8084 **Poster Session**

Digital spatial profiling for identification of prognostic genes and molecular subgroups in pleural mesothelioma. First Author: Mercedes Herrera, Hospital Universitario 12 de Octubre, Madrid, Spain

Background: Pleural mesothelioma (PM) is an aggressive malignancy that harbors significant inter- and intra-tumoral heterogeneity. Spatial transcriptomics enables the dissection of the tumor's molecular architecture by facilitating compartment-specific gene expression profiling. We performed high-resolution RNA-seq analysis of tumor (Tm) and stroma (St) compartments in PM samples to identify gene expression patterns and their association with clinical outcomes. **Methods:** Formalin-fixed paraffin-embedded (FFPE) tumor samples from untreated PM patients (pts) across three institutions were analyzed using the NanoString GeoMx Digital Spatial Profiling (DSP) platform. Regions of interest (ROIs) were selected based on histopathological features and fluorescently labeled antibodies for tumor and stromal areas. RNA expression of $>$1800 genes from selected ROIs was analyzed using GeoMx Cancer Transcriptome Atlas (CTA). Differential gene expression was assessed utilizing R "limma" package. A cutoff of absolute fold change $\geq$1 and p-value <0.05, with the Benjamini-Hochberg false discovery rate method, was applied to identify significant differentially expressed genes (DEGs). Elastic Net regression optimized through cross-validation methods was employed to identify genes associated with overall survival (OS) outcomes. Data from the TCGA PanCancer Atlas was utilized for external validation. **Results:** A total of 72 pts, 80.3% male, median age of 71y (range: 44-94) were identified for the analysis. Among them, 87.5% (63/72) were epithelioid (Ep) and 12.5% (9/72) non-epithelioid (NEp). After quality control, RNA data was available from 71 and 67 pts in Tm and St compartments, respectively. Across 132 ROIs in the Tm compartment, we identified 4 significantly DEGs between NEp (upregulated *COL5A2, THBS1*; downregulated *CLU, KRT19*) and Ep subgroups. No DEG between Ep and NEp subgroups were identified in 115 ROIs from the St compartment. Unsupervised clustering identified four molecular subgroups with distinct gene expression in the Tm compartment, of which Cluster 1 showed significantly decreased OS (6.3m vs. 16.4m; HR 3.3, p =0.001). Elastic Net regression identified 31 genes predictive of OS (R^2 = 0.43, Harrell's c-index = 0.87), including nine genes (*IFNGR2, FCER1G, MFGE8, CKLF, CBL, HLA-DRB3, HK1, PLAT, CD163*) associated with worse prognosis. Tumors in Cluster 1 demonstrated higher expression of these genes. External validation using the TCGA cohort confirmed four genes *IFNGR2* (p = 0.02), *CBL* (p = 0.01), *HK1* ($p <0.001$), *PLAT* ($p <0.001$), as significantly associated with decreased OS in PM. **Conclusions:** Spatially resolved transcriptomic profiling suggests Tm-enriched regions as the primary drivers of PM subtype and aggressiveness, identifying nine genes and a molecular subgroup associated with poorer survival outcomes. Further validation and functional studies are warranted. Research Sponsor: TRANSCAN-3 Consortium; TRNSC18004PAZ.

8086 **Poster Session**

Multiomics profiling for prediction of immunotherapy response in advanced pleural mesothelioma: Sub-study of the NIPU trial. First Author: Mehrdad Rakaee, University Hospital of North Norway, Oslo, Norway

Background: The combination of ipilimumab and nivolumab (IPI/NIVO) is a standard treatment for unresectable pleural mesothelioma. However, the objective response rate (ORR) is relatively low, and serious toxicity necessitating treatment cessation with or without steroid treatment is seen in 20%. Predictive biomarkers for IPI/NIVO in mesothelioma are needed to personalize treatment decisions. **Methods:** In the NIPU trial, 118 patients progressing after first-line chemotherapy were included in the study and were randomly assigned to IPI/NIVO alone or in combination with the telomerase UV1 vaccine. Whole-slide tumor tissues were available from 99 patients and analyzed using multiplex immunofluorescence (mIF) with a panel including CD8, CD20, CD66b, FoxP3, Granzyme-B, and pan-cytokeratin. Machine learning algorithms (XGBoost) were utilized and trained for immune cell subset classification and tissue subregion segmentation (tumor vs. stroma). Bulk RNA-sequencing (RNA-seq) was performed on 25 matched baseline fresh frozen tissues, followed by differential expression analysis (DESeq2), gene set enrichment analysis (GSEA) and immune cell deconvolution. Radiological evaluation was done by local assessment of immune version of the mesothelioma modified RECIST criteria. Disease control rate (DCR) was defined as the fraction of patients with partial response (PR) or stable disease (SD) compared to those with progressive disease (PD). **Results:** The DCR and ORR were 69% and 20%, respectively. From mIF analysis, stromal CD66b, CD20, and tumoral CD66b showed the highest area under the curve (AUC = 0.60 $\pm$ 0.1) for differentiating DCR groups. For ORR, tumoral CD8+FoxP3+ T-cells demonstrated the highest AUC (0.58) for identifying PR. Patients with tumoral CD66b% scores above the median ($>$0) had significantly longer progression-free survival (6.2 vs. 4.2 months; HR: 0.63, 95% CI: 0.42–0.97, P = 0.04) and showed a trend toward improved overall survival (HR: 0.65, 95% CI: 0.41–1.0, P = 0.07). These findings were consistent with RNA-seq-derived immune fraction scores. Lasso Cox regression identified natural killer cells, neutrophils, and CD4+ T cells as top predictive features for DCR groups. Additionally, GSEA hallmark analysis revealed significant enrichment of interferon-γ and -α pathways in the DCR PR/SD group ($Q <$ 0.001) compared to PD. **Conclusions:** High/positive levels of tumoral CD66b+ neutrophils show promise as predictive biomarkers for immunotherapy efficacy in advanced pleural mesothelioma. Larger, independent studies are needed to confirm these findings and validate their clinical utility. Clinical trial information: NCT04300244. Research Sponsor: Bristol Myers Squibb; South-Eastern Norway Regional Health Authority; Ultimovacs.

8087 **Poster Session**

Phase III study on atezolizumab versus placebo in adjuvant therapy of pleural mesothelioma patients after pleurectomy/decortication: Preliminary results of the AtezoMeso study. First Author: Maria Pagano, Medical Oncology, Comprehensive Cancer Centre, AUSL-IRCCS, Reggio Emilia, Italy

Background: AtezoMeso Study is a multicentric double-blind, placebo-controlled, Phase III trial, that aims to evaluation the efficacy of adjuvant atezolizumab therapy versus placebo in patients with pleural mesothelioma (PM), who have undergone pleurectomy/decortication (P/D) and peri-operative chemotherapy. Here, we report preliminary data on disease recurrence and Next Generation Sequencing (NGS) testing. **Methods:** Patients with PM who have undergone P/D and perioperative platinum-pemetrexed chemotherapy are randomized 2:1 to receive atezolizumab or placebo for up to 12 months, or until unacceptable toxicity or patients'/physicians' decision. The primary objective of the study is disease free survival (DFS), with a sample size of 90 patients. Surgical specimens are analyzed centrally to determine the genomic profile using FoundationOne CDx Platform. **Results:** Between December 2021 and January 2025, 64 patients were randomized in 14 Italian centers. The characteristics of patients included 46 (71.88%) males and 18 (28.12%) females. %), with a median age of 67 years (range 48-79). Sixty (93.75%) patients had epithelioid histotype, and 4 (6.25%) non-epithelioid. Sixteen (25%) patients are ongoing the adjuvant treatment. At the median follow up of 8.3 months (1-30 months), 25 (53.19%) of 47 evaluable patients experienced a disease recurrence. Sixteen (64%) of 25 patients had a local recurrence of disease, 5 (20%) patients an extra-thoracic recurrence, and 4 (16%) patients both. The median DFS of all evaluable patients was 12 months (7.4 - 16.6 months). The histotype of all relapsed patients was epithelioid. NGS testing was performed in 43 (67.19%) of 64 patients. Median Tumor Mutational Burden (TMB) was 2 mutations/megabase (0-13). The most frequent genomic alteration detected were BAP1 found in 21 (48.83%) patients, CDKNA2A-B in 18 (41.86%), NF2 in 8 (18.60%), SETD2 and TP53 in 5 (11.63 %). One (2.32%) patient had a mutation of BRCA2. The co-occurrence of BAP1 and CDKNA2A-B mutations was detected in 7 (16.27%) patients, all of whom had a disease recurrence. **Conclusions:** These preliminary dataof AtezoMeso Study, regarding all randomized patients, show a median DFS longer than expected in control arm according with the study design hypothesis (9 months). The TMB of MPM patients is low. BAP1 mutations were identified as the most frequent molecular alterations. Furthermore the co-occurrence of BAP1 and CDKNA2A-B mutations was found in patients with disease relapse. Clinical trial information: NCT04996017. Research Sponsor: None.

8088 **Poster Session**

Real-world efficacy and safety of tarlatamab in patients with relapsed extensive-stage small cell lung cancer. First Author: Mitchell Parma, Department of Hematopoietic Biology and Malignancy, The University of Texas MD Anderson Cancer Center, Houston, TX

Background: Tarlatamab, a bispecific T cell engager targeting Delta-Like ligand 3, received FDA approval in May 2024 for patients with relapsed extensive-stage small cell lung cancer (SCLC). While the clinical trials leading to its approval demonstrated impressive objective response, it has unique toxicities including cytokine release syndrome (CRS) and immune effector cell-associated neurotoxicity syndrome (ICANS). Here, we report a real-world case series of safety and efficacy data for patients treated with standard of care tarlatamab at MD Anderson Cancer Center. **Methods:** We queried the MD Anderson Lung Cancer GEMINI database for patients treated with tarlatamab and retrospectively collected demographic, clinical, and outcome data. From 7/1/2024-1/15/2025, a total of 39 patients received tarlatamab. 8 patients were excluded from analysis either due to diagnosis of extrapulmonary small cell cancer or rapid clinical deterioration due to disease progression around the time of the first tarlatamab infusion. The final cohort consisted of 31 patients. **Results:** The average age of our cohort was 66 years, 36% of patients were of non-white race, and their median lines of prior treatment was 2. 4 patients had transformed SCLC from classical EGFR-mutant lung adenocarcinoma (EGFR transformed), and 12 patients had untreated brain metastases (BM) prior to tarlatamab initiation. Safety data is summarized in the Table. At the cutoff, 17 patients had their first repeat systemic imaging: 59% had tumor shrinkage, 12% had stable or mixed tumor response, and 29% experienced tumor growth. Of the 3 EGFR transformed cases that had a repeat imaging on treatment, 2 had tumor growth. 18 patients underwent a repeat brain magnetic resonance imaging (MRI) after tarlatamab treatment. Out of 11 patients with untreated BM, 82% (9) had intracranial tumor shrinkage or stability, and 2 patients had mixed response, one of which was an EGFR transformed case. Of the 7 patients who either had no prior BM or had BM treated with radiation, only 1 had developed new BM (EGFR transformed). **Conclusions:** Preliminary data from this cohort show efficacy comparable to that observed in clinical trials. Notably, we report impressive intracranial response in patients with untreated BM. The toxicity profile reveals similar CRS but higher ICANS rates compared to those reported in the clinical trials. Additional data collection and analyses are ongoing at this time. Research Sponsor: None.

Safety data from C1D1 and C1D8 of Tarlatamab.

Adverse Event	Hospitalization for C1D1 of Tarlatamab 1 mg IV (N=31)	Hospitalization for C1D8 of Tarlatamab 10 mg IV (N=28)
Cytokine-release syndrome — no. (%)		
Overall	12 (39)	11 (39)
Grade 3 or more	1 (3)	1 (4)
Tocilizumab Administration	8 (26)	4 (14)
ICANS — no. (%)		
Overall	8 (26)	4 (14)
Grade 3 or more	3 (10)	0 (0)
Adverse event leading to ICU stay — no. (%)	4 (13)	1 (4)

8089 **Poster Session**

A phase 1 dose escalation and expansion study of ZG006, a trispecific T cell engager targeting CD3/DLL3/DLL3, as monotherapy in patients with refractory small cell lung cancer or neuroendocrine carcinoma. First Author: Qiming Wang, The Affiliated Cancer Hospital of Zhengzhou University & Henan Cancer Hospital, Zhengzhou, Henan, China

Background: ZG006 is a unique designed T cell engager, targeting CD3 and Delta-like ligand 3 (DLL3) with two distinct DLL3 epitopes, and bridges tumor cells and T cells by strongly binding to DLL3 on tumor cells and CD3 on T cells, thereby mediating T cell-specific killing of DLL3-expressing tumor cells such as small cell lung cancer (SCLC) or neuroendocrine carcinoma (NEC). Here, we report the complete results for the phase 1 study of ZG006 for the treatment of patients (pts) with refractory SCLC or NEC. **Methods:** This is a multi-center, open-label, phase 1 clinical study of ZG006 as monotherapy in pts with SCLC or NEC who failed or were intolerant to the standard therapies. A standard "3+3" design, with an accelerated approach for the first two lower dose levels was used during the dose escalation stage. Patients were treated with doses from 0.1 to 100 mg, intravenous infusion, once every 2 weeks. Tumor response was assessed by RECIST1.1. DLL3 expression was retrospectively evaluated by IHC. **Results:** As of data cut-off in Dec 2024, a total of 45 pts (41 SCLC pts and 4 NEC pts) were enrolled and received≥1 dose of ZG006, 4 at the dose group of 0.1 mg, 3 at 0.3 mg, 3 at 1 mg, 3 at 3 mg, 5 at 10 mg, 12 at 30 mg, 11 at 60 mg and 3 at 100 mg. Patients included 35 males and 10 females, with median age 59 years (range: 43-72). The majority (86.6%) had received ≥2 lines of prior treatments and 44.4% received ≥3 lines. Twenty-six pts (57.8%) had prior anti-PD-(L)1 treatment. Only one patient in 100 mg group experienced DLT events (grade 3 cytokine release syndrome and grade 4 pneumonia). Treatment-related adverse events (TRAEs) occurred in all 45 pts; most commonly: cytokine release syndrome (CRS), pyrexia, anemia, white blood cell count decreased, pruritus, decreased appetite, hyponatraemia, asthenia, neutrophil count decreased, nausea, hypoalbuminaemia, alanine aminotransferase increased and constipation. CRS occurred mostly after the first two doses and usually recovered within 2 days. Eleven pts (24.4%) experienced serious TRAEs. There was no TRAE leading to treatment discontinuation or death and no ICANS was reported. Twenty-three SCLC patients receiving ZG006 10-60 mg were efficacy-evaluable with at least one post-baseline tumor assessment, and the ORR was 60.9% (14/23, 10 confirmed) and the DCR was 78.3% (18/23). Among the 18 pts who had low/medium DLL3 expressions, 12 pts achieved PRs with an ORR of 66.7%, which demonstrated that ZG006 had a great anti-tumor activity in SCLC pts. ZG006 demonstrated a nearly dose-proportional increase in concentration with a half life of approximately 4 days after multiple doses. **Conclusions:** ZG006 exhibited a promising antitumor activity with acceptable safety profiles. Phase 2 dose expansion studies have been initiated to further investigate the efficacy and safety of ZG006 in pts with SCLC or NEC. Clinical trial information: NCT05978284. Research Sponsor: None.

8090 **Poster Session**

Efficacy and safety of envafolimab plus carboplatin and etoposide as first-line treatment for extensive-stage small-cell lung cancer: A prospective, single-arm, phase II trial. First Author: Shengjie Sun, Senior Department of Oncology, the Fifth Medical Center of PLA General Hospital, Beijing, China

Background: Extensive-stage small cell lung cancer (ES-SCLC) is related to high malignancy and the poor prognosis. At present, immunotherapy combined with chemotherapy resulted in favorable therapeutic efficacy, and had been established as the standard treatment regimen for first-line treatment of ES-SCLC. However, some patients may still experience intolerable AEs over the course of treatment, such as immune-related pneumonitis and enteritis. Additionally, currently marketed ICIs were administered by continuous intravenous infusion, which is inconvenient for patients. This trial aimed to evaluate the efficacy and safety of envafolimab, which is a subcutaneously administered fusion protein of humanized anti-PD-L1 monodomain antibody, plus chemotherapy as a first-line treatment for ES-SCLC. **Methods:** This prospective, single-arm, phase II trial was conducted at the Fifth Medical Center of Chinese PLA General Hospital. Eligible patients with histologically or cytologically confirmed ES-SCLC were consecutively enrolled. Patients were given four cycles of carboplatin (5-6 mg/mL/min, day 1 of each cycle) and etoposide (80-100 mg/m², days 1-3 of each cycle) with envafolimab (300 mg, Q3W, day 3 post-chemotherapy of each cycle), followed by envafolimab maintenance until disease progression or intolerable toxicity. The primary endpoint was progression-free survival (PFS), and the secondary endpoint included objective response rate (ORR), disease control rate (DCR), and safety. **Results:** Between October 2021 and November 2022, a total of 32 patients were enrolled in this study. 32 patients were included for safety analysis, and 31 patients were included for efficacy analysis. As of the data cutoff (September 15, 2024), the median follow-up was 27.7 months. The ORR was 87.1% (95% CI, 70.2-96.4%), and the DCR was 100% (95% CI, 88.8-100%). The median DoR was 5.47 months (95% CI, 3.43-10 months). The median PFS was 6.43 months (95% CI, 4.83-7.67 months), and median OS was 20 months (95% CI, 14.7-NA). Treatment-related adverse events (TRAEs) of any grade were reported in 59.4% of patients, with grade ≥ 3 TRAEs in 15.6% patients. No treatment-related deaths occurred. **Conclusions:** First-line envafolimab in combination with carboplatin and etoposide yielded favorable clinical efficacy with a manageable safety profile for patients with ES-SCLC, representing a promising treatment modality. Clinical trial information: ChiCTR2100044981. Research Sponsor: None.

8091 **Poster Session**

Unveiling drivers of MHC repression and therapeutic strategies to counter immune evasion in small cell lung cancer. First Author: Triparna Sen, Icahn School of Medicine at Mount Sinai, New York, NY

Background: Small cell lung cancer (SCLC) is a highly aggressive neuroendocrine malignancy with a median survival of 9–11 months. Despite the addition of immune checkpoint blockade (ICB) to frontline chemotherapy, improvements remain limited. SCLC evades anti-tumor immunity by suppressing major histocompatibility complex class I (MHC-I) and antigen presentation (AP). The variability of MHC repression across molecular subtypes of SCLC and high-grade neuroendocrine tumors is not fully understood. This study analyzed clinical SCLC and neuroendocrine tumor samples to identify molecular subtypes and regulators of MHC repression, enhancing the understanding of immune evasion. **Methods:** Molecular profiling was conducted on 944 SCLC and 5056 non-small cell lung cancer (NSCLC) tumors using next-generation DNA (592-gene panel/whole exome), RNA (whole transcriptome) sequencing, and immunohistochemistry. Transcriptomic profiling of 40 SCLC cell lines and genetically engineered mouse models (GEMMs) was also performed. **Results:** Key regulators and gene networks driving MHC-I suppression in SCLC and other high-grade neuroendocrine tumors were identified. Canonical (MHC-I and II) and non-canonical AP expression scores characterized the spectrum of MHC-I repression across subtypes. Low MHC-I scores correlated with reduced immune signatures (e.g., T cell-inflamed, NK cell, and STING pathway signatures; Spearman = 0.87, 0.58, 0.62, respectively) and predicted poor OS and PFS to immunotherapy. Enhancer network and gene expression analyses identified actionable regulators of MHC-I repression, including interferon signaling. Knockout studies of top MHC-I regulators and single cell analyses revealed non-homologous end-joining (NHEJ) genes (like DNAPKCs) inversely correlated with HLA-A/B/C expression. DNAPKCs inhibition upregulated MHC-I, TAP1, and TAP2, enhanced antigen-specific T-cell-mediated cytolysis in SCLC. This inhibition activated the STING pathway, increased CD8+ T-cell infiltration, and enhanced MHC Class-I. Combining DNAPKCs inhibitor NU1774 with anti-PD-L1 reactivated MHC-I and led to significant tumor regression in aggressive murine SCLC models, supporting new combination therapies. **Conclusions:** We identified molecular subtypes and actionable pathways to restore MHC-I expression in SCLC, advancing understanding of immune evasion mechanisms. DNAPKCs is established as a key therapeutic target, enhancing PD-L1 blockade by reactivating antigen presentation. The developed MHC-I expression scores and associated biomarkers offer predictive tools for identifying patients likely to benefit from immunotherapy. These findings support biomarker-driven, personalized approaches to improve treatment for SCLC, addressing a critical unmet need in this devastating cancer. Research Sponsor: None.

8093 **Poster Session**

Serplulimab versus placebo plus chemotherapy as first-line treatment for extensive-stage small-cell lung cancer: Efficacy and safety from the end-of-study analysis of the international phase 3 ASTRUM-005 study. First Author: Ying Cheng, Department of Oncology, Jilin Cancer Hospital, Changchun, China

Background: ASTRUM-005 is a randomized, double-blind, phase 3 trial comparing the efficacy and safety of anti-PD-1 antibody serplulimab plus chemotherapy (chemo) versus (vs) placebo plus chemo as first-line therapy for extensive-stage small-cell lung cancer (ES-SCLC). Significantly prolonged overall survival (OS) in the serplulimab arm was observed at interim analysis and sustained OS improvement at extended follow-up (2024 ASCO Annual Meeting No. 8100). Here we present end-of-study analysis of ASTRUM-005 at a median follow-up of 42.4 months. **Methods:** Patients with ES-SCLC who had not received prior systemic therapy were randomized 2:1 to receive serplulimab plus chemo (carboplatin and etoposide) or placebo plus chemo. Serpluliamb or placebo were administered intravenously at 4.5 mg/kg every 3 weeks. Up to 4 cycles of intravenous carboplatin and etoposide were given every 3 weeks. Stratification factors included PD-L1 expression level, brain metastases, and age. The primary endpoint was OS. Secondary endpoints included progression-free survival (PFS), objective response rate, duration of response, and safety. **Results:** Between Sep 12, 2019 and Apr 27, 2021, 585 patients were randomized (serplulimab group, n = 389; placebo group, n = 196) and received at least one dose of study treatment. All 585 patients were included in efficacy and safety analyses. As of data cutoff on May 7, 2024, consistent with previous reports, marked improvement in OS, PFS, ORR, and DOR were achieved by patients receiving serplulimab plus chemo than those receiving placebo plus chemo. Median OS was 15.8 vs.11.1 months (stratified HR 0.60, 95% CI 0.49–0.73) for respective arms; estimated 4-year OS rate (95% CI) was 21.9% (17.6–26.6) and 7.2% (3.8–12.1). Subgroup analysis of OS by age, sex, race, ethnicity, ECOG PS, smoking history, brain metastasis, or PD-L1 expression level revealed similar trends of improvement in the serplulimab arm. Median PFS according to independent radiology review committee (IRRC) assessment per RECIST v1.1 was 5.8 vs 4.3 months (stratified HR 0.47, 95% CI 0.38–0.57), respectively. The safety profile was consistent with previous findings. Serplulimab/placebo-related treatment-emergent adverse events of grade 3 or higher occurred in 136 (35.0%) and 57 (29.1%) patients in respective arms. No new safety signals were identified in this study. **Conclusions:** This end-of-study analysis showed that addition of serplulimab to chemo continued to confer survival benefit to previously untreated patients with ES-SCLC along with manageable safety. These results support serplulimab plus chemo for first-line treatment of ES-SCLC. Clinical trial information: NCT04063163. Research Sponsor: Shanghai Henlius Biotech, Inc.

8094 **Poster Session**

DAREONTM-9, a phase Ib study of obrixtamig plus topotecan in patients (pts) with advanced small cell lung cancer (SCLC): Interim analysis results. First Author: Martin Wermke, TU Dresden University of Technology, NCT/UCC Early Clinical Trial Unit, Dresden, Germany

Background: Delta-like ligand 3 (DLL3) is highly expressed on SCLC cells and is a promising target for new therapeutic drugs. Obrixtamig (BI 764532) is a DLL3/CD3 IgG-like bispecific T-cell engager that binds simultaneously to DLL3 on tumor cells and CD3 on T-cells leading to tumor cell lysis. We report the first safety and preliminary efficacy data for the dose escalation part of the Dareon-9 trial, investigating the combination of obrixtamig and topotecan in pts with advanced SCLC (NCT05990738). **Methods:** Pts who progressed on or relapsed after ≥1 line of platinum-based treatment (Tx) ± anti-programmed cell death protein 1 (PD-1)/programmed death-ligand 1 (PD-L1) were eligible for the trial. Obrixtamig was given as step-up dosing followed by target dose (3 dose levels). Topotecan was given per label. Dose escalation of obrixtamig was guided by a Bayesian Logistic Regression Model with overdose control. Antitumor activity was assessed using RECIST 1.1. The ongoing dose confirmation part will assess obrixtamig at the dose selected at the end of dose escalation. **Results:** As of January 2, 2025, 25 pts had received ≥1 cycle of Tx. Median number of cycles for both obrixtamig and topotecan was 4 (range 1–13); median Tx exposure was 2.6 months (range ≤1–8.5). Median age was 65 years (range 38–78); ECOG PS was 0 in 13 pts (52%), 1 in 12 pts (48%); median number of prior lines of Tx was 1 (range 1–3), 92% had received prior anti-PD-1/PD-L1. Obrixtamig-related adverse events (AEs; any grade/grade ≥3) occurred in 23 (92%) and 7 (28%) pts, with no grade 5 AEs. Topotecan-related AEs (any grade/grade ≥3) occurred in 25 (100%) and 21 (84%) of pts, with no grade 5 AEs. No pts discontinued obrixtamig due to Tx-related AEs. No obrixtamig- or topotecan-related grade ≥2 neurologic events occurred. All cytokine release syndrome cases were low grade: grade 1 (44%) and grade 2 (4%). The most frequent (≥10%) Tx-emergent grade 3/4 AEs were: neutropenia and/or decreased neutrophil count in 15 pts (60%); thrombocytopenia and/or decreased platelet count in 13 pts (52%); decreased lymphocyte count in 8 pts (32%); anemia in 6 pts (24%); and fatigue in 4 pts (16%). Grade 3 febrile neutropenia was reported in 1 pt (4%). Preliminary efficacy data from evaluable pts (n=23) showed an unconfirmed ORR of 70% (95% CI 47–87); 1 pt (4%) had a CR and 15 (65%) pts had a PR. Disease control rate was 87% (95% CI 66–97). In the 13 pts with ≥2 post-baseline tumor assessments (follow-up >13 weeks), the confirmed ORR was 69%. Median duration of response was not reached. **Conclusions:** The obrixtamig plus topotecan combination was tolerable with no unexpected toxicities. AE frequency and severity reported for the combination were consistent with the expected safety findings for obrixtamig and topotecan as monotherapy. Preliminary efficacy data for the combination are encouraging and indicate an improvement on top of topotecan monotherapy. Clinical trial information: NCT05990738. Research Sponsor: Boehringer Ingelheim.

8095 **Poster Session**

Lung cancer enrollment of demographic subgroups in US clinical trial sites. First Author: Evon Okidi, Dassault Systemes, New York, NY

Background: Most clinical trials globally are not representative of a diverse patient population and 78% of trial participants remain White. This may limit the generalizability of trial results to the broader population, create an insufficient understanding of drugs' safety and efficacy between different patient populations, and hinder equitable access to investigational drugs. We compare the racial and ethnic composition of US clinical trials sites for lung cancer to epidemiology data. **Methods:** The de-identified data was sourced from Medidata's clinical trial database. The cohort included clinical trial participants enrolled in US sites in phase 1-3 interventional lung cancer studies conducted between 2016 and 2022. Lung cancer incidence estimates were taken from the National Cancer Institute's incidence data. Sites were classified as at/above or below expected demographic composition based on a relative ratio calculation, RR = proportion of trial patients/proportion of population with lung cancer. RR ≥1 means site recruited at/above expected ratio for the demographic group and vice versa. A 10% tolerance was used to capture minor deviations. A Mann-Whitney U test was used to determine if the two site types have statistically different enrollment rates, with a p-value of 0.05 for significance. **Results:** The analysis cohort consisted of 6,988 lung cancer patients from 85 studies and 876 US sites. Most sites enrolled White non-Hispanic patients at/above the epidemiological threshold. Conversely, the majority of sites enrolled non-White patients below the threshold (Table 1). The overall enrollment performance of sites enrolling a representative cohort of Black, American Indian and White patients did not differ from their counterparts. However, sites enrolling at or above the epidemiological threshold of Asian non-Hispanic and Hispanic patients had a higher enrollment rate than sites underrepresenting these patient populations. **Conclusions:** The majority of US clinical trial sites underrepresent demographic subgroups except White non-Hispanic patients. Sites enrolling a representative pool of racial and ethnic demographic subgroups did not have a lower overall enrollment performance. Research Sponsor: None.

Enrollment rate of sites recruiting at/above vs. below epidemiological threshold.

	Enrollment Rate (pts/site/month) Median (IQR)				
	Sites Enrolling At or Above Epidemiological Threshold		Sites Enrolling Below Epidemiological Threshold		
Race/Ethnicity Sub-group	N (%) sites	Enrollment Rate	N (%) sites	Enrollment Rate	P-value
Asian (non-Hispanic)	67 (13%)	0.11 (0.03 - 0.23)	439 (87%)	0.04 (0.02 - 0.08)	<0.0001
Black (non-Hispanic)	96 (15%)	0.04 (0.02 - 0.08)	553 (85%)	0.04 (0.02 - 0.09)	0.99
American Indian (non-Hispanic)	6 (4%)	0.08 (0.06 - 0.12)	137 (96%)	0.04 (0.01 - 0.07)	0.19
White (non-Hispanic)	461 (59%)	0.04 (0.01 - 0.09)	326 (41%)	0.04 (0.02 - 0.07)	0.64
Hispanic	76 (14%)	0.07 (0.03 - 0.14)	447 (86%)	0.04 (0.02 - 0.08)	0.002

8096 **Poster Session**

Comprehensive longitudinal immune cell monitoring in patients with extensive-stage small-cell lung cancer patients treated with chemo-immunotherapy to predict early relapse. First Author: Seren Durer, University Hospitals Seidman Cancer Center, Case Western Reserve University, Cleveland, OH

Background: Small cell lung cancer (SCLC) is characterized by rapid growth, and although initial chemo-immunotherapy achieves high response rates, relapse typically occurs within 6–12 months. Emerging data suggest that myeloid-derived suppressor cells (MDSCs) and lymphocyte subsets influence immunotherapy response and relapse kinetics. We conducted a detailed immune profiling study to characterize circulating myeloid and lymphoid populations in SCLC patients, comparing those with early vs. late (>200 days) relapse. **Methods:** Purified PBMCs collected at baseline and relapse were analyzed by high-parameter flow cytometry using panels containing myeloid and lymphocytic markers. **Results:** Patients with ES-SCLC treated with chemo-immunotherapy were prospectively enrolled in this biomarker trial. A total of 32 were accrued. Among patients with early (<200 days) vs. late (≥200 days) relapse, baseline frequencies of CD33+ myeloid cells were similar. At relapse, however, a marked decrease in activated CD15+/CD16+ neutrophils was observed in both groups. PMN-MDSCs showed distinct kinetics: early-relapse patients had elevated MDSCs at baseline, whereas late-relapse patients exhibited significant MDSC expansion only at relapse. Additionally, a P-selectin–high monocytic subpopulation (M-MDSC) emerged more prominently in the late-relapse cohort, potentially reflecting a protective or anti-tumor phenotype. On lymphocyte analysis, a significant decline in CD8+ cytotoxic T-cell frequencies was observed at relapse across all patients, indicating a potential mechanism of immune evasion. The analysis of CD107 expression further supported the decrease in cytotoxic T-cell activity at relapse. Notably, higher baseline frequencies of CD57+ T-cell correlated with relapse-free intervals greater than 200 days. Lastly, lower baseline frequencies of activated B cells were associated with longer relapse-free survival. **Conclusions:** Our results reveal novel findings, suggesting that unique kinetics of myeloid and lymphoid immunophenotype levels are associated with relapse timing in SCLC treated with chemo-immunotherapy. These findings suggest potential predictive biomarkers and inform the development of targeted immunomodulatory strategies. Research Sponsor: None.

8097 **Poster Session**

Efficacy and safety of HTMC0435 combination with temozolomide in relapsed extensive-stage small-cell lung cancer (ES-SCLC): A phase Ib/II study. First Author: Yun Fan, Zhejiang Cancer Hospital, Hangzhou, China

Background: Treatment options for ES-SCLC in second-line setting are limited. HTMC0435, an oral PARP inhibitor, significantly reduced the ability of PARP to repair DNA damage and inhibited tumor cell proliferation when combined with temozolomide (TMZ) in preclinical studies. We investigated the safety and activity of this regimen in relapsed SCLC. **Methods:** This was a phase Ib/II dose-escalation (3+3 design) and dose-expansion study. ES-SCLC patients who had progressed after first- or second-line therapy were eligible. Pts were administered with HTMC0435 6 mg or 8 mg bid on days 1-21 in combination with TMZ 75 mg/m^2 on days 1-7 of each 21-day cycle. The study objectives were to evaluate safety, pharmacokinetics and preliminary efficacy of the combination regimen. **Results:** From Feb-2023 to Nov-2023, 59 eligible pts were enrolled, with 7 pts in dose escalation and 52 pts in dose expansion. No dose-limiting toxicity (DLT) occurred, and HTMC0435 8mg bid combination with TMZ was selected as recommended phase 2 dose (RP2D). As of 31 October 2024, the median follow-up time was 10.3 months. 55 pts received HTMC0435 8mg bid and TMZ. Among these patients, brain and liver metastases were in 41.8% (23/55) and 23.6% (13/55) pts, respectively. 61.8% (34/55) pts had received prior platinum-based and anti–PD-(L)1 therapy as first line therapy. Among 49 efficacy evaluable patients, the objective response rate (ORR) and disease control rate (DCR) were 24.5% (12/49, 95%CI: 12.0%-37.0%) and 63.3% (31/49, 95%CI: 49.3%-77.3%). The median duration of response (DoR) was 6.9 mos (95%CI: 1.22-12.58). The median progression-free survival (PFS) and overall survival (OS) were 2.8 mos (95%CI: 1.16-4.44) and 12.0 mos (95% CI: 7.85-14.75). 23 pts were platinum-resistant (chemotherapy-free interval < 90 days), with ORR of 25.0% (5/20, 95%CI: 8.7%-49.1%), DCR of 55.0% (11/20, 95%CI: 31.5%-76.9%), mDoR not reached, mPFS of 2.5 mos (95%CI: 1.38-5.03) and mOS of 12.6 mos(95%CI: 5.78-NC). Among the 29 platinum-sensitive pts (chemotherapy-free interval ≥ 90 days), ORR and DCR were 26.9% (7/26, 95%CI: 11.6%-47.8%) and 73.1% (19/26, 95%CI: 52.2%-88.4%), and the mDoR was 4.2 mos (95%CI: 4.14-NC). The mPFS and mOS were 4.2 mos (95%CI: 2.69-5.52) and 11.2 mos (95%CI: 8.38-NC). 96.6% (57/59) pts experienced treatment-related adverse events (TRAEs) and 55.9% (33/59) pts experienced grade 3-4 TRAEs. Most common TRAEs (grade 3-4) were neutropenia (35.6%), leukopenia (28.8%), thrombocytopenia (13.6%), anemia (8.5%). Six (10.2%) pts experienced TRAEs led to dose reduction of HTMC0435 and no TRAEs led to discontinuation of HTMC0435 were reported. **Conclusions:** This combination of HTMC0435 and TMZ showed promising anti-tumor activity and manageable safety both in platinum-sensitive and platinum-resistant SCLC patients. Clinical trial information: NCT05728619. Research Sponsor: Shanghai Yidian Pharma.

8098 **Poster Session**

Debio 0123, a highly selective WEE1 inhibitor, in combination with carboplatin (C) and etoposide (E), in patients (pts) with recurrent small cell lung cancer (SCLC): Determination of recommended dose (RD) from a phase 1 escalation. First Author: Valentina Gambardella, Department of Medical Oncology, Hospital Clínico Universitario, INCLIVA Biomedical Research Institute, University of Valencia, Valencia, Spain

Background: Debio 0123 is an oral, brain-penetrant, highly selective WEE1 inhibitor. WEE1 inhibition leads to S phase and G2/M cell cycle checkpoint abrogation, allowing mitosis without DNA repair, leading to mitotic catastrophe and subsequent cell death. Debio 0123 is in clinical development in solid tumors, as monotherapy and in combination with different therapeutic agents. Debio 0123 has shown manageable safety profile and initial signals of antitumor activity. SCLC is an aggressive disease that carries a high mutational burden and genomic instability. Debio 0123 has shown to significantly improve the antitumor activity of DNA damaging agents, C + E, in preclinical SCLC models. **Methods:** This Phase 1 study (NCT05815160) is evaluating Debio 0123 in combination with C + E in pts with recurrent SCLC after first line of platinum-based chemotherapy. Of note, pts with stable brain metastasis were eligible. In the dose escalation, pts who had a chemotherapy-free interval (CFI)>45 days since the last dose of platinum chemotherapy, received escalating doses of Debio 0123 (D1–3 and D8–10) in combination with standard C (AUC5) on D1 and E (100 mg/m2) on D1-3 in 21-day cycles. **Results:** Dose escalation data (cut-off date Oct 24th, 2024) are presented. Overall, 16 pts were treated (44% female, mean age 63.3 years). Using a Bayesian Logistic model-guided dose escalation, tested doses of Debio 0123 ranged from 200-400 mg. The RD was selected at 200 mg. At this dose level, 3/10 pts experienced a dose-limiting toxicity. The treatment was considered well tolerated with a manageable overall safety profile, in line with that expected for the chemotherapy combination. Most frequent Debio 0123 -related toxicities are shown in Table 1. PK data showed Debio 0123 plasma levels increasing proportionally with the dose. Debio 0123 CSF/plasma ratio was ~40%, suggesting that Debio 0123 crosses the blood brain barrier. At 200 mg, confirmed partial responses (PR) occurred in 4/9 evaluable pts overall, and in 4/7 pts in the subgroup with CFI>90 days, including pt with intracranial response; 4 pts had SD of which 2 had tumor shrinkage of > 20 %. mPFS at the RD (n=10) was 7.2 months. **Conclusions:** Debio 0123 combined with C + E is well tolerated, with a manageable safety profile, up to 200 mg; this combination led to promising antitumor activity in pts with recurrent SCLC after prior platinum-based therapy with CFI > 45 days. Further investigation of Debio 0123 at 200 mg in pts with a CFI > 90 days is ongoing. Clinical trial information: NCT05815160. Research Sponsor: Debiopharm International.

Summary of treatment-emergent adverse events (TEAEs) related to Debio 0123 in ≥ 2 pts at the RD (200 mg).

TEAE	Any grade (N=10) n (%)	Grade ≥3 (N=10) n (%)
Neutropenia/neutrophil count decreased	4 (40)	3 (30)
Nausea	3 (30)	0
Diarrhea	2 (20)	1 (10)
Thrombocytopenia/platelet count decreased	2 (20)	1 (10)

8099 **Poster Session**

Does early versus late initiation of immunotherapy in extensive-stage small cell lung cancer affect survival outcomes? First Author: Paresh Kumar, Indiana University School of Medicine, Indianapolis, IN

Background: Small cell lung cancer (SCLC) is an aggressive malignancy characterized by a rapid doubling time, high metastatic potential, and risk for relapse, prompting urgent treatment. Chemoimmunotherapy is the standard of care for first line treatment of extensive-stage SCLC (ES-SCLC). A study evaluating the National Cancer Database reported improvement in overall survival (OS) with initiation of chemotherapy after 28 days from a SCLC diagnosis. However, the optimal timing for initiation of immunotherapy for SCLC remains unclear. Here, we seek to understand if the timing of immunotherapy impacts outcomes for ES-SCLC. **Methods:** We retrospectively reviewed 149 charts of patients diagnosed with ES-SCLC treated at Indiana University (IU) Health and IU Simon Comprehensive Cancer Center from January 2018 to August 2024. Patients who received platinum-based chemotherapy combined with immune checkpoint inhibitor (ICI) as first line therapy were included. Patients were categorized into two groups based on ICI timing: (1) with the first cycle and (2) after the first cycle of chemotherapy. Additionally, patients were stratified by time-to-ICI-initiation from diagnosis (TII), ≤21 days vs >21 days. **Results:** A total of 75 patients diagnosed with ES-SCLC who received chemotherapy with either durvalumab (18.7%) or atezolizumab (81.3%) were identified. Across the entire cohort, median OS and progression-free survival (PFS) were 12.2 and 5 months, respectively. Patients with TII of ≤21 days had a median OS of 16.8 months, compared to 11.8 months for those with TII >21 days (P = .26). Median OS was 16 months for patients who received ICI with the first cycle of chemotherapy and 10 months for those who received it later (P = .43). Median PFS was similar between these groups. For univariate analysis, we used median OS for the entire cohort (i.e., 12.2 months) to define responders (OS ≥12.2 months, n=30) and non-responders (OS <12.2 months, n=42). In responders group, 60% received ICI with the first cycle of chemotherapy, compared to 53.3% in non-responders (P = .57). **Conclusions:** The timing of initiation of immunotherapy, either with first cycle of chemotherapy or within 21 days of diagnosis, does not significantly improve outcomes in patients diagnosed with ES-SCLC. At our institution, atezolizumab is more commonly utilized for ES-SCLC. Recent real-world data suggests a survival benefit with use of durvalumab. Further prospective investigation is warranted to understand if ICI selection and timing can impact outcomes in ES-SCLC. Research Sponsor: None.

Patients' clinical and demographic characteristics.

Variable	Overall N=75	Receipt of ICI with Cycle 1: No N=33	Receipt of ICI with Cycle 1: Yes N=42	P Value
Age	62.7 ± 9	61.5 ± 9.1	63.6 ± 8.9	0.299
ECOG PS ≥ 2	17 (25%)	9 (30%)	8 (21.1%)	0.679
Female	48 (64%)	22 (66.7%)	26 (61.9%)	0.670
Active tobacco use	43 (57.3%)	**25 (75.8%)**	**18 (42.9%)**	**0.007**
Presence of brain metastases	19 (25.3%)	6 (18.2%)	13 (31%)	0.207

8100 Poster Session

Predictive and prognostic impacts of SCLC comprehensive index (SCI) in extensive-stage small-cell lung cancer (ES-SCLC) treated with chemo-immunotherapy. First Author: Songji Oh, Cancer Research Institute, Seoul National University, Seoul, Korea, Republic of

Background: First-line (1L) chemo-immunotherapy is standard of care for ES-SCLC with improved survival outcomes (IMpower133 and CASPIAN). However, there were no reliable biomarkers associated with survival outcomes in these patients (pts). This study aimed to develop a SCI signature using RNA profiling with the nCounter system to predict chemo-immunotherapy outcomes. **Methods:** The SCI genes were selected based on IMpower133 transcriptomic data (Cancer Cell 2024;42:429) by K-means clustering to determine optimal cut-offs and risk grouping. A gene scoring system was developed with weights being assigned to genes linked to better survival rates. The validation cohort consisted of 93 ES-SCLC pts who received 1L chemo-immunotherapy (etoposide, carboplatin, and atezolizumab) at Seoul National University Hospital (SNUH). NanoString nCounter analysis was performed on all FFPE samples and RNA-seq was validated on 40 samples. Cox proportional hazards models were used for univariable and multivariable analyses. **Results:** The SCI was developed using genes related to neural (N=7), epithelial-to-mesenchymal transition (N=5), tumor-associated macrophages (N=5), and the T-cell inflamed signature (TIS) (N=18). The SCI signature also included molecular subtypes (N=3), targetable genes (N=4) and 5 housekeeping genes. Our validation cohort included 93 pts with mean age of 69 years and male-to-female ratio of 7.5:1. The median progression-free survival (PFS) and overall survival (OS) were 5.7 months and 12.9 months, respectively. SCLC molecular subtypes were as follows: SCLC-ASCL1 (39%) -NEUROD1 (24%) -POU2F3 (3%) -YAP1 (32%) and -Inflamed (TIS) (9%). The SCI model using 47 genes stratified pts into high- (N=29), intermediate- (N=48), and low- (N=16) risk groups with median PFSs of 4.8, 5.9, and 9.9 months and median OSs of 8.1, 14.3, and 24.4 months, respectively. In this cohort, the high-risk group showed significantly worse PFS (HR=4.68, $P < 0.001$) and OS (HR=5.03, $P < 0.001$) compared to the low-risk group. Similarly, in the IMpower133 cohort, the high-risk group demonstrated poorer outcomes with PFS (HR=2.33, $P = 0.001$) and OS (HR=3.47, $P < 0.001$) compared to the low-risk group. **Conclusions:** The SCI 47-gene panel based on IMpower133 transcriptome was validated through nCounter analysis system and effectively stratified ES-SCLC pts into distinct risk groups with strong predictive and prognostic capacities. It provides a practical biomarker for guiding immunotherapy in pts with ES-SCLC. Correlative analyses of nCounter with RNA-seq and AI-powered TIL will be presented. Research Sponsor: None.

8101 Poster Session

Multi-omic analysis and overall survival update of phase II TRIDENT study: Durvalumab plus olaparib in extensive-stage small-cell lung cancer (ES-SCLC). First Author: Yuanyuan Zhao, Department of Medical Oncology, State Key Laboratory of Oncology in South China, Guangdong Provincial Clinical Research Center for Cancer, Sun Yat-Sen University Cancer Center, Guangzhou, China

Background: Chemotherapy plus anti-PD1/PD-L1 therapy has revolutionized the standard first-line treatment for patients with ES-SCLC. Durvalumab plus Olaparib as maintenance therapy showed encouraging anti-tumor activity in TRIDENT study as previous report. Here, we aim to identify molecular biomarkers of ES-SCLC through multi-omic analysis. **Methods:** 60 treatment-naïve ES-SCLC patients were enrolled in the TRIDENT study (NCT05245994), receiving Durvalumab plus Olaparib as maintenance therapy after Durvalumab plus chemotherapy as first line treatment. Frozen tumor tissues were collected before treatment to employ transcriptome sequencing and high-resolution quantitative DNA methylation. Next-Generation Sequencing (NGS) and Proximity Extension Assay (PEA) of cytokine were conducted using baseline plasma. **Results:** At the data cutoff on December 31, 2024, the median duration of follow-up was 13.0 months. The median PFS was 6.77 months (95% CI, 5.75-8.97), median overall survival was 14.59 months (95% CI 12.98–22.34). The 1-2-3 survival rate was 61.7%, 21.7% and 1.7%. For DNA methylation analysis, unsupervised clustering was performed based on Non-negative Matrix Factorization (NMF) and samples were classified into two clusters, with a clear difference in methylation levels. Patients in DNA hypomethylation group demonstrated better survival outcomes. Differentially methylated genes in pathway enrichment analysis revealed that immune-related and antigen processing and presentation signaling pathways were activated, while glycolysis and oxidative phosphorylation, DNA damage and repair signaling pathways were suppressed in the hypomethylation group. Moreover, transcriptome data further indicated a significant suppression in pathways related to epithelial-mesenchymal transition (EMT), extracellular matrix (ECM) remodeling, and cell adhesion in the hypomethylation group. As for cytokine analysis, high serum levels of IL6, IL8, Gal-9, CCL23, CSF-1 and HO-1 were significantly associated with poorer OS, while pro-inflammatory cytokines MCP-2 was correlated with better survival outcomes. **Conclusions:** Our findings indicated that DNA hypomethylation levels may be associated with better efficacy and survival outcomes in ES-SCLC treated with the combination of Olaparib and Durvalumab. Clinical trial information: NCT05245994. Research Sponsor: AstraZeneca.

8102 Poster Session

Impact of immunotherapy on small cell lung cancer survival: A focus on treatment setting, race, and socioeconomics. First Author: Pranali Santhoshini Pachika, University of Louisville, Louisville, KY

Background: Immunotherapy has transformed the treatment landscape for many cancers, but its benefit in small cell lung cancer (SCLC) has remained modest. Trials like IMpower133 and CASPIAN demonstrated survival gains of only 2 to 2.7 months in patients with extensive-stage SCLC. However, the ADRIATIC trial highlighted significant survival benefits with durvalumab in limited-stage SCLC. Our study examines survival trends in SCLC across the pre-immunotherapy (PIE) and immunotherapy eras (IE) using National Cancer Database data, though it does not account for the recent advances in limited-stage SCLC due to the dataset being capped at 2021. **Methods:** Kaplan-Meier plots estimate survival probabilities, and log-rank tests compare survival between the IE (2016-2021) and PIE (2010-2015). Median overall survival (OS) and 5-year OS are reported with 95% CI, using a p-value threshold of <0.05. Cox regression analyzes the impact of demographic, clinical, and socioeconomic factors on survival, with hazard ratios (HR) indicating mortality risk. **Results:** This study analyzed 244,973 SCLC patients, divided into IE (n = 124,774) and PIE (n = 120,199). The majority were White (85%), with a median age of 68 years and a near-equal sex distribution (48% male, 52% female). Most patients were diagnosed at Stage IV (63%), and only 5% at Stage I. Survival rates were better in the IE ($p < 0.001$) except for stage IV disease. Patients treated at academic centers and Asian/Pacific Islander patients had better outcomes. Cox regression identified disease stage, immunotherapy use, facility type, insurance, and socioeconomic factors as key survival determinants. Immunotherapy improved survival, while lower income, lack of insurance, and non-academic centers worsened outcomes, highlighting the need for accessible care and financial support. **Conclusions:** Immunotherapy has modest improvement in survival outcomes for SCLC, but disparities in treatment access and outcomes persist across different populations. Ensuring equitable access to specialized care and financial support is essential to further improving survival rates. Research Sponsor: None.

Category	Group	N	Median Survival (months)	5yr OS (%)	P value
All stages	IE	124,774	8.74	11.2	<0.001
	PIE	120,199	8.48	8.3	
Stage I and II	IE	12,146	27.76	31	<0.001
	PIE	10,559	22.01	26	
Stage III	IE	28,347	15.18	19	<0.001
	PIE	29,288	13.67	15	
Stage IV	IE	79,005	6.24	5	<0.001
	PIE	74,714	6.24	3	
Facility	Academic	33,883	9.69	13.3	<0.001
	Non-Academic	90,655	8.38	10.3	
Race	Hispanic	3,169	9.30	14.2	<0.001
	Non-Hispanic - Asian/Pacific Islander	2,242	9.86	14.5	
	Non-Hispanic - Black	9,786	9.95	13.8	
	Non-Hispanic - White	106,464	8.57	10.7	
Income	< $46,277	22,397	8.31	10.5	<0.001
	$46,277 - $57,856	27,868	8.51	10.2	
	$57,857 - $74,062	25,949	8.87	10.9	
	$74,063+	28,283	9.20	12.8	
Insurance	Medicaid	11,677	9.49	13.2	<0.001
	Medicare	79,039	7.89	9.3	
	Not Insured	3,083	7.16	10.4	
	Other Government	2,730	9.56	11.5	
	Private	26,732	11.20	15.6	

8104 Poster Session

Safety, tolerability, and preliminary efficacy results of a phase 1 study of LB2102, a dnTGFβRII armored DLL3-targeted autologous CAR-T cell therapy, in patients with relapsed or refractory small cell lung cancer (SCLC) and large cell neuroendocrine carcinoma (LCNEC). First Author: Jacob Sands, Dana-Farber Cancer Institute, Boston, MA

Background*:* Delta-like- ligand 3 (DLL3) is a promising therapeutic target for SCLC and other neuroendocrine tumors. Here, we present preliminary results from the ongoing dose-escalation study of LB2102, an autologous CAR-T cell therapy engineered to target DLL3 and armored with a TGF-β receptor blockade to overcome the immunosuppressive tumor microenvironment. **Methods***:* This ongoing, open-label, multicenter, phase 1 study evaluates LB2102 in patients with SCLC/LCNEC who are relapsed/refractory to ≥1 prior line of therapy. Dose escalation follows a modified 3+3 design, with planned dose levels of 0.3, 1.0, 2.0, 4.0, 8.0, 12.0, 16.0 x 10^6 CAR+ T cells/kg. All subjects undergo 3-day lymphodepletion (LD) with fludarabine (30 mg/m^2), and cyclophosphamide (300 mg/m^2). The primary objective is to assess safety, tolerability and determine the recommended phase 2 dose (RP2D). **Results***:* As of December 13, 2024, 9 patients were treated with LB2102 across dose-level (DL) 1 at 0.3x10^6 (n=3), DL2 at 1x10^6 (n=3), and DL3 at 2x10^6 CAR+ T cells/kg (n=3). Eight subjects had SCLC and one subject on DL2 had LCNEC. The median age was 54 (range 20-61), and the median prior lines of therapy was 2 (range 1-7). Bridging therapy was administered in all patients. No Dose-limiting toxicities (DLT) and no neurotoxicity was observed. One subject in DL3 experienced grade 1 CRS. Grade >3 treatment-emergent adverse events (TEAEs) attributed to LB2102 included anemia (n=2), leukopenia (n=2) and neutropenia (n=2); none were classified as serious, and all were deemed related to lymphodepletion. At DL3, best observed response per RECIST1.1 was 1 partial response (with deepening of response over time) and 2 stable disease (SD). The best overall response for subjects at DL1 was progressive disease (n=3) and at DL2 was SD (n=3) (with increased tumor shrinkage in 1 subject). Significant CAR-T expansion in peripheral blood was observed as measured by qPCR at DL3 (n=3) with a median C_{max} of 694.4 copies/μg genomic DNA (range, 45.6-2256.7) and a median T_{max} of 15 days (range, 10-29). **Conclusions***:* LB2102 has been well tolerated with no DLT observed up to DL3 (2 x 10^6 CAR+ T cells/kg). There appears to be a dose-dependent efficacy signal observed at higher doses with responses correlating to CAR-T expansion, although the data is limited. Given no DLTs and preliminary efficacy signal up to DL3, further exploration of higher dose levels is warranted. Clinical trial information: NCT05680922. Research Sponsor: Legend Biotech USA Inc.

Dose levels (CAR+ T cells/kg)	Subject No.	Best Overall Change in Sum of Tumor Size (%)
DL1: 0.3 x 10^6	1	+22.8%
	2	Non-evaluable*
	3	+57.1%
DL2: 1 x 10^6	4	-31.6%
	5	-22.6%
	6	-4.8%
DL3: 2 x 10^6	7	-14.3%
	8	-69.8%
	9	-20.6%

*Subject had non-measurable disease at baseline and progressed during study period.

8105 **Poster Session**

Association of IFITM3 with the efficacy of anti-PD1/PD-L1 therapy and regulation of immunosensitivity via MHC-I regulation in SCLC. First Author: Shengxiang Ren, Department of Oncology, Shanghai Pulmonary Hospital & Thoracic Cancer Institute, Tongji University School of Medicine, Shanghai, China

Background: Majority of small cell lung cancer (SCLC) patients exhibit resistance to immune checkpoint inhibitors (ICIs), which is associated with the downregulation of major histocompatibility complex class I (MHC-I) molecules. This study investigates the regulatory mechanisms underlying MHC-I expression and explores potential therapeutic strategies to enhance ICI efficacy. **Methods:** Single-cell and bulk RNA sequencing data from SCLC patient tumors were analyzed to identify key regulators of MHC-I expression. The IMpower133 cohort (116 patients treated with chemotherapy plus anti-PD-L1 therapy and 131 patients treated with chemotherapy alone) and an in-house cohort (39 patients treated with chemotherapy and anti-PD-1 therapy) were utilized to assess the association between IFITM3 expression and immunotherapy outcomes. Additionally, tumor samples from 42 extensive-stage SCLC patients receiving first-line chemotherapy plus anti-PD1/PD-L1 were evaluated via immunohistochemistry (IHC) to determine IFITM3 expression as a predictive biomarker. *In vitro* and *in vivo* functional studies were conducted to elucidate the role and mechanisms of IFITM3 in modulating tumor sensitivity to PD-1 inhibitors. **Results:** Integrative analysis of multiple real-world cohorts of SCLC confirmed a significant positive association between *IFITM3* and MHC-I expression. IFITM3 overexpression elevated MHC-I-related genes, activated antigen presentation pathways, and enhanced $CD8^+$ T cell activity. In the IMpower133 cohort, high IFITM3 expression was significantly associated with prolonged progression-free survival (PFS) in patients receiving chemoimmunotherapy (HR 0.65,95% CI 0.44-0.96, p=0.014) but not in those treated with chemotherapy alone (HR 1.97,95%CI 1.19-3.25, p=0.0069). Similarly, in the in-house cohort, high IFITM3 expression conferred a PFS advantage in patients receiving chemoimmunotherapy (HR 0.42,95% CI 0.19-0.90, p=0.023). Furthermore, patients with elevated IFITM3 protein levels, as determined by IHC H-scores, exhibited improved clinical outcomes following chemoimmunotherapy. Importantly, inducing IFITM3 expression directly or through treatment with Ethyl gallate (EG), an IFITM3 activator, effectively sensitized tumors to PD-1 blockade in SCLC mouse models. **Conclusions:** IFITM3 positively regulates MHC-I expression and predicts response to ICIs in SCLC. Combining EG with PD-1 inhibitors represents a promising strategy to improve immunotherapy efficacy in SCLC patients. Research Sponsor: None.

8106 **Poster Session**

Implementation of tarlatamab treatment for small cell lung cancer using an outpatient care program. First Author: Jennifer W. Carlisle, Winship Cancer Institute, Emory University, Atlanta, GA

Background: Tarlatamab, a bispecific T-cell engager targeting DLL3, was FDA approved for relapsed small cell lung cancer (SCLC) in May 2024. It requires observation for 24 hours for the first two doses due to the risk of Cytokine Release Syndrome (CRS). We developed an outpatient program to administer tarlatamab at the Winship Cancer Institute and describe the initial experience in this report. **Methods:** Patients received tarlatamab in the outpatient infusion center then were observed in an outpatient oncology Immediate Care Center (ICC) onsite, staffed by advanced practice providers, to complete the 24-hour monitoring for CRS and immune effector cell-associated neurotoxicity (ICANS). Vital signs and ICE scores were monitored, and patients were hospitalized with $>$ grade 2 CRS or grade 1 ICANS based on American Society for Transplantation and Cellular Therapy Consensus Grading. Patients were prescribed dexamethasone 8mg to be taken at physician direction for later-onset symptoms prior to return to a health care facility. Demographics, disease characteristics, treatment history, toxicities, and outcomes were abstracted from the electronic medical record. **Results:** From June 2024 to January 2025, 29 patients with SCLC were treated, 27 of whom completed cycle 2 at data cut-off and were evaluated for safety and efficacy. Baseline demographics and clinical characteristics are shown in Table 1. Four patients were admitted prophylactically based on limited home support, distance from home, or location of administration; 6 patients required admission from the ICC during the first two cycles due to CRS/ICANS (CRS: 1, ICANS:1, both: 4) and one patient was admitted 48 hours after C1D8 for grade 1 CRS and nausea. CRS was observed 14 patients (grade 1: 7, grade 2: 4, grade 3: 3) and ICANS was observed in 10 patients (grade 1: 3, grade 2: 4, grade 3: 3). Eight patients required dose holds, with two who reinitiated step up dosing. Investigator-assessed radiographic responses included 9 partial response, 7 stable disease, 6 progressive disease, and 5 not evaluable. With a median duration of follow-up of 133 days (95% CI 91,168), the estimated median progression free survival was 101 days (95% CI 78, NA). **Conclusions:** Outpatient administration of tarlatamab is safe and feasible with appropriate monitoring, including for patients with an ECOG performance status of 2. Research Sponsor: None.

Baseline demographics and clinical characteristics.

	n (%)
Age (median, range)	64, 35-80
Gender	Male: 11 (38%); Female:18 (62%)
Primary site and histology	SCLC: 25; Transformed EGFR mutant NSCLC: 3; Unknown primary site: 1
Race:	Black: 14 (48%); White: 14 (48%); Unreported: 1 (3%)
ECOG Performance status:	0: 4 (14%); 1: 20 (69%); 2: 5 (17%)
Prior Lines of Therapy:	1: 9 (31%); 2: 9 (31%); 3: 7 (24%); 4: 4 (14%)
Metastatic sites:	Liver: 12 (41%); Brain: 17 (58%); Bone: 7 (24%)
Duration of platinum sensitivity:	$<$ 90 days: 6 (21%); 90-180 days: 12 (41%); $>$ 180 days: 11 (38%)

8107 **Poster Session**

Cataloging genomic and transcriptomic features of relapsed SCLC. First Author: Sid Devarakonda, Swedish Cancer Institute, Seattle, WA

Background: Relapsed small cell lung cancer (R-SCLC) is characterized by poor outcomes and treatment resistance. The mechanisms driving treatment resistance in R-SCLC remain poorly understood. We comprehensively profiled R-SCLC samples along with patient-matched treatment-naive samples (TN-SCLC) using whole-exome (WES), whole-genome (WGS), and RNA-sequencing (RNA-seq) to catalog mechanisms of treatment resistance and identify actionable alterations. **Methods:** We analyzed 54 R-SCLC and 27 TN-SCLC samples (with 26 patient-matched TN-R pairs) using WES. At presentation, 31 patients were diagnosed with extensive and 23 with limited stage SCLC. R-SCLC samples were also analyzed by WGS (n = 28, including 18 TN-R pairs) and RNA-seq (n = 31, including 12 TN-R pairs). Differences in mutational signatures, structural variations, gene expression, alternative splicing, and neoantigen profiles were investigated between TN and R-SCLC samples. **Results:** R-SCLC samples contained mutation signatures characteristic of platinum exposure and APOBEC mutagenesis, which were absent in TN-SCLC. MYC family genes (MYC, MYCL, MYCN) were frequently amplified at relapse. Transcriptomic analyses revealed dysregulation of WNT signaling and IDO1. Extensive differences in alternative splicing, especially intron retention (IR), were observed (96% of all IR events were in TN-SCLC). IR in TN-SCLC affected genes involved in DNA repair, RNA metabolism, WNT and MYC pathways. TN-SCLC showed a median of 86 neoantigens, and R-SCLC 90 neoantigens per sample. *TP53* was the most frequently altered gene to result in a neo-antigen (48% of analyzed samples). Immune evasion mechanisms, including upregulation of CD24 and downregulation of MHC-I, were observed in R-SCLC samples. **Conclusions:** This study highlights the heterogeneity of treatment resistance in SCLC, driven by genomic instability, WNT and MYC dysregulation, and splicing aberrations. Potential therapeutic strategies for R-SCLC include targeting splicing machinery, WNT signaling, and immune evasion pathways. These findings advance our understanding of SCLC biology and provide a foundation for biomarker-driven drug development. Research Sponsor: None.

8109 **Poster Session**

A prospective, single-arm, phase II trial of adebrelimab plus nab-paclitaxel and carboplatin in patients with unresectable advanced metastatic or recurrent thymic carcinomas. First Author: Ning Xu, School of Medicine, Shanghai Jiao Tong University, Shanghai Chest Hospital, Shanghai, China

Background: With the limited efficacy of chemotherapy (carboplatin/paclitaxel) for advanced thymic carcinomas (TCs), better treatments are in need. In this study (ChiCTR2300072705), we evaluated the efficacy and safety of adebrelimab in combination with nab-paclitaxel and carboplatin as first-line treatment for unresectable advanced metastatic or recurrent TCs. **Methods:** In this study, patients with unresectable UICC stage III or IV, recurrent, or metastatic TCs without any previous antitumor therapy were enrolled. Patients were treated with adebrelimab (20 mg/kg) plus nab-paclitaxel (260 mg/m^2) and carboplatin (AUC 5) every 3 weeks for up to 4-6 cycles, followed by adebrelimab (20 mg/kg) every 3 weeks for up to 2 years until progression or unacceptable toxicity. The primary endpoint was the objective response rate (ORR). Secondary endpoints included progression free survival (PFS), disease control rate (DCR), overall survival (OS), and safety. A Simon two-stage design was applied. If more than 4 out of the first 18 pts achieved a response, the cohort would expand to include 33 pts, and the outcome would be considered positive if more than 10 pts achieved a response. **Results:** Between August 2023 and September 2024, 18 pts were enrolled in the first stage. All pts were included in the efficacy and safety analysis. The median age was 58.0 years old (range 29-71). At data cutoff (Dec 1, 2024), 9 pts (50.0%) were undergoing treatment. Discontinuations occurred in 5 pts (27.8%) primarily due to disease progression, 2 (11.1%) due to adverse events (AEs), 2 (11.1%) due to patient's decision. Three (16.7%) of 18 pts had complete response, 9 (50.0%) had partial response, and 6 (33.3%) had stable disease. The ORR was 66.7% (12/18) and DCR was 100%. The median PFS was 10.2 months (95% CI, 8.8 - 11.6 months). AEs of any grade and of grade $\geq$3 severity occurred in 100% (18/18) and 61.1% (11/18) of pts, respectively. The most common treatment related AEs were white blood cell count decreased, neutrophil count decreased, and lymphocyte count decreased. The immune-related AEs of grade $\geq$3 severity occurred in 16.7% (3/18) of pts, including immune-mediated myositis, rash and lipase increased. None of the pts died from the treatment. **Conclusions:** In previously untreated advanced TCs, preliminary results showed that adebrelimab plus nab-paclitaxel and carboplatin is effective and safe. It provides a new treatment option in pts with advanced TCs. Clinical trial information: ChiCTR2300072705. Research Sponsor: None.

8110 **Poster Session**

Combining SBRT with GM-CSF and peg-IFNα to induce abscopal effects in previously treated patients with stage IV thymic tumors: A single arm, single center, phase II trial. First Author: Min Fan, Fudan University Shanghai Cancer Center, Shanghai, China

Background: After the failure of first-line treatment, patients with stage IV thymic tumors have a poor prognosis and few therapeutic options. Combining stereotactic body radiotherapy (SBRT) with granulocyte-macrophage colony-stimulating factor (GM-CSF) and Pegylated interferon-α (Peg-IFNα) may induce abscopal effects and improve prognosis. **Methods:** We conducted this open-label, single-arm single center, phase II trial to evaluate SBRT plus GM-CSF and Peg-IFNα in previously treated patients with stage IV thymic tumors. A 21-day treatment cycle consisted of SBRT delivered to one metastatic lesion with 30 Gy in 5 fractions from day 1, synchronous subcutaneous injection of GM-CSF 125 μg/ m^2 once daily for 14 days, and subcutaneous injection of Peg-IFNα 90 μg on day 8. If the patient has more than two metastatic lesions, another treatment cycle was repeated. After the completion of 1 or 2 treatment cycles, Peg-IFNα therapy was maintained for at least half a year with a subcutaneous injection of 90 μg once a month. The two primary endpoints were the proportion of patients with abscopal effects and the objective response rate (ORR). The secondary endpoints included overall survival (OS), progression-free survival (PFS), and therapeutic safety. **Results:** A total of 27 patients were enrolled in the trial from March 2021 to September 2024. One patient died of cardiac arrest before ORR evaluation during COVID-19 pandemic and was excluded, leaving 26 patients in the analysis, with 1 (3.8%) type A thymoma, 1 (3.8%) type AB thymoma,4 (15.4%) type B1 thymoma, 3 (11.5%) type B2 thymoma, 1 (3.8%) type B3 thymoma, 1 (3.8%) type B2+B3 thymoma, 13 (50.0%) thymic squamous cell carcinoma and 2 (7.7%) thymic neuroendocrine tumor. At a median follow-up of 26.4 months, 8 (30.8%) out of 26 patients had abscopal effects, and the ORR was 38.5%. The median OS for patients with abscopal effect has not been attained yet. The median PFS was 13.0 months. We observed that patients with abscopal effects tended to have longer OS and PFS than those without abscopal effects. 5 patients (19.2%) experienced Grade 3 treatment-related adverse events (CTCAE version 5.0). **Conclusions:** Combining SBRT with GM-CSF and Peg-IFNα was well tolerated with acceptable toxicity and may represent a promising salvage therapy for previously treated patients with stage IV thymic tumors. The occurrence of abscopal effects is likely to improve patient outcomes. Clinical trial information: NCT04517539. Research Sponsor: None.

8111 **Poster Session**

Association of immune-related adverse events with survival and treatment outcomes in thymic tumors treated with immune checkpoint inhibitors. First Author: Harold Nathan C. Tan, Department of Investigational Cancer Therapeutics, Division of Cancer Medicine, MD Anderson Cancer Center, Houston, TX

Background: Thymic tumors are rare cancers with limited therapeutic options, particularly in refractory cases. Immune checkpoint inhibitors (ICIs) such as anti-PD1 and anti-PD-L1 antibodies have transformed cancer treatment, but data in thymic tumors remain scarce. We investigated the safety, efficacy, and biomarkers of ICIs in thymic tumors, focusing on immune-related adverse events (irAEs) and clinical outcomes. **Methods:** This study included patients (pts) with thymic tumors treated with ICIs at the University of Texas MD Anderson Cancer Center. The primary objective was to assess the occurrence, type, and severity of irAEs. Secondary objectives included evaluating clinical response using RECIST 1.1 and analyzing overall survival (OS) and progression-free survival (PFS) through Kaplan-Meier analysis. Cox regression was used to identify predictors of OS. **Results:** Forty-two pts (median age 58.5 years, 55% male) were analyzed: 29 (69%) had thymic carcinoma, 8 (19%) thymoma, and 5 (12%) thymic malignancy with neuroendocrine features. Pts had a median of one prior line of therapy (range 1-6) and received ICIs as monotherapy (n=23, 55%) or in combination with chemotherapy (n=9, 21%), other immunotherapies (n=6, 14%), targeted therapies (n=2, 5%), or other agents (n=2, 5%). irAEs occurred in 60% of pts (100% of pts with thymoma), with 9 pts (21%) experiencing severe irAEs (≥G3). Median time to develop ≥G3 irAEs was 42 days. Common all-grade irAEs included fatigue (19%), musculoskeletal toxicities (17%), and rash (17%), while the most frequent ≥G3 irAEs were musculoskeletal, myasthenia gravis (MG)-like, myocarditis, and hepatobiliary toxicities. Among the three pts with thymoma who developed MG-like symptoms, only one pt had a pre-existing diagnosis of MG. Two thymoma patients developed concurrent myocarditis and MG. One treatment-related death occurred due to pneumonitis in a patient with thymoma. Clinical benefit was observed in 69% of pts, including 9 partial responses (PR) (21%) and 10 with stable disease. Most pts (84%) with any-grade irAEs had SD or PR as best response with ICI. Median PFS was 195 days, with a 1-year PFS rate of 45%, while median OS was 274 days, with a 1-year OS rate of 44%. Pts with any-grade irAEs had improved OS (HR 0.3, 95% CI 0.11 -0.98, p = 0.04). Other OS predictors included *TP53* mutations (HR 7.8, 95% CI 2.2 – 27.8, p = 0.002), *CDKN2A* alterations (HR 0.2, 95% CI 0.04-0.54, p = 0.004), African-American race (HR 10.9, 95% CI 3.7-32.3, $p < 0.001$), and lung metastases (HR 6.9, 95% CI 2.4 -19.8, $p < 0.001$). **Conclusions:** ICIs demonstrate promising efficacy in thymic malignancies, with higher toxicity rates in thymoma pts. The incidence of irAEs may serve as a prognostic marker for survival and treatment outcomes. Factors such as *TP53, CDKN2A* alterations, and lung metastases could guide patient selection for future ICI trials in thymic tumors. Research Sponsor: None.

8112 **Poster Session**

Pathomics-based prediction of thymic epithelial tumor subtypes within the French RYTHMIC network. First Author: Lodovica Zullo, Department of Cancer Medicine, Gustave Roussy, Villejuif, France

Background: Thymic epithelial tumors (TETs) are classified into primary subtypes (A, AB, B1, B2, B3, C) and mixed classes, determined by varying proportions of tumoral and non-tumoral components, and different subtypes have different prognosis. This heterogeneity, combined with their rarity, poses significant diagnostic challenges that impact tumor treatment. We aim to develop and test a multiple-instance learning (MIL) model capable of classifying TETs major histological subtypes from hematoxylin-eosin/hematoxylin-eosin-saffron (HE/HES)-stained slides. **Methods:** Cases who underwent central revision by a panel of expert pathologist between 2012 and 2016 in the context of the French national RYTHMIC network were retrospectively collected, and their HE/HES slides were digitized in whole slide images (WSIs), forming the training cohort. A MIL model was trained exclusively on digitized WSIs, without clinical features, and internally validated using 3-repeated 2-fold cross-validation for the classification of major TET subtypes: A, AB, B1, B2, B3, C. Prospectively digitized WSIs from the RYTHMIC network (2022–2024) served as the testing cohort. Class predictions were assessed using AUC scores and ROC curves. Interpretability was explored through Shapley values and heatmaps. **Results:** A total of 456 WSIs from unique histological samples formed the training cohort, with 243 (53%) samples obtained via thymectomy. The most represented subtype was AB (n=129, 28%), followed by B2 (n=110, 24%). Internal validation achieved a mean AUC of 0.94 [sd 0.005] for histological subtypes classification. High-attention regions identified on the slides featured varying proportions of epithelial cells and lymphocytes, consistent with the biological characteristics of each subtype. The test set comprised 75 WSIs from unique histological samples, with 63 (84%) obtained via thymectomy. The most represented subtype was AB (n=35, 47%), followed by B2 (n=19, 25%). In the test set, the model achieved a mean AUC of 0.89 [95%CI 0.83–0.93] for histological subtypes classification. **Conclusions:** Our model shows promise for diagnosing TET major subtypes, emphasizing the value of digital pathology in identifying and classifying rare entities. We are currently reviewing discrepancies between MIL and pathologists' diagnoses in subtype classification within the test set to evaluate the potential of artificial intelligence in aiding the diagnosis of complex cases. The final results will be presented at the congress. Research Sponsor: None.

TPS8113 **Poster Session**

Comparing impact of treatment before or after surgery in patients with stage II-IIIb resectable non-small cell lung cancer (NSCLC; Alliance A082304-SWOG S2402). First Author: Raid Aljumaily, Stephenson Cancer Center at The University of Oklahoma Health Sciences Center, Oklahoma City, OK

Background: There are currently three approved approaches for patients with resectable NSCLC including neoadjuvant chemoimmunotherapy, adjuvant chemoimmunotherapy and perioperative treatment with neoadjuvant chemoimmunotherapy followed by adjuvant immunotherapy. All regimens were approved after showing event-free survival (EFS) or disease-free survival (DFS) benefit with the addition of immunotherapy to chemotherapy compared to chemotherapy alone. Each approach has its benefits and risks. Starting immunotherapy prior to surgery may improve treatment compliance and efficacy of immunotherapy. Nevertheless, neoadjuvant chemoimmunotherapy may result in missing an opportunity for curative surgery and increase the complexity of tumor resection. PROSPECT-LUNG (NCT06632327) is a randomized study evaluating whether starting chemoimmunotherapy before or after surgery leads to better outcomes. **Methods:** This is a randomized phase 3 trial in which patients will be randomized 1:1 to surgery followed by chemoimmunotherapy (adjuvant arm) or neoadjuvant chemoimmunotherapy followed by surgery and adjuvant therapy (perioperative arm). Patients with histologic or cytologic confirmation of surgically resectable stage IIA-IIIB NSCLC (per AJCC 9th edition) or stage IIA to IIIB per AJCC 8^{th} edition up to single ipsilateral mediastinal station (N2a), ECOG PS ≤ 2 (or Karnofsky ≥ 60%), no prior treatment for NSCLC and no previous malignancy within 3 years are eligible. The dual primary endpoints are real-world event free survival (rwEFS) defined as date from randomization to date of the first of the following events: failure to undergo resection for any reason, progression prior to surgery that precludes resection, recurrence or progression at any time after surgery or death from any cause, and overall survival (OS) defined as time from randomization to death from any cause. The target accrual is 1,100 patients assuming one-sided type I error of 0.03 for OS endpoint and 0.02 for rwEFS endpoint. This sample size will enable the detection of a 3-year rwEFS improvement from 55% in the adjuvant therapy arm to 64% in the perioperative arm with an 84% power. This sample size would detect an HR of 0.73 (improvement in median OS from 8.1 to 11 years in favor of the perioperative arm, 5-year OS from 65% in the adjuvant arm to 73% in the perioperative arm, assuming exponential survival) with 83.6% power. The study has a pragmatic design with minimal data collection, reporting of adverse events that lead to discontinuation of therapy, hospitalization or death only. It allows providers to choose therapy per standard of care (FDA approved or on NCCN), includes patients with ECOG performance status 2, permits use of local laboratory testing and imaging studies and determination of recurrence/progression will be done by local treating physicians with no use of RECIST. Clinical trial information: NCT06632327. Research Sponsor: National Cancer Institute; U10CA180821.

TPS8114 **Poster Session**

GEMINI-NSCLC study: Integrated longitudinal multi-omic biomarker profiling study of non-small cell lung cancer (NSCLC) patients. First Author: Douglas C. Palmer, AstraZeneca, Gaithersburg, MD

Background: Lung cancer is the global leading cause of cancer deaths. Despite treatment advances, NSCLC outcomes remain poor. The molecular landscape of NSCLC has identified various subtypes allowing targeted therapies, but some tumors lack a biomarker-directed therapy. Identifying improved surrogates of immunotherapy (IO) response is key to stopping ineffective treatments and empowering patients to switch therapies more rapidly. Combining next-generation sequencing (NGS) and circulating tumor DNA (ctDNA) technologies with high-resolution multi-omic data may revolutionize NSCLC management by enabling non-invasive monitoring, personalized treatment strategies, and the development of next-generation therapies to improve patient outcomes. **Methods:** The Gemini-NSCLC study is a multicenter, real-world observational study profiling patients with NSCLC undergoing IO standard-of-care (SOC) therapy. Cohort 1 (C1) includes patients with early-stage disease treated with curative intent therapies. Cohort 2 (C2) includes patients with late-stage disease receiving first-line IO, excluding those with targetable genomic drivers. Patients will have blood and tissue collected at study entry and longitudinally. They will undergo testing with DNA and RNA sequencing and novel assays, including baseline spatial transcriptomic profiling, serial tumor-informed ctDNA profiling, and scRNA sequencing with T-Cell receptor seq of peripheral immune cells. All patients will be assessed with cohort-relevant real-world endpoints, allowing correlation with longitudinal multi-omic data for biomarker discovery. Information from novel multi-omic assays will be descriptive and hypothesis-generating. For C1, the primary endpoint is real-world disease-free survival (rwDFS). Secondary endpoints include pathologic complete response (pCR) rate and real-world overall survival (rwOS) stratified by ctDNA status. Molecular endpoints include sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of minimal residual disease (MRD) assay vs. conventional imaging. Patients are followed until recurrence or five years post-therapy. Patients in whom disease recurs may roll over to C2 for continued data collection. For C2, the primary endpoint is rwOS, with rwPFS as a secondary endpoint. Molecular endpoints include ctDNA dynamics with IO and correlation with rwOS. Exploratory endpoints include evolving genomic variants as resistance mechanisms. As of 01/2025, the study is enrolling and active at 49 of 60 planned sites, with accruals of 48/500 in C1, 20/700 in C2. Clinical trial information: NCT05236114. Research Sponsor: Tempus, AI, Inc.; AstraZeneca.

TPS8115 **Poster Session**

KEYMAKER-U01E: A phase 2 umbrella study with rolling arms of investigational agents with or without chemotherapy plus pembrolizumab for resectable stage II–IIIB (N2) non–small-cell lung cancer (NSCLC). First Author: Konstantin H. Dragnev, Dartmouth Cancer Center, Lebanon, NH

Background: Neoadjuvantpembrolizumab (pembro) + chemotherapy (CT) followed by adjuvant pembro significantly improved event-free survival (EFS), pathological complete response (pCR), major pathological response, and overall survival (OS) in early-stage NSCLC. Despite the expanding number of therapeutic options for early-stage NSCLC, there remains an unmet need to improve outcomes. Sacituzumab tirumotecan (sac-TMT/MK-2870/SKB264) is an antibody-drug conjugate composed of an anti-trophoblast cell surface antigen 2 antibody, a hydrolytically cleavable linker, and a belotecan-derivative topoisomerase I inhibitor payload (average drug-to-antibody ratio, 7.4). Sac-TMT monotherapy demonstrated encouraging antitumor activity in a phase 1/2 study in heavily pretreated, advanced NSCLC. The phase 2 KEYMAKER-U01E study (NCT06788912) is evaluating the addition of multiple investigational agents ± CT to pembro followed by surgery and adjuvant pembro in resectable stage II–IIIB (N2) NSCLC; the treatment arm presented here includes sac-TMT + pembro. **Methods:** This open-label, adaptive design study is enrolling participants (pts) aged ≥18 years with previously untreated, pathologically confirmed, resectable stage II, IIIA, or IIIB (N2) NSCLC (AJCC v8) with no *EGFR* mutations, and measurable disease per RECIST v1.1. Pts must be able to undergo surgery, have ECOG PS 0 or 1, and provide a tumor sample for biomarker analysis. Approximately 60 pts will be randomized 1:1 to Arm 1 or 2. In Arm 1 (reference arm), pts will receive neoadjuvant therapy of 4 cycles of pembro 200 mg intravenously (IV) + CT IV Q3W (cisplatin 75 mg/m^2 or carboplatin area under the curve 5 or 6 mg/mL/min on day 1 with gemcitabine 1000 mg/m^2 on days 1 and 8 for squamous histology, with pemetrexed 500 mg/m^2 on day 1 for nonsquamous, or with paclitaxel 175 or 200 mg/m^2 on day 1 for any histology). Pts in Arm 2 will receive 4 cycles of pembro 200 mg IV Q3W + 6 cycles of sac-TMT 4 mg/kg IV Q2W (treatment arm). Following surgery, all pts will receive up to 13 cycles of adjuvant pembro 200 mg IV Q3W. Additional agents may be included when available. Randomization will be stratified by histology (squamous vs nonsquamous) and tumor stage (II vs III). Dual primary endpoints are pCR (ypT0/ypN0) and percentage of residual viable tumor, assessed by blinded independent pathology review. Secondary endpoints are EFS and distant metastasis-free survival per investigator review, OS, objective response rate during neoadjuvant therapy, and safety. Postoperative tumor imaging occurs ≤4 weeks before the start of adjuvant therapy, with pts followed per study protocol until disease recurrence, development of new primary NSCLC, pregnancy, death, pt withdrawal, or end of study. AEs will be graded per NCI CTCAE v5.0. Enrollment is scheduled to begin in March 2025 at 34 sites globally. Clinical trial information: NCT06788912. Research Sponsor: Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA.

TPS8116 **Poster Session**

A randomized study of neoadjuvant REGN7075 + cemiplimab + chemotherapy (chemo) vs cemiplimab + chemo in patients (pts) with resectable non-small cell lung cancer (NSCLC). First Author: Ardy Davarifar, University of Tennessee Medical Center, Knoxville, TN

Background: Neoadjuvant chemo + anti–PD-1 checkpoint blockade, with/without adjuvant anti–PD-1, represents a new standard of care for pts with resectable NSCLC. However, most pts do not achieve major pathologic response (MPR) or pathologic complete response (pCR), and event-free survival (EFS) remains suboptimal; therefore, novel perioperative approaches are needed. REGN7075, a first-in-class costimulatory bispecific antibody, aims to bridge CD28+ T cells with EGFR-expressing tumor cells, facilitating T-cell activation through endogenous tumor antigens. Early efficacy and pharmacodynamic evidence suggest that REGN7075 can enhance immune responses and antitumor immunity even in "cold" tumors. In a first-in-human, open-label, Phase 1/2 study (NCT04626635), REGN7075 + cemiplimab (anti–PD-1) demonstrated clinical activity in PD-1–refractory, microsatellite stable colorectal cancer (Segal NH, et al. 2024). The addition of REGN7075 to cemiplimab + chemo may deepen antitumor responses in resectable NSCLC where EGFR is highly expressed, potentially representing a novel immunotherapy-based treatment (Tx) approach in this setting. In this perioperative platform study, multiple novel Tx approaches for resectable NSCLC will be evaluated in comparison to a control arm (cemiplimab + chemo). **Methods:** In this Phase 2, open-label, perioperative platform trial (NCT06465329), pts with resectable NSCLC will be randomized to an investigational arm (a novel antitumor agent + cemiplimab + chemo) or control arm (cemiplimab + chemo), stratified by tumor stage and PD-L1 expression. Here, we focus on the first investigational arm with REGN7075. The study will consist of neoadjuvant, surgical, and adjuvant periods. During the neoadjuvant period, pts assigned to the control arm will receive cemiplimab + chemo for up to 3 cycles before surgery. Pts in the investigational arm will receive REGN7075 with cemiplimab + chemo. Pts from both arms who proceed to surgery and undergo R0/R1 resection will then receive adjuvant cemiplimab. Eligibility criteria: histologically confirmed stage II–IIIB (N2) NSCLC considered resectable with curative intent (appropriate candidate for surgery), Tx naïve, no known *EGFR/ALK* alterations, ECOG PS ≤1. Primary endpoint: MPR. Secondary endpoints: safety, feasibility of surgery, pCR, and EFS. Pre-Tx and surgical tissue will be used for translational analysis and biomarker development. Up to 40 pts will be enrolled in each investigational arm, and the control arm will be open to enrollment throughout the study. A Bayesian statistical design will be used to evaluate the posterior probability of at least 15% improvement in MPR for investigational arms vs the control arm. This study is currently enrolling. Clinical trial information: NCT06465329. Research Sponsor: Regeneron Pharmaceuticals, Inc.

TPS8117 **Poster Session**

Phase 2 peri-operative study of fianlimab + cemiplimab + chemotherapy versus cemiplimab + chemotherapy in resectable early-stage non-small cell lung cancer (NSCLC). First Author: Ekaterine Arkania, LTD Israeli-Georgian Medical Research Clinic "Helsicore", Tbilisi, Georgia

Background: Co-blockade of lymphocyte activation gene 3 (LAG-3) and programmed cell death-1 (PD-1) may enhance the efficacy of anti–PD-1 therapies. Fianlimab (anti–LAG-3) and cemiplimab (anti–PD-1) are high-affinity, fully human, immunoglobulin G4 monoclonal antibodies. In a Phase 1 study (NCT03005782), fianlimab + cemiplimab showed promising clinical activity with durable responses and an acceptable risk–benefit profile in patients with programmed death-ligand 1 (PD-L1)-naïve, advanced NSCLC. Immuno-oncology + chemotherapy is a new standard of care in the perioperative setting, but potential improvements to outcomes in early-stage disease remain under investigation. **Methods:** This is a randomized, multicenter, double-blind, Phase 2 peri-operative study (NCT06161441) in patients with fully resectable stage II–IIIB (N2), operable, and treatment-naïve NSCLC with squamous or non-squamous histology. The aim of this study is to investigate the efficacy and safety of fianlimab + cemiplimab + chemotherapy versus cemiplimab + chemotherapy as peri-operative treatment. The study will be conducted globally at ~130 sites. Key inclusion criteria: age ≥18 years; newly diagnosed, histologically confirmed, fully resectable stage II–IIIB (N2) NSCLC; no distant metastases; evaluable PD-L1 immunohistochemistry results; no cancer treatment in the past 3 years, except adjuvant hormone therapy for hormone-sensitive cancers in long-term remission; Eastern Cooperative Oncology Group performance status ≤1; no known *EGFR* mutations or *ALK* aberrations; and adequate organ and bone marrow function. Mediastinal lymph node sampling is required for patients with mediastinal adenopathy. Enrolled patients (n=~180) will be stratified by clinical TNM stage (II vs III), histology (nonsquamous vs squamous), and PD-L1 expression (<1%, 1–49%, ≥50%), and randomized (1:1:1) to the following study arms for the neoadjuvant period (≤4 cycles; each cycle is every 3 weeks): arm A, placebo + cemiplimab 350 mg + platinum doublet chemotherapy; arm B, fianlimab dose 1 + cemiplimab 350 mg + platinum doublet chemotherapy; arm C, fianlimab dose 2 + cemiplimab 350 mg + platinum doublet chemotherapy. After surgery, in the adjuvant period (≤14 cycles), patients in all arms will continue the same IO regimen with approved maintenance chemotherapy. Treatment will last ~12 months (12 weeks' neoadjuvant therapy + 42 weeks' adjuvant therapy), or until disease recurrence, unacceptable toxicity, or a decision from the patient or investigator. Primary endpoint: pathological complete response as determined by blinded independent pathological review (BIPR). Key secondary endpoints: event-free survival and tumor response by investigator assessment, major pathological response by BIPR, safety, pharmacokinetics, immunogenicity, and patient-reported outcomes. Clinical trial information: NCT06161441. Research Sponsor: Regeneron Pharmaceuticals, Inc.

TPS8118 **Poster Session**

Safety, efficacy, and tumor immune microenvironment changes with neoadjuvant chemotherapy and cemiplimab with or without alirocumab in stage 1B-3A non-small cell lung cancer. First Author: Eziafa Oduah, Duke University, Durham, NC

Background: The addition of immune checkpoint blockade to neoadjuvant and adjuvant therapy is now standard of care in early-stage surgically resectable non-small cell lung cancer (NSCLC). However, resistance to immunotherapy limit their benefit for most patients. The pathological complete response (pCR) rate, a surrogate for long term survival, remains close to 20%, leaving many patients at a high risk of recurrence and death. Thus, there is a need to apply strategies to overcome immunotherapy resistance in earlier stages of NSCLC to improve cure. Proprotein convertase subtilisin/kexin type 9 (PCSK9), a major cholesterol regulator, has emerged as an inhibitory modulator of anti-tumor immunity. Preclinical evidence showed that PCSK9 downregulated MHC class I antigen expression on tumor cells. This effect was reversed by genetic or pharmacologic inhibition of PCSK9. PCSK9 inhibitor synergized with immune checkpoint blockade to increase cytotoxic T-cell mediated tumor death. Retrospective clinical analyses of NSCLC patients treated with immune checkpoint inhibitors also showed a correlation between higher PCSK9 levels and poorer survival. **Methods:** TOP 2301 is a multi-center, open label, two-arm, randomized, phase 2 trial of chemotherapy and cemiplimab (350mg IV every 3 weeks) with or without the PCSK-9 inhibitor, alirocumab (150 mg SC every 4 weeks), prior to surgery. Eligible patients will have stage IB-3A NSCLC, deemed surgical candidates, and have no EGFR or ALK mutations. One hundred and twenty-six patients will be randomized 1:1 to receive neoadjuvant SOC chemotherapy and cemiplimab versus SOC chemotherapy, cemiplimab and alirocumab. Approximately 64 participants are required in each arm to have 90% power to reject the null hypothesis. The primary objective is to compare the pCR rates for neoadjuvant chemotherapy plus cemiplimab versus chemotherapy, cemiplimab, and alirocumab. Secondary efficacy objectives for the experimental arm include: the objective response rate (ORR), disease free survival (DFS), and overall survival (OS). A secondary safety objective is to determine the safety and tolerability of neoadjuvant chemotherapy and cemiplimab with alirocumab in early-stage NSCLC. The correlative science objective will evaluate the difference in tumor infiltrating lymphocytes and dendritic cells through IHC, FACs analysis, and bulk RNA-seq with CIBERSORT from postsurgical specimens of patients treated with neoadjuvant chemotherapy and cemiplimab with or without alirocumab. The trial was open to enrollment on 12/15/2024. Clinical trial information: NCT06385262. Research Sponsor: None.

TPS8119 **Poster Session**

Neoadjuvant lazertinib with or without chemotherapy for patients with epidermal growth factor receptor (*EGFR*)-mutated resectable non-small cell lung cancer (NSCLC): NeoLazer trial. First Author: Hye Ryun Kim, Division of Medical Oncology, Department of Internal Medicine, Yonsei Cancer Center, Yonsei University College of Medicine, Seoul, South Korea

Background: While perioperative systemic treatment with checkpoint inhibitors plus chemotherapy has become a standard approach for resectable NSCLC, the benefit of systemic treatment in *EGFR*-mutated NSCLC remains unclear. In resectable *EGFR*-mutated NSCLC, adjuvant osimertinib has been shown to significantly improve disease-free survival and overall survival. However, neoadjuvant osimertinib alone has demonstrated limited efficacy, with a major pathologic response rate of less than 15% (NCT03433469). These data altogether highlight an unmet clinical need for optimizing perioperative systemic approach in resectable *EGFR*-mutated NSCLC. Lazertinib, a third-generation, central nervous system-penetrating EGFR tyrosine kinase inhibitor, has demonstrated superior efficacy compared to comparator EGFR tyrosine kinase inhibitor in treatment-naïve *EGFR*-mutated advanced NSCLC (NCT04248829). The NeoLazer trial (NCT06268210) is a phase II, randomized, controlled study designed to evaluate the efficacy and safety of neoadjuvant lazertinib with or without chemotherapy in patients with *EGFR*-mutated resectable NSCLC. **Methods:** Eligible patients must be ≥19 years of age, have an ECOG performance status of 0 or 1, non-squamous histology, stage IB–IIIB NSCLC based on the AJCC 8th edition, have confirmed sensitizing *EGFR* mutations (exon 19 deletion or L858R mutation), be deemed completely resectable by a multidisciplinary team, and demonstrate adequate organ and bone marrow function. The trial will enroll approximately 160 patients, who will be randomized 1:1 to receive either lazertinib (240 mg once daily) with chemotherapy (pemetrexed 500 mg/m² and carboplatin AUC5 every 3 weeks) or lazertinib alone (240 mg once daily) for three cycles before surgical resection. Randomization will be stratified by disease stage (IB–II vs. III) and *EGFR* mutation type (exon 19 deletion vs. L858R mutation). Following surgery, all patients will receive adjuvant lazertinib for three years. Neoadjuvant and adjuvant treatments will continue until unacceptable toxicity, disease progression or relapse, or patient withdrawal. The primary endpoint is major pathologic response, defined as ≤10% residual viable cancer cells in the surgical specimen. Secondary endpoints include safety based on CTCAE 5.0, type of surgical resection (segmentectomy vs. lobectomy), pathologic complete response, objective response rate based on RECIST 1.1, event-free survival, disease-free survival, and overall survival. In addition, the trial incorporates exploratory analyses, including whole-genome sequencing of tumor tissue and monitoring the dynamics of minimal residual disease through serial blood sampling. Clinical trial information: NCT06268210. Research Sponsor: None.

TPS8120 **Poster Session**

Neotrace: A multicenter phase II study of neoadjuvant sacituzumab govitecan plus zimberelimab followed by adjuvant zimberelimab with or without sacituzumab govitecan in patients with resectable non-small cell lung cancer. First Author: Friederike C Althoff, Goethe University Frankfurt, Frankfurt Am Main, Hessen, Germany

Background: Phase III trials, including KEYNOTE-671, have established combined neoadjuvant chemoimmunotherapy followed by adjuvant immunotherapy (IO) as the standard of care for resectable NSCLC. However, a notable challenge in KEYNOTE-671 and similar studies was that ~17-22% of patients did not proceed to surgery following neoadjuvant chemoimmunotherapy, highlighting the need for more tolerable regimens. Recent data from studies such as NEOpredict (which demonstrated a 100% surgical completion rate with neoadjuvant nivolumab with/without relatlimab), NeoCOAST-2 (which reported a 34% pathological complete response [pCR] rate using a neoadjuvant combination of an anti-TROP2 antibody drug conjugate [ADC], IO, and single-agent platinum, thereby surpassing the ~20% pCR rates achieved with neoadjuvant chemoimmunotherapy), and EVOKE-02 (which showed promising objective response rates of 69% and 44% with the anti-TROP2 ADC sacituzumab govitecan plus pembrolizumab in first-line metastatic NSCLC patients with PD-L1 ≥50% and PD-L1 0-49%, respectively) demonstrate that chemotherapy-sparing approaches may reduce toxicity while maintaining or enhancing efficacy. These findings highlight the potential synergistic effect of ADC plus IO, suggesting this strategy may also be an effective treatment option in the perioperative setting with potentially lower toxicity compared to chemoimmunotherapy. Additionally, long-term adverse events associated with platinum-based chemotherapy, such as neuropathy, may be lower or avoided altogether. This study aims to improve the pCR rate, reduce toxicity, enhance surgical eligibility, and personalize adjuvant treatment. **Methods:** NeoTRACE is a phase II, multicenter, open-label, single-arm study evaluating the neoadjuvant combination of sacituzumab govitecan (SG) and the PD-1 inhibitor zimberelimab (ZIM) in patients with resectable stage II to IIIB (N2) NSCLC with no known EGFR or ALK alterations. Patients will receive neoadjuvant SG 10 mg/kg IV on days 1 and 8, and ZIM 360 mg IV on day 1, every 3 weeks for 4 cycles, followed by definitive surgery as per local standards. In the adjuvant phase, patients will either continue adjuvant SG plus ZIM for up to 4 cycles, followed by ZIM only for a total of up to 13 cycles, or receive adjuvant ZIM monotherapy (as per physicians' choice). The primary endpoint is the rate of pCR in tumor and lymph nodes. Secondary endpoints include major pathological response, surgical resection rate, time to surgery, DFS, OS, safety, and quality of life. The study also explores circulating tumor DNA dynamics, TROP2 expression, and spatial transcriptomics and proteomics to identify potential biomarkers. As of June 2025, the NeoTRACE study is recruiting 50 patients across 15 sites in Germany. EudraCT: 2024-517561-16. Clinical trial information: 2024-517561-16 (EudraCT). Research Sponsor: None.

TPS8121 **Poster Session**

Efficacy of low-dose nivolumab combined with chemotherapy as neoadjuvant treatment for lung cancer. First Author: Aline Fusco Fares, University of Florida, Gainesville, FL

Background: Immune checkpoint inhibitors have revolutionized cancer treatment, providing durable responses in a substantial subset of patients. However, their high costs remain a significant barrier to access, especially in low- and middle-income countries (LMICs). Evidence from pharmacodynamic studies suggests that lower doses (LD) of anti-PD-(L)1 agents can achieve comparable receptor saturation and therapeutic efficacy without compromising outcomes. Mounting data supports the concept of treating patients with LD anti-PD(L)1 agents. For instance, the use of LD nivolumab (0.3 mg/kg) has demonstrated equivalent PD-L1 receptor occupancy and similar survival outcomes to standard doses, offering a more cost-effective alternative. Notably, at 0.3 mg/kg, up to 10 patients can be treated for the cost of treating a single patient with standard doses. While most supporting evidence pertains to advanced disease settings, data on the use of LD in curative-intent applications, such as neoadjuvant therapy for resectable non-small cell lung cancer (NSCLC), remain limited. This study investigates the efficacy and safety of LD nivolumab combined with platinum-based chemotherapy as a neoadjuvant treatment for resectable NSCLC, addressing the urgent need for affordable treatment options in LMICs. **Methods:** This is an ongoing investigator-initiated, single-arm, phase II trial conducted at Hospital de Base, São José do Rio Preto, Brazil. Eligible participants are adults with histologically confirmed stage IB-IIIA NSCLC, with known PD-L1 expression, and no actionable genomic alterations in EGFR, ALK, or ROS1. All patients will receive three cycles of nivolumab (0.3 mg/kg IV every three weeks) combined with carboplatin (AUC 5-6) and either pemetrexed or paclitaxel, selected based on tumor histology and physician preference. Surgery will be scheduled 9-12 weeks after initiating therapy. The co-primary endpoints are major pathologic response rate (MPR), defined as ≤10% viable tumor cells in the resected surgical specimen, and complete pathologic response. Secondary endpoints include disease-free survival, overall survival, and treatment-related adverse events (AEs) graded per CTCAE v5.0. Exploratory analyses will evaluate outcomes based on disease stage, PD-L1 levels, and smoking history. The trial employs a Simon two-stage design with an initial cohort of 17 patients to assess futility. If at least one MPR is observed, enrollment will expand to a total of 33 patients. This design aims to detect an improvement in MPR from 12% (null hypothesis) to 24% (alternative hypothesis), with a significance level of 0.1 and 80% power. All specimens will undergo pathological review, and blood samples will be collected for exploratory biomarker analyses, including circulating tumor DNA. Study enrollment began in January 2024, and as of December 2024, 5 patients have been screened, with 3 enrolled. Clinical trial information: NCT06667154. Research Sponsor: Hospital de Base de Sao Jose do Rio Preto.

TPS8122 **Poster Session**

Phase II study of pembrolizumab in combination with cisplatin or carboplatin and pemetrexed as induction chemoimmunotherapy in resectable epithelioid and biphasic pleural mesothelioma (CHIMERA study). First Author: Giulia Pasello, Oncology Unit 2, Istituto Oncologico Veneto (IOV-IRCCS), Padova, Italy

Background: Pleural mesothelioma (PM) is a rare cancer related to asbestos exposure, marked by complex histopathological diagnosis and dismal prognosis. Patients' survival is strongly influenced by the histological subtype and by the eligibility to a multimodal approach, which is reserved to very selected patients. Platinum-pemetrexed chemoregimen or the immunotherapy combination ipilimumab+nivolumab are the available first-line treatment options for unresectable PM patients. In this setting, pembrolizumab in combination with platinum-pemetrexed showed an improved overall and progression free survival (IND227/Keynote483 trial). In patients with resectable PM, the multimodality approach with platinum-pemetrexed chemotherapy and surgery is usually preferred, achieving pathological complete response (pCR) in 5% of cases. To date, the role of perioperative immunotherapy for PM has not yet been extensively investigated. **Methods:** This is a phase II single arm trial enrolling patients with resectable PM from 8 high volume Italian centers, with 18 months of enrollment and 12 months of follow-up. Inclusion criteria will be the histologically confirmed diagnosis of surgical resectable stage I-IIIA treatment-naïve epithelioid/biphasic PM. Patients will receive 3 cycles of pembrolizumab 200 mg plus cisplatin (75 mg/sm) or carboplatin (AUC 5) and pemetrexed (500 mg/sm) every 3 weeks. The surgical procedure of pleurectomy/decortication will be centralized in 2 centers and will be performed within 6 weeks after the last neoadjuvant cycle. The adjuvant treatment will start within 10 weeks from surgery and will be based on 14 cycles of pembrolizumab 200 mg every 3 weeks. The primary endpoint will be the pCR; secondary endpoints will include: major pathological response, objective response rate, event free survival, OS, surgery feasibility, safety. Translational analysis on tissue and blood samples will also be performed. In order to investigate an improvement of pCR from 5% to 18%, 36 patients and a minimum number of 4 pCR are needed to verify this hypothesis with a least 80% power and a probability of type I error of 0.05. Considering a 10% patients dropped-out because of disease progression precluding surgery, a total number of 40 patients will be included in the study. The trial is currently ongoing since November 2024; 5 patients have been enrolled so far. This is the first clinical trial assessing the activity and safety of pembrolizumab in combination with platinum-pemetrexed for resectable PM patients. Clinical trial information: NCT06155279. Research Sponsor: MSD.

TPS8123 **Poster Session**

Trial in progress: Sacituzumab govitecan for the treatment of patients with diffuse pleural mesothelioma. First Author: Michael Offin, Memorial Sloan Kettering Cancer Center, New York, NY

Background: Diffuse pleural mesothelioma (DPM) is an aggressive malignancy with poor outcomes and only three FDA-approved treatments (all first-line). Even when first-line treatment is effective, most patients experience progression within a year, and there are no approved, nor accepted, second-line approaches. Analysis of our novel library of DPM patient derived xenografts (PDXs) nominated TROP-2 as a candidate target for therapy. The role of TROP-2 expression in proliferation, colony formation, migration, and invasion was determined along with the antitumor efficacy of a TROP-2 targeting antibody-drug conjugate (ADC). Exogenous TROP-2 expression increased tumorigenicity *in vitro* and *in vivo* across multiple DPM models and induced upregulation of pro-oncogenic pathways. Treatment of PDXs with the TROP-2 ADC sacituzumab govitecanhziy (SG) inhibited tumor growth with higher efficacy than gemcitabine (a standard of care later-line treatment) or the cytotoxic payload alone (irinotecan; results previously presented at WCLC 2024). These data identified TROP-2 as a promising therapeutic target in DPM leading to the development of an investigator-initiated trial with Department of Defense support (HT9425-24-1-0754). **Methods:** A single arm phase 2 unblinded Simon two-stage single-institution study recently commenced at Memorial Sloan Kettering Cancer Center (MSK) assessing the primary endpoint of overall response rate to SG by modified (m)RECIST v1.1 in patients with recurrent and/or unresectable/metastatic pathologically confirmed DPM (NCT06477419). Secondary endpoints include overall survival, progression-free survival, and safety. Key eligibility criteria include receipt of at least one prior line of standard systemic therapy and agreement to undergo study biopsies at screening, prior to cycle 3, and end of treatment (optional) if safe and feasible. SG will be administered intravenously at the FDA-approved dose/schedule established in breast cancer (10 mg/kg on days 1 and 8 of a 21-day cycle). Patients will undergo imaging after the first 2 cycles and subsequently every 3 cycles until progression. In the first stage, 19 patients will be treated. If at least 4 responses are observed, then an additional 14 patients will be accrued. To date, 4 patients have been enrolled. Tumor material will undergo 1) routine histologic subtyping, TROP-2 immunohistochemistry, and next-generation sequencing (MSK-IMPACT), 2) flow cytometry, 3) proteomic analyses/mass-spectrometry, and 4) RNA sequencing/methylation analysis. These studies will characterize how SG alters tumoral expression of TROP-2 and signaling pathways supporting cancer growth and survival. Clinical trial information: NCT06477419. Research Sponsor: U.S. Department of Defense; HT9425-24-1-0754; Gilead Science.

TPS8124 **Poster Session**

TIGOS-LS, an open-label, randomized study of BMS-986489 vs durvalumab as consolidation therapy following chemoradiotherapy in limited-stage small-cell lung cancer. First Author: Melissa Lynne Johnson, Sarah Cannon Research Institute, Nashville, TN

Background: Standard treatment for limited-stage small-cell lung cancer (LS-SCLC) has recently changed to add durvalumab consolidation after concurrent chemoradiotherapy. Although durvalumab consolidation increases overall survival (OS; Cheng et al. 2024), other therapeutic agents may be able to provide further improvement. BMS-986489 is a potential first-in-class fixed-dose combination of atigotatug (BMS-986012) and nivolumab. Atigotatug binds to fucosyl-monosialoganglioside-1 (fuc-GM1), which is highly expressed on SCLC cells and is largely absent in normal tissues. This binding results in tumor cell death by antibody-dependent cellular cytotoxicity, antibody-dependent cellular phagocytosis, or complement-dependent cytotoxicity. The immune effects initiated by atigotatug may further enhance T cell activation by nivolumab, thereby improving outcomes after chemoradiotherapy. In a randomized phase II study in extensive-stage SCLC, atigotatug improved median OS when added to carboplatin, etoposide, and nivolumab (CE/NIVO): 15.6 months (95% confidence interval [CI]: 11.3-NE) vs 11.4 months (95% CI: 9.3-16.5) with CE/NIVO alone (Kalinka et al. 2024). **Methods:** TIGOS-LS is an open-label, randomized study to evaluate the safety and efficacy of BMS-986489 as consolidation therapy vs the new standard durvalumab following chemoradiotherapy in LS-SCLC. Approximately 250 participants will be enrolled at 80 sites within the US. Eligible participants will be adults (≥18 years) with an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 and histologically or cytologically confirmed LS-SCLC. All participants must have completed concurrent chemoradiotherapy for LS-SCLC without progression; prophylactic cranial irradiation (PCI) will be permitted before initiation of study treatment. Confirmation of fuc-GM1 expression will not be required. Participants will be stratified based on disease stage (I/II vs III) and receipt of PCI and will be randomly allocated in a 1:1 ratio to either the BMS-986489 or durvalumab arms. BMS-986489 or durvalumab will be administered intravenously at a fixed dose once every 4 weeks for up to 2 years or until other discontinuation criteria are met. Response will be evaluated by Response Evaluation Criteria in Solid Tumors (RECIST) v1.1. Survival follow-up will occur every 12 weeks for up to 3 years. The primary endpoint is OS. Key secondary endpoints include progression-free survival, objective response rate, clinical benefit rate, disease control rate, duration of response, and safety parameters. Enrollment is projected to start in April 2025. Clinical trial information: NCT06773910. Research Sponsor: Bristol Myers Squibb.

TPS8125 **Poster Session**

Radiotherapy integration strategy for small-cell lung cancer in extensive stage (RISE) with up to 10 metastases: A study protocol of a randomized phase II trial. First Author: Łukasz Kuncman, Department of External Beam Radiotherapy, Copernicus Memorial Hospital in Lodz Comprehensive Cancer Center and Traumatology, Lodz, Poland

Background: The standard of care (SoC) for patients with extensive-disease small-cell lung cancer (ED-SCLC) currently involves chemo-immunotherapy. Radiotherapy (RT) has proven effective as a chest consolidation therapy in ED-SCLC patients who respond to chemotherapy. However, there is limited evidence regarding the role of RT in both chest consolidation and metastasis-directed therapy for ED-SCLC patients undergoing chemo-immunotherapy. The RISE (Radiotherapy for Extensive-Stage Small-Cell Lung Cancer) study aims to evaluate the efficacy of various RT strategies targeting residual lesions in this patient population. **Methods:** A total of 165 patients with ED-SCLC will be recruited, with 55 patients assigned to each of the three study arms. Patients with stabilization or partial regression, according to the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1, during chemo-immunotherapy will be included. Arm I will serve as the control group, comprising patients who continue SoC of programmed death-ligand 1 (PD-L1)/programmed death-1 (PD-1) immunotherapy (durvalumab or atezolizumab) following platinum-based chemo-immunotherapy. Arm II will receive the SoC with consolidative RT to the chest area and potentially, according to palliative indications to metastatic lesions, delivered in 30 Gy in 3-Gy fractions. Arm III will receive SoC with RT of 45 Gy in 3-Gy fractions to the chest area and stereotactic body radiotherapy (SBRT) with 24 Gy in 8-Gy fractions to the metastatic lesions. Blood samples for circulating tumor DNA (ctDNA) will be collected before RT, during each week of treatment, and at the time of disease progression. The primary endpoint is progression-free survival (PFS) based on RECIST 1.1 or patient death. 1. Secondary endpoints are OS, treatment toxicity (frequency of G3 toxicity according to CTCAE v.5.0), area of progression (primary tumor localization/new lesions), Overall response rate (ORR), and the response rate in non-irradiated lesions. The study population of patients with ED-SCLC has a poor prognosis. Dose-escalated chest RT and SBRT (for up to 10 metastases) administered with modern techniques offer the possibility to improve OS and PFS. Trial registration: Clinicaltrials.gov NCT06529081 (Registered 26th Jul 2024). Clinical trial information: NCT06529081. Research Sponsor: Medical Research Agency; 2023/ABM/01/00040.

TPS8126 **Poster Session**

A phase 1/2 clinical trial of quaratusugene ozeplasmid gene therapy and atezolizumab maintenance therapy in patients with extensive stage small cell lung cancer (ES-SCLC). First Author: Bo Wang, Willamette Valley Cancer Institute and Research Center, Eugene, OR

Background: The addition of atezolizumab (atezo) to both induction therapy and maintenance therapy for patients with ES-SCLC has improved median progression free survival (PFS) and overall survival (New Eng J Med. 2018;379:2220-9). However, the median PFS from starting atezo maintenance was only 2.6 months (J Thoracic Onc. 2022;17:1122-9). Expression of TUSC2, a tumor suppressor gene, is absent in 41% of SCLC patients and is decreased in 100% of SCLC patients (Clin Cancer Res 2008;14(1):41–47). Quaratusugene ozeplasmid (QuarOze) gene therapy consists of a DNA plasmid expressing the *TUSC2* gene encapsulated in a positively charged lipoplex which delivers the *TUSC2* gene to cancer cells, restoring TUSC2 expression. Xenograft studies using a SCLC cell line in a humanized mouse model treated with a combination of QuarOze and atezo demonstrated significantly increased tumor cell killing compared to that of atezo alone. In addition, infiltration of immune cells was increased in the tumor tissue, whereas myeloid derived suppressor cells were decreased (Meraz IM et al, AACR/NCI/EORTC 2023). Thus, in this study QuarOze is added to atezo maintenance therapy with the aim of improving PFS after the start of maintenance therapy. **Methods:** Eligible patients have ES-SCLC and have completed 3-4 cycles of induction therapy with etoposide, a platinum agent, and atezo without disease progression, and are thus eligible for maintenance therapy. QuarOze is administered IV every 21 days in escalating dose cohorts in Phase 1 and atezo 1200 mg is also administered IV every 21 days. Dexamethasone, acetaminophen, and diphenhydramine are given prior to each treatment to prevent delayed infusion-related reactions. Efficacy is evaluated after every even cycle of treatment using RECIST 1.1 criteria. Safety is evaluated using CTCAE v5, with dose limiting toxicities generally defined as ≥Gr 3 adverse events (AEs). TUSC2 protein expression is measured by a validated immunohistochemistry assay in paraffin sections to determine if PFS is related to pretreatment TUSC2 levels. A validated assay measures pharmacokinetics in all patients. In Phase 1, two planned dose levels (0.09, and 0.12 mg/kg) of QuarOze were administered, and a standard dose escalation with 3-6 patients/dose level was used. The Phase 2 portion of the trial will enroll 50 patients which provides 80% power at a one-sided alpha level of 0.05 to detect an 18-week PFS rate of 52% compared to a historical 18-week PFS rate of 34% with atezo alone. This corresponds to a median PFS of approximately 4.3 months compared to a historical median PFS of 2.6 months with atezo alone. A Safety Review Committee (SRC) reviewed safety data at the end of each dose level of Phase 1 to make recommendations about dose escalation. The Phase 2 portion of the trial opened for enrollment in December, 2024. Clinical trial information: NCT05703971. Research Sponsor: Genprex, Inc.

TPS8127 **Poster Session**

The TIGOS trial: A randomized, double-blind phase 3 trial of atigotatug + nivolumab fixed-dose combination with chemotherapy vs atezolizumab with chemotherapy in patients with 1L extensive-stage small cell lung cancer (ES-SCLC). First Author: Luis G. Paz-Ares, Hospital Universitario 12 de Octubre, Universidad Complutense de Madrid, Madrid, Spain

Background: Atigotatug is an innate immune inducer monoclonal antibody that binds fucosyl-monosialoganglioside-1 (fuc-GM1) with high affinity and specificity, thereby inducing immune-mediated tumor cell death. Fuc-GM1, a cell surface target, is expressed in 50%–90% of SCLC tumors. In a randomized, open-label phase 2 study, atigotatug combined with nivolumab and chemotherapy vs nivolumab and chemotherapy alone has shown a promising trend in overall survival (OS) with median OS of 15.6 mo vs 11.4 mo, respectively (HR 0.71; 95% CI 0.44–1.16), as a first-line treatment in ES-SCLC. Based on these results, a confirmatory trial comparing this regimen to the standard of care is warranted. TIGOS (NCT06646276) is a randomized, double-blind, multicenter phase 3 trial to compare the efficacy and safety of atigotatug + nivolumab fixed-dose combination with chemotherapy vs atezolizumab with chemotherapy. **Methods:** Approximately 530 eligible patients will be randomized 1:1 to receive either atigotatug + nivolumab fixed-dose combination with carboplatin and etoposide Q3W (induction) followed by atigotatug + nivolumab fixed dose combination (maintenance) Q4W or atezolizumab with carboplatin and etoposide Q3W (induction) followed by atezolizumab (maintenance) Q4W. Patients will be stratified by ECOG performance status (PS) 0–1, presence of liver metastases, and presence of brain metastases at baseline. Treatment will continue until disease progression, unacceptable toxicity, death, or withdrawal of consent. Eligible patients must be ≥18 years old, have histologically or cytologically documented SCLC, ≥1 measurable lesion outside the central nervous system (CNS), any previous limited-stage SCLC treatment completed ≥6 months prior to study treatment initiation, and an ECOG PS of 0–1. Key exclusion criteria include prior treatment for ES-SCLC, untreated symptomatic CNS metastases, and prior treatment targeting T-cell co-stimulation, checkpoint pathways, and/or fuc-GM1. The primary endpoint is OS, and the secondary endpoints are time to definitive deterioration, safety, objective response, duration of response, and progression-free survival, as assessed by the investigator. Assessment of pre- and on-treatment changes in biomarkers will be part of an exploratory analysis. This study will be conducted in 180 locations, with a primary completion date expected in April 2028. Clinical trial information: NCT06646276. Research Sponsor: Bristol Myers Squibb.

TPS8128 **Poster Session**

An open-label, multicenter, phase 1/2 study of peluntamig (PT217), an anti-DLL3/anti-CD47 bispecific antibody, in patients with DLL3-expressing cancers such as SCLC, LCNEC and EP-NEC (SKYBRIDGE study). First Author: Jacob Sands, Dana-Farber Cancer Institute and Harvard Medical School, Boston, MA

Background: Neuroendocrine carcinomas (NECs) are aggressive cancers with limited median survival. Over 90% of the NEC cases originate from the lung, including small cell lung cancer (SCLC) and large cell neuroendocrine carcinoma (LCNEC) of the lung. The rest of the cases are extra-pulmonary NECs (EP-NECs), including gastroenteropancreatic neuroendocrine carcinoma (GEP-NEC) and neuroendocrine prostate cancer (NEPC). Despite the initial impressive responses to platinum-based chemotherapy with or without an immune checkpoint inhibitor (ICI), at progression, resistance and clinical deterioration are common. High mortality rates and limited treatment options with durability highlight a significant unmet medical need. NECs are known to be heterogeneous. One unifying feature is the consistent surface expression of DLL3, making targeting DLL3 an attractive treatment approach. Peluntamig (PT217) is an IgG1 based anti-DLL3/anti-CD47 bispecific antibody that activates both innate and adaptive immunity to target cells that express DLL3 and/or overexpress CD47. **Methods:** The study consists of 4 parts: Monotherapy Dose Escalation (Part A), Dose Expansion (Part B), Chemotherapy Combination Therapy (Part C), and ICI Combination Therapy (Part D). Each part includes multiple cohorts. The study is designed to evaluate the safety, tolerability, pharmacokinetic (PK), pharmacodynamic (PD), and preliminary efficacy of peluntamig. Parts A, C and D are on-going. Cohort C1 will enroll patients with first-line (1L) LCNEC of the lung and EP-NEC and patients with second-line (2L) SCLC who have (defined as progression ≥ 90 days after last dose of platinum therapy). Patients will receive peluntamig and SOC CE. Cohort C2 will enroll SCLC, LCNEC of the lung and EP-NEC patients eligible for 2L paclitaxel therapy. Patients will receive peluntamig and SOC paclitaxel. Cohort D1 will enroll 2L LCNEC of the lung, EP-NEC and ES-SCLC patients who have progressed/relapsed from their 1L treatment that may have included an ICI. Patients will receive peluntamig + atezolizumab. Cohort D2 will enroll 1L patients with ES-SCLC who have completed their induction therapy with CE plus atezolizumab and are eligible to continue with atezolizumab treatment. Patients will receive peluntamig + atezolizumab as maintenance therapy. Cohort D3 will enroll 1L patients with ES-SCLC who are treatment-naïve. Patients will receive peluntamig + CE + atezolizumab. Dose escalation, guided by a 3+3 design, will be conducted independently for each cohort. Patients will be backfilled to DLT-cleared dose levels to further evaluate safety, tolerability, PK and efficacy. Potentially active cohorts will be further investigated in dose randomization studies in Part B. Clinical trial information: NCT05652686. Research Sponsor: None.

TPS8129 **Poster Session**

A global phase III, double-blind, randomized trial of BNT327/PM8002 plus chemotherapy (chemo) compared to atezolizumab plus chemo in patients (pts) with first-line (1L) extensive-stage small cell lung cancer (ES-SCLC). First Author: Martin Reck, Thoracic Oncology Department, LungenClinic Grosshansdorf, Grosshansdorf, Germany

Background: SCLC is an aggressive form of lung cancer. Incorporating immunotherapy for ES-SCLC pts in the frontline has improved outcomes, but long-term benefit is still lacking. There is an urgent need for efficacious treatments that can extend the duration of response and improve survival in SCLC. BNT327 is an investigational bispecific antibody, targeting both PD-L1 and VEGF-A in the tumor and tumor microenvironment (TME). By binding to PD-L1 on tumor cells it is designed to restore effector T-cell function and by binding to VEGF-A within the TME it also reverses the negative impact of VEGF signaling on immune cell infiltration and activation. In addition, via VEGF-A neutralization, it normalizes tumor vasculature. This dual targeting of PD-L1 and VEGF-A aims to deliver better efficacy and safety. Preliminary results from a Phase II trial showed encouraging efficacy results and a manageable safety profile for BNT327 with paclitaxel as second-line (2L) treatment of pts with SCLC (1992P, ESMO 2023). Combining BNT327 with chemo is being investigated in several Phase II and III trials in both 1L and 2L, including a global dose optimization trial. This Phase III trial will further assess the efficacy and safety of BNT327 in combination with chemo for previously untreated pts with ES-SCLC in a global population. **Methods:** Thisglobal, randomized, double-blind, Phase 3 trial (NCT06712355) will enroll ~439 pts with histologically or cytologically confirmed SCLC, who have not received prior systemic therapy for ES-SCLC. Pts will be initially randomized 1:1:1 to receive combination therapy of atezolizumab (1,200 mg IV) plus chemo (etoposide + carboplatin) (Arm 1), BNT327 (2,000 mg IV) plus chemo (Arm 2), or BNT327 (1,400 mg IV) plus chemo (Arm 3) administered Q3W for four cycles, followed by maintenance therapy with atezolizumab (Arm 1) or BNT327 (Arm 2 and Arm 3) Q3W until confirmed disease progression, intolerable toxicity, participant withdrawal, trial termination or up to two years, whichever occurs first. Chemo will be dosed per local treatment guidelines. One of the BNT327 arms (Arm 2 or 3) is expected to be closed upon evolving insights on the optimal dose. Further pts will then be randomized (1:1) into Arm 1 or the remaining BNT327 arm. Stratification includes brain metastasis, liver metastasis, and geography. The primary endpoint is overall survival (OS). Secondary endpoints include progression-free survival (PFS), objective response rate, PFS rates and OS rates at defined timepoints, patient-reported outcomes, occurrence of treatment emergent adverse event (TEAEs) and occurrence of dose delay, infusion interruption, and discontinuation due to TEAEs; with efficacy endpoints per RECIST 1.1; safety per CTCAE v5.0. The Phase III trial is currently recruiting pts. Clinical trial information: NCT06712355. Research Sponsor: BioNTech SE.

TPS8130 **Poster Session**

IMMUNORARE[5]: A national platform of 5 academic phase II trials coordinated by Lyon University Hospital to assess the safety and the efficacy of the immunotherapy with domvanalimab + zimberelimab combination in patients with advanced rare cancers—The B3 Thymomas and Thymic Carcinomas Cohort. First Author: Michaël Duruisseaux, Louis Pradel Hospital, Hospices Civils de Lyon Cancer Institute, Cancer Research Center of Lyon (INSERM 1052, CNRS 5286), Université Claude Bernard Lyon 1, Université de Lyon, Lyon, France

Background: In patients with rare cancers, there is an unmet medical need for investigating innovative therapeutics. Indeed, these diseases are rarely assessed in clinical trials. Thymic epithelial tumors (TET) are rare heterogeneous thoracic malignancies. B3 TET and thymic carcinomas are more aggressive and prone to metastatic spreading. The standard 1st line treatment relies on platinum-based chemotherapy. Consensual 2nd line treatment has not been identified yet. Several studies showed limited efficacy of PD-1 blockade in B3 TET and thymic carcinomas. Concurrent blockage of TIGIT and PD-1 immune checkpoint B3 TET may improve outcomes according to translational studies. **Methods:** IMMUNORARE[5] (NCT06790706) is a platform of 5 single arm phase II trials testing the safety and efficacy of Domvanalimab (anti-TIGIT) and Zimberelimab (anti PD-1) in 5 independent cohorts of rare cancers. The trial, sponsored by Lyon University Hospital, is conducted in 15 French centers, in partnership with the corresponding French national reference centers. The B3 TET and thymic carcinomas cohort, led in collaboration with the RYTHMIC Network (www.rythmic.org), will enroll 26 patients after failure of at least one line of platinum-based chemotherapy, with evaluable lesions at baseline according to RECIST criteria. Patients previously treated with immunotherapy are not eligible. Patients will receive Domvanalimab and Zimberelimab intra-venous, every three weeks, until disease progression or unacceptable toxicity. The primary endpoint is the progression-free survival rate at 6 months. The secondary endpoints are overall response rate and duration of the response, progression-free survival, overall survival and tolerability. The trial is designed with a two-stage Simon design, with early termination for futility (5% one-sided alpha level, 80% power). The treatment would be considered interesting if the percentage of patients free from disease progression at 6-months is statistically higher than 40%; 65% is expected. Translational research projects will be developed aiming at deciphering cellular and molecular mechanisms involved in response to treatment. Moreover, data from the prospective database of the RYTHMIC network will be investigated to build a synthetic historical arm representative of the efficacy of the standard treatments in a similar population of patients. Clinical trial information: NCT06790706. Research Sponsor: GILEAD.

8500 **Oral Abstract Session**

First-line adagrasib (ADA) with pembrolizumab (PEMBRO) in patients (pts) with advanced/metastatic KRAS^{G12C}-mutated non-small cell lung cancer (NSCLC) from the phase 2 portion of the KRYSTAL-7 study. First Author: Pasi A. Jänne, Department of Medical Oncology, Lowe Center for Thoracic Oncology, Dana-Farber Cancer Institute, Boston, MA

Background: In the phase 2 KRYSTAL-7 study (NCT04613596), first-line ADA, a KRAS^{G12C} inhibitor, plus PEMBRO demonstrated clinical activity and a manageable safety profile in pts with advanced/metastatic *KRAS*^{G12C}-mutated NSCLC and PD-L1 ≥50% (Garassino et al. *Ann Oncol* 2023). Here we report efficacy and safety data, including the first disclosure of survival data, for pts across all PD-L1 tumor expression levels. **Methods:** Pts with advanced/metastatic *KRAS*^{G12C}-mutated NSCLC and known PD-L1 tumor proportion score received first-line ADA (400 mg orally BID) plus PEMBRO (200 mg IV Q3W). The primary endpoint was investigator-assessed objective response rate (ORR) per RECIST v1.1. Secondary endpoints included duration of response (DOR) and progression-free survival (PFS) assessed by investigator, overall survival (OS), and safety. **Results:** As of August 23, 2024, 149 pts had received ADA plus PEMBRO (median OS follow-up 22.8 mo): median age was 67 years, 48% were female, and 62% had ECOG PS 1. ORR was 44.3% (95% CI 36.2–52.7); median DOR was 26.3 mo (95% CI 14.9–not estimable [NE]); median PFS was 11.0 mo (95% CI 5.8–14.0) with an 18-mo PFS rate of 37.6% (95% CI 29.0–46.1); and median OS was 18.3 mo (95% CI 14.3–NE) with an 18-mo OS rate of 51.8% (95% CI 43.0–59.8). Efficacy outcomes per PD-L1 status are shown in the Table. Treatment-related adverse events (TRAEs) of any grade (G) were reported in 94.6% of pts (G3/4 in 68.4%); three G5 TRAEs were reported (pneumonia [n=2]; pneumonitis [n=1]). The most common hepatic TRAEs (any G) were increases in alanine aminotransferase (39.6%; G3/4 in 11.4%), aspartate aminotransferase (35.6%; G3/4 in 14.1%), and alkaline phosphatase (19.5%; G3/4 in 6.7%). The discontinuation rate due to hepatic TRAEs was 2.0% for ADA, 6.7% for PEMBRO, and 0.7% for both ADA and PEMBRO. **Conclusions:** In pts with advanced/metastatic *KRAS*^{G12C}-mutated NSCLC, first-line ADA plus PEMBRO demonstrated promising clinical efficacy and a manageable safety profile, regardless of PD-L1 status. These data represent the largest dataset evaluating a first-line KRAS^{G12C} inhibitor plus PD-(L)1 inhibitor in this population presented to date. The phase 3 portion of KRYSTAL-7, comparing first-line ADA plus PEMBRO vs PEMBRO monotherapy in pts with *KRAS*^{G12C}-mutated NSCLC and PD-L1 ≥50%, is ongoing and recruiting. Clinical trial information: NCT04613596. Research Sponsor: Mirati Therapeutics, a Bristol Myers Squibb company.

	PD-L1 <50%(n=95)	PD-L1 ≥50% (n=54)
ORR, n (%)	34 (35.8)	32 (59.3)
95% CI	26.2–46.3	45.0–72.4
Median DOR, mo (95% CI)	(n=34)	(n=32)
	18.2 (11.1–NE)	26.3 (26.3–NE)
Median PFS[a], mo (95% CI)	6.9 (3.9–12.4)	27.7 (8.1–NE)
18-mo rate, % (95% CI)	29.8 (19.8–40.4)	50.7 (35.5–64.0)
Median OS[b], mo (95% CI)	15.5 (11.1–21.0)	NE (15.4–NE)
18-mo rate, % (95% CI)	45.2 (34.3–55.6)	62.4 (47.5–74.1)

[a]Median PFS follow-up 17.5 mo (PD-L1 <50%) and 22.6 mo (PD-L1 ≥50%); [b]Median OS follow-up 21.4 mo (PD-L1 <50%) and 24.9 mo (PD-L1 ≥50%).

8501 **Oral Abstract Session**

TROPION-Lung02: Datopotamab deruxtecan (Dato-DXd) plus pembrolizumab (pembro) with or without platinum chemotherapy (Pt-CT) as first-line (1L) therapy for advanced non-small cell lung cancer (aNSCLC). First Author: Benjamin Philip Levy, Sidney Kimmel Comprehensive Cancer Center, Johns Hopkins Medicine, Baltimore, MD

Background: TROPION-Lung02 (NCT04526691) evaluated the TROP2-directed antibody-drug conjugate (ADC) Dato-DXd plus pembro combination with or without Pt-CT in aNSCLC. Here we report primary analyses of pts receiving combination therapy in the 1L setting. **Methods:** Pts across 6 cohorts were dosed with Dato-DXd (4 or 6 mg/kg) plus pembro 200 mg alone (doublet) or with pembro plus Pt-CT (triplet; cisplatin 75 mg/m^2 or carboplatin AUC 5) Q3W. PD-L1 expression (tumor proportion score) was assessed locally by immunohistochemistry (22C3 assay). Primary objectives were safety and tolerability; efficacy was a secondary objective. **Results:** As of Apr 29, 2024, 96 pts received either the doublet (n=42) or triplet (n=54) combination as 1L therapy; 29% and 15% of pts were ongoing, respectively. Median ages were 65 (doublet) and 64 years (triplet). Median treatment durations were 9.7 and 5.8 months, respectively. Stomatitis (doublet, 57%; triplet, 33%) and nausea (doublet, 42%; triplet, 48%), primarily Gr 1–2, were the most common adverse events (AEs) across both regimens. Treatment related serious AEs occurred in 5 (12%) and 12 (22%) pts in each cohort and no deaths related to study drug were seen. Efficacy outcomes, including by histology, are summarized in the Table. Biomarker analyses, including efficacy by PD-L1 status, will be presented. **Conclusions:** In this largest data set to date evaluating an ADC combined with an anti-PD-1/L1 agent in the 1L setting, the combination of Dato-DXd plus pembro treatment both with and without Pt-CT elicited durable antitumor activity in pts with aNSCLC. Tolerability of the combinations was as expected, based on known profiles of the individual agents. Clinical trial information: NCT04526691. Research Sponsor: Daiichi Sankyo, Inc.

	All 1L (n=96)		1L, Nonsquamous (n=75)		1L, Squamous (n=21)	
Response, n (%)	**Doublet (n=42)**	**Triplet (n=54)**	**Doublet (n=33)**	**Triplet (n=42)**	**Doublet (n=9)**	**Triplet (n=12)**
Confirmed objective response rate	23 (55)	30 (56)	17 (52)	24 (57)	6 (67)	6 (50)
Complete response	1 (2)	2 (4)	1 (3)	2 (5)	0	0
Partial response	22 (52)	28 (52)	16 (49)	22 (52)	6 (67)	6 (50)
Stable disease	14 (33)	18 (33)	12 (36)	14 (33)	2 (22)	4 (33)
Progressive disease	3 (7)	2 (4)	3 (9)	1 (2)	0	1 (8)
Disease control rate[a]	37 (88)	48 (89)	29 (88)	38 (91)	8 (89)	10 (83)
Median duration of response, mo (95% CI)	20.1 (9.7–NE)	13.7 (5.7–NE)	24.9 (9.7–NE)	18.0 (8.0–NE)	12.0 (5.5–NE)	5.5 (4.1–NE)
Median PFS, mo (95% CI)	11.2[b] (8.2–21.3)	6.8[c] (5.5–11.1)	11.2 (6.1–21.3)	10.8 (5.5–17.3)	10.2 (0.4–NE)	6.7 (1.0–8.2)

[a]Proportion of pts with confirmed CR + PR + SD at 12 wks. [b,c]Median (95% CI) PFS follow-up, mo: [b]17.3 (11.3−26.8); [c]23.5 (17.3−27.9).
mo, months; NE, not evaluable.

LBA8502 **Oral Abstract Session**

CAMPASS: Benmelstobart in combination with anlotinib vs pembrolizumab in the first-line treatment of advanced non-small cell lung cancer (aNSCLC)—A randomized, single-blind, multicenter phase 3 study. First Author: Baohui Han, Shanghai Chest Hospital, Shanghai, China

The full, final text of this abstract will be available at meetings.asco.org on the day of presentation and in the online supplement to the June 10, 2025, issue of the *Journal of Clinical Oncology*.

8503 **Oral Abstract Session**

Efficacy of zipalertinib in NSCLC patients with EGFR exon 20 insertion mutations who received prior platinum-based chemotherapy with or without amivantamab. First Author: Helena Alexandra Yu, Memorial Sloan Kettering Cancer Center, New York, NY

Background: Despite the approval of amivantamab (ami) for EGFR exon 20 insertion (ex20ins) mutant NSCLC, an unmet need remains for well-tolerated oral targeted therapies with durable clinical benefit. Zipalertinib (zipa, CLN-081, TAS6417) is a novel EGFR TKI which showed promising clinical activity and manageable safety in a phase 1/2a study in pts with ex20ins NSCLC that progressed on platinum-based chemotherapy (plt-chemo). Here we report the primary data from the pivotal phase 2b REZILIENT1 study of zipa in patients (pts) with advanced or metastatic EGFR ex20ins mutant NSCLC that progressed after prior plt-chemo with or without prior ami. **Methods:** Pts were enrolled in two parallel cohorts (prior plt-chemo, prior plt-chemo and ami) and treated with zipa 100 mg BID. Tumor response was assessed by blinded independent central review (BICR) per RECIST v1.1. Pts with stable, asymptomatic, or treated brain metastases (mets) were allowed. **Results:** As of 10 December 2024 data cut off, 176 pts (51 with prior ami and 125 with plt-chemo) were enrolled with median follow-up of 9.3 months: median age: 65 (33-85), median lines of prior therapy: 2 (1-7), prior PD1/L1: 100 (56.8%), history of brain mets: 68 (38.6%). Among all pts treated, zipa demonstrated a confirmed ORR (cORR) of 35.2%, mDoR of 8.8 months, and mPFS of 9.5 months (table 1). In pts with plt-chemo without ami, the cORR was 40.0%. Of the 51 pts with prior ami, 30 had no other ex20ins-directed therapy, while 21 had also received other ex20ins drugs (such as mobocertinib, sunvozertinib, BLU-451, or poziotinib), the cORR was 30.0% and 14.3%, respectively. Among all pts with brain mets, systemic cORR was 30.9%. The most common treatment-emergent AEs (TEAEs, all-grade) were paronychia, rash, anemia, diarrhea, dry skin, nausea, and stomatitis and the majority of the TEAEs were CTCAE grade 1 or 2. **Conclusions:** Zipalertinib demonstrated clinically meaningful efficacy with a manageable safety profile in pts with exon20ins NSCLC who have received prior platinum-based chemotherapy and for those who received prior amivantamab, a significant and growing unmet need. Clinical trial information: NCT04036682. Research Sponsor: None.

BICR assessed tumor responses per RECIST v1.1.

	N	CR(%)	PR(%)	SD(%)	cORR(%, 95%CI)	mDOR(m, 95%CI)	mPFS(m, 95%CI)
Plt-chemo	125	0	50 (40.0)	55(44.0)	40.0(31.3, 49.1)	8.8(8.3, 11.4)	9.5(7.7,11.5)
Prior Ami ± other ex20ins drug	51	1 (2.0)	11 (21.6)	33(64.7)	23.5(12.8, 37.5)	8.5(4.2, 14.8)	7.3(5.3,9.7)
Total	176	1 (0.6)	61 (34.7)	88(50.0)	35.2(28.2, 42.8)	8.8(8.3, 11.4)	9.5(7.4, 10.0)

CR=complete response, PR=partial response, SD=stable disease.

8504 Oral Abstract Session

SOHO-01: Safety and efficacy of BAY 2927088 in patients with advanced *HER2*-mutant non-small cell lung cancer (NSCLC) who were pretreated but naïve to HER2-targeted therapy or had not received any treatment for advanced disease. First Author: Herbert H. Loong, The Chinese University of Hong Kong, Hong Kong SAR, China

Background: The potent, reversible HER2 tyrosine kinase inhibitor BAY 2927088 has demonstrated manageable safety and anti-tumor activity in patients with advanced NSCLC with *HER2*-activating mutations. Here we report safety and efficacy data from 2 cohorts of the ongoing, open-label, multicenter Phase I/II SOHO-01 trial. **Methods:** Patients with advanced NSCLC with *HER2*-activating mutations were enrolled and received oral BAY 2927088 20 mg twice daily. Patients in expansion/extension Cohort D had disease progression following ≥1 systemic therapies and were naïve to HER2-targeted therapy; patients in expansion Cohort F had not received any systemic therapy for locally advanced or metastatic disease. Safety (MedDRA v27.1 and CTCAE v5.0) was the primary endpoint; anti-tumor activity (RECIST v1.1) was a key secondary endpoint. **Results:** As of October 14, 2024, 81 (D) and 39 (F) patients were treated. Median age was 60 years (D) and 65 years (F), 61.7% (D) and 64.1% (F) were female, 61.7% (D) and 79.5% (F) had never smoked, and 43.2% (D) had received ≥2 systemic therapies. All patients were analyzed for safety and efficacy; response was based on the full analysis set. Treatment-related adverse events (TRAEs) were observed in 96.7% of patients; diarrhea was the most common TRAE leading to dose reduction in 8.3% of patients (Table). No patients discontinued BAY 2927088 treatment because of diarrhea, and no cases of interstitial lung disease were reported. Investigator-assessed objective response rates were 59.3% (95% CI 47.8, 70.1; D) and 59.0% (95% CI 42.1, 74.4; F). Disease control rates (confirmed response or stable disease for ≥12 weeks) were 84.0% (95% CI 74.1, 91.2; D) and 84.6% (95% CI 69.5, 94.1; F). One patient in Cohort D achieved a complete response. **Conclusions:** BAY 2927088 demonstrated manageable safety in both cohorts, consistent with previous reports. Diarrhea was the most common TRAE, but it was manageable and did not lead to treatment discontinuation. Similar response rates were observed in patients with advanced *HER2*-mutant NSCLC who were pretreated but naïve to HER2-targeted therapy and in those treated in the first-line setting. Clinical trial information: NCT05099172. Research Sponsor: Bayer AG.

	Cohort D (n=81)		Cohort F (n=39)	
n (%)	All grades	Grade ≥3	All grades	Grade ≥3
Any TRAE	78 (96.3)	31 (38.3)	38 (97.4)	8 (20.5)
Most common TRAEs occurring in ≥20% of all patients				
Diarrhea	68 (84.0)	19 (23.5)	32 (82.1)	1 (2.6)
Rash	40 (49.4)	0	22 (56.4)	0
Paronychia	20 (24.7)	0	7 (17.9)	0
Stomatitis	15 (18.5)	1 (1.2)	9 (23.1)	0
Most common TRAE leading to dose reduction				
Diarrhea	9 (11.1)	3 (3.7)	1 (2.6)	1 (2.6)

LBA8505 Oral Abstract Session

Savolitinib (Savo) combined with osimertinib (osi) versus chemotherapy (chemo) in EGFR-mutant (EGFRm) and *MET*-amplification (*MET*amp) advanced NSCLC after disease progression (PD) on EGFR tyrosine kinase inhibitor (TKI): Results from a randomized phase 3 SACHI study. First Author: Shun Lu, Shanghai Chest Hospital, School of Medicine, Shan, Shanghai, China

The full, final text of this abstract will be available at meetings.asco.org on the day of presentation and in the online supplement to the June 10, 2025, issue of the *Journal of Clinical Oncology*.

8506 Oral Abstract Session

Patritumab deruxtecan (HER3-DXd) in resistant *EGFR*-mutated (*EGFR*m) advanced non-small cell lung cancer (NSCLC) after a third-generation EGFR TKI: The phase 3 HERTHENA-Lung02 study. First Author: Tony S. K. Mok, State Key Laboratory of Translational Oncology, Chinese University of Hong Kong, Hong Kong, China

Background: After disease progression on a 3rd-gen (3G) EGFR TKI for advanced *EGFR*m NSCLC, available therapies provide limited efficacy. HER3-DXd, an antibody-drug conjugate consisting of a fully human mAb to HER3 attached to a topoisomerase I inhibitor payload via a stable tetrapeptide-based cleavable linker, showed promising efficacy in HERTHENA-Lung01. **Methods:** HERTHENA-Lung02 (NCT05338970) is a phase 3, randomized, open-label study of HER3-DXd vs platinum-based chemotherapy (PBC) in patients (pts) with advanced *EGFR*m (Ex19del or L858R) NSCLC following disease progression on a 3G EGFR TKI. The primary endpoint is PFS by BICR, tested using a stratified log-rank test. The key secondary endpoint is OS. **Results:** 586 pts were randomized to HER3-DXd or PBC (median age, 64 y; 61% female; 60% Asian). At the 31 May 2024 data cutoff for primary analysis of PFS, median (range) study duration was 10.7 (5.2-21.9) mo, and treatment duration was 5.5 (0.7-16.8) mo and 4.6 (0.7-16.5) mo with HER3-DXd and PBC, respectively. HER3-DXd provided a significant improvement in PFS vs PBC (HR, 0.77; 95% CI, 0.63-0.94; *P*=.011). Median PFS (95% CI) with HER3-DXd vs PBC was 5.8 (5.5-6.8) mo vs 5.4 (5.0-5.6) mo. The PFS rate (95% CI) with HER3-DXd vs PBC was 0.50 (0.44-0.56) vs 0.38 (0.32-0.44) at 6 mo; 0.29 (0.23-0.35) vs 0.19 (0.14-0.25) at 9 mo; and 0.18 (0.12-0.25) vs 0.05 (0.01-0.13) at 12 mo. ORR (95% CI) was 35.2% (29.7%-40.9%) with HER3-DXd vs 25.3% (20.4%-30.6%) with PBC. Median DOR (95% CI) was 5.7 (5.1-7.3) mo with HER3-DXd vs 5.4 (4.1-5.6) mo with PBC. OS data were immature at this protocol-specified interim data cut. In pts with brain metastases at baseline (per CNS BICR), median (95% CI) intracranial PFS was 5.4 (4.0-5.9) mo with HER3-DXd (n=105) vs 4.2 (2.8-5.0) mo with PBC (n=95) (HR, 0.75; 95% CI, 0.53-1.06). TEAEs occurred in 100% of pts in the HER3-DXd arm and 99% in the PBC arm. TEAEs were associated with treatment discontinuation in 33 pts (11%) in the HER3-DXd arm and 27 (10%) in the PBC arm. The most common TEAEs (n [%]) in the HER3-DXd/PBC arms were nausea (168 [57.9]/118 [42.1], thrombocytopenia (151 [52.1]/76 [27.1]), and fatigue (146 [50.3]/118 [42.1]). Grade [G] ≥3 TEAEs occurred in 73% (HER3-DXd) and 57% (PBC) of pts; the difference was driven by a higher rate of G≥3 thrombocytopenia with HER3-DXd (30% vs 7.9%). Each arm had 1 G≥3 bleeding event associated with G≥3 platelet count decreased. Adjudicated drug-related ILD occurred in 14 pts (5%; 11 G1/2, 1 G3, 2 G5) in the HER3-DXd arm. **Conclusions:** HER3-DXd demonstrated statistically significant improvement in PFS vs PBC in pts with *EGFR*m NSCLC post EGFR TKI therapy. The safety profile was manageable, consistent with prior reports. Most common TEAEs were hematologic and gastrointestinal. Follow-up is ongoing, along with further exploration of secondary/exploratory/biomarker endpoints from this data cut. Clinical trial information: NCT05338970. Research Sponsor: Daiichi Sankyo Company, Limited; Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA.

8507 Oral Abstract Session

Sacituzumab tirumotecan (sac-TMT) in patients (pts) with previously treated advanced EGFR-mutated non-small cell lung cancer (NSCLC): Results from the randomized OptiTROP-Lung03 study. First Author: Li Zhang, Sun Yat-sen University Cancer Center, Guangzhou, China

Background: Sac-TMT (MK-2870/SKB264), a novel TROP2 ADC developed to conjugate a belotecan-derivative topoisomerase I inhibitor, has shown encouraging antitumor activity in EGFRm NSCLC pts in phase I trial (Fang *et al*. AACR 2024). Here, we report the results from a multicenter, randomized, controlled study comparing sac-TMT with docetaxel in previously treated EGFRm NSCLC pts (OptiTROP-Lung03, NCT05631262). **Methods:** Pts with advanced EGFRm NSCLC who had progressed after EGFR TKI and platinum-based chemotherapy were randomized (2:1) to receive sac-TMT 5 mg/kg Q2W or docetaxel 75 mg/m^2. Pts with verified progression on docetaxel could be crossed over to receive sac-TMT if eligible. Hierarchical fixed-sequence testing was employed for efficacy endpoints, including ORR (primary) and PFS, assessed by blinded independent review committee (BIRC), followed by OS. Pre-specified OS interim analysis was conducted alongside final PFS analysis, with the level at one-sided alpha of 1.23% determined by alpha spending function. The crossover-adjusted OS was derived using the rank-preserving structural failure time (RPSFT) model. **Results:** A total of 137 pts (median age 56 yrs; 43.8% male; 82.5% ECOG PS 1; 93.4% prior 3rd EGFR TKI) were randomized to receive sac-TMT (n=91) or docetaxel (n=46). At a median follow-up of 12.2 mo (data cutoff: Dec 31, 2024), 25.3% of pts (sac-TMT) vs 4.3% (docetaxel) remained on treatment. The study met its primary and key secondary endpoints. Sac-TMT achieved statistically significant clinical outcomes compared to docetaxel: confirmed ORR (BIRC: 45.1% vs 15.6%, 1-sided p=0.0004; investigator [INV]: 34.1% vs 8.7%), PFS (BIRC: median 6.9 vs 2.8 mo, HR 0.30 [95% CI: 0.20, 0.46], 1-sided p<0.0001; INV: median 7.9 vs 2.8 mo, HR 0.23 [95% CI: 0.15, 0.36]), and OS (median not reached [NR] for both groups, HR 0.49 [95% CI: 0.27, 0.88], 1-sided p=0.007), with 36.4% of pts in docetaxel group crossed over to receive sac-TMT. The RPSFT model adjusted median OS was 9.3 mo for docetaxel and NR for sac-TMT (HR for OS 0.36 [95% CI: 0.20, 0.66]). Grade ≥ 3 treatment-related adverse events (TRAEs) occurred in 56.0% of pts in sac-TMT group vs 71.7% in docetaxel group, and treatment-related SAEs were 16.5% vs 41.3%. Most common (≥ 10%) grade ≥ 3 TRAEs (sac-TMT vs docetaxel) were neutrophil count decreased (42.9% vs 58.7%), WBC count decreased (25.3% vs 52.2%), stomatitis (16.5% vs 2.2%), anemia (12.1% vs 4.3%) and febrile neutropenia (0% vs 19.6%). No cases of ILD were reported in sac-TMT group. **Conclusions:** Sac-TMT demonstrated improved ORR, PFS and OS compared to docetaxel, with manageable safety profile in pts with previously treated advanced EGFRm NSCLC. These results highlight significant survival benefits and suggest that sac-TMT could emerge as a new standard of care for this population. Clinical trial information: NCT05631262. Research Sponsor: Sichuan Kelun-Biotech Biopharmaceutical Co., Ltd.

8509 Clinical Science Symposium

First-in-class PD-1/IL-2 bispecific antibody IBI363 in patients (Pts) with advanced immunotherapy-treated non-small cell lung cancer (NSCLC). First Author: Jianya Zhou, The First Affiliated Hospital, Zhejiang University School of Medicine, Hangzhou, China

Background: IBI363 is a first-in-class PD-1/IL-2$^{\alpha\text{-bias}}$ bispecific antibody fusion protein to block PD-1 checkpoint and rejuvenate exhausted tumor-specific T cells by cis-activating α-bias IL-2. It has potential to address the unmet clinical need of patients (pts) with immunotherapy-resistant and cold tumors. Here, we report safety and efficacy results from a phase I, multicenter, first-in-human study (NCT05460767) of IBI363 in pts with advanced NSCLC. **Methods:** Eligible pts with advanced NSCLC who failed or were intolerant of standard therapy were enrolled and received IBI363 intravenously at dose levels of 2/10/300/600 ug/kg every week (QW), 0.3/0.6/1 mg/kg every two weeks (Q2W) or 1.5/2/3/4 mg/kg every three weeks (Q3W). Endpoints included safety, objective response rate (ORR), disease control rate (DCR), duration of response (DoR) and progression-free survival (PFS) by investigator per RECIST v1.1. **Results:** As of December 6, 2024, 136 NSCLC pts were enrolled (median age: 61 years; prior treatment lines ≥2: 72%). Most patients were treated with IBI363 at 0.6/1 mg/kg Q2W (n=56), 1.5 mg/kg Q3W (n=11) or 3 mg/kg Q3W (n=57). Treatment-emergent adverse events (TEAEs) occurred in 135/136 pts (≥G3: 42.6%). TEAEs led to treatment discontinuation in 9 (6.6%) pts and TEAEs led to death in 4 (2.9%) pts with only 1 (0.7%) event considered treatment-related (unexplained death). Most common TEAEs were arthralgia (51.5%; 3.7% ≥G3), anemia (43.4%; 3.7% ≥G3), and rash (38.2%; 4.4% ≥G3). In pts with squamous cell carcinoma who had at least 1 post-baseline tumor assessment, 30 (including 1 pt who had not received PD-(L)1 before enrolled) and 27 pts had been treated with IBI363 3 mg/kg and 1/1.5 mg/kg, respectively; more encouraging efficacy signals were observed in the 3 mg/kg group: ORR 43.3% vs 25.9%, confirmed ORR 36.7% vs 25.9%, DCR 90.0% vs 66.7%, median PFS 7.3 (95% CI: 6.0-11.7) vs 5.5 (95% CI: 1.5-8.3) months, with a median follow up time of 7.3 vs 11.1 months. In the PD-(L)1 treated adenocarcinoma pts with no actionable genomic alterations who had at least 1 post-baseline tumor assessment, 25 and 30 pts had been treated with IBI363 3 mg/kg and 0.6/1/1.5 mg/kg, respectively, similarly, 3 mg/kg group showed higher ORR (28.0% vs 16.7%), confirmed ORR (24.0% vs 13.3%), DCR (76.0% vs 63.3%) and median PFS (4.2 [95% CI: 3.0-not estimable] vs 2.8 [95% CI: 1.4-5.1] months, with a median follow up of 5.9 vs 16.5 months). A higher ORR of 29% versus 4% and a longer PFS of 5.3 months compared to 2.7 months were observed in smokers (N=31, 56.4%). Notably, in patients at all dose levels with a tumor cell proportion score (TPS) under 1%, the ORR was 45.5% for squamous cell carcinoma (N=22) and 29.4% for adenocarcinoma (N=17). **Conclusions:** IBI363 was well tolerated with encouraging and durable efficacy observed in pts with advanced NSCLC who progressed to PD-(L)1, especially in the squamous subtype. Clinical trial information: NCT05460767. Research Sponsor: Innovent Biologics (Suzhou) Co., Ltd.

8510 Clinical Science Symposium

Efficacy and safety of MHB088C, a novel B7-H3-targeted ADC, in patients with relapsed extensive-stage small cell lung cancer (ES-SCLC): Subgroup analysis from a phase 1/2 multicenter study. First Author: Lin Shen, Beijing Cancer Hospital, Beijing, China

Background: MHB088C is a novel B7-H3-targeted antibody-drug conjugate (ADC) containing the potent SuperTopoi payload that is 5 to 10 times more potent than Dxd. Initial findings from an ongoing phase 1/2 study indicated that MHB088C was generally well tolerated, with early signs of clinical activity (ASCO 2024, abstract #3012). This analysis presents efficacy and safety results for the subset of pts with ES-SCLC. **Methods:** This study consisted of 2 parts: dose-escalation (part 1) and expansion (part 2). Part 1 evaluated the safety and tolerability of MHB088C at doses ranging from 0.8 to 4.0 mg/kg, administered intravenously every 2 (Q2W) or 3 weeks (Q3W). Doses of 1.6 mg/kg Q2W, 2.0 mg/kg Q2W, and 2.4 mg/kg Q3W were selected for part 2. Part 2 focused on assessing safety and prospective efficacy of MHB088C in selected tumor types, including SCLC. **Results:** At data cutoff (January 3, 2025), a total of 91 pts with relapsed ES-SCLC had received ≥ 1 dose of MHB088C (1.6 mg/kg Q2W, n=28; 2.0 mg/kg Q2W, n=33; 2.4 mg/kg Q3W, n=30). MHB088C showed encouraging efficacy in relapsed ES-SCLC (Table). The objective response rates were 42.9%, 57.6%, and 46.7% in the 1.6, 2.0, and 2.4 mg/kg cohorts, respectively, with median progression-free survival (PFS) of 5.5, 5.9, 5.5 months. Safety data were consistent with previous reports. The most common grade≥3 treatment-related adverse events were neutropenia, platelet count decreased and anemia. The 1.6 and 2.0 mg/kg cohorts exhibited favorable safety profiles, with only single-digit rates of the aforementioned hematologic adverse events. One case (1.0%) of mild interstitial lung disease (ILD) was reported. **Conclusions:** MHB088C demonstrated promising anti-tumor activity and favorable safety in previously treated pts with ES-SCLC. A Phase 3 study is planned to compare the efficacy and safety of MHB088C with standard-of-care chemotherapy in relapsed ES-SCLC. Clinical trial information: CTR20231298. Research Sponsor: None.

	1.6 mg/kg Q2W (n=28)	2.0 mg/kg Q2W (n=33)	2.4 mg/kg Q3W (n=30)
Unconfirmed ORR, (%)	42.9	57.6	46.7
Confirmed ORR, (%)	21.4	42.4	43.3
DCR, n (%)	89.3	87.9	93.3
Median PFS, month	5.5	5.9	5.5

8511 Clinical Science Symposium

First report of efficacy and safety results from a phase 2 trial evaluating BNT327/PM8002 plus chemotherapy (chemo) as first-line treatment (1L) in unresectable malignant mesothelioma. First Author: Ying Cheng, Jilin Cancer Hospital, Changchun, China

Background: Malignant mesothelioma is a rare neoplasm with a high unmet medical need. BNT327 is an investigational bispecific antibody, targeting both PD-L1 and VEGF-A in the tumor and tumor microenvironment (TME). By binding to PD-L1 on tumor cells it is designed to restore effector T-cell function and by binding to VEGF-A within the TME it also reverses the negative impact of VEGF signaling on immune cell infiltration and activation. In addition, via VEGF-A neutralization, it normalizes tumor vasculature. This dual targeting of PD-L1 and VEGF-A aims to deliver better efficacy and safety. BNT327 has shown encouraging preliminary activity in thoracic malignancies incl. SCLC (ESMO 2023) and NSCLC (ASCO & ESMO 2024). **Methods:** After a safety run-in (n=6), this ongoing, multicenter, single-arm phase 2 clinical trial recruited chemo naive pts (pts) aged ≥18 yrs with unresectable malignant mesothelioma (pleural (MPM) or peritoneal (MPeM)) to evaluate BNT327 30 mg/kg Q3W IV combined with 4-6 cycles pemetrexed and platinum, followed by BNT327 maintenance. Primary endpoints were efficacy (ORR per RECIST 1.1 for MPeM, mRECIST 1.1 for MPM) and safety (CTCAE V5.0). **Results:** As of 25 Oct 2023, 31 pts, median age 58 yrs (range 43-71), 80.6% ECOG PS 1 and 83.9% with metastatic disease had been enrolled, of which 23 had MPM and 8 MPeM. At the cutoff date of 20 Dec 2024, the median exposure duration was 16.0 mo (95% CI 8.1, 19.5) and median follow-up time 19.3 mo (95% CI 17.3, 20.9). In 23 pts with MPM, 1 pt had a CR and 9 had PRs as BOR, resulting in a confirmed ORR (cORR) of 43.5%. 10 pts had SD and 1 non-CR/non-PD, giving a DCR of 87.0%. Median PFS (mPFS) was 11.8 mo, and median DOR was 11.8 mo. The 12 mo OS rate was 82.6% (95% CI 60.1, 93.1), with median OS not yet reached. Among 13 pts with MPM of epithelioid histology, cORR was 30.8%, DCR was 84.6% and mPFS was 16.6 mo. Among 8 pts with MPeM, 6 had PR as BOR, leading to a cORR of 75.0%. 2 pts had SD, resulting in a DCR of 100%; median DOR was 16.3 mo. Median PFS and OS were not yet reached, with an OS rate of 62.5% (95% CI 22.9, 86.1) at 12 mo. 6 pts with MPeM of epithelioid histology displayed a cORR of 83.3%, DCR of 100% and mPFS of 19.5 mo. All pts experienced TRAEs, 93.5% of pts (29/31) of Grade (G) 3-4. 5 pts (16.1%) had G 3-4 treatment-related SAEs. 5 pts (16.1%) experienced an irAE, 1 (3.2%) of G 3-4. The most common TRAEs were decreased neutrophil count (27 pts, 87.1%), decreased white blood cell count (26 pts, 83.9%), proteinuria (24 pts, 77.4%), anemia (23 pts, 74.2%), decreased platelet count (19 pts, 61.3%), and nausea (16 pts, 51.6%). 6 pts discontinued treatment due to TRAEs; no treatment-related deaths occurred. 9 pts remain on treatment. **Conclusions:** BNT327 plus chemo as a 1L regimen for mesothelioma showed encouraging efficacy, including in tumors of epithelioid histology. AEs were consistent with those expected for the treatment regimen. Clinical trial information: NCT05918107. Research Sponsor: Biotheus Inc.

8512 Rapid Oral Abstract Session

Telisotuzumab adizutecan (ABBV-400; Temab-A), a c-Met protein–targeting antibody-drug conjugate (ADC), in patients (pts) with advanced *EGFR*-mutated (MT) non-squamous (NSQ) non-small cell lung cancer (NSCLC): Results from a phase 1 study. First Author: David Ross Camidge, University of Colorado Cancer Center, Aurora, CO

Background: c-Met protein (also known as MET protein) expression is increased in NSCLC and is a negative prognostic indicator. Temab-A is an ADC comprising the c-Met protein–targeting mAb telisotuzumab conjugated to a novel topoisomerase 1 inhibitor payload. A phase 1 study (NCT05029882) of Temab-A in advanced solid tumors is ongoing. In dose expansion, Temab-A had manageable safety and promising efficacy in pts with NSQ *EGFR* wildtype NSCLC (*Ann Oncol*. 2024;35:1257MO). Herein, we present the results for pts with advanced *EGFR* MT NSQ NSCLC. **Methods:** Pts (≥18 yr) whose disease had progressed after platinum-based chemotherapy doublet and tyrosine kinase inhibitor(s) (TKIs) were enrolled. Pts received Temab-A at 2.4 (n=36) or 3.0 (n=5) mg/kg Q3W. Primary objectives were evaluating safety, tolerability, PK, and preliminary efficacy of Temab-A. Tumor tissue c-Met protein expression was assessed centrally by IHC. **Results:** Forty-one pts were enrolled in the *EGFR* MT cohort. Median age was 64 yr (43–88), 63% were female, and 32% had baseline brain metastases. Median prior therapies was 3 (1–8); 93% had prior anti-EGFR treatment. Median treatment duration was 9.2 months; median follow-up was 9.7 months. TEAEs of any grade/grade ≥3 occurred in 100%/73% of pts. The most common any-grade TEAEs were hematologic (83%) and gastrointestinal (81%); any-grade TEAEs in ≥30% of pts were anemia (63%), nausea (61%), vomiting (37%), decreased appetite (34%), and neutropenia (34%). Grade ≥3 TEAEs were mostly hematologic (42%), and most common were anemia (27%) and neutropenia (22%). The any-grade adjudicated interstitial lung disease/pneumonitis rate was 7% (grade ≥3: 2%). TEAEs leading to discontinuation occurred in 20% of pts. Four deaths occurred; 1 (pneumonitis) was considered related to study drug. All pts with post-baseline data had some decrease in tumor burden. ORR was 63% (Table); similarly high ORR was observed regardless of c-Met protein expression. Responses occurred irrespective of *EGFR* L858R alterations, exon 19 deletions, or TKI resistance mutations including T790M and C797S. As of the data cut (Sep 2024), 19 (46%) pts remain on treatment. Time-to-event endpoints are immature; to date, 54% of responders have a DOR of ≥6 months. Exploratory biomarker analysis is ongoing. **Conclusions:** Temab-A has a manageable safety profile with promising clinical activity in pts with 3L+ NSQ *EGFR* MT NSCLC, meriting further investigation. Clinical trial information: NCT05029882. Research Sponsor: AbbVie Inc.; n/a

Efficacy	NSQ *EGFR* MT NSCLC (n=41)
Best overall response,[a] n (%)	
PR	26 (63)
SD	12 (29)
NE/Not assessed	3 (7)
ORR,[a] n (%)	26 (63)
CBR12,[a] n (%)	34 (83)
P[PFS at 6 mo], % (95% CI)	80 (63, 89)
P[OS at 6 mo], % (95% CI)	93 (79, 98)

[a]Confirmed responses. P, probability.

8513 Rapid Oral Abstract Session

Efficacy and CNS results from a randomized subset of the phase 2 SAVANNAH study comparing savolitinib (savo) + osimertinib (osi) combination with savo + placebo (PBO). First Author: Benjamin Philip Levy, Sidney Kimmel Comprehensive Cancer Center, Johns Hopkins University School of Medicine, Baltimore, MD

Background: The MET pathway is a known mediator of EGFR-TKI resistance and represents a therapeutic vulnerability to select MET-TKIs. Savo is an oral, highly selective MET-TKI that, when combined with osi, has the potential to overcome MET-driven resistance after progressive disease (PD) on osi. The Phase 2 SAVANNAH study has demonstrated clinically meaningful activity with the combination of savo + osi in patients (pts) with EGFR-mutated (EGFRm) advanced NSCLC and MET overexpression/amplification (NCT03778229). Isolating the efficacy of savo in the use of savo + osi is a key question for this combination. **Methods:** A subset of SAVANNAH included eligible pts who had EGFRm advanced NSCLC with MET overexpression (IHC 3+ intensity in ≥90% of tumor cells [IHC3+/≥90%]) and/or amplification (≥10 MET gene copies by FISH [FISH10+]) after PD on first-line (1L) osi; asymptomatic stable brain metastases (treated/untreated) were allowed. Pts were randomized 2:1 (double-blind) to savo 300 mg BID + osi 80 mg QD, or savo 300 mg BID + PBO (stratified by investigator [INV] assessed baseline [BL] brain metastases [yes/no]), until INV-assessed PD per RECIST 1.1. Brain imaging occurred at BL and PD; pts with brain metastases were re-imaged at each tumor assessment to PD. Endpoints included objective response rate (ORR), duration of response (DoR), and progression-free survival (PFS) by BICR and INV; CNS PFS, and presence/absence of CNS lesions at PD by BICR. **Results:** Overall, 73 pts were randomized (savo + osi n=48; savo + PBO n=25). At BL, median age: 67 vs 65 years, female: 73% vs 64%, White: 73% vs 52% in the savo + osi and savo + PBO arms, respectively. Efficacy outcomes (ORR, DoR, and PFS) were higher with savo + osi than savo + PBO (Table). CNS PFS events by CNS BICR occurred in 5/14 (36% savo + osi) and 2/4 pts (50% savo + PBO). In pts without BL brain metastases, none of the 13 pts (savo + osi) with RECIST PD by BICR had a new CNS lesion; 6/11 pts in the savo + PBO arm developed a new CNS lesion. **Conclusions:** In EGFRm advanced NSCLC with MET IHC3+/≥90% and/or FISH10+ status after PD on 1L osi, efficacy of savo 300 mg BID + osi was numerically greater than savo + PBO and showed promising CNS activity. To date, this is one of the largest randomized data sets presented evaluating an oral MET-TKI in EGFRm NSCLC. Efficacy findings from SAVANNAH suggest that targeting both EGFR and MET is key and support further investigation of savo + osi and CNS activity in the Phase 3 SAFFRON study. Clinical trial information: NCT03778229. Research Sponsor: AstraZeneca.

	Assessment	Savo + osi (n=48)	Savo + placebo (n=25)
ORR, % (95% CI)	BICR	58 (43, 72)	16 (5, 36)
	INV	54 (39, 69)	24 (9, 45)
DoR, mo, median (95% CI)	BICR	11.8 (6.0, NC)	4.5 (2.6, NC)
	INV	8.0 (4.9, 11.7)	4.2 (2.6, NC)
PFS, mo, median (95% CI)	BICR	8.3 (5.8, 15.1)	3.6 (1.4, 5.7)
	INV	7.6 (5.6, 11.0)	2.7 (1.4, 4.1)

BICR, blinded independent central review; CI, confidence interval; mo, months; NC, not calculable.

8514 Rapid Oral Abstract Session

Phase 3 study of benmelstobart in combination with chemotherapy followed by sequential combination with anlotinib for the first-line treatment of locally advanced or metastatic squamous non-small cell lung cancer (sq-NSCLC). First Author: Yuankai Shi, National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences & Peking Union Medical College, Beijing Key Laboratory of Clinical Study on Anticancer Molecular Targeted Drugs, Beijing, China

Background: PD-1/ PD-L1 inhibitors plus platinum-based chemotherapy is the standard first-line therapy for locally advanced or metastatic sq-NSCLC. Improvements in clinical benefits of sq-NSCLC receiving antiangiogenic agents and immune-checkpoint inhibitors have remained elusive, highlighting an urgent need to develop new therapeutic strategies. TQB2450-III-12 is a multicenter, randomized, double-blind, parallel-controlled phase III study of benmelstobart (PD-L1 inhibitor) in combination with chemotherapy followed by sequential combination with anlotinib (multi-targeted angiogenesis inhibitor) versus tislelizumab plus chemotherapy as first-line therapy for locally advanced or metastatic sq-NSCLC. **Methods:** Patients with unresectable locally advanced or metastatic sq-NSCLC without prior systematic therapy were randomized 1:1 to receive benmelstobart (1200 mg, Q3W) plus chemotherapy for 4 cycles followed with benmelstobart plus anlotinib (10mg, P.O., D1-D14, Q3W) (group A) or tislelizumab (200mg, Q3W) plus chemotherapy for 4 cycles followed with tislelizumab (group B). Paclitaxel (175 mg/m^2, day 1) and carboplatin (area under the concentration [AUC] of 5, day 1) were given every 3 weeks. The primary endpoint was PFS per RECIST 1.1 by independent review committee and the key secondary endpoint was OS. Here we present the primary interim analysis for PFS per prespecified analysis plan. **Results:** As of March 1, 2024, 565 patients were randomized 1:1 to group A and group B. Baseline characteristics were well balanced. Median PFS was significantly improved in group A (10.12 months, 95% CI, 8.54–NE) versus group B (7.79 months, 95% CI, 6.87–9.69), HR=0.64 (98.35% CI, 0.45–0.93; P =0.0038). The subgroup analysis showed that PFS benefit favored group A in almost all subgroups, particularly in patients with ECOG PS 0 (HR 0.44, 0.23-0.84), PD-L1 expression (tumor proportion scoring) of 1-49% (HR 0.47, 0.30-0.73), and age <65 years (HR 0.59, 0.39-0.90). The ORR of group A and group B were 71.9% and 65.1%, respectively. The median DoR was longer in group A (9.69 months, 95% CI, 8.44, NE) than Group B (8.34 months; 95% CI, 5.78-NE) HR=0.58 (95% CI, 0.38, 0.88; P=0.0091). OS was immature. ≥Grade 3 benmelstobart/tislelizumab or anlotinib/ placebo-related adverse events was 61.57% in group A and 51.06% in group B. There was no difference of the grade 5 treatment-emergent adverse events (TEAE) between the treatment groups (group A: 5.69%, group B: 5.63%). The discontinuation of any treatment components by TEAE was 4.27% in group A and 5.28% in group B. **Conclusions:** Benmelstobart in combination with chemotherapy followed by sequential combination with anlotinib significantly improved PFS, with a manageable safety profile. It might be a new first-line treatment for sq-NSCLC. Clinical trial information: NCT05718167. Research Sponsor: Chia Tai Tianqing Pharmaceutical Group Co., Ltd.

8515 Rapid Oral Abstract Session

Plasma-guided adaptive first-line chemoimmunotherapy for non-small cell lung cancer (NSCLC). First Author: Julia K. Rotow, Lowe Center for Thoracic Oncology, Dana-Farber Cancer Institute, Boston, MA

Background: There is clinical uncertainty as to which patients with advanced/metastatic NSCLC require first-line treatment with chemoimmunotherapy (ChemoIO) versus treatment with immune checkpoint inhibitor (ICI) monotherapy. While PD-L1 expression can predict for ICI response, it is an imperfect biomarker. Cell-free DNA (cfDNA) clearance is a dynamic biomarker that predicts for benefit to immunotherapy in metastatic NSCLC. Here we evaluate the use of cfDNA clearance after initial cycles of first-line ICI monotherapy to guide early treatment intensification via addition of platinum-based chemotherapy. **Methods:** In this prospective clinical trial patients with advanced/metastatic PD-L1 positive (TPS ≥ 1%) NSCLC were treated with two cycles of pembrolizumab monotherapy and then assessed for plasma and radiographic response. Plasma response was defined as ≥50% reduction in the maximum variant allele fraction and/or persistent low-shedding status at cycle two day one compared to pretreatment using an amplicon-based plasma NGS assay. Patients with radiographic response or with radiographic stable disease with plasma response continued pembrolizumab monotherapy. Patients with RECIST stable disease without plasma response were intensified to carboplatin doublet (paclitaxel squamous/pemetrexed nonsquamous) plus pembrolizumab. Those with radiographic progression ended study treatment. **Results:** Forty patients were enrolled across six sites. 56.8% (n=21) had nonsquamous histology and 37.5% (n=15) were PD-L1 low (TPS 1-49%). 36 patients (90%) completed a C2D1 plasma response assessment, with plasma response to ICI monotherapy in 58.3% (n=21) patients (57.1% in PD-L1 low, 59.1% in PD-L1 high [TPS ≥ 50%]). At cycle 3, 52.8% (n = 19) continued pembrolizumab monotherapy (7 with PR, 12 with SD and plasma response). 19.4% (n=7) had radiographic SD and plasma non-response and received intensification to ChemoIO (pemetrexed in 6, paclitaxel in 1). 27.8% (n=10) went off study treatment for PD (n=4), death (n=1), adverse event (n=3), or patient/physician decision (n=2). 20% (n=3) of PD-L1 low patients and 16% (n=4) of PD-L1 high patients received treatment intensification to ChemoIO. The ORR to this adaptive treatment strategy was 50%, the median PFS was 11 months (95% CI 3.4-15.9 months), and the median OS was 14.9 months (95% CI 8.2-27.2 months). Median PFS was higher in patients with plasma response (16.4 vs 4.8 months; HR 0.34; 95% CI 0.12-0.92). Fewer patients were treated with platinum doublet chemotherapy than would have been predicted by PD-L1 status alone (17.5% vs 37.5%). **Conclusions:** The use of a cfDNA-guided adaptive treatment design resulted in a median progression-free survival which compared favorably to historical controls with less upfront exposure to platinum doublet chemotherapy. Further study within a randomized prospective trial design is needed to validate this treatment strategy. Clinical trial information: NCT04166487. Research Sponsor: Dunkin Donuts Breakthrough Grant; Dana-Farber Cancer Institute; ASCO CDA.

8516 Rapid Oral Abstract Session

Randomized trial of relevance of time-of-day of immunochemotherapy for progression-free and overall survival in patients with non-small cell lung cancer. First Author: Yongchang Zhang, Hunan Cancer Hospital/The Affiliated Cancer Hospital of Xiangya School of Medicine, Central South University, Changsha, China

Background: Recent retrospective studies across 10 cancer types suggest increased efficacy of Early rather than Late Time-of-Day (ToD) infusions of immune checkpoint inhibitors (ICIs). This first randomized controlled phase III trial aimed to determine the relevance of ToD of immunochemotherapy for efficacy in patients (pts) with non-small cell lung cancer (NSCLC). **Methods:** Eligible pts received ICI pembrolizumab or sintilimab combined with chemotherapy, as 1st line treatment for stage IIIC-IV NSCLC without driver mutation. Pts were randomly assigned in a 1:1 ratio to receive the initial four immunochemotherapy cycles either before 15:00 in the Early ToD group, or after 15:01 in the Late ToD group. We hypothesized an increase in median progression-free survival (PFS) from 6 months in the Late ToD group up to 10 months in the Early ToD group. A total of 210 pts was required to validate PFS differences, using a two-sided significance level (α, 0.05; β, 0.80). Secondary endpoints were overall survival (OS) and objective response rate (ORR). **Results:** From 09/2022 to 05/2024, 210 pts (median age, 61 y.o.; male sex, 90.5%; Stage IV, 80.5%) were randomized. The pts in each group had similar characteristics. After a median follow-up of 18.9 months (mo.), median PFS was 13.2 mo. [95% CI, 10.1-16.3] in the early ToD group and 6.5 mo. [5.9-7.1] in the late ToD group, with a hazard ratio (HR) of an earlier progression of 0.43 [0.31-0.60] ($P < 0.0001$). Median OS was not reached in the early ToD group, whereas it was 17.8 mo. [14.2-21.5] in the late ToD group (HR of an earlier death, 0.43 [0.27-0.69]; $P = 0.0003$). ORR was 75.2% [66.8%-83.6%] for early ToD and 56.2% [46.5%-56.8%] for Late ToD ($P = 0.007$). PFS, OS, and ORR were consistently improved in the early ToD group regardless of age, sex, performance status, tumor stage, histology, PD-L1 status, and ICI agent. **Conclusions:** In this randomized trial, all three efficacy endpoints of immunochemotherapy were significantly improved through Early vs Late ToD dosing in pts with previously untreated stage IIIC-IV NSCLC. The near doubling in PFS and OS in our trial support the need for further randomized trials to determine the relevance of ToD for ICI efficacy and their underlying circadian mechanisms in pts with various cancer types. Clinical trial information: NCT05549037. Research Sponsor: National Natural Science Foundation of China.

8517 Rapid Oral Abstract Session

Hypoxia-responsive CEA CAR-T cells therapy for relapsed or refractory non-small cell lung cancer: A single-arm, open-label, phase I trial. First Author: Shuang Wei, Department of Respiratory and Critical Care Medicine, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China

Background: Non-small cell lung cancer (NSCLC) is a leading cause of cancer-related mortality worldwide. Chimeric antigen receptor (CAR)-T cell therapy has achieved significant success in targeted tumor cells eradication. However, data on CAR-T therapies in NSCLC remain limited. This study evaluates the safety and efficacy of CEA CAR-T cell therapy in r/r NSCLC. **Methods:** Adult metastatic NSCLC patients with relapse after ≥2 lines of treatment were enrolled and administered intravenous CEA CAR-T cells at three dose levels (0.75×10^6, 1.5×10^6, and 3×10^6 CEA CAR-T cells/kg).Peripheral blood samples were collected on day 28 post-infusion and analyzed using 10x Genomics single-cell RNA sequencing (scRNA-seq).The primary endpoint was safety , and secondary endpoints including efficacy and pharmacological evaluation. **Results:** From August 1, 2023, to July 15, 2024, a total of 18 patients were screened, and 15 received CAR-T infusion. The median age was 60 years , with a median of 4 prior therapy lines (range 2-10 lines). Among 6 patients receiving the maximum dose (3×10^6 cells/kg), no dose-limiting toxicities, grade 4 cytokine release syndrome or ICANS were observed. No adverse events were observed during a three-month long-term safety evaluation. With a median follow-up of 5.7 months, 7 patients achieved PR, 6 had SD, and 2 experienced PD. The best DCR was 87%, and ORR was 47%. Notably, patients with ≥30% intense and complete CEA staining in tumor cells and no brain metastases showed better PFS (72.7% vs. 25.0%, p=0.03) and OS (90.9% vs. 0%, p=0.003). CEA CAR-T cells reached maximum concentration at a median of 10 days (range 7–60 days) post-infusion. At the third month, all 12/12 patients with available CAR-T cell copy number data maintained high levels of CAR-T cells, with a median of 8,236 gDNA copies/μg , and in the patient with a follow-up of 13 months, CEA CAR-T cells were still detectable at 50,760 gDNA copies/μg. The scRNA-seq was performed in 12 patients. Responders exhibited a higher percentage of NK cells in a less exhausted state, characterized by reduced activity of immunosuppressive pathways and lower expression of stress-associated genes. Further cell-cell communication analysis suggested HLA-DRB1 expression in NK cells might be influenced by interactions with the CD244 in $CD8^+$ T cells. **Conclusions:** A single infusion of hypoxia-responsive CEA CAR-T demonstrated promising efficacy and manageable safety in r/r NSCLC. The findings highlight the potential role of specific NK cell states and immune interactions in the therapeutic effects of CEA CAR-T therapy. Research Sponsor: the National High Technology Research and Development Program of China; 2021YFA1101500; the National Natural Science Foundation of China; 81873427 and 82070217; National Natural Science Foundation of China; 82473220, 81772477; Fundamental Research Program of Shanxi Province; 202303021221192; 2023 COVID-19 Research Project of Shanxi Provincial Health Commission; 2023XG005; Four"batches"innovation project of invigorating medical through science and technology of shanxi province; 2023XM003; Research and Innovation Team Project for Scientific Breakthroughs at Shanxi Bethune Hospital in Shangxi Province; 2024OAXIANG01.

Clinical response at different doses.

	All dose level (n=15)	Dose level 1 (n=3)	Dose level 2 (n=6)	Dose level 3 (n=6)
Disease control	13 (87%)	2 (66%)	6 (100%)	5 (84%)
Overall response	7 (47%)	1 (33%)	4 (67%)	2 (33%)
Partial response	7 (47%)	1 (33%)	4 (67%)	2 (33%)
Disease stable	6 (40%)	1 (33%)	2 (33%)	3 (50%)

Data are n (%).

8518 Rapid Oral Abstract Session

S1900E: A phase II study examining impact of co-mutations on sotorasib for previously treated stage IV/recurrent *KRAS* G12C mutated (MUT) non-squamous (Non-sq) non-small cell lung cancer (NSCLC) (ECOG-ACRIN led Lung-MAP Sub-study). First Author: Sukhmani Kaur Padda, Fox Chase Cancer Center/Temple Health, Philadelphia, PA

Background: In previously treated *KRAS* G12C MUT NSCLC, the allosteric KRAS G12C inhibitor sotorasib had superior outcomes compared to docetaxel (ORR 28% vs 13%). S1900E was the first to prospectively test sotorasib in *KRAS* G12C MUT NSCLC according to co-mutations (CO-MUT) in tumor suppressor genes such as *TP53*, *STK11*, and *KEAP1*. We report on the results of *TP53* and *STK11* CO-MUT cohorts of S1900E and hypothesized that CO-MUT would not impact the efficacy of sotorasib. **Methods:** Pts with *KRAS* G12C MUT identified by FoundationOne CDx tissue assay in the LUNGMAP screening master protocol were assigned to S1900E. Pts with stage IV/recurrent non-sq NSCLC who had progressed after ≥1 line of systemic therapy, and were ECOG PS 0-1 were eligible. There were 3 biomarker cohorts: 1 (*TP53* CO-MUT & wild type [WT] *STK11*, *KEAP1/NFE2L2/CUL3)*; 2 (*STK11* CO-MUT & WT *TP53*, *KEAP1/NFE2L2/CUL3)*; 3 (all others). The primary objective was to evaluate the confirmed objective response rate (ORR) per RECIST 1.1 in each cohort. Accrual goals for Cohorts 1 and 2 were 40 and 25 evaluable pts, respectively, based on a 1-stage binomial design with 90% power to rule out a 14% ORR (historical second-line docetaxel ORR) at the 1-sided 5% level. **Results:** S1900E completed accrual with 118 total pts and 103 evaluable from Apr 2021-Dec 2024; 59 (57%) were female and 86 (84%) were non-Hispanic white. In the *TP53* CO-MUT (N=48; 40 evaluable) and *STK11* CO-MUT (N=28; 25 evaluable) cohorts, respectively, 48% and 68% received only one prior line of therapy, 70% and 76% received both platinum chemotherapy and PD-(L)1 immunotherapy, 68% and 24% were female, known PD-L1 expression (≥1% / ≥50%) was 95%/45% and 43%/0%, and almost all had smoked. In the *TP53* CO-MUT cohort, confirmed ORR was 35% (CI 23-47). In the *STK11* CO-MUT cohort, confirmed ORR was 16% (CI 4-28). Disease control rate (DCR), duration of response (DOR), investigator progression-free survival (PFS), and overall survival (OS) (Table 1) had numerically higher values in the *TP53* CO-MUT cohort. Adverse event rates ≥ Grade 3 were similar to prior reports of single agent sotorasib. **Conclusions:** *TP53* CO-MUT cohort met its primary endpoint, while the *STK11* CO-MUT cohort did not, suggesting that *STK11* CO-MUT have detrimental effect on sotorasib in *KRAS* G12C NSCLC. S1900E Cohort 3, which may include *KEAP1/NFE2L2* and other CO-MUT, will be reported later, as will resistance patterns identified through ctDNA analysis. Clinical trial information: NCT04625647. Research Sponsor: NIH/NCI/NCTN grants U10CA180888, U10CA180819.

	TP53 CO-MUT (N=40)	*STK11* CO-MUT (N=25)
ORR (90% CI)	**35%** (23-47)	**16%** (4-28)
DCR (90% CI)	**78%** (67-88)	**60%** (44-76)
Follow-Up Median mo	19.5	16.8
DOR [Median mo (95% CI)]	**7.1** (2.7-11.5)	**6.2** (1.6-NA)
PFS [Median mo (95% CI)]	**5.7** (3.0-8.4)	**4.1** (2.6-7.1)
OS [Median mo (95% CI)]	**18.2** (12.2-33.7)	**8.0** (5.1-14.2)

8519 Rapid Oral Abstract Session

Safety and efficacy of olomorasib + immunotherapy in first-line treatment of patients with *KRAS* G12C-mutant advanced NSCLC: Update from the LOXO-RAS-20001 trial. First Author: Konstantin H. Dragnev, Dartmouth Cancer Center, Lebanon, NH

Background: Olomorasib, a potent, highly selective second-generation KRAS G12C inhibitor has demonstrated promising activity and a favorable safety profile in *KRAS* G12C-mutant NSCLC when combined with pembrolizumab. Here, we report updated results from LOXO-RAS-20001, a phase 1/2 trial (NCT04956640) of olomorasib, in patients (pts) with *KRAS* G12C-mutant NSCLC receiving olomorasib + pembrolizumab, and focus on pts receiving the combination as first-line (1L) therapy. **Methods:** Pts with advanced *KRAS* G12C-mutant NSCLC (tissue or plasma) in the 1L metastatic setting were eligible. Any PD-L1 level (0-100%) was permitted. Two dose levels of olomorasib (50 and 100 mg, orally twice daily) + pembrolizumab were evaluated. Adverse events (AE) were assessed across all treated pts; objective response rate (ORR) per RECIST v1.1 was assessed in pts with at least one post-baseline response assessment or who discontinued treatment before the first response assessment. **Results:** As of 13 November 2024, a total of 43 pts received olomorasib + pembrolizumab (50 mg, n=21; 100 mg, n=22) in the 1L setting with a median age of 70 years (range, 58-83); 10 (23%) were PD-L1 negative, 13 (30%) were PD-L1 1-49%, 19 (44%) were PD-L1 ≥50% and 1 (2%) was unknown. Median duration of follow-up was 5.5 months (range, 0.1-24.4). All grade TRAEs in ≥10% of pts (olomorasib- and/or pembrolizumab-related) were ALT/AST increased (33%/30%), diarrhea (28%), fatigue (16%), nausea (14%), pruritus (12%) and decreased appetite (12%); grade 3 TRAEs in ≥10% of pts were ALT/AST increased (26%/16%). Hepatic events were overall manageable with dose adjustments and/or corticosteroids. No pts had co-occurring total bilirubin increased or discontinued both study treatments due to hepatic events. Pneumonitis was reported in 2 pts (grades 2 and 4). The AE profile was generally comparable across doses. TRAEs led to olomorasib dose reduction in 16% of pts and discontinuation of combination treatment in 5% (2) pts. At time of data-cut, 33 pts remain on treatment and 10 discontinued. Among the 40 efficacy-evaluable 1L pts, at a median follow-up of 9 months (95% CI, 6-12), ORR was 70% (28/40; 95% CI, 54-83; 1 CR, 23 PR, 4 unconfirmed PR pending/ongoing) across all PD-L1 expression levels and disease control rate (DCR) was 90% (36/40; 95% CI, 76-97). In pts with PD-L1 ≥50%, ORR was 82% (14/17; 95% CI, 57-96) and DCR was 94% (16/17; 95% CI, 71-99). Median duration of response was not reached and progression free survival rate at 6 months was 80%. **Conclusions:** Olomorasib + pembrolizumab in the 1L metastatic setting demonstrated favorable safety and encouraging antitumor activity in pts with *KRAS* G12C-mutant advanced NSCLC across all PD-L1 expression levels. A global, registrational study investigating this combination in 1L NSCLC is currently enrolling (SUNRAY-01, NCT06119581). Clinical trial information: NCT04956640. Research Sponsor: Eli Lilly and Company.

8520 Rapid Oral Abstract Session

Sosimerasib monotherapy in patients with previously treated KRAS G12C–mutated non-small cell lung cancer: Primary results of a phase 2 study. First Author: Jia Zhong, Cancer Hospital, Chinese Academy of Medical Sciences, Beijing, China

Background: KRAS G12C mutation is a poor prognostic factor for Non-Small Cell Lung Cancer (NSCLC). Sosimerasib is a novel potent and highly selective KRAS G12C inhibitor. Here we report the primary results from a Phase 2 study of sosimerasib in patients with advanced NSCLC harboring the KRAS G12C mutation. **Methods:** In this open-label, multicenter, single-arm, pivotal phase 2 study, patients with locally advanced/metastatic KRAS G12C mutated NSCLC after failure with platinum-based chemotherapy and/or anti-PD-1/PD-L1 inhibitors were enrolled and treated with sosimerasib 500mg orally once daily. The primary endpoint was objective response rate (ORR) assessed by independent review committee (IRC) per RECIST v1.1. The secondary endpoints included duration of response (DOR), disease control rate (DCR), time to response (TTR), progression-free survival (PFS), overall survival (OS) and safety. **Results:** A total of 145 patients were enrolled. The median age was 63 years, 85.5% were male, and previous treatment lines ranged from 1 to 3, with 84.1% patients having received both platinum-based chemotherapy and anti-PD-1/PD-L1 inhibitors. By 3 November 2024, the median follow-up duration was 6.8 months (range: 0.4-10.9). IRC-confirmed ORR was 52.4% (95% CI: 44.0-60.8) with median TTR of 1.4 months (range: 1.2-8.4), DCR was 87.6% (95% CI: 81.1-92.5). Median PFS was 7.2 months (95% CI: 5.6-NA). Median DOR and median OS were not reached. At the data cutoff date, Treatment-related adverse events (TRAEs) were reported in 138 (95.2%) patients, grade 3-4 TRAEs occurred in 58 (40.0%) patients. No TRAE was fatal. Most common TRAEs were alanine aminotransferase increased (66.2%), aspartate aminotransferase increased (62.8%), anaemia (31.7%), gamma-glutamyl transferase increased (26.2%) and blood alkaline phosphatase increased (22.1%). TRAEs leading to drug interruption, dose reduction, and permanent discontinuation occurred in 35 (24.1%), 15 (10.3%), and 3 (2.1%) patients, respectively. **Conclusions:** Sosimerasib monotherapy has shown promising anti-tumor activity with manageable safety profile in locally advanced/metastatic NSCLC patients harboring KRAS G12C mutation. This study is still ongoing and longer follow-up will provide more solid evidence. Clinical trial information: ChiCTR2200059986. Research Sponsor: None.

8521 Poster Session

First-line (1L) datopotamab deruxtecan (Dato-DXd) + rilvegostomig in advanced or metastatic non-small cell lung cancer (a/mNSCLC): Results from TROPION-Lung04 (cohort 5). First Author: Saiama Naheed Waqar, Washington University School of Medicine in St. Louis, St. Louis, MO

Background: 1L anti–PD-(L)1 antibodies ± chemotherapy are standard of care for patients (pts) with a/mNSCLC without actionable genomic alterations (AGAs). However, not all pts experience response to treatment. Dato-DXd, a TROP2-directed antibody-drug conjugate, has shown efficacy in pts with a/mNSCLC alone or combined with PD-(L)1 inhibitors. Rilvegostomig, a bispecific antibody targeting PD-1 and TIGIT, has also shown preliminary efficacy in pts with a/mNSCLC. Consequently, the combination of Dato-DXd and rilvegostomig may have the potential to enhance responses. **Methods:** TROPION-Lung04 (NCT04612751) is a phase 1b, open-label, dose-escalation and expansion study enrolling pts with a/mNSCLC without AGAs. In cohort 5 (C5; C5a, PD-L1 tumor proportion score [TPS] ≥50% and C5b, PD-L1 TPS <50%) treatment-naïve pts received Dato-DXd (6 mg/kg) + rilvegostomig IV Q3W. Pts were treated until disease progression or unacceptable toxicity. The primary endpoint was safety. Secondary endpoints included objective response rate (ORR), duration of response (DoR) and progression-free survival (PFS) per investigator (RECIST v1.1). **Results:** At data cut-off (DCO; 24 Oct, 2024), 40 pts had received Dato-DXd + rilvegostomig (C5a, n=20; C5b, n=20); 29 (72.5%) had non-squamous histology. Median treatment duration was 5.1 months (range 0.7–18.6); 21 pts discontinued Dato-DXd (adverse events [AEs], n=9; progressive disease [PD], n=9), 20 discontinued rilvegostomig (AEs, n=8; PD, n=9) and 20 (50.0%) pts were still on any study treatment at DCO. All pts (N=40, 100%) had treatment-emergent adverse events (TEAEs); 60.0% (n=24) had grade ≥3 TEAEs and 50.0% (n=20) had serious TEAEs. The most common TEAEs were stomatitis (52.5%; grade 3, 2.5% [n=1]), fatigue (grouped term, 50.0%, all grade 1/2), alopecia (45.0%, all grade 1/2) and nausea (42.5%, all grade 1/2). Ocular surface events occurred in 12 pts (30.0%); grade 4, n=1. Adjudicated drug-related interstitial lung disease/pneumonitis was reported in 5 pts (grade 3, n=2). There were six fatal TEAEs (respiratory failure, general physical health deterioration, death, intestinal perforation, sepsis, cardiac arrest); however, none were related to either study treatment. Confirmed ORR for all pts was 57.5% (95% CI 40.9, 73.0); disease control rate was 95.0% (95% CI 83.1, 99.4). Responses were observed across both squamous (45.5%; 95% CI 16.7, 76.6) and non-squamous histologies (62.1%; 95% CI 42.3, 79.3) and all PD-L1 levels. DoR and PFS were immature at DCO. **Conclusions:** The safety profile for the combination of Dato-DXd + rilvegostomig was consistent with the expected toxicities of each agent and without new safety findings. Dato-DXd + rilvegostomig had encouraging activity as 1L treatment for pts with a/mNSCLC without AGAs, with responses seen in both histologies and across all PD-L1 levels. Clinical trial information: NCT04612751. Research Sponsor: This trial is sponsored by AstraZeneca. In July 2020, Daiichi-Sankyo entered into a global development and commercialization collaboration with AstraZeneca for datopotamab deruxtecan (Dato-DXd).

8522 Poster Session

Exploratory ctDNA analyses for the EVOKE-1 study in metastatic non-small cell lung cancer (mNSCLC). First Author: Enriqueta Felip, Vall d'Hebron University Hospital and Vall d'Hebron Institute of Oncology, Barcelona, Spain

Background: In NSCLC, ctDNA analysis complements assessment of clinical efficacy and identifies molecular alterations that may be prognostic or predictive of treatment. EVOKE-1 compared sacituzumab govitecan (SG) vs docetaxel in mNSCLC that had progressed on platinum-based and anti–PD-(L)1 therapy. Although statistical significance was not met, SG showed numerical improvement in overall survival (OS) vs docetaxel. Here, we assessed the value of ctDNA as a biomarker in available samples from EVOKE-01. **Methods:** The biomarker evaluable population (BEP) comprised 497 patients (pts), representing 82% of the ITT population. Cell-free DNA was extracted from blood collected at baseline and cycle 2 day 1 (C2D1). Samples were analyzed using the Guardant Infinity assay, a tumor-agnostic platform that measures ctDNA levels and gene variants from a comprehensive gene panel. **Results:** ctDNA was detected at baseline in 449 pts (90.3% of BEP), and higher ctDNA was a negative prognostic for OS, regardless of treatment. mOS was 12.7 vs 10.0 mos (HR 1.58, 95% CI: 1.11–2.26) for < vs ≥ median ctDNA level with SG and 10.8 vs 7.2 mos (HR 1.78, 95% CI: 1.28–2.46) with docetaxel. ctDNA was undetectable in 48 pts who had a longer survival (mOS NR in either arm) than those with detected ctDNA. At C2D1, median ctDNA reduction was 59% and 75% with SG and docetaxel (*P*=.33); ≥50% reduction was achieved in 103 (44%) vs 121 pts (51%), respectively. Changes in ctDNA levels at C2D1 were prognostic, with pts achieving ≥50% reduction having a longer OS than those with <50% reduction of ctDNA. Actionable genomic alterations identified included *KRAS*, *EGFR*, *ALK*, *ROS*, *ERBB2*, *MET*, and *NTRK* alterations. As expected from the required local/central testing for mutations at study entry, only a small number of pts with *EGFR/ALK* alterations were identified. *KRAS* mutations had a negative prognostic effect, whereas the group of pts with *EGFR/ALK/ROS* alterations was too small for conclusive results. Analysis of mutations (*TP53*, *KEAP1*, *STK11*) potentially contributing to anti–PD-(L)1 resistance showed that between SG and docetaxel, 167 (68%) and 171 pts (68%) had *TP53* mutations and 184 (75%) and 194 pts (77%) had ≥1 of these 3 mutations. The frequency of these mutations was similar across pts with PD/SD and those with CR/PR as best response to last prior PD-(L)1 therapy. Harboring *TP53* mutations was a negative prognostic factor in both arms: mOS was 11.3 mos vs NA (HR 1.67, 95% CI: 1.11–2.54) with *TP53* mutation vs wildtype with SG and 9.2 vs 13.9 mos (HR 1.71, 95% CI: 1.18–2.47), respectively, with docetaxel. *KEAP1/STK11* mutations were also negative prognostic markers. **Conclusions:** This analysis did not identify differences in ctDNA clearance with SG vs docetaxel. Regardless of treatment and in line with previous reports, high ctDNA was a negative prognostic marker for OS in mNSCLC. Furthermore, alterations of *KRAS*, *TP53*, and *KEAP1/STK11* represent negative prognostic factors. Clinical trial information: NCT05089734. Research Sponsor: Gilead Sciences, Inc.

8523 Poster Session

Whole-genome and transcriptome landscape of actionable driver-negative lung adenocarcinoma. First Author: Masahiro Torasawa, Department of Respiratory Medicine, Juntendo University Faculty of Medicine and Graduate School of Medicine, Tokyo, Japan

Background: Driver-negative lung adenocarcinoma (DN-LUAD) without actionable genomic alterations (AGAs) has a poor prognosis. A deeper understanding of its molecular background, particularly across the entire genome, is crucial for improving risk assessment and therapeutic development. **Methods:** We performed deep whole-genome sequencing (WGS; tumor depth: 100–120x, normal depth: 30x, paired-end reads: 150 bp) and RNA sequencing using fresh-frozen tissues from four institutions. DN-LUAD was defined as LUAD without known actionable mutations or gene fusions. We analyzed somatic mutations, copy number alterations (CNAs), and structural variations (SVs). Tumors were classified as whole-genome doubling (WGD) if more than half of the autosomal tumor genome showed at least two copies in the major copy numbers of somatic cells. HRDetect score ≥0.7 was used to determine the presence of homologous recombination DNA repair deficiency (HRD) (Davies H, et al. Nat Med. 2017). Gene Set Enrichment Analysis (GSEA) was used for pathway analysis. **Results:** Among the 745 patients (pts), 517 were classified as having DN-LUAD. WGS identified AGAs undetected by whole-exome sequencing (WES) in 33 (4.4%) pts (*EGFR* 13, *KRAS* 7, *BRAF* 5, *ERBB2* 4, *MET* 4, and *HRAS* 1). The frequently observed genomic alterations in DN-LUAD are shown in the Table. WGD was observed in 62.1% (n = 321) of DN-LUADs and was significantly associated with higher TMB, CNA, and SV burden. Tumor suppressor gene (TSG) mutations in *TP53*, *STK11*, and *KEAP1*, as well as *CDKN2A* copy number loss and SVs, were significantly more frequent in WGD pts. HRD was identified in 19 DN-LUAD pts (3.7%), with a significantly higher frequency in the WGD group (WGD vs. without WGD; 4.98% vs. 1.5%, p = 0.016). GSEA showed significant (q < 0.0001) upregulation of cell cycle pathways (E2F targets, G2M checkpoint, and MYC targets) and downregulation of immune pathways (allograft rejection and interferon-gamma response) in DN-LUADs with WGD. **Conclusions:** This largest-ever WGS study identified AGAs undetectable by WES and uncovered a subgroup of DN-LUAD characterized by increased genomic instability driven by multiple TSG alterations associated with WGD, which was also more likely to exhibit HRD. WGD was associated with the upregulation of cell cycle pathways and the downregulation of immune pathways. These findings highlight the critical role of WGS in elucidating the pathogenesis of DN-LUAD. Research Sponsor: None.

	All N = 517	WGD n = 321	Without WGD n = 196	*p*
Median TMB (Mutations/Mb)	6.6	10.2	3.0	<0.0001
Median No. of CNAs	101	117	77	<0.0001
Median No. of SVs	185	244	103	<0.0001
TP53	381 (74)	277 (86)	104 (53)	<0.0001
SMARCA4	59 (11)	43 (13)	16 (8)	0.094
STK11	56 (11)	42 (13)	14 (7)	0.049
CDKN2A	44 (9)	33 (10)	11 (6)	0.092
KEAP1	40 (8)	34 (11)	6 (3)	0.003
***CDKN2A* loss**	106 (21)	78 (24)	28 (14)	0.009
***MET* amplification**	44 (9)	34 (11)	10 (5)	0.045
CDKN2A	135 (26)	95 (30)	40 (20)	0.028
FHIT	125 (24)	99 (31)	26 (13)	<0.0001

8524 Poster Session

Potential biomarker of PD-L1 expression phenotypes in tumor and immune cells for combined PD-1 and CTLA-4 blockade therapies in advanced NSCLC. First Author: Jun Miyakoshi, Department of Thoracic Oncology, National Cancer Center Hospital, Tokyo, Japan

Background: Pembrolizumab-based chemo-immunotherapies (Pembro) and nivolumab plus ipilimumab-based immunotherapies with or without 2 cycles of chemotherapies (Nivo+Ipi) have improved survival in patients with advanced NSCLC compared to the conventional chemotherapy. However, biomarkers to support appropriate choice in these immunotherapies remain unclear. **Methods:** From 2019 to 2023, this multicenter, observational study retrospectively reviewed advanced NSCLC patients who received first-line Pembro or Nivo+Ipi and had evaluable PD-L1 expression status on tumor cells (tumor proportion score [TPS], 22C3) and immune cells (immune cell [IC] score, SP142). Survival curve comparisons between treatments were conducted using restricted mean survival time (RMST) estimation in place of Log-rank test, when the proportional hazard assumption was not met. Additionally, the genomic and expression profiles associated with TPS and IC score were assessed using whole-exome sequencing and RNA sequencing in available NSCLC samples. **Results:** A total of 198 patients were included (Pembro/Nivo+Ipi: 137/61). In the Pembro cohort, patients with high TPS (≥ 50%) had significantly longer progression-free survival (PFS) than those with low TPS (< 50%) (median PFS [mPFS, months]: 8.1 vs. 7.1, *P* = 0.02; hazard ratio [HR] = 0.59 [0.38–0.92]), while no significant difference in PFS was observed based on IC score (high vs. low: mPFS 7.4 vs. 6.8, *P* = 0.11, HR = 0.72 [0.49–1.07]). In the Nivo+Ipi cohort, PFS did not significantly differ by TPS (high vs. low: mPFS 4.0 vs. 4.0, *P* = 0.26; HR = 0.51 [0.16–1.68]), whereas patients with high IC score (≥ 1) had significantly longer PFS than those with low IC score (= 0) (mPFS: 7.7 vs. 2.8, *P* = 0.04; HR = 0.53 [0.28–0.98]). A durable PFS benefit of Nivo+Ipi over Pembro was observed only in patients with low TPS/high IC score (mPFS: 12.4 vs. 6.6; Schoenfeld individual test: $P < 0.05$; $RMST_{Nivo+Ipi}/RMST_{Pembro}$ [2 years] = 1.5, *P* = 0.049, Table). Sequence analyses revealed that tumors with low TPS/high IC score had significantly higher tumor mutational burden (TMB) than other tumors (median TMB: 18.2 vs. 1.9 [/mb]; $P < 0.001$) and showed distinct enrichment in antigen presentation and T-cell receptor signaling pathways. **Conclusions:** Nivolumab plus ipilimumab-based immunotherapies demonstrated superior durable response compared to pembrolizumab-based chemo-immunotherapies in patients with low TPS/high IC score. PD-L1 phenotypes based on TPS and IC score could guide the optimal selection of immunotherapies for advanced NSCLC patients. Research Sponsor: None.

Efficacy comparison in patients with low TPS (< 50%)/high IC score (≥ 1).

Treatments	mPFS (months)	PFS rate at 2 years	RMST at 2 years	$RMST_{Nivo+Ipi}/RMST_{Pembro}$ at 2 years	P value
Pembrolizumab-based chemo-immunotherapies	6.6	6%	8.5	1.5 [1.0–2.3]	0.049
Nivolumab plus ipilimumab-based immunotherapies	12.4	41%	12.9		

8525 Poster Session

Effects of immediate elevation of inflammatory cytokines after platinum, pemetrexed, and pembrolizumab on antitumor efficacy in advanced non-squamous, non-small cell lung cancer. First Author: Yuichi Ozawa, Department of Respiratory Meidcine/ Medical Oncology, Hamamatsu Medical Center, Hamamatsu-Shi, Japan

Background: Inflammatory cytokines play a crucial role in the tumor microenvironment and may serve as potential biomarkers for the sustained efficacy of PD-1/L1 inhibitors combined with chemotherapy. Numerous studies have been conducted on cytokines to date; however, studies on cytokine fluctuations immediately after administration remain notably limited. **Methods:** A prospective observational study at Wakayama Medical University enrolled 110 patients with thoracic malignancies receiving PD-1/L1 inhibitors as first line therapy from Oct 2019 to Nov 2023. We analyzed 41 patients with advanced or recurrent non-squamous, non-small cell lung cancer treated with platinum, pemetrexed, and pembrolizumab (CPP). Peripheral blood samples were collected at baseline, day 3($\pm$1), day 7($\pm$1), and day 42. 40 serum proteins were quantified using a Luminex 200 analyzer and a Milliplex MAP system. The association between cytokine increase and progression-free survival (PFS) was statistically analyzed. **Results:** Patient characteristics were as follows: median age (range), 71 (46-84) years; male/female, 33/8; adenocarcinoma/other, 36/5; performance status (PS) 0/1, 8/33; stage IV/recurrence, 31/10; cisplatin/carboplatin, 16/25; PD-L1 tumor proportional score (TPS) $<$1/1-49/$\geq$50, 14/12/15. The dose of dexamethasone at the first treatment was 6.6 mg (3.3-9.9 mg). Among the 40 measured cytokines, 10 showed an average increase of $\geq$50% from baseline to Day 3, of which 7 were inflammatory or immune-stimulatory (IL-1α, G-CSF, CXCL10, CXCL13, IL-6, IL-15, MCP-1). Five of them decreased by Day 7. Eight cytokines showed an increase of $\geq$50% from baseline to Day 7, of which 4 were inflammatory, and all of them were among those $\geq$50% elevated at Day 3 (IL-1α, G-CSF, IL-6, MCP-1). A univariate Cox proportional hazard analysis revealed that an increase in IL-6 or MCP-1 at day 3 (Day 3/0 ratio $>$1) was significantly associated with longer PFS [IL-6: HR 0.41 (95%CI 0.17-0.97), p=0.049; MCP-1: HR 0.43 (95% CI 0.19-0.97), p=0.042]. After adjustment for age, PS, and PD-L1 TPS in the multivariate analysis, MCP-1 remained a significant predictive factor (HR 0.36, 95% CI 0.13-0.97, p=0.043). PFS curves were significantly different between MCP-1 increased and decreased cases (median PFS 463 vs. 201 days, p=0.036), with 12-month PFS rates of 60% and 31%, and 25-month PFS rates of 50% and 8%, respectively. **Conclusions:** This study demonstrated that inflammatory cytokines increased immediately after CPP, despite the concomitant use of dexamethasone for antiemesis. Furthermore, the immediate increase in MCP-1 after treatment was associated with prolonged PFS, suggesting its potential as a predictor of treatment efficacy and providing insights into the mechanisms of chemo-immunotherapy. Research Sponsor: Japan Society for the Promotion of Science: JSPS; JP21K07247.

8526 Poster Session

Characterization of histology-dependent immunobiological differences in metastatic NSCLC: Implications for treatment with PD-1 and LAG-3 inhibitors. First Author: Hossein Borghaei, Fox Chase Cancer Center/Temple Health, Philadelphia, PA

Background: The treatment paradigm for metastatic non-small cell lung cancer (mNSCLC) without actionable genomic alterations does not differentiate between histologic subtypes for the use of checkpoint inhibitors. However, there is growing recognition of differences between squamous (SQ) and non-squamous (NSQ) lung cancer that may impact response to treatment. For example, in the RELATIVITY-104 study, addition of the LAG-3 inhibitor relatlimab to anti-PD-1 + platinum-doublet chemotherapy (PDCT) showed improved clinical benefit among patients with PD-L1 $\geq$1%, which was further enriched with NSQ histology. There is an unmet need to understand differences in tumor biology between NSQ and SQ histologies in patients with mNSCLC to inform on mechanisms underlying differences in clinical activity of anti-PD-1 + PDCT, alone or in combination with a LAG-3 inhibitor. **Methods:** Data were obtained from molecular profiling of baseline tumor samples of treatment-naive patients enrolled in the phase 3 CheckMate 227 (NCT02477826) study. PD-L1 (N=1739) and LAG-3 expression (N=540) were evaluated using immunohistochemistry. Somatic mutations and copy number alterations were assessed using the FoundationOne panel (N=1368). Gene expression, analyzed through RNA sequencing (N=465), was used to characterize differences in tumor immunobiology, including differential gene expression, pathway enrichment, and calculation of cell type-specific scores representing different immune and stromal cell types. **Results:** Transcriptional and mutational analyses revealed clear differences between NSQ and SQ tumors. NSQ tumors showed enrichment of immune pathways (e.g., antigen presentation and T cells), while SQ tumors exhibited enrichment of pathways consistent with rapid cell growth and numerous oncogenic alterations (e.g., p53 and PIK3CA). Differences in the relationship between tumor PD-L1 expression and the tumor microenvironment by histology were observed; PD-L1 expression was positively correlated with immune infiltration scores in NSQ but not SQ tumors, suggesting that drivers of PD-L1 expression may differ by histology. Consistent with previously published reports for mNSCLC, PD-L1 expression enriched for 1L anti-PD-1 + PDCT benefit in NSQ but not SQ tumors (CheckMate 227 Part 2). Differences in LAG-3 ligand expression by histology and PD-L1 expression were noted. Both canonical LAG-3 ligands, MHC-II and FGL-1, were expressed at higher levels in NSQ tumors. Within NSQ tumors, relative expression of each ligand varied by PD-L1 expression, with high MHC-II expression specifically in NSQ, PD-L1 $\geq$1% tumors. **Conclusions:** These data provide a supporting mechanistic rationale for the use of tumor histology in addition to PD-L1 expression to identify patients who would benefit from the addition of a LAG-3 inhibitor to PD-1 inhibitor + PDCT. Clinical trial information: NCT02477826. Research Sponsor: Bristol Myers Squibb.

8527 Poster Session

Unraveling relatlimab (RELA)-specific biology: Biomarker analyses in patients (pts) with metastatic non-small cell lung cancer (mNSCLC) treated with 1L nivolumab (NIVO) + RELA high-dose (HD) and platinum-doublet chemotherapy (PDCT). First Author: Martin Reck, Thoracic Oncology Department, LungenClinic Grosshansdorf, Grosshansdorf, Germany

Background: The addition of RELA HD, a lymphocyte activation gene-3 (LAG-3) inhibitor, to NIVO + PDCT has improved clinical benefits vs NIVO + PDCT for pts with PD-L1 expression $\geq$1% and NSQ histology in RELATIVITY-104 study. We report exploratory biomarker analyses from this study to elucidate mechanisms underlying NIVO + RELA HD + PDCT activity. **Methods:** Baseline and on-treatment blood samples were analyzed by flow cytometry for pharmacodynamic (PD) changes in immune cell populations including proliferating LAG-3-expressing CD4+ and CD8+ effector memory (EM) and central memory (CM) T cells. Baseline tumor samples were analyzed by monoplex immunohistochemistry (IHC) for tumor cell PD-L1, LAG-3, and CD8 expression. Associations between biomarkers and overall response rate (ORR) and progression free survival (PFS) were assessed. **Results:** NIVO + RELA HD + PDCT significantly modulated levels of proliferating LAG-3 expressing EM and CM T cells in the periphery on-treatment; no such PD change was observed with NIVO + PDCT. Among pts with NSQ histology, baseline tumor LAG-3 expression $\geq$1% showed improved ORR and median PFS in both treatment arms compared with LAG-3 $<$1%. Further, the benefit of RELA HD addition to NIVO + PDCT was also seen in patients with LAG-3 $<$1%, suggesting that baseline LAG-3 expression at 1%, unlike PD-L1 expression, would not help identify patients who can benefit from LAG-3 inhibition (Table). In contrast to NSQ, the same association trend of PD-L1 and LAG-3 expression with efficacy was not observed in pts with SQ histology, which could be partly attributable to the limited sample size in some SQ subgroups. Interestingly, PD-L1 $\geq$1% is more strongly correlated with CD8 T cells in NSQ as compared to SQ. **Conclusions:** These data represent the first in-depth biomarker analyses from a randomized phase 2 study to reveal that RELA can expand proliferating LAG-3 expressing T cells in NSCLC. NIVO + RELA HD + PDCT activity might be particularly robust in pts with NSQ histology and PD-L1 expression $\geq$1%, where CD8 T cells are enriched. The ongoing phase 3 RELATIVITY-1093 study is evaluating 1L NIVO + RELA HD + PDCT vs standard-of-care pembrolizumab + PDCT in mNSCLC. Clinical trial information: NCT04623775. Research Sponsor: Bristol Myers Squibb.

Efficacy of NIVO + RELA HD + PDCT vs NIVO + PDCT in pts with NSCLC by baseline histology, PD-L1 and LAG-3 expression.

NIVO + RELA HD + PDCT vs NIVO + PDCT	NSQ, PD-L1 ≥1% (n = 50 vs 48)	NSQ, PD-L1 <1% (n = 48 vs 46)	NSQ, LAG-3 ≥1% (n = 56 vs 42)	NSQ, LAG-3 <1% (n = 38 vs 42)	SQ, PD-L1 ≥1% (n = 29 vs 23)	SQ, PD-L1 <1% (n = 22 vs 21)	SQ, LAG-3 ≥1% (n = 38 vs 34)	SQ, LAG-3 <1% (n = 13 vs 10)
PFS HR (90% CI)	0.55 (0.36–0.85)	1.24 (0.84, 1.83)	0.81 (0.54, 1.22)	0.79 (0.51, 1.23)	0.78 (0.46, 1.34)	1.25 (0.7, 2.23)	0.97 (0.61, 1.52)	0.98 (0.45, 2.15)
ORR, %	58% vs 39.6%	35.4% vs 34.8%	57.1% vs 45.2%	34.2% vs 26.2%	44.8% vs 43.5%	81.8% vs 66.7%	52.6% vs 55.9%	84.6% vs 50%

8528 Poster Session

Genomic and circulating tumor DNA landscape in young-onset non-small cell lung cancer. First Author: Fatemeh Ardeshir Larijani, Winship Cancer Institute, Emory School of Medicine, Atlanta, GA

Background: To explore the underlying biology in young patients (pts) with non-small cell lung cancer (NSCLC), we analyzed the genomic diversity of serial circulating tumor DNA (ctDNA). **Methods:** We analyzed ctDNA data from a national database Guardant Health NGS panel of 83 loci from a population of 5210 NSCLC pts between the ages of 18-50 collected between 1/20-6/2020, with longitudinal samples from 931 pts (2 samples), 286 pts (3 samples), and 166 pts ($>$ 3 samples) with at least 90 days between the first and last sample. We evaluated statistical significance using Spearman correlation, the Mann-Whitney U test, the signed-rank test, or Fisher's exact test. We used Gene Ontology enrichment analysis and Ingenuity for genomics and MetaboAnalyst for metabolomic pathway analysis. **Results:** Out of 5,210 young adult (YA) NSCLC pts, 6,624 liquid NGS tests were conducted, of which 9% of pts were between 18 and 35 years old, defined as very young adults (VYA), and 91% were between 35 and 50 years old, defined as young adults (YA). Overall, mutation frequency increased significantly with age (Spearman r = 0.08, p = 1.9 · 10-10). Most pts were female (2,826, 54%).Mutation frequency was higher in males (Mann-Whitney p = 1.8 · 10^{-5}). The rate of targetable alterations was 48% in YA and 46% in VYA-NSCLC patients, with EGFR being the most common alteration (24% in YA, 18.4% in VYA). Of the 13 genes with mutation frequencies of at least 5%, there are 11 genes with more alterations in males and 2 in females. Immune-related pathways were infrequently altered (4.8%), while TP53/DNA damage (50%), EGFR/RAS (30%), PI3K (35%), and β-catenin/APC (28%) pathways were frequently altered. Endocrine resistance pathways altered second most (p=0.03), likely due to distinct biology or treatment effects. Metabolomic analysis identified methylation-related pathways (28.6%), including MAT1A, as the most prominent metabolomic pathways (p = 0.02). Longitudinal analysis revealed increased ctDNA burden with tumor progression. Comparing the first-to-last ctDNA in the same pts, we identified genes with distinct patterns of alteration in YA and VYA pts (Tab-1). TP53 and EGFR remain highly mutated but with stable mutation rates (TP53: 51% to 52%, EGFR: 41% to 41%). **Conclusions:** Targetable alterations are highly prevalent in YA and VYA NSCLC, exhibiting distinct ctDNA mutation frequencies upon serial testing. DNA methylation can potentially regulate gene expression in metabolic pathways, suggesting therapeutic avenues. Research Sponsor: None.

Highest positive and negative changes in mutation frequencies from first to last sample in YA and VYA NSCLC using Guardant serial ctDNA.

Genes in 1st and last sample (Difference range)	Young (35-50 Yo)	Very young (<35 Yo)	Uncorrected Signed Ranked Test P-Value
Rise in mut freq.			
KRAS	0.35	0.25	0.01
MET	0.65	0.16	0.00
BRAF	0.50	0.60	0.08
APC	0.16	0.33	0.33
Decline mut freq. in at least one group	0.56	-0.25	0.01
PIK3CA	0.08	-0.20	0.75
BRCA2	1.0	-0.20	0.08
MYC			

8529 **Poster Session**

Sacituzumab tirumotecan (sac-TMT) in combination with tagitanlimab (anti-PD-L1) in first-line (1L) advanced non-small-cell lung cancer (NSCLC): Non-squamous cohort from the phase II OptiTROP-Lung01 study. First Author: Wenfeng Fang, Sun Yat-sen University Cancer Center, Guangzhou, China

Background: Sac-TMT (MK-2870/SKB264) is a TROP2 ADC developed with a novel linker to conjugate a belotecan-derivative topoisomerase I inhibitor. The complementary mechanisms of action of sac-TMT and PD-1/L1 inhibitor may provide more potent antitumor activity. Sac-TMT was safety combined with tagitanlimab (anti-PD-L1, KL-A167) and demonstrated promising activity for the combination in 1L NSCLC (*Fang et al. 2024*). Here, we report updated results by PD-L1 expression with additional enrolled patients (pts) and extended follow-up from non-squamous cohort in the phase II OptiTROP-Lung01 study (NCT05351788). **Methods:** Advanced NSCLC pts with no prior systemic therapy and no actionable genomic alterations were enrolled to receive sac-TMT (5 mg/kg Q3W or Q2W) plus tagitanlimab (1200 mg Q3W or 900 mg Q2W) until disease progression or unacceptable toxicity. Tumor assessments per RECIST 1.1 were performed once every 6 weeks for the first 12 months (mo), and every 12 weeks thereafter. The PD-L1 tumor proportion score (TPS) was detected by IHC 22C3 pharmDx assay. **Results:** As of 30 Dec 2024, 81 pts (median age: 60.0 years; male: 79.0%; ECOG PS 1: 91.4%) with non-squamous histology were enrolled. The majority (66.7%) had PD-L1 TPS$<$ 50% (42.0% for $<$ 1%, 24.7% for 1% - 49% and 33.3% for $\geq$ 50%). After median follow-up of 17.1 mo, the confirmed objective response rate (ORR) was 59.3%; The disease control rate (DCR) was 91.4%; Median duration of response (mDOR) was 16.5 mo (95%CI: 11.7, 22.1); Median progression free survival (mPFS) was 15.0 mo (95%CI: 10.8, 24.8). Among pts with PD-L1 TPS$<$ 1%, the confirmed ORR was 47.1%; mPFS was 12.4 mo (95%CI: 7.6, 15.4); while for pts with PD-L1 TPS$\geq$ 1%, the confirmed ORR was 68.1%; mPFS was 17.8 mo (95%CI: 14.5, NE). Among pts with PD-L1 TPS$\geq$ 50%, the confirmed ORR was 77.8%; mPFS was 17.8 mo (95%CI: 10.8, NE). Most common ($\geq$ 10%) Grade $\geq$ 3 treatment-related adverse events (TRAEs) were neutrophil count decreased (45.7%), anemia (16.0%), white blood cell count decreased (14.8%) and stomatitis (11.1%). No TRAE led to treatment discontinuation or death. **Conclusions:** Sac-TMT in combination with tagitanlimab demonstrated promising antitumor activity in treatment-naive advanced non-squamous NSCLC. The durable clinical activities were observed regardless of PD-L1 expression. This combination therapy showed a tolerable safety profile based on known profiles of the individual agents, with no new safety signals observed. A phase 3 study comparing sac-TMT plus pembrolizumab *vs.* chemotherapy plus pembrolizumab as 1L treatment for PD-L1 negative pts with advanced non-squamous NSCLC is ongoing (NCT06711900). Clinical trial information: NCT05351788. Research Sponsor: Sichuan Kelun-Biotech Biopharmaceutical Co., Ltd.

8530 **Poster Session**

Clinical, genomic, and pathological features and therapeutic outcomes of non-small cell lung cancer with MTAP-loss. First Author: Hibiki Udagawa, National Cancer Center Hospital East, Kashiwa, Japan

Background: MTAP-cooperative PRMT5 inhibitors are under development for MTAP-loss solid tumors. However, clinical, genomic, and pathological features of non-small cell lung cancer (NSCLC) with MTAP-loss are still unclear. **Methods:** Using the large-scale clinical-genomic database of LC-SCRUM-Asia, the clinical, genomic, and pathological features and therapeutic outcomes of patients with NSCLC with MTAP-loss were investigated. MTAP-loss, CDKN2A-loss, targetable genomic alterations, and tumor mutation burden (TMB) were analyzed using FoundationOne CDx. PD-L1 TPS was evaluated using PD-L1 IHC 22C3. **Results:** MTAP status was successfully analyzed in 253 samples from NSCLC patients between February 2017 and May 2018. MTAP loss was detected in 54 of 253 (21%) NSCLCs distributed in 33 of 170 (19%) adenocarcinoma, 15 of 60 (25%) squamous cell carcinoma and 6 of 23 (26%) others. The patients with MTAP-loss NSCLC showed no significant difference in age, sex, smoking history, and ECOG PS compared to the patients with MTAP-intact NSCLC. In the patients with MTAP-loss NSCLC, the median age was 68 years old, 63% were male, 78% were ever smokers, and all had ECOG performance status (PS) 0-1. CDKN2A-loss was detected in 100% of MTAP-loss and 12% of MTAP-intact. The frequency of targetable genomic alterations did not differ significantly between MTAP-loss and MTAP-intact NSCLC (44% vs 38%). The frequencies of EGFR and KRAS mutations in MTAP-loss NSCLC were 20% and 15%, respectively, and those in MTAP-intact NSCLC were 21% and 10%, respectively. TMB was significantly lower in MTAP-loss NSCLC than in MTAP-intact NSCLC (Median 6.3 vs. 7.6 Mut/Mb, P = 0.03). MTAP-loss NSCLC tended to have lower PD-L1 TPS than MTAP-intact NSCLC (TPS $\geq$1%; 50 % vs 63%, P = 0.08). In the adenocarcinoma without targetable genomic alterations cohort, eight patients with MTAP-loss and 47 patients with MTAP-intact received platinum-based chemotherapies without immune-checkpoint inhibitors (ICIs) as the first-line treatment and six patients with MTAP-loss and 45 patients with MTAP-intact were treated with ICIs alone as any line treatment. There was no significant difference in the progression-free survival (PFS) of platinum-based chemotherapies as the first line between the patients with MTAP-loss and MTAP-intact (median 4.7 vs 4.6 months, HR [95%CI] 0.74 [0.35-1.55], P = 0.42). On the other hand, the patients with MTAP-loss treated with ICIs alone showed significantly shorter PFS compared to the patients with MTAP-intact treated with ICIs alone (median 1.9 vs 6.2 months, HR [95%CI] 3.62 [1.05-12.5], P = 0.04). **Conclusions:** The relatively low TMB and PD-L1 TPS might be involved in shortening the PFS in patients with MTAP-loss treated with ICIs alone. Other than that, NSCLC with MTAP-loss showed no distinct feature in patient characteristics, histopathology, and co-occurring targetable genomic alterations. Research Sponsor: AstraZeneca K.K.; Amgen K.K.; MEDICAL& BIOLOGICAL LABORATORIES CO., LTD.; Eisai Co., Ltd.; MSD K.K.; ONO PHARMACEUTICAL CO., LTD.; Kyowa Kirin Co., Ltd.; DAIICHI SANKYO Co., Ltd.; Taiho Pharmaceutical Co., Ltd.; Takeda Pharmaceutical Co., Ltd.; CHUGAI PHARMACEUTICAL CO., LTD.; Nippon Boehringer Ingelheim Co., Ltd.; Bristol-Myers Squibb K.K.; Janssen Pharmaceutical K.K.; Bayer Yakuhin, Ltd.; AbbVie GK; Nippon Kayaku Co., Ltd.

8531 **Poster Session**

Tumor-derived ILT5 and suppression of T cell immunity in non-small cell lung cancer. First Author: Xuebing Fu, Department of Thoracic Radiation Oncology, Shandong Cancer Hospital and Institute, Shandong First Medical University and Shandong Academy of Medical Sciences, Jinan, China

Background: Immune checkpoint inhibitors targeting PD-(L)1 pathways have revolutionized the treatment of non-small cell lung cancer (NSCLC) since last decade. However, the efficacy is still limited because the immunosuppressive tumor microenvironment (TME) restricts ICI-primed T cell immunity. Therefore, it is quite crucial to block the potential mechanisms in inducing immunosuppression to improve ICI efficacy. Immunoglobulin-like transcript (ILT) 5 is an important immunosuppressive molecule expressed in a wide range of myeloid cells and predicts tumor progression. Our group was the first to report ILT5 expression in solid tumor cells (colorectal cancer). However, the expression and function of ILT5 in NSCLC are still unknown. **Methods:** ILT5 expression in NSCLC tissues and tumor cell lines was determined by PCR, western blotting and immunofluorescence. The impact of tumor-derived ILT5 on T-cell phenotypes and functions was evaluated using flow cytometry and immunofluorescence. ILT5-regulated downstream signals and molecules were determined by RNA sequencing, PCR, western blotting, and flow cytometry. Tumor transplantation and immunotherapeutic models were established in C57/BL6 and NSG mice to explore the effect of ILT5 on tumor progression and the synergies of ILT5 blockade with ICIs. **Results:** ILT5 is highly expressed in NSCLC cells, predicting poor patient survival. ILT5 induced $CD8^+$ T cell exhaustion rather than senescence and apoptosis in the TME. Mechanistically, ILT5 upregulated PD-L1 through the activation of PI3K-AKT-mTOR signaling pathway, which in turn increased PD-1 expression in $CD8^+$ T cells and induced their exhaustion. PIR-B (ILT5 orthlog in mice) overexpression in mice induced $CD8^+$T cell exhaustion and tumor growth in vivo, while PIR-B knockdown had the opposite effect. More importantly, inhibition of ILT5 synergistically enhanced the tumoricidal effect of PD-1 inhibitor in NSCLC immunotherapeutic models. **Conclusions:** Enriched ILT5 expression in NSCLC cells induces $CD8^+$T cell exhaustion via activation of PI3K-AKT-mTOR-PD-L1 pathway. ILT5 inhibition synergistically enhanced the efficacy of PD-1 inhibitor. Our findings identifies a novel mechanism for tumor immunosuppression and develops a promising strategy for improving ICI efficacy. Research Sponsor: None.

8532 **Poster Session**

Prognostic value of baseline and dynamic circulating tumor cell monitoring in advanced lung cancer patients receiving immunotherapy. First Author: Zhihui Wang, Department of Thoracic Oncology, the Fifth Affiliated Hospital of Sun Yat-Sen University, Zhuhai, China

Background: Circulating tumor cells (CTCs) and PD-L1 expression on CTCs (bPD-L1) are emerging biomarkers for predicting immunotherapy response. This study assessed the prognostic value of baseline and dynamic CTC monitoring in advanced lung cancer patients receiving immune checkpoint inhibitors. **Methods:** We prospectively enrolled 53 advanced lung cancer patients (stages III-IV) undergoing immune checkpoint therapy from June 2023 to January 2025 at The Fifth Affiliated Hospital of Sun Yat-sen University. Baseline characteristics (age, gender, histology, treatment modality) were recorded. CTCs and bPD-L1 status were assessed at baseline, and treatment responses were evaluated using RECIST 1.1 criteria. Serial blood samples were collected at Day 42 (T1) and subsequent visits (T2, T3, or Tn) for CTC dynamics monitoring. **Results:** Baseline Characteristics and CTC Detection: Of the 53 patients, 47 (84.6%) were male and 8 (15.4%) were female, with a median age of 63 years (range: 32–89). Histological subtypes included adenocarcinoma (62.6%), squamous cell carcinoma (16.1%), and small cell lung cancer (17.2%). Treatments included PD-1/PD-L1 inhibitors and chemotherapy. At baseline, CTCs were detected in 60.9% of patients, with detection rates varying by histology: adenocarcinoma (59.6%), squamous cell carcinoma (60.7%), and small cell lung cancer (50.0%). PD-L1-positive CTCs (bPD-L1+) were found in 44.8% of patients, with subtype-specific positivity rates of 41.3%, 39.3%, and 40.0%, respectively. Among 53 patients who completed at least two cycles of immunotherapy, the bPD-L1-positive group (n=17) had an ORR of 64.7% and a DCR of 100%, while the bPD-L1-negative group (n=36) had an ORR of 13.9% and a DCR of 83.3% ($p<0.001$). Multivariate analysis identified bPD-L1 positivity as an independent predictor of ORR (p=0.04). Serial blood samples from 37 patients at Day 42 (T1) showed that all patients with DCR had stable or decreased CTC counts, while all PD patients showed an increase in CTC count. Extended monitoring in 13 patients revealed consistent patterns: CTC counts increased in PD cases and decreased or remained stable in DCR cases, supporting its role in monitoring treatment efficacy. A linear mixed-effects model showed a significant positive association between PD status and elevated CTC counts (β = 0.821, $p<0.05$), while non-PD showed a trend towards lower CTC counts (β = -0.370, p=0.1). This suggests that CTC counts may serve as a biomarker for disease progression, particularly in identifying PD patients. **Conclusions:** Baseline and dynamic CTC monitoring, particularly bPD-L1 status, provides strong predictive and prognostic value in advanced lung cancer patients undergoing immunotherapy. These findings suggest CTCs as a non-invasive liquid biopsy for treatment stratification and real-time monitoring of treatment response. Clinical trial information: ChiCTR2400080132. Research Sponsor: None.

8533 **Poster Session**

Host immune classifier to predict survival with chemoimmunotherapy in PD-L1 ≥50% metastatic NSCLC. First Author: Vamsidhar Velcheti, Laura and Isaac Perlmutter Cancer Center, New York, NY

Background: In the 1st line treatment of advanced NSCLC with PD-L ≥50%, immune checkpoint inhibitor (ICI) monotherapy and chemoimmunotherapy have demonstrated survival benefits over chemotherapy alone. However, no additional biomarkers are currently available to guide the choice between these options. Here we report an analysis from the INSIGHT study evaluating the Host Immune Classifier (HIC), a clinically validated blood-based test, to determine its potential to stratify patient survival and optimize treatment selection. **Methods:** Pre-treatment plasma samples were collected from 271 IIIB/IV NSCLC, 1st line ICI-treated (PD-L1 ≥50%) patients enrolled in the prospective, multicenter observational INSIGHT study (NCT03289780). Samples were analyzed by the HIC test, which categorizes patients as Hot or Cold based on the expression profile of eight proteins measured by MALDI mass spectrometry. Survival outcomes were compared between patients treated with ICI monotherapy (ICI-M) and chemoimmunotherapy (ICI-C), grouped by HIC result. To ensure comparable cohorts, baseline clinical characteristics were balanced using inverse probability weighting (IPW). Overall survival (OS) was evaluated using Kaplan-Meier estimates (95% CI) and the log-rank test. Hazard ratios were calculated with Cox proportional hazards models. **Results:** Among the analysis cohort, 171 subjects received ICI-M, and 100 received ICI-C. After IPW, baseline characteristics, including age, sex, smoking history, ECOG PS, and histology, were balanced. The distribution of HIC classifications was similar, with 70% Hot and 30% Cold. In HIC-Hot subjects, overall survival (OS) did not differ significantly between treatment groups (log-rank p=0.15, Table 1). In contrast, HIC-Cold subjects had significantly better OS with ICI-C than ICI-M (log-rank p=0.012, Table 1). Multivariate analysis confirmed the HIC test as an independent predictor of OS, adjusting for other prognostic factors. **Conclusions:** The HIC test is a robust, independent predictor of OS, unaffected by common prognostic factors. HIC-Hot patients had similar OS when treated with ICI-M or ICI-C, suggesting the potential for treatment de-escalation. Conversely, HIC-Cold patients experienced significantly poorer OS with ICI-M but showed improved OS with ICI-C, indicating the need for more aggressive treatment. These findings underscore the potential clinical utility of the HIC test in guiding 1st line ICI treatment strategies for NSCLC with PD-L1 ≥50%. Clinical trial information: NCT03289780. Research Sponsor: Biodesix Inc.

HIC Test Classification	Treatment	N	12 Month % OS	p value	24 Month % OS	p value	Median OS (Months)	Hazard Ratio (95% CI)	p value
Hot	ICI-M	114	58% (48%, 67%)	0.273	46% (35%, 56%)	0.448	18 (11, 31)	0.7 (0.5, 1.1)	0.14
	ICI-C	66	66% (52%, 77%)		52% (37%, 65%)		Median Not Reached		
Cold	ICI-M	47	26% (14%, 39%)	0.028	10% (1%, 32%)	0.005	3 (2, 6)	0.5 (0.3, 0.9)	0.014
	ICI-C	28	51% (32%, 67%)		36% (17%, 56%)		13 (4, NR*)		

*Not Reached.

8534 **Poster Session**

Lipid metabolic gene expression and association with decreased overall survival and immunogenicity in *KRAS-STK11* NSCLC. First Author: Joshua Pothen, University of Illinois Chicago, Chicago, IL

Background: Approximately 30% of patients (pts) with non-small cell lung cancer (NSCLC) have alterations (alt) in *KRAS*. How co-alt such as STK11 affect the tumor microenvironment and survival requires further characterization. Recently, our group found that lower expression of lipid metabolic genes in *KRAS* G12C co-alt tumors was associated with worse overall survival (OS). Here, we seek to confirm these findings utilizing a large real-world (rw) patient de-identified database. **Methods:** Approximately 2,187 pts (61%, stage IV) with *KRAS* G12C alt NSCLC who underwent sequencing via the Tempus xT/xR assay with co-alt in *TP53 (44%), STK11 (17%), or LRP1B (4%)* were selected. The groups are mutually exclusive. Single-sample GSEA (ssGSEA) based on 775 lipid metabolic genes (LMG) was used to calculate enrichment scores (LMG ES) for each pt. Pts were dichotomized into low vs. high groups based on their median LMG ES. Immune cell infiltration predicted from gene expression patterns, TMB, and PD-L1 from IHC was evaluated. Risk-set adjusted rwOS was calculated from sample collection date to death from any cause. Hazard ratios (HR) were calculated using Cox proportional hazards model, and p-values were calculated using the Wald test. **Results:** Among pts with *KRAS* G12C alt, the median age was 68, 58% were female, and 84% were White. Pts with *KRAS* G12C/*STK11* alt had the lowest TMB, neoantigen burden, and PDL-1 positivity compared to other cohorts ($p<0.001$ for all). Importantly, the proportion of total immune cells, M1, M2, NK cells, CD8 T cells and regulatory T cells was lowest in tumors with *KRAS* G12C/*STK11* alt ($p<0.001$ for all). To determine if lipid genes were associated with immunogenic changes, LMG ES was compared to immune infiltration. The ES was associated with immune cell infiltration percentages for M1 macrophages (OR 1.11 (1.03-1.21) p=0.012), M2 macrophages (OR 1.27 (1.15-1.40) $p<0.001$) and neutrophils (OR 1.12 (1.04-1.22) p=0.005), with a trend towards significant association with CD4 T cells (OR 1.08 (1.00-1.17) p=0.062). Pts with *KRAS G12C/STK11* alt and low LMG ES had decreased median rwOS (5.4 vs 18.2 months, p=0.0002) compared to pts with a high ES. Multivariate analysis demonstrated that lower LMG ES correlated with reduced rwOS (HR = 1.75 (1.22-2.51, p = 0.002) compared to pts with high ES. Individual gene analysis showed that low *LPL* (HR = 1.85 (1.147-2.97) p=0.012), *LDLRAD4* (HR = 1.72 (1.082-2.72) p = 0.022) and *LDLR* (HR = 1.58 (1.009-2.46) p=0.045) expression was associated with poorer rwOS. **Conclusions:** Low lipid gene expression in *KRAS-STK11* NSCLC was associated with decreased OS. Lipid gene expression and tumor immune cell infiltration were associated, suggesting that lipid metabolism may regulate tumor immunogenicity. These data suggest that lipid metabolic genes should be further explored as potential therapeutic targets for pts with NSCLC and *KRAS-STK11* alt. Research Sponsor: This work was funded by Tempus AI, Inc.

8535 **Poster Session**

A large validation study of AI-powered PD-L1 analyzer compared to pathologists' assessment of PD-L1 expression in lung cancer. First Author: Yoshitaka Zenke, Department of Thoracic Oncology, National Cancer Center Hospital East, Kashiwa, Japan

Background: Programmed death ligand 1 (PD-L1) expression is a useful biomarker for immune checkpoint inhibitors in advanced lung cancer. However, pathologists' manual evaluation of PD-L1 expression has practical limitations, including observer bias. The development of artificial intelligence (AI)-powered PD-L1 evaluation models has recently progressed. We evaluated the concordance rate of PD-L1 expression as assessed by pathologists and an AI-powered PD-L1 analyzer in lung cancer patients. **Methods:** This multicenter prospective observational study included patients with stage II to IV or recurrent lung cancer (LC-SCRUM-IBIS). PD-L1 Tumor Proportion Score (TPS) was assessed in lung biopsy specimens, by using a 22C-3 Immunohistochemistry (IHC) assay and scanned at ×40 magnification using a whole-slide images scanner (Hamamatsu Photonics). The results of PD-L1 TPS were evaluated independently by three lung pathologists trained in IHC assessment of PD-L1 expression. We examined an AI-powered PD-L1 TPS analyzer, namely Lunit SCOPE PD-L1. **Results:** Between February 2017 and May 2018, 1,017 lung cancer patients were enrolled. Of these, adequate tumor samples allow for PD-L1 IHC assays; 847 non-small cell lung cancer (NSCLC) patients and 102 small cell lung cancer (SCLC) patients. Lunit SCOPE PD-L1 training included annotations of a total of 64,245,935 tumor cells. Regarding patients characteristics, the median age was 66, 31% were female, 75% were ever smokers, and the distribution of stages was as follows: stage II, III, IV, or recurrence in 37, 97, 632, and 183 patients, respectively. The histological subtypes included in NSCLC, non-squamous (666 patients), squamous (181 patients). Additionally, 85% were diagnosed by biopsy specimens. In comparing PD-L1 TPS assessed by AI and pathologists, the overall concordance rate was 70% with a kappa value of 0.56 (95% confidence interval [CI], 0.49–0.61). The concordance rate according to PD-L1 TPS ≥50%, 1-49%, and <1% was 84%, 94%, and 44%, respectively. Of the 416 patients whom pathologists determined to be TPS <1%, 231 (55%) were TPS 1-49%, and only one patient was determined to be TPS ≥50% by AI analyzer. In SCLC patients' analysis, 84% of patients were determined to be PD-L1 <1% by pathologists, with a low concordance rate of 61% (k = 0.29) between pathologists and AI analyzer. **Conclusions:** PD-L1 TPS demonstrated a high concordance between pathologists and AI analyzers in lung cancer patients with TPS ≥50% and 1-49%. However, the concordance rate of TPS <1% was low regardless of histology. We will confirm if the AI analyzer accurately predicts treatment outcome, especially in TPS <1%. Clinical trial information: UMIN000026425. Research Sponsor: Lunit Company.

8536 **Poster Session**

Artificial intelligence-powered spatial analysis of tumor microenvironment in non-small cell lung cancer patients who acquired resistance after EGFR tyrosine kinase inhibitors. First Author: Yeong Hak Bang, Division of Hematology-Oncology, Department of Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, South Korea

Background: We evaluated dynamic changes in the tumor microenvironment (TME) after EGFR tyrosine kinase inhibitor (TKI) treatment using an artificial intelligence (AI)-powered spatial TME analyzer and assessed the predictive efficacy of immune checkpoint inhibitors (ICIs) as monotherapy or in combination therapy. **Methods:** An AI-powered whole-slide image (WSI) analyzer (Lunit SCOPE IO, Lunit, Seoul, Korea) segmented cancer area (CA), stromal area (CS), and identified tumor-infiltrating lymphocytes (TILs), tertiary lymphoid structures (TLS), fibroblasts (Fibs), and endothelial cells (ECs) in tumor tissue. We analyzed 143 non-small cell lung cancer (NSCLC) samples post-resistance to EGFR TKIs from two cohorts: 1) patients (pts) treated with ICIs at Samsung Medical Center, Korea (October 2015–July 2022), and 2) pts from the ATTLAS phase 3 trial comparing atezolizumab plus bevacizumab, paclitaxel, and carboplatin (ABCP) versus pemetrexed plus carboplatin (PC). Among these, 89 pts received ICI monotherapy, and 54 were from the ATTLAS trial (ABCP: 36, PC: 18). Paired pre-treatment samples were available for 89 pts (62.8%), and whole transcriptome sequencing was performed on 42 samples. **Results:** In the combined pre- and post-TKI samples, TLS area per CA correlated with the TLS signature (ρ=0.439, P=0.003), Fibs with the cancer-associated fibroblast signature (ρ=0.581, $P<0.001$), TILs with the interferon-gamma signature (ρ=0.498, $P<0.001$), and ECs with the angiogenesis signature (ρ=0.315, P=0.042), but not VEGF signatures (ρ=0.183, P=0.71). Post-TKI samples showed reduced TILs in CA (P=0.045) and increased ECs in CA (P=0.005), with no significant changes in Fibs (P=0.819) or TLS area (P=0.884). Changes differed by EGFR mutation subtype: L858R mutations were linked to increased ECs (P=0.009), while T790M mutations and exon 19 deletions (19del) were linked to reduced TILs (P=0.033, P=0.045). Higher TILs in CA were associated with better overall response rate (ORR, 41.7% vs. 9.7%, P=0.003) and progression-free survival (PFS, 4.9 vs. 1.8 months, HR=0.41 [95% CI: 0.21–0.79]). Similarly, higher EC levels in CA correlated with improved ORR (19.3% vs. 3.7%, $P<0.01$) and PFS (2.0 vs. 1.4 months, HR=0.44 [95% CI: 0.28–0.71]). In the ATTLAS cohort, these factors were associated with clinical benefits from ABCP, with a significant association for TILs (HR=0.42 [95% CI: 0.19–0.91, P=0.027]) and a marginal association for ECs (HR=0.29 [95% CI: 0.07–1.15, P=0.067]). **Conclusions:** EGFR-TKI alters the immune landscape of NSCLC. Higher TILs or ECs in CA were significantly associated with favorable outcomes to ICI or combination treatment. Research Sponsor: None.

8537 **Poster Session**

Molecular analysis of lung adenocarcinomas from the SAFIR02-Lung trial explores metastasis-associated alterations and potential prognostic markers. First Author: Abderaouf Hamza, Institut Curie Paris, Paris, France

Background: Lung adenocarcinoma (LUAD) molecular heterogeneity influences diagnosis, prognosis, and treatment. Molecular profiling of advanced lesions remains limited compared to early tumors. We analyzed tumors from the SAFIR02-Lung trial to identify molecular alterations associated with advanced LUAD. **Methods:** We analyzed 366 advanced LUAD tumor samples (250 locoregional [lrmLUAD], 116 distant metastases [dmLUAD]) from metastatic patients in the SAFIR02-Lung trial using targeted sequencing of 45 cancer-related genes and comparative genomic hybridization arrays. Data from The Cancer Genome Atlas (TCGA) and three public datasets—MSK-MET, Jee et al., and the AACR Project GENIE—validated our findings. **Results:** Advanced tumors exhibited greater chromosomal instability than early-stage lesions, (fraction of genome altered: 28.0% in lrmLUAD, 29.1% in dmLUAD and 7.2% in early-stage LUAD, $p < 0.01$). Copy-number alterations implicated *LAMB3, TNN/KIAA0040/TNR*, *KRAS, DAB2, MYC, EPHA3, VIPR2* in tumor progression and *AREG, ZNF503, PAX8, MMP13, JAM3, MTURN* and *CDKN2A* in metastasis. *CDKN2A* homozygous deletions correlated with poor outcomes in early-stage LUAD (hazard ratio = 2.17, 95% CI: 1.43–3.28, p = 0.01). *KRAS* mutant allele-specific imbalance (MASI), marked by mutant allele amplification, was enriched in advanced samples (8.4% lrmLUAD, 13% dmLUAD, 2.8% early-stage LUAD). Public cohort validation confirmed higher *KRAS* MASI prevalence in metastatic samples vs. primary tumors (3.17% vs. 1.4%; pooled odds ratio = 2.23, 95% CI: 1.43–3.51, $p < 0.01$). *KRAS* MASI tumors were enriched in *CDKN2A, MYC, TP53, and NKX2-1* alterations, and displayed less *STK11* and *KEAP1* variants. **Conclusions:** Chromosomal instability drives disease progression in LUAD. *CDKN2A* homozygous deletions are a negative prognostic biomarker in early-stage tumors. Metastasis-associated alterations, including *KRAS* MASI and *CDKN2A* deletions, highlight mechanisms of progression and potential prognostic biomarkers, warranting further investigation and therapeutic exploration. Nguyen B, et al. Genomic characterization of metastatic patterns from prospective clinical sequencing of 25,000 patients. Cell 2022;185:563-575.e11. https://doi.org/10.1016/j.cell.2022.01.003. Jee J, et al. Overall survival with circulating tumor DNA-guided therapy in advanced non-small-cell lung cancer. Nat Med 2022;28:2353–63. https://doi.org/10.1038/s41591-022-02047-z. The AACR Project GENIE Consortium, AACR Project GENIE: Powering Precision Medicine through an International Consortium. Cancer Discovery 2017;7:818–31. https://doi.org/10.1158/2159-8290.CD-17-0151. Research Sponsor: None.

8538 **Poster Session**

Clinical outcomes and characterization of HER2 alterations in non-small cell lung cancer (NSCLC). First Author: Nikita Dahake, Temple University Hospital, Philadelphia, PA

Background: Subsets of NSCLC carry alterations in the human epidermal growth factor receptor 2 (HER2) gene such as mutations (mt), amplification (amp), and protein overexpression. These alterations reflect distinct patient (pt) populations and disease biology, translating to variable outcomes with immunotherapy +/- chemotherapy. HER2-directed therapies have shown significant efficacy for HER2 mt and to a lesser extent HER2 3+ NSCLC. We describe the genomic landscape of HER2-altered NSCLC in a large cohort of tumors from the Caris database and explore pt outcomes. **Methods:** Next-generation sequencing of DNA (592-gene or WES) and RNA (WTS) was performed on NSCLC samples (n=52,690, Caris Life Sciences, Phoenix, AZ). IHC was performed on FFPE sections (HER2 staining intensity of 2+, >5%). HER2 amp was defined as copy number > 6. Tumor microenvironment studies were calculated by QuantiSeq. Significance was calculated using chi-square, Fisher's exact, or Mann-Whitney U test, with p-values adjusted for multiple comparisons ($q<0.05$). Overall survival (OS) was estimated from insurance claims data using Cox proportional hazards model to calculate hazard ratio (HR) and log-rank tests to calculate P values. **Results:** 670 tumors were HER2 mt (N=492 within the kinase domain, 133 extracellular domain, 47 transmembrane domain, 16 other, 400 HER2 amp, and 272 HER2 IHC 2+. Treatment (tx) received prior to tumor sample collection is not reported in 64.2% HER2 mt, 68.8% HER2 2+, 56.5% HER2 amp (may reflect tx naive pts). Among female pts, HER2 mt was more common than amp or overexpressed 3+ (59.7% vs. 39.8% vs 36.2% $p<0.01$). HER2 mt correlated with improved OS compared to HER2 amp and a cohort of NSCLC driverless tumors (wild type EGFR, ALK, ROS1, RET, KRAS, and HER2). When compared to ROS1+, ALK+ and EGFR mt, HER2 mt had shorter OS (Table). Higher frequency of co-mts are noted in HER2 amp vs mt, including TP53 (90% vs 57%), EGFR (10% vs 6%), SMARCA4 (12% vs 5%), CDKN2A (16% vs 5%), NKX2-1 (2% vs 0.5%) and TMB-H (47% vs 21%), all $p<0.001$. No differences in PD-L1 expression were observed. Higher frequency of co-mts for HER2 IHC 2+ vs HER2 mt, including KRAS (33% vs 3%), KEAP1 (21% vs 7%), BRAF (5% vs 0.8%), EGFR (13% vs 6%) and SMARCA4 (11% vs 5%), all $p<0.001$. HER2 mt tumors had greater infiltration of NK cells, B cells, M2 macrophages, neutrophils and Tregs (FC 1.2-1.3) vs. HER2 IHC 2+. **Conclusions:** This study highlights the significant differences in OS and co-alterations for HER2 mt vs other HER2 altered and NSCLC driverless tumors. This data confirms the unmet need to further explore these differences to optimize tx and improve OS. Research Sponsor: None.

NSCLC cohorts compared to HER2 mt cohort (22.0 months).

NSCLC Cohort	Survival (months)	HR, 95% CI	p-value
HER2 amp	12.3	0.67 (0.57-0.79)	<0.001
HER2 2+	14.1	0.92 (0.77-1.09)	0.33
Driverless	16.2	0.85 (0.77-0.94)	<0.01
ROS1 fusion	35.3	1.3 (1.0-1.7)	0.02
ALK fusion	47.4	1.9 (1.6-2.3)	<0.001
EGFR mt	30.7	1.3 (1.2-1.5)	<0.001

8539 **Poster Session**

Spatial transcriptomic profiling of the tumor microenvironment in EGFR and KRAS mutant non-small cell lung cancer. First Author: Fabian Johannes Bolte, University of Virginia Cancer Center, Charlottesville, VA

Background: Immune checkpoint inhibitors have greatly improved outcomes in advanced non-small cell lung cancer (NSCLC). However, patients with EGFR mutant NSCLC have a poor response to immune checkpoint inhibitor therapy. Emerging evidence suggests that an immunosuppressive tumor microenvironment plays an important role in this setting, however, we still lack fundamental knowledge about tumor endothelial cell biology. We hypothesized that oncogene specific changes in the expression of immune-related genes in tumor endothelial cells account for differences in the tumor microenvironment and efficacy of immune checkpoint inhibitor therapy. **Methods:** We utilized spatial transcriptomics (GeoMx Digital Spatial Profiling) on resected tumor tissue of EGFR mutant (n = 5) and KRAS mutant (n = 5) NSCLC patients to investigate the transcriptional signature of tumor, endothelial and stromal cells. Additionally, we used NicheNet to explore intercellular communication between tumor, endothelial, and stromal cells. Immune gene set enrichment analysis scores were calculated using ESTIMATE. Immune cell type proportions were estimated using CIBERSORT. **Results:** Using spatial transcriptomics, we dissected the tumor microenvironment into tumor, stromal and endothelial compartments. By analyzing predicted cellular communication, we found that tumor and stromal cells primarily affect an interferon-related gene signature in tumor endothelial cells. Notable differentially expressed interferon-related genes, that were significantly up-regulated in KRAS mutant and down-regulated in EGFR mutant NSCLC patients, included CXCL9, STAT1, WARS1, IRF1 and ICAM1. In the stromal compartment, immune gene set enrichment analysis scores were significantly lower in EGFR mutant than KRAS mutant NSCLC (median, 355 vs. 713, P = 0.026) indicating an immunosuppressive tumor microenvironment. We observed substantial heterogeneity while exploring the cellular landscape of the stromal compartment in EGFR mutant and KRAS mutant NSCLC. Notably, we found a significantly decreased proportion of pro-inflammatory macrophages in the stromal compartment of EGFR compared to KRAS mutant NSCLC (P = 0.006). **Conclusions:** We identified distinct interferon-related gene signatures in tumor endothelial cells of patients with EGFR and KRAS mutantNSCLC associated with variations in the cellular composition of the tumor microenvironment. This may provide a better understanding for the development of spatial biomarkers to identify which oncogene-driven NSCLC patients are most likely to benefit from immune checkpoint inhibitor therapy. Research Sponsor: University of Virginia (UVA) NCI-designated Comprehensive Cancer Center.

8540 **Poster Session**

Immune landscape of liver metastases in advanced lung cancer. First Author: Kamya Sankar, Cedars-Sinai Medical Center, Los Angeles, CA

Background: The liver is a frequent site of metastasis and carries a poor prognosis in patients with non-small cell (NSCLC) and small cell lung cancer (SCLC). Patients with liver metastases (LM) derive limited benefit from immune checkpoint inhibitors (ICI), due to hepatic myeloid derived suppressor cell (MDSC) mediated T cell elimination. Here, we used imaging mass cytometry (IMC) to perform single cell, highly multiplexed, analysis of LM and primary lung tumors to investigate how vascular endothelial growth factor (VEGF) influences T cell depletion within the tumor immune microenvironment (TIME) of LM. **Methods:** We comprehensively characterizedthe TIME in LM and primary lung tumors in 21 patients with NSCLC or SCLC using IMC. A panel of 40 antibodies was assembled to interrogate immune subsets and VEGF pathway markers. Each antibody was conjugated to a unique metal isotope. After validation, the antibody cocktail was used to stain the biopsies. Tissue images were segmented using Mesmer, and hierarchical clustering was applied to single-cell expression data to identify phenotypes. Similar clustering of cell neighbor profiles was applied to obtain spatial motifs. Phenotypic and motif frequencies, together with functional expression across phenotypes, were compiled from all samples and compared across conditions. **Results:** Initial visualization of the raw, unsegmented data revealed higher infiltration of $CD8^+$ and $CD4^+$ T cells in LM compared to the lung TIME. After segmentation, marker expression heatmaps uncovered complex cell-cell interaction ecosystems. The liver samples were enriched with M2 macrophages ($CD163^+$), MDSC ($CD11b^+$), and proliferative endothelial cells ($CD105^+$) whereas the lung samples were enriched in tumor cells ($TTF1^+$ for NSCLC and $INSM1^+$/synaptophysin$^+$ for SCLC) and T cells ($CD4^+$, $CD8^+$). Spatial neighborhood profiling of NSCLC liver tissues identified 12 neighborhood types, showing a general trend of mutual exclusivity between MDSCs and $CD4^+$/$CD8^+$ T cells across neighborhoods. Notably, $CD8^+$ T cells in MDSC-enriched neighborhoods exhibited consistently higher FAS expression, a key apoptotic marker. Heterogenous FAS and VEGF signaling across neighborhoods suggested a mixed immune-suppressive and vascularized response in the liver TIME, supporting VEGF's role in mediating MDSC-driven hepatic $CD8^+$ T cell depletion in patients with LM. **Conclusions:** Our findings highlight significant differences in the TIME between LM and primary lung tumors, with LM demonstrating a more immunosuppressive and VEGF-enriched milieu. The spatial association of MDSCs with $CD8^+$ T cells, along with elevated FAS expression and VEGF signaling suggests a mechanistic role for VEGF in driving immune evasion within liver tumors. These results underscore the potential of VEGF blockade as a therapeutic strategy to overcome T cell suppression and improve ICI efficacy in patients with lung cancer metastatic to liver (NCT05588388, PI Sankar). Research Sponsor: Conquer Cancer Foundation, ASCO; Cedars-Sinai Medical Center, CSRI.

8541 **Poster Session**

Biomarker testing of lung cancer in North America versus globally. First Author: Matthew Paul Smeltzer, University of Memphis School of Public Health, Memphis, TN

Background: Biomarker testing is essential to optimize lung cancer (LC) care, yet uptake of testing is suboptimal due to lack of access, cost, and long turnaround times (TAT). Recent advances now require biomarker testing in early-stage LC. In 2024, the International Association for the Study of Lung Cancer (IASLC) launched a 2nd global survey to measure improvements and barriers to implementation of testing. We compared results from North America (NA) with global results by high income (HIC) and low or middle income countries (LMIC). **Methods:** A multi-disciplinary committee of oncologists, pathologists, pulmonologists, epidemiologists, and advocacy partners created the survey. We used mixed methods, with focus groups and in-depth interviews informing the quantitative survey with IRB oversite. Chi-square tests were utilized to compare frequencies between NA v Other HIC (OHIC) and HIC v LMIC. **Results:** Of the 1677 responses globally, 1501 were from HIC and 176 from LMIC. HIC included 337 responses from NA (287 United States and 50 Canada). Nearly all NA respondents (99%) believe biomarker testing significantly impacts patient outcomes and 94% report a clear understanding of who should be tested (v 91% OHIC, p=0.09). In NA, 66% and 40% ranked biomarker testing as highly important in late- and early- stage LC, respectively (64% and 28% OHIC, p=0.68 and p<0.01). Only 45% of NA respondents were satisfied with biomarker testing conditions (v 52% OHIC, p=0.03), and 69% estimate at least half of LC patients receive biomarker testing (71% OHIC), an increase from 45% in the 2018 survey (p<0.01). We found 40% of respondents from NA sometimes or often began treatment prior to obtaining biomarker results (41% OHIC). Key barriers identified were cost (23%), time (22%), and sample quality (20%), consistent with global and OHIC trends. Mean TAT in NA was 17.1 days (SD 7.8) v 16.1 days (SD 9.0) in HIC. Insufficient tumor was the primary cause for re-biopsy in late and early-stage patients for NA (58%) and HIC (48%). Lastly, 14% of NA reported no additional training in next-generation sequencing beyond medical education (16% OHIC). Globally, conditions were worse in LMIC v HIC including those who sometimes or often begin treatment prior to obtaining biomarker results (73% v 41%, p<0.01) and those who are confident or extremely confident in the adequacy of testing at their institution (48% v 68%, p<0.01). **Conclusions:** Respondents from NA believe they understand the value of biomarker testing for LC and who should be tested. Testing practices have reportedly improved since 2018, yet less than half of NA respondents are satisfied with biomarker testing practices and many patients are still treated without biomarker information. Responses from NA were similar to OHIC, with some exceptions, but significant disparities were evident in LMIC. We identified key barriers that should be addressed to optimize testing practices and patient outcomes. Research Sponsor: International Association for the Study of Lung Cancer (IASLC), via the IASLC Partners for Thoracic Cancer Care.

8542 **Poster Session**

Prediction of site-specific immune-related adverse events of PD-L1 blockade in advanced non-small cell lung cancer through baseline organ-metastatic landscape: Pooled post-hoc analyses of two randomized controlled trials. First Author: Si-Heng Wang, The First Affiliated Hospital, Sun Yat-sen University, Guangzhou, China

Background: The patterns of immune-related adverse events (irAEs) during immunotherapy vary among tumors of different origins. However, it remains unknown whether metastases in different organs confer varying susceptibility to irAEs in a specific tumor type. Herein, we explored the impact of the baseline organ-metastatic landscape on the irAE patterns following PD-L1 blockade in advanced non-small cell lung cancer (NSCLC). **Methods:** We conducted a pooled post-hoc analysis of 708 patients with advanced NSCLC who received atezolizumab from two randomized controlled trials (OAK and POPLAR). The association between the baseline metastatic status and both overall and site-specific irAEs was analyzed using multivariate logistic regression and multivariate Cox regression. The Kaplan-Meier method with the log-rank test was leveraged to compare the cumulative risk of irAEs based on organ-specific metastatic status. **Results:** Patients harboring different organ metastases yielded varying vulnerability of irAEs (p = 0.047). Overall, irAEs were less likely to occur in patients with bone metastases (OR = 0.52, p = 0.039) and pleural effusion metastases (OR = 0.65, p = 0.039), while more frequent in patients with brain metastases (OR = 1.96, p = 0.023). Besides, patients with bone metastases experienced a significant delayed onset of irAEs compared to those with metastases to other organs (HR = 0.65, p = 0.007). In terms of the incidence of site-specific irAEs, hepatitis (OR = 0.55, p = 0.03), hypothyroidism (OR = 0.27, p = 0.008), and rash (OR = 0.63, p = 0.039) were less frequent in patients with bone metastases, whereas pneumonia (OR = 3.25, p = 0.046), adrenal insufficiency (OR = 12.71, p = 0.019) and ocular inflammatory toxic (OR = 21.17, p = 0.017) were more concentrated in patients with brain metastases; adrenal insufficiency was particularly prevalent in patients with adrenal metastases (OR = 15.22, p = 0.023). As for the onset of site-specific irAEs, patients with bone metastases experienced significantly earlier onset of hypothyroidism (HR = 0.27, p = 0.008), while those with metastases to brain (HR = 7.81, p = 0.029) and adrenal glands (HR = 12.54, p = 0.029) developed later onset of adrenal insufficiency; liver metastases were associated with earlier onset of hepatitis (HR = 1.8, p = 0.018) and colitis (HR = 5.49, p = 0.033). **Conclusions:** The baseline organ-metastatic landscape might be a predictive factor for overall and site-specific irAEs in advanced NSCLC patients received PD-L1 blockade. Our findings enhance the understanding of organ-specific immunity in immunotherapy under the metastatic setting of NSCLC and may inform personalized immunotherapy strategies. Research Sponsor: National Natural Science Foundation of China; 82373307; Natural Science Foundation of Guangdong Province; 2024A1515013214; China Postdoctoral Science Foundation; 2024M753780; the institutional funding of The First Affiliated Hospital of Sun Yat-sen University.

8543 **Poster Session**

A phase II trial to evaluate the safety and efficacy of SSGJ-707, a bispecific antibody targeting PD-1 and VEGF, as a monotherapy in patients with advanced NSCLC. First Author: Lin Wu, Hunan Cancer Hospital, Changsha, China

Background: SSGJ-707 is a recombinant humanized bispecific molecule built on IgG4 that targets the human programmed death 1 (PD-1) and vascular endothelial growth factor (VEGF). The increase of SSGJ-707 affinity for PD-1 was 10-fold more than that of Ivonescimab in the presence of VEGF. Here, we report the initial results from a phase II study of SSGJ-707 monotherapy in patients (pts) with advanced NSCLC(SSGJ-707-NSCLC-II-01, NCT06361927). **Methods:** Pts with treatment naive advanced NSCLC (without actionable genomic alterations and PD-L1 expression≥1%) were enrolled to receive SSGJ-707 monotherapy until disease progression or unacceptable toxicity. Tumor assessments based on RECIST 1.1 were performed every 6 weeks by investigators. **Results:** As of Jan 10, 2025, 83 NSCLC pts have received SSGJ-707 at dose of 5mg/kg Q3W (n=31), 10mg/kg Q3W (n=34), 20mg/kg Q3W (n=12), 30mg/kg Q3W(n=6). Overall, the median age was 64 years, 83.1% had ECOG PS of 1, 44.6% of pts with squamous cell carcinoma, 66.3% and 33.7% of pts had PD-L1 expression 1%-49% and ≥50%. Among the 76 pts completed at least one efficacy evaluation, ORR and DCR were 29.6% (8/27)/85.2% (23/27), 61.8%(21/34)97.1% (33/34), 54.5% (6/11)/90.9% (10/11) and 25% (1/4)/75% (3/4) at doses of 5mg/kg Q3W, 10mg/kg Q3W, 20mg/kg Q3W and 30 mg/kg Q3W, respectively. SSGJ-707 10mg/kg Q3W demonstrated promising efficacy results in treatment naive advanced NSCLC. Select subgroups are summarized in SSGJ-707 10mg/kg Q3W. The ORR were 54.5% (12/22) and 75%(9/12) in non-squamous and squamous pts respectively. And the ORR were 57% (12/21) and 69%(9/13) in PD-L1 TPS 1%-49% and ≥ 50% pts respectively. 25 pts completed at least two efficacy evaluation in SSGJ-707 10mg/kg Q3W, the ORR was 72% (18/25), DCR was 100% (25/25). For the 83 pts, 65 pts (78.3%) experienced treatment related adverse events (TRAEs), 20 pts (24.1%) experienced grade≥3 TRAEs. The most common TRAEs included hypercholesterolaemia (18.1%,15/83), hypertriglyceridaemia (18.1%,15/83), alanine aminotransferase increased (15.7%,13/83) and aspartate aminotransferase increased (15.7%,13/83). TRAE leading to discontinuation occurred in 6% of pts. **Conclusions:** SSGJ-707 monotherapy demonstrated promising efficacy results in treatment naive advanced NSCLC with manageable safety profile. Monotherapy and combination trials with chemotherapy for NSCLC are still ongoing. Research Sponsor: 3S BIO.COM. Clinical trial information: NCT06361927. Research Sponsor: Shenyang Sunshine Pharmaceuticals CO., Ltd.

8544 **Poster Session**

Clinical features associated with an exceptional response to immunotherapy in patients with metastatic non-small cell lung cancer (NSCLC). First Author: Yunan Nie, Yale Cancer Center, New Haven, CT

Background: Immunotherapy with PD1 axis inhibitors is approved for metastatic non-small cell lung cancer (NSCLC). Outside of tumor PD-L1 expression, which predicts immunotherapy sensitivity in metastatic NSCLC, no clinicopathologic characteristics have been identified that reliably predict long-term survival after immunotherapy. To identify clinicopathologic predictors of exceptional response, we compared patients with dissimilar outcomes after immunotherapy. **Methods:** Patients with advanced NSCLC treated at Yale Cancer Center with immunotherapy between 2010–2020 were enrolled on an IRB-approved protocol allowing chart review of clinicopathologic data and further archival tumor tissue analysis. Data collection cutoff was January 14, 2025. We defined three subsets of patients who received immunotherapy without concurrent chemotherapy: Exceptional responders (ER) (continued response without progression ≥3 years after first dose), non-exceptional responders (NER) (initial response followed by progression within 3 years), and primary progressors (PP) (best response of progressive disease). **Results:** 50 ER, 45 NER, and 62 PP were identified. At a median follow-up of 7.2 years, 25, 9, and 6 ER had continued response at 5, 7, and 10 years. ER had a lower frequency of baseline lung, bone, and liver metastases, prior chemotherapy (p=0.005), or lymph node/thoracic radiation (p=0.016) than NER and PP. ER had higher pre-treatment absolute lymphocyte count (ALC) and lymphocyte-to-albumin ratio (LAR), with lower platelet-to-lymphocyte ratio (PLR) and monocyte-to-lymphocyte ratio (MLR). Of 24 evaluable ER patients, 19 had tumor PD-L1 TPS score ≥50%, compared to 13/21 evaluate NER and 14/34 valuable PP. 47/50 ER were nonsquamous, compared to 36/45 NER and 53/62 PP. Compared to NER only, ER were less likely to have bone metastases (p=0.049) or prior lymph node/thoracic radiation (8% vs 24%, p=0.028). Variables associated with primary progression were female sex (OR = 3.73, 95% CI 1.55–8.9), lung metastases (OR 6.46, 95% CI 2.73–15.27), and low albumin (OR 0.29, 95% CI 0.12–0.72). The presence of brain metastases was not different between cohorts. **Conclusions:** Patients with metastatic NSCLC exhibiting exceptionally durable responses to immunotherapy demonstrate distinct baseline features, with higher pre-treatment ALC and LAR, lower PLR and MLR, and lower prevalence of lung, bone, or liver metastases. They were less likely to have had thoracic/lymph node radiation, suggesting lymph node radiation may influence immunotherapy response. Ongoing molecular studies of biospecimens from these patients include genomic/transcriptomic analysis, HLA typing, and tumor microenvironment analysis of archived tissue to further characterize drivers of differential immunotherapy response. Research Sponsor: None.

8545 **Poster Session**

Breaking barriers for patients with stage IV non-small cell lung cancer with brain metastases: Insight into the impact of immunotherapy on survival and survival disparities. First Author: Reema Tawfiq, Mayo Clinic Florida, Jacksonville, FL

Background: Brain metastases (BM) correlate with poor prognosis, occurring in 10% of non-small cell lung cancer (NSCLC) patients (pts) at diagnosis and up to 40% over the disease course. Immunotherapy (IO) with or without chemotherapy has become the new standard of care for stage IV NSCLC. However, the survival benefit of IO in pts with BM remains unclear as most studies are limited to small sample sizes or highly selected pts with asymptomatic or treated BMs. This study represents the largest real-world data analysis evaluating the survival benefits of IO in stage IV NSCLC pts with BM. **Methods:** Demographics, clinical features, and survival were analyzed in stage IV NSCLC pts with BM from the National Cancer Database (NCDB) from 2014-2020. A multivariate Cox proportional hazards modeling assessed factors impacting mortality. **Results:** Of 204,249 pts with stage IV NSCLC, 30% had BM. The mean age was 68 years, with 54% male. Most pts were White (82%), followed by Black (12%) and Asian (3.1%). Government insurance covered 70% of pts, and 26% had private insurance. Adenocarcinoma was the predominant histology (62%), followed by squamous cell carcinoma (SCC) (20%). Liver and bone metastases were observed in 19% and 42% of pts, respectively. Among pts with BM, 18% received immunotherapy, 53% received chemotherapy, 66% received whole-brain radiation, and 18% received limited-brain radiation. Multivariate Cox analysis showed that pts receiving IO had a 46% lower mortality risk compared to not receiving IO (HR: 0.54, 95% CI: 0.51–0.56, $p < 0.001$), demonstrating the independent benefit of IO in pts with BM, regardless of brain radiation or chemotherapy. Females had a lower mortality risk than males (HR: 0.88, 95% CI: 0.85–0.91, $p < 0.001$). Asian (HR: 0.71, 95% CI: 0.64–0.79), Hispanic (HR: 0.76, 95% CI: 0.65–0.89), and Black pts (HR: 0.88, 95% CI: 0.84–0.93) had improved survival as compared to White. Pts with private insurance have lower mortality risk (HR: 0.94, 95% CI: 0.90–0.98), compared to lack of insurance (HR: 1.19, 95% CI: 1.08–1.31). SCC was linked to worse survival (HR: 1.28, 95% CI: 1.22–1.35). **Conclusions:** IO significantly improves survival in pts with NSCLC with BM, regardless of brain radiation therapy or chemotherapy. However, survival disparities based on histology, insurance status, and demographic factors persist, highlighting the need for more equitable treatment strategies. Research Sponsor: None.

8546 **Poster Session**

Association between pretreatment emotional distress and survival outcomes in patients with advanced non–small-cell lung cancer: An individual patient data meta-analysis of 4632 patients in 7 trials. First Author: Jian-Guo Zhou, The Second Affiliated Hospital of Zunyi Medical University, Zunyi, China

Background: Emotional distress (ED) associated with worse survival outcomes in patients with melanoma and non-small-cell lung cancer treated with immune checkpoint inhibitors (ICIs). However, several preclinical studies suggest the association between stress and cancer treatment extends beyond ICIs alone. Here we used an individual patient data (IPD) meta-analysis of 4632 patients in 7 trials and a Kaplan-Meier analysis to verify broader connection between ED and survival outcomes in NSCLC patients. **Methods:** We searched Vivli data-sharing platform for studies which reported clinical trials of advanced NSCLC patients treated with atezolizumab and used the EORTC QLQ-C30 scale to define ED status of patients. Integrating IPD and grouped them into four groups according to ED status and treatment, Kaplan-Meier analysis was conducted to estimate median overall survival (mOS) and progression-free survival (mPFS) for each group. Next we utilized the Cox proportional hazards model to estimate hazard ratios (HRs) and 95% CIs for OS and PFS of each trials. The IPD meta-analysis was conducted to generate summary estimates of results of aggregated data. **Results:** Among a total of 4632 participants, 2753 (59.43%) received first-line treatment; 3162 (68.26%) received ICIs; 1802 (38.90%) classified as ED and 2830 (61.10%) classified as non-ED. Kaplan-Meier analysis indicate that ED patients associate with worse survival outcomes, regardless of ICIs or chemotherapy (CT) (HROS=1.21, p=0.01; HRPFS=1.19, p=0.01). Compared with non-ED, ED patients had worse OS in both ICIs (ED vs non-ED, mOS, 13.34 m vs 16.07 m; p=0.01; HR, 1.21 [1.09-1.34]) and CT (ED vs non-ED, mOS, 12.02 m vs 13.93 m; p=0.01; HR, 1.19 [1.04-1.37]). IPD meta-analysis indicate that the ED group exhibited worse OS outcome (HR=1.18 [1.07-1.30], p=0.01). Subgroup analysis confirmed this association in both ICIs (HR=1.18 [1.04-1.34], p=0.01) and CT groups (HR=1.18 [1.00-1.39], p=0.05). Excluded clinical trials which PFS not primary outcome, and investigated the association with ED and PFS in first-line clinical trials. Similarly, Kaplan-Meier analysis show ED patients had worse PFS regardless of ICIs (mPFS, 5.52 m vs 5.58 m; p=0.01; HR, 1.19 [1.06-1.33]) or CT (mPFS, 5.55 m vs 5.59 m; p=0.06; HR, 1.17 [0.99-1.37]). IPD meta-analysis of PFS also supported results above (HR=1.15 [1.03-1.28], p=0.02). **Conclusions:** The NSCLC patients with ED are significantly associated with adverse survival outcomes regardless of CT or ICIs. The findings recommend the implementation of ED status assessment in clinical practice for NSCLC patients to improve their survival outcomes. Research Sponsor: None.

8547 **Poster Session**

First-in-human study of CJRB-101, a live biotherapeutic product in combination with pembrolizumab in selected types of advanced or metastatic cancer. First Author: Jii Bum Lee, Division of Medical Oncology, Department of Internal Medicine, Yonsei Cancer Center, Severance Hospital, Yonsei University College of Medicine, Seoul City, South Korea

Background: CJRB-101 is a live biotherapeutic product containing a novel strain belonging in the species *Leuconostoc mesenteroides*. Preclinical data support the role of CJRB-101 in eliciting anti-tumor response via induction of macrophage and recruitment of $GZMB^+$ CD8 T cell, thereby eliciting synergy with pembrolizumab. **Methods:** This is a multi-national, open label, phase 1/2 study to evaluate the safety and preliminary efficacy of CJRB-101 with pembrolizumab in patients with non-small cell lung cancer (NSCLC), head and neck squamous cell carcinoma (HNSCC), and melanoma who are immune checkpoint inhibitor (ICI)-naïve or have progressed with ICIs. Patients were treated with pembrolizumab 200 mg every 3 weeks with dose level 1 (1 capsule QD) or 2 (2 capsules BID) of CJRB-101 until unacceptable toxicity or progression of disease. Exploratory endpoints included bulk RNA sequencing of baseline and post-treatment (prior to C2D1) FFPE samples. **Results:** As of Jan 17, 2025, a total of 32 patients were enrolled, including 13 ICI-naïve and 19 ICI-refractory patients. No dose limiting toxicity was observed in the lead in part (dose level 1, n=12) or in subsequent patients in level 2 (n=20). At a median follow-up of 59 days, the median number of treatment cycles was 3. Treatment-related adverse events accounted for 21.9% (n=7/32), mostly grade 1 or 2. Only 1 patient (3.2%) experienced grade > 3 TRAE which was anemia related to CJRB-101. Preliminary efficacy outcomes are shown in Table. Of the 20 patients deemed efficacy evaluable with at least 1 on-treatment scan (ICI naïve, n=10; ICI refractory, n=10), the ORR was 44% for ICI naïve, metastatic NSCLC (n=4/9), and DCR was 30% (n=3/10) for ICI-refractory NSCLC. Bulk-RNA sequencing of baseline samples (n=14) showed that patients who derived clinical benefit (CB, PR+SD, n=7) showed enrichment in T cell activation, and upregulation of innate and adaptive immune response compared to those with no-clinical benefit (NCB; PD, n=7). On treatment biopsied sample showed significant decrease in $PD\text{-}1^+Tim\text{-}3^+$ CD4 (P=0.002) and CD8 (P=0.006) T cells in CB group compared to the NCB group. **Conclusions:** CJRB-101 plus pembrolizumab was well tolerated with manageable safety profile. Preliminary efficacy data show anti-tumor activity in metastatic NSCLC, and early biomarker data support the role of immune activation of CJRB-101. Exploratory analysis of PBMCs, multiplex IHC, PD biomarker, and fecal microbiota metagenomics analysis are ongoing. Clinical trial information: NCT05877430. Research Sponsor: None.

Preliminary efficacy outcomes.

	Treatment status		
Confirmed ORR	**ICI naive**	**ICI refractory**	**Total**
Tumor types (n)	10	10	20
NSCLC (n)	9	10	19
ORR (%)	44%	0%	21%
DCR (%)	67%	30%	64%
HNSCC (n)	1	0	1
DCR (%)	100%	0	100%
Dose of CJRB-101 (n)	10	10	20
0 level (n=6)	4	2	6
ORR (%)	50%	0%	33%
DCR (%)	50%	0%	33%
1 level (n=14)	6	8	14
ORR (%)	33%	0%	14%
DCR (%)	83%	38%	57%

8548 **Poster Session**

Camrelizumab combined with 2 cycles of chemotherapy as first-line treatment for advanced non-small cell lung cancer (NSCLC): A two-arm, single-center, phase 2 study. First Author: Hongbing Liu, Department of Respiratory and Critical Care Medicine, The Second Affiliated Hospital of Nanjing Medical University, Nanjing, China

Background: In the treatment of advanced non-small cell lung cancer (NSCLC), the combination of anti-PD1 and chemotherapy has demonstrated an advantage over chemotherapy alone. First-line treatment of advanced NSCLC with camrelizumab in combination with platinum-based chemotherapy shows promising clinical activity. Nonetheless, the impact of varying chemotherapy cycles on efficacy and safety requires investigation through data from prospective studies. **Methods:** This was a two-arm, single-center, phase 2 clinical trial (ChiCTR2200065078) in which we assigned patients with stage IIIb-IV advanced non-small cell lung cancer (NSCLC) to receive 2 or 4 cycles of platinum-based chemotherapy combined with camrelizumab 200 mg, followed by camrelizumab maintenance therapy until 2 years. The primary endpoint was progression-free survival, and secondary endpoints were objective response rate (ORR), overall survival (OS) and safety. **Results:** As of December 1, 2024, 40 patients were enrolled in this study, including 16 patients in the 2-cycle platinum-based chemotherapy combined with camrelizumab groups (Group A), and 24 patients in the 4-cycle platinum-based chemotherapy combined with camrelizumab groups (Group B) with a median follow-up of 17.6 months. The patients in Group A are older than those in Group B (75.50 [72.75, 77.25] vs. 69.00 [63.75, 72.25]). The median progression-free survival (PFS) were 5.4 months (95% CI, 4.9 to 5.9) for the group A and 13.0 months (95% CI, 5.6 to 20.4) for the group B, respectively (P=0.195). The confirmed overall response (ORR) was 6.2%, (95% CI, 0.6% to 26.4%) for the Group A and 41.7%, (95% CI, 20.7% to 65.9%) for the Group B, respectively (P=0.036). The median OS were 11.4 months (95% CI, 8.6 to 14.2) for the group A and 24.1 months (95% CI, 17.4 to 30.8) for the Group B, respectively (P=0.079). Across the overall population, 97.5% of patients reported any grade of treatment-related adverse event (TRAE), with 6.2% experiencing grade ≥ 3 TRAEs for Group A, and 12.5% for Group B. **Conclusions:** The 2-cycle group did not show superior progression-free survival (PFS) relative to the 4-cycle platinum-based chemotherapy when combined with camrelizumab. However, the 4-cycle platinum-based chemotherapy group may have resulted in a higher probability of developing grade ≥ 3 treatment-related adverse events. A combination of a 2-cycle chemotherapy and immunotherapy may be more suitable for elderly patients with advanced lung cancer. Clinical trial information: ChiCTR2200065078. Research Sponsor: None.

8549 Poster Session

Evaluation of the combination of regorafenib + avelumab in patients with non-small cell lung cancer without oncogenic addiction: The phase II REGOMUNE study. First Author: Sophie Cousin, Early Phase Clinical Trials Unit and Thoracic Unit, Institut Bergonié, Bordeaux, France

Background: Combining anti-angiogenic agents with immune checkpoint inhibitors (ICI) in NSCLC has a strong biological rational. This strategy may enhance antitumor immunity by downregulating PD-1/PD-L1 expression, increasing TIL infiltration, and reducing immunosuppressive Tregs and MDSCs, potentially resensitizing patients to ICI therapy. **Methods:** This phase II, single-arm, multicentric trial evaluated the combination of regorafenib (160 mg daily, 3 weeks on/1 week off) and avelumab (10 mg/kg Q2W) in advanced/metastatic NSCLC patients without EGFR/ALK/ROS1 alterations. Eligible patients were previously treated with anti-PD(L)1 inhibitors for $\geq$4 months and had received $\leq$2 prior systemic lines. The primary endpoint was the 6-month progression-free rate (PFR6) per RECIST 1.1. Secondary endpoints included overall response rate (ORR), progression-free survival (PFS), overall survival (OS), and safety. Correlative studies analyzed baseline tumor samples to identify biomarkers of response. A Simon's two-stage design was used, requiring $\geq$13 non-progressions among 43 patients to demonstrate efficacy. **Results:** Between February 2021 and April 2024, 46 patients were enrolled across four centers (median age: 63, range: 41-88). Median follow-up was 13.4 months. Most patients (94%) had prior platinum-based chemotherapy. Dose adjustments for regorafenib were required in 78.3% of patients due to adverse events. Common grade 3/4 toxicities included erythroderma (15.2%) and oral mucositis/palmar-plantar erythrodysesthesia (13% each). No treatment-related deaths occurred. Among 34 evaluable patients, PFR6 was 35.3% (90% CI: 21.8-50.8), with 6 (17.6%) achieving partial responses and 16 (47.1%) having stable disease. The median duration of the response was 20.3 months (95% CI: 5.1-22.0). Median PFS was 3.7 months (95% CI: 1.9-8.7), and median OS was 25.5 months (95% CI: 8.7-NR). **Conclusions:** The combination of avelumab and regorafenib demonstrated the ability to resensitize a subset of anti-PD(L)1-exposed NSCLC patients to immune checkpoint inhibition, leading to durable responses and a promising 6-month PFR. Biomarker analyses will also be presented, providing insights into predictors of response. Clinical trial information: NCT03475953. Research Sponsor: None.

8550 Poster Session

Identification of immunotherapy early treatment failure in non-small cell lung cancer (NSCLC) using a novel cell-free DNA (cfDNA) tissue-agnostic genome-wide methylome enrichment assay. First Author: Tuan Hoang, Princess Margaret Cancer Centre, University Health Network, Toronto, ON, Canada

Background: Immune checkpoint inhibitor treatment failure constitutes a significant clinical challenge in non-small cell lung cancer (NSCLC). Molecular residual disease (MRD) detection in NSCLC may allow earlier detection of disease recurrence/progression and enable early treatment intensification or clinical trial enrolment. We have developed a novel tissue-agnostic genome-wide methylation enrichment platform based on cell free methylated DNA immunoprecipitation and high throughput sequencing (cfMeDIP-seq). Here, we present data on its application as an MRD assay to predict early recurrence or progression in patients (pts) with NSCLC receiving immunotherapy. **Methods:** The study population consists of pts with stage III/IV NSCLC at the Princess Margaret Cancer Centre, treated with definitive chemoradiation followed by consolidative durvalumab (stage III) or with PD-1 inhibitors +/- chemotherapy (stage IV). Pts underwent serial blood collection prior to initiation of treatment, 2-4 weeks after treatment initiation and approximately 6-8 weeks thereafter until progression. 5-10 ng of cfDNA was isolated from plasma. A classifier was trained on an independent set of lung and non-cancer samples to quantify relative circulating tumor DNA (ctDNA) content. The analysis considered multiple timepoints. Results were considered "positive" if there was a detected result at any follow-up timepoint. Results were considered "negative" if all follow-up timepoints were reported as not detected. Progression-free survival (PFS) was compared between groups using a log-rank test. Hazard ratio (HR) was estimated using Cox proportional hazards model. **Results:** A total of 187 samples from 63 unique pts (44% stage III and 56% stage IV) were analyzed and correlated with PFS. Pts with a positive MRD test showed significantly worse PFS than those who tested negative (HR 4.8; 95% CI, 2.1-10.8, P$<$0.0001), sensitivity 80%, specificity 91%. The lead time between MRD positivity and progression was up to 12.6 months, with a mean of 5.1 months. Secondary analysis of pts with stage III NSCLC revealed significantly worse PFS in MRD-positive pts compared to MRD-negative pts (HR 8; 95% CI, 1.4-46.7, P=0.007). **Conclusions:** MRD detection using genome-wide methylome enrichment correlates strongly with PFS in pts with advanced NSCLC receiving immunotherapy. This tissue agnostic assay shows promise for early identification of treatment failure, enabling timely selection of patients for treatment intensification or clinical trials. Research Sponsor: None.

8551 Poster Session

A phase I trial of intratumoral adenovirus-interleukin-12 (IT-ADV/IL-12) and atezolizumab in metastatic non-small cell lung cancer (NSCLC) progressed on first-line immunotherapy. First Author: Zainub Ajmal, Houston Methodist Neal Cancer Center, Houston, TX

Background: Interleukin-12 (IL-12) is a cytokine that enhances anti-tumor immunity via interferon-gamma release and has demonstrated synergistic effects with immune checkpoint inhibitors (ICIs) in immunoquiescent tumors. We report results of phase I trial of intratumoral adenovirus-interleukin-12(IT-ADV/IL-12)plus atezolizumab in metastatic NSCLC patients who progressed on prior ICI. **Methods:** This institutional single-arm, open-label phase I trial enrolled 13 patients with metastatic NSCLC who progressed on ICI from October 2021 to February 2024. First 2 patients received IT-ADV/IL-12 at 5×10^{11} viral particles (vp), while the remaining 11 patients received a reduced dose of 3×10^{11} vp as per protocol. Atezolizumab (1200 mg) was given every 3 weeks for up to 1 year or till disease progression. Endpoints were safety (as per Common Terminology Criteria for Adverse Events v5.0) and disease control rate (DCR), including complete response (CR), partial response (PR), or stable disease (SD) as defined by RECIST v1.1. **Results:** 12/13 patients were included in analysis (1 patient excluded due to rapid progression before starting atezolizumab). All patients had initial response to prior ICI (4/12 with CR and 8/12 with PR) but later developed resistance. DCR was 50% (6/12), median progression-free survival (PFS) was 2 months, and median overall survival (OS) was 10.5 months. 2/12 (25%) patients were alive at the time of analysis with median follow up time of 22 months. PD-L1 expression did not affect treatment response. Grade $\geq$3 treatment-related adverse events (TRAEs) occurred in 4 patients, who demonstrated a higher likelihood of treatment response (p = 0.06), with all 4 achieving stable disease (SD). Most common TRAE of any grade was fatigue (4/12, 33%). There were no grade 4 or 5 events, and no treatment discontinuation related to TRAE. Next-generation sequencing results were available in 10/12 patients. The most common mutation was TP53, detected in 9/10 patients. There was no statistically significant association between the presence of TP53 mutation and treatment response. **Conclusions:** IT-ADV/IL-12 plus atezolizumab was safe, tolerable, and showed promising clinical benefit in metastatic NSCLC with acquired resistance to ICI, without new safety concerns. Presence of TP53 mutation did not impact the treatment response. Research Sponsor: Genentech.

Study Characteristics	Results (n=12)
Age (median) years	69 years
Female (n)	5 (41.6%)
PD-L1	
<1%	5 (41.6%)
>1%	7 (58.3%)
Sites of progression after IL-12 therapy	
Local (lung)	9 (75%)
Distant visceral	5 (41.6%)
Brain	1 (8.3%)
Regional Lymph node	6 (50%)
IT ADV/IL-12 related Grade 3 adverse events (n)	
Fever	2
Dyspnea	1
Hyponatremia	1
Anemia/leukopenia	1
Pneumonia	1
Response	
DCR (n)	6 (50%)
Progression (n)	6 (50%)
Median PFS	2 months
Impact of PD-L1 expression on PFS	
<1%	3.6 months
>1%	3.29 months (p= .84)
Median OS	10.5 months

8553 Poster Session

Circulating CD28-KLRG1+CD8+ T cells as prognostic indicators in advanced NSCLC chemoimmunotherapy. First Author: Cihui Yan, Department of Immunology, Tianjin Medical University Cancer Institute and Hospital, Tianjin, China

Background: Chemoimmunotherapy has become the standard first-line treatment for advanced non-small cell lung cancer (NSCLC), but patient responses vary. Consequently, identifying predictive biomarkers is crucial to optimize therapeutic strategies. Circulating T cells are a promising focus due to the convenience of blood sampling and the feasibility of repeated monitoring. Deciphering the specific T-cell subsets that respond to chemo-immunotherapy is critical for personalizing treatment and improving outcomes in advanced NSCLC patients. **Methods:** We conducted unsupervised analysis using multi-color flow cytometry on peripheral blood samples from 30 NSCLC patients enrolled in a phase 2 clinical study (ClinicalTrials.gov NCT04836728) to explore correlations between immune cell subsets with therapeutic outcomes. We integrated single-cell RNA and T cell receptor sequencing data from peripheral blood, tumor, and non-tumor tissues of 8 NSCLC patients to study the transcriptional state of key cell types involved in these correlations. **Results:** Flow cytometry analysis revealed that a higher proportion of CD28-KLRG1+ CD8+ T cells was found in the peripheral blood of patients with durable clinical benefit (DCB) and improved overall survival (OS). Within these T cells, the CD57+ subset was positively correlated with OS at baseline, while the CD57- subset was negatively correlated. However, during treatment, both subsets showed a positive association with OS, highlighting the predictive value of CD28-KLRG1+ CD8+ T for chemoimmunotherapy response. Further phenotypic and functional analyses demonstrated that CD28-KLRG1+ CD8+ T cells are highly proliferative (Ki67) and produce anti-tumor cytokines (IFN-γ, IL-2, and TNF-α) upon TCR stimulation, indicating their immune-responsive role. Although these cells expressed relatively low levels of exhaustion markers such as PD-1 and TIGIT, they exhibited high expression of TCF1 and TOX, pointing to a progenitor exhausted T cell state characterized by reduced exhaustion and enhanced functional potential. Single-cell transcriptomic and TCR profiling revealed that CD28-KLRG1+ CD8+ T cells underwent significant clonal expansion in the peripheral blood during chemoimmunotherapy, evidenced by the higher clonality index and lower Inverse Simpson index, indicating their superior clonal expansion capacity upon activation. Longitudinal analysis showed that these cells had the highest proportion of expanded clones during treatment, primarily distributed in the effector T cell clusters, suggesting their anti-tumor activity during chemoimmunotherapy. **Conclusions:** Circulating CD28-KLRG1+ CD8+ T cells are a valuable biomarker for predicting outcomes in first-line chemoimmunotherapy for patients with advanced NSCLC. These findings highlight their functional activity, clonal expansion, and role in antitumor immunity during treatment. Research Sponsor: National Natural Science Foundation of China; 82273083; National Natural Science Foundation of China; 82272733.

8555 **Poster Session**

T-cell effector cytokine signature as predictor of survival and toxicity in metastatic NSCLC patients treated with immunotherapy. First Author: Varshini Odayar, University of Michigan Medical School, Ann Arbor, MI

Background: Immune checkpoint inhibitors (ICIs) have led to significant prolongation of survival in patients with advanced non-small cell lung cancer (NSCLC). However, less than 20% have durable long-term survival. Presence of a pre-existing tumor immune response that can subsequently be unleashed by ICIs predicts success to ICI. Specifically, a T- cell effector replete tumor immune microenvironment predicts for improved survival, following ICI. Given intra-tumor heterogeneity, we asked whether baseline and on treatment T cell effector mediated serum cytokines predict benefit from ICI in metastatic NSCLC. We also asked whether cytokines predicted immune related adverse events (iRAEs) from ICI in these patients. **Methods:** To assess whether serologic markers were associated with response and toxicity to immunotherapy, we conducted a multiplex ELISA for a panel of 70 innate and adaptive immune cytokines and chemokines in 100 NSCLC patients treated with PD-1 inhibitors, either as monotherapy or in combination with chemotherapy. Cytokine expression was correlated with outcomes (progression- free and overall survival, PFS/OS) and occurrence of any grade 3 or greater iRAE. Kaplan Meier analyses were performed for survival analyses, with the median value used to stratify cytokines. We then compared the predictive value of this cytokine signature with other predictive signatures for outcomes from ICIs. **Results:** Increased concentrations of baseline TRAIL correlated with improved PFS and OS; conversely, decreased baseline IL-3, IL-6, IL-8, APRIL, IL20, IL33, MCP4, IL-7, and TARC correlated with improved PFS. Increased baseline SDF1 and TRAIL correlated with OS; conversely, decreased baseline IL-6, IL-8, TPO, I-TAC, IL-3, APRIL, IL-20, IL-33, MCP4, MCP2, IL-15, MCSF, PDGFa, VEGFA, and MIP1d correlated with improved OS. Increased concentrations of TRAIL correlated with increased concentrations of SDF1, Perforin, and GzmB (T effector cell, Teff signature). A high Teff signature was associated with a statistically significant improvement in OS, in univariate and multivariate analysis. IL1b and IL-17a were statistically higher in on treatment samples taken from in patients who developed IRAE, whereas Eotaxin3 and MIP1d were lower in on treatment samples taken from in patients who developed IRAE. **Conclusions:** We report that an increase in a Teff cell cytokine signature at baseline predicts long term survival from ICI and may reflect the presence of a pre-existing immune response characterized by increased T-effector cells that are then subsequently unleashed by ICI therapy. Conversely, higher baseline levels of IL-1β and IL-17 indicate the presence of a heightened inflammatory state that predisposes to the occurrence of iRAEs, following ICI therapy. Research Sponsor: Veterans Affairs Merit Award I01CX001560.

8556 **Poster Session**

Comparative efficacy of osimertinib with and without radiation therapy in EGFR-mutated non-small cell lung cancer with brain metastases. First Author: Rafi Aibani, Charleston Area Medical Center, Charleston, WV

Background: Osimertinib has demonstrated efficacy in managing brain metastases in EGFR-mutated non-small cell lung cancer (NSCLC). However, the optimal approach—using CNS-penetrant tyrosine kinase inhibitor (TKI) therapy alone versus combining it with radiation therapy—remains uncertain. This study examines whether Osimertinib combined with radiation provides superior intracranial control and outcomes compared to Osimertinib alone. **Methods:** Patients aged $\geq$18 years with NSCLC and brain metastases diagnosed between January 2010 and December 2024 were identified via the TriNetX Research Network. Two cohorts were analyzed: those receiving Osimertinib with stereotactic radiation or radiosurgery within six months (cohort 1) and those without radiation (cohort 2). Propensity score matching balanced baseline characteristics. Outcomes included survival, hospitalization rates, CNS complications, and second-line treatment initiation. A Kaplan-Meier analysis evaluated survival and mortality while a Cox proportional hazards model assessed the effects of covariates. **Results:** A total of 76,474 NSCLC patients were identified, 13,377 had brain metastases, and 743 received Osimertinib. Kaplan-Meier analysis indicated lower mortality in cohort 1 at 3 years (HR = 0.674, p = 0.0029), 5 years (HR = 0.719, p = 0.0091), and overall (HR = 0.709, p = 0.0063). CNS complications (risk difference = 20.28%, $p < 0.0001$) were higher in cohort 1, with 11 patients diagnosed with radiation necrosis after treatment, representing a 5.28% risk. Additionally more people in cohort 1 developed interstitial lung disease (risk difference = 9.1%, p=0.0016). Second-line treatment initiation (HR = 1.741, p = 0.0166) was also higher in cohort 1. Key predictors of increased mortality included hypertension (HR = 1.366, p = 0.0047), bone metastases (HR = 1.608, $p < 0.0001$), and liver metastases (HR = 1.319, p = 0.0408). Stereotactic radiosurgery in particular was associated with a lower hazard ratio (HR = 0.487, p = 0.0031). **Conclusions:** Combining Osimertinib with stereotactic radiation or radiosurgery improves survival in NSCLC with brain metastases but may increase CNS complications and second-line treatment rates. These findings highlight the need to balance survival benefits with treatment risks to optimize patient care. Research Sponsor: None.

8557 **Poster Session**

Updated analysis from NEJ045A study: Safety and efficacy of durvalumab plus carboplatin and etoposide for previously untreated extensive-stage small-cell lung cancer patients with a poor performance status. First Author: Tetsuhiko Asao, Department of Respiratory Medicine, Juntendo University Hospital, Tokyo, Japan

Background: Although the combination of an anti-PD-L1 antibody and platinum-based chemotherapy has become the standard care for extensive-stage small-cell lung cancer (ES-SCLC) patients (pts), its safety and efficacy for those with a poor PS are unclear. In the NEJ045A study, by adjusting the doses of carboplatin (CBDCA) and etoposide (ETP), durvalumab (DUR) plus CBDCA and ETP demonstrated tolerability and efficacy for ES-SCLC pts with a poor PS, meeting the primary endpoint of tolerability. Here, we report the updated data from NEJ045A, including the long-term effects of ICIs. **Methods:** Previously untreated ES-SCLC pts with PS 2–3 were enrolled. Eligible pts received 1500 mg DUR plus CBDCA and ETP every 3 to 4 weeks for up to 4 cycles, followed by DUR maintenance therapy. Initial dosages of CBDCA and ETP were AUC 4 and 80 mg/m^2 in PS 2 and AUC 3 and 60 mg/m^2 in PS 3. The dosages for the subsequent cycles were adaptively determined based on the adverse events (AEs) of the previous cycles. **Results:** From April 2021 to October 2023, 57 pts (43 pts with PS 2 and 14 pts with PS 3) were enrolled. At the data cutoff (Oct 3rd, 2024), the median follow-up period for overall survival among patients with censored data was 23.4 months (12.9-32.7) in the FAS population. The median age was 74 years old (range 55-86). 79% was male. The median number of cycles of induction therapy was 4 (range 1-4), and the median number of cycles of durvalumab maintenance was 3 (range 1-16) in PS 2 and 7 in PS 3 (1-22). A total of 34 patients (64%) completed induction therapy, comprising 28 pts (67%) in PS 2 and 6 pts (50%) in PS 3. Doses of CBDCA and/or ETP were increased during induction therapy in 24% of PS 2, and 18% of PS 3. Updated median PFS in PS 2 and PS 3 were 4.5 months (95% CI, 3.1-5.8) and 4.5 months (95% CI, 1.4-8.2). The 1-year survival rates in PS 2 and PS 3 were 50% (95% CI, 37.0-67.7) and 18% (95% CI, 5.2-63.7). Updated median OS in PS 2 and PS 3 were 11.3 months (95% CI, 6.7- 16.1) and 5.1 months (95% CI, 2.1-8.5). Patients who completed induction therapy demonstrated longer OS compared to those who did not (median OS, 15.0 vs. 3.8 months). Treatment was discontinued in 100% of PS 2 and 93% of PS 3, and the reasons for discontinuation (PD/AE/other) were 79%/12%/9% in PS 2 and 38%/54%/8% in PS 3. **Conclusions:** DUR + CBDCA + ETP therapy was well tolerated for ES-SCLC with poor PS, and completion of induction therapy was associated with an improvement in OS. Clinical trial information: CRB3180025. Research Sponsor: Astra Zeneca.

8558 **Poster Session**

Avidity engineered multifunctional antibodies for stimulation and orchestration of innate and adaptive immune cells in tumor tissues. First Author: Robert Friesen, Avidicure B.V., Naarden, Netherlands

Background: Antibodies and ADCs are mainstays in the treatment of cancer. However, given difficulties in achieving a deep and sustained response, significant improvements are desirable. We report on first in class "Booster" molecules, based on clinically validated ADCC-competent antibodies, equipped with two immunomodulatory domains that are affinity engineered to be functional only when in contact with a tumor cell. We see strong expansion and increased cytotoxicity of immune cells in the presence of cancer cells *in vitro*, activation of relevant immune cell types *ex vivo*, and reduction of tumor burden *in vivo*, with significantly better activity than adoptive cell therapy or control antibody without these immunomodulatory domains. **Methods:** NRG mice were engrafted with luciferase-expressing SKOV3 cells via intraperitoneal injection 7 days prior to treatment. Mice received 1 million human NK cells isolated from healthy donors. Compounds were administered biweekly, and low dose IL2 thrice weekly. Blood was collected weekly, and tumor burden monitored weekly *via* bioluminescence. *ex vivo*: *in situ* activation of tumor infiltrating immune populations was evaluated by nanostring in freshly isolated tumor tissue. *in vitro*: cytotoxicity was measured by quantifying the number of alive tumor cells using automated microscopy. Expansion was performed by stimulating NK cells weekly with tumor cells that were opsonized with Booster or antibody, NK cells were counted weekly to determine expansion. **Results:** Mice treated with a TROP2 targeting Booster demonstrated superior tumor control than sacituzumab treated mice, with strong tumor remission by day 35. High NK counts were observed in the blood of Booster treated mice, and no NK cells were detected in that of sacituzumab treated mice. In the peritoneal cavity, NK counts were up to 100x higher in Booster treated mice than in sacituzumab treated mice. Our Booster reprograms the immune microenvironment *ex vivo* in freshly isolated tumor tissue, transforming a cold tumor into a hot tumor. It activates multiple cytotoxic and IFN-γ pathways, stimulates CD8+ T cell activation, downregulates pro-tumor pathways in Tregs and induces a phenotypic shift in macrophages from the immunosuppressive M2 to the pro-inflammatory M1 phenotype. In separate *in vitro* assays we saw sustained expansion and enhanced cytotoxicity of NK cells for at least 6 weeks. Cells stimulated with TROP2 Booster showed prolonged tumor control, whereas sacituzumab antibiody stimulated cells failed to sustain tumor control beyond 21 days. **Conclusions:** In correlation with extensive *in vitro* and *ex vivo* data, we observe a prolonged and significant improvement in tumor control in mice treated with Boosters compared to mice treated with control antibody. Work is ongoing to develop these molecules, with the first clinical trial expected to start next year. Research Sponsor: None.

8559 **Poster Session**

Predictive value of circulating tumor DNA detection for long-term survival in patients with advanced lung cancer undergoing chemoimmunotherapy. First Author: Hui Li, Zhejiang Cancer Hospital, Hangzhou, China

Background: Chemoimmunotherapy (ChemoIO) has emerged as the first-line standard treatment option for advanced non-small cell lung cancer (NSCLC) without drive gene mutation. However, only a portion of patients experienced long-term survival, even among those who achieved partial or complete response (PR or CR) in early assessments. This study assessed circulating tumor DNA (ctDNA) detection in predicting long-term survival in advanced NSCLC patients using a novel 2365-gene fixed panel integrating mutation, copy number variation (CNV), and fragmentomics (Frag). **Methods:** Based on the SheildingUltra panel developed by Geneseeq, using a discovery cohort composed of over 200 lung cancer and healthy plasma samples, AI-driven models were developed to improve the ctDNA detection sensitivity by incorporating mutations, CNV, and Frag. The enhanced panel was retrospectively validated in a cohort of 107 advanced NSCLC patients using plasma samples collected during PR/CR stages of ChemoIO. Moreover, the fixed panel was prospectively evaluated in an independent cohort of 38 patients who achieved PR/CR in early assessments, with blood samples collected both before treatment and on Day 1 of Cycle 5 (C5D1) of therapy. The value of ctDNA detection results for predicting long-term survival was subsequently evaluated in both cohorts. **Results:** The enhanced fixed panel demonstrated robust performance in the discovery cohort, effectively discriminating lung cancer patients from healthy individuals through the integration of mutations, CNV, and Frag. In the retrospective validation cohort including 107 patients in PR/CR status, ctDNA-negative patients had significantly longer progression-free survival (PFS) (median PFS: not reached [NR] vs. 14.1 months, hazard ratio (HR): 0.36 (95% confidence interval [CI]: 0.18-0.74), P=0.004) and overall survival (OS) (median OS: NR vs. NR, HR: 0.10 (95% CI:0.02-0.43), P≤0.001) compared to ctDNA-positive patients. In the prospective validation cohort, the ctDNA status determined from plasma collected at C5D1 successfully stratified patients into groups with long- and short- PFS and OS. The median PFS was NR for both groups, with a HR (95% CI) of 0.19 (0.04-0.92) and a p-value of 0.021. The median OS was also NR for both groups, with a HR (95% CI) of 4.56e-10 (0-infinity) and a p-value of 0.011. However, the pre-treatment ctDNA status was not significantly associated with survival. **Conclusions:** Using a novel ctDNA detection panel incorporating mutation, CNV, and Frag, we found the ctDNA status during the treatment may serve as a potential biomarker for predicting long-term PFS in advanced NSCLC patients undergoing ChemoIO. Additional prospective studies are needed to confirm these results and guide clinical decisions for optimal immunotherapy in NSCLC patients. Research Sponsor: None.

8560 **Poster Session**

Phase 2 study of pembrolizumab (pembro) plus plinabulin (plin) and docetaxel (doc) for patients (pts) with metastatic NSCLC after progression on first-line immune checkpoint inhibitor alone or combination therapy: Initial efficacy and safety results on immune re-sensitization. First Author: Yan Xu, Department of Respiratory and Critical Care Medicine, Peking Union Medical College Hospital, Chinese Academy of Medical Sciences & Peking Union Medical College, Beijing, China

Background: Immune checkpoint inhibitor (ICI)-based treatment regimens have become the standard of care for first-line treatment of EGFR/ALK wild-type NSCLC. However, >60% pts inevitably develop progressive disease (PD) from acquired resistance (AR), which could be due to T cell exhaustion and antigen presenting cell (APC) pathway mutation. For patients with PD, the standard of care (SOC) is still doc, while the efficacy is limited with ~10% ORR, median PFS 3.7 months in TROPION-Lung01. Thus, there is a huge unmet need for this setting of patients. Plin is a selective immunomodulating microtubule-binding agent which promotes dendritic cell maturation and enhances anti-tumor T cell response. The mechanism of action has been validated via *in vitro*, *in vivo* models, and human trials, suggesting that plin may have the potential to overcome immunotherapy AR. This phase 2 study was aimed to evaluate the efficacy and safety of pembro combined with plin and doc in pts with metastatic NSCLC who had progressed after ICI. **Methods:** In this single-arm phase 2 trial, metastatic NSCLC pts who developed acquired resistance on immunotherapy alone or in combination with platinum-doublet chemotherapy were enrolled. Participants received pembro 200 mg, plin 30 mg/m^2, and doc 75 mg/m^2 intravenously day 1 every 21days. The primary endpoint is investigator-based ORR per RECIST 1.1. The secondary endpoints included PFS, OS, DoR and safety. The sample size is 47 patients. The ORR and DOR was assessed in the evaluable set. **Results:** At of the 21th Jan, 2025, data cutoff, 47 pts were enrolled, the median follow-up time was 8.7 months, median age of 67.5 (rang 44-83), 80.9%(n=38) were male, 68.1% had smoking history. Histology included 66% with non-squamous, 34% with squamous cell carcinoma. Efficacy and safety were analyzed in the 45 patients, 40 patients were evaluable. The ORR was 20% (confirmed ORR was 17.5%) and the median DoR was 9.4 m; the DCR was 81.6% (defined as PR and SD> 4 months), median PFS was 8.2 m (current 6 m PFS rate was 60.2%, 12 m PFS rate was 29.9%), OS had not been reached (6 death since the first patient enrollment of 02/2023) . G3 or higher treatment-related AEs (TRAEs) were reported by 37.8% of pts, ≥5% TRAEs include diarrhea (6.7%), myelosuppression (8.9%) and hypertension (8.9%). **Conclusions:** Pembro plus plin and doc in pts with metastatic NSCLC who developed PD on ICI shows promising efficacy, with doubling PFS and DCR compared with historical data of doc. The AEs of the triple combination treatment is manageable. Further investigations into which pts would benefit from continued ICI treatment after progression is warranted. Clinical trial information: NCT05599789. Research Sponsor: BeyondSpring and MSD China. Plinabulin was provided by BeyondSpring and pembrolizumab by MSD China.

8561 **Poster Session**

A phase 2 study of HLX07 plus serplulimab with or without chemotherapy versus serplulimab plus chemotherapy as first-line therapy in advanced squamous non-small cell lung cancer. First Author: Yi-Long Lung Cancer Wu, Guangdong Provincial People's Hospital, Guangzhou, China

Background: Approved first-line therapies of PD-L1/PD-1 inhibitors plus chemotherapy conferred significant survival benefits for advanced squamous non-small cell lung cancer (sqNSCLC). However, the prognosis remains to be improved. The epidermal growth factor receptor (EGFR) is highly expressed in sqNSCLC and associated with a poor prognosis. This study aimed to compare the efficacy of HLX07, a novel humanized anti-EGFR antibody, plus serplulimab (anti-PD-1 antibody) ± chemo versus serplulimab plus chemo as first-line option for advanced sqNSCLC. **Methods:** This randomized, multicenter phase 2 study consisted of 4 parts that assessed varied combinations of HLX07 (at different doses), serplulimab, and chemotherapy. Part 3 evaluated the preliminary efficacy of the three-drug combination and is presented below. Patients with stage IIIB/IIIC or IV sqNSCLC that was not amenable to surgery or radiation therapy and high tumor expression of epidermal growth factor receptor (H score≥150) and no prior systemic therapy were randomized 1:1 to receive intravenous HLX07 at 800 mg (group A) or 1000 mg (group B), in combination with serplulimab (300 mg) and chemotherapy (carboplatin and nab-paclitaxel), once every three weeks. The primary endpoints were independent radiological review committee (IRRC)-assessed objective response rate (ORR) and progression-free survival (PFS) per RECIST 1.1. **Results:** As of 31 December 2024, 27 patients were enrolled and randomly assigned to group A (n=13) and group B (n=14) in part 3. 15 (55.6%) patients had metastatic disease. With a median follow-up of 16.0 months, IRRC-assessed confirmed ORR per RECIST 1.1 was 69.2% (95% CI 38.6–90.9) in group A and 71.4% (95% CI 41.9–91.6) in group B. Disease control rate was 92.3% (95% CI 64.0–99.8), and 100% (95% CI 76.8–100.0), respectively. Median PFS was 15.1 (95% CI 4.1–not available) months in group A and not reached in group B. The median overall survival and duration of response were not reached in either group as of the data cutoff date. All the patients in both groups reported treatment-emergent adverse events (TEAEs); most common TEAEs of any grade included neutrophil count decreased (92.3% vs. 71.4%), white blood cell count decreased (84.6% vs. 85.7%), anemia (84.6% vs. 78.6%), platelet count decreased (76.9% vs. 71.4%), hypokalemia (53.8% vs. 64.3%), rash (46.2% vs. 57.1%), alopecia and hypocalcemia (46.2% vs. 50.0% for each). 6 (46.2%) patients, and 8 (57.1%) in group A, and B reported immune-related adverse events, respectively. **Conclusions:** First-line HLX07 plus serplulimab and chemotherapy showed encouraging preliminary efficacy with a manageable safety profile in patients with advanced sqNSCLC which warrants further investigation. Clinical trial information: NCT04976647. Research Sponsor: Shanghai Henlius Biotech, Inc.

8562 **Poster Session**

Differential predictive impact of PD-L1 expression on immunotherapy outcomes and immunophenotype in squamous versus non-squamous NSCLC. First Author: Valentina Santo, Lowe Center for Thoracic Oncology, Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA

Background: PD-L1 tumor proportion score (TPS) is a key biomarker for immune checkpoint inhibitors (ICIs) efficacy in non-small cell lung cancer (NSCLC), but its predictive value in patients (pts) with squamous (SQ) histology remains uncertain, highlighting the need for histology-specific studies. **Methods:** Clinicopathologic, genomic, and outcomes data were collected and analyzed from advanced NSCLC pts treated with ICIs ± chemotherapy (CT) at Dana-Farber Cancer Institute, Memorial Sloan Kettering Cancer Center and MD Anderson Cancer Center. Cox regression tested the association between PD-L1 levels and survival to ICIs by histology, adjusting for potential confounders such as treatment regimen and line. Multiplexed immunofluorescence (mIF) on baseline tissue samples quantified CD8+, PD1+, CD8+/PD1+, and FOXP3+ densities, stratifying by PD-L1 TPS and histology. **Results:** Among 4967 NSCLC pts treated with ICIs ± CT, 727 (14.6%) had SQ histology. Among pts with available PD-L1 TPS, 1359 (37.9%) had TPS <1%, 1061 (29.6%) 1–49%, and 1167 (32.5%) ≥50%. Increasing PD-L1 TPS of <1%, 1–49% and ≥50% correlated with significant stepwise improvements in progression-free (PFS) and overall survival (OS) in pts with NonSQ NSCLC but not in those with SQ (Table 1). In SQ NSCLCs, there was no difference in PFS and OS between pts with PD-L1 TPS of 1–49% vs ≥50%, while only a dichotomized PD-L1 TPS (<1% vs ≥1%) was predictive of longer survival in this histology (PFS adjusted hazard ratio [aHR]: 0.72, p<0.01; OS aHR: 0.76, p=0.02). Comparing histologies, PFS and OS to ICIs ± CT were similar between SQ and NonSQ NSCLCs in PD-L1 TPS subgroups of <1% and 1–49%. However, among pts with a PD-L1 TPS ≥50%, those with NonSQ NSCLC had longer survival compared to SQ (PFS aHR: 1.30, p=0.01; OS aHR: 1.43, p<0.01), indicating stronger predictive value of increasing PD-L1 TPS levels only in NonSQ. mIF analysis (229 samples: 22 SQ, 207 NonSQ) showed lower intratumoral CD8+, PD1+, CD8+/PD1+, and FOXP3+ densities in SQ vs NonSQ. Increasing PD-L1 TPS significantly correlated with higher CD8+ cells in NonSQ NSCLCs (R = 0.25, p<0.01) but not in SQ (R = -0.034, p = 0.89). A similar association was observed for PD1+, CD8+/PD1+, and FOXP3+ cells. **Conclusions:** Increasing PD-L1 levels show stepwise PFS and OS improvements in NonSQ but not in SQ NSCLCs, where TPS acts as a dichotomous (<1% vs ≥1%) rather than continuous predictor. These findings have implications for treatment decision making as well as ICIs trial design and interpretation. Research Sponsor: None.

	PD-L1 TPS <1% vs 1-49%	PD-L1 TPS <1% vs ≥50%	PD-L1 TPS 1-49% vs ≥50%
SQ PFS mo	4.0 vs 6.6	4.0 vs 6.2	6.6 vs 6.2
aHR, p	*0.72, <0.01*	*0.71, 0.01*	*0.99, 0.95*
NonSQ PFS mo	4.6 vs 5.8	4.6 vs 8.2	5.8 vs 8.2
aHR, p	*0.79, <0.01*	*0.56, <0.01*	*0.70, <0.01*
SQ OS mo	13.0 vs 17.0	13.0 vs 17.5	17.0 vs 17.5
aHR, p	*0.77, 0.04*	*0.76, 0.06*	*0.98, 0.92*
NonSQ OS mo	14.7 vs 18.3	14.7 vs 27.7	18.3 vs 27.7
aHR, p	*0.81, <0.01*	*0.59, <0.01*	*0.72, <0.01*

8563 **Poster Session**

Clinical outcomes and predictors of response to PD-(L)1 blockade in patients with oncogene-driver negative NSCLC who have never smoked. First Author: Eleonora Gariazzo, Lowe Center for Thoracic Oncology, Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA

Background: Non-small cell lung cancer (NSCLC) in patients (pts) who have never smoked is associated with poor response to immune checkpoint inhibitors (ICI). However, most studies have focused on pts with actionable oncogenes (e.g., EGFR, ALK, ROS1, RET, MET), and it remains unclear whether specific clinicopathologic and genomic features can predict ICI response in those without these actionable drivers. **Methods:** Clinicopathologic characteristics and outcomes data were collected from pts with metastatic, oncogene driver-negative, NSCLC who received ICI across 5 academic cancer centers in US and EU. Single sample gene set enrichment analysis was performed on NSCLC samples from the Stand Up To Cancer (SU2C) cohort to characterize transcriptomic correlates of response to ICI monotherapy in responders and non-responders. **Results:** Of 5639 pts with metastatic NSCLC analyzed, 708 (12.6%) tested negative for actionable oncogene drivers and had never smoked. Among these, median age was 64 years, 59.5% were women, 65.2% had ECOG PS 0/1, and 83.8% had adenocarcinoma. At a median follow-up of 36.9 months (mo), objective response rate (ORR) was 21.8%, median progression-free survival (mPFS) was 4.5 mo, and median overall survival (mOS) was 16.9 mo in this patient population. Pts with PD-L1 TPS $\geq$1% had significantly higher ORR (31.1% vs. 16.1%, $p<0.01$), and longer mPFS (HR 0.74, $p<0.01$) compared to those with PD-L1 <1%. Similarly, pts with very high TMB ($\geq 90^{th}$ percentile) had higher ORR (52.2% vs 22.8%, $p<0.01$), longer mPFS (HR 0.50, $p<0.01$), and mOS (HR 0.40, $p<0.01$) compared to those with a TMB $<90^{th}$ percentile. Pts with positive PD-L1 expression $\geq$1% and very high TMB had the highest ORR and the longest mPFS and mOS compared to pts with either one of these biomarkers alone. Treatment outcomes also varied by regimen: pts receiving dual PD-(L)1+CTLA-4 blockade or PD-(L)1 blockade + chemotherapy had higher ORR compared to those receiving PD-(L)1 monotherapy (30.0% vs 36.5% vs 10.3%, respectively, $p<0.01$). Dual PD-(L)1+CTLA4 inhibition was also associated with significantly longer mPFS (9.4 vs 6.9 vs 2.9 mo, $p<0.01$) and mOS (47.5 vs 19.7 vs 14.7 mo, $p<0.01$) compared to PD-(L)1 + chemotherapy and PD-(L)1 monotherapy, respectively. These differences were validated in pts receiving these regimens as first-line therapy. In NSCLC samples from pts who had never smoked without oncogenic driver mutations in the SU2C cohort, responders to ICI showed upregulation of innate and adaptive immune responses pathways, including enhanced MHC I/II antigen presentation, as well as increased T-cell activation, proliferation, and chemotaxis. **Conclusions:** These results emphasize how PD-L1$\geq$1%, very high TMB, and use of dual checkpoint blockade are associated with improved outcomes in pts who have never smoked with oncogene-driver negative NSCLC, aiding personalized ICI use in this neglected population. Research Sponsor: None.

8564 **Poster Session**

Efficacy and safety of metronomic oral vinorelbine combined with PD-1 inhibitors as first-line therapy in advanced non-small-cell lung cancer in elderly patients. First Author: Lin Li, Department of Medical Oncology, Beijing Hospital, National Center of Gerontology, Institute of Geriatric Medicine, Chinese Academy of Medical Sciences, Beijing, China

Background: Elderly individuals aged over 70 constitute the majority of Non-small cell lung cancer(NSCLC) patients. However, their poor general status, multiple co-morbidities, and limited social support present significant challenges in antitumor treatments, especially standard platinum-based chemotherapy. Metronomic chemotherapy (MCT) involves the regular administration of chemotherapy drugs at low doses, offering improved safety, anti-angiogenic tumor effects, and immune modulation compared to conventional chemotherapy. In light of these considerations, we have designed a phase II trial to evaluate the efficacy and safety of PD-1 inhibitors plus metronomic oral vinorelbine (mOV) as first-line therapy for elderly patients with metastatic NSCLC. **Methods:** Elderly patients($\geq$70 years) with previously untreated locally advanced or metastatic NSCLC without a sensitising EGFR mutation, ALK fusion or ROS1 fusion and with an Eastern Cooperative Oncology Group (ECOG) performance status score of 0 or 1 were recruited for this study. Patients received PD-1 inhibitors combined with mOV (30mg, TIW1, day 1-3-5 per week) for 6 cycles, followed by PD-1 inhibitors maintenance until disease progression or intolerable toxicities. The primary endpoint was progression-free survival (PFS). Secondary endpoints included overall survival (OS), objective response rate (ORR), disease control rate (DCR), and safety profiles. **Results:** From March 2021 to November 2024, 37 patients were enrolled in the study. The median age was 77 with 31 (83.8%) males. Median follow-up time was 13.5 months (range 1.8 months-44.7 months). The median PFS was 10.9 months (95%CI: 1.0 months-20.9 months) and the median OS was 26.2 months (95%CI: (6.7 months-45.7 months). The ORR and DCR were 33.3% (95%C1: 17.3%-47.5%) and 86.1% (95%CI: 71.9%-95.7%), respectively. Compared to those with low PD-L1 expression (PD-L1 TPS <50%), patients with high PD-L1 expression (PD-L1 TPS $\geq$50) had significant prolonged PFS [mPFS=6.1 months vs 23.0 months, p=0.01, HR = 0.19 (95%CI 0.05-0.69)] and OS [mOS=6.1 months vs not reached, p=0.02, HR = 0.09 (95%CI 0.01-0.70)]. Adverse events (AEs) of any grade were observed in 29 (78.4%) patients of which immune-related adverse events (irAEs) occurred in 14 (37.8%) patients. Grade 3-4 adverse reactions were reported in 5 (13.5%) patients, 4 of which were irAEs, including immune-associated pneumonia, myocarditis, myositis, enteritis and hepatitis. No grade 5 adverse events were reported. **Conclusions:** The regimen of PD-1 inhibitors plus mOV as first-line therapy showed significant survival benefits and a favorable safety profile in elderly patients with driver-gene-negative metastatic NSCLC, particularly those with high PD-L1 expression. Clinical trial information: ChiCTR2300074586. Research Sponsor: National High Level Hospital Clinical Research Funding of China; BJ-2023-073.

8565 **Poster Session**

Analysis of genomic and immune microenvironment differences in Chinese populations: Revealing potential mechanisms of poor immunotherapy outcomes in patients with EGFR mutation and ALK fusion non-small cell lung cancer. First Author: Junhong Lü, Thoracic Surgery, Guangzhou Overseas Chinese Hospital, Guangzhou, China

Background: Non-small cell lung cancer (NSCLC) patients with EGFR mutations or ALK fusions often exhibit suboptimal responses to immunotherapy, yet the genomic and immunological basis for this remains poorly understood. This study aims to elucidate the genomic and immune microenvironment differences in NSCLC patients harboring EGFR mutations or ALK fusions that may contribute to their distinct immunotherapy responses. **Methods:** We analyzed tumor specimens from 12,528 NSCLC patients using a comprehensive next-generation sequencing (NGS) panel targeting 733 genes. Of these, 191 patients also underwent multiplex fluorescence immunohistochemistry (mIHC) analysis to assess the immune microenvironment. Subgroups included patients with EGFR mutations, ALK fusions, both EGFR mutations and ALK fusions, and those wild-type for both EGFR and ALK. We compared these groups for DNA damage response (DDR) gene mutation frequencies, tumor mutational burden (TMB), intratumoral heterogeneity (ITH), and immune microenvironment. **Results:** Among the cohort, 6389 (51%) harbored EGFR mutations and 300 (2.4%) had ALK fusions. Patients with EGFR mutations or ALK fusions exhibited significantly lower DDR mutation frequencies compared to their wild-type counterparts ($P<0.001$). TMB levels showed a gradient: wild-type > EGFR mutation > EGFR mutation with ALK fusion > ALK fusion ($P< 2.2e-16$), with wild-type patients having markedly higher TMB than any other group ($P< 2.22e-16$, P=0.0047, $P< 2.22e-16$). Conversely, ITH was lowest in wild-type patients and progressively higher with ALK fusions (P=0.017), EGFR mutations ($P< 2.22e-16$), and combined mutations ($P< 2.22e-16$). Lower ITH was associated with higher immunogenic neoantigen production, correlating with improved immunotherapy responses. Immunohistochemical analysis revealed that EGFR-mutant tumors had significantly fewer M1 tumor-associated macrophages (CD68+ HLA-DR+) ($P<0.001$) within the tumor parenchyma and reduced CD4+ T cell (P=0.013) infiltration in the tumor stroma compared to wild-type. **Conclusions:** Our findings suggest that low TMB, high ITH, and a suppressed immune microenvironment characterize EGFR-mutant and ALK-fusion NSCLC, potentially undermining their immunotherapy efficacy. These genomic and immunological signatures, particularly ITH and immune cell distribution, might be critical factors affecting the immunotherapy responsiveness of these patient subsets, warranting further investigation into tailored therapeutic strategies. Research Sponsor: None.

8566 **Poster Session**

A phase II study of durvalumab, doxorubicin, and ifosfamide in recurrent and/or metastatic pulmonary sarcomatoid carcinoma (KCSG LU-19-24). First Author: Bhumsuk Keam, Department of Internal Medicine, Seoul National University Hospital, Seoul, South Korea

Background: Pulmonary sarcomatoid carcinomas (PSCs) are very rare and aggressive tumors with poor prognosis. While conventional cytotoxic agents have limited efficacy in PSC, immune checkpoint inhibitors or doxorubicin showed potential efficacy. We evaluated the efficacy and safety of durvalumab, doxorubicin, and ifosfamide for recurrent and/or metastatic PSC. **Methods:** Patients with recurrent or metastatic PSC received durvalumab (1500 mg, day1), doxorubicin (20 mg/m² IV, days 1–3) and ifosfamide (1.5 g/m² IV with mesna, days 2–4) every 3 weeks for up to 4 cycles, followed by durvalumab monotherapy until disease progression or unacceptable toxicity, upto 12 months. The primary endpoint was objective response rate (ORR). The secondary endpoints included progression-free survival (PFS), overall survival (OS), duration of response (DOR) and toxicity. **Results:** A total of 20 patients (15 male, 5 female) were enrolled, and the median age was 63.5 (range, 44-75). Sixteen (88.9%) of the 18 evaluable cases were PD-L1 positive. Six (30.0%) out of 20 patients had previously received palliative chemotherapy. Among them, 18 patients were evaluable for the primary endpoint. ORR was 35.0% (95% CI, 17.7-55.8%) based on modified RECIST version 1.1. and the median DOR was 5.3 months (95% CI, 1.7-not estimated). After a median follow-up duration of 7.0 months (range, 1.2-37.6), the median PFS and OS were 4.8 months (95% CI, 2.0-6.5 months) and 9.4 months (95% CI, 5.5-26.8 months), respectively. Adverse events (AEs) of any grade were reported in 19 patients with serious AEs in 10 patients. The most common AEs were nausea (9.7%), anemia (7.5%), vomiting (5.4%). No treatment-related deaths were reported. **Conclusions:** Given its rarity and aggressiveness of PSC, the combination of durvalumab, doxorubicin, and ifosfamide demonstrated promising efficacy in recurrent and/or metastatic cases. Further studies are required to validate these findings and optimize treatment strategies for PSC. Clinical trial information: NCT04224337. Research Sponsor: None.

8567 Poster Session

Race-associated clinicogenomic correlates of outcomes to immune checkpoint inhibitors alone or with chemotherapy in non-small cell lung cancer (NSCLC). First Author: Nirosha D. Perera, Department of Cancer Medicine, The University of Texas MD Anderson Cancer Center, Houston, TX

Background: PD-L1 low and STK11 mutations are associated with immune checkpoint inhibitor (ICI) resistance in non-small cell lung cancer (NSCLC). It is unclear whether there are differences in clinicogenomic predictors by race and ethnicity. **Methods:** We retrospectively studied NSCLC patients 18 or older, without targetable EGFR or ALK alterations, treated with frontline combination chemotherapy with ICI (ICI-chemo) or ICI monotherapy (ICI-mono) between January 2014 and February 2020 at MD Anderson Cancer Center. We analyzed clinicogenomic and survival characteristics by race/ethnicity. Differences in clinicogenomic predictors were assessed through log-rank and chi-squared comparison of proportions tests. Survival differences were estimated via Kaplan-Meier method. **Results:** 1648 patients met inclusion criteria. Poor performance status (PS) frequency was statistically significantly different among groups, highest in African American (AA) (30.7%) and Native Alaskan/Hawaiian or American Indian (NAHAI) (30%) patients (Table). Steroid prescription within one month of ICI start was also more frequent in AA (46.4%) and NAHAI (40%) patients. However, heavy smoking was more frequent in White (62%) patients. Mutation rates were statistically significantly different for KRAS and STK11 but not TP53 (Table). KRAS mutations were most frequent in White (24.7%) and AA patients (24.2%). STK11 mutations were most frequent in AA (14.4%) patients. TP53 mutations were most frequent in HL and Black (43.6%, 41.8%) patients. Median overall survival (OS) was lower (21.3 and 24.5 months) for HL and NAHAI patients and higher (25.4, 26.4, and 30.7 months) for White, Black, and Asian patients, though not statistically significantly different (Table). **Conclusions:** AA and HL patients had lower rates of heavy smoking but higher rates of poor genomic prognostic factors. Asian patients had the lowest rates of heavy smoking, KRAS, TP53, and STK11 mutations, but the highest rates of PD-L1 <1%. Despite several traditional clinicogenomic prognostic factors being poor for minority racial/ethnic groups, OS difference was not statistically significant. Research Sponsor: Philanthropic Contributions to The University of Texas MD Anderson Lung Moon Shot Program; P30 CA016672.

	White	Black or African American (AA)	Hispanic or Latino (HL)	Asian	Native Alaskan/ Hawaiian or American Indian (NAHAI)	p-value
Total cohort n=1648, No. (%)	1305 (79.2)	153 (9.3)	101 (6.1)	79 (4.8)	10 (0.6)	
ECOG PS 2-3 at ICI start	265 (20.3)	47 (30.7)	23 (22.8)	20 (25.3)	3 (30)	**0.003**
Steroids within 1 mo of ICI start	480 (36.8)	71 (46.4)	39 (38.6)	29 (36.7)	4 (40)	**0.02**
20+ Pack Years Smoking	652 (62)	63 (50)	26 (46.4)	18 (43.9)	5 (55.6)	**0.001**
PD-L1 <1%	313 (24)	31 (20.3)	16 (15.8)	25 (31.6)	1 (10)	**0.01**
$KRAS_{mut}$	322 (24.7)	37 (24.2)	23 (22.8)	6 (7.6)	4 (40)	**0.001**
$TP53_{mut}$	486 (37.2)	64 (41.8)	44 (43.6)	25 (31.6)	4 (40)	0.1
$STK11_{mut}$	129 (9.9)	22 (14.4)	7 (6.9)	2 (2.5)	1 (10)	**0.005**
Median OS (mo)	25.4	26.4	21.3	30.7	24.5	0.2

8568 Poster Session

Predictive implications of immune-related adverse events after exposure to VEGF inhibitors on outcomes in patients with advanced NSCLC treated with prior immune check point inhibitor. First Author: Jinah Kim, University of Vermont Medical Center, Department of Hematology and Oncology, Burlington, VT

Background: Immune-related adverse events (irAEs) have been associated with enhanced antitumor immune activity, potentially correlating with improved clinical outcomes. Implications of delayed irAE after exposure to VEGF inhibitors on clinical outcomes remain poorly defined. We hypothesize that patients who develop irAEs during or following immune checkpoint inhibitors (ICIs) therapy will demonstrate improved overall survival (OS) and progression-free survival (PFS) compared to those who do not develop irAEs. **Methods:** We conducted a single center retrospective chart review of patients with non-small cell lung cancer (NSCLC) who had received at least one line of immunotherapy and subsequently underwent treatment with ramucirumab upon progression. Patients were categorized based on the presence or absence of irAEs during or after ICIs. 41 patients were identified. Kaplan-Meier estimates and log-rank tests were used for survival analyses, while Cox proportional hazards regression model was used to estimate hazard ratios (HRs) and 95% confidence intervals (CIs). **Results:** Of 41 identified subjects, median age was 63, 83% had adenocarcinoma, 56% had metastatic disease at presentation and 93% had received previous chemotherapy. Initial immunotherapy received was pembrolizumab 66%, nivolumab 20% and durvalumab 10%. For second line treatment, 85% received ramucirumab with docetaxel. 37% (n=15) of patients experienced irAE after ICIs. From the start of ramucirumab, the median OS was 8.0 months for patients with irAEs versus 6.0 months for those without, and the median PFS was 7.0 months versus 3.0 months, respectively. HRs suggested a trend favoring longer survival for patients with irAEs (HR for PFS = 0.52; 95% CI: 0.25–1.08; p=0.0072 and HR for OS = 0.62; 95% CI: 0.29–1.27; p=0.0192), though not statistically significant. Patients who developed delayed irAEs (after the start of ramucirumab) (n=4, 9.7%) had significantly prolonged OS, 34.5 months (HR 0.22; 95% CI: 0.05–0.94; p=0.0406) and PFS 33.5 month (HR 0.18; 95% CI: 0.043–0.80; p=0.0234) compared to those without. The most common irAEs were colitis (47%), rash (20%), and pneumonitis (13%). **Conclusions:** Our findings suggest that the occurrence of irAEs during or after immunotherapy may be associated with improved outcomes in patients with advanced NSCLC who receive ramucirumab-based treatment. Although the observed survival benefit for patients with any irAE was not statistically significant, those who developed delayed irAEs after initiating ramucirumab exhibited significant prolongation of OS and PFS. This raises the possibility that delayed irAEs after exposure to VEGF likely suggests a reinvigorated immune response and may serve as a prognostic marker. Further prospective validation in larger patient cohorts is warranted to investigate these findings. Research Sponsor: None.

8569 Poster Session

Digital pathology–based AI spatial biomarker to predict outcomes for immune checkpoint inhibitors in advanced non-small cell lung cancer. First Author: Feyisope Eweje, Department of Radiation Oncology, Stanford University School of Medicine, Stanford, CA

Background: Accurate prediction of outcomes with anti-PD-1/PD-L1 immune checkpoint inhibition (ICI) remains a significant challenge in non-small cell lung cancer (NSCLC). In this study, we develop an artificial intelligence (AI) approach for single-cell analysis of H&E-stained whole-slide images (WSIs) to predict objective response and clinical benefit of ICI in two independent cohorts of NSCLC patients. **Methods:** For biomarker discovery, we analyzed WSIs and clinical data from 118 advanced lung cancer patients at Stanford University. Of these, 46 patients (39%) were treated with ICI monotherapy and 72 (61%) patients were treated with ICI and concurrent chemotherapy. For external validation, 233 advanced lung cancer patients treated with ICI monotherapy at MSKCC were used. Deep learning models were deployed for automated tumor area detection and segmentation of cell nuclei in WSIs. We developed a fully automated cell annotation approach that leverages multiplex immunofluorescence and trained a deep learning model to classify nuclei into 10 cell types on H&E images, including tumor cells and major immune and stromal cells such as T cells, B cells, neutrophils, macrophages, fibroblasts, and endothelial cells. A total of 331 features were computed to quantify cell composition and cell-cell spatial interactions in the tumor microenvironment. Treatment outcomes were assessed using progression-free survival (PFS) and best objective response per the Response Evaluation Criteria in Solid Tumors (v1.1), with statistical significance reported at the 95% confidence level. **Results:** Five spatial features were included in the prediction model that characterize the cell-cell interactions between tumor cells, fibroblasts, T cells, and neutrophils. In the validation cohort, the spatial biomarker had a strong association with PFS (hazard ratio=5.46, $P<0.0001$), while the association of PD-L1 expression with PFS was modest (hazard ratio=1.67, P=0.002). For patients with high PD-L1 expression (TPS>50%), the spatial biomarker significantly stratified patients for PFS (hazard ratio=5.21, 95% CI 3.21-8.48, $P<0.0001$). For predicting objective response, a multivariate model consisting of the spatial features achieved AUROC=0.76 compared to AUROC=0.66 for PD-L1 TPS, while combining the spatial features with PD-L1 expression led to AUROC=0.78. **Conclusions:** A single-cell computational pathology approachidentifies interpretable spatial biomarkers that predict ICI response and outcomes in advanced lung cancer. The spatial biomarker could help to select patients with high tumor PD-L1 expression who are most suited for ICI monotherapy. Further validation of these findings is warranted. Research Sponsor: None.

8570 Poster Session

SMET12 and toripalimab combined chemotherapy in patients with advanced non-small cell lung cancer who are treatment-naive or have developed resistance to standard therapy. First Author: Jinghui Lin, Clinical Oncology School of Fujian Medical University, Fujian Cancer Hospital (China), Fuzhou, China

Background: SMET12 is a recombinant anti-EGFR and CD3 bispecific antibody independently developed by Zhejiang Shimai Pharmaceutical. This study aims to evaluate the efficacy and safety of SMET12 in combination with toripalimab and chemotherapy in treatment-naïve, post-first-line immune checkpoint inhibitor-resistant, and EGFR mutation-positive advanced non-small cell lung cancer (NSCLC) patients who are resistant to TKI treatment. **Methods:** This is a single-arm, cohort clinical study involving three cohorts. The primary inclusion criteria are histologically confirmed EGFR protein-expressing metastatic NSCLC patients, specifically divided into: (1) Cohort A: treatment-naïve subjects; (2) Cohort B: subjects resistant to first-line immune checkpoint inhibitor therapy; (3) Cohort C: EGFR mutation-positive subjects resistant to TKI treatment. All subjects will receive a combination regimen of SMET12, toripalimab, and chemotherapy after entering the treatment phase, with the chemotherapy cycle being 2-4 cycles. After chemotherapy, subjects with stable or effective results will enter the maintenance therapy phase with SMET12 and toripalimab until disease progression or unacceptable toxicity occurs. The treatment regimen is as follows:SMET12 30μg Q2W + toripalimab 3mg/kg Q2W+ chemotherapy Q3W. Specific chemotherapy regimens are: Cohort A: pemetrexed + carboplatin Q3W for lung adenocarcinoma; nab-paclitaxel + cisplatin Q3W for lung squamous cell carcinoma; Cohort B: docetaxel Q3W; Cohort C: pemetrexed + carboplatin Q3W. The primary endpoints are safety and efficacy indicators, including objective response rate (ORR), duration of response (DOR), disease control rate (DCR), and progression-free survival (PFS). **Results:** From March 7, 2024, to January 21, 2025, a total of 31 patients participated in this study, of which 27 patients were evaluable for efficacy. The results showed: the ORR for Cohort A was 83.3%, DCR was 100%, and the median PFS was 8.3 months (95%CI: 3.79, 12.8); the ORR for Cohort B was 22.2%, DCR was 66.7%, and the median PFS was 4.2 months (95%CI: 3.62, 4.78); the ORR for Cohort C was 41.7%, DCR was 100%, and the median PFS was 7.2 months (95%CI: 5.0, 9.4).Grade ≥3 treatment-related adverse events included leukopenia (19.4%), pneumonia (16.1%), immune-related pneumonitis (13.0%), immune-related hepatitis (3.2%), immune-related myositis (3.2%), and anemia (3.2%). **Conclusions:** SMET12 in combination with toripalimab and chemotherapy shows good tolerability and efficacy in treatment-naïve, post-immune therapy-resistant EGFR protein-expressing, and post-TKI treatment-resistant EGFR mutation-positive advanced NSCLC patients. Clinical trial information: NCT06208033. Research Sponsor: None.

8571 **Poster Session**

Exploratory study on the impact of intestinal low-dose radiation on the efficacy and prognosis of immunotherapy in metastatic non-small cell lung cancer. First Author: Baiyang Huang, Department of Radiation Oncology, Shandong Cancer Hospital and Institute, Shandong First Medical University and Shandong Academy of Medical Sciences, Jinan, Shandong, China

Background: Radiotherapy (RT) can be a palliative measure for metastases of metastatic non-small cell lung cancer (mNSCLC). However, RT to abdominopelvic metastases can cause additional intestinal radiation, that may lead to microbial imbalance. Recent research have revealed the influence of intestinal microbiota on immunotherapy (IO). Thus, this study aims to explore the impact of intestinal radiation doses on the efficacy and prognosis of IO for mNSCLC. **Methods:** Collect clinical data from patients with mNSCLC who underwent IO combined with abdominopelvic RT for metastases at Shandong Cancer Hospital over the past five years. Use the Varian Eclipse system to outline the contours of the large and small intestines and record the dosimetric parameter. Calculate overall survival (OS) and progression-free survival (PFS) using the Kaplan-Meier method, compare inter-group differences using the log-rank test, and analyze risk factors associated with OS and PFS through Cox regression analysis. **Results:** Exploratively, we set 1 Gy and 3 Gy as the thresholds for the mean intestinal radiation dose. A total of 232 patients were included, with 76 patients (32.8%) having small intestine mean radiation dose (SIMRD) $<$ 1 Gy, and 67 patients (28.9%) having SIMRD between 1-3 Gy. 153 patients (65.9%) received first-line IO, while 79 patients (34.1%) received second-line IO. Compared with the $<$ 1 Gy and $\geq$ 3 Gy groups, patients with SIMRD between 1-3 Gy not only had the highest objective response rate (ORR) after 3 months (21.1% vs. 43.3% vs. 7.9%), but also significantly prolonged OS (14.8 months vs. 22.6 months vs. 7.7 months, P $<$ 0.001) and PFS (7.2 months vs. 10.0 months vs. 4.3 months, P $<$ 0.001). Subgroup analysis of first-line and second-line therapy patients yielded similar conclusions. Compared with the $<$ 1 Gy and 1-3 Gy groups, patients with colon mean radiation dose $\geq$ 3 Gy also exhibit relatively poor OS (14.8 months vs. 12.6 months vs. 10.1 months, P = 0.036) and PFS (7.4 months vs. 7.3 months vs. 4.2 months, P = 0.006). Multivariate Cox regression analysis showed that SIMRD between 1-3 Gy was an independent predictive factor for OS (HR = 0.41, P $<$ 0.001) and PFS (HR = 0.56, P $<$ 0.001). We prospectively enrolled 14 patients with mNSCLC who received first-line IO combined with metastasis RT, with 9 patients undergoing efficacy evaluation. The results revealed that the ORR was highest (66.7%) in the group with SIMRD between 1-3 Gy, and both 2 patients with progression were in the group with SIMRD $\geq$ 3 Gy. **Conclusions:** In patients with mNSCLC receiving IO combined with metastasis RT, low SIMRD may significantly enhance the long-term prognosis of IO, potentially relying on the interaction between host immunity and gut microbiota. To validate this hypothesis, we are prospectively collecting blood and feces from patients before and after RT, with the prospective cohort being enrolled. Research Sponsor: National Natural Science Foundation of China; 82172720; CSCO-Nav HER2-related Solid Tumors Research Foundation; Y-2022HER2AZMS-0291; National Natural Science Foundation of China; 82403791; Natural Science Foundation of Shandong Province; ZR2024QH459; Shandong Province University "Youth Innovation Team Program"; 2024KJJ027.

8572 **Poster Session**

Artificial intelligence-powered spatial analysis of tumor infiltrating lymphocytes and tertiary lymphoid structures in non-small cell lung cancer patients treated with immune-checkpoint inhibitors±chemotherapy. First Author: Yeong Hak Bang, Division of Hematology-Oncology, Department of Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, South Korea

Background: This study evaluates the predictive utility of an artificial intelligence (AI)-powered whole-slide image (WSI) analyzer for assessing Tumor-infiltrating lymphocytes (TILs) and tertiary lymphoid structures (TLSs) in patients (pts) treated with ICIs, either as monotherapy or in combination with chemotherapy. **Methods:** An AI-powered WSI analyzer (Lunit SCOPE IO, Lunit, Seoul, Korea) was utilized to segment cancer area (CA) and cancer stroma (CS), and identification of tumor infiltrating cells (TILs) and tertiary lymphoid structure (TLS) on tumor tissues. Pre-treatment H&E-stained WSIs were obtained from Samsung Medical Center (n = 533), and other multi-center cohorts (Shen et al, 2024, n=634). After quality control, 1,144 samples (98.0%) were used included in the final analysis. Pts were stratified into risk groups; good risk (high TILs in CA and high TLS area per CA), poor risk group (low TILs in CA and low TLS area per CA), and intermediate risk group (others). Among them, 988 pts had available PD-L1 expression data, 435 underwent whole transcriptome sequencing, and 292 underwent whole exome sequencing. **Results:** TILs in CA correlated significantly with the interferon gamma pathway (ρ=0.49, P$<$0.001), and the T-cell inflamed score (ρ=0.56, P$<$0.001). Similarly, TLS area per CA was significantly correlated with TLS imprinting (ρ=0.48, P$<$0.001), and B cell receptor signature (ρ=0.42, P$<$0.001). Among 1,144 pts, 1,044 received ICI monotherapy, and 100 underwent combination therapy with ICI and chemotherapy. ICIs were administered as first-line therapy in 245 pts (24.1%), and second line in 524 (45.8%). The risk groups were distributed as follows: good risk (n=279, 24.4%), intermediate risk (n=437, 38.2%), and poor risk (n=428, 37.4%). Pts with PD-L1 tumor proportion score $\geq$50% were more frequent in the good-risk group (47.3%) than in intermediate (37.5%) or poor-risk groups (30.6%, P=0.001). Smoking history showed no significant association with risk groups (P=0.958). Pts receiving ICI monotherapy showed significant differences in overall response rate (ORR: 28.9% vs. 19.7% vs. 16.3%, P$<$0.001), median progression-free survival (mPFS: 6.1 vs. 3.5 vs. 2.4 months, P$<$0.001), and median overall survival (mOS: 26.4 vs. 14.6 vs. 11.3 months, P$<$0.001) among the good, intermediate, and poor-risk groups, respectively. Similar trends were observed in pts receiving ICI plus chemotherapy: mPFS (10.3 vs. 8.4 vs. 4.7 months, P=0.005), and mOS (27.9 vs. 22.4 vs. 17.6 months, P=0.047). Notably, *KEAP1* mutations were significantly more frequent in the poor-risk group (17.4% vs. 7.9%, P=0.020). **Conclusions:** AI-powered analysis of TILs and TLSs effectively stratifies NSCLC pts into risk groups, predicting efficacy outcomes of ICIs with or without chemotherapy. Research Sponsor: None.

8573 **Poster Session**

First-line envafolimab in combination with recombinant human endostatin and chemotherapy for advanced squamous non-small cell lung cancer: Updated results from a prospective, single-arm, multicenter phase II study. First Author: Lian Liu, Department of Medical Oncology, Qilu Hospital, Cheeloo College of Medicine, Shandong University, Jinan, China

Background: Immunotherapy combined with chemotherapy has been established as the standard first-line treatment for patients with advanced squamous NSCLC (sq-NSCLC) without oncogenic driver mutations. Antiangiogenic drugs enhance immunotherapy efficacy by normalizing blood vessels and remodeling the tumor microenvironment. However, they pose a high bleeding risk in sq-NSCLC treatment. Recombinant human endostatin (Rh-endostatin), the only approved agent for sq-NSCLC, can prolong survival without increasing bleeding risk. This trial aimed to investigate the efficacy and safety of Envafolimab, the first approved subcutaneous single-domain anti-PD-L1 antibody, plus Rh-endostatin and chemotherapy as first-line treatment for advanced sq-NSCLC. **Methods:** This prospective, single-arm, multicenter, phase II trial was conducted at 3 research centers in China (NCT05243355). Patients with pathologically confirmed primary advanced or locally advanced unresectable sq-NSCLC. were enrolled. Patients received Envafolimab (300 mg, subcutaneously, day 1) and Rh-endostatin (210 mg, continuous intravenous infusion over 72 hours, day 1-3) combined with paclitaxel (175mg/m^2, day 1) or albumin paclitaxel (260 mg/m^2, day 1), and cisplatin (75 mg/m^2 , day 1-3), or carboplatin (AUC 5, IV, day 1); every 3 weeks for 4-6 cycles, followed by maintenance Envafolimab until disease progression (PD), unacceptable toxicity, or patient refusal. The primary endpoint was the 1-year PFS rate, and the secondary endpoints included objective response rate (ORR), disease control rate (DCR), progression-free survival (PFS), overall survival (OS), safety, and tolerability. **Results:** From December 2021 to December 2024, 33 eligible patients were enrolled, 26 of whom were included in the safety and efficacy analysis. As of December 16, 2024, the median follow-up was 16.5 months (95%CI: 8.1, NA). According to RECIST v1.1, the ORR was 65.4%, and the DCR was 96.2%. The median PFS (mPFS) was 12.4 months (95%CI: 11.4, NA) with a 1-year PFS rate of 59.9% (95%CI: 43.0%, 83.3%). The median OS (mOS) was 24.6 months (95%CI: 12.2, NA) with 1-year OS rate of 70.7% (95%CI: 54.2%, 92.1%) and a 2-year OS rate of 54.7% (95%CI: 36.9%, 81.1%). Overall, adverse events (AEs) of any grade were reported in 84.8% (28/33) of patients. The most common AEs were myelosuppression, alopecia, and nausea, which were more likely to be chemotherapy-related. 33.3% (11/33) of patients experienced immune-related AEs (irAEs). No unexpected AEs were observed. **Conclusions:** Our results demonstrated that Envafolimab in combination with Rh-endostatin and chemotherapy resulted in favorable clinical outcomes with a manageable safety profile, representing a promising treatment modality as first-line therapy for advanced sq-NSCLC. Clinical trial information: NCT05243355. Research Sponsor: None.

8574 **Poster Session**

First-line immunotherapy with or without chemotherapy versus BRAF plus MEK inhibitors for patients with BRAF^{V600E}-mutated metastatic non-small cell lung cancer: The FRONT-BRAF study. First Author: Alessandro Di Federico, Lowe Center for Thoracic Oncology, Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA

Background: Patients (pts) with BRAF^{V600E} mutated non-small cell lung cancer (NSCLC) can be effectively treated with BRAF and MEK inhibitors (BRAFi+MEKi) or with immune checkpoint inhibitors ± chemotherapy (ICI±CT). Which one should be prioritized as initial systemic treatment in this population remains unclear. **Methods:** Clinicopathologic data were collected from pts with metastatic BRAF^{V600E} mutated NSCLC treated with 1st line ICI±CT or BRAFi+MEKi between 2015 and 2024 at 17 centers across the United States, Europe, and Brazil. **Results:** Of 284 patients, 88 received ICI±CT and 196 received BRAFi+MEKi. Compared to pts treated with BRAFi+MEKi, pts receiving ICI±CT were more likely to have a history of smoking (83% vs. 61%, P$<$0.001) and a higher median PD-L1 tumor proportion score (TPS) (68% vs 30%, P$<$0.001). ICI±CT, compared to BRAFi+MEKi, was associated with a lower objective response rate (ORR, 49% vs 63%, P=0.03), similar median progression-free survival [mPFS, 9.6 vs.12.2 months (mo.), HR 1.13, P=0.43], but significantly improved median overall survival (mOS, 40.9 vs 25.1 mo., HR 0.69, P=0.039), even after adjusting in a multivariable model (HR 0.66, P=0.02). Consistent results were observed in a propensity score-matched cohort (1:1 ratio, N=75 pts per treatment group), where ICI±CT, compared to BRAFi+MEKi, was associated with improved mOS (40.9 vs 22.7 mo., HR 0.63, P=0.04), but similar ORR and mPFS. In key subgroup analyses, ICI±CT, compared to BRAFi+MEKi, was associated with longer mOS in pts with a history of tobacco smoking (HR 0.60, P=0.01), PD-L1 TPS $\geq$1% (HR 0.66, P=0.039), and without brain metastases (HR 0.66, P=0.045). A shorter mPFS was noted in pts without tobacco smoking history (HR 1.94, P=0.03). In evaluating genomic correlates of treatment efficacy, pts with *TP53* co-mutations (N=107) had worse outcomes compared to pts with wild-type *TP53* (N=121) when treated with BRAFi+MEKi, including shorter mPFS (HR 1.67, *P*=0.01) and mOS (HR 1.77, *P*=0.01), but not with ICI±CT. Notably, pts with *TP53* co-mutations had longer mOS with ICI±CT compared to BRAFi+MEKi (48.4 vs 18.8 mo., HR 0.46, *P*=0.005). In contrast, pts with *IDH1* co-mutations (N=9) had worse outcomes compared to pts with wild-type *IDH1*(N=188) when treated with ICI±CT, including shorter mPFS (HR 4.04, *P*=0.03) and mOS (HR 6.12, *P*=0.007), as well as shorter mPFS with BRAFi+MEKi (HR 2.73, *P*=0.03). Safety of BRAFi+MEKi was comparable whether administered as 1st line or as 2nd line therapy following ICI±CT, with similar rates of adverse events of any grade (71% vs 76%, P=0.58) and grade $\geq$3 (22% vs 23%, P=0.92). **Conclusions:** Initial therapy with ICI±CT, compared to BRAFi+MEKi, showed a lower ORR, similar PFS, but superior OS, particularly among specific subgroups of pts. A prospective evaluation of the optimal 1st-line therapy for this population is warranted. Research Sponsor: None.

8575 Poster Session

A meta-analysis of safety and efficacy of datopotamab deruxtecan and sacituzumab govitecan for second line treatment of metastatic non-small cell lung cancer (NSCLC). First Author: Omar Shukri Yaghi, George Washington University, Department of Medicine, Washington, DC

Background: Subsequent line treatment options for metastatic NSCLC remain limited. We sought to analyze the efficacy and safety of two Anti-TROP-2/topoisomerase inhibitor antibody-drug conjugates (ADCs), sacituzumab govitecan (SG) and datopotamab deruxtecan (Dato-DXd), for NSCLC treatment via a meta-analysis. **Methods:** A systematic search in PubMed, Scopus, and Cochrane identified 2348 studies. After excluding duplicates (1263) and screening abstracts (1085), 25 studies underwent full-text review, and 5 RCTs (3 Dato-DXd, 2 SG) were included. All included studies involved patients with advanced NSCLC that progressed on first-line treatment. Binary random effects and pooled proportions were calculated separately for Dato-DXd and SG using OpenMeta. The Mantel-Haenszel method with random effects estimated risk ratios and odds ratios with 95% confidence intervals for ADCs vs. docetaxel. Heterogeneity was assessed using I^2 statistics. **Results:** 616 Dato-DXd and 353 SG patients were included. Pooled proportions (PP) for grade 3 adverse events were 34.0% (Dato-DXd) and 75.4% (SG) while drug discontinuation rates were 7.1% (Dato-DXd) and 7.0% (SG), respectively. Efficacy outcomes included event rate, disease control rate, and overall response rate. For Dato-DXd, these pooled proportions were 52.0%, 76.5%, and 29.4%; for SG, they were 44.8%, 67.6%, and 14.3%. PPs and relevant statistics are included in table 1. When compared to docetaxel, combined ADCs showed no significant risk reduction in progression [RR: 0.96 (0.89 – 1.05), p=0.40, I^2=7%] or mortality [RR: 0.90 (0.58 – 1.38), p=0.63, I^2=43%]. Odds ratios for disease control rate [1.39 (0.76 – 2.54), p=0.29, I^2=83%] and overall response rate [1.33 (0.40 – 4.42), p=0.64, I^2=94%] were also insignificant. **Conclusions:** Direct comparisons between ADC (Dato-Dxd and SG) and docetaxel did not show a significant difference in disease progression or death rate. This study was limited by the small number of participants and heterogeneity of published literature as many clinical trials are still ongoing. Despite this, SG and Dato-DXd had a promising overall response rate of 67.6% and 76.5%, respectively. Research Sponsor: None.

Pooled proportions of Dato-Dxd and SG to docetaxel.

	Datopotamab Deruxtecan				Sacituzumab Govitecan			
	Value	95% CI	P-Value	I^2	Value	95% CI	P-Value	I^2
Event Rate	0.520	(0.258, 0.782)	<0.001	97%	0.448	(0.211, 0.686)	<0.001	90.8%
DCR	0.765	(0.727, 0.803)	<0.001	0%	0.676	(0.627, 0.726)	<0.001	0%
ORR	0.294	(0.230, 0.358)	<0.001	49.6%	0.143	(0.106, 0.180)	<0.001	0%
G3AER	0.340	(0.215, 0.465)	<0.001	86%	0.754	(0.572, 0.937)	<0.001	91.1%
DDR	0.071	(0.026, 0.116)	0.002	69.1%	0.070	(0.011, 0.130)	0.20	74.2%

Abbreviations: DCR, disease control rate; ORR, overall response rate; G3AER, grade 3 adverse events rate; DDR, drug discontinuation rate.

8576 Poster Session

Efficacy of immune checkpoint inhibitors (ICIs) in advanced large cell neuroendocrine carcinoma (LCNEC) of the lung: A systematic review and meta-analysis. First Author: Parth Sharma, University of Missouri - Kansas City, Kansas City, MO

Background: LCNEC of the lung is a high-grade neuroendocrine carcinoma with characteristics of both small cell lung cancer (SCLC) and non-small cell lung cancer (NSCLC). Guidelines for optimal treatment for LCNEC are lacking due to the paucity of randomized control trials. Treatment regimens are often extrapolated from SCLC and NSCLC. Immunotherapy has revolutionized the outcomes of solid malignancies, including lung cancers, in the past decade. In this study, we assess the efficacy of ICIs in advanced LCNEC. **Methods:** A systematic literature search was conducted on PubMed, Embase, and Google Scholar for studies assessing the role of ICIs in advanced LCNEC of the lung. The study followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Guidelines. A random effects model was used to pool the outcomes along with 95% confidence intervals (CI). Statistical analyses were performed using program R version 4.4.1. **Results:** We included 12 studies- 11 retrospective and 1 prospective analysis. The total number of advanced LCNEC patients across all the studies was 470. 241 patients received ICIs in total, either as monotherapy or in combination with chemotherapy or anti-angiogenic agents. The pooled Objective Response Rate (ORR) for patients receiving ICIs was 34.71% (95% CI: 27.75-41.97, I^2: 26.2%), whereas the pooled Disease Control Rate (DCR) was 71.87% (95% CI: 59.57-82.92, I^2: 67.7%). The most common ICIs across the cohort were atezolizumab, camrelizumab, nivolumab, and pembrolizumab. A subgroup analysis of three double-arm studies comparing chemotherapy alone (n=42) versus a combination of chemotherapy and ICIs (n=42) as a first-line treatment was performed. We found a favoring trend of the combination over chemotherapy alone for ORR (RR=1.58, 95% CI: 0.92-2.70; p=0.095), although non-significant, but significant advantage for DCR (RR=1.32, 95% CI: 1.04-1.68; p=0.021). **Conclusions:** ICIs have become the standard of care for treating SCLC and NSCLC in various combinations. ICIs, based on our meta-analysis, have also demonstrated encouraging results in advanced LCNEC. However, tumor factors such as molecular subtypes, genomic profiles, and other predictors influencing the response to ICIs need to be elucidated. Further larger prospective studies are awaited to determine their potential in this rare but aggressive subtype of lung cancer. Research Sponsor: None.

8577 Poster Session

Artificial intelligence for immunotherapy response assessment in lung cancer using PET-CT reports. First Author: Ozden Altundag, Baskent University, Bahçelievler, Turkey

Background: Accurate and timely assessment of immunotherapy response is vital for optimizing lung cancer management. This study evaluates the efficacy of a large language model (LLM), Gemini 1.5 Pro, in automating response assessment using positron emission tomography/computed tomography (PET/CT) reports based on the European Organization for Research and Treatment of Cancer (EORTC) criteria. **Methods:** Google Gemini 1.5 Pro was selected due to its large context window capacity and its free availability via the web interface.The model was utilized with explicit instructions on applying EORTC criteria and fine-tuned using few-shot prompting. Pre- and post-immunotherapy PET-CT reports in text format from 33 lung cancer patients, anonymized in compliance with HIPAA regulations, were independently classified by the LLM and an experienced nuclear medicine specialist. Performance metrics, including precision, recall, F1-score, and support, were calculated for each response category. Inter-rater agreement was assessed using Cohen's Kappa. **Results:** The nuclear medicine specialist classified 5, 21, 6, and 1 cases as complete metabolic response (CMR), progressive metabolic disease (PMD), partial metabolic response (PMR), and stable metabolic disease (SMD), respectively, while Gemini 1.5 Pro classified 5, 20, 7, and 1 cases accordingly. The LLM achieved an overall accuracy of 97% and demonstrated excellent agreement with the expert (overall Cohen's Kappa: 0.945). F1-scores were 1.00 for CMR and SMD, 0.98 for PMD, and 0.92 for PMR, with per-label Kappa scores ranging from 0.904 (PMR) to 1.00 (CMR and SMD) (Table 1). **Conclusions:** Gemini 1.5 Pro exhibits strong potential for automating accurate immunotherapy response assessment in lung cancer using PET-CT reports. Its high concordance with expert evaluations underscores its utility in streamlining clinical workflows and improving efficiency. Validation with larger, more diverse datasets is warranted to support its clinical implementation. Research Sponsor: None.

Performance metrics of Gemini 1.5 Pro for immunotherapy response assessment.

Response	Precision	Recall	F1-score	Support	Cohen's Kappa
CMR	1.00	1.00	1.00	5	1.000
PMD	1.00	0.95	0.98	21	0.936
PMR	0.86	1.00	0.92	6	0.904
SMD	1.00	1.00	1.00	1	1.000

CMR, Complete Metabolic Response; PMD, Progressive Metabolic Disease; PMR, Partial Metabolic Response; SMD, Stable Metabolic Disease.

8578 Poster Session

Multimodal AI using host, tumor, and ghost biomarker for predicting immunotherapy efficacy in NSCLC. First Author: Vanja Miscovic, Fondazione IRCCS Istituto Nazionale dei Tumori di Milano, Milan, Italy

Background: Almost all NSCLC patients (pts) without driver alterations received a first-line based immunotherapy (IO). It is unclear if pts with very poor (VP) overall survival (OS <6 months) will benefit from IO, advancing the hypothesis that this population might benefit more from next-generation drugs or supportive care. Non-response to IO is often linked to host immune fitness, such as circulating immune profiling (CIP). These "ghost biomarkers" can guide clinicians in making critical decisions, such as sparing IO in VP pts. APOLLO 11 study, aimed to develop an AI multimodal tool combining real-world data (RWD), CT-radiomics (CTRAD), and CIP to identify IO survival prediction VP pts. **Methods:** Data collected at Istituto Nazionale Tumori di Milano included: CTRAD features extracted using both a CT-scan Foundation Model (FM CTRAD) and PyRadiomics (pyRAD) features. The two methods were compared. Fluorescence-Activated Cell Sorting (FACS) analysis focused on identifying circulating low-density neutrophils and myeloid cells. Machine Learning (ML) multimodal pipelines for both classification (using LASSO as feature selector) and survival (using COX-ML) were developed using respectively OS < 6 months as threshold and overall survival as continuous outcome. SHAP explainability was applied to identify the most influential features contributing to model predictions. **Results:** Among 932 screened NSCLC pts treated with IO a (720 retrospective-R, 212 prospective-P), 495 had available baseline CT scans, with 638 lesions in the lung (397), lymph nodes (208), and pleura (29). Baseline FACS analysis was performed on 236 patients (162 R, 74 P). 117 pts had all three modalities. 4000 FM RAD features were extracted and reduced to 52 using PCA, while 107 features with pyRAD. Bimodal models with RWD and FACS achieved better performance (AUC 0.71±0.11) than bimodal models with RWD and CTRAD achieving an AUC 0.66±0.07 with pyRAD and 0.62±0.08 with FMRAD). The multimodal ML model, including all data modalities, achieved AUC 0.76 (±0.12). SHAP showed that high frequency of total myeloid cells (CD11b) and of immature neutrophils (CD10-CD16-), high LDH, high ECOG, low BMI, and two rad features as the most important for predicting VP. The survival multimodal model achieved a c-index of 0.76 ±0.10. **Conclusions:** The multimodal tool including all data modalities demonstrated superior performance in predicting OS. SHAP identified all data modalities as relevant, highlighting key "ghost biomarkers" for predicting OS and identifying VP pts. Given that this biomarker is fast (results within one day) and cheap (approximately €/$300), it can be easily integrated with RWD and RAD, which are readily available in clinical practice. This tool can reduce financial toxicity by guiding pts to the appropriate treatment. Finally, pyRAD features compared to FM features seem to perform better in bimodal models. Clinical trial information: NCT05550961. Research Sponsor: FONDAZIONE IRCCS ISTITUTO NAZIONALE DEI TUMORI DI MILANO.

8579 **Poster Session**

Longitudinal plasma proteomic analysis: A monitoring strategy for NSCLC patients treated with immunotherapy. First Author: Yehonatan Elon, Oncohost Ltd, Binyamina, Israel

Background: Real-time monitoring is critical for tailoring treatments to individual patient responses in clinical oncology. Plasma proteomics offers a comprehensive systemic view of disease progression, tumor activity, immune responses, and various biological processes, making it a powerful tool for clinical decision-making. This study explores the feasibility of three specific plasma proteomic signatures for longitudinal monitoring of treatment responses in patients with non-small cell lung cancer (NSCLC) undergoing therapy with immune checkpoint inhibitors (ICIs). **Methods:** Plasma samples were collected from patients with advanced NSCLC receiving PD-1/PD-L1 inhibitor-based regimens. Cohort-1 (n=225) includes samples collected before treatment (T0) and 4-6 weeks after treatment initiation (T1). Cohort-2 (n=56) included samples collected pre-treatment and every three months, up to 36 months. Aptamer-based proteomic profiling quantified ~7,000 plasma protein analytes per sample. Three proteomic signatures were derived from T0–T1 changes in Cohort-1 and tracked in Cohort-2, then compared with radiologic imaging-based response evaluation. **Results:** Three distinct plasma proteomic signatures were identified. The first, featuring soluble PD-1 and PD-L1, indicates drug presence in circulation. The second reflects T-cell activation (e.g., CD8A, LAG3, IL2R), linked to drug uptake, without confirming a favourable tumor response. The third includes intracellular proteins indicative of lung tissue damage, allowing dynamic disease monitoring. Lung tissue damage signature correlated with radiologic imaging-based response evaluation (PR: *n* = 79, −4.19 [−12.47, 3.58]; SD: *n* = 125, 1.03 [−1.87, 5.01]; PD: *n* = 30, 3.37 [0, 7.27]; KW *P-value* = 0.01). Longitudinal analysis of these signatures facilitated early detection of non-responders in an average of 6.6 months [4 - 9.2 months, n=13] prior to radiologic evaluation. Among progressors, nine cases identified responders who later developed acquired resistance, distinguishing them from patients who did not respond to therapy at all. These findings highlight the potential of proteomic profiling to provide comprehensive systemic insights. A comparative analysis with ctDNA will also be presented to further validate these results. **Conclusions:** Our study demonstrates the feasibility of using plasma proteomic signatures to monitor responses to ICIs in NSCLC. We highlight the potential and emphasize the need to further develop these plasma-based monitoring tools through more extensive prospective studies. Such advancements are essential for establishing proteomic signatures as dependable decision-support tools in NSCLC treatment protocols. Research Sponsor: None.

8580 **Poster Session**

Phase 2 study of atezolizumab with carboplatin plus pemetrexed followed by maintenance atezolizumab with pemetrexed for elderly patients with advanced non-squamous non-small cell lung cancer: CJLSG1902. First Author: Hidetoshi Itani, Department of Respiratory Medicine, Japanese Red Cross Ise Hospital, Ise, Japan

Background: Chemotherapy, including immune checkpoint inhibitors and platinum-containing agents, is a standard of care for patients with advanced non-small cell lung cancer (NSCLC). Pembrolizumab in combination with pemetrexed and cisplatin/carboplatin is approved as first-line treatment for patients with metastatic non-squamous NSCLC based on the results of KEYNOTE-189. However, data on the efficacy and safety of this regimen are limited in patients ≥75 years old. On the other hand, the results of the post hoc integrated analysis of IMpower130 and IMpower132 suggest that the efficacy and safety of atezolizumab in combination with platinum-based chemotherapy is maintained in patients ≥75 years old. **Methods:** This multicenter, open-label, phase 2 trial was conducted at 28 institutions in Japan to evaluate the efficacy and safety of atezolizumab with carboplatin plus pemetrexed followed by maintenance atezolizumab with pemetrexed. Eligible patients had metastatic/recurrent non-squamous NSCLC without sensitizing EGFR or ALK mutations, were aged ≥75 years, had received no prior systemic chemotherapy, and had an ECOG performance status of 0 or 1. For induction therapy, patients received atezolizumab (1,200 mg/body), pemetrexed (500 mg/m^2) and carboplatin (area under concentration-time curve 5 mg/mL/min) on day 1 of each 21-day cycle. For maintenance therapy, patients received atezolizumab (1,200 mg/body) and pemetrexed (500 mg/m^2) on day 1 of each 21-day cycle. Treatment continued until radiographic progression or unacceptable toxicity was observed. The primary endpoint was progression-free survival (PFS). Secondary endpoints were objective response rate (ORR), overall survival (OS), and safety. This trial is registered with the Japan Registry of Clinical Trials (jRCTs041200032). **Results:** From July 2020 to January 2023, 60 patients were enrolled in this study. Median age was 77.0 years (range 75-86), 84.1% of the patients were male, and 25.5% had a PD-L1 TPS ≥50%. The median PFS was 7.49 months (80% CI 5.52-7.75, exceeding the threshold of 5.5 months), and the median OS was 16.82 months (80% CI 14.49-20.93). The ORR was 55.9% (95% CI 42.4-68.8). The most common grade 3 or 4 adverse events were neutropenia (40.7%), leukopenia (35.6%), anemia (35.6%), and thrombocytopenia (30.5%). Serious adverse events were observed in 19 patients (6 with pneumonitis, 6 with febrile neutropenia). No treatment-related deaths were observed. **Conclusions:** This study met the primary endpoint of PFS. Atezolizumab with carboplatin plus pemetrexed followed by maintenance atezolizumab with pemetrexed showed favorable efficacy and the safety profile was manageable. This combination therapy is an encouraging option as a first-line treatment strategy for elderly patients with metastatic non-squamous NSCLC. Clinical trial information: 041200032. Research Sponsor: Chugai Pharmaceutical Co., Ltd.

8581 **Poster Session**

Radiomic phenotypes of tumor angiogenesis compared with PD-L1 in pre-treatment prediction of outcomes across immunotherapy regimens in NSCLC: An external validation study. First Author: Vamsidhar Velcheti, Laura and Isaac Perlmutter Cancer Center, New York, NY

Background: Tumor angiogenesis is critical to cancer progression and treatment resistance, as evidenced by the success of therapies targeting both immune activation and neoangiogenesis. Conventional biomarkers like PD-L1 unreliably predict long-term patient outcomes such as overall survival (OS). Quantitative Vessel Tortuosity (QVT) isolates tumor-associated vessels and quantifies abnormal vascular architecture from pre-treatment radiography. We developed novel QVT Phenotypes of chaotic tumor angiogenesis and externally validated their use in the pre-treatment prediction of long term survival across multiple immunotherapy treatment strategies. **Methods:** QVT Phenotype is a radiomic AI biomarker developed and validated using a real-world dataset of 639 NSCLC patients from 6 institutions. Pre-treatment CT scans of 375 patients from institutions 1-3 were used for phenotype discovery (Dataset A). Deep learning models automatically extracted lung lesions and adjacent vessels. 910 QVT metrics of vascular abnormalities (e.g. curvature, twistedness, and branching) were computed and used to identify intrinsic vascular phenotypes via an unsupervised clustering agnostic. Two validation cohorts from external institutions 4-6 were used to evaluate association with 3-year OS: ICI monotherapy (Mono-ICI) recipients of mixed PD-L1 status (Dataset B, n=172) and Chemo-ICI recipients with PD-L1 TPS<50% (Dataset C, n=90). **Results:** 38% of patients were QVT High, with twisted and erratic growth patterns on pre-treatment CT scans indicating chaotic angiogenesis. Across validation cohorts (Datasets B+C), QVT-High emerged as a strong marker of poor survival (HR=2.26; p=<1E-5). In Dataset B, QVT-High better predicted poor Mono-ICI outcomes (HR=2.23, p=0.00080) than PD-L1 status (HR=1.99, p=0.032), with a 23.0 month reduction in median OS compared to QVT Low. QVT Phenotype maintained significance within the subset (n=61) of PD-L1 High patients (HR=3.02, p=0.017). In Dataset C, QVT-High stratified Chemo-ICI recipients by OS (HR=2.71, p=0.00060), while PD-L1 status failed to reach significance (HR=1.70, p=0.083). QVT-High Chemo-ICI patients had a 16.3 median OS reduction compared to QVT-Low patients. **Conclusions:** This validation study establishes QVT Phenotype as a non-invasive biomarker using standard-of-care pretreatment radiographic scans. QVT Phenotype of chaotic tumor angiogenesis is both interpretable and treatment-agnostic. QVT Phenotype predicted survival across multiple immunotherapy regimens in NSCLC, outperforming PD-L1. QVT phenotyping can be used to identify patients unlikely to benefit from existing SOC treatments. Future work will explore using QVT Phenotypes to identify patients who may benefit from escalated therapeutic strategies, including those incorporating anti-angiogenic mechanisms. Research Sponsor: None.

8583 **Poster Session**

Validation of HistoTME-predicted immune subtypes and immunotherapy outcomes using human interpretable features (HIFs) from H&E images in non-small cell lung cancer. First Author: Meghdad Sabouri Rad, SUNY Upstate Medical University, Syracuse, NY

Background: Tumor microenvironment (TME) plays a critical role in tumor progression and response to treatment, especially in improving the response to immune checkpoint inhibitors (ICIs) in non-small cell lung cancer (NSCLC). However, current methods are costly and not feasible for routine clinical use for characterizing the TME. Addressing this, we recently developed Histo-TME, an AI-powered tool that accurately characterizes TME subtypes and ICI responses from routine hematoxylin-eosin (H&E) scanned images. This study aims to validate and interpret HistoTME-predicted subtypes using a series of machine learning (ML) models (PathExplore, PathAI, Boston, MA) that output human interpretable features (HIFs) to quantitatively characterize the TME. **Methods:** We analyzed 1375 H&E images from 689 NSCLC patients using PathExplore algorithm, which yielded 171 HIFs spatially characterizing tumor-immune cell interactions. Unsupervised k-means clustering (UMAP) identified distinct patient subgroups based on these HIFs. We compared these subgroups to Histo-TME classifications from the same cohort and evaluated their association with immunotherapy response using Kaplan-Meier (KM) and Cox proportional hazards analyses. **Results:** Five distinct clusters with varying immune infiltration were identified using the 171 HIFs in UMAP clustering. Three out of five clusters characterized by the abundance of macrophages, plasma cells, lymphocytes and fibroblasts within proximity of tumor cells (i.e. 40μm radius), resembled the "Immune Inflamed" subgroup as predicted by HistoTME. There was no survival difference between HIF- and HistoTME-predicted immune inflamed and immune-desert clusters in KM analysis (p>0.05). Both HIF-defined clusters and the HistoTME subtypes had similar median overall survival times (4.33 vs. 4.18 years for "Immune Inflamed", p>0.05; 1.84 vs. 2.62 years for "Immune Desert", p>0.05) in KM analysis. Multivariate analysis adjusted for AJCC stage, age, smoking, ECOG, and CCI demonstrated that both methods have comparable predictive values for overall survival (HIF clusters; HR: 0.69, CI: 0.58-0.81; p<0.001 vs. HistoTME subtypes; HR: 0.80, CI: 0.68-0.94; p=0.008). **Conclusions:** This study independently validates our published HistoTME method, confirming its ability to accurately identify patients who are likely to respond to ICI therapy using H&E scanned images. Our findings underscore the importance of incorporating TME characteristics using AI-based approaches in routine histopathology and clinical decision-making workflows. Research Sponsor: None.

8584 Poster Session

Survival and safety of two year-fixed duration vs continuous immune checkpoint inhibitor therapy in advanced or metastatic NSCLC: A systematic review. First Author: Toshali Pandey, University of Arkansas for Medical Sciences, Little Rock, AR

Background: The optimal duration of immune checkpoint inhibitor (ICI) therapy in advanced or metastatic non-small cell lung cancer (NSCLC) is unknown. While multiple randomized clinical trials (RCTs) have shown the benefit of ICI-based regimens over chemotherapy, they were not designed to test optimal duration of ICI. Most trials opted to continue ICI indefinitely or stopping at two years if no progressive disease or treatment limiting immune-related adverse events (irAEs) emerged. There is concern for increased cumulative risk of irAEs with indefinite treatment. **Methods:** A systematic review of randomized controlled trials (RCTs) and real-world evidence (RWE) studies was performed for adult patients with advanced/metastatic NSCLC treated with ICI therapy (alone or in combination) up to August 24, 2024. Studies were included if they specifically reported on patients who completed a minimum of 2 years of therapy. Databases, conference abstracts and clinical trials were queried. Patients were divided into two cohorts: a two year-fixed cohort where ICI therapy was discontinued after 2 years, and a continuous cohort where ICI therapy was continued beyond 2 years. **Results:** The database search identified 8741 records of which 174 articles were screened. The final qualitative analysis included 20 studies (11 RCTs and 9 RWE studies) and 5027 patients. There were 23 cohorts that belonged to the 2 year-fixed group (N=2051) and 7 that belonged to the continuous group (N=2976). Outcomes of patients in the 2 year-fixed arms from RCTs were excellent with 5-year overall survival (OS) rates in the range of 69-83%. This was supported by RWEs which showed similar OS rates. Continuous treatment with ICIs had similar OS rates in both RCTs and RWE and was comparable to the 2 year-fixed arms. Four RWE studies compared hazard ratios (HR) for survival outcomes among 2 year-fixed vs continuous arms and did not find any statistically significant difference. Patients that completed 2 years of therapy in RCTs tended to have greater rates of irAEs compared to the baseline population but lower rates of grade 3 or 4 events. Three out of four RWEs reported higher rates of irAEs in the continuous vs 2 year-fixed arms. These findings were likely associated with longer exposure to immunotherapy. A large proportion of patients that developed progressive disease after the 2 year-mark in both 2 year-fixed and continuous arms was alive at data cut-off. Many of these were re-challenged with ICI therapy. Data from RWEs showed that larger/academic centers tended to favor 2 year-fixed therapy whereas the reverse was true for community centers. **Conclusions:** Survival outcomes after ICI discontinuation at 2 years are comparable to continuous therapy in advanced/metastatic NSCLC. Immune-related adverse events tend to accumulate over time. Progressive disease is often localized and amenable to ICI re-challenge. Research Sponsor: None.

8585 Poster Session

Phase 2 study of telomere-targeting agent THIO sequenced with cemiplimab in third-line immune checkpoint inhibitor–resistant advanced NSCLC: Evaluation of overall survival (OS). First Author: Tomasz Jankowski, Medical University in Lublin, Lublin, Poland

Background: Despite advancements in third line treatments, long-term survival for advanced non-small cell lung cancer (NSCLC) remains suboptimal, with median survival follow-up of only 5.8 months.[1] Among patients treated with prior platinum chemotherapy and immune checkpoint inhibitors (ICIs), the median survival was reported to be 6.47 months[2]. Treatment options for ICI-resistant patients are limited. THIO, a telomere-targeting agent that modifies telomeres in cancer cells, demonstrates improved overall survival (OS) independent of PD-L1 expression. **Methods:** NCT05208944 is a phase 2, multicenter, open-label study that enrolled 79 patients with advanced NSCLC who relapsed after 1–4 prior treatments, including ICIs. In the third line therapy 22 patients treated with THIO (60, 180, or 360 mg) were evaluated for OS and their prior PD-L1 expression at the time of study enrollment (C1D1). **Results:** In the third line therapy 22 patients have a current median survival follow-up of 13 months which significantly surpassed the benchmark value, and in the 180 mg dose group (n=10) it reached 16.9 months compared to 5.8 months for the benchmark.[1] THIO followed by cemiplimab was generally well tolerated in this difficult-to-treat population. The response to THIO and cemiplimab, demonstrated by partial response (PR) and stable disease (SD) was independent of baseline PD-L1 status. This indicates that THIO can be effective across patients regardless of their PD-L1 status. **Conclusion:** THIO demonstrates clinically meaningful OS improvement in third line patients with advanced NSCLC, independent of PD-L1 status. The improved OS observed in patients treated with THIO in sequential combination with an ICI, compared to standard chemotherapy, supports its potential to expand treatment options for ICI-resistant advanced NSCLC. Clinical trial information: NCT05208944. Research Sponsor: MAIA Biotechnology Inc.

8586 Poster Session

Efficacy profile of pembrolizumab for primary pulmonary NUT carcinoma: A systematic review and meta-analysis. First Author: Amruth Akhil Alluri, American University of the Caribbean School of Medicine, Cupecoy, Sint Maarten (Dutch part)

Background: Primary pulmonary NUT carcinoma is an exceedingly rare and aggressive malignancy characterized by chromosomal rearrangements involving the NUT gene. With limited therapeutic options and an extremely poor prognosis, treatment strategies have focused on identifying effective targeted and immunotherapeutic approaches. Pembrolizumab, an anti-PD-1 immune checkpoint inhibitor, has shown promise in various malignancies, particularly those with high tumor mutational burden or PD-L1 expression. However, despite its use, its efficacy in NUT carcinoma remains poorly understood due to the rarity of this disease and a paucity of robust clinical data. This systematic review and meta-analysis aim to explore the available evidence on the clinical data of pembrolizumab in treating primary pulmonary NUT carcinoma, focusing on progression-free survival (PFS), and overall survival (OS) by consolidating outcomes from case reports and case series. **Methods:** A systematic review and meta-analysis were conducted to evaluate the effectiveness of pembrolizumab in the treatment of primary pulmonary NUT carcinoma. A comprehensive search of PubMed, Embase, and Cochrane was performed for articles published between January 2014 and December 2024, using the keywords "pembrolizumab," "Pulmonary NUT carcinoma," and "NUT midline carcinoma." Inclusion criteria included reports of patients treated with either pembrolizumab monotherapy or pembrolizumab in conjunction with other therapies for Primary Pulmonary NUT Carcinoma for any duration. Reports that did not mention PFS or OS were excluded. **Results:** A total of 39 reports involving 56 patients with primary pulmonary NUT carcinoma treated with pembrolizumab, either in conjunction with other therapies or monotherapy, were analyzed. The median overall survival (OS) was 7.3 months (95% CI: 5.2–8.8), and the median progression-free survival (PFS) was 4.6 months (95% CI: 3.1–5.7). Among three patients receiving pembrolizumab monotherapy as a second-line or later treatment, the median PFS was 2.9 months. **Conclusions:** Pembrolizumab has been explored as second-line or later therapy for primary pulmonary NUT carcinoma based on its success in treating NSCLC. Our analysis revealed a median progression-free survival of 4.6 months and a median overall survival of 7.3 months for patients with primary pulmonary NUT carcinoma receiving pembrolizumab, illustrating the continuing challenge of treating this rare malignancy. Importantly, there are no randomized controlled trials investigating pembrolizumab in this rare malignancy, highlighting a critical gap in evidence. Prospective clinical trials and further research into biomarkers predictive of treatment response are urgently needed to optimize therapeutic strategies and improve outcomes for patients with this aggressive disease. Research Sponsor: None.

8587 Poster Session

Survival after osimertinib dose-reduction, discontinuation in 1L *EGFR*-mutated metastatic non-small cell lung cancer (mNSCLC). First Author: Adam Barsouk, Abramson Cancer Center, Penn Medicine, Philadelphia, PA

Background: Osimertinib (osi) has become standard of care in 1L EGFR mt (+) mNSCLC following the FLAURA trial in patients (pts) with classical sensitizing mutations. However, limited data are available on the effect of osimertinib dose reductions on survival outcomes compared to pts on full dose. **Methods:** We performed a single-institution retrospective analysis of pts with *EGFR*-mutated mNSCLC treated with 1L osi from 2018-2023 Clinical trial pts were excluded. Pts who underwent dose reduction were compared to those maintained on full dose (at least 80mg daily). Baseline demographics, disease characteristics, treatment history, toxicity, and clinical outcomes were abstracted from the electronic medical record (EMR) and compared using independent sample t-tests and chi-square analyses as appropriate. Median progression free survival (mPFS) and overall survival (mOS) were compared via Kaplan-Meier log-rank analysis and Cox regression analysis, with sex, race, age, PS, smoking hx, CNS involvement, and mutation status included *a priori*. **Results:** 171 pts with mNSCLC treated with 1L osi were identified. 26 (15%) required dose reduction. Patient sex (p=0.458), racial distribution (p=0.421), ECOG PS>1 at diagnosis (p=0.730) and smoking history (p=0.485) were comparable between reduced dose and full dose pts (Table 1). 44% vs 34% had CNS metastases at diagnosis (p=0.192). Rates of *TP53* (p=0.712) and atypical *EGFR* mutations (p=0.393) were also comparable. All dose-reduced pts experienced AEs, compared to 48% of full-dose pts ($p<0.001$). Dose-reduced pts had inferior mPFS (17.0 months [11.5-22.5]) compared to full-dose pts (24.6[19.2-28.8]; p=0.043. PFS with dose-reduction was inferior compared to full dose with (p=0.041) or without CNS metastases (p=0.048). On multivariable analysis, dose-reduction was associated with inferior PFS (p=0.047) regardless of baseline characteristics. OS, however, was comparable in pts with and without dose-reduction (36.7 [28.1-45.4] vs 39.2 [34.8-43.7]; p=0.749)). 14 pts (8%) discontinued osi due to AEs, of whom 9 (64%) were previously dose reduced. mPFS was comparable (p=0.334) between pts who discontinued and those who did not, as was mOS (p=0.910). **Conclusions:** Dose reduction of osimertinib was relatively uncommon and associated with inferior PFS but similar OS in 1L pts with *EGFR*-mutated mNSCLC. Research Sponsor: None.

Baseline characteristics and survival.

Baseline Characteristics	Dose reduced (n=26)	Full dose (n=145)	Sig (p)
Female	59.6%	63.0%	0.458
Race			0.421
White	63.0%	67.0%	
Black	3.7%	12.3%	
Asian	33.3%	19.1%	
ECOG PS>1	0%	6.8%	0.730
Smoking Hx	37.0%	39.7%	0.485
CNS mets	44.4%	33.5%	0.192
Mutation Status			
TP53	55.7%	53.1%	0.712
L858R	35.8%	38.2%	0.675
Exon19del	45.7%	45.0%	0.819
Atypical mutation	18.5%	16.8%	0.393
Adverse Events (AEs)			
Experienced AEs	100%	48.3%	**<0.001**
Discontinued due to AE	34.6%	3.4%	**<0.001**
Survival (months)			
mPFS	17.0[11.5-22.5]	24.6[19.2-28.8]	**0.043**
mOS	36.7 [28.1-45.4]	39.2 [34.8-43.7]	0.910

Significant findings in bold.

8588 Poster Session

Clinical relevance of starting alectinib at a reduced dose in patients with ALK-positive non-small cell lung cancer. First Author: Junkyu Kim, Division of Hematology-Oncology, Department of Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, South Korea

Background: Alectinib has been approved for Anaplastic lymphoma kinase (ALK)-positive non-small cell lung cancer (NSCLC) at a lower dose (300 mg twice daily: b.i.d.) in Japan than the rest of the world (600 mg b.i.d.). To evaluate the clinical relevance of reducing the starting dose of alectinib, we compared the clinical outcomes of patients treated with one of the two doses. **Methods:** This study included patients with advanced ALK-positive NSCLC who received alectinib at Samsung Medical Center, Korea. The progression-free survival (PFS), overall survival, cumulative incidence of central nervous system (CNS) progression, and safety profiles were retrospectively reviewed and compared. **Results:** Among 306 patients, 32 and 274 received alectinib at either 300 or 600 mg b.i.d., respectively. The 300 mg group showed a slight but not significant advantage in PFS (HR 0.82, 95% CI 0.44-1.51, p=0.51) and overall survival (HR 0.51, 95% CI 0.20-1.21; p=0.13) compared with the 600 mg group. Interestingly, the superior survival outcome in the 300 mg group was remarkable in patients with lower body weight (≤60 kg). However, this advantage diminished at higher body weights (>60~75 kg or >75 kg). In addition, there was a slight tendency toward a higher incidence of CNS failure in the 300 mg group of patients with baseline brain metastasis (HR 1.76, 95% CI 0.53-5.8; p=0.36). Although the safety profiles were mostly mild and manageable in both groups, the 600 mg group showed more frequent adverse events than the 300 mg group and required dose reduction in 137 patients (50%). **Conclusions:** Alectinib at 300 mg b.i.d. seems an acceptable dose in patients with ALK-positive NSCLC even in areas outside Japan. Notably, our data favor 300 mg b.i.d. in patients with lower body weight and no baseline brain metastasis, considering the more tolerable safety profiles and the potential to reduce medical costs. Research Sponsor: None.

8589 Poster Session

Depth of response and progression-free survival in patients with advanced *ALK*-positive non–small-cell lung cancer treated with lorlatinib. First Author: Rosario Garcia Campelo, University Hospital A Coruna HRS4R Universia gal, A Coruña, Spain

Background: After 5 years of follow-up in patients with *ALK*-positive non-small cell lung cancer (NSCLC) treated with lorlatinib, median progression-free survival (PFS) was still not reached in the phase 3 CROWN study (NCT03052608). This represents the longest PFS for any single-agent molecular targeted treatment in advanced NSCLC and all metastatic solid tumors. Depth of response (DepOR) is defined as the best percent shrinkage in tumor size compared with baseline. In this post hoc analysis of data from the CROWN study, we assessed the association between DepOR and PFS. **Methods:** The CROWN study is an ongoing, international, open-label, randomized, phase 3 trial comparing lorlatinib vs crizotinib in patients with previously untreated *ALK*-positive advanced NSCLC. Patients were randomized 1:1 to receive oral lorlatinib 100 mg once daily or crizotinib 250 mg twice daily. This analysis examined how DepOR is associated with baseline demographics, tumor characteristics, PFS, and tumor biomarkers. Patients were evaluable for DepOR if they had target lesions at baseline and ≥1 adequate postbaseline assessment up to the time of progressive disease or new anticancer therapy. A genAI tool (12/20/24; Pfizer; GPT-4o) developed the 1st draft; authors assume content responsibility. **Results:** In the lorlatinib group, 142 of 149 (95%) randomized patients were evaluable for DepOR; 29 (20%) had 0%-50% DepOR, 65 (46%) had >50%-75%, and 48 (34%) had >75%-100%. Baseline demographics and tumor characteristics were similar between the DepOR groups, although the percentage of patients with baseline brain metastases was higher in the greater DepOR group. PFS improved with increasing DepOR (Table). Key biomarker analyses evaluating *EML4-ALK* long- and short-variant subgroups and circulating tumor DNA dynamics, based on DepOR groups, will be reported. **Conclusions:** Greater DepOR was associated with PFS benefit in patients with advanced *ALK*-positive NSCLC treated with lorlatinib. Clinical trial information: NCT03052608. Research Sponsor: Pfizer.

PFS in patients evaluable for DepOR (n=142).

	0%-50% DepOR	>50%-75% DepOR	>75%-100% DepOR
DepOR in the lorlatinib group, n (%)	29 (20)	65 (46)	48 (34)
PFS			
Probability of being event free (95% CI), %			
At 3 years	41.0 (22.6-58.6)	68.2 (55.1-78.2)	77.5 (62.1-87.2)
At 5 years	36.9 (19.3-54.7)	62.3 (48.6-73.3)	74.8 (59.0-85.2)
Median (95% CI), months	12.7 (7.2-NE)	NE (60.0-NE)	NE (NE-NE)
HR (95% CI)[a]		0.39 (0.21-0.73)	0.25 (0.12-0.53)

NE, not evaluable.
[a]Unstratified analysis comparison vs 0%-50% group.

8590 Poster Session

Impact of lorlatinib dose modifications on adverse event outcomes in the phase 3 CROWN study. First Author: Geoffrey Liu, Princess Margaret Cancer Centre, Toronto, ON, Canada

Background: In an updated analysis of the CROWN study (NCT03052608), after 5 years of follow-up, lorlatinib continued to show superior efficacy over crizotinib in patients with previously untreated advanced *ALK*+ non-small cell lung cancer (NSCLC), with median progression-free survival (PFS) still not reached. A post hoc analysis of CROWN found no impact on PFS or time to intracranial progression with lorlatinib dose reductions within the first 16 weeks. These findings underscore the importance of dose modifications to mitigate toxicity and maintain long-term treatment efficacy. The objective of this analysis was to further characterize lorlatinib dose reductions and their impact on safety and adverse event (AE) outcomes. **Methods:** The CROWN study is an ongoing, international, open-label, randomized phase 3 trial comparing lorlatinib vs crizotinib in patients with previously untreated advanced *ALK*+ NSCLC. Patients were randomized 1:1 to receive lorlatinib 100 mg once daily (QD; n=149) or crizotinib 250 mg twice daily (n=147). This post hoc analysis used data from the 5-year follow-up to assess time to dose reduction, duration of treatment with reduced dose, and its impact on AEs and outcomes associated with lorlatinib. A genAI tool (12/13/24; Pfizer; GPT-4o) developed the 1st draft; authors assume content responsibility. **Results:** At 5 years of follow-up, 49 of 149 patients in the lorlatinib arm had ≥1 lorlatinib dose reduction. Treatment is ongoing in 33% of patients who had 1 dose reduction (n=24) and in 20% who had 2 dose reductions (n=25). In patients who had 1 dose reduction to 75 mg QD, median time to dose reduction was 7.1 months (range, 1.7-64.8), and median duration of treatment with the 75-mg dose was 42.2 months (range, 0.2-68.3). In patients who had 2 dose reductions (dose reduced to 75 mg QD and then again to 50 mg QD), median time to second dose reduction was 11.3 months (range, 2.5-56.9), and median duration of treatment with the 50-mg dose was 20.7 months (range, 0.5-61.8). In patients who had 1 or 2 dose reductions, all-cause AEs associated with dose reductions are shown in the table. Of the 30 AEs leading to 1 dose reduction, 27% of events resolved and 13% partially resolved. Of the 59 AEs leading to 2 dose reductions, 46% of events resolved and 5% partially resolved. **Conclusions:** This post hoc analysis of the CROWN study showed that dose reductions were effective in managing AEs associated with lorlatinib. These findings show the importance of dose modifications to mitigate toxicity and continue lorlatinib treatment for prolonged periods of time in patients with advanced *ALK*+ NSCLC. Clinical trial information: NCT03052608. Research Sponsor: Pfizer.

AEs associated with dose reductions in >2 patients, n (%)	Any grade	Grade ≥3
1 dose reduction (n=24)		
Any	23 (96)	14 (58)
Peripheral edema	4 (17)	2 (8)
2 dose reductions (n=25)		
Any	24 (96)	11 (44)
Peripheral edema	6 (24)	0
Blood triglycerides increased	3 (12)	2 (8)
Disturbance in attention	3 (12)	0
Generalized edema	3 (12)	1 (4)

8591 Poster Session

Dynamic changes in target protein expression following treatment in NSCLC: Simultaneous evaluation of MET, TROP2, HER2, B7-H4, and MDM2 expression in paired biopsies. First Author: Saori Murata, Department of Thoracic Oncology, National Cancer Center Hospital, Tokyo, Japan

Background: Antibody-drug conjugates and bispecific antibodies targeting non-small cell lung cancer (NSCLC) tumor surface antigens are under development, but the impact of prior treatments on target protein expression remains unclear. This study evaluates changes in the expression of multiple therapeutic target proteins in the same patient before and after treatments. **Methods:** Patients diagnosed with NSCLC underwent rebiopsy after treatments at the National Cancer Center Hospital between 2014 and 2023 were eligible. Tissues were obtained by surgery, bronchoscopy, or needle biopsy with an interval of at least 100 days of systemic anti-cancer therapy. We investigated clinicopathological features in paired specimens focusing on tumor-associated surface proteins potentially related to novel drug development such as MET, TROP2, HER2, B7-H4, and MDM2. TROP2, B7-H4, and MDM2 were evaluated using the H-score. HER2 was evaluated on a scale from 0 to 3+, as previously reported. For MET, a scoring system was adopted in which overexpression (OE) was defined as IHC 3+ positive cells representing 25% or more of the cells. **Results:** A total of 51 cases were included in this study. The median age was 64 years. Of the patients, 27 (57%) were male, 33 (65%) were smokers, and 45 (88%) had lung adenocarcinoma. EGFR 24 cases (47%)/ALK 8 cases (16%)/BRAF 1 case (2%)/ROS1 1 case (2%) were identified among 34 cases with actionable genetic alterations (AGAs). The proportion of MET OE before and after treatment was 33.3%/45.1% overall. In subgroup analyses, the proportions were 38.2%/47.1% (AGA positive), 23.5%/41.2% (AGA negative), 36.0%/52.0% (PD-L1 positive), and 30.8%/38.5% (PD-L1 negative). For HER2 positive (2+, 3+) cases, the overall proportions were 20.9%/11.6%, while subgroup proportions were 15.2%/12.1%, 40.0%/10.0%, 20.0%/15.0%, and 21.7%/8.7%, respectively. The proportion of patients who experienced change in protein expression after previous treatment was as follows: MET, 31.4%; TROP2, 29.4%; HER2, 27.9%; B7-H4, 0.0%; MDM2, 51.0%. **Conclusions:** MET, TROP2, HER2, and MDM2 showed expression changes before and after treatment in approximately 30% of patients. There were differences in the rate of change depending on whether AGA was present, with a higher rate of change in AGA negative patients. Based on these findings, rebiopsy after treatment is recommended when considering therapies targeting tumor surface protein antigens. Research Sponsor: None.

Percentage change in MET, TROP2, HER2, B7-H4, and MDM2 following previous treatment.

	MET (%)	TROP2 (%)	HER2 (%)	B7-H4 (%)	MDM2 (%)
Proportion changing (n=51)	31.4	29.4	27.9	0.0	51.0
AGA positive (n=34)	32.4	20.6	21.2	0.0	52.9
Elevated	20.6	17.6	9.1	0.0	32.3
Decreased	11.8	3.0	12.1	0.0	20.6
AGA negative (n=17)	29.4	47.1	50.0	0.0	47.1
Elevated	23.5	47.1	10.0	0.0	17.6
Decreased	5.9	0.0	40.0	0.0	29.4

AGA; actionable gene alternation.

8592 **Poster Session**

RC108 in combination with furmonertinib in patients with locally advanced or metastatic EGFR-mutated non-small-cell lung cancer (NSCLC) with MET overexpression: Results from a phase Ib/II trial. First Author: Yutao Liu, National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences & Peking Union Medical College, Beijing Key Laboratory of Clinical Study on Anticancer Molecular Targeted Drugs, Beijing, China

Background: Patients (pts) who have progressed on EGFR-TKI treatment have limited treatment choices when accompanied by MET overexpression. RC108 is a MET-directed ADC with the microtubule inhibitor monomethyl auristatin E (MMAE) as the cytotoxin and it may overcome primary/secondary MET-driven resistance to EGFR-TKI. We report the preliminary safety and efficacy results of RC108+furmonertinib (F, a third-generation EGFR-TKI) in pts with MET-overexpressing and EGFR-mutated locally advanced or metastatic (la/m) NSCLC who failed prior EGFR-TKI from a phase 1b/2 trial (NCT05821933). **Methods:** The key eligibility criteria were histologically or cytologically confirmed la/m NSCLC with at least one documented EGFR sensitizing mutation, MET-overexpression (defined as IHC 1+/2+/3+ in ≥10% of tumor cells), and disease progression on prior 1st/2nd/3rd-generation EGFR-TKI treatment. Pts received RC108 (at doses of 1.5 or 2.0 mg/kg, Q3W) + F (80 mg, QD) until disease progression or intolerable toxicity. Radiological tumor assessment was performed every 6 weeks by investigators per RECIST v 1.1. The primary endpoints were safety and objective response rate (ORR). Data cutoff date for this analysis was Sep 12, 2024. **Results:** A total of 31 pts were enrolled and received at least one dose of treatment, including 2 and 29 pts in the 1.5 and 2.0 mg/kg cohorts, respectively. The most frequent treatment-related adverse events (TRAEs) were nausea (51.6%), asthenia (48.4%), decreased appetite (45.2%), vomiting (45.2%), white blood cell count decreased (35.5%), alopecia (35.5%), and hypoesthesia (32.3%). Grade ≥3 TRAEs occurred in 7 (22.6%) pts. TRAEs led to treatment discontinuation in 1 (3.2%) pt. One pt died due to abnormal hepatic function, possibly related to the study treatment per the investigator's assessment. Among the 24 pts with at least one post-baseline tumor assessment in the 2.0 mg/kg cohort (79.2% with ECOG PS 1, 58.3% with exon 19 deletion, 33.3% with exon 21 L858R, and 62.5% with ≥2 prior lines of treatment), the ORR was 37.5% (95% CI: 18.8-59.4) and disease control rate (DCR) was 75.0% (95% CI: 53.3-90.2). In the 18 pts with ≥10% of tumor cells with 1+/2+/3+ membrane staining and ≤20% tumor cells with strong (3+) cytoplasmic staining, ORR was 50.0% (95% CI: 26.0-74.0) and DCR was 83.3% (95% CI: 58.6-96.4). The progression-free survival data were immature and under follow-up. **Conclusions:** RC108+F showed encouraging antitumor activity with manageable safety profile in pts with MET-overexpression. At the same time, this study demonstrated better efficacy in the population with lower MET expression in the cytoplasm. We will continue to explore more beneficial populations in future studies. Clinical trial information: NCT05821933. Research Sponsor: RemeGen Co., Ltd.

8593 **Poster Session**

Impact of standard vs reduced dosing of sotorasib on efficacy and toxicity in KRAS G12C–mutated advanced non-small cell lung cancer: A systematic review and meta-analysis. First Author: Wint Yan Aung, Zuckerberg Cancer Center, Northwell Health, Lake Success, NY

Background: KRAS is the most common oncogenic driver in lung adenocarcinoma. Advances in targeted therapies such as Sotorasib have improved outcomes, but optimizing dosing strategies is crucial to balance efficacy and tolerability. Sotorasib serves as an illustrative example, as it was the first drug for which the FDA requested a dose optimization strategy. The FDA's decision to maintain 960 mg dose was influenced by CodeBreaK100 and CodeBreaK200 trials. CodeBreaK100, which demonstrated an ORR of 36%, formed the basis for accelerated approval, while CodeBreaK200 confirmed clinical benefit. A post-approval dose randomization study comparing 240 mg and 960 mg doses found no clear exposure-safety relationships, though ORR was numerically higher for 960 mg. However, tolerability remains challenging with 960 mg dose, often requiring dose reductions in clinical practice. This systematic review and meta-analysis evaluates the impact of starting at 960 mg of Sotorasib versus reduced dose on efficacy and toxicity, with implications for optimizing dosing strategies in targeted therapies. **Methods:** We conducted a systematic search of PubMed, EMBASE, SCOPUS, CINAHL, and Web of Science up to Oct 1,2024. Eligible studies included randomized clinical trials, prospective and retrospective studies, reporting efficacy outcomes (ORR, PFS), and treatment-related adverse events. Pooled estimates for efficacy and toxicity outcomes were calculated using random effects model. **Results:** Out of 4510 studies screened, 145 full-text articles were assessed for eligibility, resulting in 14 studies, of which 9 focused on Sotorasib. The pooled ORR was 32% (95%CI 28%-36%) for patients starting at 960 mg (n=889), compared to 26% (95%CI 19%-34%) for those starting at a reduced dose (n=130) with no statistically significant difference (RR 1.26, 95%CI 0.87-1.83). The pooled hazard ratio for PFS did not show a significant benefit for starting at 960 mg compared to at reduced dose (HR 0.77, 95%CI 0.56-1.05). Adverse events leading to dose reduction and discontinuation at 960 mg were 16% (95%CI 10%-23%) and 9% (95%CI 6%-13%), respectively. Limited toxicity data were available for those who started treatment at reduced dose, precluding direct comparison. **Conclusions:** While the standard 960 mg dose of Sotorasib showed a trend toward higher ORR compared to starting at reduced doses, it is associated with significant toxicity, resulting in frequent dose reductions and treatment discontinuation. No significant PFS benefit was observed with starting at 960 mg dose, highlighting the need to optimize dosing strategies that balance efficacy with tolerability.Future studies should include subgroup analyses of efficacy and tolerability for dose reductions to guide optimal dosing regimens, aligning with initiatives like the FDA's Project Optimus to improve patient outcomes. Research Sponsor: None.

8595 **Poster Session**

Area deprivation index and EGFR-mutated non-small-cell lung cancer. First Author: Michael Seth Weinfeld, University of Illinois Chicago, Chicago, IL

Background: Survival outcomes in patients with non-small-cell lung cancer (NSCLC) have improved in recent decades with availability of immunotherapy and targeted therapies such as inhibitors of mutated epidermal growth factor receptor (EGFR). However, significant disparities in lung cancer outcomes exist, with many patients not offered biomarker testing and subsequent underuse of targeted therapies. Because it is not well known how social determinants of health (SDOH) impact the use of targeted therapies, we conducted a study to determine the association between area deprivation index (ADI) and presence of mutated EGFR in a large electronic health record (EHR) database. ADI is a validated measure of neighborhood socioeconomic deprivation, a SDOH metric. **Methods:** This retrospective, observational study used Epic Cosmos, a United States database of deidentified data derived from EHR, to measure the association between ADI and EGFR mutations in patients with stage IV NSCLC treated between January 1, 2015 and December 31, 2022. Receipt of EGFR inhibitors (EGFRIs) was used as a surrogate marker for mutated EGFR, as pathology and molecular data for individual patients were not available from aggregate data. Chi square analysis was used to compare ADI between those who did and did not receive EGFRIs. **Results:** From a total of 6866 patients meeting criteria for inclusion in our analysis, 653 (9.5%) received EGFRIs while 6213 (90.5%) did not. In the EGFR population, 210 (32.2%) were in the top two quintiles of ADI (most deprivation) while 275 (42.1%) were in the bottom two quintiles of ADI (least deprivation). For the non-EGFR population, 3137 (50.5%) were in the top two quintiles while 1373 (22.1%) were in the bottom two quintiles. Patients who received EGFRIs were more likely to be in the bottom two quintiles of ADI compared to those who did not (OR 2.99, 99% CI 2.32-3.84, $p<0.0001$). To control for confounding variables, this analysis was repeated after stratifying by geography, sex, smoking status, insurance, and race. This difference in ADI between the EGFR and non-EGFR groups persisted within strata of similar patients including White females with a smoking history in the Northeast with Medicare (OR 7.28, 99% CI 1.56-34.01, p=0.0009) and White females with a smoking history in the Midwest with Medicare (OR 4.76, 99% CI 1.19-19.10, p=0.0038). **Conclusions:** These data suggest that patients with EGFR mutations, as determined by receipt of EGFRIs, were more likely to reside in neighborhoods with less socioeconomic deprivation. Because of limitations posed by our analytic approach, we were unable to determine if there was a direct association between ADI and the molecular profile of NSCLC, or if these findings are primarily related to differential access to care. Nonetheless, the association persisted within strata of similar demographics, suggesting that it is not entirely explained by confounding related to geography, race, sex, or smoking status. Research Sponsor: None.

8596 **Poster Session**

Final results of afatinib plus chemotherapy with genomic profiling in osimertinib-refractory EGFR-mutant NSCLC: NEJ025B. First Author: Akihiko Miyanaga, Department of Pulmonary Medicine and Oncology, Graduate School of Medicine, Nippon Medical School, Tokyo, Japan

Background: Osimertinib is commonly used as a first-line treatment for EGFR-mutated advanced NSCLC. However, the optimal treatment following osimertinib failure remains unclear. This study evaluated afatinib plus chemotherapy for EGFR-mutated NSCLC resistant to osimertinib. Initial findings were presented at ASCO2023, and this report provides final data, including blood NGS analysis. **Methods:** Patients (pts) with EGFR mutations (Del19 or L858R) after osimertinib failure were treated with afatinib (20 mg daily) combined with carboplatin (AUC5 mg/mL/min) and pemetrexed (500 mg/m² every 3 weeks), followed by maintenance therapy with afatinib plus pemetrexed until progression or unacceptable toxicity. The primary endpoint was the 6-month progression-free survival rate (6M-PFSR). Secondary endpoints included PFS, OS, ORR, DOR, and safety. Blood samples were collected before and during treatment, and at progression, to evaluate biomarkers using CAPP-SEQ. **Results:** Between June 7, 2020, and January 19, 2022, 36 pts were enrolled. One pt met exclusion criteria, leaving 35 pts for efficacy analysis. The mean age was 70 years; 60% were women, and 54.3% were nonsmokers. The median observation period was 29.1 months (cutoff date: January 18, 2024). The primary endpoint, 6M-PFSR, was 57.1% (95% CI, 39.3–71.5), exceeding the threshold of 35%. Notably, 28.6% of pts achieved long-term PFS of ≥1 year. ORR was 51.4%, DCR was 88.6%, median PFS was 8.2 months, median DOR was 5.6 months, and median OS was 22.5 months. By mutation type, ORRs were similar for Del19 and L858R (46.7% and 55.0%, respectively), but median PFS was longer for Del19 than for L858R (9.6 vs. 5.2 months). Pts who had responded to prior osimertinib (CR/PR, n=29) had longer median PFS than non-responders (SD/PD/NE, n=6) (8.5 vs. 5.8 months). Adverse events (AEs) from TKI and chemotherapy were common but manageable. The most frequent AEs were diarrhea (52.8%), anorexia (47.2%), fatigue (36.1%), and paronychia (36.1%). Interstitial pneumonia occurred in 3 pts (8.3%), with one treatment-related death. In plasma NGS analysis, clearance of EGFR mutations during treatment was a key predictive factor. Pts without EGFR mutation clearance had shorter PFS and OS compared to those with clearance (PFS: 5.7 vs. 12.0 months; OS: 15.7 vs. 34.4 months). Efficacy was observed even in pts with p53 mutations, a known resistance factor. MET gene amplification was detected in 4 pts upon resistance. **Conclusions:** Afatinib combined with platinum-based chemotherapy demonstrated satisfactory efficacy and manageable toxicity in pts with tumors refractory to osimertinib. EGFR mutation clearance during treatment was predictive of therapeutic outcomes. This regimen may be a promising second-line option after osimertinib failure. Clinical trial information: 021200005. Research Sponsor: Boehringer Ingelheim.

8598 Poster Session

Final results of a phase 1 study of EP0031, a next generation selective RET inhibitor (SRI) in patients with SRI naïve or pretreated advanced RET-altered tumors. First Author: Guzman Alonso, Vall d'Hebron Institute of Oncology (VHIO), Barcelona, Spain

Background: EP0031 (A400/KL590586), a first in class next gen selective RET inhibitor (SRI) with FDA Fast Track Designation, has broad potency against common RET alterations, including resistance mutations. It has greater potency, antitumor activity, and CNS penetration/activity compared with 1st gen SRIs (Garralda et al. JCO 2024; 42:16; abstr 8556; Zhou et al. JCO 2023; 41:16, abstr 3007). We report final data from the dose finding and optimization Phase 1 trial in the US and Europe. **Methods:** The study recruited pts with RET-altered NSCLC, medullary thyroid cancer (MTC) and other solid tumors and included pts ≥ 18 years, PS 0 or 1, with/without asymptomatic, stable brain mets, who received EP0031 QD in 28 days' cycles. **Results:** A total of 40 pts (23 F, 17 M, median age 59 y), 22 NSCLC (20 SRI pre-treated, 1-6 prior lines), 12 MTC (7 SRI pre-treated, 1-4 prior lines) and 6 pts with other tumors (4 SRI pre-treated) were enrolled across 4 cohorts: 20 (n=3), 60 (n=10), 90 (n=16) and 120 (n=11) mg QD. The 60, 90 and 120mg cohorts were expanded for dose optimization. 9 pts had stable brain mets at baseline. No DLTs were observed. Most frequent G1/2 TEAEs (≥20%) were headache, anemia, ALT/AST increase, constipation, dizziness, hyperphosphatemia, blurred vision, keratitis, blood creatinine increased, dry mouth, dyspnea and fatigue. G3 TEAEs were rare and included (≥5%): hyponatremia, hypertension, anemia, AST/ALT increase, headache, diarrhea and ulcerative keratitis. Interruptions, reductions and discontinuations related to study drug were seen in 16 (40%), 8 (20%) and 1 (2.5%) pt. 25 pts with prior SRI were response evaluable. 5 PRs and 6 SDs reported in 15 NSCLC pts, with complete resolution of brain mets in 3/5 pts. Median DoR was 7.3mo (range 5.4-16.3). In 7 MTC pts, 2 PRs (DoR 6.6 – 9.2mo) and 2 SDs seen. Of 3 pts with other tumors, a pancreatic cancer pt had SD for 3.5 mo, and a pt with papillary thyroid cancer was clinically stable for 9 mo. In pts who were SRI naïve, 1 CR and 1 PR were reported in 2 NSCLC pts; and 5 PRs (1 uPR) were reported in all MTC pts. Baseline on-target RET resistance mutations were detected in 6/31 prior SRI pts (19.4%) with evidence of activity in 3, and sustained reduction and clearance of ctDNA (including RET resistant mutations: G810R solvent front and L730V, L730I roof mutations). Plasma exposures increased proportionately with dose. 90mg QD was selected as RP2D, with plasma levels $>IC_{90}$ for all relevant RET fusions/mutations. **Conclusions:** There is a need for new treatments for pts that progress on 1st gen SRIs. EP0031 was associated with durable responses in advanced RET altered solid tumors previously treated with SRI, including pts with brain mets, with a manageable safety profile. These data confirm that the first in class next gen SRI EP0031 has the potential to address a high unmet need. Phase 2 trials are evaluating EP0031/KL590586 in US, Europe, UAE and China. Clinical trial information: NCT05443126. Research Sponsor: Ellipses Pharma.

8599 Poster Session

Longer follow-up for survival and safety from the EVOKE-01 trial of sacituzumab govitecan (SG) vs docetaxel in patients (pts) with metastatic non-small cell lung cancer (mNSCLC). First Author: Niels Reinmuth, Asklepios Lung Clinic, German Center for Lung Research (DZL), Munich-Gauting, Germany

Background: EVOKE-01 (NCT05089734) assessed the efficacy and safety of SG vs docetaxel in pts with mNSCLC that progressed after platinum-based chemotherapy and anti–PD-(L)1 (IO) treatment. The study did not meet statistical significance for overall survival (OS) at final analysis. Here, we report updated survival and safety outcomes after longer follow-up, providing insight into the tolerability of SG over a prolonged period of administration. **Methods:** Pts were randomized 1:1 to receive SG (n = 299; 10 mg/kg IV, days 1 and 8) or docetaxel (n = 304; 75 mg/m^2 IV, day 1) in 21-day cycles until progression or unacceptable toxicity. OS was the primary endpoint, while safety was a key secondary endpoint. **Results:** As of Oct 21, 2024, median follow-up was 23.5 months. Median exposure with SG vs docetaxel was 3.5 vs 2.3 months; 33.4% vs 17.7% of pts, respectively, were exposed to study drug for ≥6 months. The longer follow-up preserved the numerical improvement in OS favoring SG in the intent-to-treat population (HR 0.89, 95% CI: 0.74–1.07; *P* = .1028) and in subgroups of interest, including nonresponders to prior IO, and across squamous and nonsquamous histologies (**Table**). Most common any-grade treatment-emergent adverse events (TEAEs) with SG vs docetaxel were fatigue (57.8% vs 56.6%), diarrhea (52.7% vs 33.7%), and alopecia (43.6% vs 30.2%). In line with the primary analysis, 68.6% vs 76.0% of pts receiving SG vs docetaxel experienced grade ≥3 TEAEs, mainly neutropenia (25.3% vs 36.8%), fatigue (12.5% vs 9.7%), and diarrhea (10.5% vs 3.8%). Discontinuations due to TRAEs were seen in 7.4% vs 14.2% of pts receiving SG vs docetaxel. There were no additional AEs leading to death reported with longer follow-up (Table). **Conclusions:** Consistent with the final analysis, SG showed a numerical improvement in OS vs docetaxel. Long-term safety showed SG is well tolerated, consistent with minimal increase in AE rates since prior report and an improved safety profile over docetaxel, despite longer treatment exposure. Clinical trial information: NCT05089734. Research Sponsor: Gilead Sciences, Inc.

Median OS, mo (95% CI) HR (95% CI)	SG	Doc
Nonresponsive (SD/PD) to last IO	n = 192 11.8 (9.6–12.8) 0.83 (0.66–1.04)	n = 191 8.3 (6.9–10.2)
Responsive (CR/PR) to last IO	n = 106 9.7 (8.4–14.3) 1.05 (0.78–1.43)	n = 113 10.8 (9.2–12.8)
Squamous	n = 84 10.3 (8.1–13.2) 0.89 (0.63–1.25)	n = 80 9.2 (6.9–11.0)
Nonsquamous	n = 215 11.6 (9.4–12.9) 0.89 (0.72–1.11)	n = 224 9.9 (7.9–11.2)
With prior therapy for AGA	n = 19 12.9 (7.2–23.9) 0.63 (0.31–1.29)	n = 25 7.0 (5.2–11.6)
TEAE, % (safety population)	**n = 296**	**n = 288**
Any grade	99.7	98.3
Grade ≥3	68.6	76.0
Serious TEAEs	47.6	44.4
Leading to dose reduction	29.7	39.2
Leading to discontinuation	10.1	16.7
TRAEs leading to discontinuation	7.4	14.2
Leading to death	3.4	4.2
TRAEs leading to death	1.4	1.0

8600 Poster Session

A retrospective study of anlotinib plus third-generation EGFR-TKIs in advanced non-small cell lung cancer with gradual or oligo progression after EGFR-TKIs treatment (ALTER-L058). First Author: Caicun Zhou, Shanghai East Hospital, Tongji University, Shanghai, China

Background: Despite the significant improvement in progression-free survival (PFS) for non-small cell lung cancer (NSCLC) patients with EGFR mutations, attributed to the advent of third-generation EGFR tyrosine kinase inhibitors (TKIs), the inevitable development of acquired resistance continues to pose a critical challenge that severely affects the long-term efficacy of these treatments. This study aims to evaluate the efficacy and safety of anlotinib in combination with third-generation EGFR-TKIs in advanced NSCLC patients experiencing gradual or oligo progression following EGFR-TKIs. **Methods:** ALTER-L058 was a retrospective study conducted at 16 hospitals in China. Eligible patients aged 18 to 75 years with histologically or cytologically confirmed NSCLC who tested positive for EGFR mutations and exhibited gradual or oligo progression following treatment with third-generation EGFR-TKIs. Patients continued their regimen of EGFR-TKIs with or without anlotinib after gradual or oligo progression. Anlotinib was administered orally at a dose of 8-12 mg per day for two weeks, followed by a one-week break, within a three-week cycle. The primary endpoint was PFS. Secondary endpoints included objective response rate (ORR), disease control rate (DCR), overall survival (OS), and safety profiles. **Results:** From 1/2020 to 12/2023, a total of 150 patients were enrolled in the study. Among these, 100 patients received third-generation EGFR-TKIs plus anlotinib treatment, while 50 patients only received third-generation EGFR-TKIs. From treatment initiation of EGFR-TKIs, compared with third-generation EGFR-TKIs alone, median PFS was prolonged with third-generation EGFR-TKIs plus anlotinib (23.2 versus 19.5 months; hazard ratio (95%CI): 0.56 (0.36-0.86); P = 0.0008). From gradual or oligo progression after EGFR-TKIs treatment, mPFS was significantly extended with the combination of third-generation EGFR TKIs and anlotinib compared to third-generation EGFR TKIs alone (9.2 versus 5.4 months; hazard ratio (95% CI): 0.40 (0.25-0.65); P < 0.0001). The incidence of grade 3 or higher treatment-related adverse events was 37.0% (third-generation EGFR-TKIs plus anlotinib) and 34.0% (third-generation EGFR-TKIs), respectively. **Conclusions:** Continuous treatment with anlotinib after the emergence of gradual or oligo progression during the third-generation EGFR-TKIs therapy prolonged the clinical benefit of EGFR-TKIs, demonstrating favorable survival outcomes and manageable toxicity. Clinical trial information: ChiCTR2500095741. Research Sponsor: None.

8601 Poster Session

First-in-human phase I/II study of BYS10 in patients (pts) with locally advanced or metastatic RET-altered solid tumors: Preliminary dose escalation results. First Author: Jianchun Duan, Shanxi Cancer Hospital, Beijing, China

Background: RET alterations occur in non-small cell lung cancer (NSCLC, 2%), thyroid cancer (TC, 10%–20%) and a range of tumor types (<1%). RET inhibitors substantially improved the clinical outcomes of pts with RET-altered solid tumors. BYS10 is a highly potent and RET-specific inhibitor that overcomes RET V804 and G810 mutations, and exhibits high selectivity for RET over KDR. This study is to evaluate safety, tolerability, pharmacokinetics (PK) and efficacy of BYS10 in Chinese pts with RET-altered solid tumors. **Methods:** In phase I, following an accelerated titration and BOIN design, eligible pts were treated with BYS10 at 25 to 600 mg daily dose. Primary endpoints included safety, tolerability, MTD and DLTs. Secondary endpoints included PK and preliminary antitumor activity. **Results:** As of 10 July, 2024, a total of 51 pts were enrolled in dose escalation cohorts at 25/50 mg QD (n = 1/1) and 50/100/200/250/300 mg BID (n = 3/12/12/9/13). The MTD was not reached. Treatment related adverse events (TRAEs) occurred in all subjects, the most common TRAE were elevated AST (64.7%), elevated ALT (58.8%), elevated TBIL (45.1%), decreased WBCs (43.1%), decreased NEUT (33.3%), hyperuricaemia (31.4%), hypertension (29.4%), hypoalbuminemia (25.5%), Elevated SCr (23.5%) and headaches (23.5%). Grade 3 to 4 TRAEs >5% included elevated AST (25.5%), elevated ALT (13.7%) and hypertension (9.8%) reported at 100 to 300 mg BID doses. Serious adverse events were recorded in 7 pts. Exposure of BYS10 increased in a dose-dependent manner from 25 to 600 mg. In 40 evaluable pts, the confirmed overall response rate (ORR) and disease control rate (DCR) by independent review committee per RECIST v1.1 were 62.5% and 85%, In pts with RET-fusion NSCLC (n=30), RET-fusion thyroid cancer (TC, n=6) and RET-mutant medullary thyroid cancer (MTC, n=4), the ORR/DCR were 60%/80%, 83.3%/100% and 50%/100%, respectively. Intracranial antitumor activity was observed by investigators in 4 pts with at least 1 measurable intracranial lesion (one intracranial complete response). The ORR/DCR by IRC in 200 mg and 300 mg BID cohorts were 66.7%/100% and 75%/91.7%, respectively. **Conclusions:** BYS10 was well tolerated and showed dose-dependent exposure. Preliminary antitumor activity was observed in pts with RET-altered NSCLC, TC and MTC. The study is still ongoing. Clinical trial information: ChiCTR2400085264. Research Sponsor: Baiyunshan Pharmceutical Holdings Co., Ltd. Baiyunshan Pharmceutical General Factory.

8602 Poster Session

Dysregulation of DNA damage repair in lung cancer driven by *MTAP* loss: Mechanistic insights and target discovery. First Author: Bo Jiang, The Eighth Affiliated Hospital, Sun Yat-Sen University, Shenzhen, China

Background: *MTAP* loss leads to methylthioadenosine (MTA) accumulation, disrupting downstream metabolic pathways. Targeting synthetic lethal interactions with *MTAP* loss offers a promising therapeutic strategy. The DNA damage response (DDR) pathway, essential for genomic stability, is commonly dysregulated in lung cancer, impacting treatment response and prognosis. Emerging evidence has highlighted potential association between *MTAP* loss and mutations in DDR genes, suggesting that investigating their relationship is critical for uncovering disease mechanisms and identifying novel biomarkers and therapeutic targets. **Methods:** Hybridization capture sequencing with StarPanel NGS Assay (1,326 genes) was conducted on 2,258 Chinese lung cancer patients' tumor and matched peripheral blood samples. Then somatic and germline mutations, and TMB values of each sample were obtained. Based on a depth-based algorithm, differences between tissue and control samples in CNVs from the gene level were analyzed. Besides, we utilized shifts in germline heterozygous SNPs within the gene region to assist in determining if the loss was homozygous or heterozygous. **Results:** Homozygous and heterozygous deletions of *MTAP* were detected in 11.07% and 6.95% of all samples. Notably, 61.67% of these samples exhibited co-loss of *MTAP*, *CDKN2A* and *CDKN2B*. The median TMB was significantly higher in samples with *MTAP* loss (3.85 mut/Mb) compared to those with intact *MTAP* (2.56 mut/Mb). In samples with homozygous *MTAP* loss, the top somatically co-altered genes were *EGFR* (76.00%), *TP53* (57.60%) and *CDKN2A* (52.80%). Gain-of-function (GoF) mutations were most prevalent in *EGFR* (56.80%), *KRAS* (12.00%) and *MDM2* (10.00%), while Loss-of-function (LoF) mutations were most common in *TP53* (50.40%), *RBM10* (11.60%) and *PTEN* (7.60%). Notably, LoF mutations in *MTAP*-loss samples showed a higher prevalence of DDR genes compared to *MTAP*-intact samples, including *RAD50* (2.40% vs. 0.00%, $p < .0001$) and *POLQ* (2.40% vs. 0.00%, $p < .0001$). Enrichment analysis further revealed LoF mutations unique to *MTAP*-loss samples were significantly enriched in the DDR pathway ($p < .0001$). For top germline pathogenic mutations, two DDR genes, *RECQL4* (0.80% vs. 0.38%, $p = 0.29$) and *BRCA2* (0.40% vs. 0.43%, $p = 1$), showed no significant differences between *MTAP*-loss and *MTAP*-intact samples. **Conclusions:** Potential association exists between *MTAP* loss and DDR pathway dysregulation, which may impact tumorigenic processes and therapeutic vulnerabilities. The enrichment of DDR-related LoF mutations indicates *MTAP* loss could exacerbate genomic instability by impairing DNA damage repair mechanisms, thereby increasing TMB and driving cancer progression with a distinct molecular profile. These vulnerabilities are primarily driven by somatic mutations, providing a rationale for exploring personalized treatment strategies. Research Sponsor: None.

8603 Poster Session

Real-world treatment patterns and time-to-treatment discontinuation among advanced ALK-positive non-small cell lung cancer patients. First Author: Rahul Mudumba, University of Southern California, Los Angeles, CA

Background: Advanced anaplastic lymphoma kinase (ALK)-positive non-small cell lung cancer (NSCLC) is typically treated with ALK tyrosine kinase inhibitors (TKIs) in the first-line (1L) setting. While clinical trials provide efficacy data, real-world evidence on treatment patterns and time-to-treatment discontinuation or death (TTD) remains scarce. Such evidence may better inform modern clinical practice and decision-making regarding long-term treatment planning and sequencing decisions. **Methods:** This retrospective observational cohort study analyzed patients with advanced ALK+ NSCLC in the Optum Clinformatics Data Mart (2016–2021). Eligible patients were ≥18 years of age, with ≥6 months of continuous enrollment prior to the index date, a lung cancer diagnosis identified via ICD-10 codes, and ≥1 prescription fill for an ALK TKI. Outcomes included TTD for 1L and second-line (2L) therapies, assessed using the Kaplan-Meier (KM) method. Treatment patterns, including discontinuation rates and transitions to 2L therapy, were also evaluated. **Results:** Among 680 patients, 1L therapy distribution was as follows: crizotinib (n=366, 53.8%), alectinib (n=267, 39.3%), brigatinib (n=22, 3.2%), and ceritinib (n=25, 3.7%). Lorlatinib (n=16) was excluded from the analysis due to its atypical use in 1L during the study period, potentially reflecting unique clinical scenarios. The median TTD for 1L therapy was 8.3 months overall (95% CI: 6.7–9.7). TTD by therapy was as follows: alectinib, 15.3 months (95% CI: 11.0–21.4); brigatinib, 7.8 months (95% CI: 3.6–18.1); ceritinib, 7.6 months (95% CI: 4.3–23.5); crizotinib, 5.7 months (95% CI: 4.7–6.8). Only 168 (24.7%) patients transitioned to another ALK TKI in 2L, with alectinib being the most common among 1L crizotinib recipients, and lorlatinib being the most common among 1L alectinib and brigatinib recipients. Median TTD for 2L therapies was 8.0 (95% CI: 5.7-11.7) months overall. **Conclusions:** This study provides real-world evidence on TTD and treatment patterns among advanced ALK+ NSCLC patients. Transition rates to 2L ALK TKIs were lower than expected based on clinical trials, with high rates of discontinuation without transition. With alectinib, brigatinib, and lorlatinib equally recommended as 1L options in US clinical guidelines, these findings provide real-world evidence to help clinicians differentiate among therapies and guide treatment sequencing decisions. Research Sponsor: None.

1L ALK TKI (n)	Transition to 2L ALK TKI (%)	Median 1L TTD (Months, 95% CI)
Alectinib (267)	51 (19.1%)	15.3 (11.0–21.4)
Brigatinib (22)	2 (9.1%)	7.8 (3.6–18.1)
Ceritinib (25)	14 (56.0%)	7.6 (4.3–23.5)
Crizotinib (366)	101 (27.6%)	5.7 (4.7–6.8)
Overall (680)	168 (24.7%)	8.3 (6.7–9.7)

1L first-line, *2L* second-line, *ALK* anaplastic lymphoma kinase, *TKI* tyrosine kinase inhibitor, *TTD* time-to-treatment discontinuation or death, *CI* confidence interval.

8604 Poster Session

Osimertinib plus repotrectinib phase I trial in TKI-resistant non-small cell lung cancer (NSCLC) with EGFR mutations. First Author: Andrés Aguilar Hernandez, Instituto Oncológico Dr Rosell (IOR), Dexeus University Hospital, Barcelona, Spain

Background: NSCLC patients with EGFR mutations develop resistance when treated with EGFR TKI. We previously reported that osimertinib combined with TPX-0005 (repotrectinib) ablated STAT3, paxillin, and YAP1 phosphorylation in a preclinical model. Osimertinib-induced Src and FAK phosphorylation was abrogated with TPX-0005 alone or in combination with osimertinib in H1975 (EGFR L858 and T790M) cell line. TPX-0005 potentiated the effect of osimertinib in PC9 and H1975 tumor xenografts without substantial toxicity (Karachaliou et al. eBioMedicine 2017). The findings prompted us to carry out the current study with osimertinib plus TPX-0005, which inhibit Src/FAK/JAK2, in addition to ALK, ROS1 and NTRKs. **Methods:** TOTEM (NCT04772235) is a phase I, two-part study to assess safety, tolerability, pharmacokinetics, and antitumor activity of repotrectinib plus osimertinib in EGFR-mutant patients resistant to previous lines of treatment. Phase Ia was a dose escalation (3+3). Treatment naïve patients were treated with osimertinib 80mg QD plus: repotrectinib 80mg QD, 160mg QD and 160mg BID. In part Ib, patients should have received osimertinib or osimertinib plus chemotherapy as first line treatment. Results from part Ia are presented in this abstract. **Results:** Phase Ia included 15 patients with a median age of 61 yrs (34-71). Of these patients: 10 were female (66.7%), 9 had PS1 (60%), and 7 had brain metastasis (48.7%). At the time of starting treatment, two patients had exon 18 (G719X) mutations (p.E709_T710delinsD and p.G719A), 5 had exon 21 (4 p.L858R, 1 p.L861Q) and 8 had exon 19 deletion. Eight patients had p53 co-mutations, other co-alterations included PIK3CA, RET, FAT1, FGFR3 and MYC mutations, CDK4 and EGFR amplification, and MET, ROS1, EGFR and FGFR3 over-expression. Six patients were treatment-naive, four were osimertinib progressors, and five had received two or more previous lines of treatment. With repotrectinib plus osimertinib, intracranial complete response was attained in 3 of the seven patients with brain metastasis (42.85%). The overall objective response rate (ORR) was noted in 5 patients (33.3%), and stable disease in 8 patients (53.3%). Median PFS was 4.4 mo. (95% CI 2.9-NR). Among the adverse events, transient, manageable dizziness was observed in 76% of the patients, and dysgeusia occurred in 48% of cases. Most side effects were grade 1-2, including anemia, diarrhea, fatigue, and liver enzyme elevation. Pharmacokinetic analysis indicated a favorable profile of the combination. Dose level 3 (160mg BID) was safe, therefore, part Ib continued with repotrectinib 160mg BID plus osimertinib 80mg QD in 15 patients enrolled. **Conclusions:** In Part Ia osimertinib + repotrectinib showed impressive intracranial ORR with a manageable safety profile. Part Ib with repotrectinib 160 mg BID plus osimertinib 80 mg is ongoing. Updated results will be presented. Clinical trial information: NCT04772235. Research Sponsor: None.

8605 Poster Session

MK-1084 for KRAS G12C-mutated (mut) metastatic non–small-cell lung cancer (mNSCLC): Results from KANDLELIT-001. First Author: Adrian G. Sacher, Princess Margaret Cancer Centre, University Health Network & University of Toronto, Toronto, ON, Canada

Background: MK-1084 is an oral, next-generation, selective KRAS G12C-GDP covalent inhibitor. The phase 1 KANDLELIT-001 study (NCT05067283) showed manageable safety and antitumor activity for MK-1084 monotherapy in *KRAS* G12C-mut solid tumors and MK-1084 + pembrolizumab (pembro) in *KRAS* G12C-mut mNSCLC. We report additional NSCLC and preliminary ctDNA data from this study. **Methods:** Pts had confirmed *KRAS* G12C-mut, RECIST-measurable disease and ECOG PS 0-1. Pts with any advanced solid tumor and ≥1 prior systemic therapy received MK-1084 monotherapy 25-800 mg/d in arms 1 and 3. Pts with previously untreated mNSCLC and PD-L1 TPS ≥1% received MK-1084 25-400 mg/d + pembro 200 mg Q3W in arm 2 dose escalation and expansion cohorts. Pts with previously untreated nonsquamous mNSCLC received MK-1084 50-200 mg/d + pembro 200 mg, carboplatin, and pemetrexed Q3W in arm 4. Dose-limiting toxicities (DLTs), AEs, and AEs leading to discontinuation were the primary endpoints; ORR, DCR, and PFS per RECIST v1.1 by investigator review were secondary. *KRAS* G12C variant allele fraction (VAF) and maximum somatic allele frequency (MSAF) in ctDNA were assessed in serial blood samples collected from 23 pts in arm 1 using the Guardant Health OMNI panel. **Results:** There were 99 pts in arms 1+3 (21 with NSCLC), 34 in arm 2 escalation cohorts, 26 in arm 2 expansion cohorts, and 24 in arm 4 as of the 12 Aug 2024 data cutoff. Median study follow-up was 14.8 mo, 16.2 mo, 2.5 mo, and 4.1 mo, respectively. DLTs occurred in 1 pt in arm 2 (gr 3 ALT and AST increase) and 1 pt in arm 4 (gr 3 diarrhea). Drug-related AEs occurred in 62% of pts in arms 1+3, 88% of pts in arm 2, and 96% of pts in arm 4, were gr ≥3 in 9%, 33%, and 58%, and led to discontinuation of any drug in 1%, 20%, and 17%. There was 1 drug-related death (myelosuppression and platelet count decrease in arm 2). Rates of drug-related ALT increase (any/gr ≥3) were 16%/3% in arm 1, 33%/10% in arm 2, and 33%/4% in arm 4. Rates of drug-related AST increase (any/gr ≥3) were 17%/3%, 30%/8%, and 25%/4%. Efficacy is shown in the Table. Median *KRAS* G12C VAF was 14.0% at baseline and 0.9% at week 6; median MSAF was 26.0% and 2.2%, respectively. **Conclusions:** In pts with *KRAS* G12C-mut mNSCLC, MK-1084 shows manageable safety and antitumor activity as monotherapy for previously treated disease and in combination with pembro ± chemo as first-line (1L) therapy. The >90% decrease from baseline in *KRAS* G12C VAF in ctDNA confirms MK-1084 target engagement. The phase 3 KANDLELIT-004 study is evaluating MK-1084 + pembro as 1L therapy for *KRAS* G12C-mut mNSCLC with PD-L1 TPS ≥50%. Clinical trial information: NCT05067283. Research Sponsor: Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA; N/A.

	ORR		DCR		PFS	
Arm	n[a]	% (95% CI)	n[a]	% (95% CI)	n	Med (95% CI), mo
1+3 NSCLC (MK-1084 alone)	21	38 (18-62)	21	76 (53-92)	21	8 (4-NR)
2 escalation (MK-1084 + pembro)	34	74 (56-87)	34	91 (76-98)	34	25 (9-NR)
2 expansion (MK-1084 + pembro)	20	40 (19-64)	20	80 (56-94)	26	NR (NR-NR)
4 (MK-1084 + pembro + chemo)	22	41 (21-64)	22	82 (60-95)	24	NR (5-NR)

[a]Pts with ≥1 MK-1084 dose ≥5 wk before data cutoff.

8606 **Poster Session**

Clinicogenomic analysis of *EGFR*-mutant lung cancers for identification of Rb inactivation as a hallmark of squamous transformation. First Author: Mark Yungjie Jeng, Memorial Sloan Kettering Cancer Center, New York, NY

Background: Histologic transformation to squamous carcinoma (LUSC) is a recognized mechanism of resistance in *EGFR*-mutant lung adenocarcinoma (EGFR+ LUAD) and can occur in 5-8% of patients treated with osimertinib. While our prior work identified the AKT pathway as a possible mediator of LUSC transformation, comprehensive clinicogenomic assessment of this process remains lacking. **Methods:** We performed genomic characterization of *EGFR*-mutant patient samples undergoing LUSC transformation, including: (1) pre- and post-transformation specimens transformed after TKI treatment, and (2) microdissected distinct LUAD and LUSC components obtained from adenosquamous (LUAS) tumors. Retrospective analysis of clinical outcomes such as time-to-treatment discontinuation (TTD) were evaluated in patients with EGFR+ LUAD on frontline osimertinib who have undergone MSK-IMPACT (n=181). Xenograft models (using PC9 and HCC827) mimicking squamous transformation were treated with osimertinib (5-10 mice/group). Phenotypic markers of LUSC (P40 and CK5/6) were assessed by IHC. **Results:** Among patients with EGFR+ LUAD undergoing LUSC transformation (n=20), 50% and 60% had alterations in the AKT or Rb pathway, respectively. When compared to a cohort of never-transforming EGFR+ LUAD (n=1515), patients with transforming LUAD had a higher frequency of AKT (44% vs 18%) and Rb (56% vs 32%) pathway mutations. Clinically, patients with EGFR+ LUAD on first line osimertinib harboring baseline Rb/AKT pathway mutations (n=70) experienced shorter TTD (median 18 vs 24 months, p=0.0261) compared to a Rb/AKT wild-type cohort (n=111). In xenograft models of squamous transformation, Rb inactivation through CRISPR deletion of *RB1* or upstream regulators *CDKN2A/B* led to greater *in vivo* tumor growth in immunodeficient mice treated with osimertinib compared to controls. Histologic assessment revealed induction of squamous markers P40 and CK5/6 in xenografts with Rb inactivation. **Conclusions:** Genomic alterations in Rb and AKT pathways are detected at higher frequency in patients with EGFR+ LUAD undergoing squamous transformation and are associated with worse clinical outcomes to frontline osimertinib. Rb inactivation in xenograft mouse models led to increased squamous-like phenotype and resistance to osimertinib. Detection of these mutations may help identify patients at high risk of treatment resistance and transformation. Research Sponsor: None.

8607 **Poster Session**

Shifting landscape of resistance to next-generation ALK inhibitors with evolving treatment paradigm in ALK+ lung cancer. First Author: Sarah Waliany, Massachusetts General Hospital, Boston, MA

Background: Next-generation (gen) ALK tyrosine kinase inhibitors (TKIs) are standard first-line (1L) therapy for patients (pts) with *ALK*-rearranged (ALK+) metastatic non-small cell lung cancer (mNSCLC), having supplanted crizotinib (criz). While past studies uncovered mechanisms of resistance to next-gen ALK TKIs, vast majority of analyzed biopsies (bx) were obtained from pts treated with next-gen TKIs after 1L criz, reflecting the outdated treatment paradigm. Limited knowledge exists on the mechanisms of resistance to second- (2G) and third-gen (3G) ALK TKIs received without 1L criz exposure. **Methods:** This retrospective study included pts with ALK+ mNSCLC who received 2G ALK TKIs (alectinib, brigatinib, ceritinib, ensartinib) or 3G TKI lorlatinib (lorl) and had post-progression tissue (TBx) or liquid bx (LBx) assessed by next-generation sequencing (NGS). Frequency (freq) of *ALK* mutations (mut) (on-target) or *MET* amplification (amp) and histologic transformation (off-target) was compared in pts who had vs had not received prior 1L criz. **Results:** We identified 270 pts (median age, 52; 61.1% women) who received 2G TKI (1L criz, n=116; no 1L criz, n=106) and/or 3G TKI (1L criz, n=69; no 1L criz, n=59) and underwent TKI-resistant bx (116 pts with $\geq$2 bx). In total, 436 post-next-gen TKI bx (280 post-2G TKI, 156 post-lorl) underwent NGS. Post-2G TKI bx detected lower freq of *ALK* mut in pts without vs with prior criz exposure (TBx: 36.8% vs 64.3%, p$<$0.001; LBx: 44.4% vs 71.7%, p=0.006). Of pts with post-lorl TBx, 43.8% had $\geq$1 *ALK* resistance mut detected, of which 23.6% had $\geq$2 co-occurring *ALK* mut. Post-lorl Tbx detected lower freq of *ALK* mut (29.7% vs 53.8%, p=0.024) and lower freq of $\geq$2 co-occurring *ALK* mut in pts without vs with prior criz (10.8% vs 32.7%, p=0.036), with consistent findings by LBx. In terms of off-target resistance. *MET* amp was detected by post-2G TKI TBx at higher freq in pts without vs with prior criz (17.2% vs 2.5%, p=0.002), but with no significant difference post-lorl without vs with prior criz (13.9% vs 5.8%, p=0.26). Of note, the two post-1L lorl TBx both had *MET* amp or polysomy, without *ALK* mut. Histologic transformation occurred at similar freq in pts without vs with 1L criz after 2G TKIs (4.3% vs 1.2%, p=0.33) and after lorl (2.7% vs 3.8%, p=0.99). Among pts with post-1L 2G TKI bx, on-target resistance (*ALK* mut) was more common with *EML4::ALK* variant 3a/b vs variant 1 (TBx: 56.3% vs 20.0%, p=0.038; LBx: 75.0% vs 13.3%, p=0.003). **Conclusions:** In this largest analysis of post-2G/3G ALK TKI TBx/LBx to date, on-target resistance was less freq after 2G/3G TKIs in pts treated with the current paradigm (upfront 2G/3G ALK TKIs) than the past approach (2G/3G TKI after 1L criz). These findings crystallize a shifting resistance landscape and indicate an increasing role for off-target resistance with upfront 2G/3G TKIs, highlighting a need to uncover and therapeutically address off-target resistance. Research Sponsor: None.

8608 **Poster Session**

Real-world comparative outcomes of alectinib and brigatinib in ALK-positive non–small cell lung cancer: A retrospective cohort analysis using HIRA data. First Author: Hyun Woo Lee, Department of Hematology-Oncology, Ajou University School of Medicine, Suwon, South Korea

Background: Alectinib and brigatinib are both recommended as first-line treatments for patients with ALK-positive non–small cell lung cancer (NSCLC). However, direct real-world comparisons of these agents remain limited. **Methods:** We retrospectively reviewed patients diagnosed with ALK-positive NSCLC between 2007 and 2023 who did not undergo surgical resection. Among these, 1,009 patients received either alectinib (n=868) or brigatinib (n=141) as first-line therapy on HIRA data. Baseline characteristics, comorbidities (e.g., diabetes, hypertension), and outcomes—including overall survival (OS) and progression-free survival (PFS)—were collected. Cox proportional hazards models adjusted for age $\geq$70 years, sex, and comorbidities were used to estimate hazard ratios (HRs) for death and disease progression. **Results:** The mean age was 61.56 years (SD 13.72), and 49.45% of patients were male. Patients receiving alectinib were older on average (p$<$0.001), but no significant differences in major comorbidities were observed between the two groups. In unadjusted analyses, brigatinib was associated with a lower risk of death compared with alectinib (HR 0.60, 95% CI 0.40–0.90; p=0.013), but this association was not significant after multivariable adjustment (HR 0.69, 95% CI 0.46–1.03; p=0.07). Conversely, alectinib was associated with significantly longer first and second PFS compared with brigatinib (1st PFS HR 1.53, p=0.012; 2nd PFS HR 4.02, p$<$0.001). Both alectinib- and brigatinib-treated patients who transitioned to lorlatinib demonstrated notably prolonged survival. **Conclusions:** In this real-world study, both alectinib and brigatinib provided favorable survival outcomes in patients with ALK-positive NSCLC. While brigatinib showed a trend toward reduced mortality in univariable analysis, this was not maintained in adjusted models. Alectinib conferred a longer duration of disease control (PFS) in both first- and second-line settings. Further prospective studies are warranted to clarify the optimal sequencing of ALK inhibitors and to validate these findings. Research Sponsor: None.

8609 **Poster Session**

High-dose furmonertinib combined with bevacizumab and pemetrexed in non-small cell lung cancer patients with EGFR mutations and leptomeningeal metastasis: A prospective real-world study. First Author: Qi Zhao, Department of Internal Medicine, The Affiliated Cancer Hospital of Zhengzhou University & Henan Cancer Hospital, Zhengzhou, China

Background: Leptomeningeal metastasis (LM) in lung cancer is always associated with poor prognosis. Our previous study has demonstrated that high-dose furmonertinib offers promising efficacy in non-small cell lung cancer (NSCLC) patients with epidermal growth factor receptor(EGFR) mutations and LM. In this study, we aim to further evaluate the efficacy and safety of high-dose furmonertinib combined with bevacizumab and pemetrexed in NSCLC patients with EGFR mutations and LM in the real world. **Methods:** Eligible patients had histologically or cytologically confirmed NSCLC harboring an EGFR mutation. Patients were diagnosed as LM according to the EANO-ESMO criteria. They were treated with high-dose furmonertinib (240 mg, daily), bevacizumab (15 mg/kg, every 3 weeks), and pemetrexed (50 mg, intrathecal chemotherapy or 500 mg/m², intravenous chemotherapy, every 3 weeks). The primary endpoint was overall survival (OS). Secondary endpoints included time to treatment failure (TTF), ORR-LM (objective response rate in leptomeningeal metastasis) according to the RANO-LM radiologic criteria, clinical response rate (assessed with improvement of neurologic symptoms or signs and changes in the performance status), and adverse events (AEs) (graded according to CTCAE v5.0). **Results:** Between March 10, 2023 and December 31, 2024, 33 patients were enrolled at Henan Cancer Hospital. 10 patients (30.3%) had EGFR exon 19 deletions, 18 patients (54.5%)had exon 21 L858R mutations, and the other 5 patients (15.2%) had non-classical mutations. 20 (60.6%) had an ECOG score of 1-2, while 13 (39.4%) had an ECOG score of 3. Additionally, 22 patients (66.7%) had received at least two prior lines of treatment, and 23 patients(69.7%) had previously been treated with third-generation EGFR-TKIs. 6 patients (18.2%) received pemetrexed via intravenous administration, while 27 patients (81.8%) received intrathecal chemotherapy of pemetrexed. The clinical response rate was 72.7%, the ORR-LM and disease control rate (DCR) assessed by investigator according to RANO-LM radiologic criteria were 64.7% and 94.1%.At the data cut off point of December 31, 2024, 7 (21.2%) patients had died. The median follow-up was 7.8 months. The median OS was not reached. 25 (75.8%) patients experienced treatment-related adverse events (TRAEs) of any grade. Grade 3 adverse events included: diarrhea (6.1%), leukopenia/neutropenia (9.1%), anemia (6.1%), and thrombocytopenia (3%). One patient experienced grade 4 leukopenia and thrombocytopenia. The dose of furmonertinib was reduced to 160mg in 4 patients and intrathecal chemotherapy was discontinued in one patient. **Conclusions:** High-dose furmonertinib combined with bevacizumab and pemetrexed demonstrates remarkable clinical efficacy and tolerable safety in NSCLC patients with EGFR mutations and LM. Clinical trial information: NCT06643000. Research Sponsor: None.

8610 **Poster Session**

Efficacy and safety of larotrectinib in patients with TRK fusion lung cancer: An updated analysis. First Author: Daniel Shao-Weng Tan, Division of Medical Oncology, National Cancer Center Singapore and Duke-NUS Medical School, Singapore, Singapore

Background: *NTRK* gene fusions are oncogenic drivers in various tumor types, including lung cancer. Larotrectinib is the first-in-class, highly selective, central nervous system (CNS)-active TRK inhibitor approved for tumor-agnostic use in patients with TRK fusion cancer based on a robust and durable objective response rate in patients with various cancers. Here, we report updated long-term efficacy and safety data in the subset of patients with TRK fusion lung cancer treated with larotrectinib. **Methods:** Patients with TRK fusion lung cancer enrolled in 2 larotrectinib clinical trials (NCT02122913, NCT02576431) were included. Larotrectinib was administered at 100 mg twice daily. Responses were independent review committee-assessed per Response Evaluation Criteria in Solid Tumours version 1.1. The data cutoff was July 20, 2024. **Results:** At data cutoff, 32 patients were enrolled; 12 patients had known CNS metastases at baseline. The median age was 56 years (range 25–81). One patient (3%) was systemic treatment-naïve in the metastatic/unresectable setting, and 19 (59%) patients received 2 or more prior therapies. All *NTRK* gene fusions were identified by next-generation sequencing (NGS). The overall response rate was 69% (95% confidence interval [CI] 50–84): 4 (13%) complete responses, 18 (56%) partial responses, 6 (19%) stable disease, 2 (6%) progressive disease, and 2 (6%) not evaluable. Median time to response was 1.8 months (range 1.5–7.3). Median duration of response (DoR), progression-free survival (PFS), and overall survival (OS) were 34 months (95% CI 13—not estimable [NE]), 22 months (95% CI 10–39), and 41 months (95% CI 17—NE), respectively, at median follow-ups of 37, 38, and 46 months. The 4-year rates for DoR, PFS, and OS were 33% (95% CI 7–60), 26% (95% CI 6–45), and 48% (95% CI 29–68), respectively. The median duration of treatment was 20 months (range 2–75). At data cutoff, 8 (25%) patients remained on treatment: 7 had responded and 1 was not evaluable for response. Treatment-related adverse events (TRAEs) were predominantly Grade 1/2. Grade 3/4 TRAEs were reported in 10 (31%) patients. One (3%) patient discontinued treatment due to TRAEs (increased alanine aminotransferase, aspartate aminotransferase, and gamma-glutamyl transferase). **Conclusions:** Larotrectinib demonstrates rapid and durable responses, extended survival, clinical benefit, and a favorable safety profile in patients with advanced TRK fusion lung cancer. These results support the wider adoption of NGS panels that include *NTRK* gene fusions in patients with lung cancer to identify those who may benefit from targeted treatment. Clinical trial information: NCT02122913, NCT02576431. Research Sponsor: These studies were funded by Bayer HealthCare Pharmaceuticals, Inc.

8611 **Poster Session**

Interim results of PDL1V (PF-08046054), a vedotin-based ADC targeting PD-L1, in patients with NSCLC in a phase 1 trial. First Author: Elisa Fontana, Sarah Cannon Research Institute UK, London, United Kingdom

Background: PDL1V is an investigational antibody-drug conjugate that delivers the cytotoxic agent monomethyl auristatin E to cells expressing programmed cell death ligand 1 (PD-L1). In addition to cytotoxicity, PDL1V elicits antitumor activity via the bystander effect and immunogenic cell death. Here we present the safety profile and preliminary efficacy in patients with metastatic, relapsed/refractory non-small cell lung cancer (NSCLC) enrolled in the phase 1 trial. **Methods:** C5851001 (NCT05208762) is a phase 1 study enrolling patients with relapsed or refractory solid tumors, including NSCLC, whose disease has progressed on standard-of-care therapies. Patients received the PDL1V recommended expansion dose of 1.5 mg/kg on days 1 and 8 of a 21-day cycle using adjusted ideal body weight, and were required to have measurable disease per RECIST v1.1 and ECOG PS $\leq$1. Patients with genomic alterations were not excluded. The primary objectives of this study are safety, tolerability, and pharmacokinetics, with antitumor activity as a secondary objective. **Results:** As of December 20, 2024, 30 patients with NSCLC have been treated at the recommended expansion dose. The median age was 60 years (range 44-73); 43.3% were male, 66.7% had ECOG PS 1, 23.3% had squamous histology, and 83.3% were PD-L1 positive. The median number of prior lines of therapy was 2.0 (1, 8); 96.7% and 66.7% of patients were previously exposed to anti-PD-1/PD-L1 antibodies and taxanes, respectively. There have been no dose-limiting toxicities at the recommended expansion dose. Peripheral sensory neuropathy (27.2%), nausea (25.0%), diarrhea (23.9%), and fatigue (21.7%) were the most common treatment-related adverse events (TRAEs) for all patients treated in the Phase 1 trial at the recommended expansion dose (N=92); the majority of TRAEs were grade 1-2 in severity, and 5.4% of patients discontinued therapy due to TRAEs. The most common grade $\geq$3 TRAE was anemia (5.4%). The incidence of treatment-related immune-mediated AEs by investigator assessment was 14.1%; 5.4% for grade 3, with no grades 4 or 5. The investigator-assessed confirmed objective response rate (cORR) for patients with NSCLC was 26.7%, while the cORR was 32.0% for those with PD-L1 expressing tumors. The median duration of confirmed response was 7.8 months (95% CI 4.8, –), and the median follow-up was 10.0 months (95% CI 4.9, 13.1). Objective responses were observed in patients with PD-L1 expressing squamous (n=6) and non-squamous (n=19) tumors (33.3% and 31.6% cORR, respectively). **Conclusions:** PDL1V monotherapy at the recommended expansion dose was generally well tolerated with a manageable safety profile. Encouraging preliminary efficacy in NSCLC was observed, independent of histology. Based on these results, further development of PDL1V in NSCLC is ongoing. Clinical trial information: NCT05208762. Research Sponsor: Pfizer Inc.

8612 **Poster Session**

Exploring decisional needs of patients considering first line treatment of advanced EGFR+ lung cancer: An interpretive descriptive study. First Author: Rena Seeger, Faculty of Medicine, University of Ottawa, Ottawa, ON, Canada

Background: With expanding treatment options for EGFR+ metastatic non-small cell lung cancer (mNSCLC), shared decision-making is important in aligning treatment plans with patient values. Targeted therapies like osimertinib offer convenience and independence. New studies like FLAURA2 and MARIPOSA explore therapeutic combinations with intravenous drugs, demonstrating potentially superior efficacy but more side effects, highlighting the need for unbiased and patient-centered approaches. This study explores the decisional needs of patients considering first-line treatments. **Methods:** We conducted an interpretive descriptive qualitative study guided by the Ottawa Decision Support Framework to explore the experiences and perspectives of EGFR+ mNSCLC patients. Interviews were conducted via Microsoft Teams. Inclusion criteria: 18+ years; mEGFR+ NSCLC; current/prior osimertinib therapy; proficient in English. Interviews were conducted using a standardized interview guide with inductive thematic analysis. A sample size of 10-12 was considered sufficient to saturate ideas from participant responses, with additional 3 recruited to ensure saturation. Themes were mapped onto the Ottawa Decision Support Framework. **Results:** Sixteen participants were interviewed from Sep-Nov 2024: age 48-83 (median 62 years); 11 female; 13 currently taking osimertinib; 10 diagnosed $>$1 year. Many patients reported relying on oncologist recommendation without participation in decision making. Patients with young children had an increased desire to be actively involved in treatment decisions. Key themes from preliminary analysis identified: patients overwhelmingly *trusted their oncologist*, felt *pressure to start treatment quickly*, were *overwhelmed with the diagnosis*, had *inadequate knowledge of the treatment* and potential side effects, and felt *highly responsible to ensure proper drug administration*. Patients valued e*ase and convenience of* [osimertinib] *treatment, few severe side effects, being alive, continuing day to day living*, and *remaining independent for family and travel.* When asked about combination therapy, patients valued *quality of life, avoiding increased hospital trips and side effects*, but indicated a *willingness to try*. **Conclusions:** Key themes from preliminary analysis identify crucial components at initial diagnosis, with patients feeling overwhelmed and having inadequate knowledge, thus relying on their trusted oncologists' recommendation. While patients highly valued independence, fewer visits and quality of life, they were willing to try combination therapy, highlighting the importance of oncologists understanding their patient's individual needs and goals of treatment. Treatment choices should reflect the patient's values. These results will be used to create a decision aid that we can pilot in our oncology clinics. Research Sponsor: None.

8613 **Poster Session**

MYTX-011, a cMET-targeting antibody-drug conjugate (ADC), in patients with previously treated, advanced NSCLC: Updated dose escalation results in the phase 1 KisMET-01 study. First Author: Rebecca Heist, Massachusetts General Hospital, Boston, MA

Background: MYTX-011 is a novel cMET-targeting vcMMAE ADC engineered for pH-dependent binding. This results in more efficient payload delivery, which drives efficacy in tumors over a wide range of cMET expression, including potentially $>$50% of NSCLC patients (pts). Here we report safety and preliminary efficacy from dose escalation pts who received $\geq$4.0 mg/kg (mpk), the clinically active dose range, in the Phase 1 KisMET-01 study. **Methods:** KisMET-01 (NCT05652868) is a multicenter, first-in-human study of MYTX-011 in pts with previously treated, locally advanced or metastatic NSCLC. The study comprises dose escalation in pts with NSCLC of any histology or cMET expression, followed by dose expansion in cMET-positive (cMET+) pts selected by immunohistochemistry (Ventana SP44). In dose escalation, cMET expression is analyzed whenever tumor tissue is available. **Results:** As of 7 Jan 2025, 85 pts received $\geq$1 dose of MYTX-011 (1.0–8.3 mpk Q3W), and 59 pts received doses $\geq$4.0 mpk. PK showed near dose proportional exposure and low unconjugated MMAE across dose levels. In pts who received $\geq$4.0 mpk, median age was 67 yr (43–83) and median prior lines of therapy was 3 (1–10); median follow-up was 4.2 mo (0.1–10.4). TRAEs of any grade (Gr)/Gr $\geq$3 occurred in 90%/48% of pts; the most common (any Gr TRAE $\geq$20% of pts) were blurred vision (49%), keratopathy (44%), nausea (29%), fatigue (20%), AST increased (20%), and keratitis (20%). Gr 3 or higher TRAEs that occurred in $\geq$5% of pts were keratopathy (15%), blurred vision (12%), and neutropenia (10%). Ocular events led to treatment discontinuation in 5 (8%) pts, with 3 of 5 treated at doses higher than 5.0 mpk. Unadjudicated pneumonitis/ILD was reported in 2 (3%) pts, both Gr 1 or 2 with 1 leading to treatment discontinuation. Peripheral neuropathy was reported in 15%; all were Gr 1 or 2 and did not lead to dose reduction or discontinuation. No treatment-related death was reported. 35 of 59 pts who received $\geq$4.0 mpk were cMET+ (2+ at $\geq$25% tumor cells) with a median follow-up of 3.7 mo (0.7–10.3). ORR was 38% in cMET+ pts with $\geq$1 post-baseline disease assessment (n=29). DCR at 6 wk/12 wk/24 wk was 97%/83%/53%. ORR was 44% in cMET+ Non-squamous (NSQ) EGFR wild-type (n=16), 38% in NSQ EGFR-mutant (n=8), and 25% in squamous cell carcinoma (n=4). Antitumor activity was similar in cMET+ pts across expression levels and known cutoffs, and no clear dose-response relationship was observed in doses $\geq$4.0mpk. Doses of 5.0 mpk Q3W with dose-break (2-on 1-off) and 4.0 mpk Q3W were selected for further evaluation in dose expansion. **Conclusions:** MYTX-011 is well tolerated with low rates and severity of AEs commonly associated with cytotoxic and cMET-targeting agents. Preliminary anti-tumor activity suggests MYTX-011 can potentially benefit a wide range of cMET-expressing NSCLC pts. Dose expansion is currently ongoing as of January 2025. Clinical trial information: NCT05652868. Research Sponsor: Mythic Therapeutics.

8614 **Poster Session**

GBC-11004: An AI-driven novel kinase target with potential to overcome osimertinib resistance in NSCLC. First Author: Hyunjeong Lee, Gradiant Bioconvergence Inc., Seoul, South Korea

Background: Osimertinib resistance poses a significant clinical challenge in the treatment of non-small cell lung cancer (NSCLC), with diverse mechanisms complicating patient outcomes. Conventional next-generation sequencing (NGS) analysis methods often fall short in identifying effective therapeutic targets due to the complexity and heterogeneity of resistance mechanisms. **Methods:** To address this issue, we have developed an artificial intelligence (AI)-driven target discovery platform designed to identify novel and effective drug target genes capable of overcoming Osimertinib resistance in NSCLC, thereby surpassing the capabilities of traditional NGS analysis. Our platform integrates three key components: deep learning (G-TAC), statistical significance testing (G-SET), and a large language model (G-LAT). G-TAC and G-SET evaluate and rank genes according to their responsiveness to Osimertinib and tumor-specific expression. G-LAT assesses these genes based on publications and clinical trials to ensure novelty and efficacy of the identified targets. **Results:** We identified a novel kinase target named GBC-11004, as one of the top-ranked target genes that were found to be overexpressed in patient-derived organoids (PDOs) resistant to Osimertinib. To ascertain the functional impact of GBC-11004, target validation was conducted using PDOs and CRISPR/Cas9-based gene editing. Gene editing in Osimertinib resistant PDOs resulted in a significant decrease in cell viability corresponding to increased indel frequency. Furthermore, we have initiated lead compound optimization by preliminary IC50 analyses using compounds targeting GBC-11004 and observed significantly enhanced sensitivity in the combination therapy group (Osimertinib + GBC-11004 inhibitor) compared to the Osimertinib monotherapy group in resistant PDO models. **Conclusions:** Our results demonstrate the potential of GBC-11004 as a novel therapeutic target for overcoming Osimertinib resistance in NSCLC treatment and emphasize the capability of our PDO-based AI-driven target discovery platform in identifying high-priority novel targets. Research Sponsor: None.

8615 **Poster Session**

Sacituzumab tirumotecan (sac-TMT) in patients (pts) with previously treated locally advanced or metastatic (LA/M) non-small cell lung cancer (NSCLC) harboring uncommon EGFR mutations: Preliminary results from a phase 2 study. First Author: Li Zhang, Sun Yat-sen University Cancer Center, Guangzhou, China

Background: Pts with NSCLC harboring uncommon *EGFR* mutations generally have limited treatment options compared to those with the more common *EGFR* mutations. Sac-TMT (MK-2870/SKB264) is a TROP2 ADC developed with a hydrolytically cleavable linker to conjugate a belotecan-derivative topoisomerase I inhibitor. Sac-TMT has shown encouraging antitumor activity in NSCLC pts with the more common *EGFR* mutations (Fang *et al*. AACR 2024). Here we present the preliminary efficacy and safety of sac-TMT in treating uncommon *EGFR*-mutated advanced NSCLC from the Phase 2, open-label, multiple-cohort study (NCT05631262). **Methods:** Advanced NSCLC pts harboring uncommon *EGFR* mutations, including G719X in exon 18, S768I in exon 20, L861Q in exon 21 and exon 20 insertions (ex20ins), who had progressed on or after standard systemic therapy were enrolled. Pts received sac-TMT 5 mg/kg Q2W until disease progression or unacceptable toxicity. Tumor response was assessed per RECIST v1.1 by investigator. **Results:** As of 01 Dec 2024, 42 pts (median age 61 years; 33.3% male; 85.7% ECOG PS 1) were enrolled, including 23 pts with *EGFR* G719X in exon 18, S768I in exon 20, or L861Q in exon 21 and 19 pts with *EGFR* ex20ins. Median number of prior treatment regimens for advanced disease was 2 with 35.7% of pts having ≥3. After a median follow-up of 9.2 months, the objective response rate (ORR) was 35.7% (15/42, 3 pending confirmation). The disease control rate (DCR) was 85.7%. Responses were durable with the median duration of response (mDoR) not yet reached, and the 6-month DoR rate was 90.9%. The median progression-free survival (mPFS) was 9.5 months (95% CI: 5.6, 10.9). In the subset of pts with uncommon non-ex20ins, the ORR was 34.8% (8/23, 1 pending confirmation); the mPFS was 10.9 months (95% CI: 5.6, NE). In the subset of pts with ex20ins, the ORR was 36.8% (7/19, 2 pending confirmation); the mPFS was 9.0 months (95% CI: 2.4, NE). Grade ≥3 treatment-related adverse events (TRAEs) occurred in 52.4% of pts. The most frequent grade ≥3 TRAEs (≥5%) were neutrophil count decreased (45.2%), WBC count decreased (21.4%), anemia (14.3%), and stomatitis (9.5%). No TRAE led to treatment discontinuation or death. No cases of interstitial lung disease/pneumonitis were reported. **Conclusions:** Sac-TMT monotherapy demonstrated promising clinical activity with a manageable safety profile in previously treated advanced NSCLC pts with uncommon *EGFR* mutations. These findings warrant further investigation of sac-TMT as a potential therapy for this population. Clinical trial information: NCT05631262. Research Sponsor: Sichuan Kelun-Biotech Biopharmaceutical Co., Ltd.

8616 **Poster Session**

Phase I/II study of DZD6008, a 4th-generation EGFR TKI with full BBB penetration, in EGFR-mutant NSCLC. First Author: Mengzhao Wang, Department of Respiratory and Critical Care Medicine, Peking Union Medical College Hospital, Chinese Academy of Medical Sciences & Peking Union Medical College, Beijing, China

Background: NSCLC patients whose disease progressed after 3rd generation EGFR TKI treatment often have CNS metastasis and acquired EGFR resistance mutations, such as C797S mutation. DZD6008 is a 4th generation EGFR TKI, designed to target EGFR sensitizing mutations (L858R/del19), resistant double (T790M and L858R/del19) and triple mutations (C797X, T790M and L858R/del19). Preclinical data shows that DZD6008 has high selectivity against wildtype EGFR and other kinases and is fully blood-brain-barrier (BBB) penetrant. Here we report results from the ongoing phase 1/2 studies in advanced EGFR mutation positive (EGFRm) NSCLC. **Methods:** TIAN-SHAN2 (CTR20241790) is a multi-center, first-in-human phase 1/2 study with expansion designed to evaluate the safety, tolerability, and anti-tumor activity of DZD6008 in EGFRm NSCLC patients who failed prior EGFR TKI treatment. DZD6008's BBB penetration capability was evaluated by measuring the ratio of free drug concentrations in CSF and blood, as well as tumor response of brain lesions. **Results:** Preclinically, DZD6008 showed equal potencies against multiple variants of single, double or triple EGFR mutations, with >50-fold selectivity over wild-type EGFR. In osimertinib-resistant CDX and PDX models carrying EGFR triple mutations, DZD6008 induced profound tumor shrinkage in a dose-dependent manner. As of December 24, 2024, 12 patients with EGFRm NSCLC had been enrolled into dose escalation cohorts of TIAN-SHAN2 study, and treated with DZD6008 at 20 mg to 90 mg once daily (QD). The median age was 61 years, 67% were female, and 50% had an ECOG PS of 1. All patients had adenocarcinoma and carried various types of single, double or triple EGFR mutations. The median lines of prior therapies was 5 (range 2 - 8). All patients had been treated with EGFR TKIs and chemotherapy, and 11 had received prior third-generation EGFR TKI treatment. DZD6008 was well tolerated across the doses investigated, and no dose limiting toxicities were reported. The maximum tolerated dose was not reached. DZD6008 exhibited dose-proportional and linear pharmacokinetic characteristics, with excellent blood-brain-barrier penetration (CSF to free plasma ratio >1) in patients with baseline brain metastasis. Ten out of 12 patients (83.3%) showed target lesion tumor shrinkage following DZD6008 treatment. Partial response was observed at ≥ 20 mg in patients with various EGFR mutations. Anti-tumor activity was observed in patients with brain metastasis. The longest duration on treatment was >6 months (treatment ongoing). **Conclusions:** DZD6008 is a novel, highly selective, full-BBB penetrant EGFR TKI with broad-spectrum of activity against different EGFR mutations. In heavily pre-treated EGFRm NSCLC patients, DZD6008 monotherapy was well-tolerated and showed encouraging anti-tumor activity. TIAN-SHAN2 study is ongoing and updated data will be presented at the meeting. Clinical trial information: CTR20241790. Research Sponsor: None.

8617 **Poster Session**

Patient and caregiver treatment preferences for ALK+ non-small cell lung cancer in the United States. First Author: Christopher Danes, Takeda Pharmaceuticals U.S.A., Inc., Cambridge, MA

Background: Treatment options for non-small cell lung cancer (NSCLC) with ALK rearrangement (ALK+) have distinct benefits and risks. As patients often use ALK inhibitors for years, balancing these considerations is crucial. This study quantified how benefits and risks drive treatment preference and trade-offs between them from patients' and caregivers' perspectives. **Methods:** A discrete choice experiment (DCE) was completed online by Stage 4 ALK+ NSCLC patients and caregivers, recruited via physicians and the ALK Positive advocacy group. The DCE (developed based on literature review, phase 3 trial data and qualitative interviews) repeatedly asked participants to choose between 2 hypothetical treatments described by 7 benefit/risk attributes, each with a plausible clinical level. A mixed logit model estimated the relative impact of each attribute on preferences as relative attribute importance (RAI) and maximum acceptable loss (MAL) of 3-year progression-free survival (PFS) for reduced treatment risks. **Results:** 205 patients (mean age 61.9 years old; mean time since diagnosis: 2.7 years; 34.1% with brain metastasis) and 125 caregivers participated. 29.8% patients and 33.6% caregivers chose treatments based solely on PFS. Treatment preferences were mainly driven by 3-year PFS with less importance placed on adverse events (RAI: patients 4.0-11.0%; caregivers 3.7-13.3%) (Table). Patients were willing to forgo 3.9-8.7% of 3-year PFS to reduce risks of any grade cognitive/mood effects, grade ≥3 abnormal lab results, grade ≥3 lung complications, grade ≥3 weight gain, and any grade myalgia; caregivers were willing to trade 3.7-7.2% of 3-year PFS to reduce any grade cognitive/mood effects, grade ≥3 abnormal lab results, and grade ≥3 lung complications, but not any grade myalgia or grade ≥3 weight gain. **Conclusions:** Patients and caregivers highly prioritized achieving a higher chance of 3-year PFS when choosing treatments. Most were willing to trade PFS benefit for reduced risks, although there was a subset of caregivers who were unwilling to trade any benefit for reduced risks. The extent varied between patients and caregivers. Shared treatment decision making between physicians and patients/caregivers should consider the balance between benefits and risks. Research Sponsor: Takeda Development Center Americas, Inc.

RAI and MAL.

	RAI		MAL of 3-year PFS	
Attributes (Levels)	**Patients (n=205)**	**Caregivers (n=125)**	**Patients (n=205)**	**Caregivers (n=125)**
3-year PFS (30-65%)	50.8%	51.6%	NA	NA
Any grade cognitive/mood effects (0-25%)	11.0%	13.2%	8.7%	7.2%
Grade ≥3 lung complications (0-6%)	9.3%	6.7%	5.4%	3.7%
Grade ≥3 abnormal lab results (0-30%)	8.7%	13.3%	6.8%	5.5%
Grade ≥3 weight gain (0-20%)	8.5%	4.5%	4.7%	NS
Any grade myalgia (0-20%)	7.6%	7.2%	3.9%	NS
Tumor progression in the brain within 3 years (10-55%)	4.0%	3.7%	6.1%	NS

NS: not statistically different to zero (p≥0.05), indicating unwillingness to forgo 3-year PFS to reduce these risks.

8618 **Poster Session**

LUMINOSITY, a phase 2 study of telisotuzumab vedotin in patients with c-Met protein–overexpressing non-squamous *EGFR*-wildtype advanced NSCLC: Efficacy outcomes by prior therapy. First Author: Jonathan W. Goldman, David Geffen School of Medicine at University of California, Los Angeles, Los Angeles, CA

Background: Telisotuzumab vedotin (Teliso-V) is a c-Met–directed antibody-drug conjugate comprising the mAb telisotuzumab and the microtubule polymerization inhibitor monomethyl auristatin E. In the phase 2 LUMINOSITY trial (NCT03539536), Teliso-V monotherapy 1.9 mg/kg showed durable responses and a generally manageable safety profile in patients (pts) with c-Met protein–overexpressing (OE) non-squamous (NSQ) *EGFR*-wildtype (WT) non-small cell lung cancer (NSCLC). Herein we present an analysis of efficacy outcomes according to prior platinum or prior platinum and immune checkpoint inhibitor (ICI)-based therapies. **Methods:** Pts (≥18 years) with locally advanced/metastatic c-Met protein–OE NSQ *EGFR*-WT NSCLC who had ≤2 prior lines of therapy, including ≤1 line of chemotherapy, were treated with 1.9 mg/kg Teliso-V Q2W. c-Met protein overexpression (by immunohistochemistry clinical trial assay for MET [SP44] [Roche]) was defined as ≥25% tumor cells with 3+ staining intensity (high: ≥50% 3+; intermediate [int]: 25 to <50% 3+). The primary endpoint was overall response rate (ORR) by independent central review per RECIST v1.1. **Results:** As of 21 Feb 2024, 172 pts received ≥1 dose of Teliso-V and 168 pts were included in efficacy analyses (c-Met high, n=84; c-Met int, n=84). In the c-Met OE total population, 97.6% of pts received prior platinum and 78.6% received prior platinum + ICI. Efficacy data for pts with prior platinum and platinum + ICI therapies are shown in the Table. Among the 172 dosed pts, the most common any-grade treatment-related adverse events (TRAEs) were peripheral sensory neuropathy (31%), peripheral edema (16%), and fatigue (14%). The most common grade ≥3 TRAE was peripheral sensory neuropathy (7%). **Conclusions:** This analysis demonstrated that Teliso-V elicited durable responses in pts with c-Met protein–OE NSQ *EGFR*-WT NSCLC regardless of whether they had received prior platinum or platinum + ICI therapies; the efficacy outcomes in these subgroups were consistent with those in the overall pt population. Clinical trial information: NCT03539536. Research Sponsor: AbbVie, Inc.; n/a

	Platinum	Platinum + ICI	Overall
ORR,[a] n/N (%) [95% CI]			
c-Met OE total	48/164 (29.3) [22.4, 36.9]	38/132 (28.8) [21.2, 37.3]	49/168 (29.2) [22.4, 36.7]
c-Met high	28/81 (34.6) [24.3, 46.0]	22/67 (32.8) [21.8, 45.4]	29/84 (34.5) [24.5, 45.7]
c-Met int	20/83 (24.1) [15.4, 34.7]	16/65 (24.6) [14.8, 36.9]	20/84 (23.8) [15.2, 34.3]
Median DOR,[a] mo [95% CI]			
c-Met OE total	7.2 [5.5, 11.3]	7.2 [5.5, 11.0]	7.2 [5.5, 11.0]
c-Met high	9.0 [3.8, 12.0]	9.0 [3.8, 11.3]	7.2 [4.2, 12.0]
c-Met int	7.2 [4.7, 11.5]	7.2 [5.3, 11.5]	7.2 [4.7, 11.5]

[a]Per independent central review. DOR, duration of response.

8619 **Poster Session**

EATON: A phase I trial of nazartinib (EGF816) and trametinib in EGFR-mutant (EGFRmut) non-small cell lung cancer (NSCLC). First Author: Sebastian Yves Friedrich Michels, University of Cologne, Faculty of Medicine and University Hospital Cologne, Center for Integrated Oncology Aachen Bonn Cologne Düsseldorf, Department I for Internal Medicine, Lung Cancer Group Cologne, Cologne, Germany

Background: EGFR inhibitors (EGFRi) are highly effective in EGFRmut NSCLC, but resistance inevitably emerges. Among the mechanisms of acquired resistance, RAS/MEK pathway activation has been identified in both cell models and patients. Preclinical and clinical data support efficacy of dual MEK and EGFR inhibition in this setting. In the EATON trial we investigated the combination of the MEK inhibitor (MEKi) trametinib (TMT) and the third-generation (3gen) EGFRi nazartinib (NAZ) in patients with EGFRmut NSCLC. **Methods:** EATON (NCT03516214, AIO-TRK-0216) is an academic multicenter, phase I, dose-escalation trial conducted in Spain and Germany. Primary endpoint: maximal tolerated dose (MTD)/recommended phase 2 dose (RP2D); secondary endpoints: pharmacokinetics (PK), safety, preliminary efficacy. Key eligibility criteria: Advanced/metastatic EGFRmut NSCLC, EGFR p.T790M-positive/-negative, no MET amplification, any treatment line. Dose escalation was based on a modified 3+3 up-and-down design in up to 18 patients [Storer, 1989]. TMT and NAZ were dosed once daily (qd) at pre-defined dose levels (DL) of 0.5 mg/100 mg (DL -1), 1.0 mg/100 mg (DL 1), 1.5 mg/100 mg (DL 2), 1.5 mg/150 mg (DL 3), 2 mg/150 mg (DL 4). The dose-limiting toxicities (DLT) period comprised the first 28 treatment days. **Results:** In total, 19 patients were dosed (mean age, 62 years (range, 44-81); 14 female (73.7%)). Prior EGFRi and 3gen EGFRi use were noted in 17 (89.5%) and 14 (73.7%), respectively. Patients were treated at DL -1 (N=4), DL 1 (N=13), and DL 2 (N=3), with 18 (94.7%) eligible for dose-escalation decisions. DLTs were observed in 4 (22.2%) patients (Grade 3 creatinine phosphokinase elevation, N=3; Grade 3 hypertension, N=1). The MTD was determined to be TMT 1.0 mg qd and NAZ 100 mg qd. After repeated dosing (C1D15) at the MTD, geo-mean C_{max} of NAZ was 336 ng/ml (N=14, CV % 44.8) and of TMT 19.5 ng/ml (N=7, CV% 22.6). Geo-mean AUC_{tau} of NAZ was 3950 ng/ml*h (N=14, CV% 48.7) and of TMT 301 ng/ml*h (N=7, CV% 27.3). Treatment-related adverse events (TRAEs) of any grade were observed in all patients (N=19; 100%) and of Grade ≥3 in nine (47.4%). Discontinuation rates were 26.3% (N=5) and 21.1% (N=4), for TMT and NAZ. Sixteen (84.2%) patients were evaluable for RECIST 1.1 response assessment and 19 (100%) for time-to-event outcomes. One patient had a partial response (ORR, 6.3%; 95% CI, 1.6-30.2) and six had stable disease (37.5%). Median progression-free survival was 2 months (95% CI, 1.7-2.2). Molecular determinants of response and resistance were investigated by 3' RNA and DNA sequencing. **Conclusions:** At the MTD, treatment was safe and moderately tolerable. Preliminary efficacy in this unselected and heavily pre-treated population was limited. A comprehensive biomarker-driven approach may help identify patients more likely to derive clinical benefit. Clinical trial information: NCT03516214. Research Sponsor: German Federal Ministry of Education and Research (BMBF); Novartis.

8620 **Poster Session**

Patient-reported outcomes (PRO) evaluating physical functioning and symptoms in patients with pretreated HER2-mutant advanced non-small cell lung cancer (NSCLC): Results from the Beamion LUNG-1 trial. First Author: Joshua K. Sabari, Division of Medical Oncology, Perlmutter Cancer Center, New York University Langone Health, New York, NY

Background: Zongertinib is an irreversible tyrosine kinase inhibitor that selectively inhibits HER2 while sparing EGFR, thereby limiting associated toxicities. Beamion LUNG-1 (NCT04886804) is a Phase Ia/Ib first-in-human study evaluating safety and efficacy of zongertinib in patients with HER2-mutant advanced NSCLC (Phase Ib). Here, we report PRO data on NSCLC-related symptoms, physical functioning, symptomatic adverse events (AEs) and their burden from Phase Ib Cohort 1. The PRO analysis included patients with previously treated HER2-mutant NSCLC who received 120mg QD zongertinib. **Methods:** EORTC QLQ-C30 physical functioning scale, NSCLC-SAQ (cough, dyspnea, pain, fatigue and poor appetite), EORTC IL46/Q168 (side effect burden) and nine PRO-CTCAE items (mouth and/or throat sores, taste changes, nausea, vomiting, diarrhea, rash, skin dryness, itching, and numbness/tingling) were collected at cycle 1: days 1, 8 and 15, and day 1 of cycles 2, 3, 5, 7 and 9. Change from baseline (CFB) to cycle 5 in EORTC QLQ-C30 physical functioning (0-100, higher=better) and NSCLC-SAQ total score (0-20, lower=fewer symptoms) were analyzed using mixed model repeated measures. EORTC IL46 (1 = 'Not at all', 4 = 'Very much') and PRO-CTCAE (0 Never/None to 4 Almost Constant/Very Severe) were analyzed descriptively; maximum baseline-adjusted proportions of patients were calculated. Post-hoc analysis includes contextualizing results based on clinically meaningful thresholds and exploring associations between PRO and clinical endpoints such as objective response. **Results:** The PRO analysis set comprised of 30 patients. High completion rates were observed, over 86%, across PROs and visits. Longitudinal MMRM analysis showed improvements for EORTC QLQ-C30 physical functioning and NSCLC-SAQ total score, with rapid improvement which was maintained to cycle 9; CFB to cycle 5: LS means 9.6 (95% CI: 6.3, 12.9), and -3.9 (95% CI: -4.8, -2.9) respectively. Patients reported low overall side effect burden (EORTC IL46); patients reporting side effect burden on treatment as 'Quite a bit'/ 'Very much' was equal to baseline reporting (6.7%), with the exception only at cycle 1 day 15 (10%). Patient reported adverse event frequency/severity (PRO-CTCAE items) reflected expected toxicity profiles; diarrhea was reported at the highest frequency (maximum baseline adjusted: 'Frequent'/ 'Almost constant'=30%), low percentages of patients reported high levels of severity or interference for any adverse event. **Conclusions:** Zongertinib-treated patients reported a rapid improvement followed by stability in physical functioning and NSCLC-SAQ total score. The frequency and severity of patient-reported symptomatic AEs and the overall side effect burden demonstrated favorable tolerability of zongertinib. Clinical trial information: NCT04886804. Research Sponsor: Boehringer Ingelheim.

8621 **Poster Session**

Advancing evidence-based NSCLC testing and treatment across academic and community-based settings. First Author: Gilberto Lopes, Sylvester Comprehensive Cancer Center, University of Miami, Miami, FL

Background: Comprehensive testing for guideline-recommended driver mutations in advanced non-small cell lung cancer (aNSCLC) remains underutilized. **Methods:** From Feb to Mar 2024, 20 healthcare professionals (HCPs) were surveyed from one academic and one community-based oncology system in the same region and retrospective chart audits (N=100) were performed to assess current practices, challenges/barriers, and areas for improvement in biomarker testing and use of targeted therapies in aNSCLC. Based on these baseline findings, an expert steering committee, including an oncologist, pathologist, surgeon, and site representatives, developed a NSCLC biomarker toolkit to support evidence-based testing. Clinical teams reviewed the data in audit feedback sessions and developed and implemented action plans to address identified gaps. **Results:** Both academic and community HCPs (aHCPs, cHCPs; 60%) cited *determining the appropriate molecular tests to order for treatment decisions* as their top challenge in integrating targeted therapies into practice. Significant variation was reported in which team member checks insurance authorization for molecular testing and submits the order, and how the medical oncologist is notified when test results are available. Most HCPs (93%) said molecular test results are not consistently scanned into the same chart locations. Compared to aHCPs, cHCPs were more likely to start NSCLC treatment before receiving molecular test results and reported significantly lower confidence in shared decision-making with pts. Top challenges in adverse event (AE) management were *patient communication about recognizing AEs* for aHCPS (80%), and *staying updated on AEs from targeted therapies* (50%) for cHCPs. Chart audits revealed greater variability in frontline therapies prescribed to pts treated in a community setting. Molecular testing was ordered for 86% of pts overall, including 100% in academic settings and 72% in community settings; 81% of pts had a documented mutation. As a result of this initiative, systems developed action plans to integrate the biomarker testing tool into practice, improve workflows for reflex testing, standardize molecular test documentation in EMRs, and utilize AI dashboards and dedicated phone lines to streamline communication with NSCLC patients about treatments and side effects. Additional follow-up data will be presented. **Conclusions:** This project uncovered real-world gaps in biomarker testing and evidence-based integration of targeted therapy for aNSCLC and revealed unique differences between academic and community settings, driving action plans to improve clinical workflows and communication. The biomarker testing toolkit and sustainable process changes implemented in this QI initiative represent key opportunities for improvement that can be implemented in clinics across the country to improve NSCLC care. Research Sponsor: Janssen Biotech, Inc.

8622 **Poster Session**

Novel potent and selective fourth-generation inhibitors targeting EGFR for NSCLC therapy. First Author: Gauthier Errasti, PMC Isochem, Paris, France

Background: Epidermal growth factor receptor (EGFR)-activating mutations (Del19 or L858R) are oncogenic drivers of non-small cell lung cancer (NSCLC). Most patients treated with tyrosine kinase inhibitors (TKIs) will eventually develop resistance mutations including the T790M gatekeeper mutation. Osimertinib, a third-generation covalent TKI, is efficacious against the T790M resistance mutation and prevents its onset. However, treatment with Osimertinib inevitably induces additional mutations, especially the C797S mutation, as well as various off-target resistance mechanisms. To date, there are no approved therapies capable of overcoming mutational or non-mutational resistance to third-generation EGFR TKIs. **Methods:** We have characterized the efficacy of two novel fourth-generation EGFR inhibitors, CCM-205 and CCM-308, which are potent against both mutational and non-mutational tumor resistance to Osimertinib. Enzymatic binding affinities were determined by KdELECT assay. Cell-Titer-Glo (CTG) assay was used to assess cytotoxicity (cellular IC_{50}) of CCM-205 and CCM-308 *in vitro* on EGFR triple mutant and other Osimertinib-resistant cell lines, with comparison to both Osimertinib and fourth-generation EGFR inhibitor BLU-945. *In vivo* tumor growth inhibition (TGI) was determined in Osimertinib-resistant xenografts including the triple mutant PC9-DTC (Del19/T790M/C797S) model. **Results:** In Ba/F3 EGFR DTC and LTC cells, CCM-205 / CCM-308 inhibit proliferation with IC_{50}s of 137 nM / 40 nM and 198 nM / 61 nM respectively, while Osimertinib antiproliferation is limited to 1.225 μM and 1.562 μM respectively. Moreover, CCM-205 / CCM-308 spare Ba/F3 EGFR WT better than Osimertinib with IC_{50}s of 577 nM / 294 nM (182 nM for Osimertinib). CCM-205 / CCM-308 also bind tightly to double mutants targeted by Osimertinib with K_ds for EGFR LT (L858R/T790M) of 4.9 nM / 1.2 nM. CCM-205 and CCM-308 are more potent against PC9 DTC cells (IC_{50}s: 1.02 μM and 220 nM, respectively) than Osimertinib (4.10 μM) and are comparable to BLU-945 (559 nM). In addition, CCM-205 / CCM-308 are highly potent against Osimertinib-resistant PC9 (IC_{50}s: 728 nM / 321 nM) and H1975 (IC_{50}s: 1.716 μM / 684 nM) cell lines generated through 8-week treatment with 1 μM Osimertinib (Osimertinib IC_{50} = 3.81 μM and 4.70 μM, respectively), while EGFR-specific fourth-generation inhibitors targeting C797S such as BLU-945 lose potency (IC_{50}s: 7.96 μM and $>$ 10 μM, respectively). In the PC9-DTC xenograft, CCM-205 completely inhibited tumor growth and induced tumor regression ($>$ 100% TGI) exceeding that of BLU-945, while the tumor was resistant to Osimertinib ($<$ 20% TGI), when agents were delivered orally at similar fractions of their maximum tolerated doses (MTDs). **Conclusions:** Novel fourth-generation EGFR inhibitors have been developed that can potentially overcome both on-target and off-target resistance in NSCLC and have potential clinical applications. Research Sponsor: CCM Biosciences.

8623 **Poster Session**

Final overall survival analysis for a phase 3 randomized trial comparing afatinib to chemotherapy in treatment-naïve non-small cell lung cancer with a sensitizing uncommon epidermal growth factor receptor mutation (ACHILLES/TORG1834). First Author: Kyoji Tsurumi, Department of Respiratory Medicine, Miyagi Cancer Center, Natori, Japan

Background: The phase 3 randomized trial comparing afatinib to chemotherapy in treatment-naïve non-small cell lung cancer (NSCLC) with a sensitizing uncommon epidermal growth factor receptor mutation (*EGFR*) (ACHILLES) met its primary endpoint at the interim analysis. This trial demonstrated statistically significant improvement in progression-free survival (PFS)with hazard ratio 0.421; 95% confidence interval (CI), 0.251–0.706; p = 0.0010). Here, we report the final updated survival data. **Methods:** In this open-label phase 3 study, treatment-naïve patients (n=109) with sensitizing uncommon *EGFR* mutant NSCLC were randomized 2:1 to receive oral afatinib (30 mg or 40 mg daily) or a combination of platinum (cisplatin 75 mg/m^2 or carboplatin AUC 5 or 6) and pemetrexed (500 mg/m^2), followed by pemetrexed maintenance therapy every 3 weeks. The primary endpoint was PFS according to RECIST 1.1 criteria. Overall survival (OS) was a secondary endpoint. Post-protocol treatment was administered at the physician's discretion. **Results:** As of the 2 December 2024 database lock, the median follow-up time was 33.6 months. Afatinib continued to improve PFS compared with chemotherapy (median, 10.8 months vs 7.0 months; HR [95% CI], 0.528 [0.338–0.827], p = 0.0052). The updated OS HR for afatinib compared to chemotherapy was 0.645 (95% CI, 0.359–1.160; p = 0.1433; 49/109 events, 44.9% maturity). The median OS was 45.0 months (range, 27.0–not estimated) in the afatinib group and 27.0 months (range, 15.9–50.4) in the chemotherapy group. The crossover rate to EGFR-TKI was 90.6% in the chemotherapy arm. Notably, the subgroup receiving a starting dose of 40mg afatinib and the subgroup of younger patients ($<$ 75 years) showed a favorable OS HR (HR 0.371, 95%CI, 0.140–0.986; HR 0.422, 95%CI, 0.201–0.886). No new safety signals were observed in this update analysis. **Conclusions:** This final survival analysis confirmed the superiority of afatinib compared to chemotherapy for uncommon or compound *EGFR* mutation-positive advanced NSCLC. Clinical trial information: jRCTs 031180175. Research Sponsor: None.

Treatment arm	n	Median PFS, mo [95%CI]	PFS HR [95%CI]	Median OS, mo [95%CI]	OS HR [95%CI]
Afatinib					
All	73	10.8 [8.6–13.2]	0.528 [0.338–0.827]	45.0 [27.0–NE]	0.645 [0.359–1.160]
Major uncommon (G719X, L861X, S768I/V)	44	10.0 [7.2–11.4]	0.630 [0.385–1.030]	42.0 [17.8–NE]	0.878 [0.470–1.639]
Other uncommon	5	8.6 [6.1–NR]	1.006 [0.384–2.635]	37.8 [27.0–NE]	0.814 [0.237–2.794]
Compound	24	15.5 [9.1–21.0]	0.414 [0.230–0.748]	NR [30.2–NE]	0.358 [0.132–0.972]
Chemotherapy					
Platinum+Pemetrexed	36	7.0 [4.7–8.3]	-	27.0 [15.9–50.4]	-

8624 **Poster Session**

Epigenetic and transcriptional consequences of MTAP-loss in lung adenocarcinoma. First Author: Swati Pothukuchi, Department of Internal Medicine, University of California, Davis, Davis, CA

Background: Lung adenocarcinoma (LUAD), the most common lung cancer subtype, has poor survival rates and limited treatment options. Among its molecular drivers, loss of methylthioadenosine phosphorylase (MTAP) is linked to aggressive development and poor outcomes, yet its downstream effects remain unclear. MTAP is essential for purine biosynthesis and S-adenosyl methionine (SAM) production, a key methyl donor for epigenetic regulation. MTAP-loss leads to methylthioadenosine (MTA) accumulation, which inhibits methyltransferase activity and disrupts epigenetic control. However, the impact of MTAP deficiency on transcriptional and metabolic programming in LUAD is still largely unknown, highlighting a critical gap for targeted therapy. This study examines these molecular consequences to identify potential therapeutic vulnerabilities in MTAP-deficient LUAD. **Methods:** RNA-sequencing data for 510 LUAD samples were obtained from The Cancer Genome Atlas (TCGA) via cBioPortal. Samples were classified as MTAP-loss (n=64) or MTAP-normal (n=446) based on mutational data. Differential gene expression was performed using the DESeq2 package for R and the Benjamini-Hochberg procedure was used to control for false discovery rate. DNA methylation (Illumina Human Methylation 450k) was compared between MTAP-loss (n=46) and MTAP-normal (n=404) cohorts. Significantly altered probes were mapped to differentially expressed genes (DEGs). Pathway and gene ontology (GO) analyses were conducted using KEGG, GO, and EnrichR to identify dysregulated pathways. **Results:** DNA methylation analysis revealed 581 hypomethylated and only 51 hypermethylated probes in MTAP-loss samples, underscoring a global hypomethylation phenotype likely driven by MTA accumulation. We identified 343 differentially expressed, hypomethylated genes in MTAP-loss LUAD samples. Of these, upregulated genes were highly enriched in mitochondrial function and stress response pathways, whereas downregulated genes were linked to cell differentiation and developmental processes, suggesting an epigenetically driven metabolic reprogramming. Notably, these alterations may confer heightened cellular survival and adaptability under stress, while curtailing normal differentiation programs. **Conclusions:** Our findings indicate that MTAP loss in LUAD leads to a coordinated shift in DNA methylation and gene expression, promoting survival-focused metabolic and stress responses at the expense of normal regulatory pathways. These results highlight novel vulnerabilities in MTAP-deficient tumors and suggest potential targets for precision therapies. Research Sponsor: None.

8625 **Poster Session**

Rare ALK: Clinical characteristics and efficacy of targeted therapy in NSCLC with ALK fusions other than EML4::ALK. First Author: Felix Carl Saalfeld, Department of Medicine I, University Hospital Carl Gustav Carus Dresden, TU Dresden, Dresden, Germany

Background: More than 90% of ALK rearrangements in NSCLC lead to recurrent fusions with EML4. The remainder is a heterogeneous group involving more than twenty different fusion partners. Data on prognosis and management of these patients is limited to case reports. **Methods:** This is an international, multicenter, retrospective analysis of advanced NSCLC patients with a non-EML4::ALK-fusion (*rare ALK*) compared to a control cohort of patients harboring typical EML4::ALK-translocations. **Results:** Out of 26,152 NSCLC patients tested by NGS 0.2% showed *rare ALK* with 21 distinct fusion partners identified. The prevalence of typical EML4::ALK fusions in the cohort was within the expected range (1.9%). Sufficient clinical data was available for a total of 51 *rare ALK* and 277 EML4::ALK patients. Median age within the *rare ALK* cohort was 66 years. 59% were male. The majority (88%) presented with adenocarcinoma, 10% had squamous-cell carcinoma. The choice of first-line TKI in *rare ALK* patients was similar to the EML4::ALK control cohort and with alectinib used predominantly (around 50%). Compared to EML4::ALK, patients with *rare ALK* were significantly older, more likely to have ever smoked (59% vs 35%) and, among smokers, had more pack years (15 vs 7 pack years). Objective response rate (ORR) to firstline ALK inhibitor treatment across all treatment lines in patients with *rare ALK* was 68% (95% confidence interval [CI] 53%-80%), while EML4::ALK patients had an ORR of 85% (CI 80%-89%; p=0.01). ALK inhibitors in first-line palliative treatment led to similar PFS in the *rare ALK* (23 months [mo]; CI 7.1-38.9) and the EML4::ALK cohort (25 mo; CI 19.9-30.1; HR 0.92; CI 0.6-1.5; p=0.7). Median overall survival (OS) was 40 mo (CI censored) for *rare ALK* compared to 57 mo (CI 50.7-63.3) for EML4::ALK (HR 0.9; CI 0.5-1.6; p=0.6). Within the *rare ALK* cohort, first-line treatment with platinum-doublet chemotherapy was associated with shorter PFS as compared to ALK inhibitors (5 mo vs 23 mo; HR 3.1; CI 1.2-8.0; p = 0.021) and trended towards shorter OS (24 mo vs 40 mo; HR 2; CI 0.7-5.9; p=0.2). **Conclusions:** Acknowledging the limitations of a retrospective analysis, our data suggest that, compared to EML4::ALK, patients with *rare ALK* fusions derive similar benefit from treatment with ALK inhibitors, which should be preferred over platinum-based therapies as first-line palliative treatment. Research Sponsor: None.

8626 Poster Session

Clinico-genomic characteristics of clinical trial participation and its impact on clinical outcome in metastatic NSCLC: A nationwide database analysis in Japan. First Author: Kentaro Gosho, Division of Genome Biology, National Cancer Center Research Institute, Tokyo, Japan

Background: The clinico-genomic factors influencing clinical trial participation and their impact on clinical outcomes remain unclear. We investigated which clinico-genomic characteristics predict clinical trial participation in patients with metastatic NSCLC and whether trial participation improves clinical outcomes compared to non-participation, using a nationwide database. **Methods:** We retrospectively analyzed 2,966 patients with metastatic NSCLC who underwent comprehensive genomic profiling (CGP) testing from March 2019 to December 2023 in the Center for Cancer Genomics and Advanced Therapeutics, a nationwide database. Multivariable logistic regression identified clinico-genomic factors associated with trial participation. Multivariable Cox model compared OS between trial participants and non-trial participants, adjusting for age, sex, smoking status, performance status, liver/brain metastases, FDA-approved/potentially druggable genes, PD-L1 tumor proportion score (TPS). Overall response rate (ORR) by the line of therapy was evaluated. **Results:** Of 2,966 patients, 167 (6%) participated in clinical trials. In the multivariable analysis, *EGFR* mutation (mut), non-squamous (sq) histology, and male sex were associated with a higher likelihood of trial participation, whereas *STK11* mut was associated with a lower likelihood of trial participation. After stepwise selection, biomarker factors (*EGFR* mut, *KRAS* G12C mut, *RET* fusion, *MET* exon 14 skipping mut, PD-L1 TPS $\geq$ 50%) explained 72% of the increased trial participation odds, while clinical factors (age $<$ 65, male sex, non-sq histology) accounted for 28%. Among patients with lung adenocarcinoma (LUAD), *KRAS* G12C and male sex predicted higher trial participation; among those with lung sq cell carcinoma (LUSC), *KRAS* G12C predicted higher trial participation. Participation did not confer an OS benefit in the overall NSCLC cohort (HR, 0.94; 95% CI, 0.74–1.19), in LUAD (HR, 1.03; 95% CI, 0.78–1.37), or in *EGFR*-mut patients (HR, 0.99; 95% CI, 0.52–1.88), but was significantly associated with improved OS in LUSC (HR, 0.29; 95% CI, 0.10–0.78). ORR was not significantly different between trial participants and non-trial participants in 1L (49% vs. 57%, P=0.25), 2L (30% vs. 34%, P=0.75), and 4L (25% vs. 19%, P=0.56) therapy lines, but was significantly higher among trial participants in 3L (46% vs. 23%, P=0.002) and $\geq$5L (48% vs. 18%, P=0.0001). **Conclusions:** Biomarker factors contributed to 72% of the likelihood of trial participation in patients with metastatic NSCLC, underscoring the importance of CGP. Clinical trial participants exhibited survival outcomes comparable to those of nonparticipants. Their higher ORR in later lines of therapy suggests that clinical trial participation may be a potent therapeutic option, particularly after standard treatment. Research Sponsor: None.

8627 Poster Session

Osimertinib plus anlotinib in patients with untreated, EGFR-mutated, advanced non-small-cell lung cancer with concurrent gene alterations: A single-arm, prospective, multicenter phase II study. First Author: Guanming Jiang, Dongguan People's Hospital, Dongguan, China

Background: The standard first-line treatment for advanced EGFR-mutated non-small cell lung cancer (NSCLC) is EGFR tyrosine kinase inhibitors (EGFR-TKIs). However, co-existing mutations can reduce the efficacy of EGFR-TKIs, and combination treatments may offer superior outcomes. Some studies suggest that the combination of Osimertinib and Anlotinib may enhance anti-tumor activity. This study explores the efficacy and safety of this combination as a first-line treatment for advanced NSCLC with EGFR co-existing mutations. **Methods:** This prospective, multicenter phase II trial enrolled patients (pts) with untreated, advanced NSCLC carrying EGFR exon 19 deletions or L858R mutations plus at least one additional mutation in TP53, PI3KCA, or RB1. pts received oral Osimertinib (80 mg daily) and Anlotinib (10 mg daily for 2 weeks, followed by 1 week off), repeated every 3 weeks until disease progression, unacceptable toxicity, or withdrawal. The primary endpoint was the 1-year progression-free survival (PFS) rate. Secondary endpoints included median overall survival (mOS), median PFS (mPFS), objective response rate (ORR), disease control rate (DCR), and safety. Exploratory analyses evaluated changes in circulating tumor DNA (ctDNA) and their correlation with clinical outcomes. **Results:** As of June 24, 2024, 38 pts (median age 65 years; 39.5% male; 78.9% ECOG PS 1) were enrolled. EGFR mutations included exon 19 deletions (47.4%) and L858R (52.6%), with co-existing mutations in TP53 (78.9%), PI3KCA (28.9%), and RB1 (2.6%). At baseline, 47.4% of pts had brain metastases. With a median follow-up of 14.5 months, the 1-year PFS rate was 85% (95% CI: 70%-95%), and median PFS was 29.0 months (95% CI: 22.5-NA). The ORR was 76.7%, and DCR was 97.4%. Among the 18 pts with brain metastases, the ORR was 83.3%, and median PFS was 22.3 months (95% CI: 14.6-30.4). All pts experienced treatment-related adverse events (TRAEs), with 18.3% having Grade 3 or higher TRAEs. Common TRAEs included rash (81.6%), hand-foot syndrome (71.1%), oral mucositis (50.0%), hypertension (60.5%), liver function impairment (47.4%), decreased appetite (44.7%), and diarrhea (36.8%). In the 11 pts monitored via next-generation sequencing (NGS), ctDNA clearance post-treatment correlated significantly with improved PFS (median PFS: NR vs. 17.8 months, P=0.015). **Conclusions:** The combination of Osimertinib and Anlotinib shows promising efficacy and manageable toxicity as a first-line treatment for advanced NSCLC with EGFR co-existing mutations, particularly in pts with brain metastases. Post-treatment ctDNA clearance appears to be a potential biomarker for predicting therapeutic response and prognosis. Further investigation is warranted to confirm these findings and explore personalized treatment strategies in NSCLC. Clinical trial information: ChiCTR2300070023. Research Sponsor: None.

8628 Poster Session

Association of circulating tumor DNA (ctDNA) variant allelic frequency (VAF) with outcomes on matched targeted therapies (TT) in advanced non-small cell lung cancer (aNSCLC). First Author: Amin Nassar, Yale Cancer Center, New Haven, CT

Background: There is a critical gap in our understanding of the correlation between ctDNA driver VAF and outcomes in patients (pts) with aNSCLC treated with TT. We explore the landscape of driver alterations (alts) in aNSCLC by ctDNA VAF and assess the association with outcomes in pts treated with matched TT. **Methods:** We analyzed 3,146 pts with aNSCLC with a driver positive liquid biopsy (LBx) (FoundationOneLiquid CDx) Targetable driver altswere defined as alts listed in NCCN guidelines and were stratified by VAF. Clinical outcomes were assessed for pts included in the nationwide (US-based) de-identified Flatiron Health-Foundation Medicine aNSCLC clinico-genomic database (FH-FMI CGDB) originating from approximately 280 US cancer clinics (~800 sites of care). For 224 pts receiving matched TT within 60 days of LBx collection, multivariate Cox proportional hazard models were employed to evaluate the association of VAF on real-world progression-free (rwPFS) and overall (rwOS) survival adjusting for clinical and demographic factors. **Results:** Among 3,146 pts with targetable alts detected in LBx, the frequency of drivers with VAF $<$1% in ctDNA was 36% (1,185/3,262 alts). Distribution of drivers by VAF is shown in the table. For pts in the FH-FMI CGDB treated with matched TT following driver positive LBx, clinical and demographic characteristics were balanced between pts with driver VAF $<$1% (n = 75) and those with VAF $\geq$1% (n = 147), except for the presence of liver metastases, which were more common in pts with VAF $<$1% (12% v 26%; p = 0.0002). There was no significant difference in the median rwPFS for pts with driver VAF $<$1% vs those with VAF $\geq$1% (10.8 vs 8.7 months; HR = 1.40 [0.92-2.00]; p=0.12). Similarly, there was no significant difference in median rwOS (32.4 vs 23.2 months; HR 1.20 [0.74-2.00]; p=0.45). To account for potential bias due to varying effectiveness of TT by driver, we limited the analysis to pts treated with EGFR inhibitors: VAF of the *EGFR* mutation did not affect rwPFS (10.8 vs 9.8 months; HR 1.14 [0.69-1.90]; p=0.61) or rwOS (18.3 vs 23.2 months; HR 1.1 [0.61-2.00]; p=0.74). **Conclusions:** Outcomes in pts with aNSCLC receiving matched TT after LBx were comparable between pts with driver VAF $<$1% and those with VAF $\geq$1%. Our findings highlight that the presence of a detectable targetable driver alt in aNSCLC is actionable, regardless of ctDNA VAF. Research Sponsor: Foundation Medicine, Inc.

Alteration	VAF <1% (n = 1,185)	VAF ≥1% (n = 2,077)	Percentage <1% VAF [95% Confidence interval]	VAF Range
***KRAS* G12C**	288	566	34 [31-37]	0.1% - 78%
EGFR	457	1,065	30 [28-32]	0.09% - 98%
ALK	129	126	51 [44-57]	0.04% - 49%
RET	47	32	59 [48-70]	0.04% - 36%
ROS1	41	22	65 [52-76]	0.05% - 47%
***MET* exon 14**	75	94	44 [37-52]	0.09% - 80%
NTRK1/2/3	13	7	65 [41-84]	0.11% - 17%
***BRAF* V600E**	71	59	55 [46-63]	0.09% - 35%
ERBB2	64	106	38 [30-45]	0.09% - 77%

8629 Poster Session

Safety and efficacy of ifebemtinib (IN10018) combined with garsorasib (D-1553) in KRAS G12C mutant solid tumors from a phase Ib/II study: Results from single-arm of non-small-cell lung cancer (NSCLC) and randomized part of colorectal cancer (CRC). First Author: Zhengbo Song, Zhejiang Cancer Hospital, Hangzhou, China

Background: RAS inhibitors (RASi) need to be combined with optimal partner(s) to maximize their efficacy. Ifebemtinib (ifebe) is a highly potent and selective oral inhibitor of focal adhesion kinase (FAK) demonstrating synergies with RASi both preclinically and clinically. D-1553 is a novel KRAS G12Ci approved in China for KRAS G12C mutant NSCLC. We previously reported a promising ORR of 90.3% in KRAS G12C mutant NSCLC receiving ifebe + D-1553 with pending durability of efficacy. Here we are updating the follow-up (FU) results in NSCLC and also reporting preliminary results of ifebe + D-1553 vs D-1553 in KRAS G12C mutant CRC from a randomized part to decipher the relative contribution of ifebe. **Methods:** Locally advanced or metastatic KRAS G12C mutant NSCLC patients (pts) without any prior systemic anticancer therapy were enrolled in a single arm and received ifebe (100mg QD) + D-1553 (600mg BID). Metastatic KRAS G12C mutant CRC pts with at least 1 prior line of systemic anticancer therapy were enrolled in a randomized part and randomized 1:1 to ifebe (100mg QD) + D-1553 (600mg BID) or D-1553 (600mg BID) alone. **Results:** As of 22-Jan-25, 33 front-line NSCLC pts (81.8% stage IV) were enrolled and received ifebe + D-1553, and 36 previously-treated metastatic CRC pts were enrolled and randomized 1:1 to receive ifebe + D-1553 or D-1553 alone. In NSCLC with a median FU of 13.8 months (range: 1.1, 20.9), 12-month PFS rate is 67.9%, and Kaplan-Meier curve of PFS flattens as treatment continues, predicting durable efficacy. The mDOR, mPFS and mOS are not reached by the cut-off date. In the randomized part of CRC, all 36 pts are radiologically evaluable. The ORR is 33.3% (95%CI: 13.3, 59.0) vs 16.7% (95%CI: 3.6, 41.4) and DCR is 100.0% (95%CI: 81.5, 100.0) vs 77.8% (95%CI: 52.4, 93.6) in ifebe + D-1553 vs D-1553 alone, respectively. The mDOR, mPFS and mOS has not matured yet. The safety profiles of ifebe + D-1553 in both NSCLC and CRC pts are comparable to each single agent. No ifebe- or D-1553-related death or AEs leading to drug withdrawal were reported. The incidence of SAEs and $\geq$Grd.3 AEs are listed in Table 1. **Conclusions:** Combination of ifebe and D-1553, as a dual-oral regimen, is safe and highly efficacious against KRAS G12C mutant NSCLC with ORR over 90% and durable efficacy. Preliminary results from the randomized part of CRC demonstrated ORR doubling with the combo, validating the add-on benefits of ifebe. Our data suggest that ifebe could be an ideal partner of RASi. Clinical trial information: NCT06166836; NCT05379946. Research Sponsor: None.

Incidence of SAEs and ≥Grd.3 AEs.

	NSCLC	CRC	
	Ifebe + D-1553 N=33 n(%)	Ifebe + D-1553 N=18 n(%)	D-1553 N=18 n(%)
Pts with SAE	**8 (24.2)**	**2 (11.1)**	**4 (22.2)**
ifebe-related	5 (15.2)	2 (11.1)	-
D-1553-related	5 (15.2)	2 (11.1)	1 (5.6)
Pts with ≥ Grd. 3 AE	**11 (33.3)**	**4 (22.2)**	**4 (22.2)**
ifebe-related	7 (21.2)	4 (22.2)	-
D-1553-related	7 (21.2)	4 (22.2)	2 (11.1)

8631 Poster Session

Clinical outcomes of tepotinib and immune checkpoint inhibitor therapy for MET exon 14 skipping NSCLC: A multicentric retrospective analysis. First Author: Kazuhito Misawa, Department of Thoracic Oncology, Saitama Cancer Center, Saitama, Japan

Background: The VISION study demonstrated that tepotinib, a MET inhibitor, is effective against MET exon 14 (METex14) skipping NSCLC, but the clinical data on the efficacy and safety of this drug are scarce, and the utility of immune checkpoint inhibitors (ICIs) in patients with METex14 requires further investigation. The present, multicentric, retrospective study evaluated the clinical efficacy and safety of tepotinib and ICIs in patients with METex14 skipping NSCLC. **Methods:** Data on the patient characteristics, treatment details, efficacy, and safety of tepotinib and ICIs in patients with METex14 skipping NSCLC diagnosed at any of six Japanese hospitals between August 2020 and December 2024 were extracted from electronic medical records and retrospectively analyzed. **Results:** Of the 98 patients enrolled, 57 (58.2%) and 41 (41.8%) were male and female, respectively. 60 patients (61.2%) had a smoking history. Histological data indicated adenocarcinoma in most of the patients (68.4%). There were 50 patients (51.0%) with PD-L1 $>$ 50%. Tepotinib was administered to 79 patients with a median age of 75 years (range: 55–90 years). Most of these patients had advanced-stage cancer. Tepotinib was administered as the first-line therapy in 62 patients (78.5%), with 19.0, 55.7, 17.7, 6.3, and 1.3% of this subgroup having ECOG PS 0, 1, 2, 3, and 4, respectively. The median observation period was 29.1 months (range: 1.5–51.5 months). First-line tepotinib therapy achieved a 61.4% overall response rate (ORR; 95% confidence interval [CI]: 48.8–74.0), median progression-free survival (PFS) of 8.2 months (95% CI: 6.3–10.1), and median overall survival (OS) of 24.4 months (95% CI: 9.5–39.2). The most common adverse event (AE) was edema (71.0%), with Grade 3 or higher edema occurring in 12.9% of the patients. Notably, these patients had significantly longer PFS than those without edema (10.8 months [95% CI: 8.0–13.6] vs. 4.2 months [95% CI: 2.8–5.5]; hazard ratio: 0.31; 95% CI: 0.16 to 0.60; P $<$ 0.001). Treatment-related AEs led to tepotinib discontinuation in 15.0% of the cohort, and dose interruption and dose reduction were required in 59.5% and 62.0% of the cohort, respectively. ICI therapy, which was administered to 34 patients at various times, achieved a median PFS of 28.8 months (95% CI: 9.3–52.5) and a median OS of 45.2 months (95% CI: 20.9–77.0). **Conclusions:** The present, real-world analysis corroborated the findings of the VISION study demonstrating the efficacy and safety of tepotinib therapy against METex14 skipping NSCLC. The association between tepotinib-related edema and longer PFS warrants further investigation. Importantly, ICIs appear to be a promising treatment option for this population and deserve further study. Research Sponsor: None.

8632 Poster Session

Vebreltinib plus PLB1004 in EGFR-mutated NSCLC with acquired MET amplification or overexpression after failure on EGFR-TKI treatment: A phase Ib/II study. First Author: Fei Zhou, Shanghai East Hospital, Shanghai, China

Background: MET amplification (METamp) or overexpression (METov) is the most common "off-target" mechanism that drives resistance to EGFR-TKIs. Vebreltinib is a potent and selective c-Met inhibitor, while PLB1004 is an oral, potent, irreversible, and selective EGFR-TKI with potent blood-brain barrier penetration and broad tyrosine kinase activity. **Methods:** This open-label, multicenter phase Ib/II study evaluated vebreltinib and PLB1004 in Chinese patients (pts) with EGFR-mutated NSCLC with METamp or METov after EGFR-TKI failure. Patients were eligible if they were METamp positive by NGS or FISH, or METov by IHC (3+). Phase Ib part established vebreltinib 150 mg BID and PLB1004 80 mg QD as the RP2D. Phase II further investigated the efficacy and safety of RP2D in four cohorts, stratified by MET gene status and previous EGFR-TKIs: 1: Progression after 1st-/2nd-generation EGFR-TKIs, T790M (-), with METamp (GCN $\geq$ 5 and/or MET/CEP7 $\geq$ 2 by FISH). 2: Progression after 3rd-generation EGFR-TKIs with METamp (GCN $\geq$ 5 and/or MET/CEP7 $\geq$ 2 by FISH). 3: Progression after EGFR-TKIs, T790M (-) for 1st-/2nd-generation TKIs, with METamp (GCN $<$ 5 and MET/CEP7 $<$ 2 by FISH, but positive by NGS). 4: Progression after EGFR-TKIs (1st-/2nd-/3rd-generation), T790M (-) for 1st-/2nd-generation TKIs, with METov (IHC 3+), and without METamp (GCN $<$ 5 and MET/CEP7 $<$ 2 by FISH, and negative by NGS). **Results:** There were 56 pts enrolled, with 13 in phase Ib and 43 in phase II (2/35/1/5 in four cohorts). The mean age was 58.8 $\pm$ 8.9 years, and 53.6% were male with the majority of patients having stage IV disease (98.2%). Prior EGFR-TKIs included 1st- (7.1%), 2nd- (5.4%), and 3rd-generation (87.5%) TKIs. Confirmed overall response rate (ORR) was 50.0%, and all cases (n=28) were partial response (PR). Disease control rate (DCR) was 89.3% (50/56). The median progression-free survival (mPFS) was 9.9 months. In 19 pts with brain metastases, ORR was 42.1% and mPFS was 9.5 months. There were 47 METamp-positive pts as detected by NGS (regardless of FISH), and these pts had an ORR of 53.2% and mPFS of 9.6 months. All pts (100%) reported treatment-related adverse events (TRAEs), with grade $\geq$ 3 TRAEs in 11 pts (19.6%). Serious adverse events were observed in 5 pts (8.9%), all of which were treatment-related. None discontinued treatment or died due to TRAE. The most common TRAEs were rash (64.3%), oedema peripheral (60.7%) and paronychia (48.2%). **Conclusions:** Vebreltinib and PLB1004 at RP2D demonstrates notable efficacy and manageable safety in EGFR-mutated NSCLC with METamp or METov after EGFR-TKIs failure. Findings from our phase Ib+II data suggest that NGS reported METamp+ could be utilized to identify target patients to receive combination of PLB1004 + Vebreltinib. Further studies are warranted to confirm these findings. Clinical trial information: NCT06343064. Research Sponsor: None.

8633 Poster Session

Hypothesis generative head-to-head study comparing efficacy of afatinib and osimertinib based on immunological biomarkers in Japanese NSCLC patients with *EGFR* mutations: Heat on Beat randomized phase II study. First Author: Nobuhiko Seki, Division of Medical Oncology, Department of Internal Medicine, Teikyo University School of Medicine, Tokyo, Japan

Background: Osimertinib (Osi) has been established as a standard of care for patients (pts) with *EGFR*-mutant advanced non-small-cell lung cancer (NSCLC). However, in the FLAURA study, survival superiority of Osi over first-generation EGFR-TKIs was not demonstrated especially in Japanese pts (hazard ratio [HR], 1.39; 95% confidence interval [CI], 0.83 to 2.34; P = 0.22). This is presumably due to the different impact of adverse events or tumor antigen-specific cytotoxicity of T cells on subsequent therapy between both EGFR-TKIs in Japanese pts. On the other hand, there has been no clinical trial comparing second- with third-generation EGFR-TKIs. Therefore, optimal first-line EGFR-TKI may not have been identified in Japanese pts. **Methods:** This was a randomized, open-label, multicenter, phase II study to compare overall survival (OS) between initial treatment with afatinib (Afa) (n = 50) and Osi (n = 50) in pts with advanced or recurrent *EGFR*-mutant NSCLC. Exploration of immunomonitoring through peripheral blood mononuclear cells (PBMC) was also performed, before, during, and after treatment. The co-primary endpoints were the superiority of Afa over Osi at 3-year survival rate and the exploration of immunological biomarkers for treatment outcomes. Enrollment started in May 2020 at 28 sites in Japan with a minimum follow-up of 3 years. **Results:** Overall, 95 eligible pts were analyzed (47 to Afa and 48 to Osi). Objective response rates were 63.8% for Afa vs. 62.5% for Osi. Median progression-free survival (PFS) was 16.7 months (mos) for Afa vs. 14.5 mos for Osi (HR, 1.17; 95% CI, 0.72 to 1.90; P = 0.52). Median OS was 38.8 mos for Afa and not reached for Osi (HR, 1.15; 95% CI, 0.64 to 2.05; P = 0.64), resulting in 54.7% (95% CI, 39.4 to 67.7) for Afa vs. 57.5% (95% CI, 42.2 to 70.1) for Osi at 3-year survival rate. Predominant adverse events with Afa or Osi were diarrhea (92% vs. 31%) and pneumonitis (11% vs. 21%; Grade 5, 0% vs. 6%). Treatment discontinuation rates due to adverse events were 21% with Afa vs. 29% with Osi. The efficacy of Osi varied significantly dependent on the immunological biomarkers, Th7R (stem cell-like CD4 T cells) and Th2. Pts with high Th7R (7.83% or more) had promising PFS (31.0 mos [n = 28] vs. 6.6 mos [n = 20]; HR, 0.38; P = 0.006) and OS (not reached vs. 35.5 mos; HR, 0.56; P = 0.18). In contrast, pts with high Th2 (7.20% or more) had poor PFS (6.6 mos [n = 27] vs. 31.0 mos [n = 21]; HR, 1.78; P = 0.11) and OS (35.5 mos vs. not reached; HR, 2.77; P = 0.03). On the other hand, no immunological biomarkers affected PFS and OS of Afa. **Conclusions:** Afa and Osi both demonstrated favorable clinical activity as first-line treatment in Japanese NSCLC patients with *EGFR* mutations. Although their outcomes are comparable, immunological biomarkers (Th7R/Th2) may refine treatment decisions and warrant further prospective validation. Clinical trial information: jRCTs031190221. Research Sponsor: Boehringer Ingelheim Foundation.

8635 Poster Session

Therapeutic responses in 555 advanced NSCLC patients enrolled in phase I studies at MD Anderson Cancer Center. First Author: Jeong Uk Lim, Department of Investigational Cancer Therapeutics, The University of Texas MD Anderson Cancer Center, Houston, TX

Background: Lung cancer remains the deadliest solid tumor, with non-small cell lung cancer (NSCLC) accounting for 80–85% of cases. Patients enrolling in Phase I studies are often heavily pretreated and face limited treatment options. Understanding their demographics and therapeutic responses is crucial to improving patient outcomes. This study aimed to analyze therapeutic responses in NSCLC patients enrolled in Phase I studies. **Methods:** Data on NSCLC patients treated at the Investigational Cancer Therapeutics (ICT) department, a dedicated Phase I unit at The University of Texas MD Anderson Cancer Center (MDACC), were reviewed from January 2016 to December 2024, using MDACC CHIMERA platform. Collected data included age, gender, histologic type, Eastern Cooperative Oncology Group (ECOG) performance status, prior lines of treatment, treatment regimen, trial details and best response to treatment. **Results:** A total of 555 NSCLC patients were identified, of whom 267 (48.1%) were female. The median age was 64 years. The number of prior chemotherapy lines included: one line (50.3%), two lines (16%), and three lines or more (11.0%). The most frequent histologic type was adenocarcinoma (80.0%), followed by squamous cell carcinoma (15.7%) and NSCLC not otherwise specified (3.1%). The median number of treatment cycles was three, and the median duration of treatment was 2.0 months. The best response was evaluable in 449 cases (80.9%). The overall objective response rate (ORR) was 21.2%, and the disease control rate (DCR) was 71.3%. Clinical trial enrollment were categorized into seven groups: Targeted Monotherapy (TM), 227 cases (40.9%); Targeted Combination (TC), 49 cases (8.8%); Immunotherapy Monotherapy (IM), 81 cases (14.6%); Immunotherapy Combination, 57 cases (IC) (10.3%); Targeted + Immunotherapy (TI), 70 cases (12.6%); Antibody-Drug Conjugates (ADC) Monotherapy, 64 cases (11.5%); and Others (O), 7 cases (1.3%). When the ORR was compared among these groups, the TM group demonstrated the highest ORR at 32.6%, followed by the O group at 28.6% and the TC group at 28.2%. **Conclusions:** Phase I studies, especially those involving regimens containing targeted therapy, may serve as a promising treatment option for pretreated patients with advanced NSCLC. Research Sponsor: None.

Comparison of best response and objective response rates between different regimen groups.

	Targeted Therapy (Monotherapy)	Combination with Targeted Agent	Immunotherapy (Monotherapy)	Combination with Immunotherapy	Targeted Therapy Combined with Immunotherapy	Antibody-Drug Conjugate (Monotherapy)	Others	P
CR	1.6%	0%	0%	0%	0%	0%	0%	<0.001
PR	31.1%	28.2%	4.7%	11.6%	10.5%	12.2%	28.6%	
SD	43.2%	59.0%	57.8%	44.2%	57.9%	65.3%	0%	
PD	24.2%	12.8%	37.5%	44.2%	31.6%	22.4%	71.4%	
ORR	32.6%	28.2%	4.7%	11.6%	10.5%	12.2%	28.6%	<0.001

Abbreviations: CR: Complete Response; PR: Partial Response; SD: Stable Disease; PD: Progressive Disease; ORR: Objective Response Rate.

8636 Poster Session

Artificial intelligence-powered real-time model for predicting survival in advanced *EGFR*-mutant NSCLC. First Author: Hyun Ae Jung, Division of Hematology-Oncology, Department of Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, South Korea

Background: Novel targeted therapies have led to improved survival in *EGFR*-mutant NSCLC. However, survival outcomes and cancer progression vary. Accurate and practical prediction of progression, survival, and T790M status in advanced *EGFR*-mutant NSCLC is crucial for optimizing patient outcomes and personalizing treatment strategies. This study developed and validated an AI model for predicting survival, and the T790M mutation, integrating clinical, pathological, laboratory, and radiologic data. **Methods:** The model was developed and internally validated using data from Samsung Medical Center (SMC) collected baseline data (at the time of starting EGFR-TKI) and longitudinal laboratory data (during the EGFR-TKI treatment and follow-up) of patients with *EGFR* (deletion 19 or L858R) mutant NSCLC who received EGFR-TKI between 2008 and 2023. The primary outcome was the prediction of progression-free survival (PFS) event within 3, 6, and 12 months from each monitoring point during EGFR-TKI treatment. Secondary outcomes included predicting overall survival (OS) within 3, 6, and 12 months from each monitoring points and the detection of the T790M mutation. **Results:** A total of 3,095 patients participated in the study, with a median follow-up period of 41.5 months. At the time of data lock, 2,713 (87.7%) patients had experienced disease progression, 311 (10.0%) patients continued on first-line EGFR TKI treatment, and 71 (2.3%) patients were lost to follow-up. Among the patients who progressed on first-line EGFR-TKI, 1,083 (39.9%) patients acquired the T790M mutation, and 815 patients received third-generation EGFR-TKI as second-line treatment. Of the 1,630 patients without T790M or with an unknown T790M status, 174 received third-generation EGFR-TKI (117 for leptomeningeal seeding and 57 in a clinical trial), 865 were treated with cytotoxic chemotherapy or other therapies, and 591 were lost to follow-up. A total of 2,985 patients were included in the AI model. Median PFS in total population was 24.0 months (95% CI, 22.5-25.0). and medial overall OS was 50.7 months (95% CI, 48.7-52.9). The training set consisted of 1,910 patients, the validation set had 478 patients, and the test set included 597 patients. The AUC for predicting PFS events at 3, 6, and 12 months from the monitoring point was 0.780, 0.755, and 0.698, respectively. The AUC for predicting OS events at 3, 6, and 12 months from the monitoring point was 0.924, 0.886, and 0.812, respectively. The AUC for predicting T790M detection from the monitoring point at 3, 6, and 12 months was 0.768, 0.737, and 0.666, respectively. **Conclusions:** This study demonstrates a real-time AI-powered model to predict survival outcomes and T790M mutation status in advanced EGFR-mutant NSCLC during EGFR-TKI treatment. The model's ability to accurately forecast PFS, OS, and T790M acquisition offers valuable insights for personalized treatment strategies. Research Sponsor: None.

8637 Poster Session

Efficacy and omics-based insights of TROP2 ADC in non–small cell lung cancer with or without actionable genomic alterations (AGAs). First Author: Anlin Li, Department of Medical Oncology, Sun Yat-Sen University Cancer Center, Guangzhou, China

Background: TROP2 antibody–drug conjugate (ADC) has emerged as a promising strategy for advanced non-small cell lung cancer (NSCLC). A trend of enhanced efficacy has been observed in patients with actionable genomic alterations (AGAs), but the validity of AGA status for patient selection remains controversial. Current evidence suggests that endocytosis is a key factor in TROP2 ADC activity. However, systematic analyses of clinicopathological and genetic associations with endocytosis are lacking. This study combined a meta-analysis and omics analyses to identify potential NSCLC populations that respond or are resistant to TROP2 ADC. **Methods:** For the meta-analysis, we searched for trials of TROP2 ADC in advanced or metastatic NSCLC. Overall survival (OS), progression-free survival (PFS), and objective response rate (ORR) were pooled in the overall population and AGA subgroups. For the omics analysis, given that STK11/KEAP1 mutations are generally mutually exclusive with AGAs and define special subsets, we assessed TROP2 expression and endocytosis activity in three NSCLC categories: AGA-positive (AGA+), AGA−negative/STK11 or KEAP1-mutated (AGA−/SK+), and AGA-negative/STK11 and KEAP1-wild-type (AGA−/SK−). Each NSCLC AGA and key tumor suppressor driver mutation was also evaluated independently. **Results:** A total of 1,387 NSCLC patients from two randomized clinical trials (TROPION-Lung01 and EVOKE-01) and two single-arm trials (TROPION-Lung05 and KL264-01) were meta-analyzed. TROP2 ADC did not significantly improve OS (HR = 0.89, P = 0.12), PFS (HR = 0.90, P = 0.25), or ORR (OR = 1.68, P = 0.39) compared to docetaxel. The pooled ORR for the TROP2 ADC arm was 30% [18%-42%], with higher rates in AGA+ (43% [35−50%]) and EGFR-mutant subsets (45% [37−54%]). However, there was no significant difference in the advantage of TROP2 ADC over docetaxel between patients with and without AGAs ($P_{interaction}$=0.11, 0.51, and 0.79 for OS, PFS, and ORR, respectively). AGA+ tumors exhibited significantly higher TROP2 expression (FDR=0.01) and endocytosis activity (FDR=0.001) than AGA−/SK+ tumors, but no differences were observed between AGA+ and AGA−/SK− tumors. Within AGA− populations, SK− tumors had evidently higher TROP2 expression (FDR=0.0001) and endocytosis activity (FDR=0.01) than SK+ tumors. Among common NSCLC mutations, STK11 mutations showed the lowest levels of both TROP2 expression and endocytosis activity. **Conclusions:** AGA+ NSCLC tends to be more responsive to TROP2 ADC, but AGA status is not a reliable predictive biomarker for patient selection, likely due to heterogeneity within AGA− population. AGA−/SK+ defines a subgroup with the low TROP2 expression and endocytosis activity that may confer primary resistance to TROP2 ADC. We'll present in vitro experiments and clinical data regarding the primary resistance to TROP2 ADC in SK+ NSCLC at ASCO. Research Sponsor: None.

8638 Poster Session

Real-world data on the efficacy and safety of iruplinalkib (WX-0593) in ALK-positive advanced lung adenocarcinoma patients previously treated with lorlatinib. First Author: Fen Wang, Department of Oncology, Peking University Shenzhen Hospital, Shenzhen, China

Background: Iruplinalkib (WX-0593) is a novel anaplastic lymphoma kinase (ALK) tyrosine kinase inhibitor (TKI). Here we report the results from a retrospective observational study on efficacy and safety of iruplinalkib in ALK-positive lung adenocarcinoma (LUAD) patients who had previous treatment with lorlatinib. **Methods:** Patients with ALK-positive advanced LUAD who either experienced disease progression on or were intolerant to lorlatinib were evaluated for clinical outcomes including objective response rate (ORR), disease control rate (DCR), progression-free survival (PFS), overall survival (OS), and safety profiles. **Results:** A total of 11 patients were enrolled in this study, of which five (45%) were male, eight (73%) experienced treatment failure with lorlatinib, and seven (64%) received prior two or more second-generation TKIs. The median age was 49-years old. All patients received 180 mg of iruplinalkib orally daily. The median treatment line with iruplinalkib was six. Brain metastasis and prior treatment were summarized in the table. As of the data cut-off date on December 31, 2024, the median follow-up was 8.1 months. The ORR was 27%, and the DCR was 91%. The 12-month PFS rate was 53.0%, while the median PFS and OS were not reached. Eight (73%) and one (9%) patient experienced any grade and grade $\geq$ 3 treatment-related adverse event (TRAE), respectively. **Conclusions:** Iruplinalkib exhibited promising efficacy and acceptable toxicity in patients with ALK-positive advanced LUAD patients who were previously treated with lorlatinib. Research Sponsor: None.

Parameters	Results (n=11)
Baseline brain metastasis	9 (82%)
Prior ALK TKIs	
Crizotinib + second-generation + lorlatinib	10 (91%)
Second-generation + lorlatinib	1 (9%)
Detailed second-generation ALK TKI	
Aletinib	8 (73%)
Ceritinib	6 (55%)
Brigatinib	3 (27%)
Ensartinib	3 (27%)
Prior chemotherapy	5 (45%)
Prior anti-angiogenesis	8 (73%)
Prior immune checkpoint inhibitor	2 (18%)
Best objective response	
Partial response	3 (27%)
Stable disease	7 (64%)
Progressive disease	1 (9%)
Objective response	3 (27%)
Disease control	10 (91%)
PFS event	3 (27%)
12m PFS rate	53.0%
Median PFS, months	NR
Any grade TRAE	8 (73%)
Grade ≥ 3 TRAE	1 (9%)
TRAE leading to dose interruption/reduction/discontinuation	1 (9%) /0/0

8639 Poster Session

Amivantamab plus chemotherapy vs chemotherapy in *EGFR*-mutant advanced NSCLC after disease progression on osimertinib: Outcomes by osimertinib resistance mechanisms in MARIPOSA-2. First Author: Raffaele Califano, Department of Medical Oncology, The Christie NHS Foundation Trust and Division of Cancer Sciences; The University of Manchester, Manchester, United Kingdom

Background: Amivantamab (ami), an EGFR-MET bispecific antibody with immune cell–directing activity, combined with chemotherapy (chemo) is approved for patients with *EGFR*-mutant advanced NSCLC after disease progression on an EGFR TKI. In the phase 3 MARIPOSA-2 study (NCT04988295), ami-chemo significantly improved progression-free survival (PFS) vs chemo after disease progression on osimertinib (osi; HR, 0.48; $P<0.001$). Nearly all patients develop resistance after osi, most commonly *MET* amplifications (*MET*amp) and *EGFR* resistance mutations (Chmielecki *Nat Commun* 2023; Besse *Ann Oncol* 2024; Yang *JTO* 2024). We evaluated outcomes by baseline osi resistance mechanisms in MARIPOSA-2. **Methods:** MARIPOSA-2 enrolled participants (pts) with *EGFR*-mutant (Ex19del or L858R) advanced NSCLC whose disease progressed on osi; ~1/3 received osi as 2L therapy. This analysis included pts randomized to ami-chemo (n=131) or chemo (n=263). Pathogenic alterations were identified by next-generation sequencing (NGS) of blood circulating tumor DNA (ctDNA) with Guardant360 CDx or PredicineCARE assay. **Results:** Baseline ctDNA for NGS analysis of pathogenic alterations was available for 341 pts (87%; ami-chemo, n=120; chemo, n=221). Characteristic of post-osi resistance, the most commonly detected baseline alterations for ami-chemo vs chemo were *MET*amp (10% vs 14%) and secondary *EGFR* (C797X, L718X, G724X, L792X, G796X) resistance mutations (13% vs 18%). Ami-chemo improved median PFS (mPFS) vs chemo among pts with *MET*amp (HR, 0.51; P=0.078) and secondary *EGFR* mutations (HR, 0.55; P=0.125; Table). Furthermore, ami-chemo significantly prolonged mPFS vs chemo for pts with *EGFR*/*MET* independent (HR, 0.54; P=0.025) and unknown (HR, 0.31; $P<0.001$) resistance mechanisms. **Conclusions:** Ami-chemo improved mPFS vs chemo across baseline resistance subgroups, including *EGFR*/*MET* dependent, independent, and unknown resistance. Ami-chemo is an important treatment option, regardless of baseline osi resistance mechanism, for pts with *EGFR*-mutant advanced NSCLC after progression on an EGFR TKI. Clinical trial information: NCT04988295. Research Sponsor: Janssen Research & Development, LLC, a Johnson & Johnson company.

	Ami-chemo, chemo (n)	Ami-chemo vs chemo, mPFS (mo)	HR (95% CI); *P* value
Detectable baseline ctDNA	104, 195	5.9 vs 4.2	0.49 (0.36–0.68); <0.001
***TP53* co-mutation**	59, 127	5.6 vs 4.1	0.63 (0.44–0.92); 0.014
***MET*amp present**	12, 30	4.4 vs 3.1	0.51 (0.24–1.11); 0.078
Secondary *EGFR* resistance mutations present	15, 39	5.7 vs 5.0	0.55 (0.26–1.19); 0.125
Secondary *EGFR* resistance mutations absent	89, 156	6.2 vs 4.2	0.47 (0.34–0.67); <0.001
***EGFR/MET* dependent**	27, 62	5.5 vs 4.1	0.57 (0.33-0.99); 0.042
***EGFR/MET* independent**	39, 41	5.6 vs 3.9	0.54 (0.31–0.94); 0.025
Unknown	38, 92	9.7 vs 4.2	0.31 (0.17–0.56); <0.001
Independent + unknown	77, 133	7.0 vs 4.2	0.47 (0.32–0.68); <0.001

8640 **Poster Session**

Vabametkib in MET exon 14 skipping non-small-cell lung cancer: Efficacy and safety from the open-label, phase 2, cohort-1 trial. First Author: Xiuning Le, The University of Texas MD Anderson Cancer Center, Houston, TX

Background: Vabametkib (ABN401) is a tyrosine kinase inhibitor (TKI) targeting MET. It has previously demonstrated preliminary efficacy in patients(pts) with MET genomic aberrations including MET exon 14 skipping mutation (METex14) in lung cancer. Here, we present the efficacy and safety data from cohort 1 (TKI-naïve, METex14 non-small cell lung cancer [NSCLC]) **Methods:** Phase 2 Cohort 1 trial (NCT05541822) is an open-label, global, multicenter study designed to evaluate the safety and efficacy of vabametkib in pts with NSCLC harboring METex14. METex14 status is confirmed via NGS testing and the status is further validated centrally using digital droplet PCR (ddPCR). Pts receive oral vabametkib at a dose of 800 mg once daily (QD) until disease progression or the occurrence of unacceptable toxicity. The primary endpoint is the objective response rate (ORR). Additional outcomes being evaluated include pharmacokinetics (PK), duration of response (DoR), disease control rate (DCR), progression-free survival (PFS), and overall survival (OS). **Results:** This study was conducted across 24 centers in three countries (US, South Korea, and Taiwan). A total of 40 pts with METex14 NSCLC were enrolled and treated, including 24 males (60%) and 16 females (40%), between January 17, 2023, and June 14, 2024. Pts were aged 43-86 years, with 35 Asians and 5 Caucasians. Twenty-one pts were treatment-naive, while 19 had received prior treatment. As of December 24, 2024, the objective response rate (ORR) in the evaluable population (n=37) was 43.2% (95% CI: 27.10–60.51), with 16 out of 37 patients achieving a response. The median PFS was 15.9 months (95% CI:10.9, NA) for treatment-naive pts and 6.2 months (95% CI:5.9, NA) for previously treated pts. The median follow-up for the efficacy population was 7.7 months. Vabametkib's safety was assessed in all 40 treated pts, the most common treatment-related adverse events were nausea (n=28; 70%), diarrhea (n=14; 35%), and vomiting (n=8; 20%) and peripheral oedema (n=5; 12.5%). Grade 3 or higher adverse events occurred in 5 (12.5%) pts, no grade 3 edema were reported in the study population (0%). No grade 5 events in this cohort. **Conclusions:** Vabametkib demonstrates good antitumor activity in pts with METex14 NSCLC, and better toxicity profile with excellent tolerability, compared to FDA-approved MET inhibitors, supporting vabametkib continued clinical development for METex14 NSCLC pts. Clinical trial information: NCT05541822. Research Sponsor: None.

8641 **Poster Session**

Dermatologic prophylaxis and impact on patient-reported outcomes in first-line *EGFR*-mutant advanced NSCLC treated with amivantamab plus lazertinib: Results from the phase 2 COCOON trial. First Author: Jill Libles Feldman, EGFR Resisters – Patient Advocacy Group, Deerfield, IL

Background: The phase 2 COCOONtrial (NCT06120140) is evaluating the impact of enhanced dermatologic management (DM) in combination with amivantamab (ami) + lazertinib (laz) on reduction of skin and nail adverse events (AEs). At the interim analysis, enhanced DM (COCOON DM) significantly reduced the incidence of grade ≥2 dermatologic AEs by Wk 12 vs standard of care dermatologic management (SoC DM). We assessed patient-reported outcomes (PROs) from COCOON to determine if reducing dermatologic AEs impacts the quality of life (QoL) of patients with *EGFR*-mutant advanced NSCLC. **Methods:** Participants (pts) with previously untreated *EGFR*-mutant (Ex19del/L858R) advanced NSCLC were randomized 1:1 to receive COCOON DM or SoC DM per site practice. Pts received the approved doses of IV ami + oral laz. COCOON DM included oral doxycycline/minocycline (100 mg BID Wks 1–12), clindamycin 1% lotion on scalp (QD Wks 13–52), chlorhexidine 4% to wash hands and feet QD, and non-comedogenic ceramide-based moisturizer to body and face QD. The COCOON DM arm received a digital health tool with training on dermatologic AEs and reminders to increase adherence to the DM regimen. Dermatologic symptoms and impact on pts' health-related QoL were measured with PRO instruments every 2 weeks. The Skindex-16 questionnaire assesses the impact of skin conditions on QoL using 3 subscales (functioning, emotional, symptoms) and an average score (0 – no effect to 100 – effect experienced all the time). Patient's Global Impression of Severity (PGI-S) is a self-reported 4-point rating scale (no symptoms, mild, moderate, severe) assessing severity of nail infection, skin condition, and rash over time. All *P* values reported are nominal. **Results:** As of 13 Nov 2024, 138 pts received COCOON DM (n=70) or SoC DM (n=68) and had ≥12 wks of follow-up (median, 4.2 mo). This analysis focuses on PROs through 12 wks of follow-up (three 28-day ami+laz treatment cycles). Substantial and consistent separation favoring COCOON DM was observed in all post-baseline Skindex subscales indicating lower severity of dermatologic AEs and reduced impact of those AEs on QoL. More specifically, at Cycle 3 Day 15 (~10 wks), a lower average Skindex total score was observed with COCOON DM vs SoC DM (*P*=0.02). More pts in the COCOON DM arm vs SoC DM reported mild or no PGI-S rash, skin condition, or nail infection across the first 3 cycles. At Cycle 3 Day 15, there was a meaningful 3-fold difference for COCOON DM vs SoC DM in pts reporting no symptoms for PGI-S rash (21% vs 7%; *P*=0.04) and skin condition (23% vs 7%; *P*=0.02). There was also a numeric improvement in pts reporting no symptoms for nail infections (27% vs 16%; *P*=0.13). **Conclusions:** Among pts with *EGFR*-mutant advanced NSCLC, COCOON DM reduced the severity of dermatologic AEs and reduced the impact of those AEs on QoL compared to SoC DM. Clinical trial information: NCT06120140. Research Sponsor: Janssen Research & Development, LLC, a Johnson & Johnson company.

8642 **Poster Session**

Use of targeted therapy, healthcare costs, and survival with large panel testing, narrow testing, or no molecular testing in patients with metastatic non-small cell lung cancer (mNSCLC). First Author: Julie Anna Wiedower, Guardant Health Inc., Redwood City, CA

Background: Treatment guidelines recommend broad molecular profiling for patients with mNSCLC. With the availability of molecular tests with different genes, panel sizes, and specimen types, the testing landscape has become complex. This study aimed to evaluate use of biomarker-targeted therapy, healthcare costs, and overall survival with large panel, narrow, or no molecular testing for mNSCLC. **Methods:** This retrospective analysis used de-identified administrative claims from the Optum Labs Data Warehouse from 01/01/2016 to 03/31/2023. Commercial and Medicare Advantage enrollees with claims evidence of newly diagnosed mNSCLC between 08/01/2020 and 12/31/2022 were identified (index date = first diagnosis code for metastatic disease). Using procedure codes and laboratories on claims around the index date, patients were grouped by use of molecular testing as: 1) large panel (≥51 genes) testing; 2) narrow (individual gene or ≤50 gene panel) testing, or 3) no observed molecular testing. Outcomes evaluated in the variable follow-up period were targeted therapy use, healthcare costs (2022 adjusted) per patient per month (PPPM) in the first 180 days of follow-up, and overall survival. **Results:** Of 8,783 patients, 3,634 (41%) had large panel testing, 2,660 (30%) had narrow testing, and 2,057 (23%) had no observed testing; the remaining 5% of patients had molecular testing of unknown size. Use of targeted therapy was higher with large panel testing than narrow testing (12% vs. 8%, $p<0.001$) or no observed testing (3%, $p<0.001$). For commercial patients, mean ± SD total healthcare costs PPPM were higher for patients with large panel vs. narrow testing ($43,629 ± 33,097 vs. $38,642 ± 33,948, p=0.02) and were driven by higher pharmacy costs, but total healthcare costs PPPM were similar for patients with large panel vs. patients with no observed testing ($37,545 ± 50,329, p=0.11). For Medicare Advantage patients, mean total healthcare costs PPPM were similar ($p>0.10$) for patients with large panel ($18,321 ± 18,073), narrow ($18,462 ± 25,555), or no observed testing ($17,130 ± 31,955). Patients with large panel testing had higher median overall survival than patients with narrow testing (10.6 vs. 8.5 months, $p<0.001$) or no observed testing (10.6 vs. 5.9 months, $p<0.001$). **Conclusions:** Patients with large panel testing received targeted treatment at higher rates and had better overall survival than patients with narrow testing or patients with no observed testing. Total healthcare costs were similar with large panel testing vs. no testing and similar or higher (but driven by higher pharmacy costs) with large panel vs. narrow testing. Research is ongoing to assess outcomes among patient subgroups with treatment after adjusting for baseline differences between cohorts. Research Sponsor: None.

8643 **Poster Session**

Comparable efficacy and safety of taletrectinib for advanced ROS1+ non–small cell lung cancer across pivotal studies and between races and world regions. First Author: Maurice Perol, Department of Medical Oncology, Léon Bérard Cancer Center, Lyon, France

Background: Taletrectinib is a highly potent, next-generation, central nervous system–active, selective ROS1 tyrosine kinase inhibitor (TKI) that was evaluated in 2 pivotal ROS1+ non–small cell lung cancer (NSCLC) phase 2 trials: the regional TRUST-I (NCT04395677) and global TRUST-II (NCT04919811) studies. While earlier trials suggest its safety and efficacy data are consistent across racial and geographic factors, further analysis is required to confirm the consistency of outcomes and applicability of results across regions. Here, we compare the efficacy and safety of taletrectinib within and between the pivotal regional TRUST-I and global TRUST-II studies through predefined subgroup analyses. **Methods:** The pivotal cohorts of TRUST-I (N=173) and TRUST-II (N=159) had similar study designs, which included the same primary endpoint (confirmed objective response rate [cORR] by independent review committee per RECIST v1.1) and secondary endpoints, as well as similar inclusion/exclusion criteria and safety evaluation methods. Key efficacy and safety profiles were compared in 3 ways: (a) between TRUST-I and TRUST-II, (b) across Western (North America and Europe) and Asian regions, and racial subgroups, in the pooled study population of TRUST-I and TRUST-II, and (c) between Western and Asian regions and other subgroups in the global TRUST-II study. Relative risk (RR) and associated 95% confidence intervals (CIs) via the Wald method were used to compare data (data cutoff June 2024). **Results:** When comparing TRUST-I and TRUST-II, cORRs were consistent for TKI-naive (91% vs 85%; RR: 0.94 [95% CI: 0.83, 1.07]) and TKI-pretreated pts (52% vs 62%; RR: 1.20 [95% CI: 0.87, 1.66]). Rates of grade ≥3 treatment-emergent adverse events (TEAEs) were consistent across both studies (51% vs 51%, RR: 1.0 [95% CI: 0.81, 1.24]). TEAEs leading to dose interruptions (41% vs 40%) and discontinuations (6% vs 8%) were similar. In subgroup analyses of the pooled patient population by race, Asian and non-Asian patients had similar cORRs in both TKI-naive (89% vs 84%; RR: 0.94 [95% CI: 0.77, 1.15]) and TKI-pretreated (52% vs 68%; RR: 1.30 [95% CI: 0.93, 1.82]) groups. Comparison of different efficacy and safety profiles among subgroups in the pooled data set also showed consistency among races and regions. Within the multiregional TRUST-II study, cORRs were high in TKI-naive patients regardless of region (Western: 81%; Asia: 88%), prior chemotherapy (yes: 90%; no: 84%), and race (White: 83%; Asian: 86%; other: 86%). Similarly, major safety profiles were comparable between Asian and Western patients and between races within TRUST-II. **Conclusions:** Taletrectinib showed comparable efficacy and safety that were not impacted by geographic and racial factors. Therefore, the clinical benefit of taletrectinib is broadly applicable to ROS1+ NSCLC patients globally. Clinical trial information: NCT04395677, NCT04919811. Research Sponsor: Nuvation Bio Inc.

8644 Poster Session

Efficacy and safety of pralsetinib in patients with advanced *RET*-fusion-positive NSCLC: Final data from the phase 1/2 ARROW study. First Author: Gilberto Lopes, Sylvester Comprehensive Cancer Center, University of Miami Miller School of Medicine, Miami, FL

Background: *RET* fusions are targetable oncogenic drivers in 1-2% of non-small cell lung cancers (NSCLC). ARROW (NCT03037385) study results (final data lock May 20, 2024) supported the US FDA approval of pralsetinib, a highly potent, oral, selective RET inhibitor for metastatic *RET*-altered NSCLC. Here, we present final study results. **Methods:** ARROW was a phase 1/2 open-label study conducted at 84 sites in 13 countries. Phase 2 included patients with *RET*-fusion-positive NSCLC who received 400 mg pralsetinib once daily (QD). Initially, treatment-naïve patients were not candidates for platinum-based therapy and presented with several unfavorable prognostic factors; this requirement was removed by protocol amendment in July 2019. Primary objectives were overall response rate (ORR, per RECIST v1.1) and safety. Progression-free survival (PFS) and overall survival (OS) are reported in the full efficacy population; the measurable disease population (MDP) was the primary analysis population for ORR and duration of response (DOR). **Results:** 281 patients with *RET*-fusion-positive NSCLC received pralsetinib 400 mg QD, with a median duration of treatment of 14.95 months (mos). Median age was 60 years; 46% were male. In the MDP (n=259), ORR was 70.3% (95% confidence intervals [CI]: 64.3, 75.8) and median DOR was 19.1 mos (95% CI: 14.5, 27.9; Table). In the efficacy population (N=281), median OS was 44.3 mos (95% CI: 30.9, 53.1) with median follow up of 47.6 mos (95% CI: 44.8, 49.2), and median PFS was 13.1 mos (95% CI: 11.4, 16.8). ORR (Table) and median PFS were markedly higher in the US (25.9 mos, n=64) vs. Asia (12.6 mos, n=122) or Europe (12.9 mos, n=95). In the safety population, 95% of patients experienced treatment-related adverse events (TRAEs); 66% experienced ≥grade 3. Common TRAEs included increased AST (n=128 [46%]), anemia (n=121 [43%]), increased ALT (n=98 [35%]), and hypertension (n=77 [27%]). 3 patients died due to TRAEs (pneumonia, n=2; interstitial lung disease and rhabdomyolysis, n=1 each). No new safety signals were identified with this update. **Conclusions:** Pralsetinib produced clinically meaningful and durable responses in patients with *RET*-fusion-positive NSCLC (regardless of prior therapies) with a manageable safety profile, confirming with this longer follow up previously published results. Clinical trial information: NCT03037385. Research Sponsor: Rigel Pharmaceuticals, Inc.; Blueprint Medicines; Genentech/Roche.

	All MDP (n=259)	Prior Platinum (n=130)	Treatment-naive (n=106)
ORR, % (95% CI)			
Overall	70.3 (64.3, 75.8)	63.1 (54.2, 71.4)	78.3 (69.2, 85.7)
US	(n=58) 77.6 (64.7, 87.5)	(n=31) 64.5 (45.4, 80.8)	(n=19) 100 (82.4, 100)
Europe	(n=89) 65.2 (54.3, 75)	(n=36) 63.9 (46.2, 79.2)	(n=43) 65.1 (49.1, 79)
Asia	(n=112) 70.5 (61.2, 78.8)	(n=63) 61.9 (48.8, 73.9)	(n=44) 81.8 (67.3, 91.8)
Median DOR, mos (95% CI)[a]	(n=182) 19.1 (14.5, 27.9)	(n=82) 31.8 (15.1, 40.4)	(n=83) 13.4 (9.4, 21.7)
Median DOR follow up, mos (95% CI)	46.8 (42.3, 50.2)	50.3 (46.9, 56.8)	42.3 (37.4, 44.2)

[a]Per FDA censoring rule.

8645 Poster Session

Final results of a phase II study of cabozantinib in patients with *MET*-altered lung cancers. First Author: Guilherme Harada, Memorial Sloan Kettering Cancer Center, New York, NY

Background: *MET* alterations define a subgroup of non-small cell lung cancers (NSCLC) sensitive to MET tyrosine kinase inhibitors (TKIs). Currently, only type I MET TKIs are approved for treating these patients. We evaluated the activity of cabozantinib, a type II multikinase inhibitor, in MET-altered lung cancers. **Methods:** This is a single-arm, phase 2 trial in which patients with metastatic MET-altered lung cancers received cabozantinib (60 mg daily) until disease progression or intolerable toxicity. A Simon two-stage minimax design was used, with a null hypothesis (H0) of a 10% response rate and an alternative hypothesis (H1) of 30%. With a type I error of 10% and a power of 90%, 16 patients were enrolled in the first stage, with at least two responses required to advance to the second stage, enrolling an additional nine patients. The primary endpoint was objective response rate (ORR) and would be considered met if five or more patients provided an objective response among the 25 evaluable patients treated. Secondary endpoints included progression-free survival (PFS), overall survival (OS), and safety. **Results:** Twenty-eight patients were treated. The median age was 68 (range 38–85) years. Most patients (82%; 23/28) had MET exon 14 alterations; 7% (2/28) had MET amplification only, and 12% (3/28) had concurrent MET exon 14 alteration and amplification. The median number of prior systemic therapies was two (range 1–6), and 86% had previously received a MET TKI. Among the 25 evaluable patients, the ORR was 20% (95% CI, 8.9–39.1). Four out of five patients who achieved a partial response had received prior MET TKI: two with crizotinib, one with tepotinib, and one with capmatinib. The median PFS and OS were 4.5 (95% CI, 3.3-5.7) months and 7.2 (95% CI, 2.9-11.5) months, respectively. Treatment-related adverse events were primarily grade 1 or 2, with the most common being fatigue (39%), diarrhea (39%), palmar-plantar erythrodysesthesia (36%), and anorexia (36%). Grade 3 or higher events included hypophosphatemia (14%), hypertension (11%), and elevated lipase (11%). No treatment-related deaths occurred. **Conclusions:** This trial met its primary endpoint. Cabozantinib demonstrated activity in MET-altered NSCLC, and prospective clinical proof-of-concept that type II MET TKI switching can rescue type I MET TKI progression was established. Clinical trial information: NCT01639508. Research Sponsor: Exelixis.

8646 Poster Session

Rechallenge with first-generation RET inhibitors in *RET*-rearranged NSCLC pre-treated with selpercatinib or pralsetinib: Results from the RET MAP registry. First Author: Arianna Marinello, Cancer Medicine Department, Gustave Roussy, Villejuif, France

Background: *RET* fusions occur in 1-2% of patients with advanced non-small cell lung cancer (aNSCLC). First-generation RET inhibitors (RETi, selpercatinib and pralsetinib), have improved outcomes across treatment lines. Options at progression remain limited, especially in the absence of novel generation RETi. In real-world settings, rechallenge with the same class RETi is sometimes attempted, though efficacy and safety data are lacking. **Methods:** This multicenter retrospective analysis of the RET MAP registry included patients with *RET*-rearranged aNSCLC initially treated with selpercatinib or pralsetinib, followed by rechallenge with the same or a different first-generation RETi, as a single agent or in combination therapy. Clinical features, reasons for initial RETi discontinuation, treatment outcomes, and toxicity were assessed for both treatment courses. **Results:** Among 354 patients treated with first-generation RETi, same class RETi were re-administered in later lines in 33 (9.3 %) patients. At first RETi administration vs rechallenge, median prior lines were 2 (IQR 2–3) vs 4 (IQR 3–5), ECOG PS 0–1 was observed in 26 (78%) vs 25 (76%) patients, and brain metastases in 9 (27%) vs 13 (39%). Reasons for discontinuation of the first RETi were disease progression in 25 (76%) patients and toxicity in 8 (24%). RETi re-administration involved a change of first-generation RETi in 14 (42%) patients, monotherapy in 22 (67%), combination therapy in 11 (33%) (8 with other targeted agents for by-pass resistance, 3 with chemotherapy). It was given immediately after a prior RETi in 13 (39%) patients. At subsequent RETi treatment after progression on a prior RETi, ORR and median PFS were 18% and 2.17 months (95% CI 1.63–NR), respectively, with single-agent RETi (N=17), and 20% and 4 months (95% CI 3.55–NR), respectively, with RETi combined with other targeted agents (N=8). Patients who previously discontinued RETi due to toxicity (N=8) received a different RETi, with ORR and median PFS of 57% and 9.89 months (95% CI 5.33–NR), respectively. In this subgroup, 3 (37.5%) experienced serious side effects at re-administration of a different first-generation RETi. **Conclusions:** Rechallenge a different RETi of the same class is effective after initial discontinuation due to toxicity, though recurrent toxicity may occur in one-third of patients. In contrast, RETi rechallenge after progression demonstrates limited efficacy, primarily in selected cases treated with combination therapies. Research Sponsor: None.

TPS8647 Poster Session

TROPION-Lung14: A phase 3 study of osimertinib ± datopotamab deruxtecan (Dato-DXd) as first-line (1L) treatment for patients with *EGFR*-mutated locally advanced or metastatic (LA/M) non-small cell lung cancer (NSCLC). First Author: Shun Lu, Shanghai Chest Hospital, School of Medicine, Shan, Shanghai, China

Background: Despite the benefit observed with osimertinib, most patients with LA/M *EGFR*-mutated NSCLC develop resistance and treatment options on or after disease progression are limited. Phase 3 clinical trial data, using agents with broad antitumor activity, have demonstrated the potential to extend the clinical benefit of 1L osimertinib and delay the onset of resistance. Dato-DXd, an antibody-drug conjugate composed of a humanized anti-TROP2 monoclonal antibody conjugated to a potent topoisomerase I inhibitor, has demonstrated efficacy as monotherapy in NSCLC in TROPION-Lung01, including in patients with *EGFR*-mutated advanced NSCLC. TROPION-Lung14 is evaluating the efficacy and safety of osimertinib ± Dato-DXd as 1L therapy in patients with *EGFR*-mutated LA/M NSCLC. **Methods:** TROPION-Lung14 (NCT06350097) is an ongoing phase 3, open-label, multicentre, randomized study. The study is enrolling patients (aged ≥18 years) with histologically or cytologically confirmed stage IIIB/IIIC or IV non-squamous, *EGFR*-mutated (exon 19 deletion or L858R) NSCLC, no prior EGFR tyrosine kinase inhibitor or other systemic therapy for stage IIIB/IIIC or IV disease, at least one measurable lesion per RECIST 1.1, and WHO performance status (PS) of 0 or 1. Prior to the randomized study period, ~20 patients will receive osimertinib + Dato-DXd in a non-randomized single-arm safety run-in . Following safety run-in, ~562 patients will be randomized 1:1 to osimertinib (80 mg orally [PO] QD) or osimertinib (80 mg PO QD) + Dato-DXd (6 mg/kg IV Q3W). Patients will be stratified by *EGFR* mutation type (Ex19Del vs L858R), WHO PS (0 vs 1) and central nervous system (CNS) metastasis status (yes vs no). Treatment will continue until RECIST v1.1-defined progression or unacceptable toxicity. The primary study endpoint is progression-free survival (PFS) assessed by blinded independent central review. Overall survival is a key secondary endpoint; other secondary endpoints include PFS by investigator, objective response rate, duration of response, PFS2, safety, pharmacokinetics and immunogenicity. Enrollment is ongoing. Clinical trial information: NCT06350097. Research Sponsor: AstraZeneca. This trial is sponsored by AstraZeneca. In July 2020, Daiichi-Sankyo entered into a global development and commercialisation collaboration with AstraZeneca for datopotamab deruxtecan (Dato-DXd).

TPS8648 **Poster Session**

SOHO-02: Phase III trial of BAY 2927088 in patients with locally advanced or metastatic NSCLC with *HER2*-activating mutations. First Author: Xiuning Le, The University of Texas MD Anderson Cancer Center, Houston, TX

Background: Approximately 2-4% of non-small cell lung cancer (NSCLC) harbor activating human epidermal growth factor receptor 2 (*HER2*) mutations. This represents a major area of unmet medical need as no first-line HER2-targeted therapies are currently approved for patients with locally advanced or metastatic NSCLC with *HER2*-activating mutations. BAY 2927088 is an oral, reversible tyrosine kinase inhibitor that potently targets HER2 and mutant epidermal growth factor receptor. Preliminary evidence from the Phase I/II SOHO-01 trial has demonstrated anti-tumor activity and a manageable safety profile in previously treated patients with NSCLC with *HER2*-activating mutations (PL04.03 presented at IASLC 2024 World Conference on Lung Cancer). Here we introduce the SOHO-02 trial evaluating the efficacy and safety of BAY 2927088 as first-line therapy in patients with locally advanced or metastatic NSCLC with *HER2*-activating mutations. **Methods:** SOHO-02 is an ongoing Phase III, open-label, randomized, multicenter trial of BAY 2927088 in patients with locally advanced or metastatic NSCLC with *HER2*-activating mutations (NCT06452277). Eligibility criteria include patients aged ≥18 years with: documented histologically or cytologically confirmed, locally advanced or metastatic non-squamous NSCLC; documented activating mutation in the tyrosine kinase domain of HER2; measurable disease per RECIST v1.1; no previous systemic therapy for locally advanced or metastatic disease; and eligibility to receive treatment with the selected platinum-based doublet-chemotherapy and pembrolizumab. Overall, 278 eligible patients will be randomized to BAY 2927088 p.o. 20 mg twice daily or standard of care (SoC; pembrolizumab in combination with cisplatin/pemetrexed or carboplatin/pemetrexed) in 21-day cycles. The primary endpoint is BAY 2927088 efficacy vs. SoC on progression-free survival per RECIST v1.1 as assessed by blinded independent central review (BICR). Key secondary endpoints include BAY 2927088 efficacy vs. SoC on overall survival, overall response rate, disease control rate, and duration of response per RECIST v1.1 by BICR, and BAY 2927088 safety and tolerability vs. SoC. Impact of BAY 2927088 on patient health-related quality of life and symptom severity will be evaluated using EORTC QLQ-C30 and NSCLC-SAQ. Enrollment is ongoing. Clinical trial information: NCT06452277. Research Sponsor: Bayer AG.

TPS8649 **Poster Session**

Onkoras-101: A phase 1a/1b open-label study evaluating the safety, tolerability, pharmacokinetics, and efficacy of BBO-8520 in subjects with advanced KRAS^{G12C} mutant non-small-cell lung cancer. First Author: Benjamin J. Solomon, Peter MacCallum Cancer Centre, Melbourne, VIC, Australia

Background: BBO-8520 is a first-in-class, potent, selective, directly binding, orally bioavailable, covalent inhibitor of KRAS^{G12C}. It is effective against both the active GTP-bound (ON) state and the inactive GDP-bound (OFF) state of KRAS^{G12C}. BBO-8520 is being developed to treat patients with advanced cancer harboring the KRAS^{G12C} mutation. The oncogenic KRAS^{G12C} mutation results in an increased abundance of KRAS^{G12C} in the active GTP-bound (ON) state. While recent approvals of KRAS^{G12C}-targeted therapies provide a new treatment option for patients with KRAS^{G12C}-driven cancers, these agents exclusively target the GDP-bound (OFF) state of the protein, enabling the emergence of heterogeneous adaptive resistance. Thus, there is an urgent need for agents that can provide durable treatment benefit. **Methods:** This first-in-human, multicenter, open-label, Phase 1a/1b study evaluates the safety, tolerability, pharmacokinetics and preliminary antitumor activity of BBO-8520 as monotherapy and in combination with pembrolizumab in subjects with advanced non-small-cell lung cancer (NSCLC) with a KRAS^{G12C} mutation. BBO-8520 is administered orally once daily, in a 21-day treatment cycle. Patients enrolled in the trial must have histologically documented locally advanced or metastatic NSCLC with a KRAS^{G12C} mutation. Patients with treated or stable brain metastases are allowed to participate in the study. During Phase 1a dose escalation, BBO-8520 will be evaluated at escalating doses as monotherapy and in combination with pembrolizumab. The primary objective of Phase 1a is to evaluate the safety and tolerability of BBO-8520 monotherapy or in combination with pembrolizumab and determine the optimal dose(s) for Phase 1b dose expansion. Patients with KRAS^{G12C} -mutant NSCLC who have received prior treatment with KRAS^{G12C} (OFF) inhibitors are allowed to participate in Phase 1a. During Phase 1b dose expansion, BBO-8520 will be evaluated as monotherapy in expansion cohorts of: (1) patients with advanced NSCLC and prior treatment with KRAS^{G12C} (OFF) inhibitors; and (2) patients with advanced NSCLC and no prior treatment with KRAS^{G12C} inhibitors. BBO-8520 will also be evaluated in combination with pembrolizumab in an expansion cohort of patients with advanced NSCLC and no prior treatment with immune checkpoint or KRAS^{G12C} inhibitors. The primary objective of Phase 1b is to verify safety and tolerability of BBO-8520 monotherapy and in combination with pembrolizumab and evaluate antitumor activity (objective response rate evaluation). Clinical trial information: NCT06343402. Research Sponsor: BridgeBio Oncology Therapeutics.

TPS8650 **Poster Session**

Phase 1/2 clinical trial of JIN-A02, a 4th generation EGFR-TKI in EGFR-mutated advanced/metastatic non-small cell lung cancer. First Author: Sun Min Lim, Yonsei Cancer Center, Yonsei University College of Medicine, Seoul, South Korea

Background: Epidermal growth factor receptor (*EGFR*) mutations are the predominant drivers of NSCLC. While EGFR tyrosine kinase inhibitors (TKIs) are the primary treatment for *EGFR*-mutant NSCLC patients, resistance inevitably develops, leading to disease progression. JIN-A02, a novel 4th generation EGFR-TKI, intended for oral administration, selectively and reversibly binds to *EGFR* mutations, including the C797S and/or T790M mutation that causes resistance to 3rd generation of EGFR-TKIs. Preclinical studies with *EGFR* C797S and/or T790M mutated cell lines and C797S+ xenograft mice model showed that JIN-A02 inhibits cell and tumor growth in a dose dependent manner and exhibits high selectivity over wild-type *EGFR*. Moreover, JIN-A02 has been shown to penetrate the blood-brain barrier and exhibit anti-tumor activity in an intracranial tumor model. This phase 1/2 study is designed to evaluate the safety and anti-tumor activity of JIN-A02 in *EGFR*-mutant NSCLC patients. **Methods:** JIN-A02 is under evaluation in Phase 1/2, multicenter, an open-label trial (NCT05394831) for subjects with advanced NSCLC harboring C797S and/or T790M mutation as a monotherapy. The primary objective is to assess safety, tolerability, pharmacokinetics, and anti-tumor effect for determining the recommended phase 2 dose (RP2D) of JIN-A02. Inclusion criteria are that the subject (≥ 18 years) must have advanced or metastatic NSCLC showing progressive disease post-treatment with approved standard EGFR-TKIs and/or platinum-based anticancer chemotherapy, with ECOG status 0 or 1. The study consists of 3 parts: dose escalation (Part A), dose exploration (Part B), and dose expansion (Part C). In Part A, JIN-A02 is administered orally once daily from 12.5 mg, and at least 3 subjects are recruited per cohort conducted over 28 days cycles to evaluate the maximum tolerated dose. Dose escalation between cohorts is made at up to twice the prior dose level. Dose-limiting toxicities (DLTs) are assessed over 21 days. Part B aims to further evaluate JIN-A02 safety to determine the RP2D using two preliminary effective dose levels from Part A. In Part C, subjects are divided into 5 cohorts based on the EGFR mutation status (both or single positive for C797S and T790M), and the anti-tumor activity of JIN-A02 is evaluated according to RECIST v1.1 at the RP2D. Clinical trial information: NCT05394831. Research Sponsor: None.

TPS8651 **Poster Session**

Phase 3 trial of the therapeutic cancer vaccine OSE2101 versus docetaxel in patients with metastatic non-small cell lung cancer and secondary resistance to immunotherapy. First Author: Stephen V. Liu, Georgetown University, Washington, DC

Background: OSE2101 (TEDOPI) is a therapeutic cancer vaccine composed of multiple peptides restricted to HLA-A2 phenotype targeting tumor-associated antigens (CEA, HER-2, MAGE-2, MAGE-3, P53) frequently expressed in non-small cell lung cancer (NSCLC). In prior studies, OSE2101 strongly induced T cell immune responses, with higher immune responses associated with longer survival (OS). In the randomized ATALANTE-1 study, OSE2101 significantly improved OS with a better safety profile and quality of life (QoL) compared to third-line chemotherapy (CT) in patients with NSCLC with progressive disease (PD) after at least 12-weeks of second line anti-PD(L)1 monotherapy. The aim of the phase III ARTEMIA study is to confirm the benefit of OSE2101 versus CT in second-line treatment of patients with NSCLC and secondary resistance to immune checkpoint inhibitor (ICI) given in the first line setting. **Methods:** HLA-A2 positive patients with metastatic NSCLC without known EGFR, ALK, ROS1 actionable gene alterations, no brain metastases, ECOG PS 0 or 1, who had PD ≥ 24 weeks after first line CT-ICI including at least 12 weeks of maintenance ICI without cytotoxic therapy, will be randomized 2:1 to receive either OSE2101 or docetaxel. Randomization will be stratified by histology (squamous vs non-squamous), and ECOG PS (0 or 1). Patients will receive subcutaneous OSE2101 every 3 weeks for 6 injections, then every 8 to 12 weeks up to end of year 2. In the control group, patients will receive docetaxel at 75 mg/m2 per standard of care. Primary endpoint is OS defined as time from randomization to death of any cause. Secondary endpoints include QoL Physical, Role, and Global Health Score by EORTC QLQ-C30 questionnaire, and time to ECOG PS deterioration. Other endpoints are safety, tumor assessments by RECIST 1.1 and Net Treatment Benefit. For patients who agree, biomarkers in tumor biopsies and blood are planned. The primary estimand is OS in all randomized and treated patients using treatment policy approach for intercurrent events and the hazard ratio (HR) as population-level summary.Assuming a HR of 0.70 with a power of 80% using a 2-sided log-rank test, 363 patients will be enrolled to reach 269 events. An interim analysis is planned. The ARTEMIA phase 3 study aims to confirm the benefit on survival and quality of life of the therapeutic cancer vaccine OSE2101 compared to docetaxel in second-line treatment of HLA-A2 positive patients with NSCLC and secondary resistance to immune checkpoint inhibitor. Recruitment is ongoing in North America and Europe. Clinical trial information: NCT06472245. Research Sponsor: OSE Immunotherapeutics.

TPS8652 **Poster Session**

KEYMAKER-U01 substudy 01A: Phase 1/2 study of pembrolizumab plus ifinatamab deruxtecan (I-DXd) or patritumab deruxtecan (HER3-DXd) with or without chemotherapy in untreated stage IV non–small-cell lung cancer. First Author: Charu Aggarwal, Division of Hematology-Oncology, Department of Medicine, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA

Background: A standard-of-care option for metastatic non–small-cell lung cancer (NSCLC) with no targetable genetic alterations includes pembrolizumab plus chemotherapy. However, there remains an unmet need for patients who do not respond to standard treatment. Ifinatamab deruxtecan (I-DXd) and patritumab deruxtecan (HER3-DXd) are investigational antibody-drug conjugates (ADCs) against B7 homologue 3 and human epidermal growth factor receptor 3, respectively, two proteins that are highly expressed in NSCLC tumors. Both I-DXd and HER3-DXd are conjugated with a topoisomerase 1 inhibitor payload, resulting in apoptosis of target cells. Preclinical and preliminary clinical data suggest that combining an immune checkpoint inhibitor with an ADC may provide robust antitumor activity. KEYMAKER-U01 substudy 01A (NCT04165070) is a phase 1/2, two-part, rolling arm, open-label study assessing the efficacy and safety of pembrolizumab plus an investigational agent (part A: vibostolimab, boserolimab, MK-4830, and MK-0482; part B: I-DXd and HER3-DXd), with or without chemotherapy in untreated stage IV NSCLC. We present the study design for KEYMAKER-U01 substudy 01A part B. **Methods:** Eligible participants for KEYMAKER-U01 substudy 01A part B are aged ≥18 years with previously untreated histologically or cytologically confirmed stage IV (per American Joint Committee on Cancer v8) squamous or nonsquamous NSCLC and measurable disease per RECIST v1.1 as assessed by investigator and verified by blinded independent central review (BICR). Additional eligibility criteria include ECOG PS of 0 or 1, provision of an archival tumor sample or newly obtained biopsy of a nonirradiated tumor for biomarker analysis, and no *EGFR, ALK, or ROS1* mutations for which first-line targeted therapy is indicated. In part B, 10–30 participants will be allocated to treatment arms 5–7. In Arms 5 and 6, participants will receive I-DXd plus pembrolizumab 200 mg Q3W (Arm 5) or I-DXd plus pembrolizumab with 4 cycles of carboplatin area under the curve 5 or 6 mg/ml/min (Arm 6); I-DXd dose will be at 8mg/kg. In Arm 7, participants will receive HER3-DXd 3.2, 4.8, or 5.6 mg/kg plus pembrolizumab and carboplatin. Participants can receive I-DXd and HER3-DXd until disease progression or unacceptable toxicity and pembrolizumab up to 35 cycles. The primary endpoint is incidence of dose-limiting toxicities until the start of cycle 2, and AEs and treatment discontinuations due to AEs until 40 days after last treatment (90 days for serious AEs); secondary endpoints include ORR and DOR, both per RECIST v1.1 by BICR, and pharmacokinetic parameters, including maximum concentration (C_{max}) and maximum trough concentration (C_{trough}) of I-DXd and HER3-DXd. Enrollment will be ongoing globally. Clinical trial information: NCT04165070. Research Sponsor: Daiichi Sankyo Company, Limited and Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA.

TPS8653 **Poster Session**

ARTEMIDE-Lung03: A phase 3, randomized, double-blind, multicenter, global study of rilvegostomig or pembrolizumab in combination with platinum-based chemotherapy as first-line treatment for patients with metastatic non-squamous non-small-cell lung cancer whose tumors express PD-L1. First Author: Clarissa Mathias, Oncoclínicas&Co. and Hospital Santa Izabel, Salvador, Bahia, Brazil

Background: In the United States, non-squamous histology accounts for approximately 70% of all non-small-cell lung cancers (NSCLCs), and stage IV disease with no targetable alterations is associated with poor prognosis, with a median overall survival of around 2 years. Immunotherapy targeting programmed cell death (ligand)-1 (PD-1/PD-L1) with or without platinum-based chemotherapy (PBC) is a standard of care first-line (1L) chemotherapy for patients with advanced non-squamous NSCLC. Despite the efficacy of this approach, not all patients respond to PD-1/PD-L1 immunotherapy and more effective therapeutic strategies are needed. Inhibition of the co-inhibitory T cell immunoglobulin and immunoreceptor tyrosine-based inhibitory motif domain (TIGIT) pathway in combination with PD-1/PD-L1 blockade to increase immunotherapy efficacy is being investigated in NSCLC, as well as other cancer types. Preliminary results (Hiltermann TJN, et al. *J Thorac Oncol [WCLC]* 2024; abstract OA11.03) show that rilvegostomig, a monovalent, bispecific, humanized IgG1 monoclonal antibody targeting both PD-1 and TIGIT receptors, achieved encouraging antitumor response rates and durable responses with a manageable safety profile in NSCLC. The phase 3, randomized, double-blind, multicenter ARTEMIDE-Lung03 study (NCT06627647) will assess the efficacy and safety of rilvegostomig versus pembrolizumab, in combination with platinum-based doublet chemotherapy, as 1L treatment for participants (pts) with non-squamous metastatic NSCLC (mNSCLC). **Methods:** Approximately 878 pts will be randomized 1:1 to either Arm A: rilvegostomig + PBC (pemetrexed + cisplatin or carboplatin) intravenous (IV) every three weeks (Q3W) for 4 cycles followed by rilvegostomig + pemetrexed maintenance treatment IV Q3W, or Arm B: pembrolizumab + chemotherapy IV Q3W for 4 cycles followed by pembrolizumab + pemetrexed maintenance IV Q3W. Eligibility criteria include histologically or cytologically confirmed non-squamous mNSCLC not amenable to curative treatment, tumors expressing PD-L1 (TC ≥1%), an Eastern Cooperative Oncology Group performance status of 0 or 1, no sensitizing *EGFR* mutations, *ALK* or *ROS1* rearrangements, or mutations in other oncogenes with approved 1L therapies available. Dual primary endpoints are progression-free survival (Response Evaluation Criteria in Solid Tumors v1.1 by blinded independent central review) and overall survival. Safety/tolerability and biomarkers will also be assessed. The study will be conducted across approximately 350 sites in 25−30 countries. Clinical trial information: NCT06627647. Research Sponsor: AstraZeneca.

TPS8655 **Poster Session**

Phase 1b/2 study evaluating telisotuzumab adizutecan (ABBV-400; Temab-A) in combination with budigalimab in patients (pts) with advanced non-squamous (NSQ) non-small cell lung cancer (NSCLC) with no prior treatment for advanced disease and no actionable genomic alterations. First Author: David Ross Camidge, University of Colorado Cancer Center, Aurora, CO

Background: c-Met (MET) protein expression is frequently increased in NSCLC and is associated with poor prognosis. 24% of pts with NSQ *EGFR* wildtype (WT) NSCLC exhibit increased c-Met protein expression, ie, ≥25% 3+ via IHC. Addition of programmed cell death (ligand) 1 (PD-[L]1) inhibitors to chemotherapy (CT) has improved treatment of NSCLC regardless of PD-(L)1 expression. However, more-effective therapies are needed, particularly for pts with no known actionable genomic alterations. Temab-A is an antibody-drug conjugate comprising the c-Met protein–targeting antibody telisotuzumab and the potent topoisomerase 1 inhibitor adizutecan payload attached via a stable cleavable linker. In an ongoing phase 1 study (NCT05029882), Temab-A monotherapy demonstrated manageable safety and promising efficacy in pts with advanced/metastatic (a/m) NSQ *EGFR* WT NSCLC in second line and later, with an objective response rate (ORR) of 48% (23/48) across all c-Met expression levels and clinical benefit rate of 85% (41/48) (De Miguel et al. *Ann Oncol*. 2024;35:S805-S806). Herein, we describe a study evaluating Temab-A in combination with the PD-1 inhibitor budigalimab. **Methods:** This multicenter, global,open-label, phase 1b/2, randomized (in part 2) study (NCT06772623) will enroll ~172 pts (≥18 yr) with a/m NSQ NSCLC. Eligible pts have ECOG 0 or 1, measurable disease per RECIST v1.1, and documented *EGFR* WT and PD-L1 status. Primary objectives are to evaluate safety and tolerability, assess efficacy as measured by ORR by blinded independent central review, and select the recommended phase 3 dose of Temab-A combined with budigalimab. Secondary objectives include assessment of efficacy outcomes (PFS, DOR, OS, and disease control rate), characterization of PK and immunogenicity, and evaluation of PD and potential predictive biomarkers. The study has 2 parts: a safety dose-escalation part 1 and a dose-optimization part 2. Part 1 enrolls ~12 pts who have received ≤1 prior systemic therapy for a/m NSCLC, including platinum-based CT, an immune checkpoint inhibitor, or targeted therapy. Pts receive escalating doses of Temab-A IV Q3W guided by BOIN design in combination with a fixed dose of budigalimab IV Q3W. Dose-limiting toxicities are evaluated during cycle 1. Part 2 enrolls ~160 pts who have not received prior systemic therapy for a/m NSCLC. Pts are randomized 1:1:1:1 to Temab-A at 1 of 2 doses determined in part 1 + budigalimab, to budigalimab + CT, or to SOC (pembrolizumab + CT) arms. Randomization is stratified by PD-L1 expression and history of brain metastases. Treatment continues until disease progression, intolerable toxicity, or other discontinuation criteria are met. The first dosing of the first patient enrolled is planned in March 2025. Clinical trial information: NCT06772623. Research Sponsor: AbbVie Inc.; n/a

TPS8656 **Poster Session**

Krascendo 2: A phase III study of divarasib and pembrolizumab vs pembrolizumab and chemotherapy in patients with previously untreated, advanced or metastatic, *KRAS* G12C-mutated non-small cell lung cancer (NSCLC). First Author: Ferdinandos Skoulidis, The University of Texas MD Anderson Cancer Center, Houston, TX

Background: *KRAS G12C* mutations are found in ~12% of NSCLC cases. The recommended first-line treatment for patients (pts) with advanced or metastatic non-squamous *KRAS G12C*-mutated (*G12C*+) NSCLC is immunotherapy (most commonly pembrolizumab [pembro]) ± chemotherapy (chemo); however, there is an unmet need in this pt population for more efficacious therapies with tolerable and manageable safety profiles. Divarasib is a potent KRAS G12C inhibitor that has shown efficacy and safety as a monotherapy in pts with previously treated, advanced or metastatic *KRAS G12C*+ NSCLC. Previous reports suggest that combinations of KRAS G12C inhibitors and pembro have promising anti-tumor activities with manageable safety profiles. We hypothesize that divarasib plus pembro may be an effective and well tolerated first-line chemo-free treatment option in pts with advanced or metastatic *KRAS G12C*+ NSCLC. **Methods:** Krascendo 2 (CO45042; NCT06793215) is a randomized, open-label, multicenter, global, phase III study, evaluating the efficacy and safety of first-line treatment with divarasib and pembro vs pembro and chemo (pemetrexed + carboplatin/cisplatin), in pts with advanced or metastatic *KRAS G12C*+ NSCLC. Eligible pts (≥18 years old) must have an Eastern Cooperative Oncology Group performance status (ECOG PS) of 0–1, measurable disease per RECIST version 1.1, and histologically/cytologically confirmed advanced or metastatic, non-squamous NSCLC that is not eligible for curative surgery and/or definitive chemoradiotherapy and is previously untreated. Pts must also have known programmed death-ligand 1 (PD-L1) expression status and *KRAS G12C*+ status. Asymptomatic individuals with stable and treated central nervous system (CNS) metastases are eligible. Pts will be randomized 1:1 to receive either oral divarasib daily and intravenous (IV) pembro (in 21-day cycles), or IV pembro, pemetrexed and four cycles of platinum-based chemo (in 21-day cycles), until disease progression, or unacceptable toxicity. Pts will be stratified by PD-L1 expression status (tumor proportion score or tumor cell <1% vs 1–49% vs ≥50%), ECOG PS (0 vs 1), and history of CNS metastases (yes vs no). Pts who show clinical benefit per investigator judgment may continue study treatment after disease progression at the investigator's discretion. Primary endpoints are progression-free survival by blinded independent central review (BICR) and overall survival. Secondary endpoints include confirmed objective response rate and duration of response by BICR, changes in patient-reported symptoms and functioning from baseline to Cycle 5 assessed via questionnaires, and safety. Tumor assessments will occur at screening, every 6 weeks (±7 days) for the first 72 weeks after randomization, and then every 9 weeks (±7 days). Clinical trial information: NCT06793215. Research Sponsor: This study is sponsored by F. Hoffmann-La Roche Ltd. Third-party medical writing assistance, under the direction of the authors, was provided by Tahmina S. Alam, MA, of Ashfield MedComms, an Inizio company, and was funded by F. Hoffmann-La Roche Ltd.

TPS8657 **Poster Session**

FIRST-NEC (GFPC 01-2022): A multicenter phase II study evaluating the efficacy and safety of the combination of durvalumab with etoposide and platinum as first line treatment in patients with advanced large-cell neuroendocrine lung carcinomas (LCNECs). First Author: Dominique Arpin, Hôpitaux Nord Ouest VIllefranche sur Saone, Gleizé, France

Background: LCNECs of the lung are rare lung tumors (2%) with difficult histopathological diagnosis (70-80% confirmation rate after centralized review). Platinum–based regimen is currently the recommended first-line treatment for advanced LCNECs. However it results in poor median progression-free survival (PFS) and overall survival (OS) of 5 months and 7.7 months, respectively. Retrospective studies have suggested efficacy of immune checkpoint inhibitors against LCNECs with significantly prolonged OS. In addition, the CASPIAN trial demonstrated the superiority of durvalumab plus platinum-etoposide over chemotherapy alone in patients with extensive-stage neuroendocrine small cell lung cancer, with an acceptable toxicity profile. **Methods:** This ongoing single-arm phase II trial is designed to evaluate the efficacy and safety of durvalumab in combination with platinum-etoposide as first line treatment in pts with locally diagnosed advanced LCNEC. Key selection criteria are age $\geq$ 18 years, ECOG PS 0-1, measurable disease (RECIST 1.1) and locally advanced (Stage III) ineligible for loco-regional therapy or metastatic (Stage IV). Central confirmation of the histopathological diagnosis will be performed for all pts at the start of treatment. All pts will receive 4 cycles of induction with durvalumab 1500mg, platinum (either carboplatin AUC5 or cisplatin 80mg/m² at D1) and etoposide 100mg/m² (D1-D3), repeated every 3 weeks. Durvalumab 1500mg will be continued alone every 4 weeks for a maximum of 24 additional cycles or until disease progression or unacceptable toxicity. The primary endpoint is to determine, in pts with confirmed diagnosis, 12-month progression-free rate (12M-PFR) as per central radiological review. Secondary endpoints include PFS, OS and safety. Radiological criteria will be described using the RECIST 1.1 both as per investigator's assessment and as per central radiological review. Biomarkers will be studied as predictive and prognostic factors of efficacy. Efficacy will be assessed sequentially every ten pts using a Bayesian approach. Analogous to a frequentist approach from an A'Hern-Fleming single-stage design, 51 evaluable pts will be enrolled. A futility stopping rule will stop the trial if there is a high probability ($>$80%) that the 12M-PFR is less than or equal to P0 (15%). Finally, a trial emulation will be performed as an exploratory analysis to assess PFS and OS compared to an external control arm by using real-world data from the ESME database. Since the start of recruitment (June 2024), 13 patients with a confirmed diagnosis have been included. Clinical trial information: NCT06393816. Research Sponsor: French ministry of health / French National Cancer Institute (INCa); PHRC-K23-033; Astrazeneca; Not applicable (drug supply).

TPS8658 **Poster Session**

TeliMET NSCLC-04: A phase 2, open-label, randomized, global study of 2 telisotuzumab vedotin regimens in patients with previously treated c-Met protein–overexpressing, locally advanced/metastatic non-squamous *EGFR* wildtype non-small cell lung cancer. First Author: Alona Zer, Rambam Health Care Campus, Haifa, Israel

Background: c-Met protein (also known as MET protein) overexpression is observed in ~25% of patients with non-squamous *EGFR* wildtype (WT) non-small cell lung cancer (NSCLC) and is associated with poor prognosis. Telisotuzumab vedotin (Teliso-V) is a c-Met–directed antibody-drug conjugate consisting of the monoclonal antibody telisotuzumab and the cytotoxic payload monomethyl auristatin E. The primary analysis of the phase 2 LUMINOSTY trial (NCT03539536) demonstrated that Teliso-V at 1.9 mg/kg once every 2 weeks (Q2W) was associated with durable responses in patients with previously treated c-Met protein–overexpressing (OE) advanced/metastatic (a/m) non-squamous *EGFR* WT NSCLC, and adverse events (AEs) were generally manageable. The overall response rate was 28.6% among all patients with c-Met protein overexpression and 34.6% among those with c-Met high protein overexpression (Camidge et al. *JCO* 2024; 42:3000-11). **Methods:** This global, multicenter, open-label, randomized phase 2 study (NCT06568939) evaluates the safety and efficacy of Teliso-V monotherapy at 1.6 mg/kg Q2W and 1.9 mg/kg Q2W in patients with previously treated c-Met protein OE, a/m non-squamous *EGFR* WT NSCLC. Eligible patients are $\geq$18 years old with c-Met protein OE ($\geq$25% tumor cells at 3+ intensity by immunohistochemistry assay [investigational use only assay for MET (SP44) (Roche)]), a/m non-squamous *EGFR* WT NSCLC. Patients must have measurable disease according to RECIST v1.1, ECOG PS 0–1, and documented disease progression on $\geq$1 prior lines of therapy ($\leq$1 line of prior chemotherapy) in the a/m setting. Approximately 100 patients will be randomized 1:1 to receive Teliso-V monotherapy at either 1.6 mg/kg or 1.9 mg/kg Q2W until disease progression or other protocol-specified discontinuation criteria are met. The primary safety endpoints are treatment-emergent AEs (TEAEs; any grade and grade $\geq$2), interstitial lung disease (any grade and grade $\geq$2), peripheral neuropathy (any grade and grade $\geq$2), ocular surface disorders (any grade and grade $\geq$2), TEAEs leading to discontinuation, and grade 5 TEAEs. The primary efficacy endpoint is objective response based on RECIST v1.1 by blinded independent central review (BICR). Secondary endpoints are pharmacokinetics, patient-reported outcomes, duration of response by BICR, progression-free survival by BICR, and overall survival. Clinical trial information: NCT06568939. Research Sponsor: AbbVie, Inc.; n/a.

TPS8659 **Poster Session**

Phase 2, multicenter study of frontline maintenance therapy with lifileucel plus pembrolizumab in advanced non-small cell lung cancer. First Author: Ben C. Creelan, Moffitt Cancer Center and Research Institute, Tampa, FL

Background: Tumor-infiltrating lymphocyte (TIL) therapy with lifileucel plus pembrolizumab (pembro) demonstrated durable and deepening responses with an objective response rate (ORR) of 64.3% in patients (pts) with anti–PD-1/PD-L1–naive, *EGFR* wild-type, locally advanced or metastatic non-small cell lung cancer (mNSCLC) in cohort 3A of the IOV-COM-202 phase 2 open-label study (NCT03645928), with 4 of 5 ongoing responses lasting $>$20 months from start of therapy and no new safety signals. We added two new cohorts within this basket study, 3D and 3E, which evaluate if adding lifileucel to pembro $\pm$ pemetrexed in the maintenance phase of standard-of-care (SOC) therapy (from tumors procured in treatment-naive pts [3D] versus those who had already started receiving SOC chemotherapy [3E]) is feasible and provides added benefit with an acceptable safety profile. Incorporating TIL with current SOC has the potential to address a major unmet need by improving outcomes that are not durable or adequate for many pts with NSCLC. **Methods:** Pts have tumor resection before cycle 1 (3D) or between cycles 1 and 4 (3E) of frontline platinum-doublet chemotherapy plus pembro. After completion of SOC chemotherapy, a dose of pembrolizumab will be given followed by nonmyeloablative lymphodepletion (NMA-LD) (day $-$5 to day $-$3: cyclophosphamide 20 mg/kg/day; day $-$5 to day $-$2: fludarabine 25 mg/m2/day). Lifileucel is administered on day 0, followed by IL-2 continuous infusion on days 1–4. Following lifileucel and IL-2, pembro (plus pemetrexed if nonsquamous histology) will be continued for up to 2 years or until disease progression or unacceptable toxicity. Eligible adults have histologically confirmed mNSCLC, no actionable mutations with effective targeted therapy, no prior systemic therapy for metastatic NSCLC, ECOG performance status 0–1, estimated life expectancy $\geq$6 mo, and $\geq$1 resectable lesion $>$1.5 cm in diameter to generate lifileucel. Prior organ allograft or cell transfer therapy, symptomatic brain metastases, current systemic steroid therapy $>$10 mg/day of prednisone or other steroid equivalent, and active illnesses or autoimmune disorders are not permitted. Endpoints include ORR, complete response rate, disease control rate, and PFS by investigator-assessed RECIST v.1.1, OS, percentage of manufactured lifileucel drug products that meets release specification, and incidence of grade $\geq$3 treatment-emergent adverse events. Selected exploratory endpoints include in vivo T-cell persistence, correlative biomarkers, and circulating tumor DNA. Enrollment of approximately 20 pts per cohort will take place in Europe and North America. Clinical trial information: NCT03645928. Research Sponsor: Iovance Biotherapeutics, Inc.

TPS8660 **Poster Session**

NAPISTAR 1-01: An international phase I/II trial of the novel ADC TUB-040 in platinum-resistant ovarian cancer (PROC) and relapsed/refractory adenocarcinoma non-small cell lung cancer (NSCLC). First Author: Toon Van Gorp, University Hospitals Leuven, Leuven Cancer Institute, Leuven, Belgium

Background: NaPi2b, encoded by SLC34A2, is a sodium-dependent phosphate transporter overexpressed in various cancers, particularly high levels in high-grade ovarian cancer (HGSOC) and non-small cell lung cancer (NSCLC) adenocarcinomas. This tumor-selective expression pattern makes NaPi2b a compelling target for therapeutic development. TUB-040 is an innovative antibody-drug conjugate (ADC) combining a NaPi2b-specific Fc-silenced monoclonal antibody with the cytotoxic payload exatecan, a potent topoisomerase-I inhibitor exhibiting a robust bystander effect. This ADC utilizes a cleavable dipeptide linker (P5) to achieve a uniform drug-to-antibody ratio of 8, optimizing its potency against heterogeneous tumors. **Methods:** NAPISTAR 1-01 (NCT06303505) is an open-label, multicenter, Phase I/IIa study investigating TUB-040 in platinum-resistant ovarian cancer (PROC) and advanced NSCLC adenocarcinoma . Phase I employs a stepwise dose escalation strategy using adaptive titration design (ATD), followed by a Bayesian Optimal Interval (BOIN) model. The dose escalation framework includes initial double-dosing steps, transitioning to modified Fibonacci increments with intra-patient escalation permissible at low exposure levels. An independent Dose Escalation Board manages safety oversight. Phase IIa involves randomized dose optimization at multiple dosing levels to identify the optimal therapeutic window. Enrollment of approximately 100 patients across the US, EU and UK is planned, with dose escalation currently underway. Clinical trial information: NCT06303505. Research Sponsor: None.

TPS8661 **Poster Session**

A multicenter, open-label, single-arm phase I/II study to assess the efficacy and safety of WSD0922-FU in patients with EGFR C797Sm+ advanced non-small cell lung cancer (NSCLC) in China (NCT06631989). First Author: Wei Zhong, Wayshine Biopharm Inc., Corona, CA

Background: Although 3rd-generation EGFR TKIs, such as Osimertinib, Almonertinib, Furmonertinib, Befotertinib etc. are highly effective in front-line metastatic *EGFR*-mutated (*EGFR*m) NSCLC, treatment resistance ultimately occurs, including the emergence of the on-target C797S mutation for which there are no approved TKIs. WSD0922-FU is an oral, central nervous system (CNS)-penetrant, wildtype-sparing, ATP non-competitive, reversible EGFR inhibitor targeting EGFR aberrations in NSCLC and High-Grade Astrocytoma. It has shown promising preclinical and clinical data, including antitumor CNS activity that may improve patient outcomes. Additionally, combining WSD0922-FU with standard therapies may provide enhanced disease control across multiple lines of treatment, including against heterogenous tumors, in patients with *EGFR*m+ NSCLC. WSD0922-102 (NCT06631989) is an ongoing phase 1/2, open-label, multicenter trial evaluating the efficacy and safety of WSD0922-FU in patients with EGFR C797Sm+ NSCLC in China. **Methods:** Adult patients with EGFR C797Sm+ NSCLC were initially treated with oral WSD0922-FU, with three doses selected from phase I dose escalation (MC1914, NCT04197934) as a bridging PK study in China. After DLT evaluation, expansion was initiated for each dose followed by extension for the dose selected as the recommended phase 2 dose (RP2D). Key inclusion criteria include patients $\geq$18 years of age with metastatic *EGFR* C797Sm+ NSCLC; Eastern Cooperative Oncology Group performance status 0–1; and failed in the previous 3rd generation EGFR-targeted TKI treatment for bridging PK study, with only one 3rd generation EGFR TKI for expansion and with only one first-line 3rd generation EGFR TKI for extension. All patients must harbor an EGFR C797S resistance mutation (locally assessed for tissue/liquid samples). Key exclusion criteria are tumors harboring EGFR T790M mutations, EGFR exon 20 insertions, or MET aberrations. Dose escalation primary endpoints are maximum tolerated dose, RP2D and safety. The expansion and extension primary endpoints are overall response rate (ORR) by RECIST 1.1. Secondary endpoints include ORR (dose escalation), duration of response, disease control rate, progression-free survival, overall survival, antitumor CNS activity (iORR) by RANO-BM, and safety (dose expansion and extension). The phase 1 dose escalation adopts a 3+3 design. Patients will be enrolled into 3 treatment cohorts: dose escalation (n≈12-15), dose expansion (n≈20), and dose extension (n≈70). Patients may receive treatment until disease progression, unacceptable toxicity, or other discontinuation criteria are met. Enrollment in this study for dose expansion cohorts is ongoing and 15 sites are open across China. Clinical trial information: NCT06631989. Research Sponsor: None.

TPS8662 **Poster Session**

Phase 2 cohort-2 trial in progress: Vabametkib plus lazertinib for patients with EGFR-mutant NSCLC who developed resistance to 1st-line, 3rd-gen-EGFR TKIs via C-Met dysregulation. First Author: Dae Ho Lee, Asan Medical Center, Seoul, South Korea

Background: Third-generation Epidermal Growth Factor Receptor Tyrosine Kinase Inhibitors (EGFR TKIs) have emerged as a promising first-line treatment for Non-Small-Cell Lung Cancer (NSCLC) patients with EGFR T790M mutations, as well as EGFR exon 19 deletions and exon 21 L858R mutations. Recently, lazertinib, combined with amivantamab, has been approved as a potential first-line therapy for NSCLC. Despite these advancements, there remains a significant unmet medical need for patients who develop resistance to first-line third-generation EGFR TKIs. ABN401 (vabametkib), a selective oral c-MET inhibitor, has shown anti-tumor activity in preclinical studies, both as monotherapy and in combination with other treatments. Currently in a phase 2 clinical trial, this study aims to evaluate the combination of vabametkib and lazertinib in patients who have developed resistance to 3rd generation EGFR TKIs. **Methods:** ABN401-003 phase 2 cohort-2 is a multicenter, open-label trial that evaluates the dose escalation, safety and efficacy of the combination therapy of vabametkib and lazertinib in patients resistant to first-line EGFR TKIs. Enrollment criteria include MET amplification (GCN $>$10 by NGS or FISH) or c-MET overexpression (IHC score $\geq$90). The study consists of three parts: Part 1 (safety run-in), a traditional 3+3 dose-escalation study assesses the safety of vabametkib combined with lazertinib. Up to 18 patients will be evaluated in safety run-in, with dose adjustments based on dose-limiting toxicities (DLTs). Part 2: Randomized Dose Optimization – Two combination dose levels, determined from Part 1, will be tested in 40 patients to identify the optimal dose. Part-2 may be skipped if the maximum tolerated dose (MTD) is established in Part 1. Part 3 [randomized clinical trial – The optimal dose combination will be compared to the standard of care (SOC) in 80 patients. Key secondary endpoints include objective response rate (ORR), disease control rate (DCR), progression free survival (PFS) and duration of response (DOR). Additionally, safety and patient-reported outcome will be evaluated. Clinical trial information: NCT05541822. Research Sponsor: None.

TPS8663 **Poster Session**

A phase 1/2 open-label, multicenter, first-in-human study of the safety, tolerability, pharmacokinetics, and antitumor activity of BH-30643 in adult subjects with locally advanced or metastatic NSCLC harboring EGFR and/or HER2 mutations (SOLARA). First Author: Xiuning Le, Department of Thoracic Head and Neck Medical Oncology, The University of Texas MD Anderson Cancer Center, Houston, TX

Background: Clinical outcomes for patients with metastatic *EGFR*-mutant NSCLC have steadily improved with successive generations of EGFR tyrosine kinase inhibitors (TKIs). However, there remains significant need for further advancement in progression-free survival (PFS) and overall survival (OS), as these outcomes still fall short when compared to the remarkable benefits observed with newer TKIs in *ALK* and *ROS1* driven NSCLC. BH-30643 is a first-in-class EGFR TKI with a novel macrocyclic structure offering potent, reversible, mutant selective inhibition of classical and atypical *EGFR* activating mutations without vulnerability to common on-target resistance mutations. Cellular activity of BH-30643 was recently described (AACR 2025) demonstrating sub-nanomolar potency for EGFR exon 19del and L858R classical mutations which are maintained in the presence of T790M +/- C797S. High potency was also observed against atypical *EGFR* mutations (e.g., G719X, L861Q, S768I) and exon 20 insertions, as well as mutant *HER2*. Such an OMNI-EGFR inhibitor may have the potential to overcome some of the limitations of earlier agents. **Methods:** SOLARA (NCT06706076, BH-30643-01) is a Phase 1/2, multicenter, open-label, dose escalation, first-in-human study to determine the safety, tolerability, pharmacokinetics, and antitumor activity of BH-30643, in adult subjects with locally advanced or metastatic NSCLC harboring *EGFR* and/or *HER2* mutations. Enrollment based on local molecular testing and/or liquid biopsy is permitted. Asymptomatic brain metastases (treated or untreated) are eligible. BH-30643 is administered orally twice daily until disease progression or intolerable toxicity. The study consists of an initial dose escalation part using a Bayesian optimal interval design to identify Recommended Dose(s) for Evaluation (RDE). Dose-limiting toxicities (DLTs) are evaluated for the first 21 days of treatment. A subsequent expansion part will further evaluate the RDE(s) to identify a Recommended Phase 2 Dose (RP2D), studying cohorts with or without prior systemic therapy across a range of *EGFR*/*HER2* driver mutations. Efficacy will be evaluated by RECIST 1.1 criteria and toxicity by CTCAE V5.0. Plasma is collected for circulating tumor DNA (ctDNA) analysis at baseline and on treatment. Enrollment is underway, with planned enrollment across ~35 sites in multiple continents. Clinical trial information: NCT06706076. Research Sponsor: BlossomHill Therapeutics, Inc.

TPS8664 **Poster Session**

A randomized phase 3 study of ivonescimab plus chemotherapy versus pembrolizumab plus chemotherapy for the first-line treatment of metastatic non–small cell lung cancer: HARMONi-3. First Author: Jianjun Zhang, Department of Thoracic/Head and Neck Medical Oncology, The University of Texas MD Anderson Cancer Center, Houston, TX

Background: The additionof antiangiogenic agents to standard first-line treatment with a programmed cell death protein 1 (PD-1) inhibitor and platinum doublet chemotherapy has shown efficacy in patients with metastatic non–small cell lung cancer (NSCLC). Ivonescimab is a novel tetravalent bispecific antibody that targets PD-1 and vascular endothelial growth factor. In a phase 2 trial, ivonescimab plus chemotherapy showed objective response rates (ORRs) of 71.4% and 54.2% and median progression-free survival (PFS) of 11.1 and 13.3 months in patients with metastatic squamous (SQ) and nonsquamous (NSQ) NSCLC, respectively (1). **Methods:** The multiregional, randomized, double-blind, phase 3 HARMONi-3 trial (NCT05899608) will compare the efficacy and tolerability of ivonescimab plus chemotherapy with pembrolizumab plus chemotherapy as first-line treatment in patients with metastatic SQ or NSQ NSCLC who have not previously received systemic treatment for metastatic disease and whose tumors have no known actionable mutations for which approved first-line therapies are available. Patients will be randomly assigned (1:1) to receive ivonescimab 20 mg/kg every 3 weeks (Q3W) or pembrolizumab 200 mg Q3W combined with chemotherapy (paclitaxel or nab-paclitaxel plus carboplatin for SQ or pemetrexed plus carboplatin for NSQ) for up to 4 cycles, followed by maintenance with ivonescimab or pembrolizumab alone for SQ or in combination with pemetrexed for NSQ for up to 24 months. Randomization will be done in blocks by histology (SQ and NSQ) and stratified by sex (female vs male), age ($<$65 vs $\geq$65 y), geographic region (East Asia vs rest of world), presence or absence of liver or brain metastases at baseline, previous PD-1 or programmed death ligand 1 (PD-L1) inhibitor treatment $>$6 months before the development of metastatic disease (yes vs no), and PD-L1 tumor proportion score ($\geq$1% or $<$1%). The dual primary end points are overall survival and PFS (assessed by investigators per RECIST v1.1). The secondary end points are ORR, disease control rate, duration of response, safety, pharmacokinetics, and immunogenicity. Patients are being recruited in Asia, Europe, and North America, with a target enrollment of 1080 patients (45-50% SQ and 50-55% NSQ). 1. Zhang L et al, ELCC 2024, FPN: 68P. Clinical trial information: NCT05899608. Research Sponsor: Summit Therapeutics, Inc.

TPS8665 **Poster Session**

NVL-330, a selective HER2 tyrosine kinase inhibitor, in patients with advanced or metastatic HER2-altered non-small cell lung cancer: The phase 1 HEROEX-1 study. First Author: Xiuning Le, The University of Texas MD Anderson Cancer Center, Houston, TX

Background: Oncogenic mutations and gene amplifications in the HER2 receptor tyrosine kinase are detected in approximately 2-4% and 1-5% of non-small cell lung cancers (NSCLC) in the US, respectively. Exon 20 insertion mutations (exon20ins) are the predominant *HER2* mutations in NSCLC, and ~50% of patients with *HER2*-mutant metastatic NSCLC develop brain metastases. The antibody drug conjugate (ADC) trastuzumab deruxtecan (T-DXd) has received FDA accelerated approval for *HER2*-mutant NSCLC, but no tyrosine kinase inhibitors (TKIs) are currently approved for this indication. NVL-330 is a novel, brain-penetrant, HER2-selective investigational TKI, designed to address the medical need of targeting *HER2*-mutant tumors, and treating brain metastases, while minimizing treatment related adverse events due to off-target inhibition of wild-type EGFR. **Methods:** HEROEX-1 (NCT06521554) is a first-in-human, Phase 1a/1b trial. The Phase 1a dose escalation portion employs a Bayesian optimal interval design with a 3+3 run-in, followed by a Phase 1b dose expansion. The study population includes adult patients with advanced or metastatic NSCLC with a *HER2* oncogenic mutation (Phase 1a/1b) or amplification (Phase 1a only) determined by local testing. Eligible patients must have received at least one prior systemic therapy including platinum-based chemotherapy with or without immunotherapy, or are unsuitable candidates for available therapies. Prior HER2-directed antibodies and HER2-directed ADCs are allowed. Prior HER2 TKIs are allowed in Phase 1a only. Patients will receive NVL-330 by oral administration once or twice daily. The primary objectives are to evaluate safety and tolerability, determine the recommended Phase 2 dose, and, if applicable, the maximum tolerated dose of NVL-330. Additional objectives include assessment of preliminary activity and characterization of the pharmacokinetic and pharmacodynamic profiles of NVL-330. Analyses will be performed to evaluate tumor and blood-based biomarkers of response and other relevant biomarkers. The study is open to accrual. Clinical trial information: NCT06521554. Research Sponsor: Nuvalent.

TPS8666 **Poster Session**

Neladalkib (NVL-655), a highly selective anaplastic lymphoma kinase (ALK) inhibitor, compared to alectinib in first-line treatment of patients with ALK-positive advanced non-small cell lung cancer: The phase 3 ALKAZAR study. First Author: Sanjay Popat, The Royal Marsden NHS Foundation Trust, London, United Kingdom

Background: Oncogenic *ALK* gene fusions are detected in ~5% of advanced non-small cell lung cancer (NSCLC) cases. Among these patients, the incidence of brain metastases at diagnosis is ~40%. Prior generations of ALK tyrosine kinase inhibitors (TKIs) present limitations that may influence efficacy and tolerability, such as inadequate control of brain metastases, treatment-emergent drug-resistant *ALK* mutations, or off-target adverse events, particularly neurological events associated with inhibition of the structurally related TRK kinases. Neladalkib is a potent, brain-penetrant, ALK-selective TKI with preclinical activity against diverse *ALK* fusions and resistance mutations (Lin et al., Cancer Discovery 2024). In the Phase 1/2 ALKOVE-1 study, neladalkib showed encouraging preliminary efficacy in patients with heavily pretreated *ALK+* NSCLC, including in those with *ALK* single or compound resistance mutations and brain metastases (Drilon et al., ESMO 2024). It also exhibited a favorable safety profile consistent with its ALK-selective, TRK-sparing design. The Phase 3 ALKAZAR study aims to demonstrate the superiority of neladalkib over a current standard of care, alectinib, in TKI-naïve patients with advanced *ALK+* NSCLC. **Methods:** ALKAZAR (NCT06765109) is a global, Phase 3, randomized, controlled, open-label study in adult patients with locally advanced or metastatic NSCLC harboring an *ALK* rearrangement per local testing of tissue or blood. Prior systemic anticancer treatment for metastatic disease is not allowed. Patients who received prior alectinib in the adjuvant setting are not eligible. Patients are required to have measurable disease by RECIST. Patients with untreated central nervous system (CNS) disease without progressive neurological symptoms or increasing corticosteroid doses are eligible. Patients with non-ALK oncogenic driver alterations are excluded. Approximately 450 patients will be randomized in a 1:1 ratio to receive either oral neladalkib (150 mg once daily) or oral alectinib (600 mg twice daily), stratified by brain metastases, ethnic origin (Asian vs. non-Asian), and Eastern Cooperative Oncology Group (ECOG) performance status (PS) score (0 vs.1 vs. 2). The primary endpoint is progression-free survival by blinded independent central review. Secondary endpoints include intracranial activity, objective response rate, duration of response, overall survival, safety and tolerability, and patient-reported outcomes. Additional analyses will be conducted to investigate candidate biomarkers and molecular mechanisms of response and resistance to neladalkib and alectinib. The study is open to accrual. Clinical trial information: NCT06765109. Research Sponsor: Nuvalent.

TPS8667 **Poster Session**

A phase 2 safety and efficacy study of PRT3789 in combination with pembrolizumab in patients with advanced or metastatic solid tumors and a *SMARCA4* mutation. First Author: Timothy A. Yap, The University of Texas MD Anderson Cancer Center, Houston, TX

Background: Genes encoding subunits of the switch/sucrose non-fermentable (SWI/SNF) chromatin remodeling complex are often mutated in cancer (~20% of all human cancers). The SWI/SNF complex contains either SMARCA2 or SMARCA4 enzymatic subunits for ATP-dependent chromatin remodeling. Since SMARCA2 and SMARCA4 function as mutually exclusive catalytic subunits of the SWI/SNF complex, cells exhibiting SMARCA4 loss rely on its paralog, SMARCA2, making SMARCA2 an attractive therapeutic target. In NSCLC, *SMARCA4* mutations are associated with aggressive and invasive disease. PRT3789 has been shown to increase antigen processing and presentation of unique MHC class I peptides, and increase T-cell activity and IFN-γ production in *SMARCA4*-mutated cancer cells. SMARCA2 degradation by PRT3789 promoted the effects of anti-PD1 therapy in SMARCA4-deficient mouse models, and PRT3789 combined with pembrolizumab (pembro), a humanized immunoglobulin G4 monoclonal antibody, promoted cell death of SMARCA4-deficient NSCLC cells. While inhibitors targeting the PD-1/PD-L1 axis have shown remarkable clinical activity across a broad range of tumor types, some patients demonstrate an inadequate response and disease progression consistent with the natural disease course that may be tied to innate resistance mechanisms. Other patients progressed after a period of disease control, which may be associated with acquired resistance mechanisms. PRT3789 + pembro may re-sensitize resistant cancers to subsequent anti–PD(L)-1 therapy. **Methods:** This is an open-label, 2-part, multicenter study to evaluate the safety, tolerability, efficacy, pharmacokinetics (PK), and pharmacodynamics (PD) of PRT3789 + pembro in patients who are resistant to prior anti–PD(L)-1 therapy. Adults with any advanced, recurrent, or metastatic solid tumor and any *SMARCA4* mutation are eligible to enroll into part 1, a safety run-in to establish the initial safety of PRT3789 376 mg intravenous (IV) once weekly + pembro 200 mg IV every 3 weeks. Part 2 will target adults with advanced, recurrent, metastatic NSCLC or upper gastrointestinal cancer with a *SMARCA4* loss-of-function mutation. Other key eligibility criteria include documented prior or acquired resistance to anti–PD(L)-1 therapy, or received prior standard-of-care therapy, but naive to anti–PD(L)-1 therapy due to PD-L1 negative expression. A safety review committee will evaluate dose-limiting toxicities (DLTs) in part 1 and advise on opening part 2 and regularly review accumulated safety data during the study. The primary endpoints are safety, tolerability, and incidence of DLTs in part 1, and overall response rate and duration of response in part 2. Secondary endpoints include progression-free survival, clinical benefit rate, PK, and PD of PRT3789. This study is actively recruiting. Clinical trial information: NCT06682806. Research Sponsor: Prelude Therapeutics Incorporated.

TPS8668 **Poster Session**

TACTI-004: A double-blinded, randomized phase 3 trial in patients with advanced/metastatic non-small cell lung cancer receiving eftilagimod alfa (MHC class II agonist) in combination with pembrolizumab (P) and chemotherapy (C) versus placebo + P + C. First Author: Giuseppe Lo Russo, Thoracic Oncology Unit, Medical Oncology Department, Fondazione IRCCS Istituto Nazionale Tumori, Milan, Italy

Background: Eftilagimod alfa (E), an antigen presenting cell activator, binds to a subset of MHC class II molecules to mediate T cell (CD4/CD8) recruitment/activation.Prior studies in first line (1L) non-small cell lung cancer (NSCLC) (TACTI-002 [NCT03625323]: combining E + pembrolizumab (P); INSIGHT-003 [NCT03252938] combining E with chemotherapy + P [SoC]) showed encouraging efficacy results across all PD-L1 strata & excellent safety profiles. TACTI-004 is a double-blinded, randomized, placebo-controlled phase 3 study testing E + SoC vs. placebo + SoC in 1L NSCLC patients (pts). **Methods:** Approximately 756 pts with 1L NSCLC will be enrolled, irrespective of PD-L1 status, & randomized 1:1 to receive either E + SoC or placebo + SoC. The dual primary endpoint (EP) is overall survival & progression-free survival (RECIST 1.1). Secondary EPs include ORR, disease control rate, duration of response, quality of life, safety & biomarkers. Pts will receive 30 mg E SC q2w for 24 weeks, then q3w and P IV at 200 mg (30 min) q3w; both treatments for up to 2 yrs. Chemotherapy choice will be histology-dependent: non-squamous NSCLC pts will receive IV cisplatin (75 mg/m^2) or carboplatin (AUC 5 or 6) + pemetrexed (500 mg/m^2) q3w for 3 mo, then maintenance pemetrexed q3w. Squamous NSCLC pts will receive carboplatin (AUC 5 or 6) + paclitaxel (175 or 200 mg/m^2) q3w for 3 mo. Imaging will be performed q6w until week 18, q9w until week 54 & q12w thereafter. Testing for PD-L1 (22C3) & genetic alterations will be prospectively assessed. Key inclusion criteria: Adults diagnosed with measurable advanced/metastatic (A/M) NSCLC (squamous or non-squamous), not amenable to curative treatment nor locally available oncogenic driver mutation-based 1L therapy. Treatment-naïve for systemic therapy (previous palliative radiotherapy for A/M disease acceptable). Expected survival $>$3 months & ECOG 0 or 1. Tumour tissue must be available for PD-L1 central testing. Pts may not have tumours with EGFR mutations nor ALK or ROS1 translocations. Stable brain metastasis is acceptable. Clinical trial information: NCT06726265. Research Sponsor: None.

TPS8669 **Poster Session**

A biomarker-directed, multi-center phase II/III study of ctDNA molecular response adaptive immuno-chemotherapy in patients with non-small cell lung cancer (BR.36). First Author: Valsamo Anagnostou, Sidney Kimmel Comprehensive Cancer Center, Johns Hopkins School of Medicine, Baltimore, MD

Background: Minimally invasive analyses of circulating cell-free tumor DNA (ctDNA) have shown clinical value as an early endpoint of immunotherapy response, allowing patients with primary resistance to be rapidly and accurately identified. In the first of two independent stages, the BR.36 trial demonstrated a sensitivity of ctDNA response for radiographic RECIST response of 82% and a specificity of 75%, with a median time to ctDNA response of 2.1 months. **Methods:** BR.36 is a multi-center, open-label, biomarker-directed, phase II/III clinical trial of ctDNA molecular response adaptive immuno-chemotherapy in patients with treatment-naïve metastatic NSCLC. The main objective is to evaluate if adding chemotherapy to pembrolizumab for patients who have persistent ctDNA on liquid biopsy after 6 weeks of pembrolizumab, will result in better PFS and OS compared to patients who remain on pembrolizumab until radiographic clinical progression. Key eligibility criteria include: age ≥18 years, ECOG performance status 0-2, metastatic NSCLC, EGFR and ALK mutation negative and PD-L1 Tumor Proportion Score (TPS) ≥ 50%, at least and not more than 2 cycles of the 200 mg or 2 mg/kg IV Q3W dose/schedule of pembrolizumab as first line systemic immunotherapy at the time of screening and RECIST non-PD or clinically stable PD documented prior to enrolment that can continue on immunotherapy if randomized to that arm. The phase II primary endpoint is PFS and has secondary endpoints of feasibility, overall response rate and safety/tolerability. Sex, RECIST response and ECOG status represent stratification criteria. With 110 randomized patients evaluable for progression (55 patients per arm and 71 PFS events observed in this phase of the clinical trial), we would be able to detect a hazard ratio difference of 0.67 with a 1-sided alpha of 0.2 and power of 0.80 using a phase II screening design. The trial will not stop accrual for the phase II analysis of PFS if feasibility endpoints are achieved. In the phase III portion, a total of 210 randomized patients recruited over 3 years and followed for an additional 24 months are required to detect an OS hazard ratio difference of 0.67 with 1-sided alpha of 0.05 and power of 0.8. The total number of events for the final analysis is expected to be 156, and assuming 10% of patients are lost to follow-up, we are targeting 230 patients to be included overall. The primary endpoint of the phase III portion is overall survival, with secondary endpoints of best overall response, response duration, progression-free survival and safety/tolerability. Exploratory endpoints include longitudinal ctDNA analyses by targeted next-generation sequencing and whole genome sequencing approaches. The BR.36 clinical trial is open to enrollment and to date 2 patients have been registered (ClinicalTrials.gov ID: NCT04093167). Clinical trial information: NCT04093167. Research Sponsor: Cancer Research Institute; The Mark Foundation for Cancer Research; LabCorp.

TPS8670 **Poster Session**

A global phase 2/3, randomized, open-label trial of BNT327/PM8002 in combination with chemotherapy (chemo) in first-line (1L) non-small cell lung cancer (NSCLC). First Author: Solange Peters, Centre Hospitalier Universitaire Vaudois Lausanne (CHUV), Lausanne, Switzerland

Background: The introduction of immune checkpoint inhibition for the treatment of 1L NSCLC has improved survival, however long-term outcomes remain suboptimal, highlighting the need for more efficacious treatments. BNT327 is an investigational bispecific antibody, targeting both PD-L1 and VEGF-A in the tumor and tumor microenvironment (TME). By binding to PD-L1 on tumor cells it is designed to restore effector T-cell function and by binding to VEGF-A within the TME it also reverses the negative impact of VEGF signaling on immune cell infiltration and activation. In addition, via VEGF-A neutralization, it normalizes tumor vasculature. This dual targeting of PD-L1 and VEGF-A aims to deliver better efficacy and safety. Data published on BNT327 has indicated a tolerable safety profile and encouraging anti-tumor activity in patients (pts) with NSCLC (ASCO 2023, ASCO and ESMO 2024). This global Phase 2/3 trial will further assess safety and efficacy of BNT327 plus chemo (Phase 2) and BNT327 plus chemo versus pembrolizumab plus chemo (Phase 3) in pts with advanced NSCLC. **Methods:** This Phase 2/3, multisite, randomized, open-label trial will enroll ~982 pts with stage IIIB/C and stage IV non-squamous cell (NSQ) NSCLC (Substudy A) and squamous (SQ) NSCLC (Substudy B) without actionable EGFR mutations or ALK rearrangements. Each substudy consists of a Phase 2 and a Phase 3 part. During the Phase 2 part, pts will be randomized 1:1 to receive BNT327 at either 1400 mg (Arm 1) or 2000 mg (Arm 2) plus chemo (carboplatin + pemetrexed for Substudy A, carboplatin + paclitaxel for Substudy B) Q3W IV for four cycles, followed by Q3W IV maintenance BNT327 at previously administered doses (with maintenance pemetrexed for Substudy A). In the Phase 3 part, pts will be randomized 1:1 to receive BNT327 at the selected dose (based on the Phase 2 part) plus chemo (carboplatin + pemetrexed for Substudy A, carboplatin + paclitaxel for Substudy B) or pembrolizumab 200 mg plus chemo Q3W IV, followed by Q3W IV maintenance BNT327 or pembrolizumab (both with maintenance pemetrexed for Substudy A). Chemo will be administered at approved doses. Primary endpoints include occurrence of adverse events (AE) and serious AEs, rates of dose interruption, reduction and discontinuation due to treatment-emergent (TE) AEs, objective response rate (ORR) and best percentage change from baseline in tumor size (Phase 2), and both progression free survival (PFS) per blinded independent central review and overall survival (OS) (Phase 3). Secondary endpoints include duration of response, disease control rate (Phase 2), PFS per investigator, ORR, landmark PFS and OS, patient reported outcomes and occurrence of AEs, and rates of dose interruption, reduction and discontinuation due to TEAEs (Phase 3); with efficacy endpoints per RECIST 1.1; safety per CTCAE v5.0. The trial is enrolling. Clinical trial information: NCT06712316. Research Sponsor: BioNTech SE.

9000 Clinical Science Symposium

Implementation of a fellow-led tumor board to enhance learning and support in fellow continuity clinic. First Author: Neha Hippalgaonkar, University of Illinois Chicago, Chicago, IL

Background: Hematology/oncology fellows in our program manage diverse and complex cases in continuity clinic (CC), including uncommon malignancies and challenging clinical scenarios, providing a rich educational opportunity. To further enhance case-based learning and in response to fellows' feedback from an internal program survey, we implemented a Fellow Tumor Board (FTB) to provide clinic-specific additional guidance and structured learning. **Methods:** The FTB was integrated into an existing biweekly didactic virtual didactic to minimize added burden and encourage participation. Investment in learning was fostered by focusing on fellows' own cases. Chief fellows reviewed recent CC consults, selecting cases involving new malignancies, rare conditions, or complex management scenarios, and invited guest faculty experts for targeted feedback. Each 30-minute FTB, moderated by chief fellows, included multiple 5-minute case discussions: fellows presented cases, posed clinical questions, and received expert and peer input. Chief fellows summarized key recommendations and clinical pearls while senior fellows provided insights and mentorship. This collaborative format enabled fellows to learn from their own and peers' cases. An anonymous electronic survey was distributed six months after FTB implementation to assess its impact. Fellows rated their experiences on a Likert scale (1 = strongly disagree to 4 = strongly agree). **Results:** Survey responses (12) showed positive reception. Fellows reported feeling more supported in managing CC patients (3.6 $\pm$ 0.4), empowered to seek guidance (3.6 $\pm$ 0.4), found expert input valuable (3.7 $\pm$ 0.4), that FTB fostered a collaborative environment (3.5 $\pm$ 0.5) and that case-based learning was effective (3.4 $\pm$ 0.4). However, 4/12 fellows disagreed that they learned from their co-fellows' cases. All respondents agreed that the FTB should continue as part of the didactic curriculum. Additional informal feedback highlighted improved confidence, ability to present cases in tumor boards, and mentorship while faculty praised the active learning environment. In-training exam scores to assess knowledge retention and program survey responses to evaluate supervision quality at year-end will be tracked to further evaluate FTB's impact and will be available at time of presentation. **Conclusions:** FTB is a feasible and adaptable innovation that addresses gaps in CC education. By promoting case-based learning, collaboration, and mentorship, it enhances fellows' support, knowledge, confidence and preparedness for oncology practice. To optimize its effectiveness, strategies to encourage fellows to engage and learn from their peers' cases – not just their own – should be explored. Research Sponsor: None.

9001 Clinical Science Symposium

Integration of a podcast curriculum (PC) to improve hematology oncology fellow (HOF) knowledge: A multi-center cluster randomized control trial. First Author: Vivek Patel, Vanderbilt University Medical Center, Nashville, TN

Background: Medical podcasts are widely used as learning resources, yet their integration into fellowship curricula remains unstudied. We present the final analysis of a multicenter cluster randomized trial comparing a supplemental PC with the standard curriculum (SC) to SC alone for HOFs. **Methods:** Twenty-seven U.S. HOF programs were randomized to receive a novel PC with SC (podcast arm) or SC alone (control arm). The PC arm accessed a website with links to podcast episodes (PEs) and show notes covering breast cancer (BC), myeloma (MM), bleeding disorders (BD), and heparin induced thrombocytopenia (HIT). PEs were developed by *The Fellow on Call* and *Two Onc Docs* podcasts. Show notes were developed by *The Fellow on Call*. Pre- and post-intervention qualitative surveys (QS) and knowledge assessments (KA) were administered via REDCap. HOFs rated their comfort managing topics using a 7-point Likert scale. The KA was a 16-question multiple-choice test. ANCOVA analysis was used to compared post-intervention results. This study was powered for dual primary endpoints of mean QS improvement by 0.5 and KA improvement by 10% as previously published. **Results:** Pre-intervention QS and KA were completed by 220 (52%) and 187 (45%) HOFs, respectively. Post-intervention, 53/107 (49%) HOFs in the podcast arm and 46/113 (40%) in the control arm completed assessments. PGY distribution was similar between podcast and control arms: PGY 4 25% and 37%, PGY 5 32% and 30%, and PGY 6+ 43% and 33% (p=0.38). At baseline, 37 (69%) podcast-arm and 24 (52%) control-arm HOFs listened to medical podcasts. Detailed didactic characteristics for each institution and HOF learning preferences were previously presented. Baseline mean comfort levels ($\pm$SD) were comparable in podcast vs. control: BC (4.4$\pm$1.5 vs. 4.5$\pm$1.4), MM (4.5$\pm$1.2 vs. 4.4$\pm$1.4), BD (3.9$\pm$1.2 vs. 3.7$\pm$1.2), and HIT (5.5$\pm$1 vs. 5.5$\pm$1). Post-intervention paired mean comfort level difference ($\pm$SD) significantly improved in the podcast vs. control across topics ($p<0.01$): BC (1.4$\pm$0.4 vs. 0.9$\pm$0.2), MM (1.5$\pm$0.4 vs. 0.9$\pm$0.3), BD (1.6$\pm$0.3 vs. 1$\pm$0.2), and HIT (1.2$\pm$0.6 vs. 0.8$\pm$0.4). Composite mean KA improved from 39.7%$\pm$18.9 to 62%$\pm$19.2 in the podcast arm vs. 43.5%$\pm$19.2 to 50.3%$\pm$19.8 in the control arm. The podcast arm had significantly greater improvement with an adjusted mean difference of 15.5% ($p<0.01$). In the podcast arm, 44 (83%) utilized >50% of show notes and found them helpful, and 47 (89%) planned to continue using these podcasts. Results were not impacted after adjusting for baseline podcast use. **Conclusions:** To our knowledge, this is the largest cluster randomized trial of a pragmatic educational intervention in graduate medical education. The study met its dual primary endpoints, demonstrating that the podcasts significantly improved fellow comfort and knowledge in representative topics. Despite limitations of dropout and respondent bias, findings support integrating these podcasts as a recommended resource in hematology oncology education. Research Sponsor: None.

9002 Clinical Science Symposium

Perception and concerns of the hematology and oncology (HemOnc) workforce about artificial intelligence (AI) in clinical practice (CliPr) and medical education (MedED). First Author: Guilherme Sacchi de Camargo Correia, Mayo Clinic, Jacksonville, FL

Background: The field of AI is rapidly evolving. With recent development of more user-friendly AI software, its integration into healthcare across different medical specialties, including HemOnc has emerged. Data detailing the perception and concerns of the HemOnc workforce about AI's roles is lacking and is needed if AI is to be integrated in HemOnc CliPr and MedEd. **Methods:** Questionnaires about the perception and concerns regarding AI in CliPr and MedEd were created on REDCap and approved by IRB. We surveyed the entire HemOnc workforce at the 3 Mayo Clinic major sites between 11/07/24 and 01/20/25, including physicians, both faculty (FAC) and fellows (FEL), advanced practice providers (APP), and nurses (RN). Participation was voluntary. Simple statistical analyses were employed for the results. **Results:** 344 participants (PTP) responded to the survey, 118 physicians (41 FEL and 77 FAC), 49 APP, and 177 RN. 64% of PTP report having used AI but only 31% used it in HemOnc MedEd, and 28% in HemOnc CliPr, with 67% considering themselves to have little to no knowledge about AI. 94% of PTP believe AI will be integrated in HemOnc MedEd, with such integration being seen as beneficial by 90%. Among physicians, 85% of FEL and 92% of FAC report that fellowship programs should incorporate AI training into curricula. 95% of PTP believe AI will be incorporated into HemOnc CliPr. Meanwhile, 62% of PTP (50.8% of physicians, and 68% of APP and RN) are concerned about risks it may pose to CliPr. Nevertheless, 90% of PTP would embrace AI's use in HemOnc. Table 1 details the perceptions and concerns about AI in HemOnc MedEd and CliPr. The main perceived risks are decreased time spent with patients (pts), and inaccuracies or worse pt care. Meanwhile, 33% believe AI would increase efficiency and quality of care, while 30% believe it would increase time spent with pts. 14% of PTP worry their role could be replaced by AI. **Conclusions:** To the best of our knowledge, this is the largest assessment of HemOnc workforce's perception and concerns about AI. Based on our survey, the HemOnc workforce, in general, endorses AI use, but with some concerns raised. While incorporation in MedEd is perceived with excitement, many envision the use in CliPr involves risks and challenges. Proper systematic education of the workforce about AI, with well-designed CliPr integration methods are needed to mitigate the legitimate existing concerns. Research Sponsor: None.

Perceptions & concerns about AI in HemOnc MedEd & CliPr.

	FEL %	APP %	RN %	FAC %
AI will assist documentation in CliPr	98	82	79	92
AI will be used in pt communication	73	80	78	87
AI will screen pts for clinical trial enrollment	85	86	76	96
AI will increase the efficiency and quality of CliPr	43	37	24	46
AI will increase time spent with pts	39	27	25	38
AI will decrease time spent with pts	29	41	48	23
AI will lead to inaccuracies or worse CliPr	12	20	25	20
AI may replace the HemOnc workforce	11	16	19	5

9003 Rapid Oral Abstract Session

Research productivity of international medical graduate (IMG) hematology and oncology fellows in the United States (US). First Author: Arya Mariam Roy, The Ohio State University, Columbus, OH

Background: IMGs constitute one-third of practicing oncologists in the US. However, there is limited data on their academic contributions. We analyzed the research productivity of IMG hematology-oncology fellows in US fellowship programs. **Methods:** Hematology-oncology fellows enrolled in an ACGME accredited training program as of June 2024, were identified from publicly available institutional fellowship program websites. Baseline characteristics (presumed gender, institution, additional graduate degrees [AD]) and academic profiles were abstracted. Research productivity data, including number of PubMed-listed manuscripts, original articles, review articles, first-author and senior-author manuscripts, google scholar (GS)-listed abstracts/articles, high-impact (impact factor $\geq$ 10) articles, citations, H-index, I-10 index were obtained from PubMed and GS. Fellows were categorized as IMGs or AMGs, based on whether they completed medical school outside or within the US, respectively. Chi-squared and Wilcoxon rank-sum/T-tests were used for categorical and numeric variables, respectively. Linear regression identified factors associated with higher research productivity. **Results:** Out of the total 1,858 fellows included, 42.3% were female, and 11% held ADs (e.g. master's, PhD). Among all fellows, 30.5% were identified as IMGs. AMGs were more likely than IMGs to hold ADs (12% vs. 8.3%, p=0.019) and PhDs (8.9% vs. 3.4%, $p<0.001$). However, IMG fellows exhibited significantly higher research productivity, including more manuscripts (mean, 95% CI: 14.9 [12.6, 17.3] vs. 9.5 [8.6, 10.4]), abstracts (14.9 [9.2, 20.6] vs. 7.3 [3.5, 10.9]), review articles (4.9 [3.9, 6.0] vs. 2.4 [2.2, 2.7]), first-author manuscripts (4.3 [3.6, 5.0] vs. 2.7 [2.5, 2.8]), compared to AMGs (all $p<0.001$), Table 1. IMGs had an estimated 5.7 more manuscripts on average than AMGs after adjusting for gender and ADs ($p<0.001$); this difference varied by gender (8.7 higher in males, $p<0.001$, and 2.0 higher in females, p=0.2). **Conclusions:** IMG hematology-oncology fellows exhibit higher research productivity than their AMG counterparts, despite having fewer additional degrees. Our results highlight the substantial contributions of IMG fellows, underscore their critical role in academic medicine, and emphasize the importance of addressing potential structural barriers to practice at academic medical centers upon graduation. Research Sponsor: EMORY STAT CORE, NIH21.

Research profile of IMG/AMG hematology-oncology fellows.

Research productivity (median, IQR)	IMG (N= 566)	AMG (N= 1292)	p-value
PubMed manuscripts	7.5 (3, 16)	6 (2, 11)	<0.001
GS articles	14 (6, 33)	9 (3, 18)	<0.001
Abstracts	3 (1, 13)	2 (0, 6)	<0.001
Original articles	4 (1, 11)	3 (1, 8)	<0.001
Review articles	2 (0, 5)	1 (0, 3)	<0.001
First-author manuscripts	2 (0, 5)	2 (0, 4)	<0.001
Citations	116 (28, 310)	80 (12, 346)	0.07
H-index	5 (2, 8)	4 (0, 8)	0.003
I-10 index	3 (1, 9)	2 (0, 12)	0.28

9004 Rapid Oral Abstract Session

International medical graduates (IMGs) in leadership roles within academic oncology in the United States (US). First Author: Shipra Gandhi, Roswell Park Comprehensive Cancer Center, Buffalo, NY

Background: Although IMGs comprise one-third of US oncologists, their leadership presence at academic centers with affiliated oncology fellowship training programs has not been studied. **Methods:** Using Electronic Residency Application Services website for training programs, and publicly available information on corresponding institutional websites, data were collected on leadership (cancer center director, division chair, fellowship program director (PD), subspecialty chiefs) and clinical faculty (August to December 2024). Leadership level data included whether the institution is NCI-designated, its geographic region, presumed gender, additional graduate degree (AD: Master's, PhD), H-index and citations. Leaders and faculty were categorized into American Medical Graduate (AMG) and IMG, who completed medical school within and outside the US, respectively. Logistic regression was used to assess factors associated with leadership. **Results:** Leaders (n=1057) and faculty (n=4338) from 186 oncology fellowship programs (medical, radiation, surgical oncology) were included. Among 146 cancer center directors, 26% were IMGs. IMGs represented 30% of division chairs and 32% of fellowship PDs in medical oncology; however, their representation in surgical and radiation oncology leadership and faculty was more modest (Table). There was no difference in AD (30.8% vs 30.2%), H index (44.3 $\pm$ 39 vs 45.9 $\pm$ 34.5) or citations (13,133 $\pm$ 26,228 vs 14,151 $\pm$ 23,529) between IMG and AMG leaders, respectively. IMG leadership varied regionally (Midwest 30%, Northeast 26%, South 23%, Southwest 31%, West 16%, p=0.03) and was underrepresented in NCI-centers (21.3% vs 33.3%, $p<0.05$) vs other centers. There was no difference in male AMG leaders (48.9% vs 47.1%, p=0.77), however, the proportion of female AMG leaders was higher in NCI- vs other centers (28.8% vs 19.7%, $p<0.01$). Female IMGs had lowest leadership representation (7.3% at NCI-centers, 9.2% at other centers), similar to their limited faculty presence (9.2%). Female IMGs were less likely to be leaders compared to male IMGs (odds ratio [OR] 0.66 [95% CI 0.49-0.89], $p<0.01$) and male AMGs (OR 0.71 [0.55-0.93], $p<0.05$). **Conclusions:** Despite similar academic productivity, IMGs are under-represented in leadership in NCI-cancer centers, and in the West with female IMGs having lowest representation. Our results highlight the need to address these regional, gender and institutional disparities to foster a more inclusive workforce. Research Sponsor: EMORY Stat Core, NIH21.

Leadership and faculty positions by IMG and AMG.

		Medical Oncology (n=183)		Radiation oncology (n=88)		Surgical oncology (n=39)	
		AMG	IMG	AMG	IMG	AMG	IMG
Division chair	N (%)	94 (70%)	41 (30%)	70 (90%)	8 (10%)	28 (82%)	6 (18%)
Subspecialty chiefs	N (%)	255 (71%)	106 (29%)	66 (76%)	21 (24%)	65 (82%)	14 (18%)
Fellowship PD	N (%)	116 (68%)	54 (32%)	69 (90%)	8 (10%)	24 (77%)	7 (23%)
Faculty	N (%)	1849 (69%)	848 (31%)	922 (90%)	107 (10%)	449 (86%)	75 (14%)

9005 Rapid Oral Abstract Session

Burnout, professional fulfillment, and associated factors in academic oncology physicians. First Author: Jennifer A. Ligibel, Dana-Farber Cancer Institute, Boston, MA

Background: Occupational burnout has negative consequences on the health of individual physicians (MDs), patients, and health care systems. We assessed the prevalence of burnout and professional fulfillment (PF) in academic hematologists/medical oncologists (HO), general internists (GIM), and other internal medicine subspecialties (IMS) and evaluated factors associated with burnout and PF across specialty groups. **Methods:** Academic medical institutions participating in the Healthcare Professional Well-being Academic Consortium (PWAC) administered surveys including validated measures of burnout and PF, as well as variables influencing these domains. MDs with a subspecialty of HO, GIM, or IMS were included. Descriptive statistics were used to summarize characteristics of the cohort. Logistic regression was used to assess relationships between respondent characteristics (subspecialty, gender, age) and burnout/PF. **Results:** Fifteen academic medical centers administered surveys between 10/2019 and 7/2021.Of 19,532 (50.7% response rate) respondents, 579 were HO, 1912 GIM, and 1922 IMS. No significant difference in the proportion of respondents who met criteria for burnout was observed across groups (41.7% HO, 38.0% IMS, 40.4% GIM, p=0.11). HO MDs were more likely to have high professional fulfillment (44.5% HO, 38.8% IMS, 35.8% GIM, p-value <0.001). Determinants of burnout and PF varied across groups (Table) with HO MDs reporting less favorable scores for impact of work on personal relationships ($p<0.001$), self-valuation ($p<0.001$), and electronic health record (EHR) helpfulness (<0.001), but more favorable scores for meaning in work (p=0.02), control over schedule ($p<0.001$), and perceived gratitude for their work ($p<0.001$). Factors most closely associated with risk of burnout in HO MDs included negative impact of work on personal relationships (Cohen's D 1.10), self-valuation (Cohen's D 0.98), and control over schedule (Cohen's D 0.90). **Conclusions:** In a large, multi-center study, HO MDs had similar rates of burnout but higher PF than other IM specialties. These results highlight the challenges and rewards of working in oncology and identify priority domains to improve oncologists' work environments. Research Sponsor: None.

Mean scores for determinants of burnout and PF across IM specialties.

Assessment Scale	HO n=579	IMS n=1922	GIM n=1912	Kruskal-Wallis P value
Negative Impact of Work on Personal Relationships*	3.86	3.64	3.40	<0.001‡
Self-Valuation**	4.61	5.13	5.14	<0.001‡
EHR Helpfulness**	5.22	5.56	5.82	<0.001‡
Perceived Gratitude**	7.22	6.65	6.63	<0.001‡
Control over Schedule**	4.38	3.98	4.18	<0.001‡
Meaning in Work**	8.03	7.55	7.50	0.02 ‡
Sleep-Related Impairment*	3.20	3.03	2.95	0.04
Peer Support**	6.42	6.19	6.38	0.04

‡ Statistically significant after adjustment for multiple comparisons.
*Range 0-10, higher scores = unfavorable.
**Range 0-10, higher scores = favorable.

9006 Rapid Oral Abstract Session

Who's on the podium? Geographic and career diversity of ASCO Annual Meeting presenters. First Author: Aysche Stern, Temecula Valley Hospital, Temecula, CA

Background: The ASCO annual meeting is the world's preeminent meeting of oncology professionals. Giving an oral presentation at the ASCO annual meeting is a landmark in a career. We examined the training and geographic diversity of presenters. **Methods:** We identified all oral abstract or moderator presentations from the ASCO Annual Meeting 2021-2024 using asco.org. Further information on each speaker was gathered from publicly available information through internet searches of institutional websites and professional social media. We queried degree, pronoun use, medical school, institutions of post-graduate training and years of graduation. Institutions were classified by geographic region (country, state, and U.S. Census Geographic Area), type (academic versus community) and NCI-designation. Presentations per population (PPP) of 10^6 persons were standardized by state and region level 2020 US Census data. Study was IRB exempt at investigators respective institutions. **Results:** Between 2021-2024, there were 1563 oral presentations in abstract sessions from 1310 speakers representing 491 institutions. 253 (19%) presented more than once (range: 1-5). 57% use the 'he' pronoun. Most presenters were from US institutes (66.7%; n=1043), 6.3% (n=99) from China, 4.0% (n=63) from France, and 3.2% (n=50) from the UK. 69.7% (n=1090) were from North America, 17.6% (n=275) from Europe/UK, 10.2% (n=16) from Asia, and 2% (n=31) from Australia. Few presentations were given by speakers from institutions in the Middle East (0.1%, n=2) or South America (all Brazil; 0.3%, n=4), and no presentations were given by speakers from African institutions. 22% (n=347) of presentations were from the top 5 presenting institutions, all of which were in the US and 3 of 5 on East coast. 87.1% (n=768) of presentations from US institutions were from NCI-designated centers. 21 of 33 (64%) US based plenary presenters were from New England or Mid Atlantic states, while 25% (n=11/44) were from non-US institutions. PPP were highest in northeast 6.0/10^6 compared to Midwest (2.9/10^6), South (2.6/10^6), and West (2.2/10^6). Highest PPP states were MA (15.5/10^6), DC (11.6/10^6), and CT (8.6/10^6) while 13 states had no presenters. Presenters were a median of 13.0 (SD: 9.2) years post training (YPT). By ASCO definitions, 6.8% (n=63) were students/trainees, 6.1% (n=57) were early career (<3 YPT), 53.8% (4-15 YPT) were mid-career, and 35.1% (n=326) were later career (>15 YPT). Trainee and early career speakers gave 0 plenary presentations, 9.6% (n=91) of oral abstract presentations, and 22.1% (n=40) of rapid oral abstracts ($p=<0.001$). **Conclusions:** Oral presenters were most frequently mid to late career, medical oncologists and from Northeastern, US, academic, NCI-designated centers while few speakers were from community sites or early career/trainees suggesting there is room for continued diversification to represent all oncologists and those they treat. Research Sponsor: None.

9007 Rapid Oral Abstract Session

Board certification and billing practices of international medical graduate hematologists and oncologists. First Author: Austin Wesevich, University of Chicago, Chicago, IL

Background: International medical graduates (IMGs) comprise a substantial portion of the oncology workforce in the United States (US). IMGs may help address oncology workforce shortages with an aging US population, but IMGs face considerable barriers to becoming practicing oncologists in the US. We analyzed the credentialing and billing practices of IMG hematologists and oncologists (HO) to better describe the IMG workforce. **Methods:** We linked publicly available data from the Centers for Medicare & Medicaid Services (CMS) and the American Board of Internal Medicine to describe credentialing and billing practices of all HO who billed Medicare Part B in 2022 and whose medical school was specified in CMS data. Physicians were dichotomized as IMGs versus graduates of a US, Canadian, or Puerto Rican medical school (USMGs). We defined academic as working in a teaching hospital and research as having non-federal research funds. **Results:** Of 12,019 HO identified, 48% were IMGs. Even though they had a similar median number of years since medical school graduation, IMGs more frequently obtained initial hematology and medical oncology board certification (72% vs 58%, $p<0.001$) and maintained certification (79% vs 75%, $p<0.001$) than USMGs (Table). On average, IMGs billed Medicare more and had more outpatient visits and inpatient days with Medicare beneficiaries than USMGs. Most (55%) Medicare inpatient days were billed by IMGs. While USMGs were more frequently academic researchers than IMGs (35% vs 31%, $p<0.001$), IMGs were more frequently community clinicians than USMGs (13% vs 11%, $p<0.001$); there was no difference in IMG versus USMG representation for academic clinicians or community researchers. **Conclusions:** IMGs make up almost half of the US oncology workforce. Compared to USMGs, IMGs are more frequently double-boarded and maintaining board certification. Plus, they have more clinical productivity and higher representation in community-based oncology care than USMGs. Additional efforts should be instituted at a national level to eliminate training barriers and mitigate the biases faced by IMGs so that we can meet the growing demand for oncology care in the US. Research Sponsor: None.

Hematologist & oncologist credentialing and billing by medical school location.

Characteristic	USMG, n=6,288	IMG, n=5,731	p-value
Female gender	2,267 (36%)	2,005 (35%)	0.22
Median years since medical school graduation (IQR)	24 (16-36)	25 (17-34)	0.19
Oncology Single-Boarded	2,415 (38%)	1,485 (26%)	<0.001
Hematology Single-Boarded	241 (4%)	148 (3%)	<0.001
Hem/Onc Double-Boarded	3,632 (58%)	4,098 (72%)	<0.001
Maintenance of Certification	4,704 (75%)	4,537 (79%)	<0.001
Median Medicare Payments in 2022 (IQR)	$78,938 ($35,507-$234,627)	$88,401 ($41,329-$240,705)	<0.001
Median Medicare Outpatient Visits in 2022 (IQR)	480 (216.5-902)	506 (237-925)	0.004
Median Medicare Inpatient Patient-Days in 2022 (IQR)	45 (0-138)	62 (0-171)	<0.001

9008 Rapid Oral Abstract Session

Recognizing international medical graduates: Awards and committee membership in ASCO. First Author: Karun Neupane, H. Lee Moffitt Cancer Center and Research Institute, University of South Florida, Tampa, FL

Background: International Medical Graduates (IMGs) comprise one third of practicing oncologists and half of hematology-oncology fellows in the US. This study explores the previously unexamined distribution of ASCO awards, Fellow of ASCO (FASCO) designation and ASCO committee memberships between IMGs and American Medical Graduates (AMGs). **Methods:** Between 2019-2023, we gathered data from the ASCO website on ASCO awards including career development awards (CDA), young investigator awards (YIA), MERIT and Other awards, and FASCO distinctions. Between 2021-2023 we gathered information on ASCO committee memberships. We searched for medical school and degree of each individual to classify them as IMGs, AMGs, International physicians or non-physicians. We used the world bank geographical distribution comparing IMGs' country of origin. Chi-square, Fisher's Exact, and Cochran-Armitage Trend tests were performed as appropriate using SAS v. 9.4. **Results:** Out of a total of 2,514 entries, 2,342 physicians were included for analyses (1583 ASCO awards, and 759 FASCO designation/committee memberships) and 172 non-physician entries were excluded. Among 1583 physicians with ASCO awards, 22% were IMGs (133 Female (F), 209 Male (M)), 58% were AMGs (410F, 508M) and 20% were international physicians (150F, 173M). Among 759 physicians with FASCO designation/committee membership, 18% were IMGs (61F, 77M), 71% were AMGs (293F, 245M) and 11% were international physicians (41F, 42M). IMGs were significantly underrepresented compared to AMGs ($p<0.001$) in receiving YIA (18% vs 82%), CDA (21% vs 79%), MERIT (35% vs 65%) and Other awards (15% vs 85%). The ratio of CDA-YIA to Merit/Other awards were 0.36 and 0.83 for IMGs and AMGs, respectively ($p<0.001$). This underrepresented trend of IMGs for ASCO awards remained unchanged between 2019-2023 (p=0.6).Compared to the major career awards (YIA and CDA) through these years, FASCO designation for IMGs has an increasing trend (p=0.03). The proportion of FASCO granted to IMGs increased from 9% in 2019 to 25% in 2023. Female IMGs were the least represented group for the awards (25%, p=0.07) and FASCO/committee membership (17%, p=0.03) when compared to AMGs. Majority of these IMGs were from South Asia (30%) and Europe/Central Asia (24%) while Sub-Saharan Africa had the lowest representation (3%) based on world bank classification. **Conclusions:** IMGs' receipt of major career awards (CDA, YIA) remains significantly underrepresented while their contributions to ASCO volunteering activities is on the increasing trend as evidenced by increase in FASCO designee IMGs. Barriers for major career awards for IMGs remain to be explored. Research Sponsor: EMORY Stat Core, NIH21.

Year wise trend of IMGs with ASCO CDA/YIA awards and FASCO designation.

Year	CDA+YIA n (%)	FASCO n (%)	P-value
2019	11 (84.6)	2 (15.4)	0.03
2020	17 (81)	4 (19)	
2021	21 (77.8)	6 (22.2)	
2022	22 (68.8)	10 (31.2)	
2023	21 (60)	14 (40)	
Total	92	36	

9009 Rapid Oral Abstract Session

Career transitions and practice patterns among international medical graduates in oncology workforce: A US nationwide analysis. First Author: Jiazhang Xing, Sinai Hospital of Baltimore, Baltimore, MD

Background: International Medical Graduates (IMGs) are a vital component of the US oncology workforce, representing nearly half of practicing medical oncologists. However, systemic barriers may influence their career trajectories differently. Understanding these challenges is essential for addressing workforce disparities and optimizing cancer care delivery across diverse geographic regions. **Methods:** We conducted a cross-sectional study of 13,497 medical oncologists using the 2024 Dec CMS Provider Dataset linked with the 2023 Rural-Urban Continuum Codes (RUCC). Medical oncologists were identified by their self-reported primary specialties, including Hematology/Oncology, Medical Oncology, and Hematopoietic Cell Transplant. Physicians were categorized by graduation origin (based on their self-reported medical school), career stage (early: 0–10 years, mid: 11–30 years, late: >30 years post-medical school graduation). The primary outcomes included practice at Main Campus of NCI Designated Cancer Centers (as an indicator of academic practice) and the geographical location of their practice (Metro, Non-Metro, Mixed). We employed chi-squared tests for statistical comparisons and performed stratified analyses by career stage to evaluate transition patterns over time. **Results:** 6920 IMGs constituted 48.7% of the oncology workforce, with similar gender distributions between IMG and non-IMG oncologists (37.9% vs 36.5% female, p=0.068). Notably, early career oncologists were less likely to be IMGs (IMG vs non-IMGs: 8.2% vs 12.5%, $p<0.001$). Compared to Non-IMGs, IMG oncologists are less likely to practice at main campuses of NCI Center (19.9% vs. 27.7%, $p<0.001$), especially as their career advances (all $p<0.01$). (Table). IMGs had higher representation in non-metropolitan areas than non-IMGs (11.4% vs 9.1%, $p<0.001$), particularly in late-career stages (14.7% vs 12.3%, p=0.033), indicating their unique role in serving underserved regions. (Table). **Conclusions:** Our findings reveal that, IMGs are less likely to practice at main campuses of NCI-Cancer Center than their non-IMG colleagues. Meanwhile, IMG oncologists are disproportionately serving rural communities. Supporting IMG pathways in oncology is critical to ensure a balanced cancer care delivery across the United States. Research Sponsor: None.

Practice setting distribution and academic affiliation among international medical graduates (IMGs) and US graduates (USGs) by career stage.

	IMG (N=6,577)		Non-IMG (N=6,920)		IMG (N=6,577)		Non-IMG (N=6,920)	
	NCI Center	Other	NCI Center	Other	Metro	Non-Metro/ Mixed	Metro	Non-Metro/ Mixed
Total	19.9%	80.1%	27.7%	72.3%	88.6%	11.4%	90.9%	9.1%
Career Stage								
Early (0-10y)	29.1%	70.9%	36.1%	63.9%	91.1%	8.9%	95.4%	4.6%
Mid (11-30y)	21.3%	78.7%	28.8%	71.2%	90.1%	9.9%	91.6%	8.4%
Senior (30+y)	15.0%	85.0%	22.0%	78.0%	85.3%	14.7%	87.7%	12.3%

9010 Rapid Oral Abstract Session

Productivity of National Cancer Institute K Awardees and their transition to independent funding. First Author: Mariah Malak Bilalaga, MedStar Health Georgetown University, Baltimore, MD

Background: The National Cancer Institute (NCI) mentored career development (K) awards program plays an essential role in supporting early-career scientists in the United States.Understanding factors that influence the transition from mentored to independent funding is crucial to optimize support for early-career cancer researchers. Here, we examine the productivity of K awardees and explore factors that predict a successful transition to independence. **Methods:** This retrospective cohort study utilized publicly available data from: 1) the National Institutes of Health Research Portfolio Online Reporting Tools Expenditures and Results database to obtain data on awards, total costs, and funding mechanisms, and 2) the NIH iCite database to obtain data on publications, citations, and mean relative citation ratio. We included principal investigators (PIs) who received NCI mentored K awards between 1981 and 2013 to allow for at least 10 years of follow-up. Multivariable logistic regression models were employed to explore predictors of attaining an R01-equivalent award. **Results:** Between 1981-2013, 1,778 K awards were awarded by the NCI, with a median total cost of $128,036 (interquartile range [IQR]: 89,420-138,085) per award/year. Of the 1,778 PIs, 759 (42.7%) received an R01-equivalent award over a total of 4,827 person-years, with a median time to award of 5.52 years (IQR: 3.88-7.79) and an incidence rate of 0.16 awards per person-year (95% CI: 0.15, 0.17). In multivariable logistic regression models, PIs who received a K08 (odds ratio [OR]=1.47 [95% CI=1.09, 1.99]), K22 (OR=1.72 [95% CI=1.06, 2.77]), or a K99 (OR=1.55 [95% CI=1.06, 2.29]) displayed greater odds of attaining an R01-equivalent award compared to K01 awardees. Similarly, PIs based in independent hospitals (OR=1.45 [95% CI=1.12, 1.88] vs. institutes of higher education), who focused on molecular/cellular research (OR=1.37 [95% CI=1.03, 1.81] vs. human research), had a greater number of publications per year (OR=1.40 [95% CI=1.25, 1.57]; per additional publication/year), had a higher mean relative citation ratio (OR=1.65 [95% CI=1.31, 2.15]; per 5 units increase), and published for a longer time interval (OR=1.09 [95% CI=1.06, 1.12]; per additional year), displayed greater odds of receiving an R01-equivalent award, while total cost did not (p=0.14). **Conclusions:** Between 1981 and 2013, 42.7% of K awardees received an R01-equivalent award, with a median transition time of 5.52 years. Productivity metrics, including greater publication and citation rates, were associated with a higher likelihood of successful transition. These findings underscore the crucial role of mentored awards in advancing scientific careers and emphasize the importance of providing mentorship and resources to early-career scientists to enhance their overall research impact. Research Sponsor: None.

9011 Rapid Oral Abstract Session

Trends in racial and gender diversity among adult hemato-oncology trainees over last decade and impact of Covid. First Author: Ohm Tripathi, University of Connecticut, Storrs, CT

Background: We aim to examine trends in racial and gender diversity of trainees within adult and pediatrics hemato-oncology (H-0) fellowships, and evaluate the impact of COVID on the racial and gender proportions of trainees within H-0 training programs. **Methods:** Accredited Council for Graduate Medical Education (ACGME) data were queried to identify hemato-oncology trainees between 2014 and 2024. Trainees were identified based on self-reported race and gender. We defined 2016-17 to 2019-20 and 2020-21 to 2023-24 era as pre and post COVID years. Student T-tests were used to assess differences between groups and trends. **Results:** Average number of the female H-0 fellows (44.1%) is significantly lower compared with men (55.4 %) [$p<0.005$] . There is a slow but steady increase in female representation in H-0 fellowship across the study period as the gender gap has declined from 15.4 % in 2016-2017 to 7.2 % in 2023-2024. There is a non-statistical increase in the proportion of females in H-0 fellowships (44.1%) post covid compared with pre covid era (42.3%) [p = 0.0054]. Blacks (3.4%) represented a lower proportion of H-0 fellows compared to Whites (37.2%, $p < 0.005$), Asians (34.0%, $p<0.005$), and Hispanics (5.0%, $p<0.005$). Asian H-0 fellows saw the highest increase in the percentage (12.7%) from 2014-2015 to 2022-2023 followed by white H-0 fellows (3.4%) while the Hispanics and blacks H-0 fellows (2.8 and 2.4% respectively) had miniscule increase in the same time frame . There is also a significant increase in Asian H-0 fellows (10.8%) post covid compared to Black fellows (1.5%). **Conclusions:** This study reveals persistent gender and racial/ethnic disparities within H-0 fellowships in the United States. While the proportion of female trainees has gradually increased in H-0, they remain underrepresented compared to men. Regarding diversity, the data shows underrepresentation of Black and Hispanic individuals in H-0 fellowships, with Asian trainees experiencing the greatest growth. Importantly, the COVID-19 pandemic did not significantly impact these existing disparities. These findings underscore the need for targeted efforts to address systemic barriers limiting diversity and inclusion in the hematology-oncology workforce. Potential strategies include holistic admissions, mentorship programs, and pipeline initiatives to support underrepresented minority students and trainees. Research Sponsor: None.

9012 Poster Session

A cluster analysis of clinician distress trajectories when caring for seriously ill hospitalized patients. First Author: Anessa M Foxwell, University of Pennsylvania, Philadelphia, PA

Background: Millions of Americans are hospitalized every year; many of whom are seriously ill with one or more co-morbidities. Clinicians, including physicians and advanced practice providers (APPs) care for these complex patients while also juggling competing clinical demands from fielding multiple specialty recommendations to navigating interprofessional relationship. But clinicians are distressed, which has the potential to impact the quality of healthcare delivery at the moment of care and in the future. To date there is limited empirical inquiry examining the longitudinal trajectory of clinician distress and its potential impact on healthcare quality. Study objective was to describe unique clinician distress trajectories in general medicine hospital clinicians caring for seriously ill patients based on their level of distress over time through mobile ecological momentary assessments (mEMAs). **Methods:** Latent class cluster analysis of prospective serial mEMAs. Exploratory analysis of patient and clinician variables was then performed using generalized estimating equations univariate ordinal logistic regression. Total participants consisted of 184 hospital encounters for hospital clinicians (n=68) caring for seriously ill patients (n=151). **Results:** The main outcome of clinician distress typology was identified by latent class cluster analysis. Distress was measured by serial mEMA distress thermometer levels over two days. The sample included more physicians (60.3%) than APPs (39.7%) and clinicians had an average of 8.4 years' experience (range 0-31 years). Patients average age was 65.4 years, majority were male (53.6%) and White (61.6%) The majority of patients had a primary serious illness of a solid tumor malignancy (50%), followed by hematologic malignancy (27.9%) then non-cancer chronic illness (22.1%). Clinicians fell into four typology clusters: low distress (23.2%), moderate distress (33.1%), variable distress (19.7%) or high distress (23.9%). Credentials (APP vs. physician; x^2=9.11, p=0.0025) and clinician emotional experience (x^2=11.29, p=0.0008) were significantly associated with clustering by typology. Compared to physicians, APPs were six times more likely to be in a higher distress typology (OR=6.16, p=0.003). Clinicians who had reported more emotions were more likely to be in a higher distress typology (OR=1.90, p=0.001). Mid-career clinicians were more likely to be distressed than either early or late career clinicians (OR=1.80, p 0.370). Patient and clinician demographics were not otherwise significantly related to clusters. **Conclusions:** Clinicians experience distress throughout their workday. This study identifies unique distress trajectories measured in real-time and specific characteristics of those trajectories that can be leveraged by healthcare systems when designing interventions and support resources for hospital clinicians. Research Sponsor: None.

9013 Poster Session

Oncologists' attitudes and beliefs toward crying with patients and its correlation with burnout. First Author: Hannah Z. Catzen, University of Michigan Medical School, Ann Arbor, MI

Background: This pilot study examines oncologists' perspectives on expressing emotion, particularly crying, in the presence of patients, the frequency of such moments, and their potential correlation with burnout. We developed a survey to assess these factors and hypothesized that oncologists with more positive attitudes toward emotional expression would report lower burnout scores. **Methods:** We surveyed physicians who practice oncology and administer cytotoxic therapy to adults at Michigan Medicine, identified using the cancer center directory. The survey, developed by the authors based on a literature review and expert opinion, included 28 questions to assess attitudes and behaviors towards crying, 7 demographic questions, and the 22-question Maslach Burnout Inventory for Healthcare professionals (MBI-HSS). We used Spearman correlations to analyze the relationship between survey questions about frequency and appropriateness of crying and the MBI-HSS subscales: Emotional Exhaustion (EE), Depersonalization (DP), and Personal Accomplishment (PA). **Results:** We analyzed data from 50 respondents (78.6% response rate). In response to "How often do you cry with your patients," 45% of providers indicated that they never or rarely (less than once a year) cried, 47% cried 1-3 times a year, 8% cried often (once every 1-2 months) and none cried more frequently (once a week). In response to "Is it appropriate to cry with patients," 12% of providers indicated that they disagree or strongly disagree, 43% indicated that they neither agree nor disagree, and 45% indicated that they agree or strongly agree. More emotionally expressive physicians had higher Personal Accomplishment scores. Personal Accomplishment was positively correlated with likelihood of crying (r = .36, p = .01) and perceived appropriateness of crying (r = .30, p = .03). Although not statistically significant, physicians with positive attitudes toward the appropriateness of crying showed a trend towards lower Emotional Exhaustion scores (r = -0.24, p = .1). **Conclusions:** This pilot study highlights the diverse attitudes of oncologists toward crying in the presence of patients. While nearly half of the respondents viewed crying as appropriate, 12% disagreed, and 45% expressed neutrality, suggesting a lack of consensus on the role of emotional expression in patient care. Oncologists who viewed crying more favorably or engaged in emotional expression more frequently reported higher Personal Accomplishment and showed a trend toward lower Emotional Exhaustion. These findings suggest that fostering open discussions among physicians about healthy emotional expression and its role in humanizing patient care may help address burnout. Future studies should also incorporate patients' perspectives to better understand the impact of physicians' emotional expression on the therapeutic relationship and overall care experience. Research Sponsor: None.

9014 Poster Session

The impact of burnout on oncologists and hematologists: *Nunc agendum est* (now is the time to act). First Author: Rajesh Sharma, Manage Health Foundation, Ahmedabad, India

Background: Burnout among oncologists is a pressing global issue, with prevalence rates ranging from 25% to 70%. South Asia, in particular, has reported alarmingly high rates, primarily driven by heavy patient load, long working hours, administrative demands, and very limited resources. This study aims to explore the prevalence of burnout, its associated stress symptoms, coping mechanisms, and the role of institutional support, with a focus on practical strategies to mitigate burnout. **Methods:** A cross-sectional survey involving 342 oncologists and hematologists in India was conducted using the Maslach Burnout Inventory (MBI) framework. This framework assessed 3 key dimensions of burnout: emotional exhaustion (EE), depersonalization (DP), and reduced personal accomplishment (PA). Additional variables included stress symptoms, burnout severity, contributing risk factors, and coping strategies. Statistical analyses such as Pearson correlation, logistic regression, and factor analysis were performed. Odds Ratios (ORs) were calculated to assess impact of various risk factors, while factor loadings were used to identify underlying domains contributing to burnout. **Results:** Burnout Prevalence: Moderate-to-severe burnout was reported by 43% of respondents. Emotional exhaustion was experienced occasionally by 34.4% and frequently by 31.2%. Depersonalization affected 17.6%. Key Risk Factors: Long working hours increased burnout risk by 2.45 times (OR: 2.45, 95% CI: 1.72–3.48). Administrative workload strongly correlated with emotional exhaustion ($r = 0.68$, $p < 0.01$). Core Domains (Factor Analysis): Systemic Challenges: High patient loads and administrative tasks (factor load > 0.75). Individual Resilience: Practices like meditation and yoga reduced burnout (factor load > 0.70). Organizational Support: Psychological resources and peer discussions were critical (factor load > 0.80). Coping Strategies: Meditation reduced burnout likelihood (OR: 0.64, 95% CI: 0.42–0.96). Peer discussions and group therapy eased depersonalization symptoms ($p < 0.05$). Specialty-Specific Insights: Medical Oncologists: Highest emotional exhaustion (45%). Radiation Oncologists: Moderate depersonalization (41%). Surgical Oncologists: Strongly benefited from peer support (factor load = 0.78). **Conclusions:** Burnout among oncologists requires immediate action. Effective solutions include reducing systemic burdens, providing institutional psychological support, and encouraging individual resilience strategies like meditation and peer discussions. Addressing burnout is critical to improving oncologists' well-being and ensuring quality patient care. Research Sponsor: None.

Statistical associations of risk factors with burnout.

Risk Factor	OR (95% CI)	p-value
Long Working Hours	2.45 (1.72–3.48)	<0.01
Administrative Workload	2.10 (1.56–2.89)	<0.01
Lack of Work-Life Balance	1.85 (1.34–2.56)	<0.05
Poor Institutional Support	1.96 (1.40–2.75)	<0.05

9015 Poster Session

Rethinking future workforce planning by developing novel metrics of complexity in cancer care. First Author: Philip Q. Ding, Oncology Outcomes (O2) Program, University of Calgary, Calgary, AB, Canada

Background: The decision to recruit additional oncologists is often based on simple workload measures such as new patient volumes. This approach may be appropriate previously when cancer management was less complex and at a time when attrition from cancer mortality was significant. We hypothesized that cancer care complexity has increased over time and that new metrics are needed to optimize workforce planning. **Methods:** We conducted a population-based, retrospective cohort study of adult patients diagnosed with common solid and blood cancers in Alberta, Canada. We focused on cases from 2004 to 2018 to ensure adequate follow-up. We evaluated indicators of complexity including patient characteristics at the time of diagnosis, clinical course within 2 years of diagnosis, and longevity as measured by overall survival (OS). For these complexity indicators, we used logistic and Cox regression models to estimate relative changes over the 15-year study period. **Results:** A total of 141,040 patients were included in the study cohort, with a median age of 66 years (range 18-107) and 51.7% male. Breast cancer was most common (25.6%), followed by prostate (24.0%), lung (20.2%), colorectal (17.9%) and leukemia/lymphoma (12.4%). Across all sites, annual cancer incidence rate was 249.9 per 100,000 in 2004 and 284.4 per 100,000 in 2018. Age distribution remained largely stable throughout the study period. Meanwhile, specific indicators of complexity increased over time, including polypharmacy at diagnosis (odds ratio [OR] 1.30, 95% confidence interval [CI] 1.28-1.32), multimodality treatment (OR 1.06, 95% CI 1.05-1.08), and hospital admission via the emergency department (OR 1.08, 95% CI 1.07-1.10). These metrics also demonstrated increasing complexity in multivariable analyses after adjusting for age, sex, and cancer site. Similarly, there was a trend towards greater longevity as measured by OS (hazard ratio 0.98, 95% CI 0.98-0.98). **Conclusions:** Cancer care complexity has increased over time. Workforce planning using antiquated workload metrics, such as incident patient volumes alone, may not align with the actual demands of providing increasingly complex cancer care. Recruitment strategies should consider multi-faceted indicators that reflect complexity in addition to quantity. Research Sponsor: None.

Trends in metrics of patient complexity, by time era.

	Year of diagnosis		
Characteristic	2004-2008, n = 39,465	2009-2013, n = 46,408	2014-2018, n = 55,167
Age, y (range)	66 (18, 104)	66 (18, 104)	66 (18, 107)
Stage III-IV[a]	12,706 (41.4%)	15,265 (39.2%)	17,258 (38.1%)
Polypharmacy	6,853 (17.4%)	11,175 (24.1%)	14,836 (26.9%)
Multimodality treatment	13,884 (35.2%)	17,069 (36.8%)	21,025 (38.1%)
Any admission via ED[b]	7,679 (19.5%)	9,341 (20.1%)	12,057 (21.9%)
2-year OS (95% CI)	0.70 (0.69-0.70)	0.73 (0.73-0.74)	0.76 (0.75-0.76)

[a]solid cancers only; [b]within 2 years following diagnosis.

9016 Poster Session

Parenting challenges of international medical graduate hematologists-oncologists in the United States. First Author: Vera Kazakova, UMass Chan Medical School, Worcester, MA

Background: Almost two-thirds of physicians report delaying childbearing due to medical training. Amongst hematologists-oncologists (HOs), up to 75% report burnout related to parenting. International Medical Graduates (IMGs) account for a third of all practicing HOs; yet little is known about the unique challenges they face in navigating parenthood. This cohort study aimed to explore parenting challenges of IMG HOs in the U.S. **Methods:** An anonymous survey was distributed electronically via social media and the ASCO community of practice between December 2024 and January 2025. Descriptive statistics were employed to compute frequencies and percentages of survey responses. Chi-square tests for independence were performed to evaluate associations between key survey variables. **Results:** Among 73 respondents, majority were aged 30–39 (50%) and were women (75%). At the start of their first U.S. post-graduate training, 51% of respondents were on J1/ H1B visa. The majority (77%) delayed parenthood due to medical careers with higher rates of delay in non-citizen/non-permanent resident (NCNPR) IMGs compared to those with permanent residence/citizenship (81% versus 71%). A Chi-square test indicated an association between immigration status and the likelihood of delayed parenthood (p=0.03). Parenthood delay correlated with work hours, financial strain, and lack of social support (Table 1). Key factors affecting career trajectory included decreased academic productivity (66%), reduced conference participation (64%), and declined advancement opportunities (53%). After having children, the most common challenges were achieving work-life balance (95%), lack of social support (93%), and increased burnout (92%). Visa status contributed to parenthood challenges for 38% of NCNPR IMGs. Respondents cited the need for childcare resources, enhanced leave policies, workplace accommodations, visa assistance, stronger support and mentorship. **Conclusions:** IMG HOs face significant challenges balancing parenthood and career, including higher burnout rates than previously reported amongst physicians. Within the cohort of IMG HOs, there is a significant association of immigration status with likelihood of delaying parenthood. Findings highlight the need for systemic support through improved childcare resources, workplace accommodations, mentorship, and visa assistance. Research Sponsor: None.

Correlation between parenthood delay and determinants of parenthood timing.

Factor	Chi-Square	p-value
Duty hours	44.41	<0.0001
Financial strain	22.91	0.0285
Unsupportive work environment	34.5	0.0006
Lack of accommodations during pregnancy	29.79	0.003
Lack of/unclear parental leave policy	30.1	0.0027
Lack of accommodations post parental leave	26.28	0.0098
Lack of social support	39.96	0.0001
Impact on career trajectory	31.99	0.0014
Delay in training completion	30.06	0.0027

9017 Poster Session

Communication skills training program for medical staff in cancer genomic testing: A mixed-methods assessment of an educational initiative. First Author: Shuhei Suzuki, Department of Clinical Oncology, Yamagata University, Yamagata, Japan

Background: Cancer genomic testing presents unique communication challenges for medical staff, particularly regarding low treatment access rates, the complex psychological needs of patients, and concerns about germline findings. While communication skills training (CST) has shown promise in oncology settings, it has not yet been specifically applied to genomic testing conversations. This Pfizer Global Medical Grants Initiative 2023 was designed to address this critical educational gap in the implementation of cancer genomic medicine. **Methods:** A mixed-methods evaluation was conducted of a structured CST program implemented across 10 institutions under Pfizer's educational initiative framework. The program incorporated SHARE protocol-based training (Fujimori *et al. JCO*. 2014), role-playing sessions, and specialized modules addressing genomic testing-specific challenges. The quantitative assessment utilized pre- and post-intervention 4-point categorical assessments. The qualitative evaluation employed semi-structured interviews (median duration 12 minutes, range 7-21) analyzed using a modified grounded theory approach until theoretical saturation. **Results:** Among 251 participants (22% physicians, 37% nurses, 25% other healthcare professionals, 12% administrative staff, 4% others; median experience 9 years, range 0-39), 95% initially reported a psychological burden when explaining genomic testing results. Post-intervention, 94% reported a reduced psychological burden ($p< 0.001$, Chi-square), with 84% expressing satisfaction with the training program. An ordinal logistic regression analysis revealed a significantly greater improvement in nurses than in other professionals (OR 3.52, 95%CI 1.88-6.58, $p< 0.001$). A qualitative analysis of 19 interviews (58% medical staff, 42% patients/families) revealed four major conceptual categories through a constant comparative analysis: 1) multilayered information needs with psychological support requirements, 2) experiential uncertainty in communicating germline findings, 3) perceived competency gaps in genomic counseling, and 4) organizational support needs for sustained practice changes. A thematic analysis identified a strong demand for program continuation and expansion. **Conclusions:** This educational initiative revealed significant effectiveness in addressing critical communication challenges in cancer genomic medicine. The mixed-methods evaluation provides a robust framework for implementing specialized CST programs in genomic medicine practice. These results will contribute to the evolving landscape of cancer genomic medicine education and support the value of structured, evidence-based educational initiatives in advancing the delivery of precision oncology care. Research Sponsor: Pfizer Global Medical Grants; 75412385.

9018 Poster Session

Competencies for practicing medical oncology with common sense: A global curricula review. First Author: Haydee Cristina Verduzco-Aguirre, Queen's University, Kingston, ON, Canada

Background: The Common Sense Oncology (CSO) movement advocates for high-quality, patient-centered cancer care by emphasizing evidence-based, patient-relevant outcomes and equitable access to care through improved evidence generation, interpretation, and communication. A key part of CSO's mission is training oncologists to incorporate these principles into their practice. Therefore, this study aimed to evaluate how competencies in global postgraduate medical oncology curricula align with CSO principles. **Methods:** We conducted a document analysis of publicly available postgraduate medical and clinical oncology curricula. Curricula were identified through: (1) searches in Education Source, EMBASE, and PubMed using the terms 'oncology', 'curriculum', and 'competency-based'; (2) a grey literature search; and (3) requests to medical education experts. Curricula in English, Spanish, Italian, Portuguese, or Hebrew were included to ensure regional representation, while accounting for the research team's language proficiency. Competencies were categorized into eight domains aligned with CSO principles, including critical appraisal, cost and value of cancer care, communication about outcomes and treatment risks, equity in accessing cancer care, ethical principles, and integration of psychosocial oncology, survivorship, and palliative care. Two team members reviewed each curriculum, resolving discrepancies collaboratively, with unresolved cases adjudicated by the first or senior author. **Results:** We analyzed 16 curricula (Australia/New Zealand, Brazil, Canada, the European Union, India, Ireland, Italy, Japan, Mexico, Nigeria, Pakistan, Spain, the United Kingdom, the United States, and the ESMO/ASCO joint curriculum). Ten (63%) were from high-income regions, and six (37%) were from low/ middle-income countries (LMIC). The most frequently identified domains were critical appraisal (94% of curricula), communication (94%), palliative care (94%), and cost/value of care (88%). Less frequent domains were equity in accessing cancer care (56%), ethical principles (56%), and survivorship care (63%). Four (25%) curricula, all from high-income regions, covered all CSO-relevant domains, while three (19%) addressed four or fewer. Competencies related to equity and ethics were found in 70% of high-income curricula but only in 33% of LMIC. **Conclusions:** Competencies reflecting CSO principles were identified in global oncology curricula, with emphasis on critical appraisal, communication, palliative care, and psychosocial oncology. Competencies related to equity, ethical principles and survivorship care were less frequently observed. Notable gaps were observed between high-income countries and LMIC, though language limitations may have influenced our findings. Our results will inform the development of a globally relevant competency framework for common sense in oncology. Research Sponsor: None.

9019 Poster Session

Enhancing radiotherapy planning skills through structured deliberate practice and artificial intelligence integration: A pilot study. First Author: Ivy Weishan Ng, National University Cancer Institute, Singapore, NA, Singapore

Background: In many cancer treatment protocols, radiotherapy plays a pivotal role in achieving disease control. A key component of radiotherapy planning is contour delineation, which involves accurately outlining tumors and nearby structures to target radiation effectively and minimize toxicity. However, formal training in this skill often falls short, with surveys indicating up to 80% of learners and practitioners calling for a need for more robust educational methods (Leung et al. J Med Imaging Radiat Oncol 2019). While advances in artificial intelligence (AI) can improve contouring speed and consistency, radiation oncologists must also develop the skills to evaluate AI-generated results to maintain high-quality care critically. This pilot study aimed to determine whether a structured training approach that incorporates deliberate practice, personalized feedback, and AI integration could improve the contour delineation proficiency of radiation oncology trainees and practitioners. **Methods:** A baseline survey was conducted to identify existing gaps in contour training. Participants practiced with four anonymized thoracic imaging standardized datasets offline. Each participant's initial contours were compared against expert consensus using the Dice similarity coefficient (DSC), a standard metric for spatial overlap. Slice-by-slice visual comparisons and self-reported confidence ratings provided additional qualitative feedback. Over six months, participants engaged in structured lessons, repeated practice sessions (including real clinical cases), expert mentoring, and AI contour assessments. **Results:** At baseline, 24 heart contours were consistently accurate (DSC $>$ 0.9), while tumour and oesophagus delineation showed wide variability (DSC 0.4–0.9 and 0.2–0.9, respectively). Over time, learners demonstrated measurable improvement. By the final assessment, variability in tumour and oesophagus contours decreased (DSC 0.6–0.9 and 0.7–0.9, respectively), while heart contours remained consistently accurate. Learners also demonstrated improved confidence in both manual and AI-augmented contour delineation. **Conclusions:** This study suggests that a structured training approach incorporating a deliberate practice curriculum augmented by personalized feedback and AI integration can improve contour delineation skills. Future studies with larger datasets and diverse learner populations could further validate this approach, ultimately aiming to improve patient safety and treatment outcomes across the broader oncology landscape. Research Sponsor: None.

9020 **Poster Session**

On-shift resident education about hematologic and oncologic emergencies: A needs-based assessment. First Author: Leah Ann Goldberg, University of Chicago, Chicago, IL

Background: Hematology/oncology (H/O) is a fundamental topic for the American Board of Internal Medicine (ABIM); however, there are few resources designed for resident-level education. While asynchronous approaches have gained popularity, there can be a synergistic effect to cementing understanding during clinical exposure. Rotations provide this opportunity, but limited tools exist to augment practice-based learning. Multimodal approaches, such as self-directed text and near-peer educational models, are rarely accessible on shift. The breadth and depth of such resources can make it difficult for users to distill salient information during patient care. This needs-based assessment (NBA) sought to characterize residents' attitudes towards on-shift learning as well as their comfort with diagnosing and treating 3 common H/O emergencies. **Methods:** An NBA survey was sent to 104 internal medicine (IM) and medicine-pediatrics (MP) residents at an academic medical center. Descriptive statistics are reported. **Results:** Fifty-five of 104 residents completed the survey, for a response rate of 53%. Forty-seven percent were post-graduate year (PGY) 1, 25.5% were PGY-2, 25.5% were PGY-3 and 2% were PGY-4. While 98% of respondents use educational resources on shift, only 6% had a H/O specific resource. The most used resources were Up-to-Date (98%), the Mass General Hospital WhiteBook (75%), PubMed (47%), and artificial intelligence (AI) (47%). The biggest barriers to resource utilization were lack of time due to clinical responsibilities (76%) and length of resource (69%). Ninety-one percent indicated interest in a resource designed for shift-based learning and would most value guideline inclusion (80%). While most residents (62%) were comfortable diagnosing tumor lysis syndrome (TLS) and febrile neutropenia (FN) (69%), they were neutral/uncomfortable with diagnosing hyperleukocytosis (71%). Most were comfortable treating FN (53%) but were neutral/uncomfortable with treating TLS (60%) or hyperleukocytosis (96%). There was a statistically significant difference between PGY-1 and PGY-2+ in comfort with diagnosis ($p=.0018$) and treatment ($p<.001$) of FN as well as the treatment ($p=.0132$) of TLS. There was no significant difference in comfort with TLS diagnosis, or hyperleukocytosis diagnosis or treatment among PGY. **Conclusions:** This assessment demonstrates an overwhelming interest in an easily accessible, guidelines-based, electronic resource for residents to utilize during clinical care. Though a medical emergency, hyperleukocytosis is a H/O diagnosis that our program's residents are not comfortable identifying or managing. These results highlight the opportunity for growth in H/O education of IM/MP residents and will guide the design of a digital education resource, as well as its implementation and evaluation at our institution. Research Sponsor: None.

9021 **Poster Session**

The hidden toll: Defining impacts of home call on oncology fellows. First Author: Erica Andres, Mayo Clinic Rochester, Rochester, MN

Background: Home call is an expected trainee responsibility in many hematology-oncology (HO) training programs although the specific duties and frequency vary. Home call is associated with sleep deprivation and burnout . The Accreditation Council for Graduate Medical Education (ACGME) outlines that home call should not prevent adequate rest or personal time and that the clinical time spent must be counted toward duty hours. However, little is known about the educational value or impact of home call. We sought to analyze the volume, perceived value, and effects of oncology home call on HO fellows. **Methods:** We completed a review of the pager log of the outpatient/after hours oncology pager (OP) at a single 2059 bed tertiary medical center from 1/1/23-12/31/24. The HO fellow carries the OP afterhours and on weekends except for 7am-12pm on Saturday/Sunday. The pager receives all consult calls from the emergency department and inpatient teams requesting verbal communication (in addition to the electronic order), critical results, and outpatient patient calls on matters related to oncology (hematology not included). Patient calls are not triaged and are routed through the hospital operator directly to the OP. Overnight home call is maximum 3 times per week without a post call day. An optional survey was distributed to fellows in May 2024 to assess fellows' experiences with the OP using a 5-point Likert scale and free response. **Results:** There were 80,672 and 87,605 oncology patient visits in 2023 and 2024 respectively at the analyzed institution. The OP received a total of 7,239 pages over the analyzed period. Fellows received a mean of 5.8 pages per weeknight call shift and 8.8 pages per weekend call shift. The survey response rate was 19/33 (42%) HO fellows. Respondents were 58% male and included first (42%), second (26%), and third year (32%) fellows. 89% of respondents reported that most pages overnight were from outpatients and 0 respondents felt that answering patient calls required a physician. Most fellows (79%) did not report educational value from holding the OP and 63% of fellows felt that holding the OP negatively impacted their performance at work the next day. For nights that received more than 3 calls, 95% fellows reported feeling not well rested. In addition, a majority of negative impact on their wellness including anxiety and inability to exercise or socialize when holding the OP. **Conclusions:** The results from our single-institution study indicate that home call could represent a major opportunity to improve the wellness of trainees without negatively impacting their education. More research is needed to understand what the primary contributors are for the negative experiences and perceptions while developing sustainable systems and approaches for efficiently handling oncology pager traffic. Research Sponsor: None.

9022 **Poster Session**

Successful intervention to bridge the knowledge gap in recognizing and managing chemotherapy hypersensitivity reactions among oncology fellows in southeast Michigan. First Author: Jailan Elayoubi, Oncology Department, Wayne State University, Detroit, MI

Background: Recognizing hypersensitivity reactions (HSRs) to paclitaxel and carboplatin in patients receiving multi-drug chemotherapy regimens combined with monoclonal antibodies (mAb) and distinguishing them from infusion-related reactions (IRRs) is challenging due to overlapping clinical presentations, rarity, and severity. To address this, we designed a continuing professional development (CPD) activity to enhance knowledge and awareness of these life-threatening reactions. **Methods:** The CPD activity was designed using Kern's six-step approach, targeting Hematology/Oncology (H/O) fellows, Gynecological Oncology (GO) fellows, and chemotherapy infusion center nurses (Chemo RNs). A questionnaire featuring real-life HSRs and IRRs scenarios was administered anonymously before and after a 60-minute, in-person, interactive educational lecture. Paired statistical comparisons were not performed, as both surveys were kept anonymous to encourage participation. **Results:** A total of 42 participants attended the CPD activity, including 30 H/O fellows from 3 fellowship programs, 3 GO fellows from 1 program, and 9 Chemo RNs from a comprehensive cancer center in Southeast Michigan. Participation in pre- and post-lecture questionnaires among fellows was 87.8% and 72.7%, respectively. Recognition rates among fellows improved from 82.7% to 100% for paclitaxel HSRs, 58.6% to 95.8% for carboplatin HSRs, and 93.1% to 91.6% for mAb IRRs, with the most notable improvement in recognizing HSRs to carboplatin. For Chemo RNs, paclitaxel HSRs and mAb IRRs recognition rates were 100% at baseline and post-lecture, while carboplatin HSRs recognition improved from 71.4% to 88.8%. **Conclusions:** A knowledge gap was identified among oncology fellows in recognizing HSRs to paclitaxel and carboplatin, while Chemo RNs demonstrated exceptional baseline knowledge of paclitaxel HSRs and mAb IRRs. CPD activities aimed at raising awareness of various HSRs and their management were effective and well-received by the healthcare staff, supporting their integration into H/O fellowship curricula. Research Sponsor: None.

Key points from the educational lecture.

	Carboplatin	Paclitaxel
Timing	Mostly occurs towards the end of infusion or up to days after. Cumulative effect, highest incidence by the 8th exposure.	Occurs within the first 10 minutes during the first or second infusion.
Most characteristic feature	Itching, rash on palms and soles,abdominal cramps, back pain.	Flushing and hemodynamic instability.
Pre-medications	Corticosteroids, H1/H2 antagonists do not prevent HSRs.	Dexamethasone, diphenhydramine, H2 receptor antagonists before paclitaxel infusion decrease HSRs.

9023 **Poster Session**

Introducing a capacity building model to improve cancer research in MENA. First Author: Sara Ahmad Al-Banna, King Abdullah University Hospital, Amman, Jordan

Background: The Middle East and North Africa (MENA) region faces a rising cancer burden, straining healthcare systems. The scarcity of cancer research in the region highlights the need for research-focused capacity building. Our project aims to reduce this burden by empowering scientific research for better understanding and strategic implementation. **Methods:** The Science Health Education (SHE) Center was founded by the Dana-Farber Cancer Institute in 2019 to empower cancer research in MENA by offering mentorship, fostering international scientific collaborations, and supporting the next generation of researchers. Capacity-building efforts within the past six years were implemented through 21 in-person and virtual workshops that combined interactive and theoretical approaches, with data collected via pre- and post-assessment forms. The workshops covered topics including Research Basics and Manuscript Writing, Research Administration & Gap Analysis, Mentorship, CV Writing and Leadership. Data were analysed using independent t-tests to compare pre- and post-workshop scores, with Cohen's d calculated to quantify effect sizes, demonstrating the scale of skill improvement. **Results:** A total of 573 healthcare workers from four MENA countries (Jordan (n= 267, 47%), Iran (n=187, 33%), United Arab Emirates (n=65, 11%), and Morocco (n=54, 9%)) have attended our workshops. In Jordan, over 67% of the 267 participants were women. The attendees included 96 medical students and 171 healthcare professionals (HCPs) from various departments, including Scientific Affairs (n=54, 32%%), Pharmacy (n=16, 9%), and Nursing (n=16, 9%). HCPs attended four Manuscript Writing Workshops, which covered theoretical basics, manuscript drafting, peer review, and US-based review by our editors. Fifty manuscripts from 73 participants across two workshops were edited by the Center and submitted for publication, with a publication rate of 34% thus far. Medical students participated in four Professional Development Workshops. Pre- and post-assessments conducted for 20 participants from the latest pilot analysis in Jordan showed significant improvement in manuscript writing skills. Participants reported enhanced self-rated writing ability ($P=0.003$, $d=1.072$), increased familiarity with IMRaD structure ($P=0.057$, $d=0.661$), better understanding of journal selection ($P=0.004$, $d=1.033$), greater confidence in formatting references and citations ($P=0.004$, $d=1.053$), and improved knowledge of handling peer review feedback ($P<0.001$, $d=1.382$). **Conclusions:** The SHE Center is a successful model for training cancer researchers in developing their research and publishing skills. Further capacity building will help trainees develop advanced skills, preparing them to mentor the next generation. This model has potential to be adopted in other low- and middle-income countries to enhance research productivity and improve cancer care. Research Sponsor: None.

9024 **Poster Session**

Enhancing educational experiences through standardization of inpatient hematology curriculums. First Author: Prasanth Lingamaneni, Mayo Clinic Rochester, Rochester, MN

Background: Comprehensive hematology education during fellowship is essential for delivering high-quality healthcare. Variability in individual learning experiences can lead to trainee dissatisfaction and suboptimal clinical acumen. Fellowship programs must strive for a well-rounded and equitable educational experience for all fellows to prepare them for real-world practice in the increasingly dynamic field of hematology. **Methods:** Hematology fellows (n=30) at Mayo Clinic (Rochester) were invited to complete a survey about the inpatient Fellow Hematology Curriculum (FHC) during 2021-2022. Responses were recorded in a five-point Likert scale and free-text. Using the initial results, we implemented a structured inpatient hematology curriculum starting in 2022 and conducted a post-implementation survey in Spring 2024 to assess its success and sustainability. **Results:** The initial survey was completed by twenty fellows, with a response rate of 66%. All respondents agreed that the FHC could be improved. Only 45% agreed that structured education is adequately paired with clinical duties. In the open-ended responses, a structured curriculum covering a set list of topics was the most common recommendation given to improve the FHC. This prompted a longitudinal QI initiative to implement standardized rotation-specific lectures created by fellows and distributed to faculty and fellows prior to the associated 4-week rotations. Twelve fellows (40%) completed the post-implementation survey. Summary of key responses are shown in table 1. Although there remained high variability among consultants regarding their engagement in education, significant improvements were noted. Agreement that the curriculum has well-defined objectives for each rotation increased from 25% to 58%. Additionally, 83% of fellows agreed that structured education was effectively paired with clinical duties, up from 45%. Open-ended responses highlighted variability in consultants' utilization of the curriculum but reflected overall satisfaction. **Conclusions:** The need for a well-structured FHC was identified as a gap in equitable hematology education. This was addressed through a fellow led longitudinal QI project generating easily accessible educational material relevant to weekly themes on inpatient hematology services. The introduction of a structured and clinically relevant curriculum was well-received. Research Sponsor: None.

Summary of survey responses.

	Pre-implementation	Post-implementation
Statement	Agreed or strongly agreed (%)	Agreed of strongly agreed (%)
I know what topics and to what extent I'm expected to learn	25	67
The FHC has well-defined objectives for each rotation	25	55
There is high variability among consultants with engagement in education	95	75
Structured education is paired with clinical duties	45	83
I can easily locate lectures given by hematology consultants	5	42

9025 **Poster Session**

Leveraging the power of diagnostic metrics to competency based medical education (CBME) implementation in medical oncology (MO) across Canada. First Author: Anna T. Tomiak, Queen's University, Kingston, ON, Canada

Background: MO training programs across Canada implemented CBME in 2018. Early implementation focused primarily on immediate "structural" changes, and included the adoption of new stages of training, new assessment practices and the creation of Competence Committees. To explore elements that would reflect broader and transformational change related to a true shift to an individualized and competency-based approach to education, program leaders sought to identify, develop, and pilot indicators that could be used by programs to evaluate their implementation of the Competence by Design (CBD) model. It was anticipated that implementation and evaluation of these indicators would be challenging. **Methods:** In phases one and two of the study, program leaders established a consensus regarding qualities they considered to transformative, and qualitative information regarding how these qualities are reflected in programs was obtained. In phase three, electronic resident portfolios at 2 sample sites were investigated for data regarding specific indicators to determine the feasibility of use by program directors to track implementation progress and aid in program review. Opinions of program leaders in all 14 Canadian programs were obtained through a consensus process. Educators from all sites were invited to participate in semi-structured interviews and a 100% response rate obtained. Data from the 2 sample sites was collected from portfolios, de-identified and reported in aggregate to help maintain confidentiality. **Results:** 7 key priority indicators were identified. These centered around 6 themes: direct observation, personal learning plans, curricular change, coaching, data sources used by Competency Committees and general concerns about CBD. Variability was found in the extent of implementation of these across programs and in adaptations made locally. At the 2 sample sites, extraction of key metrical indicators from resident portfolios had to be completed manually and was challenging as electronic databases had not been designed to allow easy review and analysis of these specific indicators. **Conclusions:** Program leaders of Canadian MO training programs were able to reach consensus regarding key data indicators they believe to be transformative and reflective of core CBD principles. Despite this consensus, variability was found in the implementation of these across programs and practical challenges encountered in extracting data related to key indicators from resident portfolios at 2 sample sites. To provide program leaders with data they feel is important for optimal CBD implementation, electronic databases will need ongoing attention and adaptation to facilitate access to key indicators considered important for program review and evaluation. Research Sponsor: Royal College of Physicians and Surgeons of Canada (RCPSC).

9026 **Poster Session**

Implementation of clinical trial communication skills training for oncology fellows. First Author: Carma Bylund, University of Florida, Gainesville, FL

Background: Effective physician-patient communication about cancer clinical trials (CCTs) is critical for improving participation, particularly in underrepresented populations. Most eligible patients are willing to participate when invited through clear, patient-centered discussions, yet treating oncologists often do not discuss trials or do so ineffectively. Communication skills training is well-suited for the fellowship stage; however, most Hematology/Oncology (Hem-Onc) education programs do not formally teach CCT communication skills. To address this gap, we implemented COMM-CCT, a previously developed CCT communication skills workshop for Hem-Onc fellows and assessed the acceptability and feasibility of its implementation in Hem-Onc fellowship programs. **Methods:** We implemented the COMM-CCT workshop at seven Hem-Onc programs in the U.S. The three-hour, synchronous Zoom-based workshop included a one-hour didactic session that covered barriers to patient trial participation (e.g., patient, physician, institutional) and introduced the COMM-CCT framework (Check-In, Outline Options, Make a Shared Decision, Map Out Next Steps) for discussing CCTs. This was followed by a two-hour role-play session where fellows practiced communication skills with cancer survivors who were trained to act as patients, while faculty facilitators and peers gave constructive feedback. At each site, "fellow champions" encouraged peers to participate in the workshop. We assessed implementation (i.e., feasibility and acceptability) by surveying and interviewing participating fellows. **Results:** Regarding acceptability, fellows (n=54) reported high satisfaction (on a 1-5 scale) with the workshop (M=4.30, SD=0.79), its content (M=4.28, SD=0.79), its organization and execution (M=4.5, SD=0.61), and the faculty and facilitators (M=4.56, SD=0.63). They were comfortable with communication skills taught (M=4.15, SD=0.71) and felt the skills were compatible with the realities and resources of their clinical practice (M=4.35, SD=0.70). Fellows further agreed what they learned would be useful to (M=4.33, SD=0.73) and able to be incorporated into (M=4.22, SD=0.72) their clinical practice. When interviewed, fellows (n=9) found the workshop acceptable, describing it as "well-organized," "very helpful," and relevant. The role-plays with "real survivors" were noted as a strength, as was learning by observation in a group setting. Feasibility was evidenced by fellows reporting incorporating COMM-CCT concepts into practice, such as by initiating discussions with patients about cancer clinical trials since participating in the workshop. **Conclusions:** The COMM-CCT workshop is acceptable and feasible to implement in Hem-Onc fellowship programs. Findings will inform its refinement, broader scaling, and continued integration into graduate medical education programs. Research Sponsor: The Leukemia & Lymphoma Society.

9027 **Poster Session**

GUIDE-G: An artificial intelligence-powered platform for dynamic NCCN guideline visualization in breast cancer (BC). First Author: Nataly Valeria Torrejon, Baylor College of Medicine, Houston, TX

Background: Breast cancer (BC) management has evolved rapidly, with 17 FDA approvals in the past five years. Increasing complexity in NCCN guidelines has resulted in prolonged decision-making times and complex clinic preparation processes. GUIDE-G, an AI-powered, web-based platform, was developed to address these challenges by enabling hierarchical visualization of NCCN guidelines and providing efficient, point-of-care clinical decision support. **Methods:** The primary objective was to assess the feasibility of GUIDE-G. SUMMARIZATION of NCCN Guidelines in BC was performed using Large Language Model-based feature extraction, applying targeted prompts for accurate content retrieval and generating structured markup output. Manual curation by a panel of BC experts at Baylor College of Medicine ensured alignment with the guidelines, with accuracy measured by edits per generated content. VISUALIZATION involved transforming the markup into dynamic hierarchical diagrams using markmap-lib framework, supported by Node.js. GitHub-based version control ensured automated updates, with mobile-compatible HTML enabling cross-platform accessibility. **Results:** GUIDE-G (https://elkhanany.github.io/cancer_workflow/) achieved 90% accuracy in guideline summarization, as validated by expert review. The feasibility objective was met, with seamless integration into clinical workflows. Anecdotal feedback from 20 BC fellows highlighted the platform's ability to reduce per-patient preparation time by approximately 5 min. Although formal survey data is pending, preliminary observations suggest the platform enhances learner engagement and supports real-time clinical decision-making. Visualization performance demonstrated consistent sub-second rendering on major mobile platforms, ensuring accessibility at the point of care. Formal impact evaluation is underway, with IRB approval for studies assessing workflow efficiency and learner satisfaction. **Conclusions:** GUIDE-G offers a transformative approach to BC guideline implementation, combining scalable architecture and version-controlled deployment for sustained adaptation to evolving guidelines. Learner impact is being collected via 16-point survey instruments. Preliminary findings demonstrate potential for significant improvements in clinical workflow efficiency and educational outcomes, paving the way for implementation across oncology subspecialties and transforming evidence-based care delivery. Research Sponsor: None.

9028 **Poster Session**

Implementation of a novel interdisciplinary pharmacology curriculum in a hematology/oncology fellowship program. First Author: Rebecca Forman, Yale New Haven Hospital, New Haven, CT

Background: Thoroughly understanding cancer therapeutics is a critical component of Hematology/Oncology (HO) training, with pharmacology comprising a large part of the ASCO/ESMO Recommendations for a Global Medical Oncology Curriculum. Prior studies demonstrated that interdisciplinary approaches to education lead to more teamwork and enable learners to gain from multiple perspectives. We created and implemented a novel pharmacology curriculum in our HO fellowship program using a case-based, interdisciplinary format grounded in learning science principles. **Methods:** We used a pre-post design to evaluate and transform HO fellowship pharmacology training. The pre-existing pharmacology curriculum was organized by drug mechanism of action (MOA) and delivered via a didactic lecture by a pharmacist. HO fellows completed a baseline survey assessing satisfaction and garnering feedback. Based on this feedback, a case-based curriculum was piloted, organized by disease type and given jointly by a pharmacist and clinician. Lectures involved active learning with call and response questions with guidance in treatment decision making, dosing considerations, patient counseling, and toxicity management. This was followed by a post-survey to assess changes in perceptions and effectiveness. **Results:** 34% of HO fellows filled out the initial survey (11/32) and 17 (53%) completed the post-lecture survey with results in Table 1. Among the 12 post-survey respondents who had attended pharmacology lectures the previous year, all rated the new format as an improvement. Thematic qualitative analysis emphasized increased absorption of material and increased relevance due to clinician inclusion and case-based format. Comments noted the new series as a "marked improvement" and "more clinically relevant." **Conclusions:** HO fellows found a case-based, interdisciplinary, disease-specific pharmacology curriculum conducive to learning and retaining information, and a significant improvement over a passive lecture series organized by MOA. The new format increased fellows' confidence and abilities in managing cancer-directed therapies, and improved perceived skills related to interdisciplinary patient care. This curriculum could serve as a model for implementation at HO fellowship programs in other institutions. Research Sponsor: None.

Pre- and post-intervention survey results.

Pre-survey statement	% Agree, n/total
I did not retain a significant amount from the lectures	63%, 7/11
I did not find the format conducive to learning	73%, 8/11
I would prefer a case-based approach	91%, 10/11
Post-survey statement	
The new format is conducive to my learning	94%, 16/17
The interdisciplinary format enhanced my learning	94%, 16/17
The lectures increased my confidence in prescribing/ managing therapies	88%, 15/17
The lectures improved my ability to discuss treatment options with patients/other providers	71%, 12/17

9029 **Poster Session**

Applying learning science principles (LSP) through a simulation session (SIM) for oncology trainees (OT) about fertility preservation (FP) in patients (pts) with cancer and treatment (tx) of pregnant pts (TPP) with cancer. First Author: Tanmayi Pai, Mayo Clinic, Jacksonville, FL

Background: Addressing guideline concordant FP and TPP with cancer is challenging, especially for OT. SIM, a well-known education tool, has not been traditionally used to teach these topics. As part of the hematology/oncology fellowship curriculum, we designed a SIM applying LSP to bridge this educational gap. **Methods:** Applying LSP of contrasting cases, elaboration, feedback, generation and just-in-time telling, chief OTs and faculty designed a SIM with 3 clinical scenarios (CS) and 3 standardized pts (SP): FP for a female pt hospitalized for acute lymphoblastic leukemia tx, FP for a male pt in clinic for germ cell tumor tx, and breast cancer tx for a pregnant pt in 2nd trimester. OT received written educational materials (WEM) and attended a lecture 1 week and 1 day pre SIM, respectively. OT were split into 2 groups; 1 started in the FP CS and 1 in the TPP CS, and then they switched. To reduce cognitive overload, each OT participated in 1 of 2 FP CS: half in the female FP CS and half in the male. Faculty and chiefs led debriefing sessions after all CS. The FP debrief ended with a special "learner as a teacher" part, where OT who attended the female CS taught those from the male CS about their topic and vice versa. The SIM concluded with "take-home" points. Pre (after having WEM) and post SIM anonymous surveys and verbal feedback assessed OT comfort, perceptions, and knowledge. **Results:** A 3 hour SIM with 14 OT and 5 faculty was completed successfully. SIM ended with all OT verbally sharing a learning point and positive feedback. All OT filled pre and post SIM surveys. Pre SIM, 17% reported having prior FP education, and 42% had prior TPP education. However, only 8% and 25% felt adequately prepared for FP and TPP discussions, respectively. Post SIM survey showed major improvement in comfort and knowledge about FP and TPP (see table 1). 75% of OT favored a combination of SIM and learning by teaching over other SIM formats. 83% supported having a TPP lecture before SIM. 100% reported satisfaction with FP and TPP SIM's quality and wanted similar activities in the future. 92% were satisfied with the learner as a teacher tool. 100% felt education about FP and TPP with cancer should be part of fellowship training. Moral/cultural concerns were discussed as possible challenges in FP education. **Conclusions:** The application of LSP through SIM significantly increased OTs' comfort discussing FP and TPP with cancer, and objectively enhanced their knowledge on these topics compared to after reading WEM. The SIM was largely perceived as a successful activity to educate about challenging topics and should become part of fellowship curriculum. Research Sponsor: None.

	Pre SIM %	Post SIM %
Comfortable addressing FP	17	92
Comfortable addressing TPP	8	100
Correct answers about female FP	63	83
Correct answers about male FP	67	94
Correct answers about TPP with cancer	68	98

9030 **Poster Session**

Linking comfort levels and knowledge gaps in hematology/oncology (HO) fellowship education: Insights from a multicenter survey. First Author: Ronak Mistry, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA

Background: HO fellowship programs lack standardized educational approaches. This can impact learning & self-assessment of learning gaps. This study investigates the relationship between HO fellows' (HOF) comfort levels & objective knowledge assessments across diverse HO topics, addressing a critical need for data in this area. **Methods:** HOF from 27 U.S. programs were invited to complete an anonymous survey (Sept-Oct 2023) in which they rated their comfort managing representative HO diseases, namely breast cancer (BC), plasma cell dyscrasias (PCD), hemophilia, von Willebrand disease (vWD), & heparin-induced thrombocytopenia (HIT), on a 7-point Likert scale (1 = extremely uncomfortable, 7 = extremely comfortable). An optional multiple choice knowledge quiz on these topics followed, including an option for "not sure & need to look it up." Fellows were categorized into low (1–3), moderate (4–5), & high (6–7) comfort groups. One-way ANOVA assessed differences in knowledge scores by comfort levels. **Results:** In total,222 HOF completed the comfort survey (53% response rate): 82 PGY4 (37%), 72 PGY5 (32%), & 69 PGY6+ (31%). Also, 189 HOF completed the knowledge quiz (46% response rate): 71 PGY4 (38%), 57 PGY5 (30%), & 60 PGY6+ (31%). Mean comfort levels ($\pm$SD) were: BC diagnosis 4.8$\pm$1.4, localized BC management (mgmt.) 4.2$\pm$1.5, metastatic BC mgmt. 4.2$\pm$1.5, PCD diagnosis 4.8$\pm$1.4, MGUS/smoldering myeloma mgmt. 4.7$\pm$1.4, front-line myeloma treatment 4.5$\pm$1.6, maintenance myeloma treatment 4.1$\pm$1.5, inherited/acquired hemophilia mgmt. 3.7$\pm$1.5, vWD diagnosis 4$\pm$1.4, vWD mgmt. 3.8$\pm$1.4, HIT diagnosis 5.4$\pm$1.1, & HIT mgmt. 5.4$\pm$1.1. Mean knowledge scores were 41% for BC, 39% for PCD, 47% for hemophilia, 33% for vWD, & 51% for HIT. When evaluated by comfort level groups (low, medium, & high), knowledge scores increased significantly with higher comfort levels for BC (25%, 43%, 55%; $p<0.01$), PCD (25%, 38%, 51%; $p<0.01$), hemophilia (29%, 55%, 77%; $p<0.01$), & vWD (13%, 39%, 62%; $p<0.01$). HIT scores showed no significant difference by comfort levels (p=0.89). The number of "not sure" responses (%) significantly decreased ($p<0.01$) with greater comfort across topics: BC (53%, 20%, 10%), PCD (39%, 23%, 7%), hemophilia (52%, 28%, 2%), vWD (69%, 40%, 12%). HIT "not sure" responses showed no significant difference by comfort levels. **Conclusions:** This multicenter analysis demonstrates a correlation between HOF comfort levels & knowledge assessments. Despite overall low performance on knowledge tests, comfort levels effectively discriminated between knowledge groups, underscoring their potential utility as a surrogate for educational progress. These data highlight the need for interventions to bridge gaps between perceived & actual knowledge. Future studies to validate these results across broader topics & institutions to inform optimal education strategies in HO training programs are needed. Research Sponsor: None.

9031 **Poster Session**

Enhancing bereavement education and emotional preparedness: A global survey of oncology residency programs. First Author: Giusti Raffaele, Medical Oncology Unit, Sant'Andrea Hospital of Rome, Rome, Italy

Background: Bereavement care is a vital yet underemphasized aspect of oncology, requiring both clinical expertise and emotional resilience. Despite its importance, bereavement training is rarely integrated into residency programs, leaving residents unprepared and at risk of emotional fatigue and burnout. Addressing this gap is critical to improving caregiver support and resident well-being. This study evaluates the global state of bereavement training, its impact on preparedness, and the need for tailored interventions. **Methods:** A cross-sectional survey was conducted among 115 oncology residents from 21 countries. The survey included questions on demographics, bereavement training, interactions with grieving caregivers, preparedness, barriers, and interest in education. Descriptive statistics summarized the data, chi-square tests evaluated associations between training and preparedness, and correlation analysis assessed the relationship between caregiver interaction frequency and preparedness. **Results:** Participants were 58% female and 42% male. Most worked in academic hospitals (53%), followed by the public (44%) and private centers (3%). Residents represented 21 countries, with Italy contributing 61% of responses. Other countries included the UK, Pakistan, Romania, Kenya, Portugal, Bosnia, Saudi Arabia, Germany, Malaysia, Ukraine, Ireland, Russia, France, Egypt, Turkey, Australia, Iraq, Yemen, Georgia, and Norway. Bereavement training was absent for 80% of participants. Preparedness levels were rated as "Somewhat prepared" by 44.3%, "Not very prepared" by 43.5%, "Not at all prepared" by 8.7%, and "Very prepared" by 3.5%. Barriers included emotional fatigue (62%), lack of training (48%), and time constraints (41%). Emotional distress was common, with 61% reporting occasional impact, 33% deep impact, and 38% considering leaving residency due to emotional demands. Residents with formal training declared significantly higher preparedness (χ^2 = 13.83, p = 0.003). A weak positive correlation (r = 0.19) was found between caregiver interaction frequency and preparedness. **Conclusions:** Oncology residents face significant challenges in bereavement care due to insufficient training, high emotional demands, and systemic barriers like time constraints. The finding that 38% considered leaving residency underscores the emotional toll of inadequate preparation. Integrating bereavement training into oncology curricula is essential to enhance confidence, resilience, and caregiver support. Training should address grief management, pathological bereavement, and communication skills. Experiential learning, such as mentorship and reflective practices, can further improve preparedness. These interventions aim to meet residents' emotional and professional needs while enhancing patient and caregiver outcomes. Research Sponsor: None.

9032 **Poster Session**

Evaluation of NCI Designated Cancer Centers medical student education and training initiatives. First Author: Ana I. Velazquez Manana, University of California, San Francisco, San Francisco, CA

Background: The rising incidence of common cancers, an aging oncology workforce, and workforce shortages underscore the importance of medical education in oncology. However, U.S. medical students report that cancer education is underemphasized in their curriculum, and non-surgical oncology clerkships are infrequently required. Providing medical students with exposure to cancer care and research is crucial for encouraging them to pursue careers in oncology. This study evaluates the current landscape of medical student education and training initiatives at National Cancer Institute-designated cancer centers (NCIDCCs). **Methods:** In January 2025, we conducted a qualitative evaluation of the education and training webpages of NCIDCCs. Each webpage was reviewed to identify programs and training opportunities available to medical students. Programs specifically designed for medical students, as well as those for which medical students are eligible, were included. Data were summarized using descriptive statistics. **Results:** Of the 72 NCIDCCs, 71 had evaluable education and training webpages. The majority (n = 63, 89%) listed at least one education, training, or professional development initiative for medical students. Five institutions offered more than five programs for medical students. Most NCIDCC medical student initiatives focused on research training, with the most common opportunities being summer research fellowships, Medical Scientist Training Programs (MSTP), and travel awards. Only a few NCIDCCs listed clinical electives or internships among their offerings. Additionally, only 14 (20%) NCIDCCs advertised medical student programs focused on students from diverse backgrounds. **Conclusions:** Expanding cancer education and training in medical school is essential to addressing the growing need for an oncology workforce. While multiple research training opportunities exist at NCIDCCs, few cancer centers offer clinical electives or internships that provide medical students with direct exposure to clinical cancer care. Our analysis is limited to publicly available webpage listings; as a next step, we will conduct a survey of NCIDCC offices of education and training to further evaluate medical student initiatives. Given their multidisciplinary focus and integration of research with clinical care, NCIDCCs are uniquely positioned to develop and train the next generation of oncologists and clinical researchers through enhanced oncology education and training programs for medical students. Research Sponsor: None.

9033 **Poster Session**

Advancing gender-responsive cancer control: A mixed methods evaluation of the leadership program for women in oncology. First Author: Meritxell Mallafré-Larrosa, City Cancer Challenge Foundation, Geneva, Switzerland

Background: Women constitute nearly 70% of the global health and social workforce but hold only 25% of senior leadership roles. Increasing women's representation in leadership is essential to addressing global health challenges and delivering equitable solutions. Leadership programs for women in healthcare enhance skills, confidence, and career progression. The Leadership Program for Women in Oncology (LPWO), developed by City Cancer Challenge (C/Can) in partnership with the American Society of Clinical Oncology (ASCO), aims to empower mid-career women oncologists in C/Can cities to lead transformative cancer care improvements. Combining in-person and virtual training, networking, and mentorship, the LPWO's first cohort was evaluated to assess its impact on participants, institutions, and communities. **Methods:** Data were collected through surveys and key informant interviews (KIIs) with the 10 program participants from diverse geographic and professional backgrounds. Surveys, conducted at five time points, assessed knowledge across 11 leadership domains. Descriptive and inferential statistical analyses were used to evaluate changes over time. **Results:** Significant improvements were observed across all leadership domains, with mean scores increasing ($p<0.05$). KIIs revealed broader impacts, including strengthened team dynamics, strategic institutional involvement, and community engagement. Participants emphasized mentorship and coaching as a cornerstone of the program, fostering professional growth, project development, and connections with global experts. **Conclusions:** The LPWO demonstrates the potential of targeted leadership programs to drive systemic change. By equipping women oncologists with essential leadership skills, it enables them to advance institutional practices and reduce health disparities. Furthermore, the LPWO plays a critical role in fostering gender-responsive health systems by empowering women leaders to advocate for equitable and inclusive cancer care. Continued investment in similar initiatives, paired with rigorous evaluation, is critical for achieving sustainable global health outcomes. Research Sponsor: None.

9034 **Poster Session**

Board certification practices of US hematologists and oncologists. First Author: Austin Wesevich, University of Chicago, Chicago, IL

Background: United States (US) fellowship programs train physicians in both hematology and medical oncology (HO), yet fellows often focus on only one of these specialties. Historically, single-subspecialty boarding has been viewed as a feasible career pathway for medical oncologists pursuing academic careers; single-boarding in hematology was uncommon while dual-boarding was favored for clinical practice. Real-world HO board certification practices and how these partition with career pathways are presently unknown. **Methods:** We linked Centers for Medicare & Medicaid Services (CMS) and American Board of Internal Medicine (ABIM) publicly available data to describe the credentialing practices of all US HO who billed Medicare Part B in 2022. Physicians were single-boarded (only obtained hematology or oncology certification) or double-boarded. Current position was dichotomized per CMS as teaching versus non-teaching hospital and metropolitan versus non-metropolitan per rural-urban commuting area codes (1-3 vs 4-10). Researchers had non-federal research funding in 2022 per CMS Open Payments while clinicians did not. **Results:** Of 12,394 physicians, 32% single-boarded in oncology, 3% single-boarded in hematology, and 64% double-boarded. Single-boarded hematologists were more frequently employed at teaching hospitals in metropolitan areas (Table). Researchers or those who graduated from a top 20 ranked medical school were more frequently single-boarded. Maintenance of certification was most common for those who initially double-boarded and least common for those who single-boarded in hematology. Physicians who maintained both boards or only oncology boards were most frequently clinicians at teaching hospitals while those who only maintained hematology boards were most frequently researchers at teaching hospitals. **Conclusions:** Over one-third of US HO fellowship graduates single board, with single-boarding in oncology being 10x more common than single-boarding in hematology. Single-boarded hematologists were more likely to work at teaching hospitals than single-boarded oncologists or dual-boarded physicians. Consideration could be given to tailoring US HO fellowship training requirements to more appropriately fit the interests and career pathways of HO fellows. Research Sponsor: None.

Physician characteristics by initial ABIM hematology/oncology credentialing.

Characteristic	Oncology Single-Board, n=4,012	Hematology Single-Board, n=400	Hem/Onc Double-Board, n=7,982	p-value
Female gender	1,402 (35%)	13 (34%)	2,878 (36%)	0.38
Years Since Medical School Graduation (SD)	28.8 (11.9)	29.8 (14.7)	25.0 (11.0)	<0.001
Top 20 Medical School	641 (16%)	57 (14%)	645 (8%)	<0.001
Teaching Hospital	3,317 (83%)	361 (90%)	6,549 (82%)	<0.001
Metropolitan Area	3,777 (94%)	388 (97%)	7,508 (94%)	0.04
Non-Federal Research Funds	1,586 (40%)	156 (39%)	2,602 (33%)	<0.001
Maintenance of Certification	2,859 (71%)	252 (63%)	6,450 (81%)	<0.001

9035 **Poster Session**

Exploring DORIS: A cancer-focused AI knowledge platform for diagnosis and treatment information. First Author: Joseph Monforte, Wild Type Advocates, Lincolnshire, IL

Background: Clinicians in oncology have high demands on their time due to lack of sufficient staffing, leading to the need to work additional hours outside of practice, "pajama time", and high levels of stress. Key approaches to improving the situation for clinicians include: (a) increasing staffing and resources, (b) improved teamwork, (c) utilization of ambient AI for notetaking, and (d) the use of AI assistants for medical knowledge access and interpretation. We're focused on (d). Regarding the use of AI assistants, our informal survey of oncology fellows and attendees has revealed that over 90% of them are using a general AI chat tool to help them find key medical information. The use of a general AI chat tool is problematic since there is no medical review or curation, leading to errors and gaps in the information provided. **Methods:** Our team has built an alternative to general AI chat, called DORIS (Dynamic Oncology Reference Information System). The DORIS for breast cancer prototype was built in alignment with ASCO's Guiding Principals for AI, and targets easy access to information around 5 pillars of medical knowledge needed for cancer care: molecular biomarkers, diagnostic testing, treatment pathways, drug-drug comparison, and clinical trial search. The system uses a Large Language Model (LLM) to facilitate access to a carefully curated set of medical documents covering the 5 pillars, including treatment pathways (with digitization of flow diagram logic), FDA, NIH and other publicly accessible datasets. To be accurate, the curation of DORIS' knowledgebase needs to be kept up-to-date, while removing out-of-date information (something general AI platforms don't do). To further increase the ease of use, DORIS includes different approaches to query for information while also using its embedded intelligence to suggest follow up questions. **Results:** Medical review of DORIS is ongoing. Early errors were identified related to omissions from curation. Other errors occurred due to bugs within the LLM, e.g. the responses suddenly shifted to Spanish. The reference materials have been expanded to reduce omissions and code implemented to double check responses from the LLM. We are on target for onboarding over 250 users for the early access program. **Conclusions:** Early user feedback has been positive with regards to relevance and utility. We will report on the first 6 months of use of this prototype platform, providing multiple metrics on how it is being used, and an analysis of user feedback on the value of the tool. Research Sponsor: Bridgewest Ventures New Zealand; Callaghan Innovation - Government of New Zealand.

9036 **Poster Session**

The value of observerships abroad: Lessons from UA-MED supporting Ukrainian cancer care during the war. First Author: Nataliya Kovalchuk, Stanford University, Help Ukraine Group, Stanford, CA

Background: This study evaluates the influence of international observerships organized by the coalition of healthcare professionals from academic institutions - the Ukrainian Alliance for Medical Exchange and Development (UA-MED) - on the professional development, knowledge transfer, and clinical practice improvement of Ukrainian oncology professionals during the war. **Methods:** A total of 126 international observerships were facilitated for various Ukrainian medical professionals across 17 participating institutions the US, Canada, Europe, and Australia. A survey was administered to assess the impact of observerships on oncology care in Ukraine, focusing on procedural knowledge gained, lessons learned, and challenges faced when implementing new techniques upon return. **Results:** Eighty-six respondents participated in the survey. Seventy-three percent of respondents were oncology professionals, including 30.1% radiation oncologists, 31.7% surgeons, 15.9% medical oncologists, and 14% medical physicists. The median duration of the observerships was 4 weeks with 79.7% observers attending a professional conference. The average satisfaction score for the observerships was 9.6 $\pm$ 0.7 out of 10. Importantly, 93% of respondents reported a shift in their perception of how to practice medicine, 90% learned new procedures and techniques, and 71.2% implemented these new procedures upon returning to Ukraine. However, despite this progress, significant barriers to implementation were encountered, including lack of material resources (70.7%), human resources (43.1%), and support from department leadership (43.1%) and colleagues (32.8%). Encouraged to disseminate their knowledge, participants provided informal training to colleagues (78.0%), prepared presentations for their institutions (69.5%), national conferences (44.1%), and incorporated learned materials into educational lectures (49.2%). Notably, 83.0% of participants maintained ongoing mentorship contact with their training institutions. Key institutional advancements included transition from Co-60 to linear accelerators at few centers, the launch of an allogeneic bone marrow transplant program, and the development of educational programs across various specialties. Participants emphasized improved confidence in their clinical decision-making and highlighted the value of multidisciplinary team approaches they observed abroad. **Conclusions:** The international observerships played a crucial role in enhancing the skills and knowledge of Ukrainian cancer care professionals during the war. Despite the ongoing conflict, significant improvements were made in clinical practice, medical education, and the implementation of new procedures. The success of these observerships underscores the potential for similar programs to be replicated in other LMICs/UMICs. Research Sponsor: None.

9037 **Poster Session**

Dissecting publication timelines: Insights from high-impact oncology journals. First Author: Abdulmalek Aljafari, Brody School of Medicine at East Carolina University, Greenville, NC

Background: Efficient dissemination of research findings is critical in oncology, where timely access to new knowledge impacts clinical care and outcomes. This study analyzes publication timelines of high-impact oncology journals to identify patterns and determinants, including research categories and study designs. **Methods:** This is a retrospective observational study. Journals with the highest impact factors and available publication timeline data were included: *Journal of Clinical Oncology, Molecular Cancer, Clinical Cancer Research,* and *Cancer Discovery*. All articles published in 2023 were analyzed for submission-to-acceptance, acceptance-to-publication, and total publication times. Data were processed using SPSS, and statistical comparisons were made with the Kruskal-Wallis test (significance: $p<0.05$). **Results:** A total of 875 articles were analyzed. The overall median total publication time (TT) was 7.1 months (IQR: 5.7–8.9), with submission-to-acceptance (AT) and acceptance-to-publication (PT) medians of 4.8 months (IQR: 3.5–6.3) and 2.2 months (IQR: 1.6–2.6), respectively. Among journals, *Molecular Cancer* exhibited the shortest TT (median: 4.7 months; IQR: 3.1–6.6), while *Cancer Discovery* had the longest TT (median: 8.8 months; IQR: 6.8–10.6). Similarly, *Molecular Cancer* achieved the fastest AT (median: 3.9 months; IQR: 2.2–5.4) and PT (median: 0.6 months; IQR: 0.4–1.1). Conversely, *Cancer Discovery* recorded the slowest AT (median: 6.0 months; IQR: 4.5–7.8) and PT (median: 2.8 months; IQR: 2.4–3.2). In terms of research categories, blood cancer articles accounted for the largest proportion of publications (14.4%), followed by gastrointestinal cancer (13.9%). Articles in genitourinary (median TT: 6.4 months; IQR: 5.5–8.8) and cardiac cancer (median TT: 6.5 months; IQR: 5.9–6.9) categories had the shortest TT, while endocrine (median TT: 7.9 months; IQR: 5.6–10.9) and immunotherapy (median TT: 9.1 months; IQR: 6.8–10.5) categories exhibited the longest TT ($p<0.05$). Clinical trials were the most common study design (37.6%), followed by cross-sectional studies (19.5%). Systematic reviews had the shortest TT (median: 2.4 months; IQR: 1.9–9.2), while proof-of-concept studies required the longest TT (median: 9.5 months; IQR: 8.7–10.7) ($p<0.05$). Systematic reviews and database studies also had the shortest PT (median: 1.5 months), whereas proof-of-concept studies had the longest PT (median: 2.8 months; $p<0.001$). **Conclusions:** Publication timelines in oncology journals vary significantly by journal, research category, and study design. *Molecular Cancer* demonstrates the fastest publication processes, while *Cancer Discovery* exhibits the slowest. Genitourinary and dermatologic oncology categories, as well as systematic reviews, achieve the most expedited timelines, emphasizing the need to consider category and study design in publication planning. Research Sponsor: None.

9038 **Poster Session**

The evolving landscape of academic and industry partnerships in gynecologic oncology clinical trials. First Author: Kevin Ji Li, Geisel School of Medicine at Dartmouth, Hanover, NH

Background: To determine trends in the financial relationships of study investigators in gynecologic oncology trials. **Methods:** From 2011-2024, phase III trials were identified from clinicaltrials.gov. Data was collected from the conflict-of-interest (COI) statements of 54 clinical trials. Chi-square and Fisher's exact tests were used for statistical analysis. **Results:** Of1,390 total co-authors from 54 clinical trial publications, we found that 46.3% of authors were from European nations, 28.3% were based in the United States, and 16.9% were from East Asian nations, with the remaining 8.5% from other nations (including, but not limited to, Australia, Canada, and Mexico). Of the listed authors' titles, 82.8% held MDs and 17.2% held non-MD degrees (PHD, MPH, MSc). Most (74.0%) of the trials were on ovarian cancer, with the remainder being on cervical (13.0%) and endometrial (13.0%) cancer. The majority (79.5%) of trials were sponsored by pharmaceutical companies, while the remainder were academic/cooperative-led trials. Among the pharmaceutical and industry sponsors, Roche / Genentech sponsored the most trials (27.8%), followed by Merck Sharp & Dohme (16.7%) and AstraZeneca (14.8%). Overall, 61.8% of total authors had some form of COI; of the total authors, 40.9% were consultants, 29.1% received research funding, 9.6% attended speaker bureaus, 18.6% received travel funds, and 9.8% declared employment/stock ownership. In all trials, the majority of authors disclosed COI regardless of if the trial was pharmaceutical or cooperative-led, at 63.5% and 55.2%, respectively. To evaluate trends, we divided the data into three time periods, 2011-2015, 2016-2019, and 2020-2024. Over time, there was a statistically significant increase in the number of authors who were consultants: 27% to 40% to 44% ($p<0.001$); who received research funding: 16% to 25% to 33% ($p<0.0001$); and who received travel funds: 8% to 19% to 20% ($p<0.01$). There was no change in speaker bureau participation (p=0.63) or employment/stock ownership (p=0.20). **Conclusions:** Financial relationships between study investigators and pharmaceutical companies have increased, particularly in consulting and research funding. As industry involvement grows, academic cooperative groups should maintain close collaboration to ensure scientific integrity and guide trial design. Research Sponsor: None.

9039 **Poster Session**

Addressing gender disparities in oncology and hematology education: Insights from social media engagement analysis. First Author: Viviana Cortiana, University of Bologna, Bologna, Italy

Background: Gender disparities in professional visibility pose significant challenges to equity in oncology and hematology education. Women represent only 34% of speakers at major oncology conferences and author just 37% of high-impact oncology publications. MedNews Week (MNW), a global platform dedicated to combating medical misinformation and fostering inclusivity, aims to address these gaps by amplifying diverse voices and promoting equitable professional representation. This study analyzed speaker engagement data to identify visibility disparities and propose actionable strategies to enhance representation in oncology and hematology education. **Methods:** MNW hosted 20 speakers during Years 2 and 3 of its programming. Social media engagement metrics were collected and analyzed for male and female speakers across five platforms: Twitter, LinkedIn, Instagram, YouTube, and TikTok. Metrics included average engagements per post (likes, shares, comments) and overall engagement trends. Gender-specific differences in engagement were evaluated using statistical analyses, including independent t-tests, to determine significance. Data were normalized to account for variations in platform algorithms and audience size. **Results:** Male speakers achieved nearly three times the total engagement of female speakers, averaging 123,745 engagements per event compared to 41,133 for females, a difference representing approximately 75% of total engagement by males. A t-test demonstrated a highly significant disparity in engagement levels ($t = -14.01$, $p = 3.48 \times 10^{-16}$). Twitter emerged as the dominant platform for both genders, with male speakers averaging 46,870 engagements, compared to 37,717 for females. However, female speakers excelled on TikTok (94 average engagements, with no male presence) and achieved near parity on LinkedIn (2,849 vs. 2,901). YouTube engagement favored females, with an average of 85 versus 61 for males. **Conclusions:** Male speakers demonstrated significantly higher overall engagement; however, female speakers achieved parity, or even outperformed, on emerging platforms like TikTok and YouTube. These findings underscore persistent challenges to achieving gender equity while also highlighting the potential of innovative platforms to amplify underrepresented voices. This analysis reinforces the need for targeted strategies, such as leveraging emerging platforms and expanding professional visibility initiatives, to enhance inclusivity and equity in oncology and hematology education. Research Sponsor: None.

Engagement metrics across social media platforms for speakers.

Platform	Female Engagement (Average)	Male Engagement (Average)	Difference
Twitter	37,717	46,870	24.3% higher (male)
LinkedIn	2,849	2,901	1.9% higher (male)
Instagram	203	279	37.0% higher (male)
TikTok	94	0	Female only
YouTube	85	61	39.4% higher (female)

9040 Poster Session

Harnessing social media for cancer prevention and early detection: Challenges, opportunities, and pathways to equity. First Author: Viviana Cortiana, University of Bologna, Bologna, Italy

Background: Social media is a valuable tool for cancer prevention and early detection but faces challenges like gender disparities, misinformation, and minority underrepresentation. Women receive 28% fewer views and 41% less engagement than men, while most cancer screening content on YouTube and TikTok is low quality and contains misinformation. MedNews Week (MNW), a global education platform, addresses these issues by promoting accurate and inclusive digital health communication. This study assesses engagement and platform effectiveness to improve cancer communication strategies. **Methods:** A systematic review of 225 articles from PubMed, supplemented by MedNews Week (MNW) outreach data, was conducted to evaluate the role of social media in cancer prevention and early detection. Metrics analyzed included platform effectiveness, engagement trends, content themes, and challenges related to misinformation and representation. **Results:** Twitter, utilized in 57% of studies, was effective in facilitating cancer prevention discussions. Breast cancer dominated interventions at 52%, while colorectal and lung cancers were underrepresented. Content quality was a concern, with 98% of YouTube and 100% of TikTok videos on prostate cancer screening rated low to moderate. Additionally, 88% of YouTube and all TikTok videos contained moderate to high misinformation. Representation gaps showed African American and Hispanic populations featured in only 10% and 6% of YouTube videos, and 20% and 12% of TikTok videos. Discussions of high-risk groups appeared in 46% of YouTube but just 8% of TikTok videos. Promising misinformation detection methods included linguistic models analyzing Twitter posts, achieving a macro F1 score of 79.7 for predicting unreliable information. **Conclusions:** Social media has great potential to improve cancer awareness, prevention, and early detection but is hindered by misinformation, lack of inclusivity, and inconsistent content quality. Overcoming these challenges requires platform-specific strategies, collaboration with healthcare entities and influencers, and a focus on diverse representation. MNW's efforts demonstrate the importance of providing reliable, inclusive health information to reduce disparities and promote equitable digital health communication. Research Sponsor: None.

Metrics of social media engagement for cancer awareness and detection.

Platform	Primary Use	Representation Gaps	Content Quality	Misinformation Levels	Engagement
Twitter	Prevention	N/A	N/A	N/A	Effective
YouTube	Prostate cancer screening	Black: 10%, Hispanic: 6%	98% low to moderate	88% moderate to high	Limited
TikTok	Emerging platform	Black: 20%, Hispanic: 12%	100% low to moderate	100% moderate to high	Minimal
LinkedIn	Professional engagement	N/A	N/A	N/A	Gender parity
Instagram	Awareness	N/A	N/A	N/A	Effective

9041 Poster Session

Empowering medical oncologists: Exploring the impact and engagement of telegram channels for professional development in Russia. First Author: Anastasia Danilova, Moscow City Oncology Hospital 62, Moscow, Russian Federation

Background: Social media use has gained popularity among medical professionals, with X being one of the most popular platforms globally by medical oncologists. Physicians worldwide use it for conference communication, sharing scientific articles, breaking geographical barriers, and engaging with peers globally. Recently, there has been increasing interest in leveraging former Twitter as an educational tool among medical oncologists, proving effective for accessing the latest news and sharing opinions. However, lot of social networks are unavailable in Russia, prompting a surge in interest in other social media platforms. Over the past three years, numerous Professional Medical Channels have emerged on Telegram, a popular platform among Russian speakers worldwide. Here, we describe the extensive use, engagement, and professional impact within the medical oncology community utilizing these educational channels. **Methods:** We analyzed Medical Oncology Telegram Channels with over 2 thousand followers. The authors (all practicing oncologists) share conference news, conduct tumor boards, clinical cases and other high yield educational materials. Ensuring the authors' credibility as established physicians in the oncology community, we analyzed engagement metrics, follower counts, and conducted an online survey among users to assess the channels' impact on daily medical practice. We present the results of this analysis. **Results:** We analyzed Telegram medical oncology channels with over 2 thousand followers, averaging 6,354 followers each. The average post reached 2,260 users, with 53% of followers engaging with posts. The online survey comprised 338 medical professionals, including practicing medical oncologists (41%), community-based oncologists (11.5%), surgical oncologists (19.6%), oncology residents (19.6%), medical students (9%), and other medical professions. Most respondents (95%) were based in Russia, with smaller percentages from Belarus, Kazakhstan, Uzbekistan, and Israel. When asked about the channels' impact on daily clinical practice, 33% reported significant changes, 50.6% reported slight changes, and 16.3% noticed no change. Additionally, 87.6% felt more confident in treatment choices due to shared information. Respondents also noted increased job satisfaction and support in combating physician burnout, with 83.3% expressing a sense of community and support through these channels. **Conclusions:** Telegram channels are gaining traction among Russian-speaking medical professionals, offering a new avenue for sharing medical updates, conference coverage, exchanging ideas, and fostering community. Especially during challenging times, such support is crucial. Further research is warranted to explore how social media engagement can enhance professional development among Russian-speaking medical oncologists. Research Sponsor: None.

9042 Poster Session

The bubble effect: Impact of ASCO digital promotion on *Journal of Clinical Oncology* (*JCO*) download metrics (2023). First Author: Oyepeju Folashade Abioye, Allegheny Health Network, Pittsburgh, PA

Background: The impact of digital promotion on scientific article metrics remains debated. This study examined how ASCO's digital promotion via Twitter (X) and podcasts influenced download rates for articles published in the Journal of Clinical Oncology (JCO) between January and December 2023. **Methods:** We conducted a retrospective review of articles published in print between January and December 2023 in JCO. Monthly download numbers from each article's month of publication till November 2024 were collected from the official JCO webpage. Promotions by the JCO Twitter (X) account (@JCO_ASCO) and JCO Podcasts - *JCO Cancer Stories: Art of Oncology Podcast* and *ASCO Guidelines Podcast* were tracked. Articles with print dates post-December 2023, those without print dates, and manuscript categories including Correspondence, Errata, Retractions, and Acknowledgments, were excluded. To evaluate the association between monthly downloads and digital promotion, multivariable mixed-effects Poisson regression models were employed. Articles were treated as random effects, while digital promotion and months since publication were treated as time-varying covariates. Free access options were included as fixed effects. Monthly rate ratios per unit change in each covariate, with corresponding 95% confidence intervals (CI) were used to summarize associations. **Results:** In total, 563 articles, of which 297 were original reports were analyzed. Digital promotion and free access significantly increased download rates. Articles promoted via official tweets experienced a 27.6% increase in download rates, while those featured in podcasts saw a more modest but still significant increase of 9.2%. When focusing on original reports, podcast promotion had a greater relative impact, with a 19.1% increase in downloads (Table 1). **Conclusions:** Digital promotion of scientific articles via Twitter (X) and Podcasts significantly boosts downloads. However, interpreting the impact of free access is challenging due to incomplete data on when articles became freely accessible. Future studies should address these limitations and explore broader metrics such as citation counts, journal impact factors, and author H-indices to better understand the influence of digital promotion on scientific dissemination. Research Sponsor: None.

Multivariable analysis of digital promotion and monthly paper downloads - eligible papers vs Original Reports only.

Variable*	ELIGIBLE PAPERS (N=563) Rate ratio (95%CI; p-value)	ORIGINAL REPORTS ONLY (N=297) Rate ratio (95%CI; p-value)
Official tweet (Yes vs. No)	1.276 (1.270, 1.281; p<0.001)	1.128 (1.121, 1.135; p<0.001)
Official podcast (Yes vs. No)	1.092 (1.084, 1.100; p<0.001)	1.191 (1.180, 1.202; p<0.001)
Open/free/partial access (Yes vs. No)	3.706 (2.766, 4.965; p<0.001)	1.411 (0.331, 6.020; p=0.642)

*Months since online publication and papers were included in the model for adjustment.

9043 Poster Session

Racial, ethnic, sex, and subspecialty demographic composition of initial fellow of the Fellow of the American Society of Clinical Oncology (FASCO) recipients through 2024. First Author: Victoria Shiqi Wu, Case Western Reserve University School of Medicine, Cleveland, OH

Background: Disparities in cancer care, including underrepresentation in the healthcare workforce, leadership, and recognition, remain a significant challenge. The Fellow of the American Society of Clinical Oncology (FASCO) designation honors individuals for their commitment to ASCO, the largest clinical oncology organization in the world. In 2022, the FASCO selection process transitioned to a more transparent, merit-based system requiring 100 points for FASCO designation. However, recipient demographics of FASCO recipients remain largely unexplored. **Methods:** All FASCO recipients through 2024 were identified and reviewed using publicly available data from the ASCO website, documenting name, degree, and award year. Providers with National Provider Identifiers were linked to Medicare Part B data. Race, ethnicity, sex, specialty, medical school graduation year, and fellowship graduation year were verified or determined through Medicare data and website reviews. Analyses included Pearson's chi-squared test, Fisher's exact test, and the Mann-Kendall trend test. **Results:** Among 644 FASCO recipients, 400 (62%) are male, 244 (38%) are female, 540 (84%) are White, 20 (3.1%) are Black, and 616 (96%) have non-Hispanic ethnicity. Medical oncologists constituted 512 (80%) of recipients, followed by 43 radiation oncologists (6.7%), 25 surgical oncologists (3.9%), and 64 (9.9%) from various specialties and professions, including pediatric and gynecological oncology, family practice, palliative care, radiology, urology, oral oncology, software engineering, non-profits, health policy, social work, research, and patient advocacy. The average time in practice before FASCO designation is 23 years. Between 2007 and 2024, FASCO awards increased significantly in both overall number and diversity, with non-White recipients rising from 16.1% to 22.7% ($p < 0.001$), Hispanic recipients from 4.3% to 13% ($p < 0.001$), and female recipients from 38% to 49% ($p = 0.003$). Following the 2022 selection change, recipient diversity improved, with 25.5% non-White recipients, 7.8% Hispanic recipients, and near gender parity achieved (122 men, 121 women, $p < 0.001$) from 2022 to 2024. **Conclusions:** In this first definitive review of FASCO recipients, nearly two-thirds of recipients are male, 84% are white, and 80% are medical oncologists. Over time, the diversity of recipients in terms of gender, race, and ethnicity has gradually improved, accelerated by the implementation of a more transparent, merit-based system in 2022. These changes in the FASCO selection process have significantly enhanced diversity among recipients, highlighting the critical role equitable and transparent practices play in promoting diversity and inclusion within professional organizations. Research Sponsor: None.

9044 **Poster Session**

Advancing gender equity in cancer research across north Africa: A comprehensive analysis of women's role and men's supportive efforts—Final findings from the GEORGiNA-1 study. First Author: Khalid El Bairi, Faculty of Medical Sciences, University Mohammed VI Polytechnic, Ben Guerir, Morocco

Background: Despite limited research on gender inequity in North Africa, this male-dominated region provides a unique context for exploring gender dynamics in academic oncology. The GEORGiNA-1 study (Gender Equity in Oncology Research Group in North Africa) examined the representation of female oncologists in publications, cancer societies, and editorial boards of peer-reviewed journals, while also evaluating the outcomes of a mentorship program aimed at supporting their professional development. **Methods:** An updated analysis of articles published from 2018 to 2022 was conducted. Data extraction was performed manually using a standardized template, capturing gender and publishing features. Gender representation was further evaluated in leadership roles within oncology societies, editorial boards of regional journals, and through a pilot men-led mentorship program aimed at supporting women in cancer research via training, project development, and academic publishing guidance. Factors associated with gender distribution were studied using Chi-squared and Fished Exact tests as well as logistic regression. **Results:** A total number of 7,774 publications including 6,142 original articles were analyzed. Females accounted for 50.7% of first authors position. There was a significantly higher percentage of females as first authors in Tunisia ($p<0.001$). In last author positions, male authors were more prevalent, accounting for 63.5% of publications. Male researchers were found to have significantly higher representation as principal investigators (PIs) ($p < 0.001$). Female first authors were significantly more likely to collaborate with female co-authors ($p < 0.001$). Similarly, when females held PI positions, there was a statistically significant increased number of female co-authors ($p < 0.001$) and female first authors as well ($p < 0.001$). Female first authors were found to publish significantly more original research ($p < 0.001$), but they published significantly less original research when holding PI positions ($p < 0.001$). Additionally, female PIs received significantly less funding ($p < 0.001$). The percentage of local female speakers at cancer meetings consistently outpaced that of male speakers. Male dominance was evident across most journals. Fifteen female mentees were selected for the mentorship program. Among those who achieved most of the program's goals (n=12), they produced significant outputs, including an edited book, original studies, reviews, conference abstracts, and multiple poster and oral presentations at oncology meetings. **Conclusions:** Although women in cancer research seem to hold a fair position in North Africa, barriers such as insufficient funding and limited international collaboration continue to hinder progress toward gender equity. Research Sponsor: None.

9045 **Poster Session**

A multifactorial analysis of first-author retention in ASCO accepted works. First Author: Taha Huda, HCA Healthcare/USF Morsani College of Medicine GME: Bayonet Point Hospital, Hudson, FL

Background: Ensuring clinician oncologists remain engaged with research is an important step in maintaining optimal patient care in a rapidly changing field, and can be especially difficult for clinicians of marginalized groups. To identify trends in research engagement among oncologists, we performed a retrospective analysis on first-author retention in ASCO accepted works from 2019-2024, focusing on year presented, presentation type, and gender. **Methods:** Data from publicly available ASCO works from 2019 to 2024 were obtained from ASCO online materials, including first author (or speaker/chair) and presentation type (limited to education session, oral abstract, poster discussion session, poster session, and online-only ASCO meeting publication). Gender was identified by name using Namsor, a public web-tool. Names that could not be predicted by the web-tool were identified manually by physical presentation on institutional websites, if possible. An original script was created to identify first-author retention year-to-year, outputting the proportion of first authors found in both years and appropriate statistical tests. This analysis focused on comparing one-year retention (e.g. 2019-2020, 2020-2021, etc.). **Results:** We found that the period with the highest one-year first-author retention of all works was during 2022 to 2023, with 22% retention (985 of 4445 first-authors). First-author retention remained 20-22% for all other periods analyzed, except during 2023-2024 where retention decreased to 15% (806/5568; Two-proportion test comparing 2022-2023 and 2023-2024: $p < 0.001$). Focusing on specific presentation types, education sessions were found to have the lowest one-year retention, averaging 5.1%, as compared with poster sessions, which had the highest average one-year retention of 15.3% (Two-proportion test: $p < 0.001$). Looking at gender, we found that education sessions were the least male-prevalent, with an average of 49.6% retained speakers being male across all years. For oral abstracts, poster discussion sessions, and online-only publications, 53-54% of retained first-authors were male. Notably, first-author retention in poster sessions was much more male-prevalent, with an average of 62.7% of first-authors being male (Two-proportion test comparing male proportion in education and poster sessions: $p = 0.002$). Lastly, we found that five-year first-author retention of all works from 2019 to 2024 was significantly male-dominated, with 61% of those retained being male (267/437; one-proportion test $p < 0.001$). **Conclusions:** Trends of retention at a major oncology conference were identified, including recent decreases in retention, which could be due to a relative increase in first-time authors. The male prevalence in poster sessions and decrease in first-author retention of women over longer periods of time reveal specific areas to create more equitable opportunities for women in research. Research Sponsor: None.

TPS9046 **Poster Session**

A randomized controlled trial of high-fidelity simulation versus mentoring training for residents: ACACIAS 2. First Author: Elise Deluche, CHU Dupuytren, Limoges, France

Background: In medical oncology, the "know-how-to-be" aspect of training is crucial but often underemphasized in resident education. Typically, residents develop their interpersonal skills through direct patient interactions. The challenge lies in delivering cancer diagnoses with empathy and effectively managing the patient experience through advanced communication strategies. High-fidelity simulation training has proven effective in educating professionals, including those in surgical fields. Our previous feasibility studies established a simulation framework for cancer consultation processes. This study aims to demonstrate that high-fidelity simulation training provides greater benefits for residents compared to traditional mentoring by reducing perceived stress levels. **Methods:** ACACIA2 (*n° HDH :* F20221011092723) is a prospective, randomized, open-label, national, multicenter trial that aims to enroll 100 young doctors. After one high-fidelity simulation evaluation, they were randomly assigned (1:1) to have traditional mentoring (Arm A or control arm)+/- 2 sessions of high-fidelity simulation with theoretical training with a certified coach/actor (Arm B) during 6 months. This training adapted to the announcement has been validated in preliminary studies (ACACIA programme)(Figure 1). All the cases worked on in the sessions are taken from real life. Inclusion criteria include healthcare professionals aged 18 and older, actively participating in specialties where they frequently deliver cancer diagnoses, such as surgical and medical disciplines. The primary endpoint is to compare changes in stress levels between residents receiving simulation training and those undergoing conventional mentoring. Secondary objectives include assessing stress changes as measured by a coach/actor, evaluating self-assessed attitudes and skills during simulation sessions, comparing self-assessments before and after training, monitoring heart rate variability, exploring the relationship between skill development and heart rate changes, and assessing participant satisfaction. The first resident was enrolled in November 2022. Clinical trial information: F20221011092723. Research Sponsor: None.

TPS9047 **Poster Session**

Evaluating the use of educational videos in a medical oncology sarcoma clinic to improve patient knowledge and satisfaction. First Author: Fabio Murtas, Princess Margaret Hospital, Toronto, ON, Canada

Background: The first clinic visit is a pivotal step in the journey of a cancer patient (pt), often accompanied by anxiety due to future uncertainty. During this initial visit, pts receive extensive information regarding their diagnosis, treatment plan and prognosis. Early education and tailored guidance can potentially enhance understanding, aid decision-making, and alleviate distress. This study evaluates the impact of sarcoma-specific educational videos on improving pts' knowledge of their disease and treatment options *before their first clinic appointment*. Results will help to identify ways to enhance pt education and satisfaction. **Methods:** All newly diagnosed, English speaking, sarcoma pts referred to the sarcoma medical oncology clinic at Mount Sinai Hospital and Princess Margaret Cancer Centre will be eligible. The primary objective is to assess changes in pts' and caregivers' knowledge and perceptions of sarcoma and its treatment after educational intervention as measured by changes in global responses between baseline and post educational intervention surveys. Secondary endpoints include understandability and satisfaction with the educational videos, using validated tools including Pt Education Materials Assessment Tool (PEMAT) and Suitability Assessment of Materials (SAM) instrument. A pilot study (n = 20) will first be performed to assess feasibility, acceptability and determine sample size. For the interventional study, pts will be randomized in 1:1 ratio to either view the educational videos prior to their consult, or a control arm where they will receive standard of care information. Pts on the experimental arm will view four short educational videos (approximately 5-7 minutes each) which focus on 1) what to expect at their initial visit, 2) sarcoma team composition and respective roles, 3) systemic therapy overview and 4) introduction to clinical trials. The study will involve distribution of surveys at 3 different timepoints, each consisting of 15-20 multiple choice questions and taking 3-5 minutes to complete. The first baseline survey will be completed by pts in both arms before their initial consult and is designed to assess pts' initial knowledge and perceptions of their sarcoma and treatment options. The second survey, to be completed only by pts on the experimental arm after watching the educational videos, will measure changes in pts' perceptions and overall satisfaction. A third and final survey will be completed by pts in both arms after their initial consult with the medical oncologist to assess for any further changes. A knowledge quiz will also be given to the pts on the experimental arm both before and after they watch the educational videos to evaluate changes in their understanding of sarcoma and its management. If pts are accompanied by a caregiver, they will also be invited to participate in this study. Research Sponsor: None.

LBA9500 **Oral Abstract Session**

Nivolumab plus relatlimab vs nivolumab alone for the adjuvant treatment of completely resected stage III–IV melanoma: Primary results from RELATIVITY-098. First Author: Georgina V. Long, Melanoma Institute Australia, Faculty of Medicine and Health, The University of Sydney, and Mater and Royal North Shore Hospitals, Sydney, NSW, Australia

The full, final text of this abstract will be available at meetings.asco.org on the day of presentation and in the online supplement to the June 10, 2025, issue of the *Journal of Clinical Oncology*.

LBA9501 **Oral Abstract Session**

Primary analysis of the EORTC-2139-MG/Columbus-AD trial: A randomized trial of adjuvant encorafenib and binimetinib versus placebo in high-risk stage II melanoma with a BRAF-V600E/K mutation. First Author: Alexander Christopher Jonathan van Akkooi, Melanoma Institute Australia, The University of Sydney, Sydney, NSW, Australia

The full, final text of this abstract will be available at meetings.asco.org on the day of presentation and in the online supplement to the June 10, 2025, issue of the *Journal of Clinical Oncology*.

9502 **Oral Abstract Session**

Neoadjuvant-adjuvant pembrolizumab in clinical stage IIB/C melanoma. First Author: John Miura, University of Pennsylvania, Media, PA

Background: Neoadjuvant immune checkpoint therapy has shown improvement in event-free survival outcomes in patients with resectable clinical stage III and IV melanoma. Whether there is benefit to neoadjuvant immune therapy in patients with clinical stage IIB/C melanoma is unknown. **Methods:** In a single arm multicenter investigator-initiated phase 2 trial, patients with clinical stage IIB/C melanoma received a single dose of neoadjuvant pembrolizumab (200 mg intravenously) 3 weeks prior to wide excision and sentinel lymph node (SLN) biopsy followed by 1 year adjuvant pembrolizumab every 3 weeks or until unacceptable toxicity or disease progression. Primary endpoint was SLN positivity rate. A sample size of 63 patients had 80% power detect a 50% difference when compared to a predetermined historical SLN positivity rate in treatment naïve patients (25% Stage IIB and 40% Stage IIC) weighted by proportion of clinical tumor stage in eligible study patients. Secondary endpoint included recurrence-free survival. Safety outcomes, including overall toxicity and immune related adverse events, were also assessed. **Results:** Of 63 evaluable patients (33 IIB; 30 IIC at initial biopsy), the SLN metastasis rate in the neoadjuvant study group was 27%. 28 patients (44%) had residual primary tumor after single dose pembrolizumab; 4 patients had their primary tumors upstaged to IIC. Compared to a SLN metastasis rate in a historical treatment- naïve cohort based on tumor staging at wide excision (33.1%), there was a 18% reduction in SLN positivity rate in the neoadjuvant group, although this was not statistically significant (p = 0.302). In a subgroup analysis, stage IIC patients in the neoadjuvant study group had a SLN metastasis rate of 16.7% versus 40% (p = 0.009) based on initial biopsy and 23.5% versus 40% (p = 0.0499) based on primary tumor staging at wide excision. With median follow-up of 20.4 months, the 2-year recurrence free-survival in the study group was 84% with median time to recurrence (n = 10) of 9.9 months. Overall treatment-related grade 3/4 adverse events were 14 (22%) with 9 (14%) immune-related adverse events; there was no delay in definite surgery secondary to neoadjuvant treatment. **Conclusions:** Rate of SLN metastasis among patients with clinical stage IIB/C melanoma undergoing neoadjuvant pembrolizumab did not differ significantly compared to expected historical rates in treatment-naïve patients; however, in a secondary subgroup analysis among patients with clinical stage IIC disease, a decrease in SLN positivity rate was noted. Neoadjuvant therapy in clinical stage IIB/C was safe and feasible, with no significant delay in surgery or new or unexpected toxicities noted in these patients. Translational studies are under way, including flow cytometric and transcriptional studies, that may reveal immunologic determinants of efficacy versus resistance. Clinical trial information: NCT03757689. Research Sponsor: Merck; U.S. National Institutes of Health.

9503 **Oral Abstract Session**

NeoACTIVATE arm C: Phase II trial of neoadjuvant atezolizumab and tiragolumab for high-risk operable stage III melanoma. First Author: Tina J. Hieken, Mayo Clinic, Rochester, MN

Background: Neoadjuvant ± adjuvant immunotherapy improves event-free survival relative to adjuvant immunotherapy alone for patients with high-risk resectable stage III melanoma. However, the optimal regimen balancing efficacy and tolerability is not known. T-cell immunoglobulin and ITIM domain (TIGIT) is a promising immune checkpoint but its therapeutic potential in stage III melanoma is underexplored. **Methods:** In this phase II trial, patients with resectable, macroscopic stage III melanoma received four 21-day neoadjuvant cycles of 1200mg IV atezolizumab (atezo, anti-PD-L1) + 600mg IV tiragolumab (tira, anti-TIGIT), followed by therapeutic lymph node dissection (TLND) and eight 21-day adjuvant cycles of 1200mg IV atezo. Primary endpoints were pathologic response (of all patients initiating neoadjuvant therapy) and recurrence-free survival (RFS) from the time of TLND in patients who were operated on per protocol and received adjuvant therapy. Secondary endpoint was adverse events (AEs); exploratory endpoints included event-free survival (EFS) and distant metastasis-free survival (DMFS). **Results:** Thirty-four patients, median age 59 years, were accrued and initiated neoadjuvant atezo/tira. 76.5% had >1 metastatic lymph node involved at baseline and 73.5% presented with Stage IIIC disease. All 34 patients were evaluable for AEs, pathologic response and EFS. Four patients were diagnosed with metastatic disease during neoadjuvant treatment, while 30 had TLND per protocol and 28 received adjuvant treatment and were evaluable for RFS and DMFS. Major pathologic responses (MPR, ≤10% viable tumor) were observed in 16/34 patients (47.1%, Table). With 19.9 months median follow-up from registration, 12-month EFS was 72.0% (95% CI 57.9 to 89.5%). With 16 months median follow-up from operation, 12-month RFS was 73.3% (n=28, 95% CI 56.9 to 94.5%), while 12-month DMFS was 86.0% (n=28, 95% CI 72.2 to 100%). In the 16 patients with an MPR, 2 did not receive adjuvant treatment and were followed for 33.3 and 10.8 months without recurrence/death. In the remaining 14 patients, 12-month RFS and 12-month DMFS were both 91.7% (95% CI 77.3 to 100%). 5 patients (14.7%) experienced any grade 3+ AE with 2 (5.9%) at least possibly related to the neoadjuvant regimen. **Conclusions:** Among patients with high-risk resectable stage III melanoma, neoadjuvant atezo/tira was a promising regimen with a favorable safety profile and warrants further study. Identification of predictive biomarkers will allow for optimization of neoadjuvant therapy for individual patients. Clinical trial information: NCT03554083. Research Sponsor: Stand Up to Cancer-Genentech; SU2C-AACR-CT1017; Mayo Clinic Center for Clinical and Translational Science; cCATS Award 92541640-2020/Mayo Clinic.

Pathologic response.

	N=34
Major Pathologic Response	16 (47.1%)
Pathologic complete response (no viable tumor)	13 (38.2%)
Near-pathologic complete response (0.1–10% viable tumor)	3 (8.8%)
Pathologic partial response (>10.0–50% viable tumor)	2 (5.9%)
Pathologic non-response (>50% viable tumor)	12 (35.3%)
No per protocol operation	4 (11.8%)

LBA9504 **Oral Abstract Session**

Randomized phase II study of neoadjuvant (neoadj) anti-PD-1 dostarlimab (D) vs. D + anti-TIM-3 cobolimab (C) in high-risk resectable melanoma (mel) (NEO-MEL-T): Primary analysis. First Author: Meghan Mooradian, Massachusetts General Hospital, Marblehead, MA

The full, final text of this abstract will be available at meetings.asco.org on the day of presentation and in the online supplement to the June 10, 2025, issue of the *Journal of Clinical Oncology*.

LBA9505 **Oral Abstract Session**

A phase II randomized study of neoadjuvant pembrolizumab (P) alone or in combination with vidutolimod (V) in high-risk resectable melanoma: ECOG-ACRIN EA6194. First Author: Ahmad A. Tarhini, H. Lee Moffitt Cancer Center & Research Institute, Tampa, FL

The full, final text of this abstract will be available at meetings.asco.org on the day of presentation and in the online supplement to the June 10, 2025, issue of the *Journal of Clinical Oncology*.

9506 **Oral Abstract Session**

DREAMseq: A phase III trial of treatment sequences in BRAFV600-mutant (m) metastatic melanoma (MM)—Final clinical results. First Author: Michael B. Atkins, Georgetown Lombardi Comprehensive Cancer Center, Washington, DC

Background: The DREAMseq trial compared efficacy and toxicity of the sequence of nivolumab/ipilimumab (N/I) followed by dabrafenib/trametinib (D/T) to the reverse sequence in patients (pts) with BRAFV600m MM. In 9/2021, with 59% of pts 2+ years (yr) from enrollment, the DSMC and NCI CTEP recommended halting the trial and releasing data that showed a 20% difference in 2-yr OS (72% vs 52%) favoring the N/I first sequence. Here we update data to median ~5 yr from entry and report secondary analyses including time to CNS relapse and percent unconfirmed responses (ucOR). **Methods:** Eligible pts with untreated BRAFV600m MM were stratified by ECOG Performance Status 0 or 1 and LDH, and randomized 1:1 to Step 1 treatment with either N/I (Arm A) or D/T (Arm B) and at disease progression (PD) were eligible for Step 2 alternate therapy, D/T (Arm C) or N/I (Arm D). Imaging was done at baseline and q12 weeks (wks). The primary endpoint was 2-yr OS. Secondary endpoints included: 3-yr OS, efficacy (PFS, ORR and DOR) and toxicity. **Results:** 267 out of 300 proposed pts were enrolled (135 Arm A; 132 Arm B). As of 7/23/24, median follow-up of 58 months (mo) (range:0-101), 30 pts had switched to Arm C and 52 to Arm D. 2-yr OS for those assigned to Arm A was 68.3% (95% CI: 60.8-76.9) and for Arm B 54.1% (95% CI: 46.1-63.7%) (log-rank $p < 0.01$). 3 and 5-yr OS by sequence and 2, 3 and 5-yr PFS for initial arms, and median PFS, ORR and DOR for all arms are shown in Table. There were 125 deaths (Arm A-C:47; Arm B-D:78). 76% of responders in Arm A and 24% in Arm B remain in response. At 12 wks, 59 pts on Arm A and 85 on Arm B had RECIST PR of which 10 (16.9%) and 35 (41.2%), respectively were ucOR by wk 24. CNS was the first site of PD in 24 pts on Arm A and 44 pts on Arm B. Median time to CNS PD: Arm A 12.2 mo (0.7-46.5); Arm B 8.4 mo (1.3-78.1) ($p < 0.01$). **Conclusions:** At nearly 5 yr median f/up, the N/I first treatment sequence continues to show superior efficacy over the D/T first sequence for treatment-naïve BRAFV600m MM with a near doubling (30% absolute difference) in 5-yr OS and a tripling of 5-yr PFS. While confirmed ORR were similar between Arms A and B, shorter DOR and more ucOR and more and earlier CNS PD were seen with initial D/T contributing to its worse efficacy. Clinical trial information: NCT02224781. Research Sponsor: This study was conducted by the ECOG-ACRIN Cancer Research Group (Peter J. O'Dwyer, MD and Mitchell D. Schnall, MD, PhD, Group Co-Chairs) and supported by the National Cancer Institute of the National Institutes of Health:; U10CA180820, U10CA180794, U10CA180821, U10CA180868, U10CA180888, UG1CA189953, UG1CA233184, UG1CA233193, UG1CA233196, UG1CA233234, UG1CA233290, UG1CA233331, and UG1CA239758.

Secondary Endpoint (95% CI)	Arm A to C (n=135)	Arm B to D (n=132)	Log-rank p
3 yr OS rate	65.6% (57.3, 73.9)	44.8% (36.7, 54.6)	p<0.01
5 yr OS rate	63.3% (55.4, 72.3)	33.9% (25.9, 44.3)	
2 yr PFS rate	Arm A	Arm B	
	50.8% (42.8, 60.3)	22.9% (16.5, 31.7)	p<0.01
3 yr PFS rate	45.0% (37.0, 54.8)	15.9% (10.5, 24.0)	
5 yr PFS rate	39.4% (31.3, 49.5)	12.8% (7.9, 20.7)	
Median PFS (mo)	Arm A	Arm B	
	26.7 (11.2-47.3)	8.5 (8.1-12.6)	
	Arm C (n=30)	Arm D (n=52)	
	11.2 (9.5, 22.3)	5.9 (2.9, 22.4)	
ORR	Arm A (n= 132)	Arm B (n=131)	
	51.5% (42.7, 60.3)	51.1% (42.3, 60.0)	
	Arm C (n=30)	Arm D (n= 52)	
	70% (37.4, 74.5)	46.2% (32.2, 60.5)	
Median DOR (mo)	Arm A (n=68)	Arm B (n=67)	<0.01
	Not reached	15.5 (11.2, 23.5)	
	Arm C (n=17)	Arm D (n=20)	p=0.03
	14.7 (8.2, NR)	45.2 (19.5, NR)	

LBA9507 **Oral Abstract Session**

A randomized phase 2 trial of encorafenib + binimetinib + nivolumab vs ipilimumab + nivolumab in BRAFV600-mutant melanoma brain metastases: SWOG S2000 (NCT04511013). First Author: Zeynep Eroglu, H. Lee Moffitt Cancer Center and Research Institute, Tampa, FL

The full, final text of this abstract will be available at meetings.asco.org on the day of presentation and in the online supplement to the June 10, 2025, issue of the *Journal of Clinical Oncology*.

LBA9508 **Oral Abstract Session**

Comparison of 1 year versus minimum 2 years of anti-PD1-based immunotherapy as first-line treatment for metastatic melanoma: Results of the DANTE phase III trial. First Author: Sarah Danson, Cancer Therapeutics, Division of Clinical Medicine, University of Sheffield; Department of Oncology, Sheffield Teaching Hospital NHS Foundation Trust, Sheffield, United Kingdom

The full, final text of this abstract will be available at meetings.asco.org on the day of presentation and in the online supplement to the June 10, 2025, issue of the *Journal of Clinical Oncology*.

9509 **Rapid Oral Abstract Session**

A first-in-human study of DYP688, an antibody drug conjugate delivering a direct Gq/11 inhibitor, in patients with metastatic uveal melanoma (MUM) and other GNAQ/11 mutant melanomas. First Author: Matteo S. Carlino, Sydney Medical School, Faculty of Medicine and Health Sciences, The University of Sydney, Camperdown and Melanoma Institute Australia, Sydney, and Crown Princess Mary Cancer Centre, Westmead and Blacktown Hospitals, Westmead, NSW, Australia

Background: GNAQ/11 mutations occur in up to 95% of uveal melanomas (UM) and a subset of non-uveal melanomas. Cell surface PMEL17 (gp100) is highly and broadly expressed in melanoma (including UM). SDZ475 (FR900359) is a potent GNAQ/11 inhibitor, however in vivo toxicity has precluded clinical development. DYP688 is an antibody drug conjugate that binds to PMEL17 to deliver the payload SDZ475. **Methods:** This first-in-human, open-label, multicenter, single-arm study (NCT05415072) of DYP688 in patients (pts) with MUM and other GNAQ/11 mutant melanomas aimed to evaluate safety and tolerability, determine recommended dose(s) (RDs) of DYP688 (primary objective), and evaluate antitumor activity, pharmacokinetics (PK), and immunogenicity (secondary objectives). Here we present data from the ongoing Phase I dose-escalation. **Results:** As of 25 Oct 2024, 66 pts were treated with DYP688 at 4 (n=5), 8 (n=12), 12 (n=13), 16 (n=14), and 24 (n=11) mg/kg biweekly (Q2W) and at 12 (n=5) and 16 (n=6) mg/kg once weekly (QW) in 28-day cycles. Tumor types included MUM (n=60) and non-MUM (n=6). Of the 66 treated pts, 60 (90.9%) had prior antineoplastic therapy; 38 (57.6%) received $\geq$2 lines, and 22 (33.3%) received prior tebentafusp. The majority (n=57, 86.4%) of pts had liver metastases and elevated LDH (n=43, 65.25%) at baseline. Preliminary PK demonstrated a nearly dose-proportional exposure of total monoclonal antibody and active conjugated payload. Most treatment-related adverse events (TRAEs) were grade $\leq$2 with 4 grade 3 events: hypotension, hypercalcemia, anemia, and increased GGT. One dose limiting toxicity was reported (grade 3 hypotension at 24mg/kg Q2W). Most common TRAEs (all grades/doses, $>$15%) were hypercalcemia (22.7%), dry mouth (19.7%), fatigue (18.2%) and peripheral edema (16.7%). At data cutoff, 27 (40.9%) pts remained on study treatment and 39 (59.1%) pts had discontinued, mainly due to disease progression (PD) and none due to AEs. Of the 55 pts treated at doses $\geq$8 mg/kg Q2W who were eligible for RECIST v1.1 evaluation, confirmed objective responses were seen in 12 (21.8%) pts with 1/12 at 8 mg/kg (Q2W), 3/13 (1 complete response) at 12 mg/kg (Q2W), 5/8 at 16 mg/kg (Q2W), 2/5 at 12 mg/kg (QW) and 1/6 at 16 mg/kg (QW), with evidence of deepening response over time. Best response of PD was seen in 6/55 (10.9%) pts and stable disease in 35/55 (63.6%) pts. Median (range) duration of treatment by Kaplan Meier was 7.0 ($<$1 – 20.7) months. Analysis of mutational profiles from tissue and circulating tumor DNA is ongoing. **Conclusions:** DYP688 shows favorable safety and tolerability at all doses tested and promising preliminary clinical efficacy at doses $\geq$ 12mg/kg Q2W; the RDs for dose optimization are yet to be declared and dose exploration is ongoing. Clinical trial information: NCT05415072. Research Sponsor: Novartis Pharmaceutical Corporation.

9510 **Rapid Oral Abstract Session**

A phase II study of the interleukin-6 (IL-6) receptor blocking antibody sarilumab (Sari) in combination with ipilimumab (Ipi), nivolumab (Nivo) and relatlimab (Rela) in patients with unresectable stage III or stage IV melanoma. First Author: Janice M. Mehnert, Perlmutter Cancer Center of NYU Langone Health/NYU Grossman School of Medicine, New York, NY

Background: Combination immune checkpoint inhibitor regimens, especially those utilizing anti-CTLA-4 blockade, demonstrate higher response rates compared with single agent anti-PD-1 therapy but also increased rates of immune related adverse events (irAEs). IL-6, a key cytokine in driving inflammatory and autoimmune responses, is a compelling target to reduce irAEs through the use of IL-6 receptor (IL-6R) inhibitors. We conducted a clinical trial of 1L Nivo, Rela, and Ipi combined with the IL-6R inhibitor Sari in patients with advanced melanoma. **Methods:** 33 patients with advanced stage III/IV melanoma were treated in a single arm phase II trial. Patients received Nivo/Rela 480 mg/160 mg Q4W, Ipi 1 mg/kg Q8W and Sari 200mg q2 weeks for 12 doses over 24 weeks followed by maintenance Nivo/Rela 480 mg/160 mg Q4W and Ipi 1 mg/kg Q8W. Prior adjuvant immunotherapy was allowed if $>$ 6 months before enrollment. Patients with controlled brain metastases could enroll. The co-primary endpoints were rate of grade (gr) 3-5 irAEs and antitumor activity defined by RECIST best overall response rate at 24 weeks. With 33 patients, a difference of $\geq$ 22% from the known irAE rate of Nivo, Rela, and Ipi could be detected using a binomial test (2-sided alpha = 0.05, 80% power). BORR was estimated with an exact 95% Clopper Pearson confidence interval. Circulating IL-6 signaling mediators were measured over time in 14 patients using Luminex assays. **Results:** 33 patients (40% F, 60% M, PS 0-1, median age 63) were treated. Median follow-up was 9.8 months (95% CI: 8.5, 12.6 months; data lock, 12/12/24). 3% had acral and 9% mucosal melanoma. 24% had $>$ M1c disease and 39% elevated LDH. BRAF status, known for 81% of patients, was positive in 26%. BORR at 24 weeks was 63.6% (95% CI: 45.1%, 79.6%). Median PFS and OS were not reached (25th percentile for PFS = 8.3 (95% CI: 2.77, NA) months). Median treatment duration was 28 weeks and 9% discontinued therapy for toxicity. At 24 weeks 12.1% (n = 4) experienced $>$ gr 3/4 irAEs, significantly lower than the expected known irAE rate (2-sided p = 0.0007, 95% CI: 12.1%-28.2%). 27% (n = 9) had gr 3/4 toxicity over study duration; 93.9% (n = 31) had any grade irAE. Circulating IL-6Ra and IL-4 were significantly reduced at Cycle 2 ($P < 0.05$). **Conclusions:** Nivo, Rela, Ipi, + Sari demonstrated encouraging efficacy and tolerability. At 24 weeks, 63.6% BORR and 12.1% gr 3/4 irAE rate were observed. 2 patients had gr 4 toxicity; no gr 5 events were reported. These results compare favorably with published combination regimens including CTLA-4 blockade. Decreases in IL-6Ra and the inflammatory marker IL-4 observed post-treatment will be evaluted in a larger cohort of samples. An ongoing randomized cohort of Nivo + Rela + Ipi +/- Sari will further define the impact of IL-6R blockade on clinical outcomes in metastatic melanoma. Clinical trial information: NCT05428007. Research Sponsor: Bristol Meyers Squibb; Regeneron.

9511 **Rapid Oral Abstract Session**

Clinical outcomes of the DIET study: A randomized controlled phase 2 trial of a high fiber diet intervention (HFDI) in patients with melanoma receiving immune checkpoint blockade (ICB). First Author: Yufan Qiu, The University of Texas MD Anderson Cancer Center, Houston, TX

Background: Dietary fiber intake is associated with response to ICB in melanoma. HFDIs favorably modulate the microbiome in non-cancer populations and in preclinical models. However, whether diet intervention can favorably modulate the microbiome and immune response in cancer patients is unknown. We conducted a proof-of-principal randomized trial of a fully controlled feeding study comparing HFDI with healthy control diet in melanoma patients receiving ICB. The primary objective was to establish the effects of HFDI on the structure and function of the gut microbiome. Here we report an exploratory objective of cancer-specific outcomes by arm. **Methods:** Patients initiating ICB treatment for melanomawere randomized (2:1) to either HFDI (30 g/d fiber ramped-up biweekly via whole foods to 50 g/d) or healthy control diet (20 g/d fiber). Diets in both arms met cancer prevention guidelines, were isocaloric and macronutrient-controlled, such that participants were provided all calorie-containing meals/snacks and met weekly with the dietitian for the study duration (up to 10 weeks). Objective response rate (ORR, per RECIST 1.1), pathological response rate (per INMC), progression-free survival (PFS), event-free survival (EFS, defined as the time from treatment initiation to disease progression, recurrence or death), recurrence rate (RR), recurrence-free survival (RFS) and immune-related adverse event (IRAE) rates were assessed and compared across arms. **Results:** 45 patients were randomized, of which 43 (F/M 22/21, median age 57 years, 79% cutaneous) initiated ICB and diet intervention: 28 in the HFDI arm and 15 in the control arm. ICB was administered in adjuvant, neoadjuvant and unresectable setting in 19, 12, and 12 patients, respectively. ICB regimens include pembrolizumab or nivolumab monotherapy (n = 19), ipilimumab + nivo (n = 16), and nivo + relatlimab (n = 7). At the time of data cut-off, October 2024, the median follow-up was 22.6 months (95% CI: 22.05-24.95 months). In the combined neoadjuvant/unresectable cohort (n = 24), ORR was 77% (HFDI) and 29% (control, p = 0.06). In the neoadjuvant cohort (n = 12), pathological complete response rate was 57%(HFDI) vs 50% (control, p = 1.0). Median EFS was not reached (HFDI) versus 20 months (control, p = 0.03). In the adjuvant cohort (n = 19), at a median follow-up of 27.6 months, RR was 14% (HFDI) versus 33% (control, p = 0.56). Median RFS was not reached (HFDI) versus 27.8 months (control, p = 0.49). Any grade IRAEs were observed in 71.4% of the patients in the HFDI arm versus 93.3% in the control arm (p = 0.13). Grade $\geq$3 IRAE rates were 28.6% and 40.0% in the HFDI and control arms (p = 0.51), respectively. **Conclusions:** Our study suggests potential benefits of HFDI on clinical outcomes and toxicity profile with ICB, warranting further study in Phase III trials powered for disease outcomes. Clinical trial information: NCT04645680. Research Sponsor: None.

9512 **Rapid Oral Abstract Session**

Neoadjuvant camrelizumab plus apatinib and temozolomide for resectable stage II/III acral melanoma: The CAP 03-NEO trial. First Author: Lili Mao, Department of Melanoma and Sarcoma, Peking University Cancer Hospital & Institute, Beijing, China

Background: The CAP 03 study demonstrated significant efficacy for camrelizumab combined with apatinib and temozolomide as first-line therapy for advanced acral melanoma (AM), achieving a 64.0% objective response rate and a median progression-free survival of 18.4 months. SWOG1801 and NADINA trials suggested that neoadjuvant therapy may provide greater benefits than adjuvant therapy in melanoma. CAP 03-NEO explores the efficacy and safety of this triple-drug regimen as neoadjuvant therapy in patients (pts) with resectable stage II/III AM. **Methods:** This two-stage clinical trial (ClinicalTrials.gov identifier: NCT05512481) aimed to enroll 60 pts with resectable stage II/III AM aged 18–75 years. In stage 1, 30 pts received two 4-week cycles of neoadjuvant camrelizumab (200 mg intravenously every 2 weeks), apatinib (250 mg orally once daily), and temozolomide (200 mg/m² intravenously daily on days 1–5 of each cycle), followed by surgery and 15 cycles of adjuvant camrelizumab (200 mg every 3 weeks). The primary endpoint was pathological complete response (pCR). Secondary endpoints included event-free survival (EFS), overall survival, and safety. Based on pathologic non-response (pNR) rate and risk-benefit assessment, stage 2 extended enrollment to an additional 30 pts receiving the same treatment. **Results:** As of December 2024, all 30 pts in stage 1 were enrolled, with a median follow-up of 18.5 months. The median age was 54 years (IQR: 41–61). Of 28 pts undergoing surgery, 16 (57.1%) achieved any pathological response, including 7 (25.0%) with pCR, 5 with near pCR, and 4 with partial pathologic response (pPR). Additionally, 12 pts (42.9%) achieved major pathological response (MPR), which includes both pCR and near-pCR. Surgery was canceled for two pts due to personal reasons and new metastatic disease. Among stage II pts, 3 achieved pCR, 1 achieved pPR, and the pNR was 64%. Among stage III pts, 4 achieved pCR, 5 near PCR, and 3 pPR, with pNR of 29.4%. The median EFS has not been reached, with a 12-month EFS rate of 74.1% (95% CI: 53.1-86.7%). The most common adverse events (AEs) were increased blood bilirubin (11, 37%), decreased white blood cell count (9, 30%), and constipation (8, 27%), with no grade 4-5 AEs observed. Neoadjuvant therapy did not increase surgical complications. **Conclusions:** Stage 1 results of CAP 03-NEO demonstrated the potential of neoadjuvant camrelizumab, apatinib and temozolomide in pts with resectable stage II/III AM. The pNR result support advancing to stage 2 to further assess the efficacy and safety of this regimen in pts with stage III disease. Clinical trial information: NCT05512481. Research Sponsor: None.

9513 **Rapid Oral Abstract Session**

Single dose of neoadjuvant ipilimumab and nivolumab in resectable melanoma with CD8+ cell imaging: Interim results of the C-IT Neo trial. First Author: Sarah E. Lochrin, Memorial Sloan Kettering Cancer Center, New York, NY

Background: Neoadjuvant (neoadj) immune checkpoint blockade (ICB) is standard of care for patients (pts) with resectable stage III/IV melanoma. A single ICB dose induces substantial peripheral immune activation and 1 dose of neoadj pembrolizumab has promising activity. The efficacy of 1 dose of combination ICB is unknown and clinically important to describe given the toxicity of sequential combination ICB. **Methods:** In this phase II single-arm trial, pts with resectable stage IIIB-IV melanoma received 1 dose of neoadj nivolumab (nivo) 1mg/kg and ipilimumab (ipi) 3mg/kg 4 weeks prior to resection. The primary endpoint is major pathologic response (MPR), defined as pathologic complete response (pCR) or near CR (≤10% viable tumor). Using a Simon minimax two-stage design, MPR $<$ 30% is deemed not promising and $>$ 50% promising; positive if $>$12 MPR in 28 pts. Secondary endpoints were response rate (RECIST 1.1), recurrence free survival (RFS), and safety. CD8-PET imaging was done pre-ICB and pre-surgery, using ^{89}Zr-radiolabeled crefmirlimab to evaluate association with MPR. Autoradiography and CD8 cell infiltrate by IHC were used to verify the on-target binding of crefmirlimab in surgical specimens. **Results:** Stage I successfully met the interim efficacy threshold with 5 of 12 pts demonstrating an MPR, thus advancing to stage II. Here we report interim results of the 19 pts enrolled by data cut-off 01/02/2025. Baseline stages were IIIB (53%, n = 10), IIIC (42%, n = 8) and IV (5%, n = 1); 80% cutaneous, 10% acral and 10% unknown primary melanoma. An MPR was observed in 53% (95% CI: 29,76) of pts (n = 10, 7 pCR, 3 near pCR), partial pathologic response (PR) in 21% (n = 4), and non-response in 26% (n = 5). Of the 18 evaluable, RECIST response was 28% (n = 5, all PR), 61% (n = 11) had stable disease, and 11% (n = 2) progressive disease (PD). The rate of grade $>$3 treatment-related adverse events (TRAE), in neoadj and adjuvant setting, was 11% (n = 2); 1 pt was hospitalized with adrenal insufficiency, no grade 5 events occurred on study. All pts proceeded to surgery with median time to surgery of 29 days (IQR 26,31). 14 pts (74%) received adjuvant therapy; 13 anti-PD-1 and 1 BRAF targeted therapy. Median follow-up was 16 months (IQR 8;23) and 12-month RFS from surgery was 91% (95% CI: 75, 100). Of the 3 pts with recurrent or progressive disease; 0 had an MPR and 2 died from progressive melanoma. CD8-PET was completed in 19 pts pre-ICB and 17 pts pre-surgery. SUVmax pre-ICB, pre-surgery and the percent change over-time was not significantly associated with MPR. CD8-PET tracer evaluation by autoradiography correlated with CD8+ cell infiltrate on IHC by pathologist assessment. **Conclusions:** C-IT-Neo is the first study evaluating a single dose of combination ICB in the neoadjuvant setting. Interim results show one dose has low grade 3+ TRAE and high efficacy with MPR of 53%. The trial is actively enrolling, with ongoing analysis of CD8-PET imaging and immune biomarkers. Clinical trial information: NCT05289193. Research Sponsor: Melanoma Research Alliance; ImaginAb.

9514 **Rapid Oral Abstract Session**

A phase II study of neoadjuvant lenvatinib plus pembrolizumab in Merkel cell carcinoma. First Author: Andrew Scott Brohl, H. Lee Moffitt Cancer Center and Research Institute, Tampa, FL

Background: Given the success of checkpoint inhibitor therapy in the advanced setting in Merkel cell carcinoma (MCC), there is interest in exploring immunotherapy as a neoadjuvant approach, which additionally allows a window of opportunity to assess the efficacy of new immunotherapy combinations. **Methods:** We conducted a single center, phase II open label trial (NCT04869137) in patients (pts) with resectable stage II-IV MCC. All pts were to receive six weeks of neoadjuvant therapy with pembrolizumab 200mg IV q3 weeks plus lenvatinib 20mg PO daily before planned surgery ± adjuvant radiation therapy. Following local therapy, pts were to receive continued adjuvant pembrolizumab monotherapy to complete 1 year total of systemic therapy. Target accrual was 26 pts. Pathological complete response (pCR) rate was the primary endpoint of the study, with ≥15 pCR needed for the combination therapy to be considered as promising compared to a historical benchmark of ~40% pCR for single-agent anti-PD1. **Results:** Twenty-six pts were enrolled between 06/2021 and 09/2024, including 5 (19.2%) with clinical stage II disease, 20 (76.9%) with stage III, and 1 (3.8%) with stage IV. Pts were predominantly male (77%) and with a median age of 69 (range 53-88). Following neoadjuvant treatment, 2 pts (7.7%) were unable to undergo planned surgery, one due to progressive disease (PD) and one due to toxicity. Two pts who achieved a clinical response to neoadjuvant therapy declined surgery and underwent post-neoadjuvant therapy biopsies for pathological assessment. On intention to treat, 15 of the 26 pts (57.7%) achieved a pCR. With a median follow-up of 20 months, 6 pts (23.1%) have experienced disease progression, 2 during neoadjuvant therapy, 2 during and 2 after adjuvant treatment. Among pts with pathological assessment of response, pCR was associated with a lower risk of relapse, though this result was not statistically significant (13.3% vs. 33.3%, p = 0.33). Thirteen of 15 pts who achieved pCR following surgery omitted adjuvant radiation therapy and there have been no local recurrences in pCR cases. Thirteen pts (50%) experienced at least one G3 treatment related adverse event (TRAE), most commonly G3 hypertension in 10 pts (40%) that improved with dose interruption and/or dose reduction of lenvatinib. No G4-5 TRAEs were observed. At the time of analysis, one pt (neoadjuvant PD) has died from progressive MCC. Two pts have died from other causes without evidence of recurrence at last follow-up. **Conclusions:** Lenvatinib plus pembrolizumab demonstrated encouraging efficacy with anticipated toxicity when used as neoadjuvant therapy for Merkel cell carcinoma. The primary endpoint of the study was met with 57.7% of patients achieving a pathological complete response. Pts with a pCR had a lower risk of recurrence vs those without, but recurrences were seen even after pCR. Ongoing correlative studies may help to identify biomarkers for response. Clinical trial information: NCT04869137. Research Sponsor: Merck Sharp & Dohme LLC.

9515 **Rapid Oral Abstract Session**

Lifileucel in patients with advanced melanoma: 5-year outcomes of the C-144-01 study. First Author: Theresa Medina, University of Colorado Comprehensive Cancer Center, Aurora, CO

Background: Lifileucel is a personalized, one-time tumor-derived autologous T-cell immunotherapy approved for the treatment of adult patients (pts) with advanced (unresectable or metastatic) melanoma previously treated with a programmed cell death-1 (PD-1)–blocking antibody, and, if *BRAF* V600 mutation–positive, a BRAF inhibitor with or without a MEK inhibitor. In the registrational C-144-01 study (NCT02360579), pts with advanced melanoma who received lifileucel had an objective response rate (ORR) of 31.4%. Follow-up in therapeutic trials targeting refractory patients with refractory melanoma typically span months rather than years due to lack of activity. Reflective of the durability of lifileucel, we nowreport 5-year survival outcomes from the C-144-01 study. **Methods:** C-144-01 (NCT02360579) is a phase 2, multicenter, multicohort, open-label study of lifileucel. Eligible pts had advanced melanoma that had progressed on or after immune checkpoint inhibitor and targeted therapy, where appropriate. Before lifileucel infusion, pts underwent nonmyeloablative lymphodepletion (NMA-LD; cyclophosphamide, 60 mg/kg × 2 d plus fludarabine 25 mg/m² × 5 d). Pts received cryopreserved lifileucel followed by up to 6 doses of interleukin-2 (IL-2; 600,000 IU/kg every 8–12 hours). The primary endpoint was ORR assessed by an independent review committee (IRC) using RECIST v1.1. Key secondary endpoints were duration of response (DOR), overall survival (OS), and safety. **Results:** Among pts who received lifileucel (n = 153; median age, 56 y; range, 20–79), 54% were male. All pts had an Eastern Cooperative Oncology Group Performance Status of 0 or 1 and previously received anti–PD-1/PD-L1 therapy. Pts had a median of 3 prior lines of therapy (range, 1–9) and 55% were primary refractory to anti–PD-1/PD-L1 therapy. At a median follow-up of 57.8 mo, all pts have completed or discontinued the study, with 28 (18.3%) pts having completed the 5-year study follow-up. The ORR was 31.4% (complete response, 5.9%; partial response, 25.5%). Median DOR was 36.5 mo (95% confidence interval [CI]: 8.3–not reached), with 31.3% of responders completing the 5-year assessment with a sustained response. Median time to best response was 1.5 mo (range, 1.3–30.4). Median OS was 13.9 mo (95% CI: 10.6–17.8); the 5-year OS rate was 19.7% (95% CI: 13.3–27.0). Treatment-emergent adverse events were consistent with known safety profiles of NMA-LD and IL-2. The extended follow-up revealed no new safety signals. **Conclusions:** This 5-year analysis of the C-144-01 trial is the longest follow-up of the largest group of pts with melanoma treated with tumor-infiltrating lymphocytes in a single study. This study illustrates lifileucel's continued durability of response and survival benefit up to 5 years after a single administration without any long-term safety concerns. Clinical trial information: NCT02360579. Research Sponsor: Iovance Biotherapeutics Inc.

9516 Rapid Oral Abstract Session

Infusion product characteristics to predict response to tumor-infiltrating lymphocyte (TIL) therapy in metastatic melanoma (MM). First Author: Lilit Karapetyan, H. Lee Moffitt Cancer Center and Research Institute, Tampa, FL

Background: Identification of the TIL therapy product (TILp) characteristics associated with objective response to therapy is critical to improve future adoptive TIL-based therapy. In this study we performed comprehensive phenotypic analysis of TILp in association with TIL therapeutic outcomes in consecutive patients with MM. **Methods:** Data were extracted from early-phase clinical trials of MM patients treated with TIL only, TIL plus ipilimumab, TIL plus nivolumab, and TIL plus vemurafenib at Moffitt Cancer Center. The immunophenotypic features of TILp were evaluated by flow cytometry using antibodies against checkpoints, costimulatory molecules, T cell subsets and TCRβ sequencing. Tumor reactivity was measured using HLA-matched cell lines. The relationship between TILp characteristics and both objective response and progression-free survival (PFS) was assessed in treated patients. **Results:** A total of 50 patients, 21 female (42%) and 29 male (58%), median age 49 [IQR 40–55] received lymphodepleting chemotherapy followed by TIL and interleukin-2 (IL-2). Median numbers [IQR] of infused TIL and IL-2 dose were $59e^9$ [42-$84e^9$] and 5 [4–6], respectively. Patients with objective response had a significantly higher total number of infused TIL, total number of infused $CD8^+$ TIL, and proportion of $CD8^+$ cells in the infusion product ($p < 0.05$), with high $CD8^+$ TIL being associated with improved PFS ($p = 0.0001$). The total number and proportion of infused stem cell-like memory $CD8^+$T cells ($T_{SCM,}$ $CD8^+CD45RA^+CCR7^+CD62L^+CD95^+$) were significantly higher in responders and associated with improved PFS ($p < 0.01$). TILs from responders had distinct patterns of co-inhibitory and co-stimulatory receptors' expression and were characterized by significantly higher proportion of $LAG3^+$ and $LAG3^+TIGIT^+$ co-expressed TIL of total $CD3^+$ TIL ($p < 0.05$). Proportions of $LAG3^+CD8^+$ and $TIGIT^+CD8^+$ cells were also increased in responders ($p < 0.05$) with no significant differences observed in $PD1^+CD8^+$, $BTLA^+CD8^+$, and $TIM3^+CD8^+$ cells. There was an increased proportion of $OX40^+CD8^+$ and $OX40^+4\text{-}1BB^{neg}CD8^+$ cells among responders ($p < 0.01$). T cell clonal analysis using top 20 clones revealed high persistence in responders ($p < 0.01$) measured by TCRβ overlap between ACTP and post-treatment peripheral blood. There were no significant differences in clonality, diversity and evenness in responders *vs.* non-responders. Using HLA-matched cell lines there was a trend towards HLA-matched reactive TIL and improved PFS ($p = 0.058$). **Conclusions:** Response to TIL therapy is associated with TIL persistence and distinct TILp immunophenotypic features characterized by enhanced proportion of $CD8^+$ TIL, T_{SCM} $CD8^+$ cells, and high surface expression of $LAG3^+TIGIT^+$ and $OX40^+$. Novel strategies to modulate *ex vivo* TIL expansion toward this optimal TIL phenotype may result in increased response for future trial design. Research Sponsor: None.

9517 Rapid Oral Abstract Session

OBX-115 engineered tumor-infiltrating lymphocyte (TIL) cell therapy with regulatable membrane-bound IL15 (mbIL15) in patients (pts) with immune checkpoint inhibitor (ICI)–resistant advanced melanoma: Phase 1 results of the Agni-01 multicenter study. First Author: Jason Alan Chesney, UofL Health – Brown Cancer Center, University of Louisville, Louisville, KY

Background: OBX-115 TIL are engineered to express mbIL15 regulated by the FDA-approved small-molecule drug acetazolamide (ACZ), abrogating the need for toxic high-dose IL2 after TIL infusion. Single-center phase 1 data (NCT05470283) demonstrated differentiated early safety (Amaria ASCO 2024). We report the first data evaluating OBX-115 in pts with advanced melanoma in the multicenter phase 1/2 Agni-01 study (NCT06060613). **Methods:** This single-arm, open-label study assesses safety, tolerability, and efficacy of the OBX-115 TIL cell therapy regimen in pts with advanced melanoma and NSCLC (Shoushtari AACR 2025). Phase 1 characterizes safety (treatment-emergent adverse events [TEAEs]: AEs ≤30 d after OBX-115 infusion) and tolerability in escalating dose levels of OBX-115 and ACZ to establish a recommended phase 2 dose (RP2D). Phase 2 evaluates efficacy of the regimen at RP2D (RECIST v1.1 per investigator). OBX-115 is manufactured from pt tumor tissue (core needle biopsy or surgical excision) and infused after standard- or low-dose (Cy 750 $mg/m^2/d \times 3$; Flu 30 $mg/m^2/d \times 4$) lymphodepletion (LD). No IL2 is administered. Oral ACZ starts day of OBX-115 infusion (QD up to 14 d), and is redosed (QD up to 7 d) every 6 wks after recovery from LD. **Results:** In phase 1,as of 01 Jan 2025, OBX-115 was successfully manufactured and infused for 11 pts with ICI-resistant advanced melanoma (median study follow-up, 22.3 wks [range, 13.3–52.1]) including 6 treated at RP2D (OBX-115 $1–100\times10^9$ cells, ACZ 500 mg/d). Majority (n = 10) received low-dose LD, including 1 in the outpatient setting. There was no dose-limiting toxicity (DLT), treatment-emergent ICU transfer, or treatment-related mortality (TRM). Eight pts had G≥3 nonhematologic TEAEs (events in > 1 pt: hyponatremia, hypokalemia [n = 2 each]). One pt reported 2 OBX-115–related serious AEs, including 1 CRS event (G2) without IL6 elevation (IL6 < 100 pg/mL). Across dose levels (n = 11), confirmed ORR was 36% (4 PR, 5 SD; DCR 82%). For 6 pts receiving RP2D, ORR was 67% (4 PR, 2 SD; DCR 100%). **Conclusions:** Early data support clinical benefit (RP2D ORR 67%, DCR 100%) of OBX-115regulatableengineeredTIL cell therapy in the absence of IL2, including with outpatient low-dose LD. The safety profile is highly differentiated, without TRM, ICU transfer, or high-grade CRS. ACZ redosing is well-tolerated and offers an opportunity to deepen responses by inducing re-expression of mbIL15 on engrafted OBX-115 TIL, a unique capability among adoptive cell therapies. These attributes may comprehensively address the unmet need in post-ICI advanced melanoma and other cancers, and data support continued investigation of OBX-115 in the ongoing phase 2 portion of the Agni-01 study. Clinical trial information: NCT06060613. Research Sponsor: Obsidian Therapeutics.

9518 Poster Session

Neutralizing antibodies and lymphocyte count as biomarkers in patients receiving oncolytic adenovirus TILT-123 and adoptive cell transfer of tumor-infiltrating lymphocytes for metastatic melanoma refractory to immune checkpoint inhibitors. First Author: Lyna Haybout, TILT Biotherapeutics Ltd., Helsinki, Finland

Background: Metastatic melanoma refractory to immune checkpoint inhibitors (ICI) remains a significant challenge. Adoptive Cell Transfer of Tumor-Infiltrating Lymphocytes (ACT-TILs) shows promise but can cause adverse events. Oncolytic adenovirus TILT-123 (igrelimogene litadenorepvec) coding for TNF and IL2 combined with ACT-TILs, offers an approach without conditioning therapies. We report long-term survival data from a phase I trial (TUNINTIL NCT04217473), and correlative clinical, histologic, and immunologic biomarker analyses. **Methods:** The aim was to evaluate safety of TILT-123 and ACT-TILs in patients with metastatic melanoma refractory to ICIs. Treatment was deemed safe and feasible. TILT-123 was given intravenously (IV) and intratumorally, ACT-TILs were given IV, without preconditioning chemotherapy or post-conditioning IL2. Five cohorts were completed in a 3+3 dose-incremental design without dose-limiting toxicities. Tumor biopsies were analyzed for adenoviral (Ad) genomes, PD-L1 expression and presence of CD4+ regulatory (reg), CD4+ and CD8+ T cells by multiplex immunofluorescence (mIF). TILT-123 DNA was quantified in tumors by qPCR, anti-Ad neutralizing antibodies (nAbs) analyzed in serum using luminescence titering assay. Disease control rate (DCR) was defined as Stable Disease or better using RECIST1.1, iRECIST, and PET criteria. Association of factors with survival and DCR was determined using Spearman's rank correlation and multivariate analysis. **Results:** Patients varied in melanoma subtype (cutaneous n=8, mucosal n=5, uveal n=4), with a median age of 67 years (25-75 years). Following TILT-123 monotherapy, the DCR on D36 was 35% by RECIST 1.1 and iRECIST, and 63% by PET criteria. PET responses were seen in 31% of patients by D36. In the combination phase (D78) DCR per RECIST 1.1 or iRECIST was 38%, and 47% by PET criteria. Responses were seen in 27% of patients on D78 in PET, including a partial response lasting >8 months and a durable complete response in a mucosal melanoma patient. Median overall survival (mOS) was 447 days. Virus DNA was detected post-treatment in both injected and uninjected tumors. Patients with elevated titers of nAbs (by D22) showed a decrease in metabolism in non-injected lesions by day 36 (p=0.0101). Blood lymphocyte count decrease after TILT administration was associated with better DCR (p= 0.0188). mIF data showed patients achieving disease control had a higher percentage of intratumoral CD8+ T cells (p=0.037). **Conclusions:** ICI refractory melanoma patients receiving TILT-123 and ACT-TILs without preconditioning show signs of CD8+ T cell trafficking to the tumor microenvironment. nAbs and lymphocyte count decrease can be further investigated as biomarkers. Clinical trial information: NCT04217473. Research Sponsor: TILT Biotherapeutics Oy; Jane and Aatos Erkko Foundation; HUCH Research Funds (VTR); Cancer Foundation Finland; Sigrid Juselius Foundation; Finnish Red Cross Blood Service; EU Horizon grants; 190121193; EU Horizon grants; 811693; Albert Ehrnrooth; Karl Fazer.

9519 Poster Session

OBX-115 engineered tumor-infiltrating lymphocytes (TIL) with regulatable membrane-bound IL15 (mbIL15): Translational data from a single-center phase 1 trial in patients (pts) with immune checkpoint inhibitor (ICI)–resistant advanced melanoma. First Author: Rodabe Navroze Amaria, The University of Texas MD Anderson Cancer Center, Houston, TX

Background: Non-engineered TIL cell therapy is approved for ICI-resistant advanced melanoma, but requires co-administration of toxic high-dose IL2. OBX-115 engineered TIL express mbIL15 under pharmacologic regulation using the FDA-approved small-molecule drug acetazolamide (ACZ), abrogating the need for IL2. We present data supporting OBX-115 mechanism of action. **Methods:** Trial design and clinical results were previously reported (Amaria ASCO 2024; NCT05470283); briefly, pts received lymphodepletion (Day [D] -7 to -1) followed by OBX-115 infusion (D0) and ≤7 days of orally administered ACZ (D2–9). Peripheral blood (PB) and tumor tissue samples were collected for longitudinal ddPCR analysis and immune profiling. **Results:** Eight pts received OBX-115 (fresh) and are included in this analysis. PB samples demonstrated ACZ-driven OBX-115 TIL expansion, reaching a median of 1697 cells/μL at D14 (approximate day of OBX-115 expansion peak); in 3 pts with ≥6 mo follow-up, OBX-115 remained detectable through 6 mo and ongoing up to 15 mo. In the immediate post-infusion phase (up to D14), PB flow cytometry indicated expansion of product-derived CD3+CD8+ cells expressing Ki67 (during ACZ exposure) and endogenous NK cells (CD3-CD56+), while CD4+ cell levels decreased (Table). Post-infusion tumor tissue demonstrated presence of IL15-expressing T cells (of CD3+: D21, 68.6%; D42, 88.4%). Importantly, median post-infusion serum levels of IL15 and IL7 were not significantly elevated above Baseline through D42 (paired one-tailed t-test adjusted for multiple comparisons; Table); IL6 was below limit of detection at all timepoints, even in pts with fevers. T-cell receptor (TCR) clonotypes present in the OBX-115 infusion product were enriched in post-infusion PB and tumor (Table). **Conclusions:** These data support the proposed OBX-115 mechanism of action, demonstrating ACZ-driven OBX-115 TIL expansion, engraftment, and persistence; endogenous NK cell expansion, presumably driven by transactivation via mbIL15 on OBX-115, without systemic cytokine elevation; and TCR repertoire remodeling with tumor-derived, antigen-specific T cells. Investigation of OBX-115 TIL cell therapy in pts with advanced solid tumors (NCT06060613) is ongoing. Clinical trial information: NCT05470283. Research Sponsor: Obsidian Therapeutics, Inc.

Pre- and post-infusion immune profile.

Characteristic, median (N=8)	Baseline*	D14	D28	D42
CD3-CD56+ (of live, PB),† %	14.7	27.0	35.5	56.7
CD3+ (of live, PB),† %	50.7	69.9	49.5	54.2
CD8+ (of CD3+, PB),† %	27.9	75.2	85.6	87.6
CD4+ (of CD3+, PB),† %	59.7	5.7	10.6	9.3
Ki67+ (of CD8+, PB),† %	1.5	11.1	3.7	3.2
IL15, serum, pg/mL	8.5	9.5	10.0	10.8
IL7, serum, pg/mL	2.4	3.3	3.3	2.8
OBX-115 TCR clonotypes in PB, %	14.5	80.9	69.3	59.6
OBX-115 TCR clonotypes in tumor, %	28.2	Not available	86.2‡	70.4

*Pre-lymphodepletion.
†n<8.
‡D21.

9520 **Poster Session**

Homologous recombination deficiency signature (HRDsig) in advanced cutaneous melanoma (ACM): A genomic landscape study. First Author: Nimisha Srivastava, SUNY Upstate Medical University, Syracuse, NY

Background: HRDsig can aid in identifying tumors with DNA repair deficiencies, guiding PARP inhibitor (PARPi) use. It expands treatment options beyond breast cancer gene (BRCA) mutations enabling personalized therapy. Combining PARPi with targeted therapy or immunotherapy shows promise in overcoming resistance and improving outcomes for treatment-resistant ACM. **Methods:** Formalin-fixed paraffin-embedded (FFPE) primary tumors and metastatic biopsies from 9,576 ACM cases were analyzed using hybrid capture-based comprehensive genomic profiling (CGP), evaluating all classes of genomic alterations (GA). Central pathology review was conducted for all cases. Microsatellite instability-high (MSIH) status, tumor mutational burden (TMB), genomic ancestry, and mutational signatures were derived from sequencing data. HRDsig was assessed using copy number changes and genomic scars. PD-L1 expression was determined via immunohistochemistry [Dako 22C3; tumor proportion score (TPS)]. Statistical comparisons were made using Fisher's exact test with Benjamini-Hochberg correction. **Results:** Among 9,576 ACM cases, 198 (2.1%) were HRDsig positive (HRDsig+). HRDsig+ cases when compared to HRDsig negative (HRDsig-) were older (median age: 69 vs. 67 years; p=0.034), more often female (49.5% vs. 36.2%; p=0.001), and had more GA per tumor (median: 7 vs. 6; p=0.026). HRDsig+ cases were more often of African (5.6% vs. 1.2%; $p<0.0001$) or American ancestry (8.1% vs. 4.1%; p=0.026) and less often European (84.3% vs. 94.0%; $p<0.0001$). GA more common in HRDsig+ included *IGF1R* (5.1% vs. 1.3%; p=0.003), *KIT* (11.6% vs. 5.6%; p=0.004), *KRAS* (7.1% vs. 2.7%; p=0.005), *NF1* (38.4% vs. 21.4%; $p<0.0001$), *RAD21* (6.7% vs. 3.0%; p=0.037), and *TP53* (40.4% vs. 24.3%; $p<0.0001$). HRDsig- cases exhibited higher TMB (median: 13.8 vs. 6.1; $p<0.0001$), more frequent TMB >10 mutations/Mb (60.9% vs. 39.9%; $p<0.0001$), and more UV light exposure trinucleotide signatures (57.3% vs. 36.4%; $p<0.0001$). GA more common in HRDsig- cases included *BRAF* (including V600E) (44.6% vs. 23.2%; $p<0.0001$), *CDKN2A* (49.2% vs. 36.9%; p=0.003), *NRAS* (28.0% vs. 11.6%; $p<0.0001$), and *TERT* (74.4% vs. 29.8%; $p<0.0001$). In both positive and negative groups, PD-L1 low-level expression (1-49% TPS) was comparable (43.3%-39.7%), while BRCA1/2 alterations (<2.0%) and MSIH status (0.0%-0.1%) remained rare. **Conclusions:** HRDsig+ status is rare in ACM but more frequent in non-white genomic ancestries. HRDsig+ ACM cases are less likely to have BRAF GA, more likely to have KIT GA and lower TMB levels. These findings may guide the future development of clinical trials employing combination therapies and PARPi in ACM. Research Sponsor: None.

9521 **Poster Session**

Association of KIT mutations with risk of central nervous system (CNS) metastasis (met) in patients (pts) with mucosal melanoma (MM). First Author: Afsaneh Amouzegar, Department of Melanoma Medical Oncology, The University of Texas MD Anderson Cancer Center, Houston, TX

Background: The CNS is a frequent site of distant met in pts with cutaneous melanoma (CM). Previous studies have identified clinical, pathological, and molecular risk factors for CNS met in CM pts. However, little is known about the incidence of and risk factors for CNS met in MM pts, who overall have a worse prognosis than CM pts. **Methods:** We performed an institutionally approved retrospective review of pts diagnosed with clinically localized or regionally metastatic MM at MD Anderson Cancer Center from 1/1/1988 to 12/31/2023. Pts who presented with distant met were excluded. Pt and tumor features (including clinical testing for BRAF, NRAS, and KIT mutations) and distant recurrence events (CNS met; non-CNS met) were assessed. Tumor samples from a subset of MM pts were stained and scored for expression of PTEN (Absent vs Present), PD-L1 (<1% vs ≥1%), and KIT (Above vs Below median H-score) protein by immunohistochemistry (IHC). Time-to-CNS met and Time-to-non-CNS met were computed from the date of initial MM diagnosis (dx) to date of CNS/non-CNS met. Cumulative incidence of distant met events was determined using competing risks (death); pts alive with no met at last follow-up (f/u) were censored. Group differences were evaluated by Gray's test, and associations between measures of interest were determined using proportional sub-distribution hazards regression models. **Results:** 579 MM pts with clinically localized (73%) or regionally metastatic (27%) disease were included in the analysis. At a median f/u of 34.4 months (range 0 – 525.8), 111 pts (19.2%) had developed CNS met. The cumulative incidence of CNS met at 1, 2, 3 and 5 years was 5%, 10%, 14% and 18%, respectively. For pts with CNS met, median time from MM dx to CNS met was 26.1 months (range, 2.3 – 211.0). Most pts with CNS met presented with brain met only (90%), followed by brain met and LMD (6%), and LMD only (4%). On univariate analysis, KIT mutation (Hazard Ratio [HR] 2.78; 95% Confidence interval [CI] 1.74 – 4.44), $p<0.001$), mitotic rate 5-9/mm^2 (vs. 0-4/mm^2; HR 2.22; 95% CI 1.14 – 4.34, p=0.020), and lymphovascular invasion (HR 1.63; 95% CI 1.03 – 2.56, p=0.036) were associated with increased risk of CNS met. On multivariable analysis, KIT mutation (HR 2.77; 95% CI 1.71 – 4.51, $p<0.001$) remained significantly associated with increased risk of CNS met. In contrast, KIT mutation predicted a lower risk of non-CNS met in multivariate analysis (HR 0.55; CI 0.34 – 0.87, p=0.011). Among the 87 MM pts for whom IHC was performed on tumor samples, PTEN, KIT, and PD-L1 protein expression were not associated with risk of CNS or non-CNS met. **Conclusions:** KIT mutation is significantly associated with increased risk of CNS met in patients with clinically localized or regionally met MM. These results highlight distinct CNS met risk factors, and potential surveillance strategies, for MM compared to CM pts. Research Sponsor: SPORE (NIH/NCI 5P50CA221703-05); MD Anderson Melanoma Moon Shot program; Dr. Miriam and Sheldon Adelson Medial Research Foundation (Project number FP17016).

9522 **Poster Session**

Serum thymidine kinase activity (TKa) as a potential biomarker in the sequential immunotherapy and targeted therapy for metastatic BRAF V600 mutated melanoma (SECOMBIT) trial. First Author: Hildur Helgadottir, Karolinska Institute and Karolinska University Hospital, Stockholm, Sweden

Background: In melanoma, there is a need for biomarkers for predicting treatment efficacy. Thymidine kinase 1 (TK) is a cytosolic enzyme that plays a pivotal role in DNA synthesis and repair as it is part of the reaction chain to introduce thymidine into the DNA strand. Dividing cells release TK during mitotic exit and TK can be measured in blood as a biomarker of cell proliferation. Elevated levels of TK enzyme activity (TKa) have been detected in blood samples from patients with several tumor types and correlated with disease stage, prognosis, and treatment efficacy. This study is the first to evaluate the role of TKa as a biomarker in a prospective clinical trial in patients with metastatic melanoma, the SECOMBIT study (NCT02631447). **Methods:** SECOMBIT was a randomized, three-arm, phase II trial where melanoma patients received, in ARM A: BRAF+MEK inhibitors (encorafenib (E) + binimetinib (B)) and at progressive disease (PD), immune checkpoint inhibitors (ICI) (ipimumab (I) + nivolumab (N), in ARM B: I+N and at PD E+B, and in ARM C: 8-week induction of E+B before a planned switch to I+N, and at PD E+B. Serum TKa was analyzed as DiviTum Unit of Activity (DuA) by the FDA cleared and CE-labelled assay (Biovica). **Results:** Baseline serum TKa was available from 81 (38.8%) of the patients in SECOMBIT, 25, 27 and 29 in ARM A, B and C, respectively. Patients were divided into TKa-HIGH (n=41) and TKa-LOW (n=40) by the median TKa value 110 DuA (range 39-2343, IQR 74-183). The median total progression-free survival (tPFS) was 17 months (95% CI 12 to 22), and the median overall survival (OS) was 19 months (95% CI: 12 to 26) in TKa-HIGH, while the median tPFS and OS were not reached at 76 months in the TKa-LOW group (tPFS: p=0.004 and OS: $p<0.001$). In ARM A and B, TKa-HIGH patients had significantly worse tPFS and OS while the survival difference between TKa-HIGH and TKa-LOW was not statistically significant in ARM C (Table 1). TKa predicts prognosis independently of LDH in multivariate analysis. **Conclusions:** Baseline serum TKa levels efficiently predicted the outcome of patients with BRAF V600 mutated metastatic melanoma treated with different sequences of ICI and BRAF+MEK inhibitors. Patients with elevated TKa is an evident poor prognosis group and appears to benefit from the regime received in ARM C, with an 8-week induction of BRAF-MEK inhibitors, before ICI (sandwich approach). TKa merits further study as a potential biomarker in metastatic melanoma. Clinical trial information: NCT02631447. Research Sponsor: None.

Survival according to study arm and TKa level.

	ARM A	ARM B	ARM C
tPFS at 5 years, (rate, 95% CI)			
TKa-HIGH	10.0 (0-28.6)	38.5 (12.0-65.0)	47.1 (23.4-70.8)
TKa-LOW	52.5 (26.8-78.2)	78.6 (57.0-100)	44.4 (4.6-84.2)
P value	0.010	0.019	0.51
OS, at 5 years, (rate, 95% CI)			
TKa-HIGH	20.0 (0-44.7)	38.5 (12.0-65.0)	46.3 (22.2-70.4)
TKa-LOW	60.0 (35.3-84.7)	78.6 (57.0-100)	75.0 (50.0-99.5)
P value	0.030	0.015	0.11

9523 **Poster Session**

Circulating tumor DNA (ctDNA) dynamics during anti-PD-1 based therapy to predict clinical outcomes in advanced stage melanoma: A multicenter retrospective study. First Author: Caroline Burkey, University of Wisconsin Hospitals and Clinics, Madison, WI

Background: ctDNA has shown promise as a prognostic biomarker for disease relapse in resected tumors. The significance of ctDNA changes in the advanced or metastatic disease setting for predicting treatment response and survival characteristics is still under investigation. In our study, we evaluated the association between early ctDNA changes after anti-PD-1 based therapy initiation and clinical outcomes in patients with advanced stage melanoma. **Methods:** We performed a multicenter, retrospective analysis using a personalized, tumor-informed ctDNA assay (Natera) on prospectively collected plasma samples from patients with unresectable stage III/IV melanoma treated with anti-PD-1 based therapy. Baseline ctDNA levels were assessed prior to the start of treatment and at 6-8 weeks. Patients were divided into 3 cohorts based on ctDNA changes: ctDNA clearance (6-8 week level undetectable or 0 MTM/mL), ctDNA decrease (6-8 week level decreased from baseline but detectable), or ctDNA increase (6-8 week level increased from baseline). Logistic regression models were used to evaluate the odds of disease control based on the change in ctDNA levels between both time points. Cox proportional hazard models were used to study the effects of ctDNA changes on progression-free survival (PFS) and overall survival (OS). **Results:** We identified 95 patients with unresectable stage III (18%; n=17) or stage IV (82%; n=78) melanoma with cutaneous (72%; n=68), uveal (12%; n=11), mucosal (8%; n=8), or unknown (8%; n=8) primaries who were treated with dual anti-PD-1/anti-CTLA-4 (60%; n=57), dual anti-PD-1/anti-LAG-3 (17%; n=16), or anti-PD-1 monotherapy (23%; n=22). At baseline, median age was 75, median baseline ctDNA was 363 mTM/ml, and median follow up was 13.1 months; 29% (n=28) had liver metastases, 26% (n=25) had brain metastases. Using ctDNA clearance (n=40) as reference, patients with ctDNA decrease (n=23) had lower odds of disease control (OR=0.09, 95% CI 0.01-0.85, p=0.035), and shorter PFS (HR=5.15, 2.25-11.79, $p<0.001$), and OS (HR=5.72, 1.52-21.56, p=0.010); patients with ctDNA increase (n=32) had even lower odds of disease control (OR=0.01, 0.00-0.09, $p<0.001$) and even shorter PFS (HR=5.67, CI 2.62-12.24, $p<0.001$) and OS (HR=8.76, CI 2.55-30.11, p=0.001). 12-month PFS for ctDNA clearance, ctDNA decrease, and ctDNA increase were 94.3%, 63.0%, and 48.2%, respectively. 12-month OS for ctDNA clearance, ctDNA decrease, and ctDNA increase were 95.4%, 64.6%, and 50.5% respectively. **Conclusions:** ctDNA dynamics after 6-8 weeks of anti-PD-1 therapy in patients with advanced stage melanoma may be predictive of disease control, progression-free survival, and overall survival. ctDNA clearance is associated with favorable clinical outcomes. Larger studies are needed to validate the role of ctDNA as an early response biomarker in advanced disease. Research Sponsor: NIH National Center for Advancing Translational Sciences (NCATS); UL1TR002373.

9524 Poster Session

Application of a novel multiplex imaging-based immunotherapy panel and AI-powered analysis solution for predictive spatial biomarker identification on immunotherapy-treated melanoma patients. First Author: Paolo Antonio Ascierto, Department of Melanoma, Cancer Immunotherapy and Development Therapeutics, Instituto Nazionale Tumori – IRCCS - Fondazione G. Pascale, Naples, Italy

Background: There is an urgent need for more robust methods to differentiate immunotherapy responders from non-responders. In this study, we present a novel multiplex imaging (MI)-based immunotherapy panel and a comprehensive analysis pipeline to characterize the spatial distribution and function of immune cells and its application for spatial biomarker detection in a cohort of immunotherapy-treated melanoma patients. **Methods:** We designed a 28-plex panel to perform sequential immunofluorescence (seqIF) on the COMET platform to target key biomarkers associated with tumor microenvironment (TME), immune cell infiltration, and immune checkpoint pathways. Pre-treatment biopsies were obtained from 12 patients with known long-term response or rapid progression to immunotherapy combination treatment from the SECOMBIT Trial (NCT02631447) and profiled utilizing Nucleai's deep-learning-based MI analysis pipeline, aiming to identify spatial biomarkers that can differentiate between long-term responders and non-responders. We identified 15 cell types, including 10 immune cell populations, in addition to 10 cell state markers. Cells were assigned to the tumor area or TME, and spatial features were calculated based on cell type, marker positivity, and gross area assignment. **Results:** Our novel MI panel and analysis pipeline demonstrated highly balanced accuracy (> 0.8) and F1 scores (> 0.8) in cell typing and protein quantification for most cell types and markers. This analysis pipeline enabled the quantification of known biomarkers such as T cell activation states, T cell infiltration patterns, and tertiary-lymphoid structure maturation. A comparison of calculated spatial features between long-term responders and rapid progressors revealed distinct immune cell interactions and differences in activation status across the tumor areas associated with response. Within the tumor area, the reciprocal interactions of tumor cells, cytotoxic CD8 T-cells and antigen-presenting cells (APC) were associated with a better outcome. In contrast, a high percentage of proliferating regulatory T cells within the tumor invasive margin was associated with a worse outcome. In the adjacent TME, endothelial cell interactions with T-cells and macrophage proliferation were associated with immunotherapy resistance. In contrast, the interaction between HLA-DR-expressing macrophages and APC cells was associated with an improved clinical outcome. **Conclusions:** Integrating MI with AI analysis has the potential to enhance our understanding of treatment efficacy and resistance mechanisms. Our preliminary data demonstrate that area-specific immune niches contribute to the success or failure of immunotherapy response and highlight the importance of spatial biology in predicting immunotherapy outcomes. Clinical trial information: NCT02631447. Research Sponsor: Lunaphore.

9525 Poster Session

RELATIVITY-020: Intracranial (IC) activity of nivolumab + relatlimab (NIVO + RELA) in patients (pts) with PD-(L)1 refractory melanoma with melanoma brain metastases (MBM). First Author: Hussein A. Tawbi, The University of Texas MD Anderson Cancer Center, Houston, TX

Background: NIVO + RELA is an anti-PD-1 + anti-LAG3 combination approved for the treatment of pts with advanced melanoma, but data on activity in pts with MBM are lacking. NIVO + RELA prolonged time to and decreased incidence of development of new brain lesions vs NIVO in RELATIVITY-047 (Tawbi, 2024 ASCO). Preliminary BLUEBONNET data (n = 9) showed a NIVO + RELA IC overall response rate (ORR) of 44% (Phillips, 2024 SNO/ASCO). This post hoc analysis investigated IC activity in pts with PD-(L)1–refractory melanoma treated with NIVO + RELA in the phase I/IIa RELATIVITY-020 trial (NCT01968109). **Methods:** Pts with anti-PD-(L)1–refractory melanoma treated with NIVO + RELA in RELATIVITY-020 parts C, D, or E with possible IC lesions were included. Brain imaging from these pts (eg, those with stable MBM at baseline) were interpreted by blinded independent central review (BICR) using modified RECIST v1.1 specific to the CNS. Efficacy endpoints for BICR-confirmed pts included confirmed IC response, target IC lesion reduction, and time to IC progression. **Results:** BICR analysis confirmed 27 pts had ≥ 1 MBM; of these, 59% had an ECOG PS 0, 30% had a *BRAF* mutation, and 48% had liver lesions. Pts had a median (range) of 2 (1–10) prior therapies, including anti-PD-(L)1 (100%), anti-CTLA-4 (63%, including 44% NIVO + ipilimumab), BRAF/MEKi (26%), and brain radiotherapy (81%, with 26% receiving the radiotherapy < 3 mo prior to first dose). With a minimum follow-up of 54.4 mo, confirmed IC ORR was 22% and clinical benefit rate (CBR) was 63% (table). Median duration of IC response was not reached. Target IC lesions were identified in 17 pts; 14 had both a baseline lesion and ≥ 1 on-treatment brain scan. Median best reduction from baseline for those 14 pts was 19.5%; 6 pts had a reduction $\geq 30\%$. Median time to IC progression (as first progression) was not reached, with 63% of pts event free for > 3 y (events/N = 7/27). Median overall survival was 21.5 mo (95% CI, 10.9–29.4) with rates of 70% at 1 y and 27% at 3 y (events/N = 22/27). **Conclusions:** A previous Part D report of this study showed a heavily pre-treated anti-PD-(L)1 refractory melanoma pt population with 12% ORR in response to NIVO + RELA irrespective of tumor location; here a subpopulation of similar pts with IC lesions compared favorably: 22% ORR and 63% CBR per CNS-specific modified RECIST v1.1. Prospective and larger studies are needed to confirm these findings. Clinical trial information: NCT01968109. Research Sponsor: Bristol Myers Squibb.

	NIVO + RELA (N = 27)
Confirmed IC ORR,[a] n (%)	6 (22)
(95% CI)	(9–42)
CR, n (%)	1 (4)
PR, n (%)	5 (19)
SD, n (%)	11 (41)
PD, n (%)	5 (19)
UTD, n (%)	5 (19)
Confirmed IC CBR,[b] n (%)	17 (63)
Median time to IC response, mo (range)	3.2 (1.7–53.4)
Median duration of IC response, mo (95% CI)	NR (4.6–NR)

[a]CR+PR; [b]CR+PR+SD; CR, complete response; IC, intracranial; NR, not reached; PD, progressive disease; PR, partial response; SD stable disease; UTD, unable to determine.

9526 Poster Session

Randomized dose evaluation of nivolumab + relatlimab (NIVO + RELA) in patients (pts) with advanced melanoma: Results from RELATIVITY-020. First Author: Georgina V. Long, Melanoma Institute Australia, Faculty of Medicine and Health, The University of Sydney, and Mater and Royal North Shore Hospitals, Sydney, NSW, Australia

Background: NIVO + RELA is approved at 480 mg NIVO + 160 mg RELA Q4W (480/160) dosing for treatment of advanced melanoma based on RELATIVITY-047. A higher dose of 480 mg NIVO + 480 mg RELA (480/480) is under investigation in other tumor types. Here, we report results from RELATIVITY-020 Part E, which aimed to compare efficacy and safety of first-line (1L) 480/480 vs 480/160 dosing in pts with treatment-naive advanced melanoma and evaluate 480/480 dosing in pts with advanced melanoma who progressed on prior anti–PD-1 therapy (PD-1 refractory [RF]). **Methods:** RELATIVITY-020 (NCT01968109) is a phase 1/2a, dose-escalation and cohort-expansion, open-label trial. For Part E, pts with treatment-naive advanced melanoma were randomized 1:1 to 480/480 vs 480/160 A single-arm cohort was enrolled to evaluate 480/480 dosing in pts with PD-1 RF advanced melanoma. Primary endpoints were safety and objective response rate (ORR) per BICR using RECIST v1.1. Secondary endpoints included duration of response (DOR) and PFS. Exploratory analyses included OS and pharmacodynamics. **Results:** As of clinical cutoff (May 22, 2024, min follow-up 33 mo), ORR was higher with the 1L 480/480 vs the 480/160 dose, while median (m) DOR, mPFS, and mOS were similar across the two arms, with numerically lower mPFS and 24-mo PFS/OS rates with the 480/480 dose (Table). With the 1L 480/480 vs 480/160 doses, 34% vs 36% of pts had grade 3–4 treatment-related AEs (TRAEs), and any grade TRAEs led to treatment discontinuation (d/c) in 29% vs 19% of pts, respectively. There was 1 treatment-related death (immune-mediated lung disease) in the 1L 480/480 arm vs none in the 480/160 arm. Treatment duration was shorter with the 1L 480/480 (m 5.6 mo) vs 480/160 dose (m 8.3 mo). Higher LAG-3 occupancy was observed with 1L 480/480 vs 480/160 dosing; however, there was no difference in Th1-associated cytokine levels. For the RF 480/480 arm (Table), outcomes were similar to published Part D data for RF 480/160 dosing. **Conclusions:** Although the 480/480 dose yielded higher ORR and LAG-3 occupancy levels than the 480/160 dose, it did not translate into improved survival outcomes or differences in Th1 cytokine levels. The 1L 480/480 dose also led to a higher rate of d/c due to TRAEs than the 480/160 dose. RF 480/480 dosing yielded similar results to RF 480/160 dosing from RELATIVITY-020 Part D. Clinical trial information: NCT01968109. Research Sponsor: Bristol Myers Squibb.

	NIVO + RELA 480/480 (N = 77)	NIVO + RELA 480/160 (N = 77)	NIVO + RELA RF 480/480 (N = 95)
ORR, % (95% CI)	61.0 (49.2–72.0)	48.7 (37.0–60.4)	10.6 (5.2–18.7)
mDOR, mo (95% CI)	NR (40.3–NR	NR (32.3–NR)	NR (3.1–NR)
mPFS, mo (95% CI)	26.8 (11.1–NR)	33.3 (11.0–NR)	1.8 (1.8–3.4)
PFS rate, % (95% CI)			
12 mo	61 (49–71)	61 (49–72)	19 (12–28)
24 mo	51 (39–62)	56 (43–67)	10 (5–19)
mOS, mo (95% CI)	NR (29.0–NR)	NR (40.0–NR)	12.9 (8.2–16.6)
OS rate, % (95% CI)			
12 mo	83 (73–90)	82 (71–89)	51 (40–60)
24 mo	66 (54–75)	73 (62–82)	30 (21–40)
Grade 3/4 TRAEs, %	34	36	17
Any grade TRAE leading to d/c, %	29	19	9

NR, not reached.

9527 Poster Session

Real-world comparison of survival with nivolumab (NIVO) + relatlimab (RELA) vs NIVO + ipilimumab (IPI) in advanced melanoma. First Author: Michael A. Postow, Memorial Sloan Kettering Cancer Center, New York, NY; Weill Cornell Medical College, New York, NY

Background: An indirect-treatment (Tx)-comparison (ITC) suggested first-line (1L) NIVO + RELA may have similar efficacy vs NIVO + IPI in clinical trial patients (pts) with untreated advanced melanoma. However, there is no real-world study comparing these Tx. This study compared survival outcomes among pts with advanced melanoma treated with 1L NIVO + RELA or NIVO + IPI in the Flatiron Health EHR-derived de-identified database, which includes ≥ 280 oncology clinics across the US. **Methods:** Data were extracted for pts aged ≥ 18 yrs who received 1L NIVO + RELA or NIVO + IPI between March 18, 2022 (date of NIVO + RELA FDA approval) and March 31, 2024. Pts who received adjuvant Tx, including anti–PD-1, were included, while pts with other primary cancers or treated in any clinical trial were excluded. Endpoints were OS and real-world PFS from start of 1L Tx. Outcomes were summarized using Kaplan–Meier methods, and Tx were compared using Cox models adjusted for age, sex, practice type, BRAF, brain metastases (mets), liver mets, prior adjuvant anti–PD-1 monotherapy, time from advanced melanoma diagnosis to start of 1L Tx, ECOG PS, stage, and LDH. Missing data for ECOG PS, BRAF, stage, and LDH were imputed. **Results:** Median (m) follow-up was 7.4 mo for NIVO + RELA (N = 408) and 7.7 mo for NIVO + IPI (N = 600). The NIVO + RELA group was older (m [IQR], 74.1 [65.9–81.5] yrs) than the NIVO + IPI group (66.2 [57.3–74.5] yrs), but generally had better prognostic factors (Table). Prior anti–PD-1 adjuvant Tx was 12% in both groups, while time from end of adjuvant Tx to 1L Tx and time from advanced melanoma diagnosis to 1L Tx trended longer with NIVO + RELA vs NIVO + IPI (Table). 74% of the NIVO + RELA group and 70% of the NIVO + IPI group were missing PD-L1 status, while 16% vs 20%, respectively, had PD-L1 $> 1\%$ (P = 0.61). mOS was not reached (NR) for both groups, with 95% CIs of 20.1–NR mo for NIVO + RELA vs 21.5–NR mo for NIVO + IPI (adjusted HR, 0.91 [95% CI, 0.70–1.18]). Median rwPFS was longer with NIVO + RELA (11.5 [8.9–18.7] mo) vs NIVO + IPI (4.8 [3.7–6.3] mo; adjusted HR, 0.75 [0.61–0.91]). **Conclusions:** This real-world study supports the ITC observation that NIVO + RELA and NIVO + IPI convey similar OS benefits for pts with advanced melanoma. The longer rwPFS for NIVO + RELA vs NIVO + IPI warrants additional research with longer follow-up and further evaluation of baseline characteristics, as the NIVO + IPI group had poorer prognostic factors. Important limitations included short follow-up, covariate missingness, and potential unmeasured confounding. Research Sponsor: Bristol Myers Squibb.

	NIVO + RELA (N = 408)	NIVO + IPI (N = 600)
Community practice,[a] %	62	77
Brain mets,[a] %	9	21
Liver mets,[a] %	7	11
LDH ≤ ULN,[a,b] %	76	61
***BRAF* mutant,[a,b] %**	40	50
ECOG PS,[b] %		
0–1	89	89
≥ 2	11	11
Time from advanced diagnosis to 1L Tx (mo)[a], m (IQR)	1.4 (0.8–3.0)	1.1 (0.7–2.1)
Time from end of adjuvant therapy to 1L Tx (mo), m (IQR)	13.0 (3.4–30.0)	8.3 (0.1–20.3)

[a]Between-Tx difference $P < 0.05$.
[b]Includes imputed values.

9528 **Poster Session**

Characteristics and predictors of chronic immune-related adverse events (irAEs) following anti-PD-1 (PD1) treatment for melanoma. First Author: Roma A. Kankaria, Vanderbilt University School of Medicine, Nashville, TN

Background: Adjuvant PD1 treatment improves clinical outcomes in high-risk resected melanoma. We have shown that adjuvant PD1 can lead to irAEs that become chronic in up to 46% of treated patients (pts). We performed longer follow-up (f/u) to further characterize chronic irAEs from adjuvant PD1 treatment and assessed risk factors to determine predictors for their development. **Methods:** We retrospectively analyzed pts treated with adjuvant PD1 for resected stage III-IV melanoma from 2015-2024 from 6 institutions. All pts had at least 12 months of f/u after PD1 initiation. We collected demographics, treatment details, and outcomes. We characterized type, grade, management, duration, and resolution of acute (onset during PD1) and chronic (persisting at least 3 months after PD1 cessation) irAEs. We performed Olink 96-protein inflammation assay in plasma from pts with and without chronic non-endocrine irAEs at 12 months after PD1 initiation. **Results:** We included 304 pts; 184 (61%) were male, and median age at PD1 initiation was 64 years. Among all pts, 221 (73%) developed acute irAEs, and 147 (48%) developed chronic irAEs; 59 pts had chronic endocrine irAEs, 99 had chronic non-endocrine irAEs, and 11 had both. At last f/u (median 61.4 months), 104 (34%) pts had ongoing irAEs. The most common chronic irAEs were hypothyroidism/thyroiditis (n=45, 15%), arthritis (n=25, 8%), dermatitis (n=17, 6%), hypophysitis/adrenal insufficiency (n=16, 5%), and xerostomia (n=10, 3%). Twenty (7%) pts experienced chronic toxicities outside of classical irAEs, most often fatigue (n=14, 5%), orthostasis (n=2, 1%), and headache (n=2, 1%). We then assessed risk factors for chronic irAEs compared with acute, resolving irAEs (excluding endocrine irAEs since nearly all become chronic). We found that peak steroid dose was similar in patients with and without chronic irAEs (median 50 mg for both groups, p=0.33). Time to irAE onset was similar in patients with and without chronic irAEs (median 91 vs. 114 days, p=0.78). Time to steroids from symptom onset trended longer for those with chronic irAEs (median 7 vs. 4 days, p=0.18) but was not statistically significant. In proteomic analysis, 24/96 cytokines had higher expression (0 with lower expression) in pts with chronic irAE (n=17) compared with controls (n=10), including IL-8 (p=0.02), IL-17 (p=0.049), TNF (p=0.02), VEGFA (p=0.005), and soluble PD-L1 (p=0.03). **Conclusions:** Among this large cohort of pts with melanoma treated with adjuvant PD1, chronic irAEs were common, persistent, and associated with elevated circulating cytokines, which could suggest possible therapeutics. No obvious predictors of chronic irAEs were identified outside of organ affected; analyses are ongoing. Given the long-term survival of pts treated with adjuvant PD1, monitoring and managing chronic irAEs is crucial. Research Sponsor: None.

9529 **Poster Session**

Safety and efficacy analysis of DNV3 plus toripalimab and chemotherapy in advanced melanoma: An open-label investigator-initiated trial. First Author: Jing Lin, Department of Medical Oncology, Clinical Oncology School of Fujian Medical University, Fujian Cancer Hospital, Fuzhou, China

Background: Previous studies have shown that combining LAG-3 and PD-1 inhibitors is effective in advanced melanoma. Here, we presented the safety and efficacy of DNV3, a LAG-3 inhibitor, in combination with a PD-1 inhibitor and chemotherapy for patients with advanced acral and mucosal melanoma. **Methods:** Eligible patients were adults with confirmed unresectable or metastatic melanoma and an ECOG performance status of 0 or 1. BRAF-mutant patients must had progressed after BRAF inhibitor treatment. The dosages for chemotherapy (albumin-bound paclitaxel at 260 mg/m² on Day 1 and cisplatin at 25 mg/m² on Days 1 to 3 for the first 6 cycles) and DNV3 (administered at 3 mg/kg) were based on body surface area and weight, while Toripalimab was given at a fixed dose of 240 mg. The combination therapy was administered every 3 weeks. DNV3 and Toripalimab were continued for up to 2 years or until withdrawal from the study. The primary endpoint is the objective response rate (ORR), with secondary endpoints including progression-free survival (PFS), duration of response (DOR), disease control rate (DCR), and overall survival (OS). **Results:** Overall, 27 patients participated (13 mucosal melanoma; 6 acral melanoma; 5 cutaneous melanoma; 3 unknown primary melanoma). 77.8% patients had prior anti-PD-(L)1 therapy. At a Nab-Paclitaxel dose of 260mg/m², 94.4% had treatment-related adverse events (TRAEs), with 50% facing severe TRAEs like infection and bone marrow suppression, leading to one death and a dose reduction for 9 patients. At 200mg/m², 77.8% had TRAEs, and 22.2% had severe TRAEs, mainly decreased PLT/WBC counts and bacteremia, with no further deaths. Among the 15 patients (55.6%) who experienced immune-related adverse events (irAEs), 6 (22.2%) had grade 3 or 4 irAEs, with no reported grade 5 cases. The most common grade 3 irAE was infection. An ORR of 37.0% (95% CI: 19.4% to 57.6%) was observed in 10 patients , 6 of whom had liver metastases according to RECIST 1.1 criteria. The median DOR had not yet been reached (95% CI: 3.65 months to not evaluable). Among the 27 patients, the overall ORR was 37%, with subtypes showing 38.5% for mucosal, 80% for cutaneous, and 16.7% for acral melanomas. Expression levels of BRAF or PD-L1 did not predict ORR within these subgroups. As of the cutoff date, neither median PFS nor OS had been achieved. **Conclusions:** The study provided preliminary evidence of the tolerability and potential efficacy of the combination of DNV3 plus Toripalimab with chemotherapy in patients with advanced melanoma, particularly in those with mucosal melanoma and liver metastases. Clinical trial information: ChiCTR2400079387, ChiCTR2400079543. Research Sponsor: None.

9530 **Poster Session**

Prognostic implications of glycemia in non-diabetic patients with metastatic melanoma undergoing immunotherapy. First Author: Domenico Mallardo, Istituto Nazionale Tumori IRCCS "Fondazione G. Pascale", Naples, Italy

Background: Immune checkpoint inhibitors (ICIs) have revolutionized the cancer therapeutic landscape, significantly improving the survival of patients (pts) with advanced malignancies. Previous studies have shown that diabetic pts have a higher risk of cancer-related mortality compared to those without diabetes. This retrospective study aimed to investigate the prognostic impact of glycemia on ICI treatment outcomes in non-diabetic metastatic melanoma pts. **Methods:** Glycemic levels were assessed at three distinct time points within a two-week period prior to the initiation of ICI therapy in 1079 non-diabetic metastatic melanoma pts treated with anti-PD1 and anti-CTLA4 either as monotherapy or in combination. Blood glucose concentrations were determined enzymatically using the cobas c-501 system (Roche, normal range 70-110 mg/dL). Interleukin-6 (IL-6) levels were assessed in 378 pts using Electrochemiluminescence Immunoassays and gene profiling analysis was performed on 95 baseline RNA using NanoString IO360 panel. Pts characteristics are listed in Table 1. Spearman's correlation was used to assess the association between variables. Survival rates were analyzed using the Kaplan-Meier method. **Results:** ROC curve analysis identified a blood glucose cut-point of 93.33 mg/dL. Pts with low glycemia had a better overall survival (median: 27.7 vs 14.5 months, HR=0.68, $p < 0.0001$) and progression free survival (median: 7.4 vs 4.3 months, HR=0.74; $p < 0.001$) compared to pts with elevated glycemia. This trend was confirmed in subgroups analysis (anti-PD1; anti-CTLA4), except for pts treated with the combination of anti-PD1 plus anti-CTLA4 as well as in line of treatment stratification (first, second and ≥ 3). Glycemia was found to be positively associated with elevated IL-6 levels (rho 0.16, $p<0.01$). Transcriptomic analysis showed an association between glycemia and genes related to inflammatory activity (S100A12; CD40) and cell cycle regulation (CNTFR; PTEN). Glycemia predicts prognosis independently of LDH and line of treatment in multivariate analysis. **Conclusions:** Elevated glycemia is associated with poor prognosis in pts with metastatic melanoma treated with ICIs. Biomarker analysis revealed an association between glycemia levels with pro-inflammatory cytokine IL-6 and genes linked to inflammation and cell cycle progression. Further investigations are needed in order to endorse the data and validate the glycemia cut-point. Research Sponsor: None.

Patient characteristics.

Patient characteristics	N = 1079
Median age	59 (range 19-91)
Gender: female/male, n (%)	448 (41)/631 (59)
CNS metastases at baseline, n (%)	201 (20)
BRAF Status, n (%)	
Wild type, n (%)	596 (55)
Mutation, n (%)	404 (38)
NA, n (%)	80 (7)
T2DM, n (%)	47 (4)
ORR, n (%)	261 (24)
Anti-PD1, n (%)	646 (60)
Anti-CTLA4, n (%)	272 (25)
Anti-PD1+ Anti-CTLA4, n (%)	161 (15)
First line, n (%)	623 (58)
Second line, n (%)	325 (30)
Third line ≥, n (%)	131 (12)

9531 **Poster Session**

Trick-MCC: Final results from the proof-of-concept investigator-initiated study of combination therapy with anti–PD-1, anti–LAG-3, and anti–TIM-3 in participants with advanced or metastatic PD-(L)1 refractory Merkel cell carcinoma (NCT06056895). First Author: Natalie J. Miller, University of Washington, Seattle, WA

Background: Merkel cell carcinoma (MCC) is an aggressive and highly immunogenic skin cancer associated with the Merkel cell polyomavirus. Over 50% of patients with metastatic MCC do not derive durable benefit from PD-(L)1 therapy alone. High expression of additional immune checkpoints LAG-3 and TIM-3 on MCC-specific CD8 T cells suggested that concurrent triple checkpoint blockade may overcome immune evasion in patients with PD-(L)1 refractory MCC. **Methods:** TRICK-MCC (Triple Immune Checkpoint Inhibition in MCC) is an investigator initiated, single center, proof-of-concept clinical trial studying concurrent treatment with anti-PD-1 (retifanlimab, q4w), anti-LAG3 (tuparstobart, q2w) and anti-TIM-3 (verzistobart, q2w) in patients with advanced/metastatic MCC that progressed after PD-(L)1 therapy. After receiving standard frequency dosing for the first 24w, benefitting patients are transitioned to reduced frequency dosing at q6w for up to 2 years total or until disease progression, unacceptable toxicity, or study withdrawal. Primary endpoint is objective response rate (ORR). Secondary endpoints include duration of response, disease control rate, progression free and overall survival, and incidence and severity of adverse events (AE). Serial tumor biopsies and blood samples are obtained in all patients, unless not feasible/safe. **Results:** Twelve (out of planned 20) patients were enrolled between Nov 2023 and Jan 2025, before the study was closed to enrollment for administrative reasons by the funding sponsor. At the time of abstract submission, ORR and AE data are available for 10 patients. Two of 10 patients (20%) have partial response and one (10%) has stable disease (26% decrease in tumor size) per RECIST 1.1. Therapy has generally been well tolerated, with immune-related AEs observed in 4 (40%) patients, all Grade 1-2. One patient discontinued therapy due to an AE, grade 5 encephalopathy (anti-IgLON5 disease) diagnosed 7 mo into treatment with unclear relationship to study agents. Correlative studies of pre- and post-treatment tumor and blood specimens are ongoing to characterize the prevalence and significance of cancer-specific T cell exhaustion markers (including PD-1, LAG-3 and TIM-3), and additional mechanisms of PD-(L)1 resistance. Updated translational and clinical results will be presented at the meeting. **Conclusions:** Concurrent triple immune checkpoint blockade of PD-1, LAG-3 and TIM-3 appears to be generally well tolerated and associated with clinical activity in our cohort of patients with PD-(L)1 refractory MCC. Our data suggests TIM-3 and LAG-3 are contributing to immune evasion in a subset of patients with PD-(L)1 resistant MCC, providing support for further investigation of these pathways in larger trials. Clinical trial information: NCT06056895. Research Sponsor: Incyte Biosciences; Kuni Foundation; Jacob Green Foundation.

9532 **Poster Session**

Resistance to anti-PD-1 immunotherapy for stage III and IV melanoma: Results from a global multi-site chart review. First Author: XiangLin Tan, Merck & Co, Inc., Rahway, NJ

Background: Anti-PD-1 immunotherapy has been approved for the treatment of stage III and IV melanoma. Real-world data on its resistance is needed to facilitate the development of combinatorial approaches to overcome anti-PD-1 resistance. Objectives: To estimate the percentage and understand patient/disease characteristics and survival of those receiving anti-PD1 therapy who experience primary resistance and late relapse in the adjuvant (resectable) setting, and primary, secondary resistance and late progression in the advanced (unresectable/metastatic) setting. **Methods:** A retrospective chart review was conducted in 22 sites in Australia, France, Germany, South Korea, UK and USA. Adult patients who began anti-PD-1 therapy for stage III or IV melanoma from 1 Jan 2018 until 12 months before the start of data collection were included. SITC Immunotherapy Resistance Taskforce definitions of resistance were used, and late relapse/progression defined if occurring more than 12 weeks after last dose of anti-PD-1. The percentage of patients with primary, secondary resistance or late relapse/progression were calculated. Time to death was analysed using Kaplan-Meier. Univariate tests were used to compare baseline characteristics and survival by type of resistance. **Results:** Of 981 eligible patients, 738 were included in the full analysis set. In the adjuvant setting (n=240), 53 (22.1%) patients developed primary resistance and 60 (25.0%) experienced late relapse. In the advanced setting (n=498), 222 (44.6%), 50 (10.0%) and 64 (12.9%) patients developed primary, secondary resistance, and late progression, respectively. In the adjuvant setting, a greater proportion of patients with primary resistance (66%) or late relapse (75%) were male than in those with no relapse (52%) (p=0.007). Asian patients experienced less late relapse (0.0%) than White patients (28.2%) but more primary resistance (61.5% vs. 18.4%) ($p<0.001$). In the advanced setting, 48.6% of Asian patients developed primary resistance, 37.8% secondary resistance, 5.4% late progression vs. 40.8%, 8.8% and 12.7% of White patients ($p<0.001$). No significant difference was observed in age, BMI, disease severity, Charlson index score and comorbid conditions by type of resistance. In both settings, time to death varied significantly by type of resistance ($p<0.001$). Patients with primary resistance had the poorest survival: a mean of 42 months in the adjuvant setting and 31 months in the advanced setting (39 months in those with secondary resistance). **Conclusions:** A large proportion of patients developed resistance or late relapse/progression and require alternative therapy after anti-PD-1, highlighting a substantial unmet medical need. A greater proportion of Asian patients developed resistance compared to White patients, possibly due to differences in melanoma subtype. Patients with primary resistance had the poorest survival. Research Sponsor: Merck & Co., Inc.

9533 **Poster Session**

CemiplimAb-rwlc survivorship and epidemiology (CASE): Interim results from a prospective study of the safety and effectiveness of cemiplimab in patients with advanced cutaneous squamous cell carcinoma (CSCC) in a real-world setting. First Author: Soo J. Park, Department of Medicine, Division of Hematology and Oncology, University of California San Diego, San Diego, CA

Background: Cemiplimab is the first PD-L1 inhibitor approved for the treatment of patients with locally advanced (la) or metastatic (m) cutaneous squamous cell carcinoma (CSCC) not amenable to curative therapy. Here, we present an analysis of cemiplimab-treated patients with advanced CSCC enrolled in the CASE study (NCT03836105). **Methods:** CASE is a phase IV, multicenter, prospective, noninterventional study evaluating the effectiveness and safety of cemiplimab in patients with laCSCC/mCSCC and basal cell carcinoma. Data were collected from participating US academic and community oncology centers treating patients ≥18 years of age with intravenous cemiplimab per standard of care. The protocol was reviewed and approved by an institutional review board/ethics committee at each site and patients provided informed consent for study participation. Effectiveness outcomes included investigator-assessed (both physical and radiological) ORR (CR plus partial response) and progression-free survival (PFS). Safety outcomes included treatment-related immune-related adverse events (irAEs), infusion-related reactions (IRRs), and serious adverse events (SAEs). **Results:** As of December 4, 2024, 254 patients (including 44 [17%] immunocompromised/immunosuppressed) across 65 centers with advanced CSCC received ≥1 dose of cemiplimab. Median duration of exposure was 35 weeks (interquartile range: 15.0, 65.9). Most patients were aged ≥65 years (82.7%), male (78.3%), and white (89.0%). Demographics and disease characteristics were similar to those from the EMPOWER-CSCC-1 trial, with the exception of patients with Eastern Cooperative Oncology Group Performance Status of 2-3, which were excluded from the trial but represented 10.7% (27/254) of our real-world study analysis set. 64.2% of patients had laCSCC and 35.8% had mCSCC. ORR, including all patients regardless of missing response data, was 111/254 (43.7%; 95% CI: 37.5, 50.0) patients. CR was reached by 40/254 (15.7%) patients. ORR in patients with at least 1 response assessment reported was 111/201 (55.2%; 95% CI: 48.1,62.2) patients, and CR was reached by 40/201 (19.9%) patients. The overall response rate of the clinical trial (52.7%) fell within the range of our response data (43.7-55.2%). Median PFS was 14.7 (95% CI: 12.5, 21.1) months, with survival at 12 months estimated at 59.5% (95% CI: 51.4, 66.7). Treatment-related irAEs occurred in 76/254 (29.9%) patients and treatment-related SAEs occurred in 19/254 (7.5%) patients; one patient reported an IRR. **Conclusions:** The interim results of this Phase IV study demonstrate robust effectiveness and a generally manageable safety profile of cemiplimab in patients with laCSCC/mCSCC in real-world practice that are comparable to the results of the EMPOWER-CSCC-1 trial. Clinical trial information: NCT03836105. Research Sponsor: Regeneron Pharmaceuticals, Inc.

9534 **Poster Session**

Biosafety analysis from the skin cancer cohorts in the IGNYTE clinical trial of RP1. First Author: Trisha Michel Wise-Draper, University of Cincinnati Cancer Center, University of Cincinnati, Cincinnati, OH

Background: RP1 (vusolimogene oderparepvec) is an HSV–based oncolytic immunotherapy administered intratumorally. RP1 + nivolumab (nivo) has demonstrated deep, durable responses with favorable safety in advanced melanoma. We report biodistribution and shedding data from the skin cancer cohorts of the IGNYTE trial (NCT03767348). **Methods:** Following RP1 injection into superficial and/or deep lesions, injection sites were covered with occlusive dressings. Injection sites, dressings and mucosa were swabbed, and blood and urine were collected pre-dose, during treatment, and at follow-up visits. Samples were assessed for RP1 DNA by qPCR. Swab samples positive for RP1 DNA were further assessed by TCID50 assay for live RP1. **Results:** The highest incidence of RP1 DNA was from injection-sites where RP1 was detected in ~35% of samples for up to 15 days post-injection. Blood samples showed the presence of low copy numbers of RP1 DNA (122/1573 [7.8%]) in ~20% (53/274) of pts during or after RP1 treatment. The highest levels were detected in blood within 6 hours of injection and decreased thereafter. RP1 was only very rarely detected and at low copy number in urine samples (3/1976 [0.2%]) from 0.7% (2/273) pts at 15 days post-injection, with all subsequent samples testing negative. RP1 DNA was detected on injection-site dressing exteriors less often (9.5% of 1114 samples) than from injection sites (18.4% of 1947 samples), demonstrating that the dressings act as a barrier to RP1. RP1 DNA was rarely present on oral mucosa (0.9% of 2052 samples). At follow-up (30-100 days post last dose), RP1 DNA was detected only at injection-sites. All available samples were negative for live RP1 by TCID50. Eight swab samples from 7 pts were collected from suspected herpetic infections but all tested negative for live RP1. There were no reports of systemic herpetic infections in pts, nor of transmission to contacts. **Conclusions:** RP1 DNA was primarily detected on the surface of injected lesions for up to 15 days, with no live RP1 being detected at 30, 60 and 100 days post the last RP1 dose. Collectively, these data demonstrate that RP1 is rapidly cleared from blood and urine, with negligible likelihood of environmental dissemination or transfer to contacts, and that the use of occlusive dressings contains RP1.Defining the biodistribution and shedding of RP1 is relevant to the education of healthcare providers and to the development of best practices for the proper administration, handling and clean down. Clinical trial information: NCT03767348. Research Sponsor: Replimune, Inc.

9535 **Poster Session**

Clinical and biomarker analyses of first-line nivolumab and relatlimab (nivo-rela) in advanced or resectable melanoma (mel). First Author: Lilit Karapetyan, H. Lee Moffitt Cancer Center and Research Institute, Tampa, FL

Background: Simultaneous blockade of lymphocyte activation gene-3 (LAG-3) and programmed death-1 (PD-1) pathways enhances antitumor activity in patients (pts) with mel. While efficacy of nivo-rela has been demonstrated in a large cohort of therapy-naïve advanced mel, it remains important to assess clinical activity of this combination in real-world settings focusing on resectable mel and on tumor microenvironment (TME) factors impacting response to nivo-rela. In this study we report the clinical activity of nivo-rela and the relation of TME characteristics to response to therapy. **Methods:** This study included pts with mel treated with first-line nivo-rela in the neoadjuvant or advanced settings between 2022-2024 at Moffitt. Safety, progression-free (PFS), overall survival (OS) and pathologic response rates were evaluated in relation to mel characteristics. To assess the impact of TME on response to nivo-rela in advanced mel, we performed NanoString GeoMx proteomic analysis using immune cell profiling, immune cell typing, and IO drug target panels. Differential proteomic analysis (fold change ≥0.05, FDR <0.05) was performed using selected baseline samples (n=16) from responders (R) and non-responders (NR). **Results:** The study included 128 mel pts treated with nivo-rela in the advanced (n=101, [C1]) and neoadjuvant (n=27, [C2]) settings, 48 female (38%) and 80 male (62%), median age 71 [IQR 62–78]. In C1, with a median follow up of 13 months, mPFS and mOS with 95% CI were 19m (10-NR), and NR (25-NR), respectively. In C2, 6 (22%) of pts did not undergo definitive surgery due to disease progression (n=4) and clinical response to therapy (n=2). Among path-evaluable pts (n=21), major pathologic response rate was 10 (48%) including 6 complete (29%) and 4 near-complete responses 19%), with partial response in 3 (14%) and non-response in 8 patients (38%). Adverse events included adrenal insufficiency and myocarditis in 12 (9%) and 4 (3%) of all pts. TME assessment revealed no significant differences in expression of LAG3, PD-1, PDL-1, $CD8^+$ among R vs NR. Baseline tumors from NR were characterized by high expression of B7-H3 in both tumor and immune compartments. No significant correlations were found between B7-H3 and PDL-1, LAG-3, and CTLA-4. High B7-H3 ROIs were enriched by $CD163^+$, $CD68^+$, $CD14^+$, and fibroblast activation protein alpha. **Conclusions:** In a real-world setting, first-line nivo-rela in advanced mel resulted in potentially better PFS while in resectable pts the major pathologic response rate was lower than previously reported in clinical trials. Mel TME with high B7-H3 protein expression was enriched with M2-skewed macrophages and fibroblasts in association with non-response to nivo-rela. This finding warrants further investigation of B7-H3 targeting agents in mel pts. Research Sponsor: None.

9536 **Poster Session**

Final results of POD1UM-201, a phase 2 study of retifanlimab, a humanized anti–PD-1 antibody, in patients with advanced or metastatic Merkel cell carcinoma (MCC). First Author: Giovanni Grignani, Candiolo Cancer Institute, FPO – IRCCS, Candiolo, Torino, Italy

Background: Retifanlimab is approved in the United States and Europe for treatment of adults with metastatic or recurrent locally advanced MCC, based on previously reported results from the open-label single-arm POD1UM-201 study (NCT03599713). As previously reported, objective response rate (ORR) was 54% (95% confidence interval [CI], 43, 64) and probability of remaining progression free at 12 months was 71% (Grignani G, et al. *Ann Oncol.* 2023;34(suppl 2):S686). Safety profile was as expected for the PD-(L)1 inhibitor class. Here, we present the final results from POD1UM-201 based on extended follow-up. **Methods:** Eligible patients were aged ≥18 years with metastatic or recurrent unresectable locoregional MCC, an Eastern Cooperative Oncology Group performance status (ECOG PS) of 0-1, and measurable disease per Response Evaluation Criteria in Solid Tumors (RECIST) v1.1. Prior systemic treatment for MCC was not allowed. Retifanlimab 500 mg was administered intravenously once every 4 weeks for up to 2 years. Premedication prophylaxis was not routinely administered. The primary endpoint was ORR assessed by independent central review per RECIST v1.1. Key secondary endpoints were duration of response (DOR), disease control rate, progression-free survival, overall survival, and safety. **Results:** The study enrolled 101 patients in North America and Europe between February 12, 2019, and June 16, 2021. Patients had a median age of 71 (range: 38, 90) years, 68 (67%) were male, 77% were White, 74 (73%) had an ECOG PS of 0, and 1 (1%) patient was HIV positive. 91 patients (90%) had stage IV disease, 69 (68%) had prior surgery, and 37 (37%) had prior radiotherapy. Merkel cell polyomavirus and PD-L1 expression were detectable in 73 (72%) and 83 (82%) patient tumor samples, respectively. Median follow-up duration was 36 (range: 1, 60) months. Summary efficacy results are shown in the Table. ORR was 55% (95% CI, 44, 64), with complete response observed in 18 patients (18%). Median DOR was not reached and probability of remaining progression free at 36 months was 57%. Most common immune-related adverse events (irAEs) were skin reactions (10%), including pruritus (4%) and rash (3%), and hypothyroidism (8%); 11% of patients had grade ≥3 irAEs and 9% discontinued treatment due to irAEs. **Conclusions:** Retifanlimab is a highly active treatment for advanced MCC with a safety profile that is representative of the PD-(L)1 inhibitor class. Clinical trial information: NCT03599713. Research Sponsor: Incyte Corporation.

Summary of efficacy.

Study Endpoint	N=101
Overall response rate (95% CI), %	55 (44, 64)
Complete response, n (%)	18 (18)
Partial response, n (%)	37 (37)
Disease control rate (95% CI), %	60 (50, 70)
Duration of response, median (range), months	NR (23, NE)
Progression-free survival, median (range), months	16 (9, 32)
Overall survival, median (range), months	NR (45, NE)

CI, confidence interval; NE, not estimable; NR, not reached.

9537 **Poster Session**

Response analysis for injected and non-injected lesions and of the safety and efficacy of superficial and deep/visceral RP1 injection in the registrational cohort of anti–PD-1–failed melanoma patients of the IGNYTE trial. First Author: Gino Kim In, University of Southern California Norris Comprehensive Cancer Center, Los Angeles, CA

Background: The IGNYTE trial (NCT03767348) primary analysis of RP1 (vusolimogene oderparepvec) plusnivolumab (nivo) showed clinically meaningful durable efficacy (ORR, 32.9%; median DOR, 33.7 mos, by RECIST 1.1 and independent central review) in patients (pts) with advanced melanoma, including deep responses in non-injected visceral lesions, demonstrating systemic efficacy. Here we present an analysis of efficacy in injected and non-injected lesions and safety and efficacy in pts receiving superficial and/or deep/visceral RP1 injections. **Methods:** Pts with confirmed progression during anti–PD-1 ± anti–CTLA-4 for ≥8 weeks were enrolled. RP1 (1×10^6 PFU/mL x1, then Q2W 1×10^7 PFU/mL x7, up to 10 mL) was injected into superficial and/or deep/visceral tumors using imaging guidance. Nivo was given (240 mg Q2W) from the 2nd dose of RP1 through dose 8, then alone (240 mg Q2W or 480 mg Q4W) for 2 yrs, with additional RP1 injections allowed if indicated. **Results:** For the 46 responding patients by RECIST 1.1 (of the 140 enrolled) 197 lesions were measured, 78 injected, 119 non-injected of which 98.7% and 96.6% had any reduction and 93.5% and 79.0% >30% reduction, respectively. For visceral lesions, 85.7% of injected and 96.2% of non-injected lesions had any reduction and 85.7% and 65.4% had >30% reduction, respectively. 104 patients had superficial only injections, and 36 had deep/visceral +/- superficial injections. Treatment-related adverse event (TRAEs) rates were comparable in patients who were injected superficially compared to patients who received deep/visceral injections, except for chills, influenza-like illness, and injection-site pain, which were numerically higher in the deep/visceral +/- superficial group. Grade ≥3 TRAEs occurred in 14.4% of pts by superficial injection and 8.3% by deep/visceral +/- superficial injection. Grade 1/2 pneumothorax occurred in 3/52 (5.8%) lung injections. No liver function abnormalities or significant bleeds were reported after liver injections. The ORR for pts with superficial injection only was 29.8%, and 41.7% for deep/visceral +/- superficial. **Conclusions:** Meaningful systemic responses were observed independent of the injection status of individual lesions or their anatomical site. Overall response was therefore driven by the response of both injected and non-injected lesions. The safety profile of deep/visceral injection was comparable to that of superficial injections, with efficacy also being similar. Clinical trial information: NCT03767348. Research Sponsor: Replimune, Inc.

9538 **Poster Session**

Long-term outcomes after discontinuation of retifanlimab in patients with advanced or metastatic Merkel cell carcinoma (MCC) in the POD1UM-201 trial. First Author: Giovanni Grignani, Candiolo Cancer Institute, FPO – IRCCS, Candiolo, Torino, Italy

Background: Retifanlimab is a humanized programmed cell death protein-1 (PD-1)–blocking antibody that is approved for treatment of adults with metastatic or recurrent locally advanced MCC in the United States and Europe. Approval was based on primary results from the phase 2, open-label, single-arm POD1UM-201 study (NCT03599713). Here, we present long-term outcomes in patients with MCC who discontinued retifanlimab for reasons other than confirmed disease progression, as previous studies have suggested high rates of recurrence in patients discontinuing treatment after initial response. **Methods:** POD1UM-201 enrolled patients with metastatic or recurrent unresectable locoregional MCC who had not received prior systemic treatment. Retifanlimab was administered every 4 weeks (q4w) intravenously (IV) for a maximum of 2 years, or until progressive disease (PD) or unacceptable toxicity. Patients with complete response (CR) were permitted to discontinue treatment after a minimum of 6 months at investigator discretion. Patients who discontinued retifanlimab for reasons other than PD were closely followed for disease status by independent central review (ICR) until disease progression or death. **Results:** The study enrolled 101 patients with a median (range) follow-up duration of 36 (1, 60) months. Objective response rate was 55% and disease control rate was 60%, including 18 patients (18%) with CR, 37 (37%) with partial response (PR), and 6 (6%) with stable disease (SD) for ≥6 months. Sixty-four patients (63%) discontinued treatment prior to completion of therapy, most commonly due to tumor progression. Forty-one patients were continuing to demonstrate ICR confirmed benefit when treatment was discontinued (CR, n=15; PR, n=21; SD, n=5). Of these patients, 26 (63%) completed the protocol-defined maximum 2 years of therapy, 3 (7%) discontinued at the discretion of the investigator after CR was achieved, and 12 (29%) discontinued due to toxicity. Among the patients with CR or PR, 30 (83%) were alive without disease progression at time of last follow-up after a median (range) of 18 (2, 46) months. Patients who achieved a CR or PR had a lower rate of PD or death compared with those with SD; 7% of patients with a CR experienced PD during follow-up vs 24% of patients with a PR and 60% of patients with SD. **Conclusions:** Retifanlimab 500 mg administered q4w IV for up to 2 years led to durable clinical responses in the majority of patients with advanced MCC. Most patients with an ongoing objective response (CR or PR) remain progression free beyond discontinuation of therapy, suggesting sustained benefit is possible in patients with this highly aggressive disease. Clinical trial information: NCT03599713. Research Sponsor: Incyte Corporation.

9539 **Poster Session**

Updated analyses from a global meta-analysis in metastatic uveal melanoma (mUM) to determine progression free and overall survival benchmarks by line of therapy: An international rare cancers initiative (IRCI) ocular melanoma study. First Author: Leila Khoja, University of Birmingham, Birmingham, United Kingdom

Background: PUMMA is an individual trial patient level meta-analysis that established survival and prognostic benchmarks in metastatic uveal melanoma (Khoja et al, 2019) in 912 patients treated 2000-2016. **Methods:** Herein we describe the dataset further by line of treatment to assist in establishing benchmarks of activity needed to satisfy synthetic control arm surrogates for regulatory purposes for benchmarks of PFS (Progression Free Survival) and OS (Overall Survival) in months (m). **Results:** Within the PUMMA dataset, 567 (62.2%) received 1st line treatment, 161 (17.7%) received 2nd /3rd line treatment. OS was comparable by line of treatment (P=0.2513) with 12m OS rates being 41.3% and 40.5% respectively. Median OS by line of treatment was 9.95 m (95% CI 9.23-10.74) for 1st line and 10.15 m (7.69-11.60) for 2nd/3rd line. PFS was also comparable by line of treatment (p=0.51) with 12m PFS rates being 11.7% and 7.2% respectively. Median PFS by line of treatment was 2.76 m (95% CI 2.66-3.38) for 1st line and 2.86 m (95% CI 2.73-3.52) for 2nd/3rd line. Multivariable analysis of the 1st and 2nd/3rd line treatments separately suggested statistically significant ($p<0.05$) variables associated with inferior PFS in the first line setting included male sex, LDH>2X ULN, ALP>2X ULN whilst inferior PFS in the 2nd/3rd line was predicted by LDH>2X ULN only. Inferior OS in the 1st line setting was statistically significantly associated with ECOG>2, Age > 65, male sex, LDH>2X ULN, ALP>2X ULN whilst inferior OS in the 2nd/3rd line was associated with ECOG>2, LDH>2X ULN, and ALP>2XULN. **Conclusions:** PUMMA continues to show value in providing benchmarks of activity for future clinical trials or regulatory purposes in mUM. The prognostic ability of LDH>2XULN retains important value across multiple lines of treatment scenarios in the PUMMA dataset. Research Sponsor: None.

9540 Poster Session

A phase II, open-label study to improve compliance and time of treatment after obtaining complete response (CR) through a tailored schedule of sonidegib in locally advanced basal cell carcinomas (laBCC): The SONIBEC trial. First Author: Carlo Resteghini, Department of Biomedical Sciences, Humanitas University; IRCCS Humanitas Research Hospital, Pieve Emanuele, Italy

Background: Sonidegib is an efficacious treatment of LA laBCC but is associated with a high risk of treatment-related adverse events (TRAEs) causing treatment discontinuation. Following a CR, treatment discontinuation rate reaches up to 60% after a year, leading to 3 years relapse free survival rate of 35%. We aimed at evaluating sonidegib tailored schedule (TS) after CR to increase treatment duration by reducing TRAEs, thus allowing CR maintenance. **Methods:** We conducted a multicenter, open-label, single-arm phase II study enrolling adult patients (pts) with laBCC who obtained a CR to sonidegib regardless of the tumor's subtype and burden. Eligible pts received TS1 with sonidegib 14 days on and 14 days off. Pts on TS1 who experienced grade 2-3 toxicity (except alopecia) lasting >28 days moved to TS2 (7 days on and 21 days off). Treatment continued until progression or unacceptable toxicity. Primary endpoint was the rate of pts maintaining sonidegib 12 months after study enrolment (H0 31%, H1 60%). Evaluable pts were defined as all pts who were either on treatment or suspended treatment for reasons other than treatment-unrelated adverse events or death. Secondary endpoints were safety, treatment compliance, rate of disease relapse at 1 and 2 years, overall survival, quality of life, use of concomitant medications and of medical resources, and translational analysis. **Results:** Between Jan 2021 and Dec 2023, 22 pts from 10 Italian centers were enrolled; the data cut-off was Jan 2025. Pts characteristics are reported in table 1. The median follow-up was 22 months (range 2-33). Three disease and treatment-unrelated deaths occurred before completing 1 year of TS and therefore 19 pts were evaluable. At data cut-off, 12 pts had discontinued treatment: 26% (5) due to disease progression, 11% (2) to sonidegib's unacceptable toxicity, the remaining either to personal or physician's choice. Twelve out of 19 evaluable pts (63%) were still on treatment after 1 year from TS start (median duration 20 months, range 2-29), meeting the primary endpoint. The most common TRAEs episodes were muscle cramps (13), alopecia (6), dysgeusia (5) with overall TRAEs grade G1 (29), G2 (11), G3 (3). Twelve pts had dose reduction to TS2. **Conclusions:** Tailored maintenance schedule with pulsed sonidegib allows for longer treatment duration and fewer relapses in CR laBCC pts. Study follow up to evaluate secondary endpoints outcome and translational analysis are ongoing. Clinical trial information: 2020-002613-17. Research Sponsor: This is an investigator initiated trial partially supported by an unconditional grant by SunPharma.

Patient characteristics.

Characteristic	N (%)
Male : Female	14 (64) : 8 (36)
Median age	76y (range 56-93y)
ECOG PS 0-1	15 (68): 7 (32)
Histology sub-type	
Nodular	8 (36)
Superficial	2 (9)
Infiltrative	7 (32)
Mixed	1 (5)
Other	4 (18)

9541 Poster Session

AI-detected tumor-infiltrating lymphocytes and response to PD-1 based treatment in advanced melanoma. First Author: Mark Schuiveling, University Medical Center Utrecht, Utrecht, Netherlands

Background: Biomarkers to predict response to immune checkpoint inhibition (ICI)-treated melanoma are limited. This study evaluates AI-detected tumor-infiltrating lymphocytes (TILs) on pretreatment metastatic pathology specimens as a biomarker for response and survival in ICI-treated patients. **Methods:** Patients treated with first-line anti-PD1 ± anti-CTLA4 for advanced melanoma were retrospectively identified from 11 Dutch melanoma centers. Pretreatment TILs were quantified on H&E stained slides using the Hover-NeXt algorithm trained on an independent melanoma dataset with 166.718 pathologist checked manually annotated cells. The average percentage of TILs per 200 μm^2 tumor area was calculated. The primary outcome was response to ICI per RECIST 1.1 with overall survival (OS) and progression free survival (PFS) as secondary outcomes. Univariable and multivariable logistic and Cox regression analyses assessed associations between a 10% increase in TILs present in pretreatment metastatic slides and clinical outcomes. Multivariable analyses were adjusted for age, sex, disease stage, BRAF mutation, LDH and performance score. Objective response rate and Kaplan Meier survival analysis were stratified by TIL tertiles. **Results:** Metastatic melanoma specimens were available for 1246 patients, 441 received anti-PD1 + anti-CTLA4. Median TIL percentage was 10.2% (interquartile range 5.5% – 17.2%). A 10% higher baseline TIL percentage was associated with response (adjusted OR 1.39 [95% 1.21-1.58]), PFS (adjusted HR 0.87 [95% CI 0.81 – 0.94]) and OS (adjusted HR 0.84 [95% CI 0.77 – 0.93] in univariable and multivariable analysis (Table 1). Stratified analysis showed significant associations between TILs, response, and survival in both anti-PD1 monotherapy and combination therapy. **Conclusions:** AI-quantified TILs in pre-treatment melanoma metastases are correlated with improved response rates and survival in ICI treated patients. This correlation is independent of known clinical predictors. Research Sponsor: The Netherlands Organization for Health Research and Development (ZonMW); 848101007; Stichting Hanarth Fonds.

Outcome	ICI	Lowest Tertile	Middle Tertile	Highest Tertile	Univariable OR / HR [95% CI]	Multivariable OR / HR [95% CI]
Response (%)	All	47.9%	57.8%	64.5%	1.35 [1.21 – 1.52]	1.39 [1.21 – 1.58]
	Anti-PD1	45.2%	57.1%	66.7%	1.42 [1.24 – 1.64]	1.37 [1.17 – 1.60]
	Anti-PD1 + Anti-CTLA4	51.4%	62.2%	58.7%	1.23 [1.00 – 1.53]	1.48 [1.13 – 1.94]
PFS (months)	All	5.4	9.7	15.3	0.87 [0.81 – 0.93]	0.87 [0.81 – 0.94]
	Anti-PD1	5.4	11.8	16.5	0.85 [0.79 – 0.92]	0.89 [0.81 – 0.97]
	Anti-PD1 + Anti-CTLA4	5.3	11.0	10.2	0.89 [0.78 – 1.02]	0.80 [0.69 – 0.94]
OS (months)	All	21.4	38.4	49.2	0.81 [0.75 – 0.88]	0.84 [0.77 – 0.93]
	Anti-PD1	21.1	36.5	51.4	0.79 [0.71 – 0.87]	0.86 [0.77 – 0.96]
	Anti-PD1 + Anti-CTLA4	21.4	77.8	46.4	0.88 [0.75 – 1.03]	0.82 [0.69 – 0.97]

9542 Poster Session

Real-world clinical outcomes of patients with BRAF-mutated melanoma with or without brain metastases receiving frontline immune-checkpoint inhibitors in the US community oncology setting. First Author: Wolfram Samlowski, Comprehensive Cancer Centers of Nevada, Las Vegas, NV

Background: Patients with BRAF-mutated melanoma are at increased risk of melanoma brain metastasis (MBM) which has historically led to worse outcomes. The prognosis of patients with MBM has improved with approval of immune checkpoint inhibitors (ICI) and targeted therapy. However, there is limited information on the impact of the MBM on outcomes in patients with BRAF mutations treated with frontline (1L) ICI. This study aims to describe clinical outcomes of patients with BRAF-mutated metastatic melanoma treated with 1L ICI in the community oncology setting, with a focus on patients with MBM. **Methods:** This was a retrospective observational cohort study of patients with BRAF-mutated metastatic melanoma who initiated 1L ICI (index) between 1/1/16-6/30/22 in The US Oncology Network and non-Network practices and were followed through 6/30/24. Patient characteristics and genomic alterations were sourced from structured electronic health records data and genomic testing results. Patients with mucosal or uveal melanoma, clinical trial participation, treatment for other primary cancers or evidence of co-mutations were excluded. Kaplan-Meier analyses of overall survival (OS), real-world time to treatment discontinuation (rwTTD) and time to next treatment (rwTTNT) were assessed from index, overall and in patients with MBM. **Results:** Of 798 metastatic melanoma patients with a BRAF mutation, 41 (5%) had documentation of a co-mutation and were excluded, resulting in 757 patients in the final analysis set. Median follow-up was 14.6 months, and median age at index was 64 years. Among patients with available data, most were male (63%), White (97%) and had an ECOG of 0-1 (87% among reported) within 60 days prior to index. Among patients with mutation-specific data (n=704), the most common mutation types were V600E (83%) and other V600 (13%) point mutations. The most common 1L ICI regimens were nivolumab+ipilimumab (45%), pembrolizumab (30%), and nivolumab (22%). MBM was documented in 46 (6%) patients at 1L ICI treatment initiation, and an additional 28 (4%) patients developed MBM during the follow-up period, resulting in a total of 74 (10%) patients with MBM. **Conclusions:** Although lower-than-expected rates of MBM were observed, in this large real-world dataset from the community setting, patients with a BRAF mutation had similar rwTTD, rwTTNT, and OS following ICI therapy, irrespective of the presence of MBM. It is reasonable to consider combination ICI therapy in BRAF mutant melanoma patients diagnosed with MBM who lack known contraindications. Further research on the impact of the somatic mutational background on MBM outcomes is ongoing. Research Sponsor: None.

Outcome, median (95% CI)	Overall (N=757)	MBM, any time (N=74)
OS, months	20.3 (16.6, 25.8)	20.3 (10.4, 33.8)
rwTTD, months	3.5 (2.9, 3.9)	3.7 (2.4, 5.6)
rwTTNT, months	5.7 (4.9, 6.5)	5.6 (3.7, 7.5)

9543 Poster Session

Real-world safety and effectiveness of avelumab in immune-compromised (IC) and non-IC patients with Merkel cell carcinoma (MCC): Results from a prospective German registry (MCC-TRIM). First Author: Jurgen Becker, University Hospital Essen, German Cancer Consortium (DKTK), Partner Site Essen/Düsseldorf, German Cancer Research Center (DKFZ), Heidelberg, Germany

Background: MCC is a rare and aggressive form of skin cancer. Avelumab was the first immunotherapy approved for patients with metastatic MCC in Europe. Immunosuppression is an established risk factor for developing MCC, but IC patients have typically been excluded from clinical trials of immunotherapies. We report an analysis of clinical characteristics, survival outcomes, and safety in IC and non-IC patients with MCC treated with avelumab in routine clinical practice in Germany. **Methods:** This prospective, noninterventional, multicenter, dynamic cohort study (MCC-TRIM; EUPAS25338) enrolled patients with MCC in Germany between April 2019 and September 2023. Primary data from a study-specific electronic case report form and secondary data from the German national skin cancer registry were combined. For this analysis, avelumab-treated patients were grouped as IC or non-IC based on prespecified comorbid conditions and concomitant medications. Survival outcomes with first-line avelumab treatment were assessed using the Kaplan-Meier method. **Results:** Among 875 patients with MCC (various disease stages) enrolled in the study, 243 were treated with avelumab, of whom 189 (77.8%) were considered non-IC and 54 (22.2%) were considered IC. Patient characteristics are summarized in the Table. At data cutoff (March 2024), median follow-up (IQR) was 14.3 months (6.4-29.4) in the non-IC subgroup and 8.9 (4.2-22.8) in the IC subgroup. In non-IC and IC subgroups, median (95% CI) overall survival from start of first-line avelumab was 38.2 (15.7-not estimable) and 9.9 (4.8-29.8) months, and median progression-free survival was 7.9 (4.0-11.6) and 4.3 (1.0-7.8) months, respectively. The incidence rate of ADRs related to avelumab was 1.01 (95% CI, 0.75-1.34) events per person-year in the non-IC subgroup and 0.71 (95% CI, 0.32-1.45) events per person-year in the IC subgroup. **Conclusions:** Results from this German nationwide registry showed the safe and effective use of avelumab in routine clinical practice for IC and non-IC patients with MCC. Research Sponsor: the healthcare business of Merck KGaA, Darmstadt, Germany (CrossRef Funder ID: 10.13039/100009945).

	Non-IC (n=189)	IC (n=54)
Mean age at diagnosis (SD), years	74.8 (10.2)	76.4 (8.1)
Male, n (%)	122 (64.6)	35 (64.8)
Stage at diagnosis, n (%)		
Early stage (I, II, or unknown)	38 (20.1)	13 (24.1)
III	80 (42.3)	19 (35.2)
IV	71 (37.6)	22 (40.7)
ECOG performance status ≤1, n (%)	153 (81.0)	40 (74.0)
Comorbidities, n (%)		
Diabetes	36 (19.0)	14 (25.9)
Chronic obstructive pulmonary disease	5 (2.6)	4 (7.4)
Cerebrovascular disease/stroke	2 (1.1)	3 (5.6)
Moderate or severe renal disease	11 (5.8)	5 (9.3)
Ischemic heart disease/myocardial infarction	21 (11.1)	8 (14.8)
Moderate or severe liver disease	3 (1.6)	0
Thyroid disorder	17 (9.0)	4 (7.4)
Inflammatory bowel disease	4 (2.1)	2 (3.7)
Rheumatoid arthritis	5 (2.6)	5 (9.3)

9545 **Poster Session**

Progression-free survival (PFS) assessment by blinded independent central review (BICR) versus local investigator (LI) in metastatic melanoma (MM) randomized controlled trials (RCT): A systematic review and meta-analysis. First Author: Islam Eljilany, Department of Cutaneous Oncology, H. Lee Moffitt Cancer Center and Research Institute, Tampa, FL

Background: Although BICR may reduce assessment variability, it introduces additional financial and logistical burdens to trial operations. This study analyzed the discrepancy indexes (DIs) to evaluate differences between PFS assessments evaluated by LIs and BICR in RCTs of patients (pts) with MM. **Methods:** A comprehensive literature search was conducted on PubMed, Embase, and Cochrane databases until June 30, 2023. Studies were eligible for inclusion in the meta-analysis if they were 1) Phase II or III RCTs with accessible, published data; 2) inclusion of pts diagnosed with MM; 3) availability of PFS data assessed through both LI and BICR; and 4) publication in English. The study complied with the PRISMA guidelines to ensure methodological rigor. Two independent researchers performed data extraction to minimize bias and ensure accuracy. A fixed-effects meta-analysis approach was applied to summarize treatment outcomes, producing pooled estimates and corresponding 95% confidence intervals (CIs). The primary outcome was DI, which was calculated for each trial as a ratio of the hazard ratios $(HR)_{BICR}$ by HR_{LI}. The agreement between PFS HRs was also evaluated using the intraclass correlation coefficient (ICC) and Pearson's correlation coefficient (r). The risk of bias was evaluated using the Cochrane Risk of Bias tool v.2 (RoB 2). **Results:** A total of 12 studies comprising 4,915 pts were included in the meta-analysis that spanned from 2012 to 2023. Of these, 10 studies (83%) were Phase III , 11 (92%) were cutaneous melanoma and all identified PFS as the primary endpoint. Most studies (n = 8, 75%) had a DI $>$ 1 and the overall combined DI was 1.08 (95% CI: 1.01–1.15), indicating a statistically significant numerically small difference (8%) in PFS evaluations conducted by the two assessments, suggesting that BICR tended to be more conservative in PFS assessments. These results were primarily driven by the Phase II or double-blinded studies, which showed a higher median (interquartile range) (IQR) DI [1.14 (o.o8) and 1.16 (0.13), respectively] than phase III or open-label trials [DI 1.04 (0.12) or 1.0 (0), respectively] . However, there was an overall significant strong correlation [ICC: 0.87, $p < 0.001$); r= 0.89, 95% CI 0.67-0.96, $p < 0.0001$)] between BICR and LI assessments and most (86%) of the PFS comparisons led to the same statistical inference. Finally, 10 studies had a low risk of systematic bias, and none had publication bias. **Conclusions:** This study demonstrated a slim statistically significant difference in PFS assessments between LI and BICR, but with strong agreements overall. These findings challenge the necessity of universally implementing BICR in all RCTs, supporting appropriate use in selected scenarios, primarily Phase II RCT. Also, supports the value of double-blinded studies. Research Sponsor: None.

9546 **Poster Session**

Efficacy and safety of transcatheter arterial infusion of immune checkpoint inhibitors in locoregional unresectable or in-transit acral melanoma: A multi-center real-world study. First Author: Ziluan Chen, Sun Yat-sen University Cancer Center, Guangzhou, China

Background: Acral melanoma (AM) is highly invasive. Standard treatment options, including surgical resection and systemic immunotherapy, frequently yield insufficient control over local lesions. Although various local treatment strategies are currently available, such as isolated limb perfusion (ILP), isolated limb infusion (ILI), intralesional therapies, and radiotherapy, there is still no universally recognized safe and effective method. Previous studies have suggested that transcatheter arterial infusion (TAI), as a locoregional therapeutic strategy, may enhance the management of local lesions through targeted drug delivery. However, the existing literature on the efficacy and safety of TAI utilizing immune checkpoint inhibitors (ICIs) is limited. The aim of this study was to assess the efficacy and safety of TAI of ICIs in patients diagnosed with AM, as well as to investigate clinical factors that may affect treatment outcomes. **Methods:** This study involved a retrospective analysis of patients with AM who underwent TAI of ICIs across multiple centers. Participants received TAI of PD-1 inhibitors or a combination of PD-1 and CTLA-4 inhibitors every three weeks, in conjunction with systemic therapy. The primary endpoint was the objective response rate (ORR), while secondary endpoints included the disease control rate (DCR), progression-free survival (PFS) of locoregional lesions, duration of response (DoR), and overall survival (OS). **Results:** A total of 44 patients with AM were enrolled and analyzed between May 2019 and January 2025. All participants had received at least two TAI treatments and had at least one evaluable locoregional lesion in the extremities, as determined by enhanced MRI or CT imaging. The cohort consisted of 23 females (52%) and 21 males (48%), with a median follow-up period of 10.6 months. The overall ORR was 36.4%, and the DCR was 86.4%. The ORR and DoR for lesions treated with TAI were 40.9% and 90.1%, respectively. Five patients (11%) achieved a complete response (CR), one of whom demonstrated a pathological complete response. The median DoR and OS were recorded at 11.8 months and 32.2 months, respectively. First-line treatment exhibited a significantly higher ORR (82.4% vs. 14.8%, P $<$ .001) and longer PFS (24.9 months vs. 3.5 months, P $<$ .001) compared to subsequent-line treatments. Adverse events were primarily classified as grade 1-2, with no instances of grade 4-5 events, and there were no treatment-related discontinuations or fatalities. **Conclusions:** This study provides evidence for the safety of TAI of ICIs and suggests that it may represent an effective first-line treatment option for Chinese patients with locoregional unresectable lesions of AM, demonstrating significant local control efficacy in real-world clinical settings. Research Sponsor: None.

9547 **Poster Session**

The phase 1 clinical trial of anti–PD-1 ab plus intrahepatic injection of oncolytic virus (OH2) combined radiotherapy of liver metastasis in stage IV melanoma. First Author: Xuan Wang, Department of Melanoma and Sarcoma, Key Laboratory of Carcinogenesis and Translational Research (Ministry of Education/Beijing), Peking University Cancer Hospital and Institute, Haidian District, China

Background: Patients with melanoma and liver metastases generally exhibit reduced responses to systemic immunotherapy. Oncolytic herpes simplex virus 2 (OH2), is an oncolytic virus with potential therapeutic benefits. Preliminary clinical trials have demonstrated the efficacy of combining PD-1 antibody therapy with intrahepatic intralesional injections of OH2. Additionally, liver metastasis radiotherapy may modulate the tumor microenvironment, potentially enhancing the efficacy of immunotherapy combinations. In this phase I study, we aim to evaluate the safety and efficacy of OH2 and Pucotenlimab, in combination with liver metastasis-directed radiotherapy in patients with melanoma. **Methods:** Eligible pts included those over 18 with injectable liver metastasis confirmed by biopsy with or without extrahepatic metastasis; the ocular melanoma and brain metastasis were excluded. Pts received intravenous Pucotenlimab Q3W combined with ultrasound guided intrahepatic injection of OH2 Q2W (10^7CCID50/mL, 8ml per injection) after SBRT (24-30Gy/3Fx) of liver metastasis. The primary endpoint was ORR. Clinical trial: NCT05068453. **Results:** From Dec 2021 to Jan 2025, 20 pts were enrolled. 77.8% had received at least one prior treatment; 52.9% presented with extrahepatic metastases. The median size of enrolled lesions was 34.56 mm (13.0–271.0 mm). The median number of liver metastases was 5.5. Among these patients, 17 were evaluable for efficacy. One iCR, four iPR, resulting in an ORR of 29.4% and a DCR of 52.9%. Nearly 60.0% of pts exhibited a reduction in target lesions, including 65.2% of intrahepatic lesions, and 41.7% of extrahepatic lesions with a maximum reduction of 100.0%. Among injection target lesions, 58.3% demonstrated shrinkage,. In non-injection target lesions, 54.5% exhibited shrinkage. The median follow-up was 17.0m. The 1-year survival rate observed was 60.0%, while the 2-year was 51.4%. The OS has not been reached. Interestingly, no clear correlation has been established between imaging evaluations and patient prognosis. Among the pts classified as having PD, 10 individuals continued treatment due to clinical benefits. Notably, their OS was comparable to that of the overall population, with 2-year survival rate 60.0%. No treatment-related deaths reported. Adverse events were minimal, with only two grade 3 TRAEs observed: pneumonia and colitis. Biopsies of 17 pts with injected lesions were analyzed 8 to 12 weeks after the first injection. Of these, five pts (1 iCR, 1 iPR, and 3 SD) showed no residual tumor cells, accompanied by TIL infiltration. All five pts exhibited long PFS. **Conclusions:** The combination of systemic anti-PD-1 therapy with intralesional injection of an oncolytic virus and radiotherapy has demonstrated a remarkable ORR and excellent OS in patients with melanoma and liver metastases, with manageable toxicity. Clinical trial information: NCT05068453. Research Sponsor: None.

9548 **Poster Session**

Influence of tumor infiltrating lymphocytes (TIL) monotherapy on persistent clinical and immunological responses in Asian metastatic melanoma patients with specific CD8+ TIL proportions: A phase I trial. First Author: Chuanliang Cui, Key Laboratory of Carcinogenesis and Translational Research (Ministry of Education/Beijing), Department of Renal Cancer and Melanoma, Peking University Cancer Hospital & Institute, Beijing, China

Background: TIL therapy, as one of the most promising adaptive cellular immunotherapy, has shown success in metastatic melanoma, with a median overall response rate (ORR) of 28% and median PFS (progression free survival) of 7.2 months. This phase I clinical trial aimed to explore the safety, feasibility, and efficacy of TILs monotherapy in Asian metastatic melanoma pts. **Methods:** Pts with metastatic melanoma who had progressed on standard therapies, had both resectable and measurable tumors were eligible to be enrolled. Pts received a lymphodepletion regimen which consisted of cyclophosphamide (30mg/kg) for 2 days, followed by Fludarabine (25mg/m^2) for 5 days, approximately 24 hours before receiving the intravenous autologous LM103 (TILs) infusion and then high dose IL-2 for 6 doses (200000IU/Kg, 1 dose per day. Doses can be adjusted based on pts tolerance to support T cell survival and proliferation. **Results:** Twelve pts (aged 26-68 yrs) with metastatic melanoma were enrolled and treated, including 8 males. Among the primary melanoma types, 6 were acral, 3 mucosal, 2 unknown, and 1 cutaneous. 7 pts had distant organ metastases. As of Jan 2025, 8 out of 12 pts were assessable, one could not be evaluated due to rapid brain metastases and 3 remained under safety observation (median follow-up, 6 wks; range, 2-48 wks). Resected tumors used for TIL production were from 8 metastatic lymph nodes and 4 subcutaneous nodules. The infused autologous TIL contained 8.24-19.47X10^{10} viable cells. The median duration of IL-2 infusion were 5.08 days, with a median dose of 13.75 IU/Kg/day. The most frequent treatment-emergent adverse events (TEAEs) were myelosuppression (100%), fever (100%), anemia (100%), and hypotension (100%). Grade 3-4 TEAEs included neutropenia (100%), lymphopenia (100%), leukopenia (100%), fever (75%), thrombocytopenia (62.5%), and anemia. The ORR was 50% (4/8, 4PR, 2SD, 2PD) per RECIST v1.1. The median PFS was not reached and the longest PFS was 11.4 months. Responders demonstrated a larger number of T cell clones, higher T cell receptor (TCR) diversity (Inverse Simpson Index), and lower TCR clonality compared to non-responders (P=0.031,*P=0.049* and *P=0.033*), based on real time peripheral monocytes analysis. These findings suggest that the LM103 in responders recognized a broader antigen spectrum. Notably, about 50% of initial TCR clones can be detected 18 wks post-infusion, suggesting LM103 persistence. Post-hoc analysis revealed that responders had a CD8+ T-cells proportion of 60-80%, while non-responders exhibited extreme proportions ($<$10% or $>$80%). **Conclusions:** LM103 was well tolerated and demonstrated durable responses in Asian patients with advanced melanoma. Patients with 60-80% CD8+T-cell proportions are more likely to respond to TIL therapy. Clinical trial information: CTR20233999. Research Sponsor: None.

9549 Poster Session

Intensive surveillance and aggressive multi-modal treatment for liver metastases from uveal melanoma. First Author: Hemant M. Kocher, Queen Mary University of London, London, United Kingdom

Background: We report utility of diagnostic laparoscopy and long-term survival outcome for patients undergoing multi-modal treatment for liver metastasis from uveal melanoma (LMUM). **Methods:** All consecutive patients with suspected oligo-metastatic LMUM diagnosed on screening ultrasound were discussed at Hepato-Pancreatico-Biliary (HPB) Tumour Boards (Jan2010-Nov2024) and were offered multiple lines of surgical / ablation, liver directed and systemic therapies as appropriate, with data censored on 30th November 2024. Liver specific overall survival was calculated from date of index liver resection to date of last follow-up (censored) or death. **Results:** Out of the 58 patients LMUM, 13 (22%) patients had multifocal disease or other concurrent cancer diagnosed on further imaging assessments (dedicated MRI liver and FDG-PET scan). Of the remaining 45 patients assessed with diagnostic laparoscopy a further 15 (33%) had multifocal hepatic metastasis. Thus 27 patients (46%) had multifocal disease precluding liver resection / ablation (Group A). 21 of 58 patients with LMUM had liver resection as a primary modality with majority (18/21) achieving a R0 resection margin and a further 10 had liver ablation (Group B). Both groups received additional lines of treatment. Patients with oligo-metastatic disease undergoing liver resection / ablation as primary modality of treatment (Group B) had longer overall survival (median liver-specific OS = 45.1 (95% CI: 31 – not reached) months; $p<0.0001$, log-rank (Mantel-Cox) test, Hazard ratio (HR): 7.86, 95%CI: 3.52-17.5) after treatment of metastatic disease compared to multi-focal disease treated with immunotherapy as primary modality (Group A, median 18.6 (95% CI: 13-26) months). Whilst the age of diagnosis of LMUM was similar for both Groups A (multifocal metastasis, median 68 years) and B (oligometastatic disease, median 63 years) (two-tailed Mann Whitney U test, p=0.12), patients group B were younger at time of diagnosis of primary UM (median 57 (B) versus median 66 years (A), two tailed Mann Whitney U test, p=0.03) with a longer interval to metastatic progression (median 1325 days (B) versus median 704 days (A), two tailed Mann Whitney U test, p=0.006). **Conclusions:** This largest series of patients with LMUM from the United Kingdom emphasises the vital role of diagnostic laparoscopy to rule out bi-lobar miliary disease. We report impactful overall survival with multimodal treatment for LMUM and highlight prognostic features for further validation. Research Sponsor: The London Clinic.

9550 Poster Session

High-dose 1,3-bis-(2-chloroethyl)-1-nitrosourea (BCNU) chemoembolization for treatment-naïve patients with limited uveal melanoma hepatic metastases. First Author: Carin F. Gonsalves, Sidney Kimmel Comprehensive Cancer Center, Thomas Jefferson University, Philadelphia, PA

Background: Nearly 50% of patients with uveal melanoma (UM) develop metastases with the liver being the primary site of disease in $>$ 90% of cases. Control of hepatic tumors is crucial to prolonging overall survival (OS) for metastatic uveal melanoma (MUM) patients. We report results of aPhase II prospective trial [NCT04728633] using high-dose BCNU chemoembolization (TACE) as first-line treatment for limited UM hepatic metastases. **Methods:** MUM patients with $<$ 50% hepatic tumor burden and no significant extrahepatic disease were treated with hepatic artery infusion of 300mg of BCNU diluted in ethiodized oil followed by gelatin sponge embolization until maximum clinical benefit, hepatic and/or extrahepatic disease progression (PD), or development of significant adverse events (AE). Tumor response (RECIST 1.1) was assessed using CT and MRI. Treatment breaks were allowed for patients with disease control (partial response [PR] + stable disease [SD]) to reduce toxicities and optimize quality of life. Retreatment with TACE was permitted if PD occurred during treatment breaks. OS, progression-free survival from liver (PFS-L) and systemic metastases were analyzed. Toxicities were assessed using CTCAE v5.0. **Results:** Twenty-eight patients (17 men; median age, 62; range, 39 - 84) were enrolled from October 2021 to January 2025. Bilobar (n=25) or unilobar (n=3) BCNU TACE was performed every 4 or 7 weeks (+/- 7 days), respectively. Median follow-up was 11.6 months (range, 1.8 – 37.6). Median OS was 14.1 months (range, 1.8 – 37.6) with 13 surviving patients. Best treatment response included PR in 8, SD in 18, and PD in 2 patients for an overall response rate of 28.6% and a disease control rate of 92.9%. Twenty-two (78.6%) patients with disease control had treatment breaks. One patient withdrew from the trial to pursue percutaneous hepatic perfusion despite SD for 25 months. Median PFS-L was 9.9 months (range, 1.8 – 36.8). Sixteen (57.1%) patients developed new/nontarget hepatic tumor progression (n=13) or progression of target and nontarget lesions (n=3). Treatment-related grade 3 AEs included pain (n=5), hypertension (n=4), incidental pulmonary emboli (n=3), thrombocytopenia (n=1) and an infected biloma. Self-limiting grade 3 or 4 liver enzyme elevation occurred in 6 patients. Fifteen (53.6%) patients developed extrahepatic disease (median, 7.3 months); 11 patients (7 with stable liver tumors) started systemic therapy off-trial. Three patients developed life-limiting AEs due to checkpoint inhibitor therapy. **Conclusions:** High-dose BCNU TACE provided disease control in the majority of treatment-naïve patients with limited UM hepatic metastases. PD typically occurred during treatment breaks, as expected. Future trials exploring the combination of BCNU TACE with systemic therapies to address both hepatic and extrahepatic metastases are warranted. Clinical trial information: NCT04728633. Research Sponsor: Guerbet.

9551 Poster Session

Gotistobart in combination with pembrolizumab in patients with advanced melanoma who have progressed on PD-1 inhibitors with or without CTLA-4 inhibitors. First Author: Siwen Hu-Lieskovan, University of Utah Health, Salt Lake City, UT

Background: Patients with advanced melanoma who progress on PD-1 and CTLA-4 inhibitors (IO-R/R) have poor prognosis. Gotistobart is a pH-sensitive anti-CTLA-4 mAb and we hypothesized that gotistobart in combination with pembrolizumab (pembro) could improve outcomes for ipilimumab plus nivolumab (ipi/nivo) treatment failure. PRESERVE-001 (NCT04140526) is a phase 1/2 study that evaluates safety and efficacy of gotistobart with pembro in patients with IO-R/R advanced melanoma. **Methods:** Patients with IO-R/R advanced melanoma were treated with 3 mg/kg or 6 mg/kg gotistobart plus 200 mg of pembro, Q3W. Treatment beyond progression was allowed at the physician's discretion. Primary endpoints were ORR (RECIST 1.1) and safety. Exploratory endpoints included OS and an ad-hoc analysis of next-treatment free survival (NTFS; next treatment was identified as initiation of a new antineoplastic agent). **Results:** As of December 19, 2024, 33 and 34 patients received 3 mg/kg and 6 mg/kg gotistobart plus pembro, with median follow up associated with OS of 14.7 and 10.7 months, respectively. Of these, 67% (22/33) and 68% (23/34) had progressed on ipi/nivo. 30% (20/67) had tumors $\geq$10cm at study entry. Unconfirmed ORR (uORR) was 25.0% (8/32) and 26.5% (9/34), respectively, with 2 patients achieving CR in the 6 mg/kg group. Of patients who had prior ipi/nivo, uORR was 23.8% (5/21) and 21.7% (5/23), respectively. Efficacy was noted regardless of BRAF mutation status. NTFS rates at 12 months were 45.3% (95% CI 26.0–62.7) and 38.5% (95% CI 20.3–56.4), respectively. OS rates at 18 months were 61.7% (95% CI 40.1–77.5) and 51.9% (29.3–70.4), respectively. Grade $\geq$ 3 TRAEs were observed in 51.5% and 61.8% of patients in the 3 mg/kg and 6 mg/kg groups, respectively, with colitis/diarrhea or AST/ALT increase being most common. 30.3% and 32.4% of patients, respectively, were able to continue treatment after dose reduction. **Conclusions:** Gotistobart 3 mg/kg or 6 mg/kg plus pembro 200 mg, Q3W, provided durable response and clinically meaningful OS benefit, regardless of prior ipi treatment, with nearly half of patients being next-treatment free at one year follow up. To our knowledge,this is one of the largest cohorts ever studied in patients with advanced melanoma R/R to ipi/nivo. Clinical trial information: NCT04140526. Research Sponsor: OncoC4 Inc; BioNTech SE; SBIR; R44CA250884; National Cancer Institute.

Additional parameters	Gotistobart 3 mg/kg (N = 33)	Gotistobart 6 mg/kg (N=34)
Median age (range)	62 (29–83)	66 (24–81)
Female n (%)/Male n (%)	12 (36%)/21 (64%)	12 (35%)/22 (65%)
ECOG score = 1 (of 0 or 1)	18 (55%)	16 (47%)
Prior treated with ipi/nivo	22 (67%)	23 (68%)
Gotistobart treatment duration in weeks, median (range)	19.0 (3–96)	8.9 (3–130)
uORR % (n)	25.0% (8/32)	26.5% (9/34)
uORR in patients prior treated with ipi/nivo % (n)	23.8% (5/21)	21.7 (5/23)
DCR % (95% CI)	50 (31.9, 68.1)	50 (32.4, 67, 6)
NTFS rates at 12 months % (95% CI)	45.3 (26.0, 62.7)	38.5 (20.3, 56.4)
OS rate at 18 months % (95% CI)	61.7 (40.1–77.5)	51.9 (29.3–70.4)

9552 Poster Session

Nautilus, a phase 1b/2 trial of combining oral HDAC inhibitor (HDACi) with MEK inhibitor (MEKi) in patients with NRAS-mutated metastatic melanoma (MM). First Author: Rodabe Navroze Amaria, The University of Texas MD Anderson Cancer Center, Melanoma Medical Oncology, Houston, TX

Background: Activating NRAS mutations occur in 15-20% of MM cases. The MEK inhibitor binimetinib has modest single agent activity with 15% objective response rate (ORR) and 2.8 month progression-free survival (PFS). Bocodepsin (OKI-179) is a novel Class I-selective, oral histone deacetylase inhibitor that was found to have synergistic efficacy with MEKi in preclinical models of NRAS-mutated melanoma. Cells displayed unrepaired double strand DNA breaks and cellular apoptosis, while regressions were observed in xenograft models. Here we present the results of the phase 2 portion of a clinical trial of this combination in NRAS-mutant MM (NCT05340621). **Methods:** In this Phase 2 study, only patients with NRAS-mutant MM previously treated with immunotherapy were enrolled and treated with bocodepsin at the recommended phase 2 dose (300 mg daily, 4 days on, 3 days off, continuously) with binimetinib (45 mg twice daily, continuously). Primary endpoint was ORR, with secondary endpoints including safety and PK analyses. **Results:** As of 1/3/2025, 36 total patients were enrolled; 14 in phase 1b dose escalation and 22 in phase 2, including a total of 24 NRAS-mutant melanoma patients. Median age of NRAS-mutant MM patients was 69 years, and 47% of patients were males. Median numbers of prior therapies was 3 and LDH elevations were found in 41% of patients. There were no grade 3/4 toxicities seen in $>$10% of patients, including no episodes of high grade rash. Of the 20 evaluable patients with NRAS-mutant MM, ORR was 30%. The median PFS was 7.25 months (5-92 weeks). **Conclusions:** The combination of bocodepsin and binimetinib in patients with NRAS-mutant melanoma is tolerable with manageable AEs and no high grade rash. Initial response data in patients with NRAS-mutant melanoma are supportive of potential combinatorial activity of a MEK inhibitor and HDACi bocodepsin. Further investigation is crucial as MM patients with disease progression after immunotherapy remain in need of rational therapeutic options. Thus, MEKi + HDACi warrants further study in a larger patient cohort. Clinical trial information: NCT05340621. Research Sponsor: OnKure.

9553 Poster Session

First-line lenvatinib plus pembrolizumab versus placebo plus pembrolizumab in Chinese patients with unresectable or metastatic melanoma: Results from LEAP-003. First Author: Jun Guo, Beijing Cancer Hospital, Beijing, China

Background: Results of the global, phase 3 LEAP-003 study, showed that lenvatinib (len) + pembrolizumab (pembro) significantly improved PFS compared with pembro alone in participants (pts) with predominantly cutaneous melanoma at the first interim analysis, but this benefit was not maintained with additional follow-up and there was no improvement in OS. Previous studies have shown that mucosal and acral melanomas, which are the predominant subtypes in Chinese patients, may benefit from combination therapy. Here, we present results for Chinese participants (pts) enrolled in the LEAP-003 global (NCT03820986) and China extension (NCT04889118) studies. **Methods:** Eligible pts were aged ≥18 y, had previously untreated unresectable stage III or IV melanoma, an ECOG PS of 0 or 1, and measurable disease per RECIST v1.1. Pts were randomly assigned 1:1 to len 20 mg or placebo (pbo) PO QD + pembro 200 mg IV Q3W for ≤2 y. Dual primary end points were PFS per RECIST v1.1 by BICR and OS. Secondary end points were ORR, DOR, and safety. **Results:** 131 pts from China enrolled and received treatment (len + pembro, n = 64; pbo + pembro, n = 67). Median time from first dose to data cutoff (Jan 18, 2023) was 18.1 mo (range, 12.7-29.5). In the overall China subgroup, median PFS was 6.1 mo (95% CI, 4.1-8.1) for len + pembro vs 2.0 mo (95% CI, 2.0-2.1) for pbo + pembro (HR, 0.55; 95% CI, 0.37-0.81); 18-mo PFS was 20.0% vs 12.8%. Median OS was 19.9 mo (95% CI, 11.9-26.8) for len + pembro vs 17.0 mo (95% CI, 12.7-25.7) for pbo + pembro (HR, 0.93; 95% CI, 0.58-1.48); 18-mo OS was 53.4% vs 49.6%. ORR was 26.6% (95% CI, 16.3-39.1; 4 CR, 13 PR) for len + pembro vs 16.4% (95% CI, 8.5-27.5; 4 CR, 7 PR) for pbo + pembro; median DOR was 13.7 mo (range, 3.8-21.4) vs NR (range, 4.2-21.4+). Among 30 pts with mucosal melanoma, median PFS was 8.1 mo (95% CI, 5.9-12.4) for len + pembro (n = 16) vs 2.0 mo (95% CI, 1.9-4.1) for pbo + pembro (n = 14; HR, 0.44; 95% CI, 0.20-0.97); 12-mo PFS was 33.5% vs 21.4%. Median OS was 26.8 mo (95% CI, 10.6-NR) for len + pembro vs 14.3 mo (95% CI, 9.0-NR) for pbo + pembro (HR, 0.51; 95% CI, 0.17-1.55); 18-mo OS was 68.8% vs 49.0%. ORR among pts with mucosal melanoma was 50.0% (95% CI, 24.7-75.3; 1 CR, 7 PR) for len + pembro vs 7.1% (95% CI, 0.2-33.9; 1 PR) for pbo + pembro. Treatment-related AEs occurred in 96.9% in the len + pembro arm vs 97.0% in the pbo + pembro arm (grade 3-5: 62.5% vs 16.4%). One pt (1.5%) in the pbo + pembro arm died due to treatment-related immune-mediated lung disease. **Conclusions:** In Chinese pts, the efficacy and safety profile observed with len plus pembro vs pembro alone was consistent with the global population. Numerical improvements in PFS and ORR in the mucosal melanoma subtype treated with len + pembro were notable, although the data should be interpreted with caution due to the limited sample size. These results support first-line pembro monotherapy as a standard-of-care for this population. Clinical trial information: NCT03820986, NCT04889118. Research Sponsor: Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA, and Eisai Inc., Nutley, NJ, USA.

9554 Poster Session

Efficacy and safety of first-line (1L) nivolumab plus relatlimab (NIVO + RELA) versus NIVO plus ipilimumab (NIVO + IPI) in advanced melanoma: An updated indirect treatment comparison (ITC) with 4-year follow-up data. First Author: Dirk Schadendorf, University of Essen and the German Cancer Consortium, Essen, Germany

Background: An ITC comparing NIVO + RELA and NIVO + IPI, approved dual immunotherapy treatment options for patients (pts) with advanced melanoma, was previously conducted using pt-level data from the pivotal RELATIVITY-047 (RELA-047; NIVO + RELA vs NIVO) and CheckMate 067 (CM-067; NIVO + IPI or NIVO vs IPI) trials (Long JCO 2024). Here we present updated results using 4-year follow-up data from RELA-047. **Methods:** Inverse probability of treatment weighting was used to adjust for cross-trial imbalances in baseline characteristics. CM-067 follow-up was truncated (median 41.0 mo) to best align with the follow-up length in RELA-047 (median 34.9 mo). Progression-free survival (PFS) per investigator, confirmed objective response rates (ORRs) per investigator, overall survival (OS), and melanoma-specific survival (MSS) were analyzed. Outcomes were also evaluated across key subgroups. The weighted NIVO arms from each trial were compared for internal validation. **Results:** After weighting, key baseline characteristics were balanced for NIVO + RELA (n=339) and NIVO + IPI (n=297). Outcomes after weighting were similar between NIVO + RELA and NIVO + IPI (hazard ratio [HR] [95% CI]: PFS 1.08 [0.89–1.33]; OS 0.95 [0.76–1.19]; table). Outcomes were similar between the NIVO arms, validating the ITC methodology. Across subgroups, efficacy appeared similar between treatments, although trends favoring NIVO + IPI were observed for ORR among pts with BRAF-mutant disease or serum lactate dehydrogenase >2x the upper limit of normal. Results when NIVO + IPI follow-up was untruncated were consistent with the truncated analyses. **Conclusions:** Consistent with previous results, this updated ITC with longer follow-up from RELA-047 suggests that 1L treatment with NIVO + RELA may have comparable efficacy to NIVO + IPI in pts with advanced melanoma, including most—but not all—subgroups. Results should be interpreted with caution given differences in study design and changes in the treatment landscape over time. Research Sponsor: Bristol Myers Squibb.

Efficacy outcomes after weighting.

	NIVO + RELA (n = 339)	NIVO + IPI (n = 297)	HR/odds ratio [OR] (95% CI)	NIVO RELA-047 (n = 338)	NIVO CM-067 (n = 288)	HR/OR (95% CI)
Median PFS per INV, mo (95% CI)	12.0 (8.2–17.1)	11.2 (8.5–18.1)	1.08 (0.89–1.33)	6.6 (4.6–10.1)	5.7 (3.9–9.1)	0.96 (0.79–1.16)
Confirmed ORR per INV, %	48	50	0.91 (0.73–1.14)	40	40	1.00 (0.79–1.28)
Median OS, mo (95% CI)	64.5 (38.6–NR)	NR (37.1–NR)	0.95 (0.76–1.19)	35.1 (27.3–48.8)	35.7 (26.4–NR)	1.02 (0.83–1.26)
Median MSS, mo (95% CI)	NR (NR–NR)	NR (NR–NR)	0.87 (0.68–1.12)	51.2 (34.7–NR)	44.8 (32.3–NR)	0.96 (0.76–1.21)

NR: not reached; HR/OR are NIVO+RELA vs NIVO+IPI.

9555 Poster Session

Phase 2 study of axitinib + nivolumab in mucosal melanoma with pilot addition of stereotactic body radiotherapy or ipilimumab in select progressors. First Author: Sarah E. Lochrin, Memorial Sloan Kettering Cancer Center, New York, NY

Background: Mucosal melanoma (MM) is an aggressive subtype of melanoma with distinct biology, and outcomes in advanced disease are inferior compared with cutaneous melanoma. Frontline Chinese studies in MM have shown efficacy of combined VEGF/R and PD-1 blockade, but studies in more diverse populations and options in PD-1 resistance are lacking. **Methods:** We conducted a phase 2/1b single-center trial in patients (pts) with untreated, unresectable or advanced MM. Pts received standard nivolumab (nivo) plus axitinib (axi) 5mg PO twice daily. Primary endpoint of the phase 2 doublet arm was objective response rate (ORR) by RECIST 1.1 (H0=23%, Ha=48%). Clinical benefit rate (CBR) was defined as ORR or stable disease (SD) >6 months (mos). Upon progression with good tolerance, the phase 1b triplet arm pts received the addition of either stereotactic body radiotherapy (SBRT, 30Gy/5 fractions) or ipilimumab (ipi, 1mg/kg < 4 doses) to ongoing nivo + axi. The primary endpoint of the triplet was safety by CTCAE v5.0 and adverse events (AEs) of special interest (AESIs). Kaplan-Meier methods estimated time to event outcomes; ORR and AEs were reported as proportions with exact 95% confidence intervals. **Results:** N=21 pts were enrolled; N=20 were evaluable for efficacy. See Table for baseline population characteristics. Median follow up was 15 mos (IQR 6, 21), 45% of pts (95% CI: 23, 68) had an objective response; 3 complete and 6 partial responses. Median duration of response was 13 mos (8.6, not reached (NR)). SD persisted ≥ 6 mos in 2 of 7 pts; CBR was 55% (95% CI: 32,77). Median progression free survival (PFS) was 6.3 mos (3.5, NR), and 12-mos estimated PFS and overall survival was 37% (20,67) and 71% (52, 96), respectively. Rate of grade ≥3 treatment related AEs (TRAE) in the doublet arm (n=21) was 67% (95% CI: 43,85), most commonly hypertension & hepatitis, with two pt deaths; 1 nivo-related myasthenia gravis / myositis, and 1 nivo-related pancreatitis with steroid-related PJP pneumonia. 14 pts (70%) progressed on doublet therapy, of which 7 enrolled on the triplet arm. N=5 received ipi and N=2 SBRT (both to anorectal primaries and adjacent lymph nodes). There were 2 grade ≥3 TRAEs in the ipi triplet arm (hepatitis), 0 in the SBRT arm, no grade 5 events, and no AESIs. Zero of 4 evaluable pts in ipi triplet and 1 of 2 in the SBRT triplet responded (4+ mos, ongoing). **Conclusions:** The frontline combination of nivolumab and axitinib was effective in patients with unresectable or advanced outside of China, and a prospective global study randomized against immune checkpoint blockade is warranted. Adding either ipi or SBRT to nivo-axi appears safe in select pts with progressive disease and further studies are needed for pts with PD-1 resistant MM. Clinical trial information: NCT05384496. Research Sponsor: National Comprehensive Cancer Network (NCCN); Pfizer.

Characteristic (n=21)	N (%)
Age (median)	73 years (IQR: 67, 82)
Sex	
Female	13 (62%)
Male	8 (38%)
Race	
Caucasian	16 (76%)
Asian	3 (14%)
Black	2 (10%)
Primary Site	
Anorectal	10 (48%)
Sinonasal	8 (38%)
Vulvovaginal	3 (14%)
Stage	
Locoregionally advanced	14 (67%)
Metastatic	7 (33%)
LDH (median)	195 (IQR: 171,201)

9556 Poster Session

Phase I dose escalation trial of STX-001, an LNP-encapsulated self-replicating mRNA expressing IL-12, in patients (pts) with advanced solid tumors. First Author: Sarina A. Piha-Paul, The University of Texas MD Anderson Cancer Center, Houston, TX

Background: STX-001 is a lipid nanoparticle-encapsulated self-replicating mRNA that activates innate immunity, promotes immunogenic cancer cell death, and expresses IL-12 to induce immune responses against tumors. Preclinical models demonstrated significant immune modulation and antitumor activity. **Methods:** Eligible pts had treatment-refractory advanced solid tumors with ≥ 1 clinically injectable lesions. Bayesian Optimal Interval design was used with an initial 3 + 3 run-in for dose escalation. STX-001 was administered intratumorally every 3 weeks. Dose-limiting toxicities (DLTs) were assessed during the first treatment cycle and response was evaluated by RECIST 1.1. **Results:** From May 29, 2024 to data cutoff (Dec 16, 2024), 14 pts were enrolled across four dose levels (30 - 900 μg). Common Gr ≥ 3 treatment-related adverse events, which included transient neutropenia (4 pts; 29%), lymphopenia (3 pts; 21%), ALT increase (2 pts; 14%), and AST increase (2 pts; 14%), were largely acute and self-limiting, and allowed ongoing dosing. There was no febrile neutropenia or drug-induced liver injury. One pt in the 900 μg cohort experienced DLTs (Gr 3 cytokine release syndrome and Gr 4 lymphopenia) but remained on study. IL-12 expression and robust IFN-γ induction were observed in the plasma. Tumor biopsies showed robust increases in PD-L1 and CD4/CD8 T cell staining post-treatment in both injected and non-injected lesions compared to baseline. 7 pts had undergone on-treatment disease assessment. 5 out of 7 pts had melanoma and were all refractory to PD-1 + CTLA-4 or LAG-3 inhibitors. 3 out of 5 melanoma pts had shrinkage of non-injected lesions (abscopal effects) including one with a confirmed RECIST complete response (CR; 100 μg cohort; prior treatments: PD-1 + LAG3, CTLA-4, and PD-1 inhibitors; metastases in skin and lymph nodes; subcutaneous lesion injected), one with a RECIST partial response (PR; 30 μg cohort; prior treatments: PD-1 + CTLA-4, PD-1, PD-1 + LAG3, and CTLA-4 inhibitors; metastases in skin, lung, and muscle; subcutaneous lesions injected), and one with 100% target lesion reduction with pronounced inflammatory response across multiple cutaneous/visceral lesions (30 μg cohort; prior treatments: PD-1 and CTLA-4 + PD-1 inhibitors; metastases in skin, lymph nodes, and lung; [sub]cutaneous lesions injected) and on-going clinical benefit (despite initial RECIST progression). ctDNA analysis, peripheral blood and tumor microenvironment profiling, PK, and other translational analyses are ongoing. **Conclusions:** STX-001 demonstrates promising preliminary efficacy, robust immune activation, and a favorable safety profile. These results support the continued development of STX-001 both as monotherapy and in combination with immune checkpoint inhibitors. Dose optimization is ongoing. Clinical trial information: NCT06249048. Research Sponsor: None.

9557 **Poster Session**

Outpatient treatment-related toxicity after hospital discharge among patients receiving lifileucel for advanced melanoma. First Author: James William Smithy, Memorial Sloan Kettering Cancer Center, New York, NY

Background: While inpatient toxicity associated with tumor infiltrating lymphocyte (TIL) therapy and IL-2 administration is well characterized, risks facing patients after hospital discharge are less understood. Better characterization of outpatient adverse effects (AEs) could guide the optimal frequency and duration of follow up for this growing patient population. **Methods:** We conducted a retrospective analysis of all patients with advanced melanoma discharged from Memorial Sloan Kettering Cancer Center after receiving investigational or commercial lifileucel from October 2020 to October 2024. We reviewed incidence and timing of new Grade 3+ treatment-related AEs (TRAEs), blood product administration, and readmission among all patients from the time of hospital discharge to the time of the start of a subsequent systemic therapy or death. **Results:** Fifty-three patients successfully discharged after lifileucel administration were identified; patient demographics are included in Table 1. The median follow up time from discharge in survivors was 5 months (interquartile range (IQR): 3, 18). Two patients (4%) developed new Grade 3+ TRAEs following hospital discharge, including new Grade 3 neutropenia 73 days after discharge and new Grade 3 hypoxia 104 days from discharge. Hypoxia was secondary to pleural effusions that developed in the setting of renal thrombotic microangiopathy. Four patients (7.5%) were readmitted for TRAEs including cytopenias, dyspnea, and syncope while 7 patients (13%) were readmitted for melanoma progression. Readmissions occurred a median of 85 (IQR: 39, 128) days after lifileucel infusion and 69 days (IQR: 19, 98) after initial discharge. Twelve patients (23%) received at least one outpatient blood product transfusion, including packed red blood cells (PRBCs; 10 patients) and platelets (6 patients). Within 30 days of initial discharge, six patients (11%) received at least one PRBC transfusion and 3 patients (5.7%) received at least one platelet transfusion. The median number of transfused PRBC units was 2 (IQR: 1,4) and the median number of platelet transfusions was 4 (IQR: 2, 4). **Conclusions:** Rates of new severe toxicity and treatment-related readmissions were low among patients discharged post-lifileucel. About one in four patients required blood products after discharge. Identification of risk factors for the development of outpatient TRAEs may inform personalized care following lifileucel administration. Research Sponsor: None.

Patient demographics.

Characteristic		N = 53[1]
Age at TIL infusion		61 (42, 66)
Sex	Male	29 (55%)
	Female	24 (45%)
Melanoma subtype	Cutaneous	19 (36%)
	Uveal	9 (17%)
	Acral	8 (15%)
	Unknown primary	8 (15%)
	Mucosal	5 (9.4%)
	Other	4 (7.5%)
BRAF status	Mutated	13/51 (25%)
	Wild type	38/51 (75%)
Treatment setting	Investigational	45 (85%)
	Standard of care	8 (15%)

1. N (%); Median (interquartile range).

9558 **Poster Session**

Results of phase III clinical trial of novel biosimilar of pembrolizumab (RPH-075). First Author: Ilya Pokataev, Moscow City Oncological Hospital No. 1 Named After S.S. Yudin, Moscow, Russian Federation

Background: Pembrolizumab is a high-affinity humanized antibody to the PD-1 receptor. This study investigated the efficacy and safety profile of RPH-075, a biosimilar of original pembrolizumab, in patients with advanced skin melanoma. **Methods:** CL01860211 was an international, multicenter, double-blind, randomized, phase III comparative study. The study was based on the following hypothesis: RPH-075 is non-inferior to pembrolizumab (Keytruda) in objective response rate (ORR) at 24 weeks from the start of therapy in patients with unresectable or metastatic melanoma as 1st or 2nd line therapy, not previously treated with pembrolizumab or other anti-PD-1/PD-L1/PD-L2 agents. Pembrolizumab was administered intravenously at a dose of 200 mg Q3W until progression or intolerable toxicity (but no longer than 2 years). ORR was assessed in the per protocol (PP) population according to RECIST 1.1 and iRECIST criteria by an Independent Radiology Review Committee. Disease control rate (DCR), progression-free survival (PFS), were the secondary endpoints. Safety assessment was carried out throughout the study. Adverse events (AE) were assessed by CTCAE v5.0. Immunogenicity was also evaluated over 24 weeks of therapy. **Results:** A total of 266 patients were randomized in 2 groups (n=137 in RPH-075 group and n=129 in pembrolizumab group). The median age was 66 years (range 27–87). The majority of patients had ECOG 0-1 – 96.24%. Most of the patients (90.60%) received pembrolizumab as 1st line treatment. Metastases in the CNS were identified in 10.53% patients. ORR was 28.35% [95% CI: 21.23; 36.73] in RPH-075 group and 24.56% [95% confidential interval (CI): 17.57; 33.21] in pembrolizumab group (p = 0.604). The relative risk was 1.154 [95% CI: 0.755; 1.764]. The lower margin of the obtained 95% CI is higher than the lower margin (0.664) established in the hypothesis. DCR was 48.03% in RPH-075 group and 35.09% in pembrolizumab group (p = 0.057). Median PFS was 3.02 months in RPH-075 group and 2.76 in pembrolizumab group (p = 0.058). Treatment-related adverse events of any grade were registered for 39.13% of patients in RPH-075 group and for 43.75% of patients in pembrolizumab group (p = 0.457). During the main period, anti-drug antibodies (ADA) were detected in 6 patients: 3 (2.36%) in the RPH-075 group and 3 (2.46%) in the pembrolizumab group. None of the patients with detected ADA had neutralizing activity of antibodies to pembrolizumab and no imAEs were registered. **Conclusions:** The non-inferior efficacy of RPH-075 relative to pembrolizumab had been confirmed along with similar safety profile. Clinical trial information: NCT06320353. Research Sponsor: None.

9559 **Poster Session**

ctDNA versus 18F-FDG PET-CT in predicting long-term disease control in patients with advanced melanoma undergoing immune checkpoint blockade therapy. First Author: Milton Jose De Barros E Silva, A.C. Camargo Cancer Center, São Paulo, Brazil

Background: Imaging remains the gold standard for assessing response to systemic immunotherapy in patients with advanced melanoma. Several studies have demonstrated a strong correlation between metabolic response evaluation using 18F-FDG PET-CT and long-term prognosis in patients with advanced melanoma treated with immunotherapy. Meanwhile, ctDNA kinetics has emerged as a promising alternative method to support the evaluation of patients receiving immunotherapy. **Methods:** We prospectively collected blood samples for liquid biopsy assessments using next-generation sequencing (NGS-Ion S5 platform; Thermo Fisher) to detect tumor somatic mutations with a 409-gene panel, and tumor mutations were tracked in plasma samples collected from advanced melanoma patients undergoing immune checkpoint blockade therapy at AC Camargo Cancer Center at baseline, Day 30 (D30), and Day 60 (D60). ctDNA was considered positive if the variant allelic fraction (VAF) exceeded 0.5% and was at least twice that in negative controls. ctDNA results were compared with Day-90 PET-CT and correlated with long-term disease control outcomes. Assessments at D30 and D60 were classified into three categories: molecular responders (MR), molecular non-responders (MNR), and negative pattern (NP), following the framework of the KEYNOTE-942 study. **Results:** This analysis included 15 stage IV melanoma patients treated with nivolumab (3 mg/kg) and ipilimumab (1 mg/kg). Seven patients (47%) showed an objective response on PET-CT. After a median follow-up of 26 months (range: 1–44 months), 31% of patients exhibited controlled disease. PET-CT demonstrated 78% accuracy in predicting long-term disease status (controlled vs. uncontrolled). Baseline ctDNA analysis showed that 10 patients (67%) were ctDNA-positive. The accuracy of baseline ctDNA (positive vs. negative) in predicting long-term disease control status was 71%. On D30, 13 cases were analyzed and classified as follows: 4 (MR), 6 (MNR), and 3 (NP). The accuracy of the D30 liquid biopsy analysis in predicting long-term disease status was only 31%. On D60, 11 cases were analyzed and classified as follows: 5 (MR), 4 (MNR), and 2 (NP). The accuracy of the D60 liquid biopsy analysis in predicting long-term disease status was 73%. **Conclusions:** ctDNA status at baseline and D60, as well as 18F-FDG PET-CT at D90, appear to have similar accuracy in predicting long-term disease control in patients with advanced melanoma treated with immune checkpoint blockade. Research Sponsor: Oncomine Clinical Research Grant.

9560 **Poster Session**

Electronic health records (EHR)-based machine learning (ML) approach to predict risk of progression to metastatic melanoma after initial diagnosis. First Author: Ryan Pindale, ConcertAI, Cambridge, MA

Background: Strategies to predict progression to metastasis in early-stage melanoma patients have relied on a limited sample size and a limited set of clinical or genomic features. Prior studies were able to achieve good discrimination in small cohorts, but applying advanced machine learning techniques to large datasets with deep clinical and molecular data may yield tools with enhanced generalizability and clinical utility. **Methods:** We employed a machine learning approach to predict the likelihood of progression to metastatic melanoma for a cohort with an initial diagnosis of stage 0-3 (n=7477) using both structured and human-curated information in the ConcertAI Patient360 melanoma EHR dataset. Patients with uveal melanoma, a second primary malignancy, or clinical trial participation status were excluded. A total of 68 features including staging, demographic, testing, biomarker, and clinical tumor information recorded within 30 days of initial melanoma diagnosis were used to train several machine learning frameworks to predict the likelihood of progression to metastatic melanoma. A logistic regression, random forest classifier, gradient boosting decision tree, and XgBoost framework were compared using the AUC from a 20% hold-out set to determine the optimal framework after hyperparameter tuning. Additional evaluation metrics, which include accuracy, precision, recall, and F1 were computed for the final model. Feature importance measures were determined using Shapley Additive Explanation (SHAP) dependence plots. Permutation (N=1000) was utilized to evaluate the predictive power of the final model. **Results:** An XgBoost approach produced a test AUC of 0.708 with a pseudo-p value = 0.001 from permutation. Notably, the model produced a precision of 0.709 on the hold-out set. SHAP dependence measures showed that the most important features used for predictions include those involving initial staging and clinical measures of the tumor. Specifically, lower initial stage corresponded with lower predicted probability of metastatic progression. Similarly, higher values of mitotic rate and tumor thickness corresponded with higher predicted probability of progression. In addition, more complex interactions between features also contributed to the improved performance of the XGBoost framework. **Conclusions:** An XgBoost framework trained on a large set clinical features for 7477 melanoma patients predicted metastatic progression with significant predictive power (p = 0.001) yielding an AUC of 0.708. The model relied heavily on staging information at initial diagnosis and information on tumor size, mitotic rate, and ulceration status to make predictions, which were typically reported in unstructured EMR. These results indicate the clinical utility for machine learning models trained on real world data for both providers and patients. Research Sponsor: None.

9561 **Poster Session**

Delineating the role of the microbiome and tumor microenvironment interactions driving mucosal melanoma (MM) response and resistance to immune checkpoint inhibitor (ICI) treatment. First Author: Florentia Dimitriou, Department of Surgical Oncology, The University of Texas MD Anderson Cancer Center, Houston, TX

Background: MM is a rare melanoma subtype with distinct biology and low response rates to ICIs. We seek to prospectively profile a cohort of MM patients to determine the interplay of gut, mucosal and tumor microbiome and modifiable risk factors on ICI response and resistance. **Methods:** Patients (pts) with MM presenting at MD Anderson are being prospectively enrolled for longitudinal collection for molecular, microbiome, and lifestyle factor profiling. Planned analyses will evaluate (1) fecal specimens [whole metagenome shotgun (WMS) sequencing, microbiome profiling and 16S rRNA gene sequencing (16S)]; (2) mucosal surface swabs (WMS sequencing); (3) formalin-fixed paraffin embedded (FFPE) tumor specimens [Bruker Digital Spatial Profiling (DSP)]; and (4) fresh tumor samples [whole exome (WES) and whole genome (WGS) of normal and tumor tissue, RNA sequencing, and T cell receptor sequencing]. **Results:** 82 pts with sequenced fecal specimens and mucosal surface swabs were enrolled as of 12/2024. MM primary sites included 25 (30%) naso-oral (including sinonasal), 14 (17%) urogenital, 30 (37%) anorectal, 10 (12%) conjunctival and 3 (4%) other. Disease stages were IVM1a/M1b in 9 (9%) pts, and IVM1c/M1d in 27 (33%) pts. Initial analysis of gut and mucosal surface swabs' microbiome by MM primary site displayed a wide range of intrasample heterogeneity and microbial signatures that correlate with the MM primary site. WES and WGS data analysis indicate low tumor mutational burden (TMB) of 1.34mut/Mb (median, range 0.52 – 14.72). Common mutations included *SF3B1* (23%), *KIT* (15%) and *NRAS* (8%). Anorectal and urogenital tumors contributed to mutational signatures associated with DNA mismatch repair and microsatellite instability (COSMIC v3.211). Conjunctival and naso-oral tumors showed an association with UV exposure. Results in the gut microbiome analysis from 78 pts treated with ICIs showed compositional differences in the presence and proportion of bacterial taxa in responders (R), compared to non-responders (NR). Distinct bacteria such as *Streptococcus, Collinsella*, and *Blautia* were identified in R, and *Butyricicoccus* in NR. DSP analysis by treatment response showed higher expression of CD56 and CD20 in the immune and tumor compartments in R. **Conclusions:** This is an ongoing prospective study that is expected to drive insights into the tumor/microenvironment/host interactions and factors regulating immunogenicity to predict response and resistance to ICIs in a rare and understudied melanoma subtype. Interrogation of the role of the gut microbiome and its modifiable determinants will lead to the investigation of new therapeutic strategies to modulate the microbiome to improve treatment outcomes in MM. Research Sponsor: U.S. Army Medical Research and Development Command; W81XWH2210973.

9562 **Poster Session**

Multidimensional, spatially resolved immunologic hallmarks of response to neoadjuvant immune checkpoint blockade (ICB) therapies. First Author: Zichao Liu, The Jackson Laboratory for Genomic Medicine, Farmington, CT

Background: The groundbreaking neoadjuvant ICB clinical trials have established beyond doubt that ICB before surgery will become the new standard of care for metastatic melanoma. Importantly, the shift from radiographic to pathologic response scoring offers an unprecedented window of opportunity to interrogate a goldmine of 'on-treatment' biospecimens. To date, single-cell profiling and region-based spatial transcriptomics (ST) have highlighted the importance of tertiary lymphoid structures (TLS) and stem-like T-cells as positive predictors of ICB response. However, the molecular mechanisms by which tumor infiltrating lymphocytes communicate and organize multicellular immune hubs within the spatial context of the tumor ecosystem remains poorly understood. **Methods:** To identify robust biomarkers of response to neoadjuvant ICB, we assembled a cohort of 58 stage III melanoma patients treated with neoadjuvant ICB [24 ipilimumab-nivolumab (IPI-NIVO), 21 NIVO-relatlimab (RELA), 13 PD1 mono] and deployed transformative technologies and computational methods, including single-cell FFPE sequencing, multiplexed FISH single-cell ST (MERFISH 305 genes), digital pathology, 3D open-top light-sheet imaging and AI-based computational pathology, to decipher the complex neoadjuvant ICB tumor ecosystem in response to therapy. We also developed 2 critical computational tools, SCIRA (Spatial Cellular Interaction and Receptor Activation), to compute receptor-ligand (R-L) interactions in whole slide images, and GC-SCAN (graph-based spatial clustering against noise), a graph-based algorithm that quantifies locally clustered structures from spatial -omics data. **Results:** Our results showed that the quantity and size of hyper-expanded germinal center/TLS, with increased GC: non-GC B-cell ratio, plasma cells and spatially resolved stem-like T-cells are strongly associated with response. IPI-NIVO elicited significantly stronger GC proliferation compared to NIVO-RELA and PD1 monotherapy, suggesting anti-CTLA4 can robustly induce germinal center/TLS proliferation. SCIRA spatial R-L analyses revealed the critical chemokine R-L interactions that organize the GC- and T-cell zones in response to therapy. Lastly, 3D light-sheet imaging revealed remarkable morphologic heterogeneity in 3D, with interconnected GC-TLS networks that are indicative of long-range molecular gradients. **Conclusions:** Our investigations herein have provided a comprehensive characterization of the immune architectures, cellular communications and 3D large-scale morphologic organizations of the TME that drive response to neoadjuvant ICB therapy. We believe the results of this study will enable the development of robust predictive biomarkers to guide the design of next generation combination ICB therapies in the clinical trial setting for melanoma and other cancer types. Research Sponsor: None.

9563 **Poster Session**

Long-term outcomes following melanoma metastasectomy categorized by response to immune checkpoint inhibitor (ICI) therapy. First Author: Aravind Sreeram, Johns Hopkins University School of Medicine, Baltimore, MD

Background: Patients undergoing surgical resection of Stage III/IV melanoma after response to ICIs show favorable survival, particularly with pathologic complete response (pCR). However, long-term outcomes of such patients stratified by ICI response remain undescribed. As surgery is increasingly employed in both PD-1 sensitive and refractory settings (e.g. tumor-infiltrating lymphocytes (TIL) therapy), better-defined outcomes and a clearer understanding of surgery's role are much needed. **Methods:** Patients treated with ICI (2003-2023) followed by metastasectomy were identified from a prospectively maintained database. Pre-surgery ICI response was assessed radiographically, and patients were categorized as having either stable/responding disease (R), an isolated site of disease progression (IP), or multiple progressing sites of disease (MP) for which surgery was pursued due to acute symptoms or palliative intent. Clinicopathologic factors examined included response to ICI, resection to no evidence of disease (NED), and pCR. Kaplan-Meier analyses with log-rank tests were used to compare disease-specific survival (DSS) from surgery date. Cox proportional hazards models identified independent predictors of DSS. **Results:** Among 513 patients, 426 (83%) had stage IV and 87 (17%) had stage III disease at ICI initiation. Patients were categorized as either R (n=76), IP (n=227), or MP (n=210). Fifty-three percent of patients received subsequent systemic therapy including 20 TIL patients, 12 of whom were in the MP group. Median follow-up after surgery among survivors was 2.51 years (IQR 0.93, 6.72). Median DSS following surgery was 4.1 years (95% CI: 2.5, NR). Resection to NED at the first operation post-ICI (n = 202, 39%) was associated with improved 5-year DSS [81% (75%, 88%) vs. 26% (20%, 33%); $p < 0.001$], with similar findings in only Stage IV patients (n = 426) [75% (67%, 84%) vs. 24% (19%, 32%); $p<0.001$]. Patients who underwent resection for an R or IP tumor had a 5-yr DSS of 89% (80%, 98%) or 62% (55%, 70%), respectively, compared to 20% (14%, 28%) for MP lesions ($p < 0.001$). Independent predictors of DSS also included NED resection and pCR (Table 1). **Conclusions:** Disease control after metastasectomy following ICI is durable, especially in patients with responding, stable, or isolated progressing disease, in addition to those achieving resection to NED or pCR. Alternative therapeutic strategies should be considered for patients with MP tumors as DSS remains poor after surgery alone. Research Sponsor: None.

Multivariate model of DSS.

	p-value	HR [95% CI]
NED Status	**<0.001**	0.31 [0.20, 0.49]
Pre-operative Neutrophil-Lymphocyte Ratio	**0.014**	1.02 [1.01, 1.04]
Response to ICI (R, IP, MP)	**<0.001**	1.31 [0.65, 2.65] (R v. IP) 2.75 [1.35, 5.63] (R v. MP)
pCR Status	**<0.001**	0.22 [0.08, 0.65]
Surgery Site	0.074	1.33 [0.97,1.83]
Time from ICI Initiation to Surgery	**0.006**	0.85 [0.76, 0.97]
M Stage	**0.003**	2.01 [1.21, 3.34]

9565 **Poster Session**

Immunological phenotype as a predictor for response after isolated limb perfusion for patients with melanoma in-transit metastasis. First Author: Anna Constantinescu, Sahlgrenska Centre for Cancer Research, Department of Surgery, Institute of Clinical Sciences, Sahlgrenska Academy, University of Gothenburg, Gothenburg, Sweden

Background: Isolated limb perfusion (ILP) is a regional treatment for patients with melanoma in-transit metastases (ITM) confined to extremities, using a high dose of melphalan. ILP has a high response rate, with approximately 60% having a complete response (CR). This study aimed to validate if pre-operative immunological phenotype could be a predictive factor for CR after ILP. **Methods:** A total of 132 patients undergoing ILP as a first treatment for melanoma ITM between January 2012 and March 2023 were included in this study. The number and percentage of naïve and memory T and B cell subtypes, as well as natural killer (NK) cells were characterized by analyzing pre-operative blood samples using fluorescence activated cell sorting (FACS). Univariable and multivariable analysis were used to investigate if any of these subtypes were predictive for response after ILP. **Results:** Out of the 132 patients included in the study, 53% achieved a CR. Immunological and clinical factors significantly and independently associated with an CR after ILP were: number of metastases (OR 0.98, 95% CI 0.97-1.00, p=0.036), size of largest metastases (OR 0.96, 95% CI 0.93-0.99, p=0.009), percentage of CD3+8+ cells (OR 1.07, CI 95% 1.02-1.13, p=0.012) and percentage of CD3+8+45RA+ cells (OR 1.11, CI 95% 1.01-1.22, p=0.029). **Conclusions:** Immunological phenotype described as percentage of cytotoxic T-cells and naïve cytotoxic T-cells are together with tumor burden important predictive factors for response after ILP for patients with melanoma in-transit metastasis. This could potentially contribute to better patient selection and individualized treatment algorithms, but might also be a foundation for future novel treatment combinations, where an ongoing trial is currently combining ILP with a PD-1 inhibitor (ClinicalTrials.gov NCT03685890). Research Sponsor: None.

9566 Poster Session

Anxiety, depression, fear of cancer recurrence (FCR) and health-related quality of life (HRQL) in people with melanoma receiving adjuvant therapies. First Author: Julia Elizabeth Lai-Kwon, Peter MacCallum Cancer Centre, Melbourne, VIC, Australia

Background: One year ofadjuvant anti-programmed cell death protein-1 (anti-PD1) or dabrafenib-trametinib are standards of care for patients (pts) with resected stage III-IV melanoma. Emotional distress has been linked to inferior disease outcomes following neoadjuvant immunotherapy for stage III melanoma. We aimed to assess the anxiety, depression, FCR and HRQL in a real-world population up to 2 years post initiation of adjuvant therapy. **Methods:** A prospective, longitudinal study of pts with resected stage IIB-IV melanoma receiving adjuvant anti-PD1 or dabrafenib-trametinib at an Australian comprehensive cancer center. The Patient-Reported Outcomes Measurement Information System (PROMIS) Network Emotional Distress-Anxiety 7a and Depression 8b, Fear of Cancer Recurrence Inventory-Short Form (FCRI-SF), and Functional Assessment of Cancer Therapy-General (FACT-G) were collected pre-treatment, and at 1, 3, 6, 12, and 24 months post treatment initiation. PROMIS t-scores were categorized as mild (55-59), moderate (60-69) and severe ($\geq$70). Clinically significant FCR was categorized as a FCRI-SF score $\geq$22. **Results:** From September 2021-December 2024, 70 pts were eligible and 52 (74%) consented: 17 (33%) female, median age 64 years (IQR 60-71), 46 (89%) resected stage III, 32 (62%) on adjuvant anti-PD1. 41 pts had completed treatment and 11 were still receiving treatment at data cut off (17 December 2024). 51 pts completed at least 1 set of surveys. The prevalence of mild, moderate or severe anxiety, depression and clinically significant FCR up to 2 years post initiation of adjuvant therapy is shown in the table. People experiencing anxiety or depression at 24 months reported worse HRQL compared to those without (mean FACT-G score- anxiety: 67.8 vs 82.8; depression: 69.7 vs 84.2). Of the 18 pts with data at both 12 and 24 months, all those with clinically significant FCR at 12 months continued to report FCR at 24 months. All those with clinically significant FCR at 24 months reported worse HRQL compared to those without clinically significant FCR at 24 months (mean FACT-G score: 67.7 vs 80.5). **Conclusions:** A significant number of pts report anxiety, depression, and clinically significant FCR up to 2 years post initiation of adjuvant therapy, which is associated with worse HRQL. Screening for psychological issues can identify those who may benefit from psychological and/or pharmacological intervention to improve disease outcomes. Research Sponsor: None.

	Pre-treatment (n= 51)	1 month (n= 46)	3 months (n=44)	6 months (n= 38)	12 months (n=31)	24 months (n=18)
Anxiety (n, %)	20 (40%)	19 (41%)	16 (36%)	15 (39%)	13 (42%)	7 (39%)
Depression (n, %)	16 (31%)	17 (37%)	13 (30%)	17 (45%)	14 (45%)	9 (50%)
Clinically significant FCR (n, %)	10 (20%)	12 (26%)	9 (20%)	10 (26%)	6 (19%)	5 (28%)

9567 Poster Session

Identification of patients at high risk for relapse by Merlin assay (CP-GEP) in an independent cohort of melanoma patients (pts) that did not undergo sentinel lymph node biopsy: An H&N subgroup analysis. First Author: Teresa Amaral, Skin Cancer Center, Eberhard Karls University of Tübingen, Tübingen, Germany

Background: Sentinel lymph node biopsy (SLNB) is still the gold standard for nodal assessment used in the clinical staging of cutaneous melanoma (CM) pts by AJCC v8. Recently, we showed in a small cohort that CP-GEP also has the potential to risk stratify pts who did not undergo SLNB in low and high-risk for recurrence (Amaral et al, EJC 2023). SLNB may be challenging in pts with head and neck (H&N) melanoma, due to the regional course of cranial nerves and lymphatic drainage. Here we focus on the ability of CP-GEP to stratify pts with H&N melanoma in particular those with lentigo maligna, who did not undergo SLNB, for their risk of recurrence. **Methods:** We analyzed formalin-fixed paraffin-embedded primary tumor samples of 930 pts of which 206 were localized in the H&N region, with stage I/II CM diagnosed between 2000-2017 who did not receive SLNB. The CP-GEP model used combines the expression of 8 genes (SERPINE2, GDF15, ITGB3, CXCL8, LOXL4, TGFBR1, PLAT and MLANA) by quantitative reverse transcription polymerase chain reaction with age and Breslow thickness to obtain a binary output: CP-GEP Low- or High-Risk. Relapse-free survival (RFS), distant metastasis free survival (DMFS) and Melanoma Specific Survival (MSS) were evaluated using Kaplan-Meier curves. **Results:** We included 930 pts (stage IA-IIC) of which 206 pts (22.3%) were diagnosed with H&N melanoma. Patient characteristics: 41% were females, median age was 73-year-old, median Breslow thickness was 0.5 mm and 75.6% were lentigo maligna melanomas. Median follow up was 51 months (RFS). All H&N pts showed the following survival: 5-year RFS 82.5%, DMFS 94.0 and MSS 95.5%. CP-GEP risk stratification identified 17 patients as CP-GEP High-Risk and 188 as CP-GEP Low-Risk. The 5-year RFS rate was 86.7% for CP-GEP Low-Risk and 39.7%% for CP-GEP High-Risk pts (HR 7.85; $p<0.001$), 5-year DMFS was 96.3% for CP-GEP Low-Risk and 68.9% High-Risk pts (HR 10.26; $p<0.001$) and the 5-year MSS was 98.5% for CP-GEP Low-Risk pts and 64.7% for CP-GEP High-Risk pts (HR 24.45; $p<0.01$). **Conclusions:** Pts with H&N CP-GEP Low-Risk tumors have a good long-term survival compared to High-Risk pts even though SLN status was not assessed. This prognostic information may allow the clinicians to skip SLNB in this difficult anatomic localization and in frail and/or older pts. Research Sponsor: SkylineDx.

9568 Poster Session

Distinct effect of neoadjuvant PD1 alone, PD1+IPI, and PD1+lenvatinib in the peripheral immune profile of melanoma patients (pts) and correlation with pathological (path) response. First Author: Ines Esteves Domingues Pires da Silva, Melanoma Institute Australia, The University of Sydney, Sydney, Australia, Wollstonecraft, Australia

Background: Neoadjuvant immunotherapy (NeoIT) has significantly improved clinical outcomes for pts with macroscopic stage III resectable melanoma and is the current standard of care for these pts. Here, we analysed longitudinal peripheral immune profiles and their correlation with path response for 3 different PD1-based NeoIT regimens. **Methods:** Pts with macroscopic stage III resectable melanoma treated with neoadjuvant PD1-based regimens (PD1 alone, PD1+IPI and PD1+Lenvatinib) for 6 weeks, followed by surgery, were included. Cytometry by time-of-flight (CYTOF; 39-marker panel) was performed on peripheral blood mononuclear cells (PBMCs) at baseline and week 6 (wk 6; pre-surgery). **Results:** Of 64 pts included, 17 PD1 alone (7 [41%] had major pathological response [MPR; $\leq$ 10% of viable tumour cells at the surgical specimen]), 26 PD1+IPI (20 [77%] had MPR) and 21 PD1+Lenvatinib (12 [57%] had MPR). We analysed >200 peripheral immune cell types/phenotypes, and present the statistically significant treatment effects (from baseline to wk 6), overall and based on path response (MPR vs. non-MPR), in patients treated with PD1 alone, PD1+IPI and PD1+lenvatinib (see Table). **Conclusions:** IPI+PD1 and PD1+Lenvatinib induced stronger peripheral blood immune activation, compared with PD1 alone, irrespective of path response. There were differences in the MPR vs non-MPR pts, particularly for PD1 alone. A more in-depth analysis of the effects of these PD1-based regimens and their association with recurrence is underway to identify key immune cell types/phenotypes associated with response & resistance to NeoIT. Research Sponsor: None.

Effect of neoadjuvant PD1 alone, PD1+IPI and PD1+lenvatinib in the peripheral immune profile of melanoma patients.

	Overall treatment effect	MPR (vs. non-MPR)	Non-MPR (vs. MPR)
PD1	Increase in: - OX40+ / ICOS+ regulatory T cells (Tregs) - KI67+ ICOS+ CD4 T cells	Increase in: - GZM+ CD4+ & CD8+ T cells - Double negative [CD27- IgD-] B cells	Increase in: - Non-classic [CD14low+CD16++] HLA-DR+ monocytes Decrease in: - CD4 T effector memory cells - Th1 cells
PD1+IPI	Increase in: - Tregs - Activated [ICOS+ / LAG3+ / TIGIT+] CD4+ T cells - TIM3+ CD4+ & CD8+ T cells - Non-classic [CD14low+CD16++] monocytes - Cytotoxic [CD56dim CD16+] NK cells Decrease in: - Stem-like [TCF7+] CD4+ & CD8+ T cells		Increase in: - OX40+ / T-BET+ CD127- CD8+ T effector memory cells
PD1+lenvatinib	Similar changes seen with PD1+IPI, as well as an increase in: - Th1 - Th17 - CD8+ T effector memory cells Decrease in: - Double negative [CD27- IgD-] B cells	Increase in: - CD127- Tregs	Increase in: - HLA-DR+ non-classic [CD14low+CD16++] monocytes

9569 Poster Session

Rational use of adjuvant anti-PD-1: Multi-omics model of recurrence in stage III melanoma. First Author: Tuba Nur Gide, Melanoma Institute Australia, Faculty of Medicine and Health, The University of Sydney, Sydney, NSW, Australia

Background: Stage III melanoma patients (pts) undergoing adjuvant anti-PD-1 immunotherapy have a high risk of recurrence (43% within one year) and treatment-related adverse events (25% severe). This study developed multi-omics models that accurately identify pts at high risk of recurrence who may benefit from alternative treatment strategies or closer surveillance. **Methods:** We analyzed a cohort of 131 pts with stage III melanoma (47% IIIA/B and 53% IIIC/D) who received adjuvant anti-PD-1 therapy. The nodal burden was micrometastatic (35%) and macrometastatic (54%), with in-transit metastases in 11% of pts. Comprehensive multi-omics profiling included DNA sequencing (tumor mutational burden [TMB]), whole-transcriptome sequencing (gene expression profiling [GEP]), and multiplex immunohistochemistry (tumor microenvironment [TME]) of the baseline tumor sample. We developed predictive models for 12-month recurrence using multivariable penalized logistic regression with consensus-nested cross-validation incorporating clinical, TMB, GEP, and TME features. Internal validation was performed using optimism bias through 500 bootstrap iterations. **Results:** Clinical factors (nodal burden, stage, and site of primary melanoma) alone achieved a modest AUC of 0.66 (95% CI: 0.56-0.75) for predicting recurrence. Addition of TME features, particularly CD16+ cells interacting with PD-L1+CD16+ macrophages, significantly improved predictive accuracy (AUC: 0.81, 95% CI: 0.72-0.91). Further enhancements were observed with TMB and BRAF mutation status (AUC: 0.83, 95% CI: 0.74-0.92) and GEP-derived natural killer (NK) cell and interferon-gamma (IFNg) signatures (AUC: 0.83, 95% CI: 0.73-0.93). A consensus model integrating these features achieved an optimal AUC of 0.86 (95% CI: 0.78-0.94). This model demonstrated robust performance across macroscopic (AUC: 0.88, 95% CI: 0.78-0.98) and microscopic (AUC: 0.86, 95% CI: 0.70-1.00) nodal diseases. **Conclusions:** This study demonstrates the potential of multi-omics profiling to significantly enhance recurrence risk prediction in stage III melanoma pts receiving adjuvant anti-PD-1 therapy. We developed a robust model with high predictive accuracy by integrating clinical data with TME, TMB, and GEP features (AUC, 0.86). This model can help identify pts at high risk of recurrence who may benefit from alternative treatment strategies or closer surveillance. Research Sponsor: None.

AUC scores of various models.

Model	AUC
Clinical	0.66
Clinical+TME	0.81
Clinical+TMB	0.83
Clinical+GEP	0.83
Consensus Model	0.86

9570 **Poster Session**

Combining machine learning with the immunohistochemical expression of AMBRA1 and loricrin to identify non-ulcerated AJCC stage I/II melanomas at high-risk of metastasis. First Author: Penny Lovat, Newcastle University, Newcastle upon Tyne, United Kingdom

Background: Precision-based personalised biomarkers able to identify both low-risk and high-risk patient subpopulations with localised cutaneous melanoma are urgently needed to guide clinical follow up and treatment stratification. The combined immunohistochemical expression of AMBRA1 and Loricrin (AMBLor) in the epidermis overlying non-ulcerated AJCC stage I/II melanomas as prognostic biomarker able to accurately identify genuinely low-risk patient subpopulations (NPV >96%, clinical sensitivity >95%, Ewen *et al* Brit J Dermatol. 2024). To further identify distinct subsets of patients at high risk of metastasis, the present study aimed to develop a machine learning (ML) risk-prediction model combining AMBLor 'at-risk' status with six specific patient clinical and tumour pathological features. **Methods:** Using common and widely used ML models a Naïve Bayes and a Generalized Linear Model with adaBoost, ML algorithms were trained and tested using three geographically distinct retrospective-prospective cohorts of AMBLor at-risk non-ulcerated AJCC stage I/II melanomas from Australia, USA and Spain (n=552), with validation studies performed in a 4th independent retrospective-prospective cohort of 120 AMBLor at-risk non-ulcerated localised melanomas derived from the UK. **Results:** Based on a training: test data split of 50:50, 20% of patients were defined as high-risk, with a 5-year recurrence-free survival (RFS) probability of 56% (Log-rank [Mantel-Cox) $P < 0.0001$, HR 6.88, 95% CI 3.03-15.63, clinical specificity 87.2%, PPV 44.4%). Further validation of the ML algorithms in the UK validation cohort identified 24% patients as high-risk, with a 5-year RFS of 56.3% (Log-rank [Mantel-Cox) $P < 0.0001$, HR 7.59, 95% CI 2.94-19.6, clinical specificity 82.1%, PPV 50%). **Conclusions:** Through the proven negative predictive power of AMBLor with the cumulative power of prognostic clinical and pathological features these data provide a novel and improved risk- prediction model to stratify patients with non-ulcerated localised melanomas at low or high risk of tumour recurrence thereby aiding optimal personalised patient management and treatment stratification. Research Sponsor: Newcastle University; AMLo Biosciences.

9571 **Poster Session**

Longitudinal ctDNA monitoring for post-surgical molecular residual disease in patients with stage I-IIIb melanoma. First Author: George Ansstas, Division of Medical Oncology, Department of Medicine, Washington University School of Medicine, St. Louis, MO

Background: Circulating tumor DNA (ctDNA) has emerged as an important biomarker for early recurrence detection and monitoring disease status in patients with cancer, including melanoma. Here, we evaluate the prognostic value and utility of post-operative ctDNA detection in patients with stage I-IIIb melanoma using a clinically validated, personalized, tumor-informed ctDNA assay. **Methods:** We conducted a retrospective analysis of real-world data of patients with stage I-IIIb melanoma (N=197), including ctDNA results using a personalized, tumor-informed, 16-plex mPCR-NGS assay (Signatera, Natera, Inc.). Adjuvant treatment decision and post-surgical plasma (N=1,718) sample collection during treatment for ctDNA analysis was at the provider's discretion. ctDNA results were correlated with clinical outcomes. **Results:** Across 197 patients analyzed for ctDNA, a median of 7 tests (range: 2-44) per patient were performed over a median period of 24.7 months (range: 3.7-74.7).ctDNA-positivity at any postoperative timepoint was significantly associated with shorter relapse-free survival (RFS; hazard ratio [HR]: 15.0, 95% CI: 7.3–31.0, $P < 0.0001$). This finding was pronounced for patients with distant/regional recurrence (HR: 27.0, 95% CI: 10.0–71.0, $P < 0.0001$). Multivariate analysis confirmed ctDNA-positivity to be the most significant prognostic factor associated with RFS when compared with other clinicopathologic factors such as adjuvant treatment, stage, sex, and mitotic rate (N=163, HR: 10.50, 95% CI: 3.891–28.32 $P < 0.001$). Finally, we explored the utility of ctDNA-positivity and its impact on clinical decision-making and observed that ctDNA-positivity influenced changes in treatment management in 73.7% (N=28/38) of patients, ranging from imaging escalation to treatment initiation, switch, or escalation. **Conclusions:** Our findings highlight the prognostic value of post-surgical, personalized ctDNA detection and monitoring of molecular residual disease in stage I-IIIb melanoma and provide information on real-world clinical decision practices based on ctDNA changes. Research Sponsor: None.

9572 **Poster Session**

Efficacy of adjuvant anti-PD-1 antibodies and interferon in patients with nail apparatus melanoma: A retrospective, multicenter study (ADJ-NAIL study). First Author: Takaya Komori, Department of Skin Oncology/Dermatology, Saitama Medical University International Medical Center, Saitama, Japan

Background: The clinical efficacy of anti-PD-1 antibodies (PD-1) for nail apparatus melanoma (NAM) is less effective than that for advanced cutaneous melanoma. Despite the significant need for effective adjuvant (adj) therapies to improve survival in NAM, the efficacy of adj PD-1 and interferon (IFN) is unknown because of the rarity of NAM. Thus, this study aimed to investigate the efficacy of adj PD-1 and adj IFN therapies for NAM. **Methods:** Thisretrospective study reviewed data of patients with stage IIB, IIC, and III NAM without adj therapies (observation: OBS), who received adj PD-1 therapy (adj-PD-1) and adj IFN therapy (adj-IFN) after complete resection across 42 Japanese institutions. The Kaplan–Meier analysis and multivariable Cox proportional hazard models were used to estimate survival probabilities. Propensity-score matching (PSM) was employed to adjust for differences in the baseline characteristics between each group. **Results:** A total of 397 patients with NAM (OBS, n = 219; adj-PD-1, n = 99; adj-IFN, n = 79) were included. The baseline characteristics were significantly different among the three groups in terms of age ($P < 0.001$) and stage ($P < 0.001$). The other baseline characteristics were comparable. A significant difference was noted in the recurrence-free survival (RFS) among the OBS, adj-PD-1, and adj-IFN groups (5-year RFS 42% vs. 21% vs. 48%; $P = 0.02$). However, distant metastasis-free survival (DMFS) and overall survival (OS) were not significantly different among the three groups (5-year DMFS 50% vs. 44% vs. 54%; $P = 0.15$, 5-year OS 59% vs. 46% vs. 58%; $P = 0.28$). Multivariable Cox proportional hazard models revealed that adj-PD-1 and adj-IFN did not positively affect survival outcomes compared with OBS (adj-PD-1: RFS hazard ratio [HR] 1.14; $P = 0.47$, DMFS HR 1.04; $P = 0.84$, OS HR 1.19; $P = 0.50$, adj-IFN: RFS HR 0.73; $P = 0.11$, DMFS HR 0.77; $P = 0.21$, OS HR 0.96; $P = 0.84$). After PSM, the patient backgrounds were balanced at a 1:1 ratio between the OBS and adj-PD-1 groups (n = 71 each) and adj-IFN groups (n = 75 each). No significant differences were found in the survival outcomes between the OBS and adj-PD-1 groups (5-year RFS 30% vs. 20%; $P = 0.96$, 5-year DMFS 39% vs. 39%; $P = 0.95$, 5-year OS 49% vs. 39%; $P = 0.53$) and between the OBS and adj-IFN groups (5-year RFS 35% vs. 48%; $P = 0.06$, 5-year DMFS 41% vs. 54%; $P = 0.09$, 5-year OS 56% vs. 57%; $P = 0.73$). In patients who experienced a relapse and were treated with nivolumab/ipilimumab combination therapy, the progression-free survival from the initiation of combination was significantly shorter in the adj-PD-1 group than in the OBS group (median PFS 1.8 months vs. 4.0 months; $P = 0.03$). **Conclusions:** In NAM, adj-PD-1 and adj-IFN did not improve survival. Furthermore, the use of adj-PD-1 may attenuate the efficacy of nivolumab/ipilimumab combination therapy after relapse. Research Sponsor: National Cancer Center Research and Development Fund; 2023-J-03; Japan Agency for Medical Research and Development; JP24ck0106765h0003.

9573 **Poster Session**

The 31-gene expression profile as a guide to better risk-aligned care decisions for patients with stage I–III cutaneous melanoma: An NCI-SEER analysis. First Author: Merve Hasanov, The Ohio State University Comprehensive Cancer Center, The James, Columbus, OH

Background: Current management guidelines for cutaneous melanoma (CM) are based on AJCC staging to stratify patients into risk groups. However, this approach can result in under- and over-estimation of risk for individual patients. The 31-gene expression profile (31-GEP) test has been prospectively validated to provide a more personalized likelihood of sentinel lymph node positivity, as well as risk of recurrence, distant metastasis, and mortality, than AJCC staging alone (Class 1A=low risk, Class 1B/2A=intermediate risk, and Class 2B=high risk). Using expanded SEER registry cohorts, we assessed the ability of the 31-GEP to independently stratify patients with high and low mortality risk categories, and to evaluate whether 31-GEP testing itself was associated with improved patient outcome. **Methods:** SEER registry data for patients with stage I–III CM (2013–2019) were linked to patients with 31-GEP test results provided by Castle Biosciences (N=13,560) using a registry trusted independent third party. Five-year melanoma-specific survival (MSS) was estimated using Kaplan-Meier analysis; survival differences between groups were compared using log-rank test. Multivariable analysis was performed to determine significant predictors of melanoma-specific mortality (MSM). Survival differences between 31-GEP tested and untested patients were performed by matching tested and untested patients according to clinicopathological factors, diagnosis year, ethnicity, and socioeconomic status. **Results:** Patients with a Class 1A 31-GEP result had a significantly higher 5-year MSS than those with Class 1B/2A or Class 2B results (99.1%, 92.5%, vs. 85.9%, $p<0.001$). Multivariable analysis showed that a Class 2B result (HR=4.20, $p<0.001$), Class 1B/2A result (HR=3.21, $p<0.001$), a positive lymph node (HR=2.78, $p<0.001$), Breslow thickness (HR=1.10, p=0.001), ulceration (HR=1.41, p=0.033), age (HR=1.04, $p<0.001$), and mitotic rate (HR=1.05, p=0.022) were significant predictors of MSM. In staging subset analyses, patients with a Class 1A 31-GEP result had a significantly higher 5-year MSS than those with Class 2B results in stage I-IIA CM (1A=98.8%, 1B/2A=95.5% vs. 2B=93.0%, $p<0.001$), stage IIB–IIC CM (1A=94.2%, 1B/2A=91.2% vs. 2B=82.3%, p=0.002), and stage III CM (1A=94.8%, 1B/2A=75.0% vs. 2B=77.6%, $p<0.001$). Among all stages, 31-GEP-tested patients had a lower MSM (HR=0.68, $p<0.001$) than untested propensity score-matched patients. **Conclusions:** In a large, real-world cohort of clinically tested patients with stage I–III CM, the 31-GEP stratified mortality risk within all staging groups, which could better help clinicians and patients make risk-aligned treatment and clinical management decisions. Research Sponsor: Castle Biosciences, Inc.

9574 Poster Session

Comparison of surveillance circulating tumor DNA and Merkel polyomavirus antibody titer for detection of Merkel cell carcinoma recurrence. First Author: Joshua Elbridge Chan, Stanford University School of Medicine, Stanford, CA

Background: Circulating tumor DNA (ctDNA) is emerging as a robust biomarker for detecting recurrences in Merkel cell carcinoma (MCC). This study aims to compare the performance of ctDNA against the Merkel polyomavirus antibody titer (AMERK) test in predicting MCC recurrence risk. **Methods:** We conducted a longitudinal, multi-center observational study involving 171 MCC patients undergoing disease surveillance, including serial ctDNA and AMERK testing (median testing interval: 92 days). All patients had detectable antibodies by AMERK at initial diagnosis and both tests were conducted within 45 days of each other. ctDNA tests were classified as positive if ctDNA was $>$ 0 MTM/mL. An AMERK test was positive if antibody titers rose $\geq$ 30% from the prior titer. Clinical recurrences were identified through routine imaging and clinical examinations. The diagnostic performance of ctDNA and AMERK tests was assessed using positive and negative predictive values (PPV and NPV), recurrence-free survival after any positive test vs. all negative tests, and corresponding hazard ratios (HRs) from Cox regression. **Results:** 718 pairs of ctDNA and AMERK tests were collected from 171 patients. Over a median follow-up of 445 days, there were 38 clinical recurrences, 91/718 (13%) positive ctDNA tests, and 73/718 (10%) positive AMERK tests. A significantly increased clinical recurrence rate was observed in patients with a positive ctDNA test compared to those with consistently negative results (HR: 27.4, 95%CI: 11.0-68.3) (Table 1). Although a positive AMERK test was similarly associated with higher clinical recurrence (HR: 5.8, 95%CI: 3.0-11.1), the rate was distinctly lower than that for a positive ctDNA test (HR: 5.8 vs. 27.4; $p < 0.001$). The PPV for clinical recurrence at 1 year after a positive test was significantly higher for ctDNA vs. AMERK (PPV: 73% [95% CI: 58-84%] vs. 51% [95% CI: 29-70%]; p=0.014). NPV for recurrence within 4 months of a negative test for the ctDNA test was similarly higher for ctDNA vs. AMERK (NPV: 98% [95% CI: 97-99%] vs. 95% [95% CI: 92-97%]; p=0.001). The median lead time between the first positive test and a clinically detected recurrence was 3.1 months for ctDNA (among 30 recurrences preceded by a positive test) and 1.9 months for AMERK (among 19 recurrences preceded by a positive test) (p=0.063). **Conclusions:** Our results indicate that, in a cohort of AMERK positive patients, ctDNA outperforms AMERK for detection of MCC recurrence. ctDNA may be a viable alternative to AMERK in clinical practice and may better identify high-risk patients who benefit from more aggressive monitoring or adjuvant therapy trials. Research Sponsor: None.

Hazard ratios for subsequent MCC clinical recurrence: Comparison of positive ctDNA and AMERK tests.

Test	HR	(95% CI)	P-value
Positive ctDNA	27.4	(11.0, 68.3)	$<$0.001
Positive AMERK	5.8	(3.0, 11.1)	$<$0.001
Difference (ctDNA / AMERK)	4.7	(2.1, 15.9)	$<$0.001

9575 Poster Session

Overall survival outcomes in stage III melanoma patients treated with adjuvant immunotherapy vs targeted therapy: A National Cancer Database analysis. First Author: Siavash Bolourani, Providence Saint John's Cancer Institute, Santa Monica, CA

Background: Adjuvant therapy with immunotherapy (IO) and targeted therapy (TT) has significantly improved outcomes in Stage III melanoma following surgical resection. While both approaches demonstrate efficacy, head-to-head comparisons remain limited, and real-world evidence on overall survival (OS) across diverse subgroups is sparse. This study compares OS between adjuvant IO and TT using data from the National Cancer Database (NCDB) from 2018 to 2020, offering insights into subgroup-specific benefits. **Methods:** We conducted a retrospective cohort study of Stage III melanoma patients from the NCDB diagnosed between 2018 and 2019 who underwent definitive surgical resection followed by either IO or TT. Patients receiving neoadjuvant therapy were excluded. OS was analyzed using Kaplan-Meier survival curves and compared using log-rank tests. Hazard ratios (HR) with 95% confidence intervals (CI) were derived from Cox proportional hazards models, adjusted for demographic and clinical covariates. Subgroup analysis was performed to identify populations deriving differential benefit from IO. **Results:** A total of 1,493 patients met the inclusion criteria (IO: 1,352; TT: 141). Overall survival (OS) was significantly higher in the IO group (74.9%; 95% CI: 72.2–77.8% at 3 years) compared to the TT group (62.1%; 95% CI: 52.5–73.3% at 3 years) ($p = 0.0055$). Subgroup analysis revealed that the survival benefit with IO was more pronounced in patients aged $<$65 years (HR 0.49; 95% CI: 0.32–0.75), males (HR 0.54; 95% CI: 0.37–0.77), those with private insurance (HR 0.45; 95% CI: 0.27–0.76), and primary tumors located on the head and neck (HR 0.44; 95% CI: 0.22–0.89). No subgroup demonstrated superior outcomes with TT. **Conclusions:** In this NCDB-based analysis, adjuvant IO was associated with a significant OS advantage compared to TT in Stage III melanoma patients. However, NCDB limitations, including lack of information on specific agents (e.g., BRAF/MEK inhibitors or checkpoint inhibitors), must be acknowledged. Additionally, this analysis reflects OS rather than melanoma-specific survival (MSS). In the NCDB sample, there was a 10:1 preference for IO over TT, reflecting marked community preference for IO. These findings appear to indicate that IO is the preferred adjuvant strategy, though further prospective studies are required to validate subgroup-specific outcomes and confirm these results. Research Sponsor: None.

9576 Poster Session

Survival impact of adjuvant treatment in resected stage III cutaneous melanoma patients: Results from a real-life cohort study (TAMARIS). First Author: Charlee Nardin, Université de Franche-Comté, Inserm 1098 RIGHT, Besançon, France

Background: Anti-PD-1 immunotherapies and BRAF+MEK inhibitors (BRAFi/MEKi) (specifically for BRAF V600E/K-mutant melanoma) have been shown to improve recurrence-free survival (RFS) in patients (pts) with resected stage III metastatic melanoma in phase III trials. However, none of these studies has demonstrated a significant improvement in overall survival (OS). Notably, adjuvant BRAFi/MEKi therapy has shown better OS only in the BRAF V600E subgroup of patients. In this context, we evaluated the real-world impact of adjuvant therapies on OS. **Methods:** TAMARIS is a national multicenter retrospective study designed to evaluate the efficacy of adjuvant treatment (anti-PD-1 or BRAFi/MEKi) in pts with resected AJCC 8th edition stage III melanoma using data from the French RIC-Mel prospective database. The primary endpoint was OS analyzed using the Kaplan-Meier method, comparing pts who received adjuvant treatment (adjuvant group) within 3 months of surgery to those who did not (control group). Demographic and clinical characteristics were compared using chi-square analyses. Secondary endpoints included OS in specific subgroups and RFS. **Results:** A total of 1,172 pts (median age: 65 years [IQR: 53–74]) with resected stage III melanoma were included between 2018 and 2023. Among them, 796 pts (68%) received adjuvant treatment with anti-PD-1 (n=676) or BRAFi/MEKi (n=120). The median treatment duration was 10.8 months (IQR: 5.6–11.9). Most pts had a history of SSM (54%) with a median Breslow thickness of 2.8 mm [range, 0-47] and stage IIIB (31%) or IIIC disease (49%). Surgical interventions for metastases prior to adjuvant treatment included lymph node dissection in 53% of cases, sentinel lymph node biopsy in 38%, and cutaneous metastasis resection in 8%. Pts in the control group were older (median age: 69.7 vs. 63.0 years, $p < 0.0001$). The median follow-up was 30.4 months (IQR: 16.7-43.3). OS was significantly longer in the adjuvant group compared to the control group (HR: 0.617; 95% CI: 0.474-0.802; $p = 0.0003$), with a 2-year OS of 90% (95% CI: 88-92) in the adjuvant group versus 79% (95% CI: 74-83) in the control group. There was a trend toward better OS with BRAFi/MEKi compared to anti-PD-1 (HR: 0.569; 95% CI: 0.312-1.037; $p = 0.065$). Subgroup analyses demonstrated a significant positive impact of adjuvant treatment on OS across most subgroups, except for pts aged $\leq$75 years, those with stage IIIA disease, primary melanomas with a Breslow thickness $<$2.8 mm, or without ulceration. RFS also favored the adjuvant group (HR: 0.545; 95% CI: 0.458-0.649; $p < 0.0001$), with a 2-year RFS of 67% (95% CI: 63-70) and 45% (95% CI: 40-50) in the control group. **Conclusions:** Adjuvant treatment appears to provide an OS benefit in patients with resected stage III melanoma in real-world settings. Further research is required as age-related differences may influence prognosis. Research Sponsor: None.

9577 Poster Session

Financial toxicity and employment outcomes in people with melanoma receiving adjuvant therapies. First Author: Julia Elizabeth Lai-Kwon, Peter MacCallum Cancer Centre, Melbourne, VIC, Australia

Background: One year ofadjuvant anti-programmed cell death protein-1 (anti-PD1) or dabrafenib-trametinib are standards of care for patients (pts) with resected stage III-IV melanoma. The impact of adjuvant therapy on a pt's employment, income, and level of financial toxicity are unknown. We examined these outcomes up to 2 years post initiation of adjuvant therapy. **Methods:** A prospective, longitudinal study of pts with resected stage IIB-IV melanoma receiving adjuvant anti-PD1 or dabrafenib-trametinib at an Australian comprehensive cancer center. Two customized employment surveys assessed impact on employment and income. Survey 1 (7 items) was administered pre-treatment, Survey 2 (11 items) at 12 and 24 months post treatment initiation. The Comprehensive Score for Financial Toxicity (FACIT-COST) was collected pre-treatment and at 1, 3, 6, 12, and 24 months post treatment initiation. FACIT-COST scores were categorized into none ($\geq$26), mild (14-25), moderate (1-13) and severe (0) financial toxicity. **Results:** Between September 2021-December 2024, 70 pts were eligible and 52 (74%) consented: 17 (33%) female, median age 64 years (IQR 60-71), 46 (89%) had resected stage III, 32 (62%) on adjuvant anti-PD1. 41 pts had completed treatment and 11 were still receiving treatment at data cut off (17 December 2024). Employment surveys were completed by 51 pts pre-treatment, 31 at 12 months and 18 at 24 months. Most (18/31, 58%) were working at 12 months, with the majority (17/18, 94%) in the same job as pre-treatment. Only half (9, 50%) were working the same number of hours or earning the same income (10, 56%) as pre-treatment (the remainder, less). Barriers to returning to work at 12 months were ongoing symptoms (45%), financial concerns (26%), and work environment (21%). 18 pts completed both the 12 and 24 month surveys. 9 (50%) had returned to work by 12 months and the majority (n=8) were still working at 24 months. At 24 months, 6 (75%) were working the same number of hours but only 5 (63%) were earning the same income as pre-treatment (the remainder, less). The prevalence of financial toxicity is shown in the table and ranged from 16% at 6 months to 36% at 12 months. **Conclusions:** Half of pts reported reduced working hours and income 12 months post therapy initiation, mostly due to ongoing symptoms. A third reported financial toxicity at 12 months, even with universal healthcare. This data can inform shared decision-making about risks and benefits of adjuvant therapy and highlights the importance of screening for financial toxicity to identify pts who require support. Research Sponsor: None.

FACIT-COST category	Pre-treatment (n= 51)	1 month (n=46)	3 months (n=44)	6 months (n=38)	12 months (n=31)	24 months (n=18)
None	37 (72.5)	32 (69.6)	35 (79.5)	32 (84.2)	20 (64.5)	13 (72.2)
Mild	13 (25.5)	11 (23.9)	6 (13.6)	5 (13.2)	10 (32.3)	2 (11.1)
Moderate	1 (2.0)	2 (4.3)	3 (6.8)	1 (2.6)	1 (3.2)	3 (16.7)
Severe	0	1 (2.2)	0	0	0	0
Any	14 (27.5)	14 (30.4)	9 (20.5)	6 (15.8)	11 (35.5)	5 (27.8)

9578 **Poster Session**

A pooled analysis of clinical outcomes with anti-PD1-based neoadjuvant immunotherapy (NeoIT) in cutaneous squamous cell carcinoma (cSCC). First Author: Ines Esteves Domingues Pires da Silva, Melanoma Institute Australia, Faculty of Medicine and Health, Charles Perkins Centre, The University of Sydney, Sydney, NSW, Australia

Background: Anti-PD1 immunotherapy has shown improved clinical outcomes in patients (pts) with advanced cSCC, and recently, in the neoadjuvant setting for resectable disease. Pathological (path) response is predictive of recurrence in melanoma and recent NeoIT trials suggests the same in cSCC; however, an analysis of clinical outcomes in pts with resectable cSCC treated with intended anti-PD1-based NeoIT in larger datasets remains unknown. **Methods:** Pts with resectable cSCC treated with intended anti-PD1-based NeoIT from 17 cancer centres globally were included. Baseline patient and disease characteristics, treatment regimen, path response and recurrence-free survival (RFS) or progression-free survival (PFS) were collected and examined. **Results:** 134 pts with resectable cSCC were treated with intended anti-PD1-based NeoIT. Median age was 75 years old (range, 39-97), 72% (n=97) were male. One fifth (22%, n=29) were immunocompromised and 43% (n=58) had ECOG PS of $\geq$1. Of 125 (93%) pts with known primary cSCC, 82% (n=102) were from the head & neck. Most pts (79%, n=106) were stage III/IV. The majority had anti-PD1 monotherapy (91%, n=122) and 9% (n=12) had anti-PD1+/-investigational agent. Median follow-up from commencement of NeoIT was 10 months (95% CI, 9 - 12). Nearly half of the pts (49%, n=66) underwent surgery; 37 (56%) pts had major pathological response (MPR; $\leq$10% viable tumour cells at the surgical specimen; 31 [47%] had complete path response [0% of viable tumour cells] and 6 [9%] had near complete path response [1-10% of viable tumour cells]), 6 (9%) had partial path response (pPR; $>$10% and $\leq$50% of viable tumour cells), and 23 (35%) had path non-response (pNR; $>$50% of viable tumour cells). Of the 66 pts who underwent surgery, 11% (n=7) had recurrence (5 loco-regional and 2 distant recurrence), all non-MPR pts (1 pPR and 6 pNR). 12-months RFS was improved with MPR vs non-MPR (100% vs 79%, p=0.004). 52% (n=34) pts had adjuvant treatment (23 anti-PD1 alone, 7 anti-PD1+/-investigational agent, 2 platinum and 2 cetuximab). Within non-MPR pts, 12 had adjuvant treatment (3 recurred; 25%), while 17 did not have adjuvant treatment (4 recurred; 24%). Fifty-one percent (n=68) of pts did not have surgery; 9 (13%) due to progressive disease (PD) and 53 (78%) due to clinical response. Of the 53 pts with a clinical response, 5 (9%) subsequently progressed. Fourteen (10%) pts have died, 6 (4%) related to cSCC; 2 had surgery (non-MPR) and 4 did not have surgery (all due to PD). **Conclusions:** Anti-PD1-based NeoIT is an active regimen in resectable stage II-IV cSCC and is associated with high clinical response and MPR rates. No pts with MPR from NeoIT has recurred to date, however, 9% of pts who did not have surgery due to clinical response eventually progressed. These findings highlight the importance of further research to investigate the role of surgery in this subgroup of patients. Research Sponsor: None.

9579 **Poster Session**

Use of artificial intelligence to identify high risk profiles in early stage melanoma patients from pathology slides. First Author: Christina Kanaan, Department of Pathology, Gustave Roussy, Villejuif, France

Background: To refine prognostication in primary cutaneous melanoma (CM) and optimize adjuvant treatment decisions, we evaluate SmartProg-MEL (SPM), an AI-based histology-driven algorithm developed by DiaDeep and applied to H&E-stained whole-slide images (WSI) at the time of diagnosis. SPM provides a risk stratification score, under 15 minutes, for overall survival (OS) and relapse-free (RFS) outcomes to support clinical decision-making. **Methods:** SPM was evaluated on a retrospective cohort of 383 primary CM with 5-year follow-up (46% IA, 15% IB, 9% IIA, 7% IIB, 6% IIC, 13% III, 4% IV). The model stratifies patients into high- or low-risk groups based solely on the WSI of the primary tumor. Kaplan-Meier curves are used to compare RFS and OS between risk groups, with statistical significance assessed using the log-rank test. A multivariable Cox regression analysis was performed to evaluate the independent prognostic value of SPM after adjusting for pathological factors. The negative and positive predictive values (NPV and PPV) of the SMP are explored. **Results:** Patients with a low risk score had a significantly higher 5-y OS and RFS than patients of the high risk group (93.1% vs 62.5%, $p<0.001$ and 92.8% vs 47.1%, $p<0.001$). In multivariable analysis, SPM risk score was the strongest predictor (OS: HR=3.95, $p<0.005$, RFS: HR=5.03, $p<0.005$). In the I-IIA group, 29% (n=78) were assigned to the high risk profile with a decrease of the OS and RFS compared with the low risk group (OS: 95.4% vs 86%, $p<0.05$; RFS: 94.3% vs 74%, $p<0.01$). SPM has a NPV of 96%, 100% and a PPV of 17% and 69% in stages I/IIA and IIB/C respectively. **Conclusions:** The AI-based risk stratification algorithm, SPM, demonstrates greater performance than stage in identifying high and low risk profiles, especially in early-stage CM patients. This new prognostic tool opens avenues for a routine clinical application to precise therapeutic decisions in an adjuvant setting. Research Sponsor: None.

Cohort statistics: Event occurrences and five-year OS and RFS endpoints survival rates, segmented by AJCC stage and SPM risk stratification.

		RFS		OS	
	# patients	# events (%)	5-y RFS [CI]	# events	5-y OS [CI]
I/IIA	266	21	88.1 [82.1 to 92.2]	14	92.5 [87.6 to 95.6]
SPM Low Risk	188 (70.7%)	8(38.1%)	94.3 [88.9 to 97.2]	5(35.7%)	95.4 [89.8 to 98.1]
SPM High Risk	78(29.3%)	13(61.9%)	74.1 [58.4 to 84.4]	9 (64.3%)	86.1[73.8 to 92.8]
IIB/IIC	51	34	24.3 [11.7 to 39.3]	22	47.8 [31.2 to 62.7]
SPM Low Risk	1 (2.0%)	0(0.0%)	100 N/D	0 (0.0%)	100 N/D
SPM High Risk	50(98.0%)	34(100.0%)	22 [9.7 to 37.4]	22 (100.0%)	46.6 [29.9 to 61.7]
III	49	39	32.8 [19.3 to 47.2]	25	100 N/D
SPM Low Risk	5(10.2%)	2(5.1%)	60.1 [12.6 to 88.2]	2(8.0%)	60.1 [12.6 to 88.2]
SPM High Risk	44(89.8%)	34(87.2%)	29.5 [14.4 to 42.3]	20 (80.0%)	51.4 [35.2 to 65.4]

SPM: DiaDeep SmartProg-MEL; CI: confidence intervals.

9580 **Poster Session**

Identification of novel RNA biomarkers for the differential diagnosis of cutaneous melanoma and nevi. First Author: Igor Samoylenko, FSBI "N.N. Blokhin National Medical Research Center of Oncology" of the Ministry of Health of the Russian Federation, Moscow, Russian Federation

Background: The differential diagnosis of nevi and melanomas remains a significant clinical challenge, as misclassification can result in overtreatment or delayed care. Despite advances in clinical, dermatoscopic, and histopathological methods, benign lesions are frequently misclassified as nevi, SAMPUS, or MELTUMP, while atypical melanomas are often mistaken for nevi. This study aimed to identify novel RNA markers for the differential diagnosis of nevi and melanomas. **Methods:** Ninety histological samples of melanocytic neoplasms were analyzed, including 45 morphologically confirmed nevi and 45 melanomas. Massive parallel sequencing was performed using the NextSeq 550 system (Illumina, USA) with the "NextSeq High Output 150 Cycles Kit" reagent set, following the manufacturer's protocol. Data normalization employed FPKM and TPM metrics, and differential gene expression analysis utilized 26 algorithms on the RNA-Seq 2G web server. Selected RNA markers were further validated on an independent cohort of 120 samples (60 verified nevi and 60 melanomas) using RT-PCR. **Results:** The study analyzed the expression of over 18,000 coding and 42,000 non-coding RNAs (primarily long non-coding) in histologically confirmed melanomas and nevi, balanced between "classical" and dysplastic nevi. Initial RNA-Seq quality control confirmed high data integrity and sufficient sequencing depth in 87 of 90 samples. Melanoma-specific markers identified included CSAG1, CXCL1, CXCL8, CXCL9, DUXAP8 + DUXAP9 + DUXAP10, FCRL3, IGHA1, IGHG1, LRP2, MAGEA3 + MAGEA6 + MAGEA12, MMP1, OR2I1P, SPP1, and VGF, while nevus-specific markers included CD44-AS1, CDR1-AS (LINC00632), DSCAS, and ENSG00000287270. For RNA marker testing at the next stage, all 120 samples were deemed suitable for analysis. Modeling of multimarker tests achieved an AUROC of 0.94, with a model incorporating only 5 preselected markers outperforming those with a larger number of markers. The most informative logistic regression model included the following marker combinations: MAGEA3 + MAGEA6, CXCL8 + LINC00632, DUXAP8 + DUXAP9 + DUXAP10, CSAG1, and CXCL1. **Conclusions:** The model, incorporating only 5 markers, achieved an AUROC of 0.94 in an independent validation cohort. It is now positioned for further validation in cohorts enriched with samples of uncertain malignant potential based on histological evaluation. Clinical trial information: NCT04353050. Research Sponsor: Ministry of Health of the Russian Federation.

9581 **Poster Session**

Animated patient's guide to melanoma: Assessing patient understanding, shared decision-making, and health outcomes. First Author: Kyleigh LiPira, Melanoma Research Foundation, Washington, DC

Background: Patients with melanoma who participate in informed, personalized-care discussions with their healthcare providers are better prepared to carry out shared decision-making (SDM) and achieve best attainable health outcomes. In a 2018 Cancer Registry Experience study of 114 melanoma survivors, a majority of respondents did not feel knowledgeable or prepared to discuss treatment options with their healthcare team. The complexity of melanoma treatments and patients' limitations due to poor health literacy are obstacles to SDM. In November 2018, the *Melanoma Research Foundation* introduced *An Animated Patient's Guide to Melanoma (APGM),* an online resource aimed at improving patient knowledge, informed SDM, and achieving best outcomes. **Methods:** APGM was developed with highly visual formats of learning on a website, comprised of melanoma educational animations, expert videos, patient experience videos, slide shows, infographics, and self-assessment tools. Learners on the website have the option to voluntarily participate in evaluations, including pop quizzes and surveys. From the website, learner responses were collected from surveys over a period of 72 months, ending January 2025. Patient responses to these questions were aggregated to measure outcome-based questions, and patient intention to discuss key decisions with healthcare providers. **Results:** Our 6-year reported data is based on 443,015 total views and 272,191 unique visitors aggregated from the APGM online resource. Unique US visitors were 54% (N=146,983); and 46% (N=125,208) from other countries. In terms of US participants/learners: 72% (N=105,828) were patients; 12% (N=17,638) were family and caregivers; 6% (N=8,819) were healthcare providers; and 10% (N=14,698) were other/undisclosed. Of the respondents who volunteered to complete the surveys, 95% (N=1,059) were patients who reported they *'will use information learned to better self-manage their melanoma'*; 93% (N=969) of patients *'will discuss information learned with their doctor'*; and 95% (N=694) of patients *'will discuss melanoma treatment options with their doctor'*. **Conclusions:** Our data shows that animated formats of learning tailored to the needs and learning styles of patients with melanoma provide effective translational learning resources, improve self-management skills, and facilitate engagement in SDM. Visual formats of learning are effective resources in helping inform patients with melanoma and improving outcomes. Our APGM initiative validates the utility of visual formats of learning which may be utilized in other oncology settings to benefit patient outcomes. Research Sponsor: None.

9582 Poster Session

A phase II trial of perioperative oral itraconazole for the management of low risk basal cell carcinoma. First Author: Rodrigo Perez Pereira, Unidade de Pesquisa Clínica em Oncologia, Porto Alegre, Brazil

Background: Recently, new treatment options have emerged for advanced basal cell carcinoma (BCC), including oral Hedgehog pathway inhibitors like Vismodegib. Itraconazole has also shown promising clinical activity in these cases by targeting the SMO receptor. This study aimed to assess the clinical and molecular efficacy of oral Itraconazole in BCC patients with low-risk disease. **Methods:** Patients with localized BCC who were eligible for surgical excision were enrolled. They received 200 mg of Itraconazole twice daily for 60 days prior to resection. Clinical assessments were based on the RECIST 1.1 criteria, with target lesions measuring at least 10 mm following a confirmatory biopsy. Molecular markers associated with cellular activity and angiogenesis (Ki67, GLI, CD105) were evaluated using immunohistochemical staining. Adverse effects were graded according to NCI-CTC v4. **Results:** A total of 26 patients were treated, with 61% female and a mean age of 62 years. The most common BCC subtype was nodular (54%), and the most frequent tumor location was the trunk (65%). Patients presented with stable disease (92%), partial response (4%), and complete response (4%). Notably, no disease progression occurred during the treatment period, and all patients underwent the planned surgical excision. The median tumor diameter prior to treatment was 14 mm (range: 11–16 mm), and after treatment, it was 13 mm (range: 11–15 mm). This reduction was statistically significant, as determined by the Wilcoxon test ($p < 0.0001$). Additionally, biological activity of Itraconazole was demonstrated through the measurement of Ki67, GLI, and CD105. The percentage of the stained area for CD105 or Endoglin decreased significantly following Itraconazole treatment, from 0.11 [0.01–1.86] to 0.03 [0.00–0.22], with this reduction also being statistically significant ($p \leq 0.0001$). **Conclusions:** Preoperative oral Itraconazole demonstrated both clinical and molecular activity in localized, low-risk BCC lesions, with no patients showing disease progression and two patients exhibiting partial and complete responses, respectively. The median tumor diameter significantly decreased after the treatment period. In addition to the reduction in tumor size, there was a notable decrease in the expression of CD105, marking the first study to demonstrate this correlation in this context. Endoglin, a well-established marker for endothelial cell proliferation, particularly in angiogenesis in regenerating tissues or inflamed tumors, underscores the anti-angiogenic potential of Itraconazole. These findings align with previously published results and suggest that oral Itraconazole could be a promising candidate for managing low-risk BCC, while also opening the opportunity for further investigation in advanced disease settings. Clinical trial information: NCT03972748. Research Sponsor: None.

9583 Poster Session

Comparison of the tolerability and safety of hedgehog inhibitors in real-life: A cohort of 330 patients with locally advanced basal cell carcinoma. First Author: Florian Herms, APHP, Hôpital Saint Louis, Paris, France

Background: Two hedgehog pathway inhibitors (HHIs) have been approved for the treatment of locally advanced basal cell carcinoma (laBCC): vismodegib and sonidegib. Efficacy of both seem similar, even though no head-to-head comparison has been performed. However, adverse events (AEs) in pivotal trials seemed less frequent with a later onset with sonidegib. CARADERM is a French national database created in 2013 to improve the management of rare skin tumors, including laBCC. The objective of our study was to compare the safety profile of HHIs in this real-life cohort. **Methods:** LaBCC patients from the CARADERM database were reviewed. Patients who started either vismodegib or sonidegib at least one year before analysis were included. Type and grade of AEs were collected when available. Cumulative incidence of the first occurrence of adverse events was estimated, with treatment discontinuation as a competing event. **Results:** In the total cohort of 452 laBCC patients, 330 met the inclusion criteria: 280 (85%) treated with vismodegib and 50 (15%) with sonidegib. The median follow-up was 22.3 months. Clinical characteristics (including age, gender, performance status, localization and tumor size) were similar for both groups. The cumulative incidence of the first AE was significantly lower with sonidegib (43.5%, 95% confidence interval (95%CI) = 29.0-57.2 at 12 months) than with vismodegib (63.5%, 95%CI = 57.5-68.9 at 12 months, p=0.0014) (Table 1). For vismodegib treated patients, 191 (68%) experienced at least one AE. The most frequent were cramps (n=123, 44%), dysgeusia (n=123, 44%) and alopecia (n=88, 31%). For sonidegib treated patients, 22 (44%) experienced at least one AE. The most frequent were cramps (n=8, 16%), alopecia (n=7, 14%) and dysgeusia (n=6, 12%). Major AEs seemed to be less frequent and to appear later with sonidegib, with a significant difference for cramps (p=0.007) and dysgeusia (p=0.001), but not significant for alopecia (p=0.059). **Conclusions:** We present here the largest real-life comparison of HHIs in a real-life cohort of laBCC patients. The cumulative incidence of the first AE was significantly lower with sonidegib. Even though the range of AEs was similar with both HHIs, dysgeusia and cramps were less frequent with sonidegib. These data highlight the difference in terms of tolerance of both HHIs, with a later onset and lower frequencies of AEs with sonidegib. However, though both groups were clinically comparable, vismodegib was overrepresented compared to current prescriptions of HHIs, and further analyses are mandatory to confirm these data. Research Sponsor: None.

Cumulative incidence of first adverse event at 3, 6 and 12 months.

	3 months [95CI]	6 months [95CI]	12 months [95CI]
Sonidegib	16.3 % [7.5 ; 28.0]	26.8 % [15.2 ; 39.8]	43.5 % [29.0 ; 57.2]
Vismodegib	31.6 % [26.2 ; 37.2]	55.5 % [49.5 ; 61.2]	63.5 % [57.5 ; 68.9]

95CI = 95% confidence interval.

9584 Poster Session

Sensitivity of circulating tumor DNA (ctDNA) for disease recurrence or relapse in melanoma patients. First Author: Vincent The-Luc Ma, Division of Hematology, Medical Oncology, and Palliative Care, Department of Medicine, University of Wisconsin, Madison, WI

Background: ctDNA has emerged as a biomarker for minimal residual disease (MRD) detection in colorectal cancer and other cancer types. Its role in MRD monitoring and disease detection for melanoma patients merits further investigation. We aimed to assess the sensitivity of a commercially available ctDNA test to detect recurrence or relapse in patients with melanoma. **Methods:** A retrospective cohort analysis was performed using a personalized, tumor-informed, ctDNA assay (Natera) on prospectively collected plasma from patients with a diagnosis of melanoma from December 2021 to January 2025 with longitudinal follow up. Inclusion criteria were patients with no evidence of disease (NED) following definitive surgery or clinical remission with systemic therapy; and an undetectable ctDNA level. We evaluated the sensitivity of ctDNA detection of patients who had biopsy and/or radiographic confirmation of recurrence or relapse; and further stratified this based on anatomic sites of recurrence or metastasis (mets). Sensitivity was computed and logistic regression models were conducted to assess predictors of ctDNA detection. **Results:** 116 patients met the inclusion criteria. 48% (n=56) had confirmed recurrence or relapse. Among these patients, 82% (n=46) had NED following surgery and 18% (n=10) had clinical remission with systemic therapy. 75% (n=42) were resected stage II/III, 7% (n=4) were resected stage IV, 4% (n=2) were unresectable stage III in remission, and 14% (n=8) were unresectable stage IV in remission. Melanoma primaries included: 82% (n=46) cutaneous, 7% (n=4) mucosal, 5% (n=3) uveal, 5% (n=3) unknown. ctDNA was detected in 30 out of 56 patients with confirmed recurrence/relapse, with an overall sensitivity of 53.6%. Sensitivity varied by site of recurrence/relapse. Sensitivity for ctDNA detection of brain mets was 33.3% (4/12); skin/mucosa/muscle recurrence or mets was 37.5% (6/16); lung mets was 61.5% (8/13); bone mets was 75% (3/4); liver mets was 87.5% (7/8), and lymph node mets was 87.5% (14/16). The odds of detecting ctDNA at relapse or recurrence were significant amongst patients with lymph node mets (OR=10.5, 95% CI 2.10-52.58, p=0.004) and patients with multiple anatomic sites (2+) of mets (OR=7.61, 95% CI 1.27-66.67, p=0.032). **Conclusions:** ctDNA monitoring shows potential in detecting recurrence or relapse in patients with melanoma. We found that location of metastatic disease impacts the shedding of ctDNA and its detection of macroscopic disease. Larger studies are needed to refine the role of ctDNA monitoring and its clinical application in melanoma surveillance. Research Sponsor: Clinical and Translational Science Award (CTSA); UL1TR002373.

9585 Poster Session

Multiomic analysis of cutaneous squamous cell carcinoma (cSCC) and association with response to anti-PD1 therapy (PD1). First Author: Yu-Ju Kuo, Melanoma Institute Australia, The University of Sydney, National Taiwan University Hospital Hsin-Chu Branch, Sydney, Australia

Background: PD1 induces a durable response and improves the survival of patients (pts) with advanced cSCC; however, about 40% of pts are resistant to this treatment. Multiomic analysis (e.g., tumor mutational burden [TMB] and gene expression profiling [GEP]) has shown predictive value for PD1 response in various cancer types. This study aims to perform multiomic analysis of cSCC and study its association with the response to PD1. **Methods:** cSCC pts were prospectively enrolled in the PIP-PREDICT study (NCT06536257). Baseline tumor tissues were sent for: a) targeted TSO500 DNAseq (NGS), for TMB and mutational status, and b) NanoString Pancancer 360IO, for GEP. Baseline characteristics and clinical outcomes were collected. Pts treated with PD1 were categorized as responders (complete/partial response) or non-responders (progressive disease) based on RECIST 1.1. Pts with stable disease were further categorized into responders/ non-responders based on PET response (PERCIST). **Results:** 26 cSCC pts were enrolled; the median age was 79 (range 39-98) and 73% (n=19) were male. 7 pts (27%) were immunocompromised and 4 were on immunosuppressants. Head and neck (HN) primaries were present in 54% (n=14), and 58% (n=15) of the pts had stage IV disease. NGS was performed on 21 pts, revealing a median TMB of 39.2 mut/Mb (range 17.3-122.2). TP53 mutations were present in all cases (100%), with other frequent mutations observed in CDKN2A (43%), TERT promoter (43%), FAT1 (38%), NF1 (24%), PIK3CA (24%), TGFBR2 (19%), and CREBBP (19%). GEP of 22 pts showed that cSCC with HN primaries exhibited higher cancer-associated fibroblast (p=0.018) and stromal (p=0.035) signatures (sig), compared to non-HN pts. Pts on immunosuppressants demonstrated lower expression of cytokine (p=0.031), effector cell (p=0.019), and NK cytotoxicity (p=0.0498) sig compared to those not on immunosuppressants. 18 pts received PD1 for advanced cSCC with evaluable disease; ORR was 61.1% and DCR was 72.2%. After a median follow-up of 12.4 months (95% CI, 4.1-20.7), the 12-months PFS and OS rates were 57.9% and 94.7%, respectively (the median PFS and OS were not reached). Responders to PD1 exhibited higher expression of MHC-I (p=0.003), T cells (p=0.039), NK cells (p=0.009), interferon-gamma (p=0.03), cell adhesion molecules (p=0.039), and antigen presentation (p=0.03) sig. Conversely, non-responders showed higher levels of angiogenesis (p=0.005), endothelium (p=0.005), hypoxia (p=0.039), and CCR8 (p=0.017) sig. No differences were observed in the expression of immune checkpoints (e.g. PD-1, LAG3), TMB, or specific mutations in responders vs. non-responders. **Conclusions:** cSCC responsive to PD1 have higher expression of immune sig and lower expression of stromal and hypoxic sig. Well-known predictive features of response to immunotherapy (e.g. TMB, PD-1 sig) were not associated with response in this cohort. Research Sponsor: None.

9586 **Poster Session**

Immunoembolization for patients with uveal melanoma hepatic metastasis: A single-institution real-world data analysis. First Author: Rino S. Seedor, Sidney Kimmel Comprehensive Cancer Center, Thomas Jefferson University, Philadelphia, PA

Background: Metastatic disease occurs in up to 50% of patients with uveal melanoma (UM) despite successful treatment of the primary eye tumor. The liver is the predominant organ of involvement in more than 90% of patients, and control of liver metastases is essential to prolonging overall survival (OS). Immunoembolization (IE) with granulocyte-macrophage colony-stimulating factor +/- interleukin-2 is considered a 1st line liver-directed therapy for those with <50% hepatic tumor burden at our institution. It is well tolerated, has limited side effects, no cumulative toxicities, and affords good quality of life between scheduled treatments. **Methods:** A retrospective single-institution chart review was performed on consecutive series of metastatic UM (MUM) patients with hepatic metastasis who were treated at Thomas Jefferson University with IE treatment. The following data were collected from medical records: age, gender, IE treatment history, treatment history before and after IE, last follow-up date, and date of death. **Results:** 604 MUM patients (median age 62, range 19-91) received IE treatment for UM hepatic metastasis from 11/2000 to 01/2025 for a total of 3,715 IE treatments. 22 patients continue to receive IE. Patients received a median of 4 IE treatments (range 1-45) over 4 months (range 1-118 months). With a median follow-up of 18.3 months (range 0.1-176.4), median OS after IE treatment initiation was 20.0 months (95%CI 18.2-22.3). OS was 73.2% at 1 year, 41.8% at 2 years, 25.3% at 3 years, and 11.2% at 5 years. 30% of patients had treatment of metastatic disease prior to IE and 83% had treatment after IE. 134 patients (22%) had concurrent therapy with IE, most commonly checkpoint inhibitor therapy (48%). Median OS was 21.5 months (95%CI 18.9-23.4) for patients who received IE as first-line metastatic therapy. Except for one patient who died of takotsubo cardiomyopathy after the first IE treatment, IE treatments were well tolerated without serious or long-term complications. Of the subset of patients that experienced a prolonged OS of ≥3 years with IE (n=117), they received a median of 10 treatments over 16 months. Of the patients with prolonged OS of ≥5 years with IE (n=33), they received a median of 12 treatments over 19 months. Patients that experienced prolonged OS with IE ≥3 years were more likely to be female (69%). The longest patient treated with IE was a female who received 45 IE treatments over 10 years. **Conclusions:** We conducted the largest retrospective study of MUM patients who have received IE treatment. Our real-world data indicates that IE is a safe and effective liver-directed therapy for UM hepatic metastases, and IE should be considered a mainstay of treatment for patients with limited hepatic tumor burden. Research Sponsor: None.

9587 **Poster Session**

Real-world outcomes of immunosuppressed patients with Merkel cell carcinoma treated with immune checkpoint inhibitors. First Author: William J Mullally, Department of Medical Oncology, Princess Alexandra Hospital, Brisbane, QLD, Australia

Background: Merkel cell carcinoma (MCC) is a rare, aggressive neuroendocrine skin cancer that disproportionately affects older adults & the immunosuppressed. Immune checkpoint inhibitors (ICI) are highly effective in advanced MCC (aMCC), but pivotal ICI trials excluded immunosuppressed patients, highlighting an unmet need for this cohort. **Methods:** Clinical databases from 10 centers across 3 countries, were retrospectively analysed to identify immunosuppressed patients with aMCC who have received ICI. These patients were categorized into solid organ transplant (SOT), human immunodeficiency virus (HIV), hematological malignancies (HM) & autoimmune (AI) diseases. The overall aim was to assess treatment outcomes in patients excluded from trials. **Results:** This retrospective multicenter study identified 46 immunosuppressed patients (80% male) with aMCC and treated with ICI. The median age was 72 years (Table 1). The objective response rate (ORR) to anti-PD1/PDL1 ICI was 47.8%, with median progression-free survival (PFS) & overall survival (OS) of 23.4 & 40.9 months, respectively. 56.5% of patients have died at data cutoff. Cause of death included MCC (69.2%), comorbidities/others (15.4%), hematological malignancies (11.5%), and ICI-pneumonitis (3.9%). There were no deaths from graft failure, AI diseases or HIV. 8.7% developed ≥ grade 3 ICI-related adverse event (irAE). There was no difference in ORR (44% vs. 40%), OS (43.6 vs. 40.5 months, p = 0.68) or PFS (26.7 vs. 22.6 months, p = 0.18) in patients who experienced any grade irAE compared to those who did not. Clinicians were less likely to offer first line ICI to SOT patients (60%), particularly non-renal SOT patients 50%, compared with non-SOT immunosuppressed patients (89%). SOT patients had numerically lower response rates vs. non-SOT patients (ORR 30% vs 56%), significantly shorter PFS & OS at 6.5 months vs. 34.6 months (p= 0.001) & 13.1 months vs. 47.6 months (p = 0.002), respectively. **Conclusions:** Real world data shows that immunosuppressed MCC patients derive significant clinical benefit from ICI with acceptable rates of irAEs. Majority of immunosuppressed MCC patients (69%) died of disease progression, with 3.9% dying from an irAE & 11.5% from deterioration in HM. This suggests pre-existing immunosuppression should not significantly deter the use of ICI in patients with MCC. Patients with SOT have worse outcomes when treated with ICI compared with other immunosuppressed groups. Clinicians were more likely to reserve ICI use beyond first line. Research Sponsor: None.

Study cohort.

	SOT (n=10)	HIV (n=4)	Autoimmune disease (n=16)*	Hematological malignancy (n=16)
Median Age (Range)	72 (18-90)			
Male, n (%)	37 (80)			
ORR (%)	30	100	56	38
Use of ICI First Line (%)	60	100	81	94
PFS months (95% CI)	6.5 (0.6 – 12.5)	41.1 (15.4 – 66.8)	34.9 (13.3 – 56.5)	20.8 (8.1 – 33.5)
OS months (95% CI)	13.1 (2.3 – 24.0)	Not reached	44.2 (22.8 – 65.5)	39.1 (23.4 – 54.8)

*15 on treatment.

9589 **Poster Session**

Tobacco smoking as a risk for cutaneous squamous cell carcinoma in skin of color. First Author: Tahira Naqvi, WVU Medicine, Morgantown, WV

Background: Ultraviolet radiation (UVR) along with immunosuppression, tobacco smoking and age are the major risk factor cutaneous squamous cell carcinoma (cSCC) in White individuals. However, the risk factors for cSCC in skin of color (SOC), where UVR may be less important, remain inadequately explored. **Methods:** A retrospective cohort study of real-world aggregate patient data from the TriNetX global federated research network was used to identify patients with cSCC. Cohorts were created for Asian, Black/African American, White/Caucasian, and Hispanic patients with ICD-10 codes for cSCC. These cohorts were then 1:1 propensity matched with a control group of the same race/ethnicity with ICD-10 codes for benign skin lesions. Propensity matching was performed for age at cSCC diagnosis and patients' sex. The number of patients in the smokers in the cSCC group was then compared to the number of smokers in the control group. **Results:** We identified 2122 Asian subjects, 5237 Black subjects, 4256 Hispanic subjects and 227,683 White subjects with cSCC. We also identified a control cohort of each race/ethnicity with a diagnosis of benign neoplasm of the skin. After propensity matching for age at diagnosis and sex, White subjects diagnosed with cSCC were 2.3 fold more likely to have a previous history of cigarette smoking than White subjects with the control diagnosis ($P<0.001$). When looking at SOC, Black subjects were 3.3 fold ($p<0.001$), Asians 3.6 were fold ($p<0.001$), and Hispanics were 2.5 fold ($p<0.001$) more likely to have a cigarette smoking diagnosis than subjects of the same race with the control diagnosis. **Conclusions:** This study suggests that smoking is a major risk factor in for cSCC in SOC. These findings emphasize this importance of tailored preventative strategies to address disparities in tobacco smoking behaviors. Future research should seek to further elucidate the underlying socioeconomic, cultural, and healthcare access factors contributing to differences for optimization of equitable care. Research Sponsor: None.

9590 **Poster Session**

Independent validation of a 16-protein test to assess malignant potential of small uveal melanocytic tumors. First Author: David Alan Reichstein, Tennessee Retina, Nashville, TN

Background: Uveal melanocytic tumors of indeterminate malignant potential (UMTIMP) are usually managed by a "watch and wait" approach before the decision to treat. Although the aggressiveness of these lesions can be assessed by tumor-biopsy based molecular testing, serial tumor biopsies may be impractical and not always feasible for routine clinical management of UMTIMPs. In contrast, aqueous humor (AH) sampling can be safely performed as an outpatient procedure and is repeatable. AH protein biomarkers strongly associated with aggressive UM could be used as a sensitive and objective biological marker of malignant transformation, facilitating earlier tumor biopsy and treatment when clinically indicated. The purpose of this study was to validate a previously developed 16-protein algorithmic test for identification of high-risk tumor biology in AH sample. **Methods:** All study participants were clinically diagnosed with UM and had the 15-GEP, PRAME and 7-gene UM panel next-generation sequencing (NGS) test results available. AH samples (N=71) were prospectively collected at 3 independent sites under IRB approved protocols. The samples were analyzed with the Olink Target 96 Oncology II panel. The low-risk group included Class 1 and BAP1 wild type samples, and the high-risk group included Class 1 BAP1-mutant samples and all Class 2. Algorithmic analyses were performed in R and demographics analysis was performed in GraphPad Prism (version 10). **Results:** The sample distribution was representative of a typical UM patient cohort: average age was 62.4±15.1 years, tumor diameter 11.16±3.56 mm, and tumor thickness 4.85± 2.94 mm. The 15-GEP identified 48/71 of tumors as Class 1, and 23/71 tumors as Class 2. There was a significant difference in tumor diameter (P=0.003) and tumor thickness (P=0.001) between Class 1 and Class 2 patients. The proteins primarily belonged to Signal Transduction, Disease, and Cytokine Signaling pathways, based on Olink's Pathway Browser. The 16-protein test had a sensitivity of 92%, specificity 52%, NPV 92%, and PPV 51%. **Conclusions:** A novel 16-protein algorithmic test for predicting high-risk tumor biology of the uveal melanocytic lesions was independently validated in a multi-center study. This high sensitivity test would help to accurately identify high-risk melanocytic lesions based on AH sample and provide a clinically useful ancillary approach for guiding decisions for definitive tumor biopsy and treatment. Research Sponsor: None.

9591 **Poster Session**

PD-1–directed intratumoral immunotherapy for cutaneous carcinomas: Interim results from an ongoing study of INTASYL PH-762. First Author: Mary C Spellman, Panclarity LLC, San Francisco, CA

Background: Immune checkpoint-targeted antibodies directed at PD-1 or PD-L1 block co-inhibitory receptors expressed by anti-tumor T cells, breaking immune tolerance against tumor cells and generating cancer immunity. PH-762 is an INTASYL compound designed to precisely silence PD-1 mRNA. INTASYL is a patented, self-delivering RNAi technology designed to impart specific properties to small interfering RNAs. PH-762's unique structural and chemical modifications ensure an optimized cell and tissue uptake profile with intratumoral (IT) administration. Local delivery of immunotherapy minimizes systemic exposure and off-target toxicities and may decrease tumor size and improve surgical morbidity. The efficient uptake of PH-762 by human T cells, silencing of PD-1 mRNA and subsequent protein reduction has been demonstrated preclinically. Murine-targeted PH-762 (mPH-762) injections are able to silence PD-1 mRNA in T cells within the murine tumor and increase the secretion of IFN-γ. **Methods:** This open-label Phase 1 clinical study (NCT 06014086) is designed to evaluate the safety and tolerability of neoadjuvant use of IT PH-762 in cutaneous squamous cell carcinoma, melanoma, or Merkel cell carcinoma, to determine the pharmacokinetic profile of PH-762 after IT injection, to observe pathologic and immunologic tumor responses, and to determine the recommended dose for development. Escalating dose concentrations of PH-762 (from 1.14 mg/mL through 22.00 mg/mL) are tested serially in cohorts of 3 patients each. Patients receive IT PH-762 once weekly, 4 times over a 3-week period prior to surgical excision, which occurs 5 weeks after the initial injection. Tumor changes are evaluated per iRECIST criteria and pathological response. **Results:** Seven patients in two dose cohorts have received IT PH-762 (1.14 or 2.39 mg/mL). No dose-limiting toxicities or serious adverse events have been reported. Pathologic response was reported following surgical excision of the tumor (or tumor site). Of the 6 patients with SCC, 2 had complete response, 2 had partial response (1 near complete with $<$10% viable tumor), and 2 were non-responders. One patient with metastatic melanoma had no response. **Conclusions:** IT PH-762 has been well tolerated, with no evident safety signals or reported systemic or off-target toxicities, and dose escalation has resumed per protocol. Clinical and histologic evidence of tumor response is encouraging. PH-762 may decrease tumor bulk or provide a non-surgical alternative in specific circumstances, while minimizing systemic exposure and off-target toxicities. Clinical outcomes, coupled with pharmacokinetic and immunologic response data will inform continued clinical development of PH-762. Clinical trial information: 06014086. Research Sponsor: Phio Pharmaceuticals.

TPS9592 **Poster Session**

Phase I/Ib study of concurrent intravenous (IV) and intrathecal (IT) nivolumab (N) and relatlimab (R) for metastatic melanoma (MM) patients (pts) with leptomeningeal disease (LMD). First Author: Isabella Claudia Glitza, University of Texas MD Anderson Cancer Center, Houston, TX

Background: Pts with LMD face dismal prognosis, with median overall survival (OS) measured in months. We previously reported the safety and efficacy data from an open label, single arm and center phase I/IB trial for MM pts with LMD, using IT/IV N (*Nature Medicine*, Glitza et al.). 50 pts were treated. Median OS was 7.5 months and the toxicity was minimal. This approach was adopted into the NCCN guidelines, as these data suggest a subset of pts benefit from IT/IV N without high toxicity. N (anti-PD1) and R (anti-LAG3) represents a fixed- dose combination (FDC) approved by the FDA in 2022 for the treatment of unresectable MM. IV N/R has shown improved outcomes vs N in MM pts, and we identified LAG3 expression on CD8 T cells in the cerebrospinal fluid (CSF) of MM pts with LMD, in a pattern very similar to the expression of PD1. Subsequent work on C57BL/6 murine models with B16 and YUMM3 established LMD confirmed that combined treatment with IT/systemic anti-PD1/anti-LAG3 was the only treatment to significantly improve OS versus IT/systemic control treatment. We therefore added a non-randomized arm of concurrent IT/IV N/R to the previous study. Based on the prior tolerated dose of IT N 50mg, and the approved FDC ratio for IV N/R, we chose a FDC of IT N/R 50mg/16.7mg with concurrent with IV N/R at 480mg/160mg. We hypothesize that IT/IV N/R will be safe and an effective treatment for MM pts with LMD. **Methods:** This is a Phase Ib, non- randomized, single center trial of concurrent IT/IV N/R in adult ($\geq$18 years) MM pts with LMD (NCT03025256). Up to 20 pts will receive IT N/R every 28 days, and Cycle 1 (C1) will consist of IT N/R only. In subsequent cycles the IT dose will be followed by an IV dose of N/R. Most pertinent inclusion criteria are radiographic and/or CSF cytological evidence of LMD, ECOG PS of $\leq$ 2, $\leq$ 4 mg per 24 hours of dexamethasone (or the equivalent), with adequate organ function. Prior radiation and treatment with immunotherapy is allowed, as is the use of concurrent BRAF/MEK inhibitors. Primary endpoint is safety, and Bayesian toxicity monitoring rule will be used. Secondary endpoints are OS, survival rates at 3,6 and 12 months, and median duration of treatment. CSF, blood and microbiome samples will be collected at various time points. The first patient was enrolled in October 2024 and accrual of patients is ongoing (NCT03025256). Clinical trial information: NCT03025256. Research Sponsor: Bristol Myers Squibb.

TPS9593 **Poster Session**

Phase I/IIa dose finding study of triplet regimen of relatlimab (RELA), ipilimumab (IPI), and nivolumab (NIVO) in first-line therapy of metastatic melanoma (TRINITY). First Author: Elizabeth M. Burton, Department of Genomic Medicine, The University of Texas MD Anderson Cancer Center, Houston, TX

Background: NIVO (anti-PD1) alone or in combination with IPI (anti-CTLA-4) or RELA (anti-LAG3) are approved immune checkpoint blockade (ICB) agents for the treatment (tx) of patients (pts) with advanced, unresectable metastatic melanoma. Doublet combinations induce higher rates of durable disease control vs single agent, translating into nominal improvements in survival. While there is no established dose-response relationship for NIVO alone or with RELA, IPI at higher doses induces higher objective response rate (ORR) but increased grade $\geq$3 immune-related adverse events. Deeper mechanistic understanding points towards potential synergy given IPI's role in expanding the TCR repertoire and modulating suppressive T cell populations while NIVO+RELA regulate the exhaustion signatures of activated T cells and allow for improved effector function. Recently, results from RELATIVITY-048 combining all three ICB agents (NIVO 480 mg Q4W + RELA 160 mg Q4W + IPI 1 mg/kg Q8W) demonstrated impressive efficacy with high response rates (59% ORR) and seemingly improved progression free and overall survival (PFS, OS) over previously reported doublet regimens. This study evaluated a markedly lower IPI dose than the approved regimen and did not include a dose escalation component to optimize the IPI dosing strategy. Our team seeks to optimize the dose and schedule of IPI to combine with NIVO+RELA in order to determine the recommended phase II dose (RP2D) for triplet ICB and maximize clinical benefit while maintaining a toxicity profile comparable to approved regimens. **Methods:** In this single center, investigator initiated, phase I/IIa study evaluating triplet ICB (NCT06683755), all pts will receive FDA approved regimen of NIVO 480mg + RELA 160mg IV Q4W along with escalating doses of IPI . Dose escalation (DE) with IPI will begin at 0.5mg/kg Q4W 4 induction doses and will incrementally escalate up to 2mg/kg Q4W. Maintenance tx will consist of NIVO+RELA Q4W. Bayesian optimal interval (BOIN) design will be used to identify the maximum tolerated dose (MTD) and RP2D (primary objective) in the DE portion, accruing an estimated 12-18 pts. The PhIIa portion will accrue an additional 12-18 pts at the RP2D to better characterize safety, and determine the ORR, (primary objective) by RECIST 1.1. Secondary objectives include PFS, OS, and tumor and immunological correlatives obtained on pre and post tx blood and tumor samples. Pts must be previously untreated, unresectable, or advanced melanoma. Non IPI containing prior adjuvant or neo-adjuvant tx will be permitted if the last dose has been $>$6 months. Pts with asymptomatic brain metastasis are allowed, provided no immunesuppressive doses of corticosteroids are required. Safely biopsiable lesions are required for pts enrolled in the PhII portion. This study is open for accrual at MD Anderson Cancer Center in Houston, Texas. Clinical trial information: NCT06683755. Research Sponsor: BMS.

TPS9594 **Poster Session**

A multicenter, randomized, controlled, open-label, phase 2 study of the PD-1/IL-2$^{\alpha\text{-bias}}$ bispecific antibody fusion protein IBI363 in mucosal and acral melanoma. First Author: Bin Lian, Peking University Cancer Hospital & Institute, Beijing, China

Background: Although several immune checkpoint inhibitors have been approved for advanced melanoma, there remain significant unmet clinical needs, particularly for immune-cold subtypes such as mucosal and acral melanoma, which are frequently observed in Chinese patients (pts). IBI363 targets and activates tumor-specific T cells that express both PD-1 and IL-2Rα, leading to enhanced antitumor activity and reduced toxicity. Previous phase 1 studies of IBI363 reported manageable safety profiles with encouraging efficacy in advanced melanoma (2024 ASCO Annual Meeting [9562], ESMO Virtual Plenary [VP4-2024], SITC [1502]). Here, we present the trial in progress of a phase 2 study evaluating efficacy and safety of IBI363 monotherapy versus pembrolizumab in mucosal and acral melanoma. **Methods:** This multicenter, randomized, controlled, open-label, phase 2 study planned to enroll 180 pts. Main inclusion criteria are: 1) locally advanced unresectable or metastatic mucosal or acral melanoma; 2) no previous systemic treatment for melanoma; 3) at least one measurable tumor lesion (target lesions) per RECIST v1.1. Pts with active or symptomatic central nervous system metastasis are excluded. Pts are randomized in a 1:1 ratio to receive IBI363 1 mg/kg Q2W (with a priming dose of 100 μg/kg administered 7 days before the full dose) in the experimental arm or to receive pembrolizumab 200 mg Q3W in the control arm. Stratification factors include subtype (mucosal vs acral) and M staging (M0 vs M1a(0)/M1b(0) vs M1a(1)/M1b(1) or M1c/M1d, (0) indicating baseline lactate dehydrogenase [LDH] $\leq$ upper limit normal [ULN] and (1) indicating baseline LDH $>$ ULN). The primary endpoint is progression-free survival (PFS) assessed by independent radiological review committee (IRRC) per RECIST v1.1. The secondary endpoints include investigator-assessed PFS, IRRC-assessed and investigator-assessed objective response rate (ORR), disease control rate (DCR), duration of response (DoR), time to response (TTR) per RECIST v1.1, overall survival (OS), safety, pharmacokinetics (PK) and immunogenicity. No interim analysis is planned. A total of 118 PFS events among 180 pts is estimated to demonstrate the superior efficacy of IBI363 compared to the control, with a power of 90% (α=0.025, one-sided). Clinical trial information: CTR20250280. Research Sponsor: Innovent Biologics (Suzhou) Co., Ltd.

TPS9595 **Poster Session**

NivoReach: Integrated study to demonstrate similarity of JPB898 to reference nivolumab in combination with ipilimumab in patients with advanced melanoma. First Author: Piotr Rutkowski, Department of Soft Tissue/Bone Sarcoma and Melanoma, Maria Sklodowska-Curie National Research Institute of Oncology, Warsaw, Poland

Background: JPB898 is being developed as a biosimilar to reference nivolumab. Analytical and functional in vitro similarity of JPB898 to reference nivolumab has been demonstrated. NivoReach will assess the pharmacokinetic (PK) and efficacy similarity of JPB898 to reference nivolumab in patients with untreated advanced melanoma. Induction therapy with nivolumab 1 mg/kg and ipilimumab 3 mg/kg is approved for advanced melanoma, before nivolumab maintenance therapy. However, the unfavorable toxicity profile of this regimen, attributed mainly to ipilimumab, has led to investigation of alternative regimens. The Phase IIIb/IV CheckMate 511 trial compared the approved regimen with an "inverse dosing" regimen comprising nivolumab 3 mg/kg and ipilimumab 1 mg/kg. Similar response and overall survival rates were observed between the treatment groups, as well as a lower incidence of immune-related toxicities and a lower rate of discontinuation due to treatment-related adverse events with the inverse regimen versus the approved regimen (Lebbé C, et al. J Clin Oncol 2019;37:867–75). Therefore, inverse dosing is an appealing combination regimen for use in NivoReach, providing a treatment option with a more favorable risk–benefit ratio to a broader advanced melanoma patient population versus the approved regimen. Currently, the study is approved in 19 countries, including the USA and some EU member states. **Methods:** This global, randomized, double-blind, parallel-group study is recruiting participants with untreated, unresectable Stage III or metastatic Stage IV melanoma, measurable per RECIST v1.1. Participants must have an ECOG performance status ≤1. Participants will not be eligible if they have active brain metastases, ocular melanoma, or other active malignancy that is untreated or requires concomitant systemic therapy. Eligible participants will be randomized 2:1:1 to JPB898, or US-licensed or EU-authorized nivolumab, in combination with ipilimumab. Randomization will be stratified by *BRAF* V600 mutation status, PD-L1 expression status, and metastasis stage. In the 12-week induction phase, participants will receive 4 cycles of the inverse regimen (nivolumab 3 mg/kg + ipilimumab 1 mg/kg, Q3W). In the maintenance phase, participants will receive fixed-dose monotherapy (480 mg, Q4W) with JPB898 or reference nivolumab from Week 16 to 48. The co-primary PK endpoints are area under the serum concentration–time curve (AUC) after the first dose and AUC after the fourth dose in the induction phase. The primary efficacy endpoint is best overall response (complete or partial response) up to 28 weeks. Other PK, efficacy, safety, and immunogenicity endpoints will also be assessed up to 52 weeks. The planned randomized sample size is 720 participants. Clinical trial information: NCT06587451. Research Sponsor: Sandoz.

TPS9596 **Poster Session**

A randomized phase 2 peri-operative (neoadjuvant plus adjuvant) study of fianlimab (anti–LAG-3) plus cemiplimab (anti–PD-1) versus anti–PD-1 alone in patients with resectable stage III and IV melanoma. First Author: Rodabe Navroze Amaria, The University of Texas MD Anderson Cancer Center, Houston, TX

Background: Prior studies demonstrated use of neoadjuvant plus adjuvant immune checkpoint inhibitors (ICIs) improves event-free survival (EFS) compared with upfront surgery and adjuvant ICI therapy alone, supporting that peri-operative (neoadjuvant plus adjuvant) ICI therapy improves survival outcomes in patients (pts) with clinical stage III and resectable IV melanoma (Mel). Initial efforts in Mel trials to explore combined blockade by anti-programmed cell death-1 (anti–PD-1) and anti-lymphocyte activation gene 3 (anti–LAG-3) antibodies produced incrementally better efficacy than blockade of the PD-1 pathway alone. However, these efforts may not have provided optimal blockade of the two pathways. We have utilized VelocImmune technology to create potentially best-in-class, high-affinity, fully human immunoglobulin G4-blocking antibodies, fianlimab (FIAN; anti–LAG-3) and cemiplimab (CEMI; anti–PD-1). In a multicohort study (NCT03005782), FIAN + CEMI demonstrated reproducibly high clinical activity (objective response rate [ORR]: 57%; median progression-free survival: 24 months; N=98) in three independent cohorts of pts who were naïve to anti–PD-1 treatment in the advanced Mel setting, with an acceptable safety profile. Thus, the combination of FIAN + CEMI warrants an investigation as a peri-operative regimen in resectable, clinically detectable, high-risk, stage III and IV cutaneous Mel. **Methods:** This is a randomized Phase 2 peri-operative study (NCT06190951) in pts with clinical stage III/IV Mel with resectable disease. Pts will receive 3 cycles of neoadjuvant therapy followed by complete surgical resection, and continue with an optional 15 cycles of adjuvant therapy, based on pathological response. The primary objective is to compare the effect of FIAN + CEMI versus CEMI alone as measured by the pathological complete response (pCR) rate. Approximately 150 pts will be randomized 1:1:1 to three arms (intravenously once every 3 weeks): Arm A, CEMI 350 mg + placebo; Arm B, High Dose FIAN + CEMI 350 mg; Arm C, Low Dose FIAN + CEMI 350 mg. Pts will be stratified based on tumor, node, metastasis (TNM) stage and geographical region. Key inclusion criteria: age ≥18 years; resectable clinical stage III/IV histologically confirmed Mel; pts with stage III Mel must have clinically detectable disease; Eastern Cooperative Oncology Group performance status 0 or 1; adequate bone marrow, hepatic, and kidney function. The primary endpoint is pCR rate by blinded independent pathological review performed centrally. The secondary endpoints are pCR rate (by local assessment), major pathological response (by local and central review), EFS, overall survival, distant metastasis-free survival, relapse-free survival, ORR, safety, pharmacokinetics, immunogenicity, and patient-reported outcomes. Clinical trial information: NCT06190951. Research Sponsor: Regeneron Pharmaceuticals, Inc.; NA.

TPS9597 **Poster Session**

A randomized, phase 2/3 clinical trial investigating RP2 plus nivolumab vs ipilimumab plus nivolumab in immune checkpoint inhibitor-naïve patients with metastatic uveal melanoma. First Author: Joseph J Sacco, The Clatterbridge Cancer Centre and University of Liverpool, Wirral and Liverpool, United Kingdom

Background: Uveal melanoma (UM) is the most common primary intraocular malignancy, accounting for nearly 90% of ocular melanomas and up to 5% of melanomas overall. Approximately 50% of patients (pts) with UM will develop metastatic disease, with the liver being the most common site of metastases (~90%). The prognosis for pts with metastatic UM (mUM) is poor, with a median overall survival (OS) of approximately 1 year. Effective treatment options for mUM are limited as it responds poorly to single-agent immune checkpoint inhibitors (ICIs; <10% response rate). Response rates are slightly higher with combination therapies (12%–18%), but often at the expense of increased toxicity. Tebentafusp is FDA approved for mUM based on survival benefit; however, its use is restricted to pts who are HLA-A*02:01 positive, and only ~10% of pts achieve an objective response. RP2 is a selectively replication-competent herpes simplex virus type 1–based oncolytic immunotherapy expressing GM-CSF, a fusogenic glycoprotein (GALV-GP-R–), and an anti–CTLA-4 antibody-like molecule. Prior phase 1 preliminary clinical data of RP2 as monotherapy or in combination with nivolumab (nivo) demonstrated a promising safety profile and anti-tumor activity with an ORR of 29.4% in 17 patients with mUM, most of whom had received prior ICIs. This study will assess the efficacy and safety of RP2 + nivo vs ipilimumab (ipi) + nivo in pts with ICI-naïve mUM (NCT06581406; RP2-202). **Methods:** This is a randomized, controlled, phase 2/3 study. Key eligibility criteria include age ≥18 years and confirmed unresectable mUM with lesions amenable to injection. Pts with metastatic disease who have had prior exposure to ICIs since the time of UM diagnosis, involvement of >33.3% of the liver, or a history of prior liver- or lesion-directed therapy are not eligible for enrollment. Enrolled pts (N = ~280) will be randomized 1:1 to receive either RP2 + nivo or ipi + nivo. In the RP2 + nivo arm, RP2 will be given intratumorally initially at 1 x 10^6 PFU/mL, then every 2 weeks (Q2W) at 1 x 10^7 PFU/mL for 7 doses in combination with intravenous (IV) nivo (240 mg). In the ipi + nivo arm, pts will receive IV ipi (3 mg/kg) and IV nivo (1 mg/kg) Q3W for 4 doses. Pts in both arms may then receive IV nivo at 240 mg Q2W or 480 mg Q4W for up to 2 years from the first dose. The co-primary endpoints are OS and progression-free survival by independent central review using RECIST 1.1. Secondary endpoints are overall response rate, duration of response, disease control rate, clinical benefit rate, duration of clinical benefit, and safety, including incidence of treatment-emergent adverse events (AEs), serious AEs, and immune-mediated AEs. Clinical trial information: NCT06581406. Research Sponsor: Replimune, Inc.

TPS9598 **Poster Session**

The MATRiX trial: A multicenter, randomized, phase II study of ATR inhibition (via tuvusertib) with or without avelumab in patients with advanced anti-PD-(L)1–refractory Merkel cell carcinoma. First Author: Rashmi Bhakuni, University of Washington Medicine Dermatology, Seattle, WA

Background: Merkel cell carcinoma (MCC) is a rare neuroendocrine skin cancer driven by UV mutations or the Merkel cell polyomavirus (MCPyV).It is aggressive, with a high Ki-67 proliferative index.Despite an initial high response rate (~55%) to PD-1 pathway inhibitors, >50% of patients exhibit primary or acquired resistance.ATR (ataxia telangiectasia and Rad3-related) kinase, a critical cell cycle checkpoint regulator, ensures genome fidelity in cancer cells experiencing high replication stress, including MCC.Our preclinical findings suggest anticancer activity of ATR inhibition via transcriptional induction of NF-κB-associated proinflammatory mechanisms.The potent, selective, orally administered ATR inhibitor tuvusertib (M1774) has shown antitumor activity in patients with unresectable solid cancers in Phase I trials, with a recommended Phase II dose of 180 mg daily on an intermittent schedule.We hypothesize that tuvusertib ± anti-PD-(L)1,may induce tumor regression in advanced anti-PD-(L)1-refractory MCC. **Methods:** The multicenter, randomized Phase II MATRiX trial tests the safety and efficacy of tuvusertib monotherapy (Arm 1) and tuvusertib plus avelumab (Arm 2) in patients with metastatic MCC refractory to PD-(L)1 blockade. Patients with progressive disease per Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 within 120 days of their last anti-PD-(L)1 therapy are eligible. Subjects randomized to Arm 1 receive tuvusertib 180 mg QD on days 1-14 of each 21-day cycle. Subjects in Arm 2 also receive avelumab 1600 mg IV on day 1 of each 21-day cycle. Imaging studies performed 9 weeks after treatment initiation and every 12 weeks thereafter will be assessed per RECIST v1.1. Patients in Arm 1 with progressive disease may receive tuvusertib + avelumab. Treatment-emergent adverse events are graded per Common Terminology Criteria for Adverse Events version 5.0. The primary endpoint is progression-free survival (PFS). Between June 2024 and January 2025, 13 subjects were enrolled across 10 centers. With a targeted enrollment of 50 patients, this trial has 83% power to observe a statistically significant (one-sided level of 10%) difference in PFS if the true hazard ratio for failure is 2.0. A stratified (primary vs. acquired resistance) log-rank test will be used, and binary outcomes will be compared using a Mantel-Haenzel test. A Wieand-like futility rule will be used for an interim analysis after the 23rd event occurs. Tumor biopsies, blood, and stool specimens will be profiled to gain integrated insight into transcriptomic, proteomic, and metabolic signatures associated with immune-mediated therapeutic outcomes. This orthogonal approach to solid tumor immunotherapy, relevant to analogous cancers, will guide future combination strategies to better harness the anti-tumor immune response. Clinical trial information: NCT05947500. Research Sponsor: NCI Cancer Therapy Evaluation Program-Experimental Therapeutics Clinical Trials Network; P30CA015704.

TPS9599 **Poster Session**

A randomized, controlled, multicenter, phase 3 study of vusolimogene oderparepvec combined with nivolumab vs treatment of physician's choice in patients with advanced melanoma that has progressed on anti–PD-1 and anti–CTLA-4 therapy (IGNYTE-3). First Author: Jason J. Luke, UPMC Hillman Cancer Center and University of Pittsburgh, Pittsburgh, PA

Background: Melanoma is the fifth most common cancer, with ~100,000 new cases and ~8000 related deaths estimated in the US for 2024. First-line systemic treatment with immune checkpoint inhibitors improves the objective response rate (ORR) and extends progression-free survival (PFS) and overall survival (OS) for patients with advanced disease. Among available treatments, combination anti–PD-1 (nivolumab) + anti–CTLA-4 (ipilimumab) therapy is associated with the highest ORR and best PFS and OS. However, only ~50% of patients respond to treatment, and limited options exist for patients whose melanoma progresses following anti–PD-1–based therapy. Vusolimogene oderparepvec (VO; also known as RP1) is a selectively replication-competent herpes simplex virus type 1–based oncolytic immunotherapy that expresses human granulocyte-macrophage colony-stimulating factor and a fusogenic glycoprotein (GALV-GP-R–). Data from a registration-intended cohort of the IGNYTE study (NCT03767348) showed that intratumoral VO + intravenous nivolumab was well tolerated and demonstrated durable, clinically meaningful antitumor activity (ORR, 32.9% per independent central review using Response Evaluation Criteria in Solid Tumors 1.1) in patients with advanced melanoma and confirmed progression on prior anti–PD-1 therapy. IGNYTE-3 will evaluate the OS and clinical benefit of VO + nivolumab for patients with advanced cutaneous melanoma whose disease has progressed after anti–PD-1 and anti–CTLA-4 therapy (or who are ineligible for anti–CTLA-4 therapy) vs physician's choice. **Methods:** IGNYTE-3 (NCT06264180) is a global, randomized, controlled, multicenter, phase 3 trial (currently recruiting). Key eligibility criteria include age ≥12 years; stage IIIb–IV/M1a–M1d cutaneous melanoma; disease progression on ≥8 weeks of an anti–PD-1 and anti–CTLA-4 treatment (administered in combination or in sequence, with anti–PD-1 last); ≥1 measurable and injectable tumor (≥1 cm); and adequate hematologic, hepatic, and renal function. Patients who are not candidates for anti–CTLA-4 therapy may enroll following progression on anti–PD-1 therapy alone. Patients with BRAF V600-mutant melanoma must have received anti-BRAF ± anti-MEK targeted therapy prior to enrollment. Patients (N = ~400) will receive VO + nivolumab or physician's choice (nivolumab + relatlimab, anti–PD-1 monotherapy rechallenge [nivolumab or pembrolizumab], or single-agent chemotherapy [dacarbazine, temozolomide, or paclitaxel/albumin-bound paclitaxel]). The primary endpoint of the study is OS; the key secondary endpoints are PFS and ORR per RECIST 1.1. Clinical trial information: NCT06264180. Research Sponsor: Replimune, Inc.

TPS9600 **Poster Session**

A phase 1, open-label, dose expansion cohort of the tolerability of tolododekin alfa (ANK-101) in combination with cemiplimab in cutaneous squamous cell carcinoma. First Author: Jong Chul Park, Massachusetts General Hospital, Boston, MA

Background: IL-12 stimulates innate and adaptive tumor immunity. Tolododekin alfa (ANK-101) is an anchored drug conjugate that creates a strong link between full-length IL-12 and aluminum hydroxide through an alum-binding protein (ABP) which localizes IL-12 to the tumor microenvironment (TME), resulting in sustained drug release, prolonged antitumor immune activation, increased PD-L1 expression, and minimal systemic adverse events. Cemiplimab is an anti-PD-1 monoclonal antibody approved in several countries worldwide for the treatment of metastatic or locally advanced cutaneous squamous cell carcinoma (CSCC) who are not candidates for curative surgery or radiation. This phase 1 clinical trial is designed to combine tolododekin alfa and cemiplimab to determine tolerability and initial biologic and clinical activity. **Methods:** This is an open-label study to evaluate locally administered tolododekin alfa and cemiplimab in patients with advanced CSCC who progressed on, are refractory to, or intolerant of prior SOC treatment. The combination cohort will consist of 15 participants. Participants will be treated with tolododekin alfa in combination with cemiplimab. Treatment will consist of up to eight cycles of tolododekin alfa in combination with cemiplimab followed by cemiplimab alone for up to one year. Follow-up imaging assessments will be performed every 12 weeks. Eligible participants must have histologically confirmed high-risk locally advanced or metastatic CSCC not amenable to surgical management, accessible tumors for injection and biopsy, and measurable disease by RECIST v1.1. Key exclusion criteria include tumors close to vital structures, uncontrolled bleeding disorders, and prior ≥ Grade 3 immune-mediated adverse events (imAEs) following treatment with an agent that blocks the PD-1/ PD-L1 pathway. Primary objectives include safety and tolerability of tolododekin alfa and cemiplimab. Secondary objectives include immunogenicity (ADA), and preliminary clinical activity measured by ORR, DCR, DOR, and PFS by RECIST v1.1. Exploratory objectives include QOL using FACT-G and immune pharmacodynamic (PD) changes. This clinical trial is in progress. Clinical trial information: NCT06171750. Research Sponsor: Ankyra Therapeutics.

TPS9601 **Poster Session**

The TIME trial: Phase II randomized controlled trial of time-of-day–specified immunotherapy for advanced melanoma. First Author: Zachary Buchwald, Department of Radiation Oncology, Winship Cancer Institute of Emory University, Atlanta, GA

Background: Ipilimumab + nivolumab is standard of care for advanced melanoma patients based on data from the CheckMate 067 trial. The recent 10-year outcomes results were reported with a melanoma specific survival of 52%. While data are very encouraging, 50% of patients still succumb to their disease by 10-years. Preclinical data suggests that the circadian rhythm may influence the anatomic localization, function and activity of T cells, the target of immunotherapy. More T cells in the tumor or tumor-draining lymph node during initial immunotherapy administration may improve clinical responses and long-term outcomes. To investigate this idea, we performed a retrospective analysis, the MEMOIR study, finding that more evening infusions of immunotherapy were associated with significantly worse progression free and overall survival for metastatic melanoma patients. These findings have now been reproduced in other cancer types, in a large meta-analysis, and in pre-clinical mechanistic studies. In light of these data, we hypothesize that patients receiving morning or midday infusions of immunotherapy will have better outcomes than patients receiving infusions in the evening. **Methods:** The TIME trial is a three-arm phase II study of time-of-day specified administration of standard dose ipilimumab + nivolumab for metastatic melanoma. Newly diagnosed unresectable metastatic melanoma patients will be randomized to receive 4 cycles of ipilimumab + nivolumab every 3 weeks between either 8:00-11:00 (Arm A), 11:00-14:00 (Arm B), or 14:00-17:00 (Arm C). Following these 4 cycles, they will receive standard of care maintenance nivolumab in a time-of-day agnostic fashion. Eligible adult patients must have Stage III-IV unresectable cutaneous, acral or mucosal melanoma, no prior immunotherapy within 1 year, ECOG performance status of 0-1, and only asymptomatic brain metastases less than 2 cm. The primary objective is to determine whether progression free survival for Arm A or Arm B is superior to Arm C. Secondary objectives include assessments of adverse events, melanoma specific survival and overall survival. We also plan to evaluate the immune profiles of blood and tumor, when available, to assess the impact of time-of-day administered ipilimumab + nivolumab on the circulating immune responses and the tumor immune microenvironment. A sample size of 99 patients (33 in each arm) was selected for at least 80% power to detect a HR of 0.50 with a Type 1 error rate of 0.1 (2-sided) for a comparison of A vs. C and B vs. C. Research Sponsor: None.

TPS9602 **Poster Session**

Phase I dose escalation and expansion study of PRAME T-cell receptor (TCR) engineered IL15-transduced cord blood–derived natural killer (NK) cells in patients with recurrent and/or refractory melanoma (PRAMETIME-Mel). First Author: Derrick Law Tao, The University of Texas MD Anderson Cancer Center, Houston, TX

Background: For patients with relapsed and/or refractory metastatic melanoma (RRFM), there is a critical need to test novel strategies with improved anti-tumor response and safety profile. Adoptive cell therapy (ACT) has been recognized as a promising avenue for addressing the unmet need for more potent anti-tumor approaches. Allogeneic cord blood (CB)-derived natural killer (NK) cell therapies have emerged as a therapeutic alternative to adoptive T-cell therapies given decreased toxicity and feasibility as an "off-the-shelf" therapy, bypassing the manufacturing time and treatment delays associated with autologous T-cell products. PRAME (PReferentially expressed Antigen in MElanoma), a cancer-testis antigen expressed on approximately 95% of cutaneous melanomas and not expressed outside of immune-privileged sites such as the testis, ovary, placenta, and endometrium, is a promising target for allogeneic NK cells engineered with a T cell receptor (TCR) to selectively target melanoma cells. In contrast to autologous T cell therapies that require exogenous systemic IL-2 as a supportive factor, NK cells engineered to express IL-15 have been observed to have minimal side effects while significantly enhancing the in vivo expansion and persistence of the transduced NK cells. PRAME TCR/IL-15 NK, an engineered TCR NK cell therapy, has demonstrated efficacy against melanoma cell lines in vitro and in vivo and safety against normal human cell lines. Building upon these preclinical findings, we propose this trial to explore the safety and efficacy of PRAME TCR/IL-15 NK cells in patients with RRFM. **Methods:** This phase I, single-center, open-label trial will assess the safety, tolerability, and efficacy of PRAME TCR/IL-15 cells in patients with HLA A*02:01 positive RRFM, with no prospective PRAME testing. The primary endpoints are to determine the safety, tolerability, maximum tolerated dose and recommended phase II dose. The secondary endpoints are to assess response and survival. The study will be comprised of dose escalation (4 dose levels, with a dose level -1 in case of excessive toxicities observed in dose level 1) and dose expansion. A maximum of 39 patients will be enrolled, including 24 patients in the dose escalation cohort and up to 15 patients in the dose expansion cohort. Enrolled patients will receive lymphodepletion chemotherapy (fludarabine 30 mg/m^2 and cyclophosphamide 500 mg/m^2) on days -6 to -3, followed by a single dose of PRAME TCR/IL-15 NK cells on day 0. Longitudinal blood and tissue samples will be collected for correlative immune analysis. Clinical trial information: NCT06660420. Research Sponsor: None.

TPS9603 **Poster Session**

Multicenter, randomized, double-blinded, placebo-controlled trial of IFx-Hu2.0 (IFx) as adjunctive therapy with pembrolizumab (pembro) in checkpoint inhibitor (CPI)-naïve patients with advanced or metastatic Merkel cell carcinoma (MCC). First Author: Andrew Scott Brohl, H. Lee Moffitt Cancer Center and Research Institute, Tampa, FL

Background: CPIs have revolutionized the treatment of a wide variety of cancers. Despite their success, the majority of cancers do not respond primarily due to tumor-intrinsic mechanisms allowing immune evasion, and obviating activation of tumor specific cytotoxic T cells (cTc), which are required for CPIs to work. Activation of tumor-specific cTc is thus the goal for most therapies aiming to overcome primary resistance to CPIs. IFx is an innate immune agonist designed to overcome primary resistance to CPIs. It consists of a plasmid DNA, pAc/emm55, encoding for an immunogenic gram+ bacterial protein streptococcal Emm55, combined with a cationic polymer that facilitates cellular uptake of DNA. Intralesional injection of IFx results in Emm55 expression on the surface of tumor cells. Pathogen-associated molecular patterns on gram+ bacteria are recognized by toll-like receptors (TLRs) on innate immune cells. TLRs with CD14 as a co-receptor binds to these bacterial proteins, activating an innate immune response against the tumor cell and the expressed bacterial protein. This causes non-self tumor neoantigen presentation to naïve B and T cells, resulting in activation of tumor specific cTc and antibodies. Unlike oncolytic viral approaches which rely on tumor lysis and distribution of tumor neoantigens into the tumor microenvironment, IFx causes phagocytosis of intact tumor cells and may provide more comprehensive and efficient antigen presentation, promoting inter-antigenic epitope spreading. In a Phase 1b trial among 23 patients with MCC or cutaneous squamous cell carcinoma (cSCC) that failed to respond to anti-PD(L)-1 therapy, intralesional IFx was well tolerated at weekly injections x3 dosing regimen. Post-protocol rechallenge with CPI resulted in 7 of 11 (63%) patients with MCC experiencing durable (median 19 mos.) complete or partial responses, despite prior failure of the same class of CPI. Based on these results, a randomized, double-blind, placebo-controlled trial to evaluate the potential for adjunctive IFx and pembro to improve response rates in the first-line treatment of CPI naïve patients with advanced or metastatic MCC is planned. **Methods:** 118 CPI naive adults with MCC will be assigned via 1:1 randomization to IFx (0.1mg) or placebo given weekly x3 concurrent with pembro 200 mg IV q3w for up to 2 years, or progression or toxicity. Responses assessed by blinded independent central review per RECIST v1.1 q12w during the first 24 months and q24w thereafter up to 5 years. Adverse events (AEs) will be assessed per CTCAE v5.0 up to 90 days after final treatment. Primary and key secondary endpoints include objective response rate and progression-free survival respectively. Other secondary endpoints are safety, duration of response, and overall survival. Clinical trial information: Pending as of submission deadline. Research Sponsor: TuHURA Biosciences, Inc.

TPS9604 **Poster Session**

TeLuRide-006: An adaptive phase 2/3 study of EIK1001, a Toll-like receptor 7/8 (TLR7/8) agonist, in combination with pembrolizumab in patients with advanced melanoma. First Author: Jason J. Luke, UPMC Hillman Cancer Center, Pittsburgh, PA

Background: Immune checkpoint inhibitors (ICIs) relieve immunosuppression of tumor-reactive T cells and enhance antitumor response. Significant advances for the treatment of advanced melanoma have been made using ICIs, with overall survival (OS) benefit conferred by ICI monotherapy. While encouraging results have been observed with combinations of ICIs, no α-controlled, statistically significant OS benefit of combinations over monotherapy has been demonstrated in Phase 3 studies. Despite these advances, 5-year survival for advanced disease is only 15 to 20%, motivating development of new therapies. EIK1001 is a TLR7/8 agonist that stimulates myeloid and plasmacytoid dendritic cells, activating immune and inflammatory responses. This dual activity, distinct from effects on checkpoint proteins, enhances antitumor T-cell activity alone or in combination with ICIs. **Methods:** TeLuRide-006 (NCT#06697301) is a global, multicenter, randomized, double-blind, adaptive Phase 2/3 study of EIK1001 or placebo in combination with pembrolizumab (pembro) as first-line therapy in participants (pts) with advanced melanoma. This study includes dose-optimization (DO), in which pts are randomized 1:1:1 to receive 1 of 2 doses of EIK1001 or placebo in combination with pembro, followed by adaptive Phase 2/3 expansion at the Selected Dose of EIK1001 + pembro or placebo + pembro. Interim analyses will determine whether the study advances from DO to Phase 2 to Phase 3. EIK1001 or placebo is administered intravenously QW until the end of Week 27 then Q3W. Pts are stratified by prior anti-PD-1 adjuvant therapy, LDH level, and BRAF mutational status. Key eligibility criteria: pts $\geq$ 18 years of age with a life expectancy of $\geq$ 3 months, Stage 3 (unresectable) or Stage 4 metastatic melanoma, known BRAF V600 mutational status (or consent to BRAF mutation testing), $\geq$ 1 measurable lesion by RECIST v1.1, and no history of or current pneumonitis/interstitial lung disease. Primary objectives are to evaluate the efficacy and safety of 2 doses of EIK1001 in combination with pembro (DO only) and to compare progression-free survival per RECIST 1.1 by blinded independent central review (BICR) and OS of pts receiving EIK1001 + pembro relative to pts receiving placebo + pembro (at Selected Dose). Secondary objectives include evaluation of the safety and tolerability of the Selected Dose of EIK1001 + pembro relative to placebo + pembro, as well as evaluation of objective response rate and duration of response per RECIST 1.1 by BICR. Exploratory objectives include evaluation of time to objective response, evaluation of potential EIK1001 exposure-response relationships, and evaluation of health-related quality of life, health utilities, and melanoma concerns in pts receiving EIK1001 + pembro relative to placebo + pembro. This study opened on 24 December 2024. Clinical trial information: 06697301. Research Sponsor: None.

TPS9605 **Poster Session**

A phase II study of binimetinib plus imatinib in patients with unresectable KIT-mutant melanoma. First Author: Katy K. Tsai, Helen Diller Family Comprehensive Cancer Center, University of California, San Francisco, San Francisco, CA

Background: Patients (pts) with melanoma refractory to immune checkpoint inhibition (ICI) remain in need of rational therapeutic options. Pts with rare melanoma subtypes (acral, mucosal) are in particular need given lower objective response rates (ORR) to ICI, and lower incidence of BRAF V600-mutant disease. Such BRAF mutations are found in only 5-10% of acral/mucosal melanomas, while KIT mutations/amplifications are found in 10-20%. Even when present, a KIT alteration does not guarantee response to KIT inhibition, with only one-third responding as shown in previous phase II studies. A significant number of KIT-mutant melanomas have been shown to demonstrate NF1 or SPRED1 loss, with recent preclinical work showing these alterations to be associated with loss of negative suppression of RAS, resulting in RAS activation and MEK dependence. We hypothesize that NF1 or SPRED1 loss cooperates with KIT mutations to drive melanomagenesis and resistance to KIT inhibition, and propose to target this vulnerability with a combination targeted therapy approach. This phase II study will be the first to evaluate the efficacy and safety of binimetinib plus imatinib in pts with KIT-mutant melanoma. **Methods:** This is a multicenter, investigator-initiated phase II study of binimetinib in combination with imatinib in pts with KIT-mutant unresectable melanoma who have progressed on or who are ineligible for ICI. Pts will be $\geq$18 yo with performance status ECOG 0-2, and have unresectable Stage IIIB/C/D or Stage IV melanoma that is KIT-mutant by CLIA-certified testing platform. Pts will have progressed on prior ICI or other standard-of-care (SOC) therapies, or be ineligible for/unable to tolerate SOC therapies. Pts with brain metastasis will be eligible if clinically stable with no need for CNS-specific treatment required prior to study start. Pts previously treated with a MEK inhibitor will be excluded. A Simon 2-stage Minimax design will be used; the null hypothesis that the true response rate is 0.1 will be tested against a one-sided alternative. 15 pts will be accrued in the Stage 1. If there are $<$1 responses, the study will be stopped. Otherwise, 10 additional pts will be accrued in Stage 2 for a total of 25. The null hypothesis that the true response rate is 0.1 will be rejected if $\geq$6 responses are observed. This yields a type I error rate of 0.05 and power of 0.8017 when the true response rate is 0.3. Primary endpoint: ORR (RECIST). Secondary endpoints: duration of response, progression-free survival, overall survival, clinical benefit rate (CR, PR, or SD $\geq$16 weeks), safety profile (CTCAE). Exploratory objectives include investigation of association between clinical response and baseline NF1 and SPRED1 status, and pathologic correlates of acquired resistance. 11 pts have been screened; 8 of planned 15 pts in Stage 1 have been enrolled. Enrollment is ongoing at UCSF and UCSD. Clinical trial information: NCT04598009. Research Sponsor: None.

TPS9606 **Poster Session**

Neoadjuvant cemiplimab in cutaneous basal cell carcinoma of the head and neck. First Author: Eric Mastrolonardo, Department of Otolaryngology Head & Neck Surgery, Thomas Jefferson University, Philadelphia, PA

Background: Surgical resection of locally advanced basal cell carcinoma of the head and neck (laBCCHN) is often not feasible due to tumor size and proximity to vital structures with risk of significant deformity. Prior data suggest that neoadjuvant therapy could have a major impact on preserving critical structures, especially in the head and neck. The PD-1 inhibitor cemiplimab (REGN2810) has shown significant response rates for metastatic BCC after progression or intolerance of Hedgehog inhibitor (HHI) therapy. However, cemiplimab has not been investigated in the neoadjuvant setting for laBCCHN. To address this gap, this multi-center phase II study seeks to assess the response to neoadjuvant cemiplimab in the treatment of HHI-naïve laBCCHN. **Methods:** Patients with HHI-naive laBCCHN will receive response-adaptive, neoadjuvant IV cemiplimab 350mg every 3 weeks for an initial 2 cycles. The primary endpoint is the fraction of patients demonstrating clinical response after 2 cycles. All patients will undergo RECIST v1.1 response assessment by CT or MRI, and if not radiographically measurable, caliper measurement will be utilized to evaluate the primary endpoint. Those with RECIST v1.1 progression or stable disease with $>$5% growth will be considered non-responders and will proceed with surgery or other standard of care (e.g. HHI). Patients with stable disease (+5% to -20%) and RECIST v1.1 response will be considered responders and will continue to additional cycles of therapy and clinical assessment (imaging every 2 cycles, total cycles = 6). Patients with complete clinical response prior to completing 6 cycles may proceed to surgery for resection or biopsy of tumor site. Secondary endpoints include rate of functional organ preservation, pathologic response, safety, and quality of life. Correlative analyses will be performed on pre- and post-cemiplimab tumor specimens and peripheral blood samples to assess treatment-related changes in the immune microenvironment related to functional changes in immune cell composition. This study is open with 22 patients enrolled at the time of submission, with a planned total enrollment of 35 patients. Clinical trial information: NCT05929664. Research Sponsor: Regeneron Inc.

TPS9607 **Poster Session**

A phase 1/2 study of vusolimogene oderparepvec (RP1) in primary melanoma (mel) to reduce the risk of sentinel lymph node (SLN) metastasis. First Author: Urvashi Mitbander Joshi, UPMC Hillman Cancer Center, Pittsburgh, PA

Background: The majority of 100,000 annual new U.S. cases of mel consist of localized early-stage disease that undergo wide local excision (WLE) +/- SLN biopsy (SLNB). The tumor draining lymph node is the initial site of immune response including formation of tumor mediated immune suppression and pre-metastatic niches. SLN positivity is a key prognostic factor in early stage mel. Thus, the SLN is a target for local immune intervention to boost the antitumor response. Vusolimogene oderparepvec (RP1) is an intratumorally administered oncolytic immunotherapy with unique potential for neoadjuvant therapeutic application. RP1 is constructed from a high potency HSV1 strain (RH018A) modified to replicate selectively in tumors (deletion of neurovirulence factors ICP34.5 and ICP47). RP1 encodes GM-CSF and a fusogenic GALV-GP R- protein to maximize oncolytic potency and induce immunogenic cell death. Preclinical and clinical data demonstrate robust antitumor efficacy (including non-injected lesions) of RP1 alone and in combination with checkpoint inhibitors in advanced mel. This trial addresses a crucial gap in understanding the impact of RP1 on SLN dynamics and preventing disease recurrence in high-risk patients (pts). We hypothesize that in pts with high risk, clinically node negative mel (pT3b-T4b), RP1 will reduce rates of SLN positivity as compared to a historic control by favorably reshaping the immune landscape of the primary tumor, SLN, and the peripheral blood. **Methods:** This is an investigator-initiated, single arm phase 1/2 trial (NCT06216938) designed to assess efficacy and safety of neoadjuvant RP1 in high-risk, clinically node-negative, non-uveal mel. Eligibility criteria: pT3b, T4a, or T4b non-uveal mel with visible residual tumor or positive biopsy margins, ECOG $\leq$1, and no prior oncolytic virus therapy. Pts receive 3 doses of neo-adjuvant RP1 (10e6 PFU day 1, 10e7 PFU on days 15 and 21), injected at the primary tumor site followed by standard WLE and SLNB within 35 days of dose 1. Biopsy of residual tumor or archival tumor tissue is obtained pre-RP1 and archival tissue from WLE and SLNB is obtained post-RP1. Blood samples are obtained with each RP1 dose and 3 months post-therapy. Pts are followed for 3 years. Primary endpoint: rate of SLN positivity in the overall cohort. Secondary endpoints: treatment related adverse events (per CTCAE), recurrence free survival, and overall survival. Exploratory endpoints: immunophenotype and microenvironment of the primary tumor, SLN and peripheral blood pre- and post-RP1 (via IHC, IF, and flow cytometry). The observed rate of SLN positivity will be compared to the predicted rate (Melanoma Institute of Australia Prediction Tool for SLN metastatic risk) with a one-sided, one-sample proportion test. Kaplan-Meier estimates will be provided for survival endpoints. The trial is active with 13 of 25 pts enrolled in January 2025. Clinical trial information: NCT06216938. Research Sponsor: Replimune.

TPS9608 **Poster Session**

Lymph node excision (LNEx) for patients with stage III melanoma with one clinically positive node: Excision of Lymph Node trial (EXCILYNT). First Author: Craig L. Slingluff Jr., University of Virginia, Charlottesville, VA

Background: When melanoma metastases are detected clinically in regional lymph nodes (cLNs) without distant metastasis, standard surgical management is therapeutic lymph node dissection (TLND), which can cause lifelong lymphedema, delay return of function, and reduce quality of life (QOL). Among patients with cLN, 40-50% have metastasis confined to just 1 LN. The goal of this trial is to test a limited lymph node excision (LNEx) for patients with 1 cLN. In a multicenter retrospective analysis of 21 patients treated with LNEx rather than TLND, only 1 (4.8%) developed a LN recurrence in the same node basin, prior to distant disease (same node basin-only recurrence: sNBoR) over ~3 years. Also, only 1 (4.8%) developed lymphedema. To provide more precise estimates of sNBoR and lymphedema rates in a prospective study, and to collect data on HRQOL and return to normal activity after surgery, the EXCILyNT trial was initiated in 2024. The primary hypothesis is that LNEx will provide regional control, with sNBoR of $\leq$5% at 3 years. The secondary hypothesis is that LNEx will induce lymphedema in $\leq$6% at 3 years. Exploratory objectives are to assess overall morbidity and HRQOL, to identify features of tumors that may most accurately identify patients with only 1 pathologic LN, and to estimate overall DFS, MSS, and overall survival rates. **Methods:** EXCILyNT is a multicenter, phase II clinical trial for patients with 1 cLN, enrolled on either of two cohorts. All are treated surgically with LNEx: those undergoing surgery first (cohort 1) and those treated with neoadjuvant systemic therapy prior to LNEx (cohort 2). Participants on cohort 2 may receive standard of care neoadjuvant therapy or may be concurrently enrolled in a clinical trial of neoadjuvant therapy, as long as that trial does not mandate TLND. Major eligibility criteria: informed consent, age $\geq$18 years, ECOG PS 0-2, confirmed metastatic melanoma to only 1 cLN in the axilla, groin, or iliac basin; able to undergo LNEx. The following are excluded: prior LND or radiation therapy of the cLN basin; in-transit or satellite metastases within 1 year; distant metastasis; pre-existing lymphedema that precludes assessment of lymphedema; systemic or intratumoral therapy within 3 months of enrollment. Correlative studies include: evaluation of tumor-involved nodes for immune infiltrates, tumor cell proliferation rates, and somatic mutations; serum collection for cell-free tumor DNA; Health-related quality of life (HRQOL) surveys, FACT-M and Work Productivity and Activity (WPAI) Questionnaire: General health (WPAI:GH) V2.0. The target sample size of 60 eligible participants is chosen to estimate the 3-year rate of sNBoR with an upper CI precision of 7.5% (upper CI limit of 12.5%) using a one-sided Clopper-Pearson exact test. Enrollment is planned to include 7 centers. Thus far, 12 of planned 60 patients have been enrolled at the first 2 centers. Clinical trial information: NCT05839912. Research Sponsor: Philanthropy.

TPS9609 **Poster Session**

NEOSENT: Neoadjuvant anti-PD-1 therapy for patients with high-risk clinical stage II melanoma with a scheduled sentinel lymph node biopsy. First Author: Milton Jose De Barros E Silva, A.C. Camargo Cancer Center, São Paulo, Brazil

Background: High-risk clinical stage II melanoma patients are already indicated for adjuvant anti-PD-1 therapy, regardless of the sentinel lymph node biopsy (SLNB) result, due to the high risk of relapse associated with pathological stages IIB/IIC or IIIC. Additionally, sentinel lymph node biopsy (SLNB) has no therapeutic effect, although studies have highlighted its prognostic value. Recent data also emphasize that delays in initiating adjuvant anti-PD-1 therapy are linked to poorer relapse-free survival rates. This study aims to investigate whether the early initiation of adjuvant anti-PD-1 therapy, or neoadjuvant anti-PD-1 therapy (for cases where sentinel node biopsy is subsequently classified as positive), is associated with improved outcomes. **Methods:** NEOSENT is a prospective cohort study with a historical control (quasi-experimental study). The inclusion criteria for the prospective cohort are as follows: high-risk clinical stage II melanoma (IIB/IIC) after excisional biopsy with negative margins, age over 18 years, absence of significant concomitant diseases, indication for sentinel lymph node biopsy (SLNB), and access to anti-PD1 treatment. Patients will undergo wide excision margins (WEM) and SLNB, scheduled for week 5 after initiating anti-PD1 therapy. A total of 1 year of anti-PD1 treatment is planned, consisting of either pembrolizumab (200 mg IV every 3 weeks for 18 cycles) or nivolumab (480 mg IV every 4 weeks). The protocol was reviewed and approved by the Institutional Review Board (IRB) prior to implementation. The historical cohort (control arm) includes patients with clinical stage IIB/IIC melanoma who were treated at the AC Camargo Cancer Center with WEM and SLNB, followed by at least one cycle of adjuvant anti-PD1 therapy. The primary objective of the study is to reduce the median time to initiation of anti-PD1 therapy by more than 30 days in the NEOSENT arm compared to the historical cohort. Secondary objectives include comparing relapse-free survival rates between the NEOSENT arm and the historical cohort using propensity score matching, as well as describing the pathological findings of SLNB after neoadjuvant anti-PD1 therapy and their correlation with survival outcomes. Research Sponsor: None.

TPS9610 **Poster Session**

A phase 2 study to determine the clinical and pathological (path) response to neoadjuvant nivolumab (nivo) and relatlimab (rela) in stage II to IV (M0) resectable cutaneous squamous cell carcinoma (Neo-SCC). First Author: Maria Gonzalez, Melanoma Institute Australia, Sydney, NSW, Australia

Background: Cutaneous squamous cell carcinoma (cuSCC) is the second most common skin cancer worldwide (Bray et al. 2018). While 90% of cases are cured surgically (Kauvar et al. 2015), approx. 5% spread regionally or distantly, with an OS rate $<$ 20% at 10 years if regional lymph nodes (LN) are involved (Ogata et al. 2019). Immunotherapy trials have shown efficacy in advanced disease. Neoadjuvant therapy (NAT) is a powerful treatment platform to rapidly assess drug activity in resectable cancers. In melanoma, a major path response to immunotherapy ($\leq$10% viable tumor) correlates with low risk of recurrence in resectable stage III disease (Menzies et al. 2021), and improved OS and EFS when anti-PD1 monotherapy or in combination with anti-CTLA-4 is given neoadjuvantly vs. monotherapy adjuvant (adj) treatment (Patel et al. 2023; Blank et al. 2024). In a study of NAT anti-PD1 monotherapy with cemiplimab, in pts with resectable stage III or IV (M0) cuSCC (N = 20), 55% of pts had a path complete response (pCR) (0% viable tumour) (Ferrarotto et al. 2021). In a larger NAT cemiplimab trial (N = 79) 51% pts achieved pCR (Gross et al. 2022). The De-Squamate cuSCC trial, evaluating NAT anti-PD1 monotherapy with pembrolizumab (N = 27), showed a 63% combined rate of pCR and clinical complete response (CCR) resulting in the de-escalation of surgery and post operative radiotherapy (RT) in 48% of pts, and avoidance of post-operative RT in 15% of pts (Ladwa et al. 2024). The Neo-SCC trial will evaluate if combined PD-1 plus lymphocyte-activation 3 (LAG3) checkpoint inhibition achieves high path response, while allowing for response-driven surgical and RT de-escalation in pts with resectable cuSCC. **Methods:** Pts with histologically confirmed, resectable cuSCC AJCC (8th ed, head/neck) or UICC (9th ed, non-head/neck) clinical stage II, III or IV (M0) are eligible (N = 20). All pts undergo resection (RES) at week 6 following NAT with 2 doses of nivo (480 mg, IV) plus rela (160 mg, IV) at week 0 and 4. LN disease pts undergo baseline index-LN marking and RES at week 6, with subsequent total LN RES if there is no pCR in the index-LN. Synchronous primary/in-transit metastases undergo wide excision during index-LN resection. Non-LN disease pts showing CCR at week 6 receive an incisional biopsy of the baseline tumor site. All non-LN pts undergo definitive excision except those with CCR or pCR on biopsy. RT follows standard care. Imaging includes CT and FDG PET/CT at BL, prior to RES, and during the 5-year follow-up period. Tumor, blood and faecal samples are collected at BL, RES, and recurrence. The primary endpoint is the pCR rate at RES. The sample size is powered to detect a difference $>$ 25% in pCR rate with the historical control. Secondary endpoints include surgical/RT de-scalation rates, RFS, OS, safety/tolerability, surgical outcomes, QOL, and biomarker analyses. Clinical trial information: NCT06288191. Research Sponsor: Bristol Myers Squibb (drug only).

TPS9611 **Poster Session**

A phase Ib study to assess the safety and efficacy of autologous tumor infiltrating lymphocytes (lifileucel) with adjuvant pembrolizumab (PEMBRO) for treatment of immunotherapy naïve patients with high-risk clinical stage IIIb-d resectable melanoma (MEL). First Author: James Isaacs, Cleveland Clinic, Cleveland, OH

Background: Despite significant advances in the treatment (Tx) of stage III MEL, there remains a high risk of recurrence after surgical resection. Adjuvant immune checkpoint inhibitors (ICI) are a standard of care, but recurrence rates remain greater than 40% at 5 years. Neoadjuvant ICI have shown improved event-free survival compared to adjuvant ICI. However, at time of surgery a significant proportion of patients' (PTS) MEL still do not show a response. Lifileucel is an autologous tumor infiltrating lymphocyte therapy (TIL) that was recently FDA-approved after showing sustained high tumor response rates for pts with ICI-refractory metastatic MEL. For patients with IO naïve stage IV MEL, ORR was 65% for lifileucel + PEMBRO. Offering TIL at earlier stages of MEL may offer several potential benefits to anti-PD-1 alone. In the Tx-naïve setting, T cells are not previously exposed to ICI that can impact the quality of the TIL product. After curative-intent resection, pts will be rendered clinically tumor-free. When TIL are then utilized to address residual microscopic MEL, they will be less impacted by an immunosuppressive tumor microenvironment often accompanying larger disease burden. Earlier stage also limits tumor heterogeneity that can emerge in more advanced Tx-refractory metastatic MEL. Here we share details of a first clinical trial to evaluate lifileucel with adjuvant PEMBRO for resectable clinically detected high-risk MEL. **Methods:** This phase 1B trial is enrolling pts with clinically detectable stage IIIB-D MEL who are planned to undergo surgical resection and eligible for standard adjuvant anti-PD1. Pts' MEL must be considered fully resectable and pts cannot have previously received ICI. Pts proceed to standard of care resection after enrollment at which time tumor is procured for lifileucel/TIL manufacturing. Once the TIL product has completed manufacturing, pts will receive lymphodepleting chemotherapy followed by TIL infusion and IL2, for up to 6 doses. At week 12 after receiving lifileucel, pts start adjuvant PEMBRO to complete 1 year of Tx. The primary endpoints of this trial are disease free survival at 1 year and safety. The trial is planned to enroll 12 pts. Sample size justification is aimed on detecting 20% improvement on 12-month RFS for lifileucel+ PEMBRO compared to standard Tx. Based on Simon's two-stage design with a one-sided type I error of 0.05 and power of 80%, if 7 or fewer of 11 pts remain relapse-free at 12 months, futility is determined. If 8 or more of 11 are still relapse-free at 12 months, then futility is rejected. Correlative studies include analysis of the phenotype, function and TCR repertoire of baseline TIL samples. Serial PBMC will be collected to monitor TIL persistence (based on TCR analysis) and functional activity. Clinical trial information: NCT06190249. Research Sponsor: Iovance.

TPS9612 **Poster Session**

Trial in progress: A phase 3 randomized study of low-dose intralesional cemiplimab versus primary surgery for patients with early-stage cutaneous squamous cell carcinoma (CLEAR CSCC). First Author: Michael Robert Migden, The University of Texas MD Anderson Cancer Center, Houston, TX

Background: Cemiplimab 350 mg administered intravenously every 3 weeks is approved for the treatment of advanced cutaneous squamous cell carcinoma (CSCC). Surgery is the standard of care for early-stage CSCC; however, for patients who prefer non-surgical management of early-stage CSCC, low-dose intralesional (IL) cemiplimab has demonstrated promising clinical activity in a pilot study (NCT03889912). The purpose of this study (NCT06585410) was to determine the non-inferiority of IL cemiplimab versus primary surgery, along with its safety, tolerability, and efficacy in patients with early-stage CSCC. **Methods:** In this phase 3, randomized, open-label, multicenter study, approximately 369 patients with early-stage CSCC will be randomized 2:1 to cemiplimab (5 mg IL every week for 6 weeks) versus primary surgery. Key inclusion criteria include: patients aged $\geq$18 years; a histologically confirmed invasive CSCC target lesion that is $\geq$1.0–$\leq$2.0 cm (longest diameter) located in the head and neck, hand, or pre-tibial surface; adequate performance status; and adequate hepatic, renal, and bone marrow function. Key exclusion criteria include target lesion of keratoacanthoma, autoimmune disease requiring treatment with systemic autoimmune suppressants, concurrent or prior solid tumor or hematologic malignancy (except for protocol-allowed exceptions), and a history of solid organ transplant. Patients will be followed for approximately 3 years. The primary objective is to assess the non-inferiority of IL cemiplimab versus primary surgery by event-free survival. Secondary objectives include safety, tolerability, longest diameter of surgical defect after resection in both arms, and composite complete response in the experimental arm. Study recruitment is planned to start in 2025. Enrollment is planned at study sites across North America, Australia, and Europe. Clinical trial information: NCT06585410. Research Sponsor: Regeneron Pharmaceuticals, Inc.

TPS9613 **Poster Session**

A phase II randomised study to evaluate the antitumour activity of roginolisib, a novel non-ATP competitive and allosteric modulator inhibiting PI3Kδ, in patients with metastatic uveal melanoma (OCULE-01). First Author: Paul D. Nathan, Mount Vernon Hospital, Northwood, United Kingdom

Background: Uveal melanoma (UM) is a rare malignancy that develops from melanocytes in the eye. At least half of the patients develop metastases, primarily in the liver, and survival outcome from the time of metastatic disease is poor. Patients with second or third line systemic therapy may have a median Overall Survival (OS) ranging from 7 to 12 months. The small molecule roginolisib (IOA-244) is a novel highly selective, non-ATP competitive, allosteric modulator targeting phosphoinositide 3-kinase delta (PI3Kδ). The clinical development of roginolisib investigates its role in PI3Kδ-dependent malignancies. PI3Kδ in solid tumours, including cutaneous and uveal melanoma. Based on previous non-clinical studies, PI3Kδ appears to be up-regulated in tumour cells through inflammation and cellular transformation. In addition to this tumour-cell intrinsic mechanism, roginolisib is designed to block tumour-cell extrinsic mechanisms, including T regulatory (Treg) cells, B cells, and, to a lesser extent, myeloid-derived immune cells. **Methods:** The study OCULE-01 is a Phase II open-label, randomised, parallel-arm, multicentre study, which will assess the clinical efficacy of oral roginolisib as monotherapy against a control consisting of Investigator´s treatment in patients with metastatic UM who have progressed on prior first line treatment. Eighty-five patients will be enrolled across 20 sites in the EU, UK, and US. Patients will have progressed following at least 1 prior immunotherapy treatment. Patients will be randomised to one of 3 treatment arms; Arm 1: (n=50) IOA-244 80mg daily, Arm 2: (n=25) Investigator's choice of therapy, Arm 3: (n-10) IOA-244 40 mg daily. The primary objective is to assess the overall survival of roginolisib versus Investigators' choice of therapy. Secondary endpoints include PFS, OR, Safety, and Quality of Life impact. Correlative aims include assessing blood and tissue biomarkers (i.e. Treg, ctDNA, gene expression, proteomics etc.) for association with clinical benefit and radiomic analysis of imaging. A final analysis will be performed to assess efficacy after 72 patients become evaluable. Study Centres are currently being opened for enrolment. Clinical trial information: NCT06717126. Research Sponsor: iOnctura.

10000 **Oral Abstract Session**

Association of immunotherapy of high-risk neuroblastoma patients with long term infusion of dinutuximab beta with survival over short term infusion: Results from the HR-NBL1/SIOPEN trial. First Author: Ruth Lydia Ladenstein, St. Anna Children's Hospital and St. Anna Kinderkrebsforschung, Department of Paediatrics, Medical University Vienna, Vienna, Austria

Background: Dinutuximab beta (DB) delivered as long-term infusion is associated with a lower frequency and magnitude of side effects compared to short-term infusion (STI). Here, we evaluated the efficacy (event free survival- and cumulative incidence of relapse-rates at 5 years) of LTI compared to STI within the HR-NBL1/SIOPEN trial (EudraCT:2006-001489-17). **Methods:** High-risk patients as defined by metastatic disease (stage M) or local stage with MYC-N amplification received high intensity induction, surgery, high dose therapy with busulfan/melphalan followed by autologous stem cell transplantation (HDT/SCT) and local radiotherapy. Patients who achieved at least a partial response prior to HDT/SCT within equal or less than 9 months between diagnosis and HDT/SCT without progression were randomized to receive 5 cycles of 100 mg/m^2 DB per cycle either as STI (20 mg/m^2 per day as 8 h infusion; days 1-5) with or without subcutaneous interleukin-2 (scIL2) (6 $\times$ 10^6 IU/m^2 per day; days 1-5 and days 8-12) (R2 randomization) or as LTI (10 mg/m^2 per day as 24h infusion; days 1-10) (d8-17) $\pm$ 3x10^6 IU/m^2 scIL2 (d1-5; d8, d10, d12, d14, d16) (R4 randomization). All patients received 160 mg/m^2 oral isotretinoin (d19-32). **Results:** From 2009-2018, 705 patients (pts) from 18 countries were randomized and eligible for this analysis. The median follow-up time is7.7 years. Key patient characteristics were age 1.5-5yrs: 65% (460 pts), disease status before HDCT: CR 56% (396 pts) versus non-CR 38% (268 pts), MYC-N amplification (MNA): 43% (304 pts); $>$ 1 metastatic compartment (MC): 78% (553 pts); time between diagnosis to DB treatment start: $>$ 9 months 48% (302 pts). There were no significantly different patient characteristics between STI and LTI cohorts, except for time to DB start $>$ 9 months: 59% in the LTI cohort vs. 37% in STI.The 5yr EFS was 0.65$\pm$0.03 for LTI vs. 0.56$\pm$0.03 for STI (p = 0.041). The cumulative incidence of relapse was 0.33$\pm$0.03 for LTI vs. 0.42$\pm$0.03 for STI (p = 0.034). Multivariable pseudovalue-regression analysis for 5-year EFS found a significantly worse outcome for stage 4 patients with $>$ 1MC (p = 0.025; cHR = 1,97), $<$ CR (p = 0.059; cHR = 1.32) and for STI (p = 0.044; cHR = 0.74). **Conclusions:** We previously reported that LTI of DB increased the safety profile (less pain and inflammation) (Lancet Oncol 2018;19(12):1617-1629; J Clin Oncol 37, 2019 (suppl; abstr 10013). Here we demonstrate that LTI is also associated with an improved outcome. Clinical trial information: 2006-001489-17. Research Sponsor: None.

10001 **Oral Abstract Session**

A phase 2 randomized study of chemoimmunotherapy with or without eflornithine (DFMO) in relapsed/refractory neuroblastoma: A Children's Oncology Group (COG) report. First Author: Margaret E. Macy, Department of Pediatrics, University of Colorado and Center for Cancer and Blood Disorders, Children's Hospital Colorado, Aurora, CO

Background: Dinutuximab, irinotecan, temozolomide and GM-CSF (DIT) is widely used in first relapsed/ refractory high-risk neuroblastoma (r/r HRNB), however $<$50% of patients (pts) respond. ODC1 is a key enzyme important for NB cell survival. Difluoromethylornithine (DFMO) irreversibly inhibits ODC1, suppressing polyamine biosynthesis and driving anti-NB activity. DFMO also inhibits arginase and may enhance immunotherapy in r/r NB. COG ANBL1821 was a randomized phase 2 study for pts with r/r NB that evaluated response to DIT with or without DFMO (NCT03794349). **Methods:** Patients with first episode of r/r NB were randomized 1:1 to DIT (Arm A) or DIT with DFMO (6750 mg/m^2 divided TID; Arm B). They were stratified by measurable/evaluable disease, *MYCN* status, prior anti-GD2 therapy, and prior DFMO therapy. Cycles were 21 days. On Arm B, DFMO was initially given continuously; discontinuous DFMO dosing (days 1-7 and 15-21) was instituted due to ototoxicity in the initial cohort. Objective Response Rate [(ORR); sum of complete (CR), partial (PR), and minor (MR) responses per the 2017 International Neuroblastoma Response Criteria (INRC)] was determined based on central review of imaging. Toxicities were graded per CTCAE v5.0. **Results:** 91 eligible and evaluable pts (44 Arm A, 47 Arm B) were randomized May 2019-Jan 2024. 28/44 (63.6%) of Arm A pts and 32/47 (68.1%) of Arm B pts had relapsed or progressive disease (RPD); the remaining pts had refractory disease. The ORR was 61.4% (27/44) for Arm A and 57.4% (27/47) for Arm B (p=0.566). On Arm A, 22/44 (50%) achieved CR or PR compared to 23/27 (48.9%) on Arm B. Response rates for pts with RPD were similar to those with refractory disease in both arms. The 1-year progression-free survival (PFS) for Arm A was 70.0$\pm$8.0% and 56.8$\pm$8.2% for Arm B. Overall survival was 87.0$\pm$5.7% and 81.4$\pm$6.3% for Arms A and B, respectively. The most common toxicities reported on both arms were hematologic and gastrointestinal. Fewer pts on Arm B (n=7) had Grade 3+ pain than on Arm A (n=15) (p=0.0326). Hearing loss was a toxicity of interest; with continuous dosing, 55.6% (5/9) of Arm B pts developed hearing loss requiring DFMO dose hold. With discontinuous dosing, hearing loss was 15.8% (6/38) on Arm B compared to 6.3% (2/32) on Arm A (p=0.275). 14/16 (87.5%) NB+ marrows were GD2+ at enrollment; loss of GD2 was not detected on persisting NB cells in on therapy marrows analyzed. **Conclusions:** The addition of DFMO to DIT did not improve response rates in pts with first r/r HRNB, though the response rates in both arms confirmed DIT activity in this population. The ORR to DIT is higher than previously reported, likely due to use of the 2017 INRC that includes MR in calculation of ORR. Rates of CR+PR in this trial were similar to those previously reported. DFMO was associated with an increased incidence of hearing loss which was partially mitigated by discontinuous dosing. Clinical trial information: NCT03794349. Research Sponsor: National Cancer Institute/U.S. National Institutes of Health; U10CA180886; National Cancer Institute/U.S. National Institutes of Health; U10CA180899.

10002 **Oral Abstract Session**

Vincristine and topotecan versus carboplatin-, etoposide-, and vincristine-based chemotherapy for ocular salvage in group D and group E intraocular retinoblastoma: A randomized, comparative trial. First Author: Prashant Prabhakar, Division of Pediatric Oncology, Department of Pediatrics, AIIMS, New Delhi, India

Background: India has the highest burden of retinoblastoma worldwide. The access to Intra-arterial chemotherapy is limited and systemic chemotherapy remains the standard of care in low-middle income countries(LMIC) like India. There is a need to find alternative systemic chemotherapy due to growing concerns of long-term toxicities with standard Carboplatin and Etoposide based therapy. Topotecan is an attractive option as it is devoid of late toxicities and found to be effective in retinoblastoma. However, the data is very limited. **Methods:** We did a randomised comparative trial in children with group D/E intraocular retinoblastoma (IORB) to compare 2 different chemotherapy regimens. Between October 2021 and March 2023, participants fulfilling the inclusion criteria were randomised to receive either vincristine, topotecan(VT-arm) or high dose carboplatin, etoposide, and vincristine(HDCEV-arm) chemotherapy every 3-weekly for 6 cycles with focal therapy after 2-cycles. The reassessment was done every two cycles.The primary objective was to compare the treatment failure rates at the end of 6-cycles, which was defined as need for non-protocol therapy, enucleation or external beam radiotherapy(EBRT). The secondary objectives were to compare final globe salvage rates (which includes all forms of therapy except EBRT) and toxicities. **Results:** Forty(42 eyes) newly diagnosed cases with group D/E IORB were enrolled. Out of which 19 children(20 eyes) received VT and 21(22 eyes) received HDCEV- based regimen. Baseline parameters were comparable in both arms. After a median follow up of 12.4 months (range, 5.7-22.6), the treatment failure rate was significantly less in HDCEV-arm compared to VT-arm (45.5% vs 75%,HR-2.64, 95% CI, 1.13-6.13, p = 0.02). The 24 months enucleation free-survival was 54.5% in HDCEV-arm and 35% in VT-arm ($p < 0.01$). There were no deaths in any arm and both treatments were tolerated well. However, the incidence of febrile neutropenia (73.6% vs 43%, p = 0.05) and episodes of grade 3/4 diarrhoea (13 vs 4,p = 0.02) was more in VT-arm compared to HDCEV-arm.The response after 4-cycles was comparable with 90% and 85% showing partial response in HDCEV and VT-arm respectively(p = 0.92) but this effect could not be sustained in VT-arm. **Conclusions:** Administration of Topotecan is feasible even in LMIC setting without therapeutic drug with manageable toxicity in children. VT is inferior to HDCEV in globe salvage and has slightly more toxicity. The initial response achieved with VT could not be translated into globe salvage. There is a need to find alternative therapy and the combination of VT with carboplatin can be an attractive option. Clinical trial information: 2021/09/047121. Research Sponsor: None.

10003 **Oral Abstract Session**

Safety and efficacy of the EZH1/2 inhibitor valemetostat tosylate (DS-3201b) in pediatric patients with malignant solid tumors (NCCH1904): A multicenter phase I trial. First Author: Ayumu Arakawa, Department of Pediatric Oncology, National Cancer Center Hospital, Tokyo, Japan

Background: Valemetostat tosylate (DS-3201b; valemetostat) is a first-in-class dual inhibitor targeting the epigenetic regulators EZH1 and EZH2. In Japan, valemetostat has been approved for the treatment of r/r adult T-cell leukemia/lymphoma and peripheral T-cell lymphoma. These enzymes are implicated in tumors characterized by SMARCB1/INI1 deficiencies, such as malignant rhabdoid tumors or epithelioid sarcoma, which frequently occur during childhood and adolescence. Valemetostat is expected to show antitumor activity against such malignancies. **Methods:** This open-label, multicenter phase I trial evaluated the safety, efficacy, and recommended phase 2 dose (RP2D) of valemetostat in pediatric patients with malignant solid tumors. Valemetostat was administered orally once daily in 28-day cycles. The dose-escalation phase used a 3 + 3 design, testing three dose levels (150, 200, and 250 mg/1.7 m^2). Following RP2D determination, 15 patients were enrolled in the expansion cohort. The primary endpoint was dose-limiting toxicity (DLT) incidence in the dose-escalation cohort. **Results:** Between March 2020 and January 2023, 30 pediatric patients were enrolled (median age: 8 yr; range: 3–19 yr). Among these, 13 (43.3%) patients were INI1-negative by immunohistochemistry. Diagnoses included atypical teratoid/rhabdoid tumor (AT/RT, *n* = 6), malignant rhabdoid tumor (*n* = 1), neuroblastoma (NB, *n* = 8), and chordoma (*n* = 3). No DLTs were observed among 12 evaluable patients, and 250 mg/1.7 m^2 was established as the RP2D. Common grade $>$3 adverse events included lymphocytopenia (26.7%), neutropenia (26.7%), and anemia (16.7%). Notable treatment-related adverse events included grade 3 pneumocystis pneumonia (*n* = 1, 3.3%) and pneumonitis (*n* = 2, 6.7%). One patient with NB developed acute lymphocytic leukemia as a secondary malignancy. Pharmacokinetic analysis revealed no significant differences in T_{max} and T1/2 compared with the phase II study in Japanese adults (J201 study); however, C_{max} and AUC_{tau} were lower within the range of variation in adults. Objective response was observed in two of 14 patients (14.2%) with measurable disease, both with AT/RT. Long-term disease control exceeding 1 yr were noted in NB (*n* = 2), chordoma (*n* = 1), rhabdoid tumors (AT/RT; *n* = 1), and glioma (*n* = 1). **Conclusions:** Valemetostat was safe in Japanese pediatric patients, demonstrating antitumor activity against INI1-negative tumors, such as AT/RT. These findings support further exploration of valemetosat in combination therapies targeting SMARCB1/INI1-deficient tumors. Additionally, the durable control of tumor observed in NB suggests potential efficacy of valemetostat against this malignancy. This study was supported by the Japan Agency for Medical Research and Development and Daiichi Sankyo Co., Ltd. Clinical trial information: jRCT2031190268. Research Sponsor: Japan Agency for Medical Research and Development.

10004 **Oral Abstract Session**

Alectinib in children and adolescents with solid or CNS tumors harboring ALK-fusions: A data update from the iMATRIX alectinib phase I/II open-label, multi-center study. First Author: Francois Doz, SIREDO Center (Care, Innovation, Research in Pediatric, Adolescent and Young Adults Oncology), Institut Curie and University Paris Cité, Paris, France

Background: Alectinib is a next generation oral inhibitor of ALK-fusion proteins, being investigated in children and adolescents with ALK-fusion bearing tumors at diagnosis or relapse. Here we present updated safety and efficacy data from the iMATRIX Alectinib phase I-II study (NCT04774718). **Methods:** Patients, less than 18 years of age, with ALK fusion-positive solid or CNS tumors for whom prior treatment had proven to be ineffective or for whom there was no satisfactory treatment available were eligible. Patients were recruited to Part 1 to confirm the recommended phase 2 dose (RP2D) and to monitor drug pharmacokinetics. Investigators reported Best Overall Response according to RANO (CNS tumors) or RECIST v1.1 (solid tumors) criteria with a data cut off of July 2024. **Results:** In total 22 patients with a median age of 8 years were enrolled. Fourteen patients were diagnosed with solid tumors: inflammatory myofibroblastic tumor (n = 9), renal cell carcinoma (n = 2), mesothelioma (n = 1), nephroblastoma (n = 1), and atypical melanocytic tumor (n = 1). Six patients were diagnosed with CNS tumors: high grade glioma (n = 5) and pleomorphic xanthoastrocytoma (n = 1). Two patients had ineligible conditions: histiocytosis (n = 1) and anaplastic large cell lymphoma (n = 1). Among the 22 patients, 14 had not received prior systemic therapy. ALK fusion partners were EML4 and CLTC in 3 patients, TPM3 and KIF5C in 2 patients, and DCTN1, FN1, KIF5B, NPM, PPP1CB, STRN, CLIP1, RANBP2, ZEB2, PLEKHA7, CDC42BPB and HNRNPA3 in 1 patient each. In the 21 safety evaluable patients, only 1 DLT of Grade 3 increased alanine aminotransferase, in the context of multiple viral infections, was reported. The DLT resolved after treatment interruption and Alectinib was restarted at a reduced dose level, and then tolerated well. Eighteen patients (86%) experienced at least one Adverse Event (AE) reported as related to Alectinib, the majority being of Grade 1 and 2 severity. Grade $\geq$ 3 AEs related to alectinib were reported for 5 patients (23.8%) and there were 2 patients with serious AEs related to Alectinib. There were no new safety signals detected. Investigator reported Best Overall Response rate in 16 patients was 87.5%; (14 PRs) and 2 patients were reported to have stable disease. A partial response was observed in 5/5 evaluable patients with CNS tumors and in 9/11 evaluable patients with solid tumours. Six patients were excluded from the efficacy analysis due to ineligible tumor type (n = 2), not dosed (n = 1), no measurable disease according to RANO criteria (n = 1) or lack of response assessment by the analysis cut-off date (n = 2). **Conclusions:** Alectinib continues to have a favourable safety profile in pediatric patients. Despite this being a very challenging population to treat, clinical efficacy results are transformational with the majority of patients experiencing a tumor response. Clinical trial information: NCT04774718. Research Sponsor: Hoffmann-La Roche.

10005 **Oral Abstract Session**

Results of a phase II trial of olaparib in combination with ceralasertib in patients with recurrent and unresectable osteosarcoma. First Author: Suzanne J. Forrest, Dana-Farber/Boston Children's Cancer and Blood Disorders Center, Boston, MA

Background: Osteosarcoma is the most common bone tumor of children, adolescents, and young adults and patients with recurrent osteosarcoma have very poor outcomes. The observed response to cisplatin in osteosarcoma, in vitro susceptibility of osteosarcoma cell lines to ATR and PARP inhibitors, and the presence of mutations in genes involved in DDR served as the basis for the development of this trial. **Methods:** In this single arm, open label phase II trial of olaparib and ceralasertib patients aged 12-40 weighing $>$ 40 Kg with recurrent osteosarcoma and measurable unresectable disease were eligible for Cohort 1. The primary endpoint for Cohort 1 was event-free status at 4-months. Secondary endpoints included objective response rate (ORR) and event-free survival (EFS). After an early study amendment changing the dosing strategy based on clinical data generated from other trials, patients received Olaparib 150mg twice a day on days 1-28 and ceralasertib 80mg twice a day on days 1-14 of a 28-day cycle. Using a two-stage design and a planned sample size of 34 evaluable Cohort 1 patients receiving the amended dosing strategy there is 90% power to detect a 20% increase (39% vs 19%, selected based on a historical benchmark) in the proportion of patients who are event-free at 4-months. Interim analysis required $\geq$2 of 15 patients to be 4-months event-free to proceed to Stage 2; at Stage 2, $\geq$11 of 34 patients 4-months event-free for evidence of efficacy. **Results:** The study proceeded to full accrual based on the interim analysis. As of 1/21/2025 data-cut off, 38 patients from four centers were enrolled in Cohort 1 between November 2020 and November 2024; 37 were eligible and evaluable for safety, objective response, and survival analyses. Excluding four patients enrolled before the study amendment updating dosing, 33 patients were evaluable for the primary objective. Median age was 19.6 years (range 12.7-38.2). Patients received an average of 4.2 (range 1-9) prior therapy regimens, including 26 (70%) patients with prior multi-tyrosine kinase inhibitor treatment. Four of the 33 evaluable were event-free at 4-months (12%; 95% CI: 4%-29%). One of 37 patients had an objective response (ORR: 2.7%; 95% CI: 0.14%-16%). The 4-month EFS$\pm$SE was 13.5$\pm$5.6% (n = 37). The most common $\geq$ grade 3 adverse events were platelet count decreased and anemia (38% and 27%, respectively). **Conclusions:** The study did not meet the predetermined threshold for efficacy for Cohort 1; however, a subset of patients may be benefit from this combination treatment. Results of Cohort 2 (resectable osteosarcoma limited to the lung parenchyma) will be reported separately. Assessment of potential biomarkers of response is underway. Clinical trial information: NCT04417062. Research Sponsor: The Osteosarcoma Institute; AstraZeneca.

10006 **Oral Abstract Session**

Phase II assessment of carboplatin with etoposide and high-dose ifosfamide in rEECur, an international randomised controlled trial of chemotherapy for the treatment of recurrent and primary refractory Ewing sarcoma (RR-ES). First Author: Martin McCabe, University of Manchester, Manchester, United Kingdom

Background: rEECur, the first randomised controlled trial (RCT) in RR-ES, has previously defined high dose ifosfamide (IFOS) as the most effective regimen in this setting compared to gemcitabine-docetaxel, irinotecan-temozolomide and topotecan-cyclophosphamide. Platinum drugs show activity in RR-ES and are frequently given with etoposide in this setting. **Methods:** Patients aged at least 2 years with RR-ES were randomised to 3-week cycles of either IFOS 15 g/m^2 by continuous intravenous (IV) infusion over 5 days or IV carboplatin 400 mg/m^2 day 1 and etoposide 120 mg/m^2 days 1 to 3 (CE). Primary outcome was event-free survival time (EFS). Secondary outcomes included overall survival time (OS), toxicity and quality of life (QoL). A probability-based Bayesian approach was used. **Results:** 139 patients recruited between 22/03/21 and 28/05/24, were randomised 1:1 to IFOS (n = 69) or CE (70). Median age was 18 years (range 3-59). Patients had refractory disease (14%), 1st recurrence (81%), $>$ 1strecurrence (6%). Sites of progression were primary site only (21%), pleuropulmonary metastases only (24%), and other or combined metastatic disease (55%). More CE patients had baseline GFR $<$ 90 ml/min/1.73m^2(41% versus 23%). Median follow-up (reverse Kaplan-Meier) was 18 months (mos). Median EFS was 5.1 mos (95% CI 3.1, 6.3) for IFOS and 3.5 mos (95% CI 2.5, 6.1) for CE. Median OS was 14.4 mos (95% CI 11.5, 20.7) for IFOS and 19.0 mos (95% CI 11.2, 24.6) for CE. Given the observed data the posterior probabilities that EFS and OS were better after IFOS than after CE (ie Pr[true hazard ratio $>$ 1 | data]) were 87% and 55% respectively. Grade 3+ adverse events present in $>$ 5% of patients randomised to IFOS (left hand values) compared with CE were febrile neutropenia (30% v 10%), anaemia (9% v 9%) and thrombocytopenia (3% v 7%). Acute kidney injury was present in 2% v 0% and encephalopathy in 5% v 0%. There were no measurable differences in QoL. **Conclusions:** There was insufficient evidence of efficacy with CE compared to IFOS to continue recruitment to phase III in this first RCT of a platinum-etoposide combination in RR-ES. IFOS remains the most effective regimen in this disease setting. The trial remains open, comparing IFOS with and without the tyrosine kinase inhibitor lenvatinib. Funded by Cancer Research UK (C22436/A28028, CTUQQR-Dec22/100006, A28474). Clinical trial information: ISRCTN36453794. Research Sponsor: None.

10007 **Oral Abstract Session**

ONITT: A phase I study of nanoliposomal irinotecan with talazoparib or temozolomide in children and young adults with recurrent or refractory solid tumors. First Author: Sara Michele Federico, St. Jude Children's Research Hospital, Memphis, TN

Background: Talazoparib (TAL), a potent PARP inhibitor, demonstrated preclinical activity in Ewing sarcoma when combined with irinotecan (IRN) and temozolomide (TMZ). A phase I study (BMNIRN, NCT02392793) showed clinical benefit of TAL + IRN + TMZ; but dose escalation was limited due to hematologic and gastrointestinal toxicity. We therefore evaluated, for the first time in children, nanoliposomal irinotecan (nal-IRI) in combination with either TAL or TMZ. **Methods:** Patients (pts) aged 1-30 with recurrent or refractory solid tumors were eligible to receive nal-IRI + TAL (Arm A) or nal-IRI + TMZ (Arm B) using a Bayesian keyboard design. Nal-IRI dosage was escalated with fixed TAL and TMZ doses. Each cycle was 21 days. Maximum tolerated dosage(s) (MTD) and recommended phase 2 dosage(s) (RP2D) were determined. Nal-IRI and TAL plasma pharmacokinetics (PK) were evaluated. Toxicities were assessed using CTCAE v.5 and responses were evaluated by RECIST 1.1. UGT1A1 polymorphisms and serial circulating tumor DNA (ctDNA) samples were evaluated. **Results:** Forty-six pts enrolled at 5 sites. The first 9 (5 Arm A; 4 Arm B) received nal-IRI days 1, 8. Four pts had dose limiting toxicities (DLTs), so day 8 nal-IRI was removed (Amend 1). After Amend 1, 37 pts (23 male; median age 14 years, range 1-23) enrolled (19 Arm A; 18 Arm B). The most common diagnosis was Ewing sarcoma (n = 16, 35%). Table 1 summarizes DLTs in Cycle 1 and response. The most common serious adverse events included febrile neutropenia (12 Arm A; 2 Arm B), colitis (4 Arm A; 2 Arm B), vomiting (4 Arm A), and diarrhea (3 Arm A). Confirmed responses were seen in five Arm A (1 CR, 4 PR) and five Arm B (1 CR, 4 PR) pts with Ewing sarcoma, CIC-DUX4 sarcoma, synovial sarcoma, and rhabdomyosarcoma. Seven pts (5 Arm A; 2 Arm B) had stable disease. Results of PK, UGT1A1 and ctDNA will be presented. **Conclusions:** The MTDs were nal-IRI 160mg/m^2 plus TAL (Arm A) and nal-IRI 200mg/m^2 plus TMZ (Arm B). The RP2Ds are pending FDA review. These regimens are feasible with evidence of anti-tumor activity and warrant further investigation. Clinical trial information: NCT04901702. Research Sponsor: None.

Dose level	Nal-IRI mg/m^2 IV	Arm A Nal-IRI + TAL (po, 600mcg/m^2/dose) Days (D)	# of pts	Arm B Nal-IRI + TMZ (po, 100mg/m^2) Days (D)	# of pts	DLT Cycle 1 (# of pts)	Confirmed Response (CR, PR, SD, PD)
1	120	D 1: nal-IRI + TAL divided BID D 2-6: TAL daily	7	D 1: nal-IRI + TMZ D 2-5: TMZ daily	3	Arm A: 1 pt - neutropenia (1)	Arm A: CR (1), SD (1), PD (2) Arm B: PR (1), SD (1), PD (1)
2	160	D 1: nal-IRI + TAL divided BID D 2-6: TAL daily	10	D 1: nal-IRI + TMZ D 2-5: TMZ daily	3	Arm A: 3 pts - anemia (1), thrombocytopenia (1), sepsis (1), colitis (1)	Arm A: PR (3), SD (4), PD (3) Arm B: PR (1), PD (1)
3	200	D 1: nal-IRI + TAL divided BID D 2-6: TAL daily	2	D 1: nal-IRI + TMZ D 2-5: TMZ daily	12	Arm A: 2 pts – abd pain (1), thrombocytopenia (1), neutropenia (1), diarrhea (1) Arm B: 3 pts – nausea (1), neutropenia (1), sepsis (1), thrombocytopenia (1)	Arm A: PR (1) Arm B: CR (1), PR (2), SD (1), PD (6)

10008 Oral Abstract Session

Phase Ib study of the combination of regorafenib with conventional chemotherapy in patients with newly diagnosed multi-metastatic Ewing sarcoma: The Rego-Inter-Ewing-1 study. First Author: Pablo Berlanga, Department of Pediatric and Adolescent Oncology, Gustave Roussy Cancer Campus, Villejuif, France

Background: Regorafenib monotherapy has shown interesting but limited activity against relapsed Ewing sarcoma. We present the first results of the phase Ib study to identify the maximum tolerated dose (MTD) of regorafenib in combination with standard multimodal treatment in patients with newly diagnosed multi-metastatic Ewing sarcoma (NCT05830084). **Methods:** International multi-center phase Ib study of the combination of regorafenib with interval-compressed chemotherapy (VDC/IE) in patients aged 2-50 years with newly diagnosed metastatic (excluding lung/pleura only) Ewing sarcoma. VDC/IE chemotherapy was administered at the standard doses. Regorafenib was given orally for 21 days of a 28-day cycle (from day 5) at a starting dose level of 66 mg/m^2/day (capped at 120 mg, DL0, 80% of the pediatric recommended phase 2 dose (RP2D)) and escalated to 82 mg/m^2/day (100% RPD2, capped at 160 mg, DL1) or de-escalated to 50 mg/m^2/day (60% RPD2, DL-1). The study implemented the Bayesian Optimal Interval (BOIN) design (Yuan et al, Clin Cancer Res 2016). Primary tumour local treatment was surgery and/or radiotherapy. Adjuvant therapy consisted of VC/IE cycles or high dose chemotherapy consolidation with Busulfan/Melphalan (BuMel) and autologous stem cell rescue (ASCR). Regorafenib was given concomitant to adjuvant VC/IE cycles and primary tumor radiotherapy to the extremities but permanently discontinued in those receiving BuMel/ASCR or primary tumour radiotherapy to sites other than extremities. **Results:** Thirteen patients (DL0: n=2, DL1: n= 11) with a median age of 15.2 years (range, 8.1-23.5), were enrolled between June 2023 and December 2024 in 7 centres and 3 countries. All were evaluable for toxicity. One dose-limiting toxicity (DLT) occurred in one patient at DL1 (pressure ulcer grade 2, requiring regorafenib dose interruption and reduction in a 17-year old patient). After the DLT period, one patient had regorafenib dose interruption/reduction. One patient presented with a grade 3 veno-occlusive disease after Bu-Mel/ASCR. Detailed toxicity data after the DLT period and pharmacokinetic data will be presented. At data cut-off of 21/01/2025, two patients had experienced disease progression before primary tumour local treatment, eight patients had finished all treatment cycles (three received Bu-Mel/ASCR consolidation) and three patients were on therapy. **Conclusions:** Regorafenib combined with VDC/IE chemotherapy is well tolerated with a MTD of 82 mg/m^2/day (capped 160 mg). The efficacy of the addition of regorafenib to standard multimodal treatment in newly diagnosed patients with metastatic Ewing sarcoma will be tested in the Inter-Ewing-1 trial developed by the Euro Ewing Consortium (planned initiation in Q3 2025). Recruitment to the Rego-Inter-Ewing-1 continues at DL1 (maximum 24 patients), until Inter-Ewing-1 initiates. Clinical trial information: NCT05830084. Research Sponsor: Fight Kids Cancer 2021 Call; Bayer (drug supply and partial funding for drug labelling/shipping).

10009 Oral Abstract Session

Promoting Resilience in Stress Management (PRISM): A randomized controlled trial of a psychosocial intervention for adolescents and young adults with advanced cancer. First Author: Abby R. Rosenberg, Dana-Farber Cancer Institute, Boston, MA

Background: Adolescents and Young Adults (AYAs) with advanced cancer report poor quality of life (QOL), high psychological distress, and minimal engagement in their healthcare decisions. We assessed the effect of a novel resilience coaching program with embedded elements of advance care planning (Promoting Resilience in Stress Management for Advanced Cancer, PRISM-AC) on AYA outcomes. **Methods:** We conducted a multisite randomized trial of PRISM-AC vs Usual Care (UC) among English-speaking AYAs aged 12-24 years and diagnosed with advanced cancer within 2 weeks before enrollment. PRISM-AC consists of 4 core sessions targeting AYA-endorsed "resilience resources" (skills in stress-management, goal setting, cognitive reframing and meaning-making) plus an optional session focused on elements of advance care planning (i.e., communication preferences and priorities). Participants completed surveys at baseline, 3-, 6-, 9-, and 12-months post-enrollment. The primary outcome was QOL (Pediatric Quality of Life scale) at 3-months; secondary outcomes included 3-month changes in resilience (Connor-Davidson Resilience scale) and hope (Snyder Hope scale) and trajectories of QOL, anxiety and depression (Hospital Anxiety and Depression Scale) over 12-months. We explored PRISM-AC's impact on AYA-engagement in critical healthcare conversations as documented in the electronic health record. We applied linear mixed effects regression models to examine the association between PRISM and changes in patient-reported outcomes. **Results:** We enrolled and randomized 195 AYAs (96 UC, 99 PRISM) between April/2019 and January/2024. They were mean aged 16.5 years (SD 3.9), mostly White (63%), non-Hispanic (59%), and publicly insured (53%). At 3-months, PRISM-AYAs reported significantly more improved resilience [mean change-score +1.3 (5.9) vs -1.4 (7.5), p=0.038] and hope [+2.4 (10.4) vs -2.8 (11.2), p=0.001] than UC-AYAs, although we detected no significant differences between study arms in QOL, anxiety, or depression. Over the 12-month study period, PRISM-AYAs reported progressively more improvements in QOL and anxiety, with significant differences at later time points [i.e., PRISM-associated improvements in QOL at 6 months: +3.4 (95% CI 0.1, 6.6, p=0.043) and 12 months: +6.8 (95% CI 3.3, 10.3, p$<$0.001)]. Over time, PRISM-AYAs also appeared to participate more in key healthcare discussions. **Conclusions:** A novel resilience coaching intervention led to immediately improved resilience and hope, and longer-term improvements in quality of life among AYAs with advanced cancer. Clinical trial information: NCT03668223. Research Sponsor: National Institutes of Health; National Cancer Institute; R01 CA222486.

10010 Oral Abstract Session

Longitudinal change in cardiac function after doxorubicin and dexrazoxane: A report from COG ALTE11C2. First Author: Erin Michele Mobley, Department of Surgery, University of Florida College of Medicine Jacksonville, Jacksonville, FL

Background: Dexrazoxane (DRZ) has been associated with reduced adverse left ventricular (LV) remodeling shortly after doxorubicin (DOX) treatment ($<$5y) and preserved LV function in long-term ($>$15y) survivors of childhood cancer. What remains less clear are longitudinal changes in echocardiographic (echo) measures in this population. **Methods:** ALTE11C2 analyzed participants who received DOX treatment and were enrolled on COG protocols P9404, P9425, P9426, P9754, and Dana Farber Cancer Institute 95-01. Except for P9754, all other protocols featured upfront 1:1 randomization with DRZ (10:1mg/m^2 DRZ:DOX dose). Central echo remeasurements were used when possible, otherwise we used data from abstracted echo reports. Echo values were converted to age- or BSA-specific z-scores. Differences in z-scores by $\pm$DRZ were estimated as a function of time using generalized estimating equations, adjusting for age, sex, DOX dose, chest radiotherapy, and data type (directly remeasured vs report). **Results:** 895 patients (67% male; 67% white non-Hispanic; mean age at diagnosis 11.4y; median DOX dose 360 mg/m^2; 32% chest radiotherapy) had evaluable echo data (n=2279 echos; 1581 centrally remeasured; 698 report only; mean of 1.0-1.7 echos per patient per time period, with an average of 1.4 echos per patient $\geq$15y). In multivariable analysis, DRZ was overall associated with more normal LV fractional shortening and less LV end-diastolic and end-systolic dilation, a pattern consistent with less subclinical dilated cardiomyopathy directionality. These cardioprotective changes associated with DRZ were seen most clearly in patients treated with DOX $\geq$250 mg/m^2 with this length of follow-up. **Conclusions:** DRZ exerts significant DOX cardioprotective effects on cardiac function and remodeling, detectable within 5y and persisting beyond 10y of follow-up. Research Sponsor: National Cancer Institute; P01 CA068484, R01 CA211996, U10 CA098543, U10 CA098413, U10 CA180886, U10 CA180899, U10 CA095861, UG1 CA189955; St Baldrick's Foundation, Leukemia and Lymphoma Society, Sofia's Hope, Rally Foundation.

Z-score difference by $\pm$DRZ as a function of time, adjusted for sex, age, echo type, DOX dose, chest radiotherapy.

LV measure	Overall	Pre-treatment	<2y	2-4y	5-9y	≥10y
Fractional shortening	0.4 (0.2, 0.5) *	0.1 (-0.2, 0.5)	0.1 (-0.2, 0.5)	0.7 (0.4, 0.9) *	0.5 (0.2, 0.9) *	0.4 (0.2, 0.7) *
End-diastolic dimension	-0.2 (-0.4, -0.1) *	-0.2 (-0.4, 0.0)	-0.0 (-0.3, 0.2)	-0.4 (-0.6, -0.2) *	-0.2 (-0.5, 0.1)	-0.3 (-0.6, 0.0) *
End-systolic dimension	-0.3 (-0.5, -0.2) *	-0.2 (-0.5, 0.0)	-0.1 (-0.3, 0.1)	-0.5 (-0.7, -0.3) *	-0.4 (-0.7, -0.1) *	-0.4 (-0.7, -0.2) *
End-diastolic posterior wall thickness	0.0 (-0.1, 0.2)	-0.4 (-0.7, -0.2) *	-0.1 (-0.3, 0.2)	0.4 (0.2, 0.6) *	0.1 (-0.3, 0.5)	0.0 (-0.2, 0.3)
End-diastolic septal wall thickness	0.1 (-0.1, 0.2)	-0.2 (-0.5, 0.1)	-0.1 (-0.3, 0.2)	0.3 (0.1, 0.5) *	0.2 (-0.1, 0.5)	0.2 (-0.1, 0.4)
Thickness-to-dimension ratio (adverse remodeling=negative)	0.1 (-0.1, 0.2)	-0.3 (-0.5, 0.0)	-0.1 (-0.3, 0.2)	0.4 (0.2, 0.7) *	0.1 (-0.3, 0.6)	0.1 (-0.2, 0.4)
Mass	-0.1 (-0.2, 0.1)	-0.4 (-0.6, -0.1) *	-0.0 (-0.3, 0.2)	0.1 (-0.2, 0.3)	-0.3 (-0.9, 0.3)	0.2 (-0.1, 0.6)

*$p<0.05$.

10011 Oral Abstract Session

Long-term off-label MAPK inhibitor therapy in children with severe/refractory Langerhans cell histiocytosis: An international observational study of 277 cases. First Author: Jean Donadieu, Hopital Trousseau, Paris, France

Background: Long-term off-label use of MAP kinase inhibitors (MAPKi) to treat, refractory childhood Langerhans cell histiocytosis (LCH) was evaluated within the European consortium for histiocytosis network (www.echo-histio.net). **Methods:** 277 patients from 26 countries treated with MAPKi were classified according to the clinical indication: refractory risk organ positive/negative (RO+/RO-), isolated lung destruction (Lung), sclerosing cholangitis (SC), neurodegeneration (ND), and diabetes insipidus (DI). 252 patients had received one or several lines of chemotherapies prior to MAPKi: VBL/steroids (n = 243) then 2CdA/AraC (n = 48), 2CdA alone (n = 52), clofarabine (n = 5), VCR/AraC (n = 70) before being considered refractory. The 25 treated front line by MAPKi were newborn with aggressive disease (n = 7), or had chronic manifestations like ND, SC or DI. *BRAFV600E* was detected in 95% of the cases. **Results:** Median age at diagnosis was 1.3 years. MAPKi indication was RO+ (n = 138); RO– (n = 72); Lung (n = 7); SC (n = 9), ND (n = 45), DI (n = 2). Median age at MAPKi onset was 2.3 years, with median follow-up of 3.5 years (IQR 1.6-5.9). Vemurafenib (n = 177), Dabrafenib (n = 105), Encorafenib (n = 3), Cobimetinib (n = 41), Tramatinib (n = 41), and Binimetinib (n = 1) were prescribed mainly in monotherapy, sometimes (n = 44) with various chemotherapies or HSCT (n = 5). The short-term response (before wk 8) varied from 98% in RO+ and RO-, to 30% in Lung to a null response in ND, DI and SC, although some long-term response (after 6 months) was observed in Lung and ND. Skin rash was the most frequent adverse event (AE), affecting 55% of patients. Other AEs were observed in 7 (cardiomyopathy n = 1, retinitis n = 6). Five tumors or malignancies were observed not related to MAPKi; only in patients heavily treated by 2CdA, AraC or Clofarabine. Six deaths were observed; 5-year survival was 98%. MAPKi discontinuation for 111 patients led to LCH 66 reactivations. None of the various empirical maintenance therapies used was able to prevent secondary reactivation. Among the 133 assessable patients free of ND at MAPKi initiation, ND was observed in 52 with a 5-year risk of 55%. In some cases, ND was reversible after MAPKi dose adaptation. **Conclusions:** MAPKi appeared quick, safe and effective in children with refractory LCH while the response to Lung, SC, DI and ND was limited or delayed. Further studies are needed to find effective maintenance therapy. ND should be monitored in the follow up of patients treated by MAPKi. Research Sponsor: Association Histiocytose france.

10012 Oral Abstract Session

Understanding the molecular landscape of rare tumors through the CCDI-COG Molecular Characterization Initiative. First Author: Lauren Marie Vasta, WRNMMC, Bethesda, MD

Background: Through collaboration with the National Cancer Institute as part of the Childhood Cancer Data Initiative, the Children's Oncology Group offers prompt paired tissue and germline sequencing for newly diagnosed rare tumor subtypes. **Methods:** Individuals are eligible for paired germline and somatic blood/tissue sequencing if they are age 25 or younger, have been diagnosed with a rare tumor in the past 6 months and have both germline and tissue samples available. The paired samples undergo DNA and RNA extraction, followed by whole exome sequencing (paired tumor and germline) of cancer associated genes and RNA targeted fusion analysis. Results are returned to the primary institution within 2-3 weeks of receipt of both samples. **Results:** Between 09/12/2022 and 11/01/2024, 490 individuals from 123 institutions were enrolled with a total of 98 distinct diagnoses reported. The most common diagnosis groups were thyroid carcinoma (n = 120), neuroendocrine tumors (n = 53), sex cord stromal tumors (n = 41), and other carcinomas (n = 83). Of the 490 patients enrolled, 438 had submitted samples with successful return of exome results in 351/438 (80.1%) and fusion results in 302/438 (69.1%) by the data cut. Tier I/II germline single nucleotide (SNV) or copy number (CNV) variants were identified in 88 (25.1%) of patients that completed sequencing. The most prevalent germline alterations included SNVs in DICER1 (n = 20, 5.7%), TP53 (n = 7, 2.0%), RB1 (n = 7, 2.0%), CHEK2 (n = 6, 17%), SDHB (n = 5, 1.4%) and VHL (n = 5, 1.4%). 98% of samples demonstrated a Tier I/II somatic variant across 26 genes, most commonly found in DICER1 (n = 39, 11.1%), BRAF (n = 30, 8.5%), TP53 (n = 22, 6.3%) and CTNNB1 (n = 14, 4.0%). RNA fusion analysis identified positive results in 22.8% of samples. Testing identified over 33 distinct fusions. Fusions were most commonly associated with thyroid cancer; RET in 16 and NTRK in 12, or desmoplastic small round cell tumor; EWSR1::WT1 in 8. In 16.5% (n = 58) of the samples, the final diagnosis was refined based on the results of the molecular testing and 6.8% (n = 24) of the centers reported using a commercially available treatment targeting an identified molecular alternation. **Conclusions:** The MCI has enabled access to genetic sequencing to patients across the Children's Oncology Group across a wide range of rare tumor diagnoses. Information about the available data can be accessed through the CCDI Hub Explore. Germline cancer predisposition was identified in a quarter of these samples, highlighting the importance of tumor-normal profiling to allow genetic counselling in these patients and appropriate surveillance. These results have the potential for lasting impact on understanding and treating individuals with rare cancers and the development of targeted future clinical trials. Research Sponsor: National Cancer Institute.

10013 Oral Abstract Session

CCDI-COG molecular characterization initiative: The expanding data on childhood cancer. First Author: Erin R. Rudzinski, Indiana University, Indianapolis, IN

Background: The Molecular Characterization Initiative (MCI), a collaboration between the Children's Oncology Group (COG) and the NCIs Childhood Cancer Data Initiative (CCDI) which is intended to define a standardized genomic characterization of pediatric cancer, provides rapid, clinical sequencing for newly diagnosed central nervous system (CNS) tumors, rare tumors, soft tissue sarcomas (STS), or advanced stage neuroblastoma (NB) to guide diagnosis and treatment for these children. **Methods:** Patients enrolled on APEC14B1-MCI who are $\leq$25 years of age with an eligible tumor type treated at national or international COG sites with available snap frozen or FFPE tissue and paired germline samples undergo RNA/DNA extraction. Whole exome sequencing (paired tumor and germline), targeted RNA fusion (excluding NB) and methylation array (CNS clinical / STS, NB and rare tumor research only) analyses are performed, with clinical results returned in 2-3 weeks. **Results:** Between 3/31/22 and 11/1/24, MCI provided results for 3,972 patients, including 2,666 with CNS tumors, 781 with STS, 372 with rare tumors and 153 with NB, across 188 institutions. 89% of the $>$ 10,000 individual tests resulted within 2 weeks of receiving nucleic acids for sequencing. Tier I/II germline single nucleotide (SNV) or copy number (CNV) variants were identified in 528 (14.1%) patients [10.4% (NB) to 25.1% (rare tumors)]. The most common germline alterations included SNVs in *TP53* (n = 52,1.4%), *CHEK2* (n = 50,1.3%), *DICER1* (n = 35,0.93%), *NF1* (n = 29,0.78%) and *ATM* (n = 24, 0.64%). Somatic SNVs or CNVs were identified in 85% of samples overall. Somatic SNVs most commonly involved TP53 (n = 309,8.3%), BRAF (n = 222,6.9%), or CTNNB1 (n = 166,4.4%). Targeted RNA sequencing identified gene fusions in 30% overall (23% rare, 27% CNS, 40% STS). Methylation array resulted in positive subclassification of CNS tumors in 90% of patients, including 522 patients with medulloblastoma. Additional characterization of residual nucleic acid samples is planned, with data available through the database of Genotypes and Phenotypes (dbGaP). Follow up data has been collected for 1236 patients (NCI-CCDI Hub), including frontline treatment (chemotherapy and/or radiation), response to therapy, and vital status. Additionally, 749 reported on the utility of MCI testing six months following enrollment. MCI results were used for: enrollment on a clinical trial (n = 86,11.5%), treatment with a targeted therapy (n = 8,10.7%), and/or refining the pathologic diagnosis (n = 223,29.5%). **Conclusions:** The MCI has resulted $>$ 10,000 sequencing assays from 3,972 children with cancer in 31 months. This has directly impacted the diagnosis and/or management of patients with newly diagnosed tumors, providing access to timely molecular testing (including methylation in CNS tumors and fusion testing in STS), and guiding therapy and clinical trial enrollment for many patients. Research Sponsor: None.

10014 Oral Abstract Session

Genomic newborn screening for cancer risk: A retrospective cohort study. First Author: Lisa Diller, Dana-Farber/Boston Children's Cancer and Blood Disorders Center, Boston, MA

Background: Population-based newborn screening (NBS) improves outcomes through early detection of rare pediatric conditions. Cancer is a leading cause of pediatric morbidity and mortality, but biomarkers for cancer risk are not included in NBS. NBS for detection of germline variants in genes associated with elevated risks of early onset childhood cancer could promote surveillance and early detection. **Methods:** Infants born in Michigan between 1987 and 2020 who developed a solid or CNS tumor before age 8 were identified through the Michigan Cancer Registry and linked to the state dried blood spot (DBS) biobank. DNA was extracted from 3.2 mm DBS punches and underwent t-NGS of 11 early-onset cancer predisposition genes (*RB1, TP53, WT1, RET, SMARCB1, PTCH1, SUFU, APC, DICER1, ALK* and *PHOX2b).* Deleterious single nucleotide, short insertion and deletion variants (SNV/indels) and copy number variants (CNVs) were identified using an automated variant classification platform (Fabric Genomics) including Clinvar classification. CNV's were manually reviewed for evidence of deletion of at least one exon in a targeted gene. **Results:** 1948 DBS from infants who developed a solid or brain cancer before age 8 were identified. DNA extraction and tNGS with $>$ 20X coverage was successful for 99.9% of DBS. A heterozygous deleterious variant was detected in 133 infants (116 SNV/indels and 17 CNVs), or 6.8% of the cohort. The distribution, by diagnostic group and gene is shown below. No activating ALK variants were detected. Germline deleterious predisposition variants (PV) in *RB1* were detected in 40/50 bilateral retinoblastoma cases. 14/132 (11%) of medulloblastoma cases demonstrated a PV involving *SUFU* (6), *PTCH1* (3), *SMARCB1* (4) or *TP53* (1). Heterozygous PV in *RET* were detected in 6/6 medullary thyroid carcinoma cases. Median age at cancer diagnosis was 14 months in cases with PV compared to 32 months in cases without PV ($p < .001$). Lower overall survival was noted in sarcoma cases with PV vs. those without PV and in brain tumor cases with PV vs. those without (Logrank test, p = .04 and $p < .004$, respectively). PV carriers developed proportionally more second cancers (9.5% vs 5%; p = 0.02) and 20% of PV carriers who received radiation therapy developed second cancers. **Conclusions:** Population-based genomic NBS could identify newborns at risk for early onset childhood cancers, enabling early surveillance, diagnosis and treatment. Inclusion of *RB1* in a NBS test would identify 80% of children at risk for bilateral retinoblastoma. Further research focused on implementation of NBS for cancer risk is needed. Research Sponsor: Bridge Foundation.

Diagnosis Group	Overall N=1948	No (%) with a variant	Count of deleterious variants (combined CNV and SNV/indel) for each gene									
			RB1	*TP53*	*WT1*	*PTCH1*	*SUFU*	*DICER1*	*SMARCB1*	*RET*	*PHOX2b*	*APC*
CNS tumors	667	28 (4%)	1	9		3	6	1	7		1	
Renal Tumors	309	10 (3%)		1	7			1	1			
Sarcoma	193	13 (7%)		10		1		2				
Retinoblastoma	167	67 (40%)	67									
Liver Tumors	87	3 (3%)		1								2
Neuroblastoma	450	1 (<1%)										1
Rare/Other	75	11 (15%)	1	3				1		6		

10015 Oral Abstract Session

The gut microbiome in pediatric diffuse midline gliomas: Correlative study results from the PNOC022 trial. First Author: Raoull Hoogendijk, Princess Máxima Center for Pediatric Oncology, Utrecht, Utrecht, Netherlands

Background: The gut microbiome exerts a multifaceted influence on treatment outcomes across various cancers, yet its potential role in diffuse midline gliomas (DMGs) remains under-explored. In this report, we present the gut microbiome findings from cohort 2 in the DMG–Adaptive Combination Trial (DMG-ACT, PNOC022). **Methods:** PNOC022 is an open-label, multi-institutional, international clinical trial using a Bayesian drug combination platform trial design. This report focuses on the combination therapy arm involving dordaviprone and paxalisib, administered to patients (aged 2–39 years) who had completed standard-of-care radiation therapy (Cohort 2). Stool samples were collected at baseline (n = 22), cycle 1 day 1 (n = 15), cycle 7 day 1 (n = 9), and at progression (n = 4). Microbiome profiling was performed with shotgun metagenomic sequencing (NovaSeq X Plus Series, PE150). Progression-free survival (PFS) and overall survival (OS) were analyzed using the Kaplan-Meier method. Longitudinal shifts in microbial communities were evaluated using α-diversity (Shannon-index) and β-diversity (Bray-Curtis dissimilarity index). Baseline α-diversity associations with PFS and OS were examined with log-rank tests and further validated through age-adjusted Cox regression analysis. **Results:** Between November 2021 and October 2023, 69 biopsy-confirmed DMG patients enrolled (median age 9 years [range 3-37], n = 42 female [61%]) in cohort 2. Median OS from time of diagnosis was 15.6 months (95% CI 12.9-19.5), with a median follow-up time of 19.5 months (95% CI 17.9-23.9). Microbiome analyses were performed for 33 DMG patients (48%). Alpha-diversity and β-diversity remained stable across timepoints. Using baseline samples (n = 22) and a median α-diversity cutoff of the respective group's values, patients were stratified into two categories (low- vs. high-diversity). Low-diversity was associated with significantly worse PFS and trended worse for OS, resulting in a 6-month PFS: 73% (95%CI 51-100) vs. 100%; $p < 0.001$) and 12-month OS: 46% (95%CI 24-87) vs. 78% (95%CI 55-100; p = 0.19). Validation using age adjusted Cox regression analysis confirmed a decrease in the risk of progression or death with increasing α-diversity. PFS hazard ratio (HR) was 0.2 (95% CI: 0.1–0.5; $p < 0.01$) and OS HR was 0.3 (95% CI: 0.1–0.7; $p < 0.01$). **Conclusions:** Baseline high alpha-diversity in the gut microbiome is significantly associated with improved PFS and trended towards improved OS in pediatric patients with DMG in cohort 2 of PNOC022. Age-adjusted survival models reinforced its prognostic value for PFS and OS. These findings highlight the potential impact the gut microbiome has on outcomes and will be explored further and warrant our ongoing investigation in PNOC022. Research Sponsor: PNOC FOUNDATION; ChadTough Defeat DIPG; DDRFA; Storm the Heavens; Musella Foundation.

10016 **Oral Abstract Session**

Cognitive outcomes following proton vs. photon radiotherapy for CNS non-germinomatous germ cell tumors: A Children's Oncology Group study. First Author: David Y. Mak, Princess Margaret Cancer Centre - University Health Network, Toronto, ON, Canada

Background: The Children's Oncology Group (COG) study ACNS1123 (stratum 1) treated children with localized non-germinomatous germ cell tumors (NGGCT) of the brain with chemotherapy followed by whole ventricular (WV) radiotherapy (RT, 30.6 Gy) followed by a focal tumor bed boost (54 Gy total dose). Previous work has shown that WVRT with proton therapy, compared to photon RT, resulted in lower RT doses to the brain. However, it was unclear whether this dosimetric difference led to superior cognitive outcomes. **Methods:** The ACNS1123 study was a prospective, phase II trial conducted by the COG that enrolled 107 patients. Evaluation of cognitive functioning of children was a co-primary objective of the study. Cognition was prospectively examined at 9, 30 and 60 months post-diagnosis, using the COG Standard Neuropsychological and Behavioral Battery. The primary endpoints were attention/concentration, estimated intelligence quotient (IQ), and processing speed. Linear mixed-effect models were created to model cognitive endpoints with treatment exposures, including RT modality (proton vs. photon RT) or RT dose to brain structures. Cognitive evaluations completed post-recurrence were excluded. **Results:** Seventy patients were evaluable and received WVRT followed by RT boost, of which 20 received proton therapy. Mean age of all patients was 11.8 $\pm$ 4.3 years old at the start WVRT, and were predominantly male (n = 52). Mean doses to the brain were significantly lower with proton vs. photon RT (mean 18.8 $\pm$ 1.8 [SD] vs. 24.7 $\pm$ 3.7 Gy, $p < 0.0001$), left hippocampus (41.1 $\pm$ 5.2 vs 46.2 $\pm$ 5.3 Gy, p = 0.0005), and right hippocampus (41.8 $\pm$ 5.1 vs 46.0 $\pm$ 5.3Gy, p = 0.0038). A total of 56, 60 and 61 patients were evaluable for attention/concentration, estimated IQ and processing speed, respectively, with 1 or more evaluation. Nine, 20 and 20 patients had data at all 3 time points for attention/concentration, estimated IQ and processing speed, respectively. Multivariable modelling demonstrated that photon therapy was associated with a decline in IQ over time (p = 0.0401), as compared with proton RT, adjusted for age at RT and gender. In a separate multivariable model, higher mean brain dose was also associated with poorer recovery of IQ over time (p = 0.0216), adjusted for gender. There were no identified associations between use of proton RT or hippocampal dose with processing speed or attention/concentration. **Conclusions:** Compared to proton therapy,WVRT delivered with photons was associated with a significant decline in IQ and adverse recovery of IQ over time. To our knowledge, this data is the first to demonstrate such an association for children with NGGCT. Research Sponsor: None.

10017 **Oral Abstract Session**

Efficacy and safety of dordaviprone (ONC201) in prospective clinical trials of adult and pediatric recurrent H3 K27M-mutant diffuse glioma patients. First Author: Ashley Love Sumrall, Levine Cancer Institute, Charlotte, NC

Background: Dordaviprone (ONC201), a first in class imipridone, has demonstrated safety and efficacy in an integrated analysis of patients with recurrent H3 K27M-mutant diffuse midline glioma across clinical studies. Here, we report efficacy and safety findings from two prospectively defined clinical trial arms that evaluated single-agent dordaviprone response in recurrent H3 K27M-mutant glioma. **Methods:** Phase 2 trialONC013 (Arm B) and Phase 1 trial ONC014 (Arm F) were designed to evaluate the objective response rate (ORR) by RANO-HGG criteria of dordaviprone in adult and pediatric patients, respectively, with recurrent H3 K27M-mutant diffuse glioma. Open label dordaviprone was administered once weekly at 625 mg for adults and at a dose scaled by body weight for pediatrics. Responses were investigator-assessed by RANO criteria. Eligibility required measurable enhancing recurrence by RANO-HGG criteria, radiotherapy completed $\geq$90 days prior to dordaviprone unless unequivocal progression qualified per RANO, Karnofsky or Lansky performance status $>$60. DIPG, spinal tumors, leptomeningeal disease, and CSF dissemination were excluded. **Results:** ONC013 Arm B enrolled 30 patients (median age 32, range, 21-66 years) with the majority having a primary midline non-brainstem tumor (n = 19, 63.3%) and one prior recurrence (n = 22, 73.3%). The ORR was 16.7% (95% CI, 5.6-34.7) with 5 partial responses (PR). The median duration of response (DOR) and time to response (TTR) were 15.1 months (7.5-not reached) and 3.8 months (1.8-4.6), respectively. Three patients experienced a grade $\geq$3 treatment-related adverse events (TR-AE), none had treatment-related serious AEs (TR-SAEs), and 1 had TR-AE leading to dose reduction (ALT increase). ONC014 Arm F enrolled 11 patients (median age 14, range 11-19 years). Most had a primary midline non-brainstem tumor (n = 7, 63.6%) and 1 prior recurrence (n = 6, 65.6%). Two (18.2%) radiographic responses were reported, 1 response (9.1%) qualified by RANO criteria. One PR occurred with $>$ 95% tumor regression and an 8.5-month DOR (1.9-month TTR). Another patient experienced a $>$ 50% tumor regression (4.3-month TTR) that did not meet RANO PR criteria due to initiation of 2.5 mg dexamethasone post-baseline. 12-month PFS rate was not reached; 12-month OS rate was 27.3% (6.5, 53.9). One patient experienced a grade $\geq$3 TR-TEAE (9.1%); no TR-SAEs, treatment-related deaths, or TR-AE leading to treatment discontinuation occurred. **Conclusions:** In prospective clinical trials designed to evaluate ORR, single-agent dordaviprone response and safety in adult and pediatric recurrent H3 K27M-mutant diffuse glioma were similar to previously pooled analyses. Clinical trial information: NCT03295396 and NCT03416530. Research Sponsor: Chimerix, Inc.

10018 **Rapid Oral Abstract Session**

Metabolic-only response assessment for omission of residual node radiation therapy (RNRT) for patients with classical Hodgkin lymphoma (cHL) and impact on event free (EFS) and overall survival (OS): A report from the Pediatric Hodgkin Consortium's phase 2 study cHOD17 (NCT03755804). First Author: Jamie Flerlage, University of Rochester, Rochester, NY

Background: The AEPA/CAPDac (brentuximab vedotin, etoposide, prednisone, doxorubicin [cumulative dose = 160mg/m^2], cyclophosphamide, vincristine, prednisone, and dacarbazine) regimen results in excellent EFS and OS rates for pediatric cHL but resulted in 65% of patients requiring RNRT using metabolic and anatomic response criteria. We aimed to determine if use of a metabolic-only response assessment would allow omission of consolidative prednisone and RNRT for the majority of high-risk patients while maintaining a high EFS. **Methods:** cHOD17 is an open-label, single-arm, multicenter, phase 2 trial with a stratum for patients $\leq$25 yrs of age at diagnosis of high-risk (stage IIB, IIIB, or IV), CD30+ cHL. ^{18}FDG-PET only (rather than + anatomic) was used to guide therapy following 2 cycles of AEPA [adapted from the HLHR13 trial (NCT01920932), without mandated growth factor] at the early response assessment (ERA). Complete (CMR) and inadequate metabolic responses (IR) were defined as Deauville $\leq$3 and $\geq$4, respectively. Patients in overall CMR received 4 CADac cycles without prednisone or RNRT. IR patients received 4 CAPDac (with prednisone) followed by consolidative IR site directed RNRT (25.5 Gy). The primary objective was to estimate EFS utilizing this approach. **Results:** 114 patients were enrolled at 7 institutions from January 2019 to February 2024. Median (range) age at diagnosis was 16.4 (6.7-24.1) yrs and follow-up 2.5 (0.4-5.7) yrs. Most (79.8%) were nodular sclerosing histology. Stages included 22.8% IIB, 16.7% IIIB, 20.2% IVA, and 40.4% IVB. One patient discontinued therapy due to treatment-related toxicity and was unavailable for response assessment. Of 113 remaining, 69 (61.1%) achieved a CMR at ERA and were spared RNRT and glucocorticoids during the CAPDac cycles. The 2-yr EFS was 94.7% (95% CI: 90.3%-99.4%) and OS 100% (95% CI: 100%-100%). Five of six relapses ($<$ 3 mo (N = 1), 3-12 mo (N = 2), and $>$ 12 mos (N = 3) following therapy) occurred in individuals with an IR. The most frequent grade $\geq$3 toxicities were lymphopenia (84.2%) and neutropenia (91.2%). Grade 3 and 4 febrile neutropenia occurred in 21.1% and 1%, respectively. Neuropathy grade $\geq$3 was not observed. Serious adverse events were rare (n = 4) and included: multi-organ failure during cycle 1 that recovered (n = 2), therapy-related myeloid leukemia in remission following allotransplant (n = 1), and infection-related death during allotransplant for relapse (n = 1). **Conclusions:** A metabolic-only response assessment in the AEPA-CAPDac regimen results in high rates of omission of consolidative RT and glucocorticoids while limiting cumulative anthracycline exposure and maintaining excellent 2-year EFS of 94.7% and OS of 100%. Clinical trial information: NCT03755804. Research Sponsor: Supported by Seagen Inc, which was acquired by Pfizer in December 2023.

10019 **Rapid Oral Abstract Session**

Second malignant neoplasm risk after mediastinal radiotherapy for pediatric Hodgkin lymphoma on Children's Oncology Group AHOD1331. First Author: Sarah Milgrom, University of Colorado School of Medicine, Aurora, CO

Background: The reported incidence of second malignant neoplasms (SMN) in long-term survivors of Hodgkin lymphoma (HL) is derived from patients treated with outdated radiation therapy (RT) techniques. We modeled the risk of SMN in pediatric patients with high-risk classic HL treated with modern mediastinal RT. **Methods:** In patients who received mediastinal RT on the Children's Oncology Group study AHOD1331, we modeled the lifetime attributable risk (LAR) at 70 years of age of thyroid, lung, and breast carcinoma. This value indicates the absolute increased risk of SMN at 70 years of age due to RT, above the baseline population risk (mean baseline rates at 70 years of age are 0.7%, 3.3%, and 8.9% for thyroid, lung, and breast carcinoma, respectively, https://seer.cancer.gov/data/). **Results:** In 296 patients who received protocol-directed mediastinal RT, median age at diagnosis was 15.1 years, 55% were female, and 98% had large mediastinal adenopathy. Following 5 cycles of chemotherapy, patients received RT targeting the mediastinum based on criteria of this study; in addition, some patients received RT to other supradiaphragmatic sites that contained slowly responding lesions, including the axilla (n = 3, 1%), lung (n = 7, 2.4%), upper neck (n = 4, 1.3%), and lower neck (n = 8, 2.7%). The RT modality was proton therapy in 25.3%, photon intensity modulated RT (IMRT) in 45.6%, and photon 3-dimensional conformal RT (3D-CRT) in 27.7%. The RT prescription dose was 21 Gy in 83% and 30 Gy in 16% who had a partial metabolic response at the completion of chemotherapy. The mean (range) doses to the thyroid, lungs, and breasts were 12.8 Gy (0-30.3), 8.0 Gy (0.1-15.2), and 4.2 Gy (0.2-14.5), respectively. For the complete cohort, the mean LAR at 70 years of age of thyroid carcinoma was 0.063% and of lung carcinoma was 5.34%. For females, the mean LAR at 70 years of age of breast carcinoma was 2.92%. The Table summarizes the LAR for each SMN, stratified by RT modality. **Conclusions:** In patients treated with mediastinal RT on a recent multi-institutional study of pediatric HL, the predicted long-term risk of SMN is substantially lower than in historical cohorts. Clinicians should consider the toxicity associated with a current RT approach when selecting therapies and counseling patients. Clinical trial information: NCT02166463, this is a post hoc modeling study that includes patients enrolled on this study. Research Sponsor: None.

Mean [range] lifetime attributable risk (%) at an attained age of 70 years for thyroid, lung, and breast carcinoma.

	Thyroid	Lung	Breast (females)
3D-CRT	0.046 [0.002-0.332] N=81	5.07 [0.12-10.82] N=82	1.82 [0.67-5.98] N=46
IMRT	0.064 [0.001-0.386] N=135	6.24 [2.22-11.79] N=135	4.36 [0.66-8.43] N=76
Proton	0.086 [0-1.160] N=74	4.15 [0.94-7.77] N=75	1.45 [0.17-7.23] N=40

10020 Rapid Oral Abstract Session

Mortality in survivors of childhood cancer diagnosed with subsequent thyroid cancer: A report from the Childhood Cancer Survivor Study. First Author: Dana Barnea, Tel Aviv Sourasky Medical Center, Tel Aviv, Israel

Background: Childhood cancer survivors are at increased risk of developing a subsequent thyroid cancer, particularly following radiotherapy. In the general population, thyroid cancer has a very low mortality rate. Mortality after a diagnosis of subsequent thyroid cancer in survivors is unknown. **Methods:** We calculated the standardized mortality ratio (SMR) following the development of subsequent thyroid cancer in a cohort of 24,683 5-year survivors of childhood cancer diagnosed between 1970 and 1999 using the age-sex-calendar-year-specific general population all-cause mortality rates from the CDC as the reference rates. We estimated all-cause mortality post the diagnosis of thyroid cancer (time-dependent covariate), adjusting for development of other subsequent malignant neoplasms (SMN) and chronic health conditions (CHC), using a piecewise exponential model. Thyroid cancer-specific mortality among survivors was compared to SEER cases with thyroid cancer, adjusting for age, sex, race and calendar-year. SEER data was also used to compare thyroid cancer characteristics in childhood cancer survivors with thyroid cancer patients without a history of childhood cancer. **Results:** Among 397 survivors with subsequent thyroid cancer, 63% were female, 83% had received radiotherapy for treatment of their primary childhood cancer with fields that included the thyroid gland, and 92% had at least one severe or life-threatening chronic condition. Thyroid tumor size was significantly smaller in survivors, with 33% of cases in survivors and 24% in SEER being less than 1 cm ($p < 0.001$). There were 82 deaths with 7 deaths due to thyroid cancer. Within the cohort of survivors of childhood cancer, the rate of all-cause mortality did not increase with a diagnosis of thyroid cancer, adjusting for development of other SMNs and CHCs (RR = 1.0, p = 0.96), but it was 7 times higher than that of the general population (SMR = 6.9, 95% CI 5.5-8.5). Compared to adults diagnosed with thyroid cancer in the general population, survivors with subsequent thyroid cancer did not have an increased risk of thyroid cancer-specific death (RR = 0.9, 95% CI 0.4-1.9). Mortality risk was higher among those with older age at subsequent thyroid cancer diagnosis, male sex, Black and Hispanic race and ethnicity and tumor size $>$ 1 cm. **Conclusions:** The rate of all-cause mortality does not increase with a diagnosis of subsequent thyroid cancer in childhood cancer survivors. This finding suggests that thyroid cancer screening in this population should be based on reducing morbidity since it likely will not provide survival benefit. Enhanced attention to CHC management may be critical for long-term survival. Research Sponsor: U.S. National Institutes of Health.

10021 Rapid Oral Abstract Session

Social determinants of health (SDOH) and late mortality among survivors of childhood cancer: A report from the Childhood Cancer Survivor Study (CCSS). First Author: Cindy Im, University of Minnesota, Minneapolis, MN

Background: Neighborhood-level SDOH may increase disparities in adverse cancer-related outcomes. The US CDC-constructed Social Vulnerability Index (SVI) reflects 4 SDOH domains (socioeconomic status [SES]; household composition; minority status/language; housing/transportation) and captures the vulnerability of underserved communities. The impact of neighborhood-level SDOH on late mortality among survivors of childhood cancer is not known. **Methods:** Analyses included 5-year survivors in the US diagnosed in 1970-1999 participating in the CCSS, a multi-institutional retrospective cohort study. We evaluated geocoded SVI quintiles (Q1 to Q5, from least to most vulnerable) based on residential addresses and personal SES factors including income, education level, and health insurance status collected at CCSS baseline. The impact of SVI and personal-level SES on all-cause and cause-specific mortality rates were evaluated using cumulative incidence and relative rates (RRs) from piecewise exponential regression models adjusted for age, sex, diagnosis age, and treatments. **Results:** Among 20,261 survivors with geocode data (mean age at cancer diagnosis and baseline evaluation, 7y and 24y respectively, with a mean follow up of 17y), 2,439 survivors died. All-cause late mortality was greater in survivors living in more vulnerable areas (Q5 vs. Q1, at 20y: 14.7% vs. 10.8%, $P<0.001$). We observed a dose-response relationship between worsening SVI and the all-cause mortality rate (Q5 vs. Q1 RR 1.52, 95% CI 1.32-1.76, $P_{trend}<0.001$) as well as for mortality rates due to specific health causes (Table). Among the SDOH domains, neighborhood SES (Q5 vs. Q1 RR 1.68, 95% CI 1.45-1.95) showed the strongest association with all-cause mortality followed by household composition (RR 1.43, 95% CI 1.24-1.66). Notably, these findings remained largely consistent after adjusting for personal-level SES as well as in analyses stratified by income and insurance coverage. **Conclusions:** Living in socially vulnerable neighborhoods during young adulthood is associated with a ~50% increased risk for late mortality among survivors of childhood cancer and is largely unaffected by favorable personal-level SES. Policies and interventions targeting neighborhood-level SDOH during the transition to survivorship care are needed to reduce mortality risk in this population. Research Sponsor: None.

Adjusted RRs and 95% confidence intervals for overall and cause-specific mortality.

SVI	All cause	Subsequent neoplasm cause	Cardiovascular cause	Other health causes
Q2	1.00 (0.88 - 1.14)	0.90 (0.74 - 1.11)	1.09 (0.76 - 1.55)	1.09 (0.85 - 1.39)
Q3	1.16 (1.02 - 1.32)	1.03 (0.84 - 1.27)	1.18 (0.82 - 1.70)	1.24 (0.97 - 1.59)
Q4	1.24 (1.08 - 1.42)	1.12 (0.90 - 1.39)	1.29 (0.88 - 1.90)	1.44 (1.11 - 1.86)
Q5	1.52 (1.32 - 1.76)	1.35 (1.07 - 1.69)	1.54 (1.02 - 2.33)	1.83 (1.38 - 2.42)

SVI Q1 (least vulnerable) is the referent.

10022 Rapid Oral Abstract Session

Five-year cardiomyopathy risk prediction in survivors of childhood cancer using electrocardiogram. First Author: Luke Patterson, Wake Forest School of Medicine, Winston-Salem, NC

Background: Childhood cancer survivors (CCS) face an increased risk of developing cardiomyopathy during adult life due to late onset of treatment (e.g. anthracyclines and chest directed radiation) associated cardiotoxicity. Early identification of survivors at elevated risk using low cost and easily accessible data modalities can identify survivors in need of echocardiographic screening. Our goal is to utilize 12-lead electrocardiogram (ECG) develop and externally validate an artificial intelligence model (ECG-AI) for prediction of five-year risk for cardiomyopathy among CCS. **Methods:** We developed three deep learning models including a modified ResNet (a convolutional neural network architecture), an encoder-attention network, and a dual attention network to predict cardiomyopathy risk from 10 second 12-lead ECGs. We used the St Jude Lifetime Cohort Study (SJLIFE) for model building using a 60/20/20 patient-level split for training, validation, and holdout testing. We evaluated model performance for all cardiomyopathy grades (Common Terminology Criteria for Adverse Events) and specifically grade 3 (severe) cases. The final model was externally validated in the Dutch Childhood Cancer Survivor Study (DCCSS-LATER) cohort. For the DCCSS-LATER cohort, we evaluated accuracy of ECG-AI for the five-year cardiomyopathy risk prediction. **Results:** SJLIFE analytical cohort included 7,632 ECGs from 4,795 unique participants with no cardiomyopathy. 228 participants developed cardiomyopathy at least one year after index ECG date. Participants were 79% white, 11% Black, and 49% male with mean age at ECG of 33 ± 10 years. In SJLIFE holdout, the encoder-attention model achieved the highest performance (area under the receiver operating characteristic curve (AUC) 0.75 for all grades and 0.84 for $\geq$grade 3 cases). The modified ResNet and dual attention models achieved AUCs of 0.69 and 0.72, respectively. DCCSS-LATER data included 749 ECGs with from 330 unique patients (48% male, age at ECG of 28 ± 10 years). 22 patients developed cardiomyopathy at least one year after index ECG date. The encoder-attention model achieved an AUC of 0.74 for 5-year cardiomyopathy risk prediction. We note that the cardiomyopathy grading was not available in DCCSS-LATER, this study instead used a broader cardiomyopathy diagnosis information. **Conclusions:** ECG-AI analysis of standard 10 second 12-lead ECGs can identify childhood cancer survivors at risk for future cardiomyopathy with moderate to high accuracy depending on the cardiomyopathy severity. Future studies will focus on improving accuracy by incorporating clinical data such as B-type natriuretic peptides, left ventricular ejection fraction. Research Sponsor: National Cancer Institute; R01CA261834.

10023 Rapid Oral Abstract Session

Does early phase study enrollment for pediatric oncology patients have an impact on symptom burden and quality of life (QOL)? A national Canadian study report. First Author: Kendra Rodden, The Children's Hospital of Eastern Ontario, Ottawa, ON, Canada

Background: There are few therapeutic options for pediatric patients with relapsed or refractory cancers. The impact of early phase trial enrolment on the quality of life (QOL) and symptom burden in this patient population is unknown. We hypothesized that this information could inform future clinical trial design and would be of value to clinicians, patients and their families. The primary aim was to determine if those enrolled on a phase I or II trial had improved QOL measured using the PedsQL 3.0 Acute cancer Module compared to those eligible, not not enrolled on a trial. **Methods:** In this Canadian multi-site study, we included patients 2-18 years of age who were enrolled on a phase I/II clinical trial and those who would have been eligible but did not enroll. The PedsQL 3.0 Acute Cancer Module was completed at baseline, week 4 and week 8 by guardians and by patients, for those age 5 and older. The PedsQL 3.0 Acute Cancer Module total scores were compared separately for patients and guardians using a mixed linear registration model with a random effect for a patient. **Results:** Of the 80 patients, 31 (39%) patients were enrolled on an early phase trial and 49 (61%) were not enrolled. The majority of patients had a brain tumor (63.3% of those enrolled; 32.7% of those not), followed by a bone tumor (16.7% of those enrolled; 24.5% of those not). In both groups, the majority of patient were included at the time of their first relapse (64.5% of those enrolled and 69.9% of those not). No significant difference was found between PedsQL3.0 patients or guardians; p = 0.09). The PedsQL3.0 total scores were significantly higher for patients enrolled on an early phase trial compared to those patients not enrolled (p = 0.01). However, after adjusting for baseline levels, the difference between enrolled patients vs not was not statistically significant (p = 0.8). **Conclusions:** Being enrolled on an early phase trial does not appear to have a negative effect on one's quality of life. The results have also demonstrated that it is feasible to evaluate patients enrolled and not enrolled on early phase trials and compare their symptom experience using the PedsQL 3.0 Acute cancer Module. Continued efforts will focus on more recruitment and using SSPedi to further investigate differences in QOL. This research is supported through C17 Council, Kindred Foundation and the CHEO Research Institute. Research Sponsor: C17; Kindred Foundation; The Children's Hospital of Eastern Ontario Research Institute.

10024 **Rapid Oral Abstract Session**

Determining the recommended phase 2 dose (RP2D) of dose-intense irinotecan combined with IVA chemotherapy (I_RIVA) in newly diagnosed very high risk rhabdomyosarcoma: A phase Ib study within the EpSSG Frontline and Relapsed Rhabdomyosarcoma study (FaR-RMS). First Author: Hans Merks, Princess Máxima Center for Pediatric Oncology, Utrecht, Netherlands

Background: Event-free survival for patients in the highest risk groups of rhabdomyosarcoma (RMS) remains poor. The COG ARST0431 study showed that dose-intensified chemotherapy benefits a subset of metastatic RMS patients. This phase Ib trial defined the safety profile, highest tested dose (HTD), and recommended phase 2 dose for dose intense irinotecan on days 8-12 combined with the standard European 3-weekly Ifosfamide, Vincristine, Actinomycin D (IVA) regimen within the European *paediatric* Soft tissue sarcoma Study Group (E*p*SSG) Frontline and Relapsed Rhabdomyosarcoma (FaR-RMS) study (ClinicalTrials.gov: NCT04625907). **Methods:** Patients aged >1 to ≤25 years with Very High Risk (VHR) RMS (FOXO1 fusion-positive, node-positive, Subgroup G and metastatic, Subgroup H) were included in designated Phase I centres. Participants received IVA (Ifosfamide 3000 mg/m² on days 1–2; vincristine 1.5 mg/m2 on days 1 and 8 and on day 15 in cycle 1 and 2 only; actinomycin D 1.5 mg/m2 on day 1 with irinotecan on days 8–12. The irinotecan starting dose was 20 mg/m²/day, with dose escalation/de-escalation to a maximum of 50mg/m2/day utilising a rolling six design. The Dose Limiting Toxicity (DLT) period was defined as up to 28 days after the start of cycle 2. All Adverse events (AEs) were assessed against the DLT definition during this time. DLTs included Grade 3 diarrhoea, enterocolitis, ileus or oral mucositis persisting > 3 days; Grade 4 diarrhoea; neutropenia or thrombocytopenia delaying treatment > 7 days; Grade 3/4 toxicities resulting in treatment discontinuation, or any Grade 5 toxicity (death) related to trial treatment. First radiological response assessment was after cycle 3 I_RIVA. **Results:** A total of 22 patients (Subgroup G, 3; Subgroup H, 19) were enrolled across 4 dose levels (20 mg/m2/day (n = 5); 30 mg/m2/day (n = 5); 40 mg/m2/day (n = 6); 50 mg/m2/day (n = 6)). Median age was 13.4 years; interquartile range, 5.2-16.3 years. All patients were evaluable for DLTs. One DLT of Grade 3 enterocolitis was observed at dose level 50 mg/m². The HTD and RP2D of irinotecan in combination with IVA were established as 50 mg/m²/day. The most common Grade 3/4 AEs occurring in > 30% of patients, during the first 3 treatment cycles were: febrile neutropenia 13 (59.1%), neutropenia 13 (59.1%); leukopenia 12 (54.5%); anaemia 10 (45.5%), and lymphopenia 7 (31.8%). The overall Response Rate (Complete or Partial Response) at first assessment was 81.8% (18/22). **Conclusions:** The RP2D for irinotecan on days 8-12 within I_RIVA was identified as 50 mg/m²/day. The intensified I_RIVA regimen is under evaluation in randomised questions, in adults and children with paediatric-type RMS, within the FaR-RMS trial in High Risk patients (IVA vs I_RIVA) and VHR patients (IVA plus doxorubicin vs I_RIVA). Clinical trial information: NCT04625907. Research Sponsor: Cancer Research UK.

10025 **Rapid Oral Abstract Session**

Integrated molecular characterization of pediatric soft tissue sarcomas: A report from the COG and CCDI molecular characterization initiative. First Author: Sapna Oberoi, CancerCare Manitoba, Winnipeg, MB, Canada

Background: The Molecular Characterization Initiative (MCI), a partnership between the Children's Oncology Group (COG) and the NCI's Childhood Cancer Data Initiative (CCDI), provides standardized genomic profiling of tumors and germline for subjects with newly diagnosed pediatric soft tissue sarcomas (STS). Here, we report on STS patients <25 years enrolled in MCI from July 2022 to July 2023. **Methods:** MCI enrollment was offered to COG institutions through APEC14B1 (Project: EveryChild), enabling patient consent, collection of clinical data, and submission of tissue/blood samples. Bio-pathology Center centrally managed sample processing, quality control, and nucleotide extraction, while molecular assays were performed at Nationwide Children's Hospital's Institute for Genomic Medicine. Whole-exome sequencing (WES) of tumor/normal, DNA methylation arrays and RNA fusion analysis were conducted in a CLIA-certified environment. Clinical reports, except methylation results, were returned to treating institutions within 21 days, and clinical, sequencing and methylation data were deposited in NCI's Cancer Data Service. **Results:** In total, 226 rhabdomyosarcoma (RMS),158 non-rhabdomyosarcoma soft tissue sarcoma (NRSTS), and 36 non-malignant soft tissue tumors (21 desmoid tumors) from 129 institutions were enrolled. Of 172 RMS patients, 56 were fusion-positive (FP) (46 with *FOXO1* fusion and 10 with fusions of other genes). WES of 179 RMS patients identified somatic mutations in 33 genes in 110 patients (61.4%). Most frequently mutated genes included *FGFR4* [25/179,14%; FN (fusion-negative) RMS:21%, FP RMS:2%), *TP53* (21/179,12%; FN RMS:15%, FP RMS: 7%), and *NRAS* (18/179, 10%; FN RMS:14%, FP RMS: 3%). Somatic copy number variants (CNVs) were detected in 164/179 (92%) of RMS patients. Germline variants were identified in 18 of 179 RMS (10%; FN RMS:15%, FP RMS: 2%); and most commonly germline altered genes included *TP53* (4/179, 2%), *APC* (2/18, 1%), and *ATM* (2/179,1%). Among 158 NRSTS > 20 histologies were enrolled, most common being synovial sarcoma (n = 16, 8%). Of 49 patients with an initial diagnosis of undifferentiated sarcoma, round cell sarcoma, spindle cell sarcoma and sarcoma NOS, 32 underwent fusion testing, and 28 had WES: in 13 (40%) sequencing resulted in specific diagnosis [CIC::DUX4 in 5, BCOR::CCNB3 in 4, *NTRK* rearrangement in 2, SS18::SSX2 in 1 and EWSR1::ETV1 in 1], and 5 (15%) had rare fusions involving *NUTM1*, *NSD3*, *EGFR* and *COL1A1* genes;16 exhibited somatic CNVs; 5(18%) had somatic mutations; and 2 (7%) carried germline variants in *TP53* and *RET* genes. Overall, MCI results, as reported by institutions, facilitated clinical trial enrollment in 15%, receipt of targeted therapy outside trials in 17%, and diagnostic refinement in 25% of tested patients, respectively. **Conclusions:** CCDI's MCI program provides comprehensive genomic profiling of pediatric and adolescent STS, uncovering distinct somatic genetic alterations, rare fusions, actionable genomic targets and germline variants. Research Sponsor: St. Baldrick's Foundation; NCTN Operations Center Grant; U10CA180886; Statistics and Data Center Grant; U10CA098413.

10026 **Rapid Oral Abstract Session**

Gut microbiome changes in pediatric AML and association with event free survival. First Author: Oren Gordon, Children's Hospital of Colorado, Aurora, CO

Background: Pediatric acute myeloid leukemia (AML) is characterized by months of hospitalization with a high risk for infections and a higher rate of relapse than many pediatric leukemias. Recent studies have highlighted the relationship between gut microbiome changes, long term cancer outcomes, and development of comorbidities. However, no study to date has examined the longitudinal changes in the gut microbiome in pediatric AML patients. **Methods:** In this retrospective study, longitudinal stool samples were taken from 14 pediatric patients with AML treated at Children's Hospital Colorado. Sample collection started after initial diagnosis for 11 patients and after first relapse for 3 patients. These samples were analyzed using 16S ribosomal RNA (rRNA) gene sequencing along with clinical data extracted via manual chart review. **Results:** We found that the relative abundance of genus *Fusobacterium* was associated with relapses. Analysis indicated that Fusobacterium was significantly elevated in the stool of 3 of 6 newly diagnosed patients who relapsed within 5 years (using a linear model that also accounted for risk stratification based on genetics and treatment response (p = 0.03)). These patients had elevated *Fusobacterium* at multiple timepoints during treatment. Samples from the 5 newly diagnosed patients who did not relapse showed minimal *Fusobacterium*. *Fusobacterium* has previously been associated with other cancers, oncogenesis and immune evasion. Of the 14 patients, 5 experienced 1-4 cases of *Streptococcus mitis* bacteremia (SMB) during the sample collection period. Genus *Streptococcus* abundance in stool samples collected immediately prior to SMB did not correlate with positive blood cultures, although this genus was highly prevalent in the gut microbiome of patients with repeated episodes. Using mixed effects random forest model (MERFM) to broadly survey whether changes in any other gut bacteria predicted a positive SM blood culture, we found evidence for a negative relationship between SMB and change in relative abundance of genus *Blautia*, and a positive relationship with the genera *Marvinbryantia, Anaerococcus, Parabacteroides* and *Dielma*. This suggests that other aspects of microbiome composition may influence whether *Streptococcus* can translocate into the bloodstream. Of the 14 patients, 4 developed *Clostridioides difficile* infections (CDI) during the collection period. Increases in genus *Clostridioides* relative abundance occurred prior to clinical CDI. Using MERFM, Faith Phylogenetic Diversity was negatively related to development of CDI and presence of the genera *Anarofustis, Bilophila, Alistipes* and was positively related to CDI. **Conclusions:** These results show that the gut microbiome may be implicated or serve as a prognostic indicator for relapse in pediatric AML. Additionally, longitudinal gut microbiome changes in patients may be associated with various clinical complications. Research Sponsor: None.

10027 **Poster Session**

New pediatric formulation of asciminib in children with chronic myeloid leukemia in chronic phase: Second interim analysis of pharmacokinetics and safety from the ASC4Kids study. First Author: Nobuko Hijiya, Pediatric Hematology, Columbia University Irving Medical Center, New York, NY

Background: More treatment (tx) options to improve efficacy and long-term safety to minimize adverse effects on growth are needed for pediatric patients (pts) with Philadelphia chromosome-positive (Ph+) chronic myeloid leukemia in chronic phase (CML-CP). Asciminib (ASC) is the first BCR::ABL1 inhibitor that Specifically Targets the ABL Myristoyl Pocket (STAMP), approved for adults with newly diagnosed or previously treated CML-CP. The phase Ib/II, multi-center, open-label ASC4Kids study (NCT04925479) aims to identify the pediatric formulation (PF) dose (with food) leading to ASC exposure comparable to the adult formulation (AF) dose (fasted) of 40 mg twice daily (BID) and assess its safety. **Methods:** Pts aged 1– < 18 years (yrs) with CML-CP, without the T315I mutation, treated with ≥1 prior tyrosine kinase inhibitors are included. The primary objective is to characterize the pharmacokinetic (PK) profile of ASC in pediatric pts. Secondary endpoints include safety and molecular responses. In an exploratory AF group, pts 14– < 18 yrs were treated with the AF. In Part 1 (dose determination), the PF dose of 1.3 mg/kg BID was confirmed based on exposure in adult studies (40 mg BID) and no observed dose-limiting toxicities (DLTs) over the first 28 days. In Part 2 (dose expansion), additional pts are treated with the confirmed PF dose for further evaluation of exposure and DLTs (across Parts 1+2; 10 pts per group: 1– < 12 yrs and 12– < 18 yrs). In Part 3, 10 more pts will be enrolled to receive PF 2.6 mg/kg once daily (QD). This interim analysis was conducted after 10 pts in the PF 12– < 18 yrs group had completed 28 days of tx in Parts 1+2. **Results:** 19 pts were enrolled in the PF group (7 in 1– < 12 yrs and 12 in 12– < 18 yrs groups, respectively). At data cutoff (19-Aug-2024), all pts continued to receive tx. For the PF group (12– < 18 yrs), 10 pts were evaluable for PK. Averaged ASC exposure with PF 1.3 mg/kg BID was comparable to that observed in adult studies (median last measured concentration [AUClast]: 7091 vs 5130 hr*ng/mL; median maximum plasma concentration [Cmax]: 1031 vs 939 ng/mL, respectively). For all pts in the PF group, no DLTs were observed. With a median duration of exposure of 36.7 weeks, 18 pts experienced adverse events (AEs; any grade); 2 had Grade ≥3 AEs. From baseline (BL) to data cutoff for height percentile shift in the PF group; 9 pts stayed in the same percentile, 4 dropped and 6 increased. Four of 19 pts had notably low bone age at BL; 3 of these also at Week 52. At BL,16/18 pts in the PF group had *BCR::ABL1*^{IS} ≤10% and 6 were in major molecular response (MMR). Of 11 and 9 pts evaluable for efficacy at Weeks 28 and 40, 10 and 9 had *BCR::ABL1*^{IS} ≤1%, and 7 and 6 were in MMR, respectively. **Conclusions:** The confirmed PF ASC dose of 1.3 mg/kg BID was well tolerated in pediatric pts, with evidence of efficacy and no new safety signals. In Part 3, a 2.6 mg/kg dose QD will be evaluated. Clinical trial information: NCT04925479. Research Sponsor: Novartis Pharmaceuticals.

10028 **Poster Session**

Financial toxicity and association with treatment outcomes during pediatric CAR T therapy. First Author: Daniel J. Zheng, Children's Hospital of Philadelphia, Philadelphia, PA

Background: Chimeric antigen receptor T cell (CAR) therapy has revolutionized the treatment of relapsed/refractory pediatric B cell malignancies. However, the financial toxicity (FT) experienced by families is unknown despite the likely high burden imposed by clinic visits, hospital admissions, and potential travel/relocation to referral centers. We present the first report of pediatric FT among families of children receiving CAR therapy including prevalence, trajectory, and impact on outcomes. **Methods:** This is a prospective cohort analysis of patient (pt) and caregiver-reported FT outcomes for pediatric and young adult pts receiving CD19-directed CAR therapy at the Children's Hospital of Philadelphia. Caregivers (for pts $<$ 18 years old) or pts (if $\geq$ 18 years old) completed the Comprehensive Score for Financial Toxicity (COST) prior to CAR infusion (baseline), 1 month, and 3 months post-infusion. COST is a self-report FT measure that has been used in adults with specific validated grading criteria (0-3) anchored on independent differences in health-related quality of life. We described baseline FT and tested its association with treatment-related toxicity (occurrence of any cytokine release syndrome [CRS]) and outcomes (complete response [CR] at day 28) using multivariable models adjusted for time from diagnosis, prior CAR exposure, and disease burden at infusion. FT was hypothesized to impact outcomes through physiologic stress affecting immunologic response. In pts with COST data through 3 months, we described longitudinal FT trajectories. **Results:** From 9/2019-12/2024, 144 pts (33% racial/ethnic minority, 8% public insurance) or their caregivers (28% less than college degree, 22% annual household income $<$ $50,000) completed baseline COST measures. 94% of the cohort had caregiver-reported FT. 81% of pts were external referrals. The median baseline COST score was 20.0 (IQR: 11.0-29.0), which corresponds to Grade 1 FT. Two-thirds of pts reported FT, with 37%, 29%, and $<$ 1% of families experiencing grades 1-3 FT, respectively. 80% of pts had CRS; 89% had CR at day 28. Baseline FT was not associated with CRS or day 28 response (all $p > 0.2$). A subset of n = 80 had complete longitudinal data and follow up of at least 3 months. In this cohort, median COST score at baseline, month 1, and month 3 was 19.5 (IQR: 10.0-29.3), 18.5 (IQR: 11.0-27.3), 16.0 (IQR: 9.8-27.0), respectively. Strikingly, 23% and 25% of pts had clinically worse grades of FT at 1 month and 3 months post-infusion (compared to baseline), respectively. Race/ethnicity, language, insurance, caregiver education, and income were not associated with worsened FT over time. **Conclusions:** There is a high prevalence of FT at time of CAR infusion for families of pediatric and young adult pts. Reassuringly, FT at the time of infusion was not associated with two key treatment outcomes, but more investigation is needed. For a notable proportion of families, FT worsens over time and highlights the need for interventions to address cumulative financial burden. Research Sponsor: American Cancer Society.

10029 **Poster Session**

Growth recovery in patients with *BRAF* altered pediatric low-grade gliomas (LGG) after discontinuation of tovorafenib. First Author: Cassie Kline, Children's Hospital of Philadelphia, University of Pennsylvania, Philadelphia, PA

Background: Tovorafenib is a selective, CNS-penetrant, type II RAF inhibitor that targets BRAF and CRAF. Based on preclinical data, CRAF plays an essential role in chondrocyte maturation, a required step in linear bone growth. Children treated with tovorafenib in early phase studies demonstrate a reversible decrease in growth velocity consistent with CRAF inhibition with no signs of premature closure of growth plates or adverse effects on bone such as fractures or treatment emergent osteopenia. Here we report a combined analysis of off-treatment growth recovery in patients treated with tovorafenib in 3 clinical studies. **Methods:** Patients aged $<$ 18 years with *BRAF* altered relapsed/refractory LGG treated with tovorafenib in the Phase 1 PNOC014 study (NCT03429803), Phase 2 FIREFLY-1 study (NCT04775485), or Expanded Access Program (EAP) for patients (NCT05760586) were included. Relevant medical history, neuroendocrine medications, growth parameters, and tovorafenib dosing were collected. Pre- and post-treatment annualized growth velocity (AGV) was calculated for all patients with growth data available $\geq$90 days post-discontinuation of tovorafenib. **Results:** As of 17-Jan-2025,38/167 (23%) patients were evaluable for growth recovery. Among these evaluable patients, median age at start of treatment was 9.5 yrs (range 3.5 -16.5). Eighteen (47%) patients had a tumor associated endocrinopathy or comorbidity that may affect growth including growth hormone deficiency (8), thyroid disease (8), precocious puberty (6) and panhypopituitarism (4) at baseline. Four (11%) were receiving a gonadotropin-releasing hormone analogue for precocious puberty and 2 (5%) were receiving growth hormone replacement concurrent with tovorafenib. Median baseline height Z-score was -0.13 (range -2.57, 2.64) with 4 patients having Z-score $>$ 2 or $<$ -2. Median on-treatment AGV was 1.7 cm/yr [n = 36, interquartile range (IQR) 0.4 - 2.2] at 12 mo and 2.3 cm/yr (n = 25, IQR 0 - 3.3) at 24 mo. Median age at end of treatment was 11 yrs (range 4.4 - 17.5), and median off-treatment follow up was 10.3 mo (range 3.2 - 37.2). Median off-treatment AGV was 4.3 cm/yr (n = 38; IQR 1.8 - 7.6) at 3 mo, 10.2 cm/yr (n = 26, IQR 2.3 - 13.8) at 6 mo and 7.7cm/yr (n = 5, IQR 4.1 - 13.9) at 12 mo. Thirty-four (89%) patients had recovery of AGV, and 28 (74%) had an increase in Z-score towards baseline indicating catch-up growth. Patients with slow AGV recovery tended to be $>$ 15 years, younger females with precocious puberty/Tanner stage 4, or have only 3 months of off-treatment follow up. **Conclusions:** Decreases in growth velocity were common during tovorafenib treatment. Majority of patients to date demonstrate AGV recovery as early as 3 months with signs of catchup within 6-12 months after stopping tovorafenib. Preliminary findings indicate tumor-associated precocious puberty/Tanner stage 4 in females may be a risk factor for slow AGV recovery. Research Sponsor: Pacific Pediatric Neuro-Oncology Consortium; PLGA Fund at Pediatric Brain Tumor Foundation; Team Jack Foundation; National Cancer Institute; Day One Biopharmaceuticals.

10030 **Poster Session**

Cerebrospinal fluid proteome during chemotherapy for childhood leukemia: Identifying pathways associated with treatment and system toxicity. First Author: Justin Tanner, St. Jude Children's Research Hospital, Memphis, TN

Background: Acute Lymphoblastic Leukemia (ALL) is the most common childhood cancer with a 5-year survival rate $>$ 90%. Survivors treated on contemporary chemotherapy-only protocols are at heightened risk for musculoskeletal, endocrine, cardiac, and neurological/neurocognitive late-effects. Chemotherapy treatment doses and administration routes (i.e., intrathecal) are associated with the late-effects and alterations in targeted cerebrospinal fluid (CSF) proteins. We aimed to identify CSF proteome pathways linked to patient variables, treatment exposures, and early adverse events (AE). **Methods:** At diagnosis and the end of induction, CSF samples were collected from 178 ALL patients (71 females, mean age [range] 7.6 [0.5-18.8] years at diagnosis) treated on a chemotherapy-only protocol. Expression of 3188 proteins was measured via tandem-mass-tag mass spectrometry and clustered via Weighted Gene Co-expression Network Analysis (WGCNA). Severe/life threatening (CTCAE grade 3/4) AEs across multiple organ systems were compiled per patient. Trait-Cluster association was assessed by generalized linear models, linking cluster-specific eigenvalues to final treatment risk stratum (Standard/High vs Low) and AE occurrence, with false discovery rate corrected significance threshold of $p < 0.2$. Protein-Protein Interaction (PPI) network and enrichment analysis were performed by STRING within target clusters. **Results:** Patients experienced AEs in 24 organ systems (86% post-induction) and $>$ 5% of patients experienced toxicities in 6 systems during and 11 after induction. A total of 1770 proteins were measured at both time points and WGCNA revealed 8 clusters at diagnosis (T1; 1046 proteins) and 13 after induction (T2; 1184 proteins). Four T1 clusters were associated with post-induction Hepatobiliary/Pancreas AEs ($p < 0.022$). Five T2 clusters were associated with treatment risk ($p < 0.055$) and eight were associated with AEs: Hepatobiliary/Pancreas ($p < 0.184$), Musculoskeletal/Soft Tissue ($p < 0.151$), or Neurology ($p < 0.196$). In four T2 clusters associated with both risk and AEs, PPI analysis revealed 251 pathways involved in nervous system development, skeletal/cardiac development, and immune regulation. **Conclusions:** The associations of Musculoskeletal/Soft Tissue, Neurology, and Hepatobiliary/Pancreas AEs with risk-associated clusters suggest pathological protein dynamics exacerbated by treatment intensity. These changes are reflected in different T1 and T2 cluster composition and the emergence of new clusters after induction. Associations between protein clusters, treatment risk, and AEs biologically connect treatment exposures to toxicities, providing mechanistic targets to reduce late-effects. Future work includes isolating enriched pathways and hub proteins to gain insight into specific protein dynamics contributing to AEs. Research Sponsor: None.

10031 **Poster Session**

Unraveling gut gram-negative antibiotic-resistant colonization dynamics in hematologic cancers: Insights from bioinformatics and immune signatures. First Author: Mahdi Malekpour, Shiraz University of Medical Sciences, Shiraz, Iran

Background: Infections account for ~60% of cancer-related deaths. Hematologic cancers have a 3x higher infection-related mortality than solid tumors, with resistant Gram-negative (GN) bacteria causing ~50% of bloodstream infections, highlighting the need to study the microbiome, antibiotic resistance, and infection risks. **Methods:** Stool samples from newly diagnosed hematologic cancer patients were collected at baseline, post-chemotherapy, and subsequent admission at Amir Hospital, a referral cancer center in southern Iran, to analyze microbial colonization dynamics. Patients enrolled in a 16-month observational program to investigate the correlation between clinical factors and infectious outcomes. Carbapenem-resistant and ESBL-producing were cultured on MacConkey agar with meropenem and ceftriaxone. ESBL and carbapenemase production assessed adhering to CLSI guidelines. To support our findings, we used the microbioTA database to identify highly elevated 16S rRNA expression in blood and lymph nodes of hematologic cancer patients, exploring microbiome-host interactions worldwide. We used gutMgene, GIMICA, and AMIDIS databases to explore key microbe-immune factor associations trough network centrality analysis of the immune factors. Central factors further examined in the Amir Cancer Registry datasets to assess their association with infectious events. STATA v27 used for statistical analyses. **Results:** Among 73 pediatric patients, GN drug-resistant bacteria was detected in 51 before hospitalization. *Escherichia coli* (86.6% of positive samples) and *Klebsiella pneumoniae* (9.5%) were the predominant pathogens. Drug-resistant E. coli persisted across samples, indicating gut colonization, consistent with microbioTA data showing E. coli detection at baseline and post-induction therapy. ESBL and carbapenemase-producing strains were 56.8% and 15.8%. Colonized patients had a 13.8% mortality rate, with bloodstream infections and typhlitis more common in K. pneumoniae and carbapenem-resistant strains. Previous antibiotic exposure, malignancy relapse, and colonization status were risk factors for mortality and infection. Investigation of the microbioTA database identified 10 datasets from Asia, Europe, and America revealed the detection of *Bacillus cereus* in 9 datasets, followed by E.coli (8) and Enterobacterales like *Salmonella enterica* (5) and K.pneumoniae (3), approving the high impact of E.coli worldwide. IL-4, IL-6, and TNF-α showed high centrality, with retrospective analysis linking their upregulated serum baseline levels to infection outcomes in Amir hospital datasets. **Conclusions:** Our study links GN microbial colonization, traced by elevated immune markers, to infectious complications, highlighting the need for microbiota-specific diagnostic and treatment protocols. Research Sponsor: None.

10032 **Poster Session**

Association of baseline clinical factors with outcomes in patients with localized Ewing sarcoma treated on frontline trials with interval compressed chemotherapy (ICC): A report from the Children's Oncology Group. First Author: Ajay Gupta, Roswell Park Comprehensive Cancer Center, Buffalo, NY

Background: Identifying clinical and biological factors associated with outcomes in localized Ewing sarcoma (ES) will enable risk-stratified clinical trials with the goal of improved outcomes for high-risk patients and decreased treatment toxicity for low-risk patients. The specific aims of this analysis in localized ES patients were 1) to classify extraosseous (EO) primary tumors with subdivisions into deep (viscera, glands, body cavities, muscle, nerves) and superficial (cutaneous and subcutaneous) sites, and 2) to understand the relationship between baseline clinical factors (age, sex, primary tumor site, size (maximum dimension and volume)) and event-free survival (EFS). **Methods:** The analytic cohort included ES patients treated with ICC on AEWS0031 and AEWS1031. Primary tumor sites were defined as pelvic, non-pelvic, and EO (deep vs. superficial). Post-enrollment EFS was the primary endpoint. Univariate analyses used the Kaplan–Meier method (logrank test). Multivariable analyses used Cox proportional hazards models. To assess the impact of tumor volume as a continuous variable, a subgroup analysis was conducted using AEWS1031 only, as tumor volumes were collected prospectively on this study. Visual exploration of effects of continuous variables on EFS event hazard used restricted cubic splines with 3 knots. Tests were performed at the 5% level. **Results:** AEWS0031 (n = 628) and AEWS1031 Regimen B (n = 283) yielded 911 patients. In univariate analyses, difference in risk of EFS event was observed between tumor sites (P= 0.03). EO tumors had the highest estimated EFS compared to pelvic and non-pelvic (5 year EFS 84.7% vs. 72.4% and 75.9%). Superficial EO appeared to be a very low-risk group, albeit interpretations are limited by the small group size and singular event (one second malignant neoplasm among 15 patients). In multivariable analysis of the combined cohort, sex, race, and ethnicity were not prognostic. EO tumors may be associated with decreased hazard compared with non-pelvic bone primaries (HR 0.58, P= 0.07), and tumors $\geq$200 mL with increased hazard (HR 1.56, $P<$ 0.01). In the subgroup analysis, tumor volume and age were prognostic and in visualizations age was non-linearly related to the hazard of EFS event, increasing until approximately 15 years. Tumor volume was non-linearly related to the hazard of EFS event and increased until approximately 400 mL. **Conclusions:** Patients with ES and primary tumors $\geq$200 mL continue to be at higher risk of an EFS event when treated with ICC, and EO tumors may be lower risk compared with other sites. Risk of an event appears to remain constant in ES patients $\geq$15 years or with primary tumors $\geq$400 mL. These findings should be validated in prospective trials and tumor biology integrated with clinical factors to improve risk stratification for localized ES. Research Sponsor: None.

10033 **Poster Session**

Demographic characteristics and survival outcomes of pediatric clear cell sarcoma of the kidney: A National Cancer Database retrospective study. First Author: Assal Sadighian, UC Riverside, Riverside, CA

Background: Clear Cell Sarcoma of the Kidney, CCSK, is a rare malignancy diagnosed during childhood. Compared to other pediatric renal neoplasms, CCSK is particularly aggressive due to its propensity for bone metastasis, resulting in a poorer overall survival rate. CCSK has a higher incidence in males than females. Given its rarity, investigating diagnostic patterns may reveal important epidemiological insights. This study analyzed the demographic factors in CCSK patients from the National Cancer Database (NCDB). **Methods:** A retrospective National Cancer Database (NCDB) from 2004 to 2020 analyzed patients who had a histologically confirmed diagnosis of CCSK (ICD-O-3 8964). Descriptive statistics were used to analyze Demographic factors (age, sex, race, Hispanic status, educational attainment, insurance status, facility type, distance from facility, and Charles/Deyo score). Regression analysis was utilized to interpret incidence trends. **Results:** Between 2004 and 2020, the NCBD identified 237 patients with confirmed CCSK, indicating a stable incidence rate (R^2 = 0.0043). The median age at diagnosis was 3 years old (SD = 24.83; range, 0–86). Males comprised 56% of the cohort, and 44% were females. Most patients were White (78%) and non-Hispanic (79%). Nearly all primary tumors (99%) occurred in the kidney and renal pelvis, with a median tumor size of 120 mm (SD = 42.33; range, 13–202). Over half of patients (54%) had private insurance, while 27% were on Medicaid. The majority (93%) had a Charlson/Deyo comorbidity score of 0. Most patients (99%) did not receive palliative therapy. 71% of the patients underwent a surgical procedure at the primary site, 70% received radiotherapy, and 76% received it as part of their primary treatment. Most patients (90%) lived in metropolitan areas, and they resided a median distance of 15 miles (SD = 57.1; range, 0.5-377.3) from the reporting hospital. The two-year, five-year, and ten-year survival rates were 86%, 81%, and 76%, respectively, with a mean survival of 163 months. **Conclusions:** To the best of our knowledge, this is the first NCDB analysis of CCSK, addressing a significant knowledge gap. Nearly all CCSK cases originated in the kidney or renal pelvis, consistent with literature indicating the kidney as the primary site with a stable incidence over time. These are the first socioeconomic factors of CCSK patients that have been described in the literature: CCSK patients are more likely to be white and non-Hispanic, male, have private insurance, and live in metropolitan areas. Further research is essential to better understand how demographic and socioeconomic factors influence the diagnosis, treatment choices, and overall survival of patients. Research Sponsor: None.

10034 **Poster Session**

Late effects in high-risk neuroblastoma survivors who received MIBG therapy. First Author: Prerna Kumar, University of Illinois College of Medicine, Peoria, Peoria, IL

Background: Meta-iodobenzylguanidine radiolabeled with iodine-131 (^{131}I-MIBG) is used to treat high-risk neuroblastoma (HRNB) as monotherapy as well as in combination with other therapies, however associated late toxicities have not been well studied. The aim of this study was to describe the characteristics of HRNB survivors who received ^{131}I-MIBG and determine if ^{131}I-MIBG is associated with subsequent malignancy, growth impairment, thyroid toxicities, and other major organ (musculoskeletal, gonadal, gastrointestinal, cardiac, or pulmonary) toxicities. **Methods:** The Children's Oncology Group LEAHRN study, ALTE15N2, evaluated HRNB survivors diagnosed after 2000 and at least five years from diagnosis. Clinical history was abstracted via study questionnaires. Clinical characteristics, treatment history, and the prevalence of late effects were descriptively summarized for subjects treated with ^{131}I-MIBG (cases). Subjects who did not receive ^{131}I-MIBG therapy were randomly selected and matched by age at diagnosis and relapse history (controls) in a 1:2 case-control study design. Chi-squared analysis was used to evaluate the association between ^{131}I-MIBG and late toxicities. P-values were adjusted using the Holm-Bonferroni approach. **Results:** Of 375 subjects enrolled in LEARHN, 32 (8.5%) received ^{131}I-MIBG. Of these, 17 (53%) reported relapsed or refractory disease. Mean age at ^{131}I-MIBG treatment was 5.1 years. 56% were male. Disease extent included an adrenal primary in 62%, multiple bone metastases in 72%, and bone marrow involvement in 63%. Thyroid toxicity (hypothyroidism, hyperthyroidism, or thyroid nodules) was similar in both groups, reported in 10/32 cases compared with 11/63 controls. One case (1/32) and four controls (4/64) reported a subsequent malignancy. Growth failure was reported in 35% of cases (11/31) and 23% of controls (16/63). Other major organ toxicities were also similar with no significant differences between cases and controls. **Conclusions:** In survivors of HRNB, the burden of late toxicities appeared similar in those treated with ^{131}I-MIBG compared to those who were not. This provides critical information for long-term follow-up care and clinical trial design. Research Sponsor: Children's Oncology Group National Clinical Trials Network Statistics and Data Center; NCTN Operations Center; Grant U10CA180886; St. Baldrick's Foundation Consortium Grant; Grant No. 353158; NCORP; Grant No. UG1CA189955.

10035 **Poster Session**

Survival and prognostic factors of patients with Ewing sarcoma at first recurrence following modern era multimodal therapy: A report from the Children's Oncology Group (COG). First Author: Sarah Cohen-Gogo, The Hospital for Sick Children, Toronto, ON, Canada

Background: Ewing sarcoma (EwS) is a rare malignancy of children, adolescents and young adults for which outcomes have progressively improved through intensification of conventional chemotherapy, including interval compression of cycles. Prior cooperative group reports of relapsed EwS included patients treated less intensively and with fewer treatment options at relapse. Here, we report overall survival (OS) and prognostic factors post-first recurrence in patients with EwS treated with frontline interval-compressed chemotherapy. **Methods:** We included patients treated on the last three phase 3 COG EwS studies treated with interval compressed chemotherapy, which accrued from 2001-2019. Patients with initially localized disease (L-EwS) were treated on AEWS0031 arm B and AEWS1031. Patients with initially metastatic disease (M-EwS) were treated on AEWS1221. The primary outcome was OS from first relapse. Demographic and clinical data from original diagnosis and from relapse were analyzed as potential prognostic factors. Kaplan-Meier survival curves were constructed and groups compared with log-rank tests. **Results:** 366 patients experienced disease recurrence as first event and were included in this analysis (AEWS0031 arm B, n = 69, AEWS1031, n = 115, for a total of 184 with L-EwS; AEWS1221, n = 182, all with M-EwS). Median age at relapse was 16 years. Median time from initial enrollment to first relapse was 1.52 years and was shorter for patients with M-EwS (Kruskall-Wallis, $p < 0.001$). First relapses were isolated local, isolated distant, and combined in 24%, 70%, and 6.4% of patients, respectively. Metastatic stage at initial diagnosis was associated with increased risk of post-first recurrence OS event ($p < 0.0001$). Two-year OS post-first recurrence (OS_{2y}) was 25.6% for patients with M-EwS and 48.5% for patients with L-EwS. Time to first recurrence was also a predictor of post-recurrence survival ($p < 0.0001$): patients with initial L-EwS and relapse $<$ 2 years from diagnosis had OS_{2y} of 31.4% vs. 70.8% for later relapses. Patients with initial M-EwS and relapse $<$ 2 years from diagnosis had OS_{2y} of 18.9% vs. 71.2%. Patients with combined relapses had higher risk of post-relapse death compared to other patterns of failure ($p = 0.003$), an effect that was largely driven by the one seen in patients with initial L-EwS. **Conclusions:** Overall survival of patients with first recurrent EwS after having received modern era therapy with interval compressed chemotherapy on recent COG trials remains poor, particularly for M-EwS, early relapse and combined relapses. These data will inform the design of trials for this relapsed population and provide critical data to help counsel patients about goals of care at first relapse. Research Sponsor: NCTN; U10CA180886; NCTN; U10CA180899; St. Baldrick's Foundation; Children's Oncology Group; U10CA098543; Children's Oncology Group; U10CA098413.

10036 Poster Session

Neurocognitive outcomes following 30.6-Gy whole-ventricular radiotherapy with 54-Gy total dose focal tumor bed boost for CNS non-germinomatous germ cell tumors: A Children's Oncology Group study (ACNS1123). First Author: Sunita K. Patel, City of Hope Comprehensive Cancer Center, Duarte, CA

Background: COG ACNS1123 stratum 1 was a prospective, phase II trial treating children with localized non-germinomatous germ cell tumors of the brain with chemotherapy followed by whole ventricular (WV) radiotherapy (RT, 30.6 Gy) and a focal tumor bed boost (54 Gy total dose) Given the potential adverse impact of RT on survivors' neurocognitive development, ACNS1123 had a co-primary objective to evaluate and longitudinally model cognitive and behavioral outcomes. **Methods:** Cognition was prospectively examined at 9, 30, and 60-months post-diagnosis via COG protocol ALTE07C1. Attention/concentration, processing speed (PS), and estimated intelligence quotient (est. IQ) were assessed by Wechsler Intelligence tests. Survey-reported attention and executive functioning (EF) were also obtained. Multivariable linear mixed-effects models examined trends over time, as well as associations and interactions with age, gender, tumor location (pineal gland versus other) and insurance type (private versus other and private versus public). **Results:** Seventy patients were evaluable and received WVRT followed by focal RT boost. Mean age at initiation of RT was 11.8 $\pm$ 4.3 years; 74% were male. A total of 56, 60, and 61 patients had at least one valid assessment score across 3 time points for attention/concentration, est. IQ and PS, respectively. Nine, 20 and 20 patients had data at all 3 time points for attention, est. IQ and PS, respectively. The average PS scores fell below the normative mean at all three time points. The average Est.IQ was below the normative mean at 9 months only. Males had higher attention scores on average ($p < .01$), while patients with other insurance had lower attention compared to the private group ($p < .01$). For the model-estimated longitudinal trajectories and their interactions with clinical factors, younger children had declining processing speed (p = 0.012), females had declining est.IQ scores ($p < .01$) and patients with tumors at pineal gland had improving est.IQ scores (p = 0.010) over time. For survey-reported outcomes, there was no change in attention while younger children had improved EF over time (p = 0.045). **Conclusions:** Treatment associated with the ACNS1123 stratum 1 protocol had variable impact on patient's longitudinal neurocognitive functioning. Younger age at irradiation and female gender were risk-factors for worse neurocognitive outcomes on examiner-administered measures. Only average PS was significantly below the normative mean at all 3 times in the collective sample. Patients should be proactively monitored for cognitive and educational supportive care services. These data could potentially serve for comparison of neurocognitive outcomes in future clinical studies that modify treatment approaches; however, the notable attrition must be considered as a limitation. Research Sponsor: U.S. National Institutes of Health; NCTN Operations Center Grant (U10CA180886); U.S. National Institutes of Health; NCTN Statistics & Data Center Grant (U10CA180899); St. Baldrick's Foundation.

10037 Poster Session

Post hoc analysis of rashes reported in patients (pts) with *BRAF*-altered relapsed/refractory (r/r) pediatric low-grade glioma (pLGG) treated with the type II RAF inhibitor tovorafenib in FIREFLY-1. First Author: Olaf Witt, Hopp Children's Cancer Center Heidelberg (KiTZ), German Cancer Research Center (DKFZ), Heidelberg University Hospital, German Cancer Consortium (DKTK), National Center for Tumor Diseases (NCT), Heidelberg, Germany

Background: Targeted therapies have become a mainstay in the treatment of pLGG. While effective, toxicities, including cutaneous adverse events (AEs), are common. Tovorafenib received accelerated FDA approval in April 2024 for the treatment of *BRAF*-altered r/r pLGG in pts $\geq$6 months of age based on FIREFLY-1 (NCT04775485) trial results. Maculopapular rash, dermatitis acneiform, and erythematous rash were the most commonly reported rashes (Kilburn LB, et al. *Nat. Med.* 2024). An update on the incidence, recurrence, and resolution of rash AEs in pts who received tovorafenib in FIREFLY-1 is provided. **Methods:** This post hoc analysis included 137 pts with pLGG (arm 1/registrational: 77; arm 2/extension: 60) treated with $\geq$1 dose of tovorafenib. Treatment-emergent rashes, graded by investigators, were grouped as maculopapular/erythematous/eczematous (M/E/E) or acneiform/pustular (A/P) (May 10, 2024 data cutoff). A rash episode included all rash events occurring over continuous days. A new rash was any subsequent episode occurring a day or more after the prior episode end date. **Results:** Median duration of tovorafenib treatment was 21.0 months (mos). 93% (128/137) of pts had a treatment-emergent rash. Of those, 59% (76) had only M/E/E rashes, 11% (14), only A/P rashes, and 30% (38), both types. As expected, A/P rashes occurred more often in pts $\geq$12 years of age (y/a). The rash was graded as G1 in 36% (46), G2 in 50% (64), and G3 in 14% (18) of pts. Most experienced 1 (53% [68]) or 2 (31% [40]) rash episodes. First rash episode median time to onset (TTO) was 0.43 mos, with 47% (60) G1, 41% (52) G2, and 13% (16) G3. First rash episodes resolved for 74% (95/128) of pts within a median of 2.67 mos. Resolution of first rash was more common among pts with M/E/E vs A/P rashes. Among any rash episodes (27% [58/219]) that remained unresolved, final severity was G1 (22% [48/219]) or G2 (5% [10/219]). All G3 rashes resolved. 47% (60) of pts experienced $\geq$2 rash episodes, of which 82% (49) were the same/lower grade episode. Of the 11 pts with a more severe second episode, 8 (73%) resolved completely. 80% (102) of pts received standard of care (SOC) treatments for rash, primarily topical steroids/antibiotics, oral antihistamines, and emollients. Only 1 (1%) pt had a rash-related tovorafenib discontinuation. 18% (23) of pts had dose interruptions due to rash. 11% (14) of pts had a dose reduction due to rash; of those, 57% (8) required no additional dose reductions due to rash. **Conclusions:** Rashes were common in pts treated with tovorafenib in FIREFLY-1. They typically occurred early in treatment, most were G1 or G2, resolved within a median of ~3 mos, and were manageable with SOC treatment and/or tovorafenib dose modifications. A/P rashes occurred more frequently in pts $\geq$12 y/a; there were no other significant trends in rashes experienced between the two age groups. Clinical trial information: NCT04775485. Research Sponsor: Day One Biopharmaceuticals, Inc.

10038 Poster Session

Safety and efficacy of pucotenlimab combined with standard chemotherapy regimens in the neoadjuvant treatment of pediatric patients with intermediate or high-risk rhabdomyosarcoma: A phase I/II study. First Author: Yi Que, Sun Yat-sen University Cancer Center, Guangzhou, Guangdong, China

Background: Previously, we defined the pathological complete response rate (pCR) for pediatric patients with intermediate or high-risk rhabdomyosarcoma who underwent preoperative chemotherapy alone (SIOP- 2024-ID 582). In this study, we aimed to determine the effect of preoperative pucotenlimab combined with the standard chemotherapy regimen as neoadjuvant treatment on the safety and pCR of rhabdomyosarcoma. **Methods:** In this single-arm phase I/II trial (NCT06456892), patients with rhabdomyosarcoma received neoadjuvant chemoimmunotherapy with pucotenlimab combined with standard chemotherapy intravenously on the first day of each three-week cycle for three cycles. During the dose-escalation phase, patients were infused with pucotenlimab at doses of 1, 3, and 6 mg/kg respectively. The primary endpoints in phase I were dose-limiting toxicities (DLTs) as well as the evaluation of safety and tolerability. Secondary endpoints included pathological complete response (pCR), major pathological response (MPR), and survival outcomes. **Results:** Herein, we report the adverse events and pCR in the phase I study. At the time of data analysis, the survival outcomes were not yet mature. Between June 2024 and September 2024, 15 patients were enrolled and received neoadjuvant chemoimmunotherapy. Among them, 7 patients have proceeded to surgical resection. The pCR rate was 3/7 (42.9%) , and 1/7 (14.3%) patients achieved an mPR. Treatment-related adverse events of grade 3 or 4 occurred in 11 patients , which mainly due to the chemotherapy. By the safety data cutoff, no DLTs were observed in the three dose groups. Most immune-related adverse events were grade 1 or 2, including hyperthyroidism (2/15), hypothyroidism (1/15), and fever (11/15). **Conclusions:** This study demonstrates the safety and potential efficacy of neoadjuvant pucotenlimab plus chemotherapy, with an acceptable safety profile, in patients with pediatric rhabdomyosarcoma. Clinical trial information: NCT06456892. Research Sponsor: None.

Summary of safety profile of 15 patients received pucotenlimab combined with the standard chemotherapy regimen.

Adverse effects	Grade 1	Grade 2	Grade 3	Grade 4
Decreased White Blood Cell Count	0	0	2	9
Decreased Platelet Count	3	0	1	2
Toothache	1	0	0	0
Limb Pain	2	0	0	0
Abdominal Pain	4	0	0	0
Headache	2	0	0	0
Oral Pain	0	1	0	0
Taste Disorder	1	0	0	0
Dizziness	2	0	0	0
Dysphagia	1	0	0	0
Epistaxis	1	0	0	0
Fatigue	2	0	0	0
Fever	11	2	0	0
Cough	2	0	0	0
Decreased Hemoglobin Concentration	2	8	4	0
Nausea	5	0	0	0
Vomiting	5	0	0	0
Decreased Appetite	1	0	0	0
Decreased Granulocytes	0	1	0	1
Decreased Total Bilirubin	8	0	0	0
Constipation	1	0	0	0
Diarrhea	2	0	1	0
Increased Alanine Aminotransferase	3	0	1	0
Increased Aspartate Aminotransferase	1	0	1	0
Increased Bilirubin	0	0	1	0
Hyperthyroidism	2	0	0	0
Hypothyroidism	1	0	0	0
Hypoproteinemia	5	0	0	0
Increased Uric Acid	5	0	0	0
Hypokalemia	1	0	0	0

10039 Poster Session

Irinotecan, temozolomide and naxitamab plus GM-CSF (HITS) and naxitamab plus GM-CSF and ifosfamide, carboplatin, etoposide (NICE) for patients with relapsed or refractory high-risk neuroblastoma: A single center, open-label phase 2 clinical trial. First Author: Jaume Mora, Hospital Sant Joan de Deu, Barcelona, Spain

Background: Patients with relapsed/refractory (R/R) high-risk neuroblastoma (HR-NB) have a poor prognosis, underscoring the need to explore new therapies. In this single institution, Phase 2 clinical trial (EudraCT 2020-000538-17), we evaluated the safety and efficacy of HITS and Naxitamab (NAX) in combination with ICE (NICE) in patients (pts) with R/R HR-NB with incomplete response (partial response (PR), minor response (MR), or stable disease (SD)) to HITS. **Methods:** Eligible pts received 2-4 cycles of HITS. Patients achieving a complete response (CR as per 2017 INRC) to HITS after 2 or 4 cycles had the CR consolidated with 5 cycles of NAX+GM-CSF. Patients with an incomplete response to HITS transitioned to NICE (up to 4 cycles) and those with progressive disease (PD) discontinued. CRs to NICE were consolidated with 5 cycles of NAX+GM-CSF. HITS consisted of Irinotecan 50 mg/m2/day IV from day 1-5 concurrently with temozolomide 150 mg/m2/day orally; NAX 2.25mg/kg IV on days 2, 4, 9 and 11; and GM-CSF 250 mcg/m2/day SC on days 7-11. NICE cycles consisted of NAX 2.25 mg/kg IV on days 2, 4, 9 and 11; GM-CSF 250 mcg/m2/day SC on days 7-11; ifosfamide 1.5 gr/m2/day IV from day 1-3 concurrent with etoposide 100 mg/m2/day IV and carboplatin 400 mg /m2/day IV on day 1. HITS/NICE cycles were administered out/inpatient, respectively. NAX was infused according to the Step-Up protocol. Treatment cycles were repeated every 4 weeks. Follow-up continued quarterly after end of treatment visit for up to 3 years. **Results:** From September 2020 until December 2022, 47 patients were screened and 34 enrolled. Of the 34 pts, 2 (5.9%) had primary refractory and 32 (94.1%) relapsed refractory disease. Prior treatments included chemotherapy (34; 100%); surgery (29; 85.3%); radiotherapy (17; 50%); autologous stem cell transplant (11; 32.4%); and anti-GD2 immunotherapy (15; 44.1%. 11 NAX and 4 dinutuximab beta). Of the 19 pts with an incomplete response after HITS, 13 (68.4%) received at least one cycle of NICE, and 5 completed all therapy. For HITS, the objective response rate (ORR) was 50% and best overall response (OR) was CR = 8 (23.5%); PR = 9 (26.5%); SD = 10 (29.4%); and PD = 7 (20.6%). For NICE ORR was 53.8% and OR: CR = 2 (15.4%); PR = 5 (38.5%); and SD = 6 (46.2%). No treatment related deaths occurred. All pts receiving NICE experienced grade 3-4 AEs (most frequent were pain (29.5%); urticaria (27.4 %); and thrombocytopenia (6.8%)), one leading to treatment discontinuation. **Conclusions:** Our clinical trial results suggest different chemotherapy combinations with naxitamab have the potential to rescue patients with R/R HR-NB. No unexpected toxicities were found when combining NAX with different chemotherapeutic agents. Clinical trial information: EudraCT 2020-000538-17. Research Sponsor: None.

10040 **Poster Session**

Pembrolizumab in pediatric participants with relapsed or refractory microsatellite instability-high solid tumors: Results from the phase 1/2 KEYNOTE-051 trial. First Author: Alberto S. Pappo, St. Jude Children's Research Hospital, Memphis, TN

Background: KEYNOTE-051 (NCT02332668) is an open-label, multicohort, phase 1/2 study evaluating pembrolizumab in children with advanced cancers. Results from participants with melanoma, PD-L1–positive solid tumors, or PD-L1–positive lymphomas showed pembrolizumab had a manageable safety profile, encouraging antitumor activity in relapsed or refractory (R/R) Hodgkin lymphoma, and limited efficacy in most other tumor types. Here, we present results from the cohort of participants with R/R microsatellite instability–high (MSI-H) solid tumors. **Methods:** Eligible participants were aged 6 months to <18 years and had advanced R/R MSI-H solid tumors determined locally by immunohistochemistry or polymerase chain reaction, measurable disease per RECIST v1.1, and a performance status of ≥50. All participants received pembrolizumab 2 mg/kg (up to a maximum of 200 mg) every 3 weeks for up to 35 doses or until other discontinuation criteria were met. The primary end points were safety and objective response rate (ORR) per RECIST v1.1 by investigator. Secondary end points included duration of response, disease control rate (DCR), and progression-free survival (PFS) per RECIST v1.1, and overall survival (OS). **Results:** Seven participants with MSI-H solid tumors were enrolled and received treatment. At the data cutoff (Jan 18, 2022), 6 had discontinued treatment and 1 was ongoing. Median age was 11.0 years (range, 3-16), 5 were female, 6 had a central nervous system malignancy (glioblastoma, n = 4; anaplastic astrocytoma, n = 1; high-grade glioma, n = 1), and 1 had an adenocarcinoma. Median time from first dose to data cutoff was 27.6 months (range, 0.3-47.5). Treatment-related AEs occurred in 3 participants; grade 3 or 4 events occurred in 1 participant and included grade 4 lymphocyte count decreased and grade 3 pyrexia. No participants died due to AEs. The ORR per RECIST v1.1 was 0% (95% CI, 0-41); the DCR was 14% (95% CI, 0-58), with 1 participant with adenocarcinoma exhibiting stable disease. Among 6 participants with a postbaseline assessment, 2 had any reduction from baseline in target tumor size, of whom 1 had a reduction of ≥30%. Median PFS was 1.7 months (95% CI, 0.4-NR); 6-month PFS was 17%. Median OS was 7.7 months (95% CI, 1.9-NR); 6-month OS was 50%. One participant with glioblastoma had a complete response at cycle 6 after initial progression, and the complete response was maintained through cycle 20. **Conclusions:** The safety profile of pembrolizumab in children with MSI-H R/R solid tumors was manageable and consistent with other tumor types. One participant with glioblastoma had a prolonged complete response after initial progression. Further evaluation of pembrolizumab in pediatric MSI-H central nervous system malignancies is ongoing. Clinical trial information: NCT02332668. Research Sponsor: Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA.

10041 **Poster Session**

Socioeconomic disparities in survival outcomes among children with non-metastatic Ewing sarcoma treated on upfront Children's Oncology Group clinical trials. First Author: Rahela Aziz-Bose, Dana-Farber/Boston Children's Cancer and Blood Disorders Center, Boston, MA

Background: Poverty is emerging as an adverse risk factor for relapse and death across many pediatric cancers. Socioeconomic disparities have not been comprehensively investigated in Ewing sarcoma. We leveraged Children's Oncology Group (COG) data to investigate socioeconomic disparities in survival outcomes in children with non-metastatic Ewing sarcoma treated on upfront phase III clinical trials from 2001-2005 and 2010-2017. **Methods:** This was a retrospective cohort study of US patients aged 0-21 years with non-metastatic Ewing sarcoma enrolled on COG AEWS0031 and AEWS1031. The analytic cohort was restricted to participants with complete data on exposures and covariates. Poverty was the primary exposure of interest, defined at the household (sole means-tested public insurance) and neighborhood (census-defined high-poverty ZIP code with ≥20% of population below 100% Federal Poverty Level) levels. Cox proportional hazards regression models evaluated associations between poverty exposures, event-free survival (EFS), and overall survival (OS) from time of trial enrollment. Multivariable models adjusted for age (as a continuous variable), sex, race/ethnicity (non-Hispanic White vs Other), initial tumor volume (≤200 ml vs > 200 ml), primary disease site (pelvic/non-pelvic/extraosseous), and assignment to interval compressed chemotherapy (yes/no). **Results:** Among 551 complete cases, 23% (n = 128) were household poverty-exposed and 19% (n = 106) were neighborhood poverty-exposed. Median age at trial enrollment was 12 years; median event-free follow-up time was 8.7 years. In multivariable models, household poverty-exposed children experienced a 52% increased hazard of EFS-event compared to unexposed children (adjusted hazard ratio [aHR] 1.52, 95% CI 1.03, 2.26, p = 0.04), and a 64% increased hazard of death compared to unexposed (aHR 1.64, 95% CI 1.03, 2.62, p = 0.04). Neighborhood poverty-exposure was not associated with increased hazard of EFS or OS event. **Conclusions:** Household poverty, as proxied by public insurance, is an adverse risk factor for EFS-event and death among children and young adults with non-metastatic Ewing sarcoma despite standardized treatment on national clinical trials. Investigation of mechanisms driving these disparities—including treatment delays and differential local control approaches—is ongoing. These data highlight an immediate need to evaluate poverty-targeted interventions alongside new therapeutic agents to improve outcomes. Research Sponsor: None.

10042 **Poster Session**

HLA allele, TCR V- and J-gene segment usage combinations and their association with survival in neuroblastoma. First Author: Eddie Fung, USF Morsani College of Medicine, Tampa, FL

Background: Neuroblastoma has variable outcomes across different risk groups. In children with stage 4 neuroblastoma, five-year overall remains around 50% in high-risk children despite the emergence of anti-GD2 antibodies. T- and NK-cell infiltration is prognostic in therapy-resistant neuroblastoma, and higher HLA class I expression is linked to better overall survival (OS). In other cancers, specific HLA alleles and T-cell receptor (TCR) V, J- gene segments have been associated with survival. Thus, we conducted a retrospective study in stage 4S neuroblastoma patients to assess whether specific HLA allele, TCR V- and J-gene segment usage combinations correlated with OS in NBL. Among combinations that were associated with OS, we also identified changes in expression of immune marker genes. **Methods:** We obtained HLA allele data from exome files of the TARGET-NBL dataset using the xHLA software. The TCR recombination reads were obtained from the TARGET-NBL RNAseq files representing tumor specimens from 99 cases, utilizing a high-stringency search algorithm. The TCR recombination reads were translated, and the complementarity determining region-3 (CDR3) amino acid sequences were obtained. HLA and TCR datasets were integrated to assess OS probabilities, comparing cases with and without specific HLA allele, TCR V- or J-gene usage combinations. Significance was determined only if independent HLA allele or V- and J-gene usage assessments were not statistically significant, but significant in the corresponding HLA allele, TCR V- or J-gene segment usage combinations. HLA allele and TCR usage combinations were grouped by association with better or worse OS probabilities, and immune marker gene expression correlations were assessed via Student's t-test and Mann-Whitney U test with a Bonferroni-corrected threshold of p = 0.00114. **Results:** We identified 73 HLA allele, TCR V- and J-gene usage combinations with significant OS distinctions: 20 associated with improved OS and 53 with worse OS. For example, 20 TARGET-NBL cases with the HLA-DQB1*04:02 and TRAJ29 usage combination did not reach the median compared to the 1319-day OS median for all remaining cases (log-rank p = 0.009). Among the cases with at least one HLA allele, TCR V- or J-gene segment usage combination with improved OS, we found that the RNAseq values for the immune markers *CD4, CD22, CD38, RPH1*, *TNFRSF17*, and *TNFRSF13B* were upregulated, as assessed via a Mann-Whitney U analysis. **Conclusions:** Identifying specific HLA allele, TCR V- and J- gene segment usage combinations associated with survival may further indicate patients who could benefit from immunologic-boosting treatments. Studies employing functional assays, immunogenomic profiling, and targeted immune pathway analyses may advance immunotherapeutic strategies and predictive biomarkers for neuroblastoma, particularly in high-risk patients. Research Sponsor: None.

10043 **Poster Session**

MYC amplification and protein expression as prognostic markers in pediatric and young adult osteosarcoma. First Author: Matthew Nagy, Boston Children's Hospital, Boston, MA

Background: Risk stratification in osteosarcoma relies on metastatic status and tumor necrosis after chemotherapy. Despite a complex genomic landscape, genomic biomarkers are not yet used for predicting therapy response. *MYC* amplification has previously been identified as a potential biomarker for chemotherapy resistance but studies of MYC expression are limited. This study evaluated the relationship between *MYC* amplification and protein expression and between these biologic features and survival in pediatric and young adult osteosarcoma. **Methods:** In a cohort of 93 patients with high-grade osteosarcoma, *MYC* copy number was evaluated using a targeted sequencing panel, and MYC protein expression was quantified via IHC with an H-Score. The relationship between copy number and protein expression were evaluated via spearman correlation. Amplification (AMP) was defined as > 7 copies, and high expression (EXP) as > 175 H-score. The primary outcome, overall survival (OS), was assessed using Kaplan Meier analysis (median [IQR]) for unadjusted models and cox proportional hazard analysis (HR±SE) with models adjusted for metastatic status at diagnosis. **Results:** Among the 93 patients, 64% were male, with a median age of 14 years [range: 4–29]. *MYC* AMP was present in 16 (17%) patients, high MYC EXP in 19 (20%), and both AMP + high EXP in 8 (9%) patients. Copy number status was positively correlated with expression (r = 0.57, p < 0.0001). Patients with AMP were more likely metastatic at diagnosis (75% vs 38%, p = 0.011) and more so for AMP + high EXP (100% vs 39%, p = 0.0009), but not high EXP alone (63% vs 39%, p = 0.11). OS was reduced for AMP compared to non-AMP (median OS: 1.3 [1.0, 2.6] vs 6.2 [2.8, 12.8] years, p < 0.0001; Adj HR 3.2±0.4, p = 0.001) and high EXP compared to low EXP (median OS: 1.5 [1.0, 3.1] vs. 6.2 [2.8, 12.8] years, p < 0.0001; Adj HR 5.6±0.4, p < 0.0001). A dose-response relationship was seen with higher copy number or expression linked to reduced OS. Compared to non-AMP + low EXP (median OS: 7.23 [3.1, 12.8] years) there was reduced OS for AMP-only/high EXP-only (median OS: 3.1 [2.0, 4.0] years, p = 0.01; Adj HR 2.8±0.4, p = 0.009) and further reduced OS for AMP + high EXP (median OS: 1.0 [0.5, 1.0] years, p < 0.0001; Adj HR 15.3±0.5, p < 0.0001). Metastasis at diagnosis predicted reduced OS compared to localized disease (median OS: 2.0 [1.0, 4.5] vs 6.2 [4.0, 12.8] years, p < 0.0001), but age, sex, and tumor necrosis were not associated with OS. **Conclusions:** *MYC* amplification and protein expression are positively correlated, and both independently and synergistically predict poor OS in osteosarcoma, even after adjusting for metastatic status at diagnosis. Incorporating *MYC* amplification and expression status into risk stratification may help identify patients with worse prognosis. These data also underscore the need for therapeutic approaches tailored to the genetic basis of osteosarcoma tumor biology. Research Sponsor: None.

10044 **Poster Session**

Updated data of efficacy and safety of luvometinib (FCN-159) in pediatric participants with neurofibromatosis type 1 from a multi-center, open-label, single-arm phase 2 study. First Author: JinHu Wang, The Children's Hospital of Zhejiang University School of Medicine, Hangzhou, China

Background: Neurofibromatosis type 1 (NF1) is an autosomal dominant genetic disease characterized by multiple progressive tumor and non-tumor manifestations, with abnormal activating MAPK pathway. Plexiform neurofibromas (PN) presents in 20-50% of NF1 patients (pts) and may cause serious complications. One MEK1/2 inhibitor was approved for pediatric pts with NF1-related PN in US, EU and China, but therapeutic options remain limited. Luvometinib is a highly potent selective anti-tumorigenic inhibitor of MEK1/2, potentially effective in NF1-related PN. Previous studies have confirmed that luvometinib is expected to be a targeted therapy for neurofibromatosis type 1 in pediatric patients (pts). **Methods:** This multi-center, open-label phase 2 clinical trial is to assess safety and efficacy of luvometinib in pediatric pts with NF1- related PN. The primary endpoint was objective response rate (ORR) evaluated by investigators (INV). The key secondary endpoint was ORR evaluated by Blinded independent review committee (BIRC), and other secondary endpoints include 1-year PFS and others. Preliminary findings from the phase 2 trial were previously disclosed at ASCO 2024. Here, we present the updated efficacy and safety results in pediatric participants. **Results:** As of data cut-off (September 23, 2024), 46 pediatric pts were enrolled and treated with a dose of 5 mg/m^2 (the recommended phase 2 dose according to phase 1 study). The median follow-up time was 25.1 months. ORR evaluated by INV was 60.5% (95%CI: 44.4, 75.0), and 26 pts had partial response. ORR evaluated by BIRC was 44.2% (95%CI: 29.1, 60.1), and 19 pts had partial response. 11 of 14 pts (78.6%) with tumor pain at baseline (overall tumor pain NRS$\geq$2) decreased to 0 points. The median DOR and median PFS were still not reached. 1-year PFS rate evaluated by INV was 95.3%. 45 pts (97.8%) experienced treatment-related adverse events (TRAEs). Among these, grade $\geq$3 TRAEs occurred in 10 pts (21.7%), including folliculitis(4.3%), dermatitis acneiform (4.3%), blood creatine phosphokinase increased (4.3%), ejection fraction decreased (2.2%), upper respiratory tract infection (2.2%), pneumonia (2.2%), anemia (2.2%) and gastrointestinal disorders (2.2%). 2 pts (3.1%) reported treatment-related serious adverse events. 14 pts (30.4%) experienced TRAEs led dose interruption. No reported TEAE led to dose reduction, discontinuation or death. No new safety signal was observed. **Conclusions:** Overall, luvometinib was well-tolerated and demonstrated promising anti-tumor activity in pediatric participants with NF1-related PN. Long-term efficacy and safety follow-up are ongoing. Clinical trial information: NCT04954001. Research Sponsor: Shanghai Fosun Pharmaceutical Industrial Development Co., Ltd.

10045 **Poster Session**

***MYC* amplification as a prognostic biomarker in osteosarcoma: A report from the Children's Oncology Group.** First Author: Sarah Whittle, Texas Children's Cancer Center/Baylor College of Medicine, Houston, TX

Background: Osteosarcoma is characterized by complex chromosomal alterations and genomic instability. *MYC* copy number (CN) gains are observed in 10%-60% of cases, and *MYC* amplification is associated with poor outcomes in single-center cohorts and genomic studies of relapsed or high-risk patients. This study aimed to validate the prognostic role of *MYC* amplification in a large, multi-center cohort of patients enrolled on Children's Oncology Group (COG) up-front treatment and biobanking protocols. We also assessed other genes linked to survival. **Methods:** This retrospective, IRB-approved case-control study used banked FFPE DNA from 137 osteosarcoma samples from the COG biorepository for SNP microarray (Affymetrix OncoScan). Patients were enrolled on INT-0133, P9754, AOST0331 and APEC14B1 from 1993-2024. Amplifications of *MYC, CCNE1*, *CDK4*, and the 6p21.1 locus, as well as chromosome 6, 8, 12, and 19 ploidy were assessed. Gene amplification was defined as the ratio of gene to chromosome copies (e.g. *MYC* CN/chr8 CN) $>$ 2.0. The primary outcome was occurrence of event-free survival (EFS) event. Patients were matched on metastatic status and follow-up time. Univariate conditional logistic regression models were fit for each genetic feature to obtain the odds ratio (OR) of EFS event associated with amplification (95% confidence interval (CI)) and to conduct one-sided tests for the null hypothesis OR £ 1 at the 5% level. **Results:** Sixty-five case-control pairs for *MYC, CDK4*, and 6p21.1, and 63 for *CCNE1* were analyzed. *MYC* amplification was estimated to have a 1.87-fold increase in odds of EFS event (95% CI: 0.79, 4.42; p = 0.08). *CDK4* amplification was associated with a 5-fold increase in odds of event (95% CI: 1.10, 22.82; p = 0.02). Neither amplification of 6p21.1 or *CCNE1* were associated with increased odds of event, with ORs of 1.33 (95% CI 0.56, 3.16; p = 0.26) and 0.73 (95% CI: 0.29, 1.81; p = 0.25), respectively. **Conclusions:** *MYC* amplification may be associated with increased odds of EFS event in this cooperative group cohort. Though the result did not reach statistical significance, this finding aligns with prior studies demonstrating increased EFS-event risk for patients with *MYC* amplification. While our selection of a ratio cut point $>$ 2.0 to define amplification was informed by prior studies, the optimal cut point has not been determined and cut points may be assay dependent. Although *CDK4* amplification appears associated with increased odds of event, confidence in this finding is limited by a sparse-data bias, due to a low number of control patients with *CDK4* amplification. Future analyses will explore *MYC* and *CDK4* copy number ratio as a continuous variable and assessing the relationship between additional genomic features and EFS events in this population. Research Sponsor: Children's Oncology Group.

10046 **Poster Session**

A phase I dose-escalation study to assess the oncolytic virus VCN-01 safety and efficacy in refractory retinoblastoma patients. First Author: Jaume Català-Mora, Hospital Sant Joan de Deu, Barcelona, Esplugues De Llobregat. Barcelona, Spain

Background: Preclinical work demonstrated antitumor activity of VCN-01 (oncolytic adenovirus targeting the E2F pathway and expressing hyaluronidase) for retinoblastoma. We report this first-in-children study aiming to assess its safety and efficacy. **Methods:** Patients with intraocular retinoblastoma who failed conservative therapy facing imminent enucleation were eligible for this phase I, dose-escalation study (NCT03284268) with two dose levels of VCN-01 intravitreal injection (2E+9 vp/eye per dose for the first patient) and 2E+10 vp/eye dose in two doses every two weeks for the remaining 8. Dose limiting toxicity (DLT) was defined as $\geq$ grade IV ocular toxicity or $\geq$ grade III systemic toxicity according to CTCAEv04. Response assessed by RB-RECIST criteria and toxicity were evaluated at day 42 of the first injection. **Results:** Thirteen patients (4 screening failures) were enrolled. Out of the 9 treated patients, five had bilateral retinoblastoma. There was no DLT. 7/9 patients experienced adverse reactions. being uveitis the most common (7/9 patients, G3 in four). From the second patient onwards, all patients received pre-emptive oral and/or topical steroids to prevent uveitis. Uveitis was improved or resolved at day 42 in 7 patients. One patient with G3 uveitis did not receive the second dose because of medical decision and also experienced glaucoma requiring treatment. No systemic toxicities occurred. VCN-01 caused reversible changes in electroretinograms due to turbidity. Viral particles were not found in the healthy retina in enucleated eyes. No VCN-01 genomes in peripheral blood were detected in any case. At 42 days of the first injection, 5 patients achieved partial response, 3 stable disease and one progressive disease. Subsequent eye-conservative treatment was administered to 5 patients and 3 eyes are preserved with vision (follow-up 12-49 months). The remaining 6 eyes were enucleated because of refractory tumor. No extraocular relapse occurred. **Conclusions:** VCN01 was safe, being uveitis the most common adverse effect. VCN-01 did not cause retinal toxicity. The response in these heavily pre-treated eyes was encouraging. Clinical trial information: NCT03284268. Research Sponsor: None.

10047 **Poster Session**

Multi-omics evaluation of relapsed pediatric cancers: What information do these sequential analyses yield? First Author: Caroline Bellavance, Département de Pédiatrie, CHUS, Université de Sherbrooke, Sherbrooke, QC, Canada

Background: While cure rates for children with cancer have significantly improved, relapses remain a challenge, requiring deeper understanding to address them. Nowadays, genomic analyses are widely used at diagnosis and in relapse settings, becoming a standard-of-care in pediatric. The aim of this study is to describe the genomic evolution of relapsed pediatric tumors in search of clonal selection and pathway identification. We also want to assess the clinical value of these new data obtained in relapsed tumors. **Methods:** This is a retrospective analysis from canadian pediatric oncology precision medicine projects. We selected patients aged $<$ 30 years with sequencing data available at diagnosis and relapse. Clinical and genomic data were collected, and each patient was paired with a non-relapsed patient. The incidences of genomic alterations were compared in the two populations and for each patient. For patients who relapsed, patient-adjusted longitudinal mixed models assessed differentially expressed genes at relapse vs diagnosis. Gene set enrichment analyses were performed, using GLMMSeq results, to study metabolic pathways that undergo significant dysregulation over time ($p < 0.05$). Electronic surveys were sent to the treating physicians of relapsed patients. **Results:** A total of 45 patients with 1 or more relapses were compared with 44 patients without relapse. Longitudinal analysis was performed on 35 relapsed patients. Our population has a median age of 10 y.o., a majority had leukemia (47 %) or sarcoma (31%). Among relapsed patients, the mutational burden at diagnosis was 0.82 mut/MB and 1.21 mut/MB at first relapse, compared with 0.47 mut/MB in non-relapsed patients (p = 0.02). 33% of relapsed patients had or acquired a TP53 alteration, compared with 16% without relapse (p = 0.084). MAPK pathway alterations were more prevalent among relapsed patients (p = 0.004). Longitudinal analyses showed enrichment in MAPK pathway at relapse. Other pathways were also significantly enriched at relapse (Wnt, TP53, TNFa, TGFb), while immune pathways (immunoglobulin/lymphocyte complex and activation) were downregulated. Although, 45% of clinicians considered that genomic analysis at relapse was useful, only 18% actually integrated the genomic data into clinical decisions due to better options available than targeted therapies. Indeed, when targeted therapies were used as proposed, it was mostly for a 2nd or 3rd relapse and for sarcoma. **Conclusions:** This study describes the evolution of the genomic landscape, showing an enrichment in mutation and pathways, and increased mutational burden in relapsed pediatric tumors. Longitudinal differential analyses brought more information about genomic evolution than the usual genomic reports sent to clinicians. Overall, the analyses performed are useful for clinicians, and a small subset of patients benefited from this information to guide therapies. Research Sponsor: None.

10048 **Poster Session**

Efficacy, safety and pharmacokinetics (PK) of zurletrectinib, a next-generation pan-TRK inhibitor, in pediatric and adolescent patients (pts) with NTRK fusion-positive (NTRK+) solid tumors. First Author: Yizhuo Zhang, Sun Yat-sen University Cancer Center; State Key Laboratory of Oncology in South China; Collaborative Innovation Center for Cancer Medicine, Guangzhou, Guangdong, China

Background: NTRK gene fusions are significant oncogenic drivers in pediatric tumors (e.g. infantile fibrosarcoma). Zurletrectinib is a highly selective next-generation TRK inhibitor. Preclinical data of zurletrectinib showed strong activity against resistant mutations, e.g., G595R. Promising efficacy was observed in a phase I/II clinical trial (NCT04685226). The pivotal phase II clinical trial (NCT05745623) is currently ongoing. Here we report an integrated analysis by combining pediatric and adolescent pts from the two clinical trials. **Methods:** Eligible pts with locally advanced or metastatic solid tumor harboring NTRK fusions, who failed from standard of care or for whom there was currently no effective therapy were included in the efficacy analysis. Adolescent pts (12-18 years) received zurletrectinib tablet at fixed dose, and pediatric pts ($<$ 12 years) received zurletrectinib orally disintegrating tablet (ODT) based on body surface area (BSA). The primary endpoint was confirmed objective response rate (ORR) per independent review committee (IRC). Tumor responses were assessed by IRC and investigators per RECSIT1.1 and RANO (BM) criteria. Treatment-emergent adverse events (TEAEs) were evaluated and graded according to CTCAE v5.0. **Results:** As of 23 Nov 2024, 18 pts in total were enrolled, including 8 pediatric pts and 10 adolescent pts. Median age was 5.0 (range: 3-9) and 13.5 (range: 12-15) respectively. ECOG performance status was between 0-1. Among the 18 pts, 6 TRK inhibitor treatment-naïve pts with central lab confirmed NTRK+ were efficacy evaluable. The confirmed ORR assessed by IRC was 100% (95% CI 54.1, 100.0). All of the pts achieved partial response (PR) at the 1st tumor assessment and maintained the remission as of the cutoff date. Median time to response were 1.0 month (95% CI: 0.99, NE) in adolescent pts and 0.9 (95% CI: 0.89, NE) month in pediatric pts. It is worth noting that one pediatric patient who progressed on prior first-generation TRK inhibitor achieved complete response after receiving zurletrectinib. The most common treatment related adverse events (TRAEs) were ALT increased (n = 8) and anemia (n = 6), the majority of which were Gr 1 or 2. There were no TRAEs leading to dose reduction or discontinuation, and no serious TRAEs were reported. PK results indicated that zurletrectinib PK profiles in pediatrics and adolescents at the recommended phase 2 dose (RP2D) were similar to that in adults. **Conclusions:** The integrated analysis demonstrated that zurletrectinib had significant efficacy and good safety profile in pediatric and adolescent pts with NTRK+ solid tumors. Zurletrectinib also showed the potential to overcome the resistance to 1st generation TRK inhibitors. These findings support zurletrectinib is a better treatment option for NTRK+ pediatric and adolescent pts. Clinical trial information: NCT04685226. Research Sponsor: Beijing InnoCare Pharma Tech Co., Ltd, Beijing, China.

10049 **Poster Session**

Phase I study of mitoxantrone hydrochloride liposome in relapsed and refractory pediatric tumors. First Author: Junting Huang, Sun Yat-sen University Cancer Center; State Key Laboratory of Oncology in South China; Collaborative Innovation Center for Cancer Medicine, Guangzhou, Guangdong, China

Background: Compared with solvent-based mitoxantrone, mitoxantrone hydrochloride liposome has been found to reduce bone marrow toxicity. This open-label, single-arm phase I clinical trial was designed to evaluate the safety and efficacy of mitoxantrone hydrochloride liposome monotherapy in the treatment of pediatric tumors. **Methods:** To explore the maximum tolerated dose (MTD) of mitoxantrone liposome in pediatric cancer patients, using a "3+3" design, patients received three dose levels (16mg/m^2, 20mg/m^2, 24mg/m^2, d1) of mitoxantrone hydrochloride liposome monotherapy every 3 weeks. Patients were observed for dose-limiting toxicity (DLT) during the first cycle. The primary endpoint was MTD, and the secondary endpoints included objective response rate (ORR) and disease control rate (DCR), DLT, adverse events (AE), etc. **Results:** From October 2022 to September 2023, total of 7 pediatric cancer patients were enrolled and completed treatment, of which 6 patients received 16mg/m^2 and 1 patient received 20mg/m^2 mitoxantrone liposome monotherapy. The median age of the patients was 13.0 years (range: 8.0, 17.0). The tumor types included soft tissue sarcoma, hepatoblastoma, T-cell lymphoma, etc. The median number of treatment cycles was 2.0 (range: 1.0, 6.0). 1 patient (16mg/m^2 dose group) developed DLT, which was a grade 3 febrile neutropenia lasting more than 7 days after G-CSF. All patients could be evaluated for toxicity, and 5 patients could be evaluated for efficacy based on imaging findings. The AE of all grades with high incidence ($\geq$50%) were white blood cell decreased (85.7%), anemia (71.4%), neutrophil count decreased (71.4%), platelet count decreased (57.1%), and anorexia (57.1%), respectively. The overall safety was acceptable. Six patients (85.7%) discontinued treatment early, of which 3 (42.9%) were due to disease progression confirmed by imaging, and 3 (42.9%) were due to limited efficacy considered by the investigators. The overall ORR and DCR were 20% (95%CI: 0.5%-71.6%) and 40% (95%CI :5.3%-85.3%), respectively. After the observation of 7 patients, the investigators thought that the efficacy of mitoxantrone liposome monotherapy was not as expected, and the study protocol was revised to continue the study of mitoxantrone liposome combined therapy. **Conclusions:** Mitoxantrone liposome has an acceptable safety profile in pediatric cancer patients, but the preliminary efficacy is not up to expectations, and further studies on combination therapy are needed. Clinical trial information: NCT05620862. Research Sponsor: CSPC Ouyi Pharmaceutical Co., Ltd.

10050 **Poster Session**

Updated efficacy and safety of entrectinib in children with extracranial solid or primary central nervous system (CNS) tumors harboring *ROS1* fusions. First Author: Ami V. Desai, University of Chicago Medical Center, Chicago, IL

Background: Entrectinib is a TRK and ROS1 inhibitor that has shown rapid and durable responses in children with *NTRK1/2/3* or *ROS1* fusion-positive (fp) extracranial solid or primary CNS tumors in an integrated analysis of the STARTRK-NG (NCT02650401), TAPISTRY (NCT04589845) and STARTRK-2 (NCT02568267) trials. These data led to FDA and EMA approval of entrectinib in pediatric patients $>$ 1 month with NTRK fp tumors. Here we present updated data on pediatric patients with ROS1 fp tumors based on the trials listed above to further describe the efficacy and safety of entrectinib in this population. **Methods:** Eligible pts were TRK/ROS1 inhibitor-naïve, $<$ 18 years old, with locally advanced/metastatic extracranial solid or primary CNS tumors, with measurable or evaluable-only disease. All pts who received $\geq$1 daily dose of oral entrectinib are included in the safety-evaluable population. Pts who had a ROS1 fusion and were followed for $\geq$6 months are included in the ROS1 efficacy-evaluable population. Pts received entrectinib until disease progression, unacceptable toxicity, or consent withdrawal. Tumor responses were confirmed by blinded independent central review (BICR) per RECIST v1.1 or RANO criteria. Primary endpoint: confirmed objective response rate (ORR) per BICR. Key secondary endpoints: ORR in pts with baseline measurable disease per BICR; duration of confirmed response (DoR); time to confirmed response (TTR); clinical benefit rate (CBR); progression-free survival (PFS); overall survival (OS); safety. **Results:** At clinical cut-off (16 July 2024), of the 113 safety-evaluable pts, there were 26 pts in the *ROS1* efficacy-evaluable cohort. ORR was 69.2% (95% CI 48.2, 85.7). Median TTR was 1.84 months. Median OS was not evaluable. Median duration of survival follow-up was 29.4 months (range 1–80). Efficacy outcomes are shown in the table. The most common related adverse events were weight gain (37.2%), anemia (36.3%), and AST increase (26.5%). Related fracture events occurred in 23% of pts. **Conclusions:** Entrectinib yielded rapid and durable responses in pediatric pts with *ROS1* fp extracranial solid or primary CNS tumors. The safety profile of entrectinib was consistent with previous reports. Clinical trial information: NCT02650401; NCT04589845; NCT02568267. Research Sponsor: F. Hoffmann-La Roche Ltd.

Efficacy	*ROS1* (N=26)
Confirmed ORR*, N, % [95% CI]	18, 69.2 [48.2- 85.7]
Complete response	4, 15.4 [4.4- 34.9]
Partial response	14, 53.8 [33.4- 73.4]
Median confirmed DoR*, months (95% CI)	NE (16.2- NE)
Median TTR*, months (range)	1.84 (1.6- 4.0)
CBR*, % (95% CI)	84.6 (65.1- 95.6)
Median PFS*, months (95% CI)	NE (21.8- NE)
Median OS, months (95% CI)	NE (NE- NE)

*Per BICR; CI, confidence interval; NE, not evaluable.

10051 **Poster Session**

A phase 1 trial of the FACT inhibitor CBL0137 in pediatric patients with relapsed or refractory solid and CNS tumors: A report from the Children's Oncology Group study PEPN2111. First Author: David Simon Ziegler, Kids Cancer Centre, Sydney Children's Hospital, Sydney, NSW, Australia

Background: CBL0137 is a novel agent that targets the FAcilitates Chromatin Transcription complex (FACT), a histone chaperone that regulates chromatin remodeling during transcription, replication, and DNA repair. CBL0137 has been shown to have anti-tumor activity in multiple preclinical models of pediatric cancer. We report the phase 1 trial of CBL0137 in children with relapsed or refractory solid tumors including central nervous system (CNS) tumors or lymphoma (NCT04870944). **Methods:** Patients (age 12 months to 21 years) with relapsed/refractory solid tumors, central nervous system tumors or lymphoma were eligible. In the dose escalation phase, a rolling-six design was used to evaluate CBL0137 administered intravenously (IV) once per week on Days 1 and 8 of a 21-day cycle. The starting dose was 400 mg/m^2, with escalation to the adult phase 2 dose (RP2D) of 540 mg/m^2. The maximum tolerated dose (MTD) was determined based on cycle 1 dose limiting toxicity (DLT) using Common Toxicity Criteria for Adverse Events (v5). Pharmacokinetics (PK) and cytokine analyses were performed during cycle 1. Seven additional patients ($<$ 18 years old) were accrued to a PK expansion cohort at the RP2D. **Results:** Sixteen patients were enrolled; 14 were evaluable for DLT assessment (12 at 400mg/m^2 [6 in dose escalation and 6 in PK expansion] and 2 at 540mg/m^2). The median (range) age was 10 (4-20) years. Diagnoses included high grade glioma (n = 6), osteosarcoma (n = 5), ependymoma (n = 2), neuroblastoma, hepatoblastoma and Burkitt's lymphoma (1 each). One of 12 evaluable patients treated at 400 mg/m^2 experienced a DLT: Grade 3 photosensitivity. At 540 mg/m^2, the two evaluable patients both had fever and dose limiting Grade 3 hypotension. Non-dose limiting Grade 3-4 toxicities included anemia, lymphopenia, neutropenia, thrombocytopenia, hypokalemia, anorexia, photosensitivity and fever. For both dose levels, a total of 12 patients were reported to have at least one episode of Grades 1-3 fever and/or Grade 1 cytokine release syndrome (CRS). PK parameters (mean$\pm$SD) for CBL0137 (400 mg/m^2) were T_{max}= 0.7 $\pm$ 0.5 h, C_{max}= 1310 $\pm$ 417 ng/mL, and $AUC_{0\text{-}24h}$ = 15300 $\pm$ 6790 h·ng/mL. Given the unexpected toxicities of fever, hypotension, and CRS, cytokine samples were collected in patients enrolled in the PK expansion cohort; all had Grade 1 CRS and significantly elevated levels of both IL-10 (adj p = 0.001) and IL-1RA (adj p $<$ 0.001) at 24 hours vs pre-infusion. **Conclusions:** The RP2D and MTD of CBL0137 in children and adolescents with solid or CNS tumors is 400mg/m^2 IV weekly on Days 1 and 8 of 21-day cycles. CBL0137 leads to immune activation, with cytokine elevation and the possibility of CRS, an unexpected toxicity not previously reported in adults. A Phase 2 cohort in patients with Diffuse Midline Glioma is ongoing and includes further assessment of immune activation. Clinical trial information: NCT04870944. Research Sponsor: Cookies for Kids' Cancer; National Cancer Institute; UM1CA228823.

10052 **Poster Session**

Factors associated with survival following relapse of high-risk neuroblastoma: A study from the International Neuroblastoma Risk Group (INRG) Data Commons. First Author: Daniel A. Morgenstern, The Hospital for Sick Children, Toronto, ON, Canada

Background: Outcomes for high-risk neuroblastoma (HR-NBL) following relapse are poor, although there is a paucity of data on overall survival post-relapse (OSPR) in the contemporary era. Prognostic factors associated with OSPR across all neuroblastoma risk groups (INSS stage, MYCN status and time to first relapse) have previously been described. Here we present an analysis focussed specifically on HR-NBL. **Methods:** We conducted a retrospective analysis using INRG Data Commons including HR-NBL patients diagnosed $\geq$1985 with relapse/progression $\leq$2022. HR-NBL was defined as age $\geq$547days at diagnosis with INRGSS M; or INRGSS L2 MYCN-amplified disease. The final cohort excluded patients without relapse/progression and with death as first event. Primary endpoint was OSPR, with Kaplan-Meier estimates of survival and sub-group comparisons using log-rank tests. **Results:** Of the 25,245 NBL patients in the INRG Data Commons, 4045 were included in the final analysis. The majority had INRGSS M disease (96%) and were $<$ 5 years at diagnosis (74%), with MYCN amplification in 36% of those with available data. OSPR was 22$\pm$0.7% at 2 years and 8$\pm$0.4% at 5 years, with median OSPR 0.76 years (95% CI: 0.73-0.82). OSPR improved over time; for example, 2-year OSPR was 16+/-2.8% for patients diagnosed 1985-1989 vs 32%$\pm$2.8% for 2015-2019 ($p < 0.0001$). Across the whole cohort, patients with a diagnosis of NBL (vs nodular ganglioneuroblastoma), greater number of involved metastatic compartments (MSI) or elevated LDH at diagnosis, tumors with MYCN amplification, higher MKI, 1p LOH and presence of ALK mutation had statistically significantly worse OSPR than respective counterparts. OSPR for INRGG M was significantly better than for INRGSS L2. Serum ferritin, tumor grade and ploidy were not associated with OSPR, while 11q LOH and age showed non-proportional hazards, with patients aged $\geq$5 years at diagnosis having a better early OSPR but poorer long-term outcome than those $<$ 5 years. **Conclusions:** In this, the largest analysis of patients with relapsed HR-NBL, multiple factors at diagnosis were associated with OSPR, emphasising the importance of tumor biology and disease burden. The finding of improved OSPR for INRG M vs L2 is unexpected but may relate to MYCN amplification. Further analyses will focus on changes in prognostic factors over time, non-proportional hazards and the impact of upfront and relapse treatment paradigms on OSPR and prognostic factors. Research Sponsor: Garron Family Cancer Centre.

10053 **Poster Session**

Whole genome-based circulating tumor DNA analysis as an ultrasensitive biomarker in pediatric sarcomas. First Author: Claire Johns, Stanford, Palo Alto, CA

Background: Disease monitoring in pediatric sarcomas relies on invasive surgical biopsies and radiologic imaging, which often trail disease activity. Circulating tumor DNA (ctDNA) is an attractive potential biomarker, but studies in pediatric sarcomas have reported low detection rates by tracking copy number alterations or recurrent genetic alterations. We aim to establish a personalized ctDNA pipeline in pediatric sarcomas based on identification of tumor-specific single nucleotide variants (SNVs) from whole genome sequencing (WGS) to enhance ctDNA detection. **Methods:** Patients $<$ 25 years old with new or relapsed sarcoma treated at our institution are eligible to enroll in our study, which is ongoing. Plasma is collected at imaging response evaluations. Matched tumor and germline DNA are collected at baseline and undergo paired WGS to identify tumor-specific SNVs, and personalized hybrid capture panels are designed to track up to 5000 mutations per patient. Cell-free DNA from each time point is analyzed with CAncer Personalized Profiling by deep Sequencing (CAPP-Seq) using duplex sequencing to minimize the background error rate and maximize sensitivity. **Results:** This approach was piloted in 8 pediatric patients with osteosarcoma (5), Ewings sarcoma (2), and rhabdomyosarcoma (1). A median of 619 tumor-derived SNVs (range 160-4937) were tracked per patient. ctDNA was detected in all patients at baseline with mean allele fractions ranging from 0.000937-27.1. Table 1 summarizes characteristics, number of SNVs tracked, and mean allele fraction for each patient. Seven patients had longitudinal ctDNA samples available for analysis. In all patients, ctDNA broadly correlated with radiologic response with ctDNA becoming undetectable in patients with an imaging response and ctDNA remaining detectable in patients who experienced progression. One patient achieved initial remission with undetectable ctDNA and relapsed with ctDNA re-emergence. **Conclusions:** Personalized whole genome-based ctDNA analysis may improve ctDNA detection in pediatric sarcomas. In this pilot, ctDNA was detected at baseline in 8/8 patients, and ctDNA levels correlated with treatment response on imaging. A personalized approach for ctDNA detection in pediatric sarcomas has the potential to aid in disease monitoring and treatment selection. Research Sponsor: Conquer Cancer, the ASCO Foundation; Stanford Maternal and Child Health Research Institute; Dianne Taube Family Foundation.

Patient characteristics and baseline ctDNA allele fraction.

Disease	New (N) v Relapsed/ Refractory (R)	Localized (L) v Metastatic (M)	Sex (M, F)	Age (years)	SNVs (n)	Baseline ctDNA Mean Allele fraction
Osteosarcoma	N	L	M	17	692	0.25
Osteosarcoma	N	L	M	14	301	4.29
Osteosarcoma	R	M	M	20	4937	0.00094
Osteosarcoma	R	M	F	11	1684	27.10
Osteosarcoma	R	M	M	12	546	2.70
Ewings sarcoma	N	L	M	5	160	14.11
Ewings sarcoma	N	L	M	6	198	0.78
Rhabdomyosarcoma	R	M	F	19	935	2.79

Each row represents 1 patient with disease and ctDNA detection characteristics displayed.

10054 **Poster Session**

A phase 2 study of sirolimus in combination with metronomic chemotherapy (CHOAnome) in children with recurrent and/or refractory solid and CNS tumors. First Author: Kathryn S. Sutton, Aflac Cancer and Blood Disorders Center, Children's Healthcare of Atlanta, Emory University School of Medicine, Atlanta, GA

Background: Outcomes for recurrent and/or refractory (R/R) solid and central nervous system (CNS) tumors remain poor. Sirolimus, an mTOR inhibitor, has both antiproliferative and antiangiogenic effects, and the mTOR pathway is activated in many cancers. Low-dose metronomic chemotherapy also decreases neovascularization and has demonstrated activity in many pediatric tumors. We previously conducted a phase 1 trial establishing the dose (2 mg/m^2), safety and tolerability of sirolimus in combination with metronomic chemotherapy. The current study is a prospective, multi-institutional phase 2 trial to determine the objective response rate (ORR) in children with R/R solid and CNS tumors treated with this regimen (NCT02574728); herein we report the results of the solid tumor stratum. **Methods:** Patients aged 12 months to 30 years with R/R extracranial solid tumors were eligible. Patients were required to have measurable disease and no known curative therapeutic options. Treatment consisted of continuous sirolimus (2 mg/m^2/dose PO daily), celecoxib (100 mg PO BID), and oral etoposide (50 mg/m^2/day; max: 100 mg) alternating every 21 days with oral cyclophosphamide (2.5 mg/kg/day; max: 100 mg) in 42-day cycles. Sirolimus was dose-adjusted to maintain a serum trough concentration of 10-15 ng/ml. Response was determined using Response Evaluation Criteria in Solid Tumors (RECIST) v1.1. Enrollment proceeded using a Fleming's two-stage design based on best overall response (BOR), requiring 2 objective disease status determinations. **Results:** Twenty-four solid tumor patients were enrolled; 20/24 were evaluable for response. Median age was 14.6 years (range: 2.5–20.5); 9 (45%) were female. Diagnoses included desmoplastic small round cell tumor (DSRCT; n = 3), osteosarcoma (n = 4), Wilms tumor (n = 2), neuroblastoma (n = 5), and one each of Ewing sarcoma, rhabdomyosarcoma, CIC-rearranged sarcoma, clear cell sarcoma-like tumor of the GI tract (CCST), juvenile xanthogranuloma (JXG), and hemangiopericytoma. Median number of cycles was 2 (range: 1-13). Best response after any cycle was partial response (PR) in 2 (CCST and JXG), stable disease (SD) in 8, and progressive disease (PD) in 10 for an objective response rate of 10%. BOR was PR in 2 (10%), SD in 5 (25%), PD in 11 (55%), and unknown in 2 (10%). Median PFS was 3.6 months (range: 1.0-26.2) and median OS was 15.5 months (range: 1.0-55.4). One-year PFS was 26.2% [95% confidence interval (CI): 11.9-57.8%) with 1-year OS of 59.6% (95% CI: 35.1-77.4%). Six patients had $\geq$SD for $\geq$6 months [CCST (n = 1), DSRCT (n = 1), JXG (n = 1), hemangiopericytoma (n = 1), and neuroblastoma (n = 2)]. **Conclusions:** The combination of sirolimus with metronomic chemotherapy showed limited activity in patients with R/R solid tumors, although prolonged disease stabilization was seen across multiple histologies consistent with a metronomic approach. Clinical trial information: NCT02574728. Research Sponsor: Cannonball Kids' Cancer Foundation; Hyundai Hope on Wheels; Carter Samuel Martin Innovative Therapy Research Fund.

10055 **Poster Session**

Association of neurocognitive impairment and financial hardship in adult survivors of childhood cancer: A report from the Childhood Cancer Survivor Study (CCSS). First Author: Daniel J. Zheng, Children's Hospital of Philadelphia, Philadelphia, PA

Background: Adult survivors of childhood cancer are at high risk for financial hardship due to the cumulative lifetime costs of cancer-directed therapy and chronic health conditions. Whether neurocognitive impairment increases the risk for financial hardship is unknown. **Methods:** Childhood cancer survivors ($\geq$ 5-year survivors, diagnosed $<$ 21 years of age between 1970-1999) enrolled in CCSS completed a validated self-report Neurocognitive Questionnaire (NCQ) in 2014 and a subsequent financial hardship survey (age $\geq$ 26 at survey completion) 3 years later. The NCQ measured neurocognitive impairment in four domains: (1) memory; (2) task efficiency; (3) organization; (4) emotional regulation. NCQ was the exposure and operationalized as the number of impaired domains (0-4); in each domain, impairment was defined as a Z-score $>$90th percentile. Financial hardship outcomes were measured in behavioral (e.g., delaying care due to cost), material (e.g., high out-of-pocket costs), and psychological (e.g., worry about financial situation) domains, as well as two discrete outcomes of debt collection and bankruptcy. Multivariable linear and logistic regressions were used to analyze associations adjusting for age, sex, and race/ethnicity. **Results:** 3023 survivors completed the NCQ (mean age 38.8, SD=8.6 years) and a subsequent financial hardship survey (mean age 41.5, SD=8.7 years). 13.9%, 8.1%, 6.0%, and 2.6% of survivors had neurocognitive impairments in 1-4 domains, respectively. Individuals with NCQ impairment had significantly higher mean standardized scores across all three financial hardship domains than those without NCQ impairments (Table). Each ordinal increase in the number of impaired NCQ domains was associated with a higher mean standardized score for both behavioral and material financial hardship. Individuals with impairments in all four NCQ domains were more likely to be sent to debt collection (54% vs. 25%, OR=3.82, 95% CI: 2.27-6.43) and file for bankruptcy protection (21% vs. 8%, OR=2.81, 95% CI: 1.53-5.17) compared to those without impairments. **Conclusions:** Cancer survivors with neurocognitive impairment are particularly vulnerable to financial hardship. This survivor population should be specifically assessed for these outcomes and offered support to prevent and mitigate financial challenges. Research Sponsor: Childhood Cancer Survivor Study; National Cancer Institute; CA21765, C. Roberts, Principal Investigator; American Lebanese-Syrian Associated Charities (ALSAC).

Standardized mean differences (SMD) of each financial hardship domain by number of NCQ impairments compared to no NCQ impairments.

Number of NCQ domains impaired	Behavioral Domain SMD (95% CI)	Material Domain SMD (95% CI)	Psychological Domain SMD (95% CI)
1	0.21 (0.11-0.31)	0.20 (0.10-0.29)	0.41 (0.31-0.50)
2	0.39 (0.27-0.51)	0.32 (0.20-0.44)	0.38 (0.25-0.50)
3	0.48 (0.34-0.63)	0.35 (0.20-0.49)	0.44 (0.30-0.58)
4	0.72 (0.51-0.93)	0.72 (0.52-0.94)	0.74 (0.53-0.94)

10056 Poster Session

Psychologic distress amongst adolescent and young adult cancer survivors' and parents. First Author: Kaille Meguiar, Vanderbilt University Medical Center, Nashville, TN

Background: Increasing survival in adolescent and young adult (AYA) cancer patients has led to a growing population at risk for poor psychological outcomes. We sought to identify risk factors for the development of psychologic distress and post-traumatic stress (PTS) in AYA survivors and their parents. **Methods:** In a single-institution prospective cohort study, survivors ages 10-25 years old completed a self-report review of systems (ROS) and psychosocial surveys at initial and follow up visits, including the Youth (YSR) or Adult Self Report (ASR) assessing psychologic distress and the Impact of Events Scale (IES) assessing PTS. Parents of patients ages 10-18 years completed the Childhood Behavior Checklist (CBCL) assessing their child's psychologic distress. Parents completed the Beck Anxiety (BAI) and Depression (BDI) Index and IES assessing their personal anxiety, depression, and PTS. Psychologic distress and PTS were defined dichotomously with an internalizing problems T-score $\geq$ 60 on YSR/ASR/CBCL and IES $\geq$ 24, respectively. Psychologic distress and PTS were further analyzed as continuous variables in multivariable linear regression models with age, diagnosis, gender, time from end of therapy (EOT), substance use, sexual dysfunction, ROS, and therapy intensity. Spearman correlation coefficients were computed to assess relationships between patient and parent scores. **Results:** The study enrolled 135 patients and 72 parents, of which 37 were parents of 10-18-year-olds. Median age of patients at diagnosis was 15 years and median time from EOT was 3.2 years. 50% were female, 65% had a hematologic malignancy, and 92% were white. 20% of patients reported psychologic distress. 17% of patients and 17% of parents reported PTS. 10% and 13% of parents reported at least moderate anxiety and depression, respectively. In multivariable regression analyses, psychologic distress was associated with a higher number of patient-reported systems (Slope estimate = 2.98, $p < 0.01$) and shorter time since EOT (-0.45, p = 0.03). PTS was associated with a higher number of patient-reported system (1.46-fold, $p < 0.01$). Multivariable regression analyses in parent data showed parent-reported psychologic distress of patient was associated with a higher number of patient-reported systems (6.01, p = 0.03). Positive correlations were seen between parent-reported psychologic distress of patient and patient self-reported psychologic distress (R = 0.58, $p < 0.01$) and also with patient self-reported PTS (R = 0.51, $p < 0.01$). Parent reported psychologic distress of patient was positively correlated with parent self-reported anxiety (R = 0.45, p = 0.01) and also with parent self-reported PTS (R = 0.42, p = 0.02). **Conclusions:** A meaningful minority of survivors and parents face psychologic distress and PTS. A larger study is ongoing to expand upon our preliminary findings and examine the trajectory of psychologic distress and PTS in survivorship. Research Sponsor: NIH/NIGMS; T32GM108554.

10057 Poster Session

Longitudinal associations between chronic health condition burden and financial hardship among adult survivors of childhood cancer: A report from the Childhood Cancer Survivor study (CCSS). First Author: Tara Suntum, MedStar Georgetown University Hospital, Washington, DC

Background: Childhood cancer survivors experience a large burden of chronic health conditions (CHCs) with the progression of these conditions facilitating potential economic burden. This study examined the association between CHC progression and financial hardship in adult survivors of childhood cancer. **Methods:** The study included CCSS participants diagnosed with pediatric cancer (1970–1999) who survived $>$ 5 years post-diagnosis and were $\geq$26 years old at the assessment of financial burden. Participants completed surveys (2017-2019) assessing three financial hardship domains: behavioral, material, and psychological. CHCs were self-reported at baseline and on up to 4 follow-ups. CHC severity was graded using CTCAE v4.03. To estimate the impact of multiple CHCs, a severity score was calculated based on published methods (PMID: 17595271) accounting for the frequency and grade of conditions. Notable CHC burden was defined as any CHC above low severity grade. Multivariable logistic regression evaluated associations of CHC burden with financial hardship adjusting for age at diagnosis, attained age, sex, insurance, personal income, education, marital status, smoking status, and body mass index. Additional analyses examined whether neighborhood deprivation using the Area Deprivation Index (ADI) (range 0-100) modified the relationship between CHC burden and financial hardship. **Results:** Among 3,638 evaluable participants, the prevalence of notable CHC burden was 66%, material hardship 16%, psychological hardship 26%, and behavioral hardship 21%. Survivors with very high CHC burden had 2.6-fold (95%CI 1.6-4.1) higher odds of material and 1.6-fold (95%CI 1.0-2.4) higher odds of psychological hardship vs. those with low CHC burden. Survivors who progressed to moderate, high, or very high CHC burden had 1.7-fold (95%CI 1.2-2.5) higher odds of material hardship and 1.6-fold (95%CI 1.1-2.2) higher odds of psychological hardship vs. those with persistent low CHC burden. For survivors living in more deprived neighborhoods (ADI$\geq$50), having notable CHC burden was associated with 2.5-fold (95% CI 1.5-4.3) higher odds of material hardship vs. those without notable CHC burden. For survivors living in less deprived neighborhoods (ADI $<$ 50), having notable CHC burden was associated with 1.5-fold (95%CI 1.1-2.2) higher odds of psychological hardship and 1.6-fold (95%CI 1.1-2.1) higher odds of behavioral hardship vs. those without notable CHC burden. **Conclusions:** Longitudinal CHC burden shows strong temporal associations with material and psychological financial hardship. Neighborhood deprivation is associated with financial hardship, beyond individual sociodemographic factors. Multi-level interventions will be crucial to address financial hardship in survivors who develop CHCs earlier than peers. Research Sponsor: National Cancer Institute; U24 CA055727.

10058 Poster Session

Treatment and lifestyle profiles of healthy aging survivors: A report from the Childhood Cancer Survivor Study. First Author: Timothy James Daeeun Ohlsen, Department of Pediatrics, Seattle Children's Hospital, University of Washington, Seattle, WA

Background: Survivors of childhood cancer are at elevated risk for adverse health outcomes, but many maintain excellent health throughout adulthood. We sought to characterize the trajectories of, and examine factors associated with, healthy aging across the lifespan. **Methods:** We longitudinally surveyed $\geq$5 y cancer survivors (18-64 y) and sibling controls enrolled in the Childhood Cancer Survivor Study. "Healthy aging" was defined by 1) having a cumulative number of severe or life-threatening (i.e., grade 3+) chronic health conditions (CHCs) less than or equal to the mean of same age, same sex sibling controls; and 2) having no functional impairment or activity limitations. We then examined prevalences of healthy aging and its 2 component domains across survivor age groups ($<$ 30, 30-39, 40-49, $\geq$50 y). Multivariable logistic regression models adjusted for demographic, treatment, and lifestyle factors at cohort entry estimated risk factors for healthy aging among survivors. **Results:** We analyzed 17,263 survivors (median age 39 y, IQR 32-46) and 3,378 siblings. Among all sibling age/sex groups, mean grade 3+ CHC counts were $<$ 1. Of survivors, 53.4% (95% CI 52.7-54.2) had no Grade 3+ CHC, and 71.4% (95% CI 70.7-72.1) reported no functional impairment. Overall, 45.0% (95% CI 44.2-45.7) of survivors met criteria for healthy aging, but this prevalence decreased with age (Table). In multivariable analysis, treatment factors associated with lower odds of healthy aging included anthracycline dose ($\geq$250 mg/m^2 vs none: OR 0.60, 95% CI 0.52-0.69), alkylator dose ($\geq$8 g/m^2 vs none: OR 0.76, 95% CI 0.67-0.86), and stem cell transplant (OR 0.60, 95% CI 0.41-0.89). High doses of radiation to any site were also associated with less healthy aging (e.g., $\geq$30 Gy to brain vs none: OR 0.22, 95% CI 0.19-0.26). Baseline physical activity $>$ 180 min/week was associated with healthy aging (vs $<$ 180 min: OR 1.23, 95% CI 1.11-1.37). Underweight, overweight, and obese baseline BMIs had lower odds of healthy aging compared with normal BMI (ORs 0.54 to 0.82, each $p < 0.05$). Survivors treated in more recent decades were more likely to experience healthy aging (1990s vs 1970s: OR 1.26, 95% CI 1.06-1.50) even after adjusting for attained age. **Conclusions:** Among childhood cancer survivors, the prevalence of healthy aging declines with age but has improved in more recent treatment eras. Higher levels of exercise and normal BMI at baseline were associated with subsequent healthy aging, suggesting that the trajectory of aging could be improved through targeted interventions. Research Sponsor: National Cancer Institute; CA55727; National Cancer Institute; CA21765.

Prevalence (%) of outcomes across survivor age groups (95% CI).

	<30 y	30-39 y	40-49 y	≥50 y
CHC count ≤ sibling mean for age/sex	67.4 (65.8, 69.0)	59.3 (58.1, 60.5)	47.5 (46.2-48.9)	34.4 (32.6-36.2)
No functional impairment	76.0 (74.6, 77.5)	73.9 (72.8, 74.9)	69.4 (68.2-70.7)	64.1 (62.3-65.9)
Healthy aging	58.0 (56.3, 59.7)	50.8 (49.5, 52.0)	39.2 (37.8-40.5)	27.2 (25.5-28.9)

10059 Poster Session

US population-level costs and cost-savings associated with long-term follow-up (LTFU) screening for survivors of childhood cancer. First Author: Matthew J. Ehrhardt, St. Jude Children's Research Hospital, Memphis, TN

Background: Children's Oncology Group's (COG) LTFU Guideline adherence is poor. We evaluated the impact of universal payer coverage on patient costs associated with adherence to COG-directed cardiomyopathy (CM), breast (BC), and colorectal cancer (CRC) screening. **Methods:** We reviewed coverage guidelines for Medicare, Medicaid, and commercial plans for COG screening for exposure-based CM (echocardiogram [echo] every 2-5 yrs based on cumulative chest radiation (RT) and anthracyclines), BC (yearly mammography [MAM] and magnetic resonance imaging [MRI] beginning at age 25 or 8 yrs from chest RT), and CRC (colonoscopy [COL] every 5 yrs or multitarget stool DNA [MTSD] every 3 yrs, starting 5 yrs from abdominopelvic RT or age 30). The eligible US population was estimated from SEER and American Cancer Society cancer survival rates. Cost of screening was derived from the Center for Medicare & Medicaid Services (CMS) and of lifetime treatment from published data. Net costs vs. benefits (in US $) were calculated, assuming 100% adherence, as the sum of cost-savings (i.e., treatment costs averted) and monetary value of quality-adjusted life-yrs (QALYs) gained minus costs (e.g., screening, false positives). **Results:** Screening coverage varied by payer (Table). BC screening for all US survivors with prior chest RT (n = 42,847) yielded a net benefit ranging from $0.5 to $3.4 billion, with patients paying 19.3% of costs. Among 138,702 survivors at-risk of CRC, net benefit from COL and MTSD was $5.7 and 5.0 billion. Patients nationally bore 0% of MTSD but 60% of COL costs. Among 218,322 at-risk of CM, costs exceeded cost-savings by $1.7 billion when using the median echo cost by payer but yielded a $400 million benefit when using the average cost of CMS and the lowest commercial plan. Patients bore 90% of CM costs. **Conclusions:** Screening for CM, BC, and CRC per the COG guidelines results in substantial cost savings and benefits. However, as adherence is $<$ 100% due to copay, inadequate coverage, and low provider awareness, interventions and policies focused on boosting adherence could yield cost savings to the health system and reduce disease burden in this population. Research Sponsor: None.

		By Payer (Subset)			Cost Bearer, % (Aggregated across Payers)		Value of Cases Averted	Value of QALYs Gained	Total Cost	Net Costs (-) or Benefit (+)
COG Screening		**Medicare**	**Medicaid**	**Commercial**	**Patient (Pt)**	**Payer**	**Billion US $, Range**			
BC MAM & MRI	**Coverage**	Full, at physician's discretion	**MAM:** Full **MRI:** None	Full	19.3	80.7	NA*	2.6 - 5.9	2.1 - 2.5	0.5 - 3.4
	Pt Cost	20% copay after Part B deductible	20% copay	**MAM:** 0% **MRI:** 15-30% copay after deductible						
CRC COL or MTSD	**Coverage**	**COL:** None **MTSD:** Full	None Full	None Full	**COL:** 60	40	3.7	4.4	2.4	5.7
	Pt Cost	**COL:** 100% **MTSD:** 0%	100% 0%	100% 0%	**MTSD:** 0	100	2.9	4.0	1.9	5.0
CM Echo	**Coverage**	None	None	≤2 covered after age 18	90.3	9.7	0.01	0.74	0.36 - 2.5	-1.7 - 0.4
	Pt Cost	100%	100%	15%-30% copay after deductible						

*Not available in published models.

10060 **Poster Session**

Food insecurity, dietary quality, and cardiovascular risk in early childhood cancer survivors. First Author: Rahela Aziz-Bose, Dana-Farber/Boston Children's Cancer and Blood Disorders Center, Boston, MA

Background: Childhood cancer survivors (CCS) experience cardiovascular (CV) mortality 7 times higher than the general population. Low-income and Black CCS experience significantly higher all-cause and CV mortality than peers. Food insecurity, a modifiable CV risk factor associated with lower dietary quality, has not been investigated as a potential driver of adverse CCS CV outcomes. We characterized and assessed associations between food insecurity, dietary quality, and CV risk conditions in a prospective cohort of early CCS. **Methods:** Children< 18 years with a hematologic, solid, or central nervous system malignancy < 12 months from completion of cancer-directed therapy were recruited at a quaternary academic pediatric cancer center. Parents/guardians completed a single-timepoint survey including validated measures of food insecurity and dietary quality. Clinical CV risk (systolic or diastolic blood pressure $\geq 95^{th}$ percentile, body mass index $\geq 85^{th}$ percentile, dyslipidemia, or impaired glucose tolerance) and therapeutic CV risk (receipt of anthracycline, chest radiation, or total body irradiation) was abstracted from the medical record. Descriptive statistics summarized dietary quality and prevalence of food insecurity. A t-test compared associations between food security status and dietary quality, followed by multivariable linear regression adjusted for age, sex, race/ethnicity, income, and diagnosis type. Logistic regression compared associations between food security status and presence of clinical CV risk conditions. **Results:** Of 135 eligible participants, 119 (88%) consented to participation and 115 (97%) completed surveys, with no missing food security or dietary data. Participants were a mean age 6.5 years and mean 4.8 months from end of therapy. Twenty-seven percent (n = 31, 95% CI: 19-36%) of participants lived in food-insecure households. Mean child dietary quality was 27.6 (SD 5.3) on a 52-point scale (higher scores reflect higher quality, US adult mean score 35.0). Dietary quality was significantly lower for participants in food-insecure households compared to food-secure households on univariate analysis (25.9 vs 28.2, p = 0.04); in multivariable analyses, this difference was no longer significant. Among the subcohort (n = 97) consented to medical record abstraction, 84% (n = 81) had a CV risk factor (47% [n = 38] clinical conditions, 26% [n = 21] therapeutic exposures, and 27% [n = 22] both). Frequency of clinical CV risk conditions did not differ between children with and without food insecurity (58% vs 63%, p = 0.61). **Conclusions:** One in four children in early cancer survivorship lives with food insecurity. These children concurrently experience multiple CV risk factors and suboptimal dietary quality. Interventions targeting food insecurity and other modifiable CV risk factors are urgently needed to mitigate CV late effects and advance equity in survivorship outcomes. Research Sponsor: Conquer Cancer, the ASCO Foundation; St. Baldrick's Foundation.

10061 **Poster Session**

Risk assessment and development of a machine learning–based prediction model for survival in patients with medulloblastoma. First Author: Yu Su, Capital Medical University, Beijing, China

Background: While clinical risk factors have long guided medulloblastoma (MB) treatment, the significance of genetic events in therapeutic strategies has not been fully elucidated. We aimed to explore whether molecular risk categories could inform management by analyzing long-term follow-up profiles, and concurrently to establish and validate an explainable prediction model for MB based on machine learning (ML) approaches, and to assess its prognostic implications in patients. **Methods:** A multicenter cohort of 729 patients from 2001 to 2023 was enrolled as a discovery cohort. Data from 511 patients from international MB consortia were used to validate. Multivariate survival analyses assessed the associations between radiotherapy dose and survival by different molecular risk stratifications which integrated clinical and genetic events, followed by training and internal and external validation of models. The area under the receiver-operating-characteristic curve (AUROC) and decision curve analysis (DCA) were used to compare the predictive performance of six ML models. The SHapley Additive exPlanation method was used to explain the final model. **Results:** Fifteen-year OS and DFS rates were 64.1% (95% CI, 57.9%-71.0%) and 59.1% (95% CI, 53.2%-65.5%) for clinical average-risk group (n = 554), and 55.9% (95% CI, 44.4%-70.2%) and 60.6% (95% CI, 51.9%-70.7%) for clinical high-risk group (n = 175), respectively. Within the high-risk stratification of SHH-MB, higher posterior fossa tumor bed (PFTB) total dose (≥ 55.8 Gy) combined with reduced craniospinal irradiation (CSI) dose (23.4 ~ < 30.6 Gy) was associated with better prognosis. In Gr.3-MB, MYC amplification (activation), as a high-risk marker of dissemination, indicated that CSI dose should be escalated to high intensity (36.0 Gy, p = 0.03) for survival benefits. In the model of Gr.4-MB, CDK6 activation well stratified patients, with 10-year OS of 71.0% (95% CI, 54.0%-93.5%) for average-risk and 52.1% (95% CI, 39.5%-68.8%) for high-risk group. The XGBoost method demonstrated the most optimal predictive efficacy among the six ML models, as evidenced by the training set AUROC of 0.75 (95% CI 0.70-0.80) for 5-year survival rates, 0.75 (0.69-0.80) for 10-year survival rates, and 0.80 (0.72-0.87) for 15-year survival rates in all patients. The final model could accurately predict survival rates in both internal and external validations, and has been deployed through a free, publicly available online software interface. **Conclusions:** The molecular risk stratification was suggested to potentially guide risk-adapted radiotherapy. Except that 36.0 Gy CSI dose is warranted for Gr.3-MB with MYC amplification, CSI reduction is recommended. Furthermore, this study, based on clinical and molecular information, constructs an available survival prediction tool for MB patients. Research Sponsor: National Natural Science Foundation of China; 82273343; Capital Medical Fund for Excellent Young Scholars; KCB2304.

10062 **Poster Session**

Retinoblastoma patient outcomes in the contemporary era: The RIVERBOAT Consortium. First Author: Murali M. Chintagumpala, Texas Children's Cancer and Hematology Center, Baylor College of Medicine, Houston, TX

Background: Retinoblastoma (RB) is the most common childhood eye tumor. Intraocular RB cure rates approach 100%. Therefore, treatment now focuses on globe salvage and preserving functional vision. The Research into Visual Endpoints and RB Health Outcomes After Treatment (RIVERBOAT) consortium was established to examine patient outcomes in the transitional era from systemic to intraocular therapy. **Methods:** Patients with RB treated at 13 North American centers from 2008-2022 were identified. Medical record abstraction was performed for disease presentation, visual acuity, treatment, globe salvage and functional outcome. Enrollment on the study included submission of retrospective data and prospective data on newly diagnosed patients as well as retrospective data from chart reviews. **Results:** 830 patients (68% white race, 77% non-Hispanic ethnicity) were enrolled. In 420 of these, data was limited to chart review. Median age at diagnosis of the 830 patients (1165 eyes) was 1 year (0 - 16.3) and at enrollment was 7.8 years (0 - 28.6). 60% had unilateral disease and the eye group distribution (International Intraocular Retinoblastoma Classification) was 10% A, 16% B, 12% C, 31% D, 27% E, and 4% unknown (UK). Of the 1165 affected eyes, major treatment modalities included primary enucleation (15%), systemic chemotherapy (SC) (36%), intraarterial chemotherapy (IAC) (10%), SC followed by IAC in 9%, and intravitreal chemotherapy in combination in 6%. SC only was used in 55-59% of those with A-C eyes compared to 29% of D eyes. IAC only was used in 20% of D eyes and 16% of C eyes. Secondary enucleation occurred in 151 eyes (14%): 63/416 (15%) of SC; 34/120 (28%) of IAC; 25/106 (24%) of SC followed by IAC; 29/523 (6%) other treatments. The overall globe salvage rate was 86%. Second malignancies occurred in 5, metastatic disease in 8 and pineoblastoma in 3 patients. Eleven patients died of RB (1%). Visual acuity after treatment was reported in 229 eyes: 106 (eye group 24 A, 37 B, 22 C, 19 D, 3 E, 1 UK) had normal vision (20/20-20/40). 38 eyes, (6 A, 11 B, 4 C, 10 D, 5 E, 2 UK) had moderate vision loss (> 20/40 – 20/70). Twenty-five eyes (5 B, 2 C, 16 D, 2 E) had low vision (> 20/70 < 20/200), and 60 eyes (12 B, 7 C, 32 D, 8 E, 1 UK) were legally blind (>20/200). In those treated with IAC only, normal vision was found in 30% of eyes, moderate vision loss in 22%, low vision in 13%, and legal blindness in 35%. In those treated with SC only, normal vision was noted in 53% of eyes, moderate vision loss in 11%, low vision in 11%, and legal blindness in 25%. In those treated with SC followed by IAC, normal vision was reported in 32%, moderate vision in 26%, low vision in 5% and legal blindness in 37%. **Conclusions:** We demonstrate the significant benefits witnessed by the evolution of RB therapy. Cure rates remain high, with a very low incidence of second malignancies, metastatic disease or trilateral RB. Eye salvage rate was excellent, avoiding low vision or legal blindness in two-thirds of the patients. Research Sponsor: None.

10063 **Poster Session**

Genome-wide association study of neurocognitive outcomes among childhood cancer survivors. First Author: Jennifer N. French, St. Jude Children's Research Hospital, Memphis, TN

Background: Long-term survivors of childhood cancer experience heightened risk of late effects, with about 40% developing cognitive impairment. Established risk factors include cranial radiation and specific chemotherapies. Variability in treatment-related outcomes has been associated with genetic factors, though prior studies examined targeted pathways and not whole genome approaches. **Methods:** Participants included 4,077 childhood cancer survivors with whole genome sequencing and direct neurocognitive testing from the St. Jude Lifetime Cohort Study (SJLIFE). The mean (standard deviation) age at primary cancer diagnosis was 7.8 (5.7) years, and 28.5 (10.3) years at neurocognitive testing; 52.3% were male; 78.9% were Non-Hispanic White. Linear regression evaluated associations between common genetic variants (minor allele frequency, MAF≥1%) and 20 neurocognitive measures (as age-adjusted Z-scores). Analyses were adjusted for sex, age at primary childhood cancer diagnosis, age at neurocognitive testing, cumulative doses of high-dose methotrexate, intrathecal methotrexate, anthracyclines and cranial radiation, and genetic ancestry . Loci with $P \leq 5x10^{-8}$ were considered genome-wide significant and evaluated in stratified analysis by genetic ancestry and treatment exposures. **Results:** 21 SNPs met genome-wide significance for associations with ≥1 neurocognitive measure, 9 SNPs with a MAF ≥1% in EUR (n = 3,312) and AFR (n = 636) survivors. All 9 SNPs had 1.1-3.6 times larger effect sizes in AFR compared to EUR. The biggest differences in ancestry groups were seen when stratifying analyses by anthracycline exposure. An intronic variant in *ERG*, rs1309269486, had a 2.0-times larger effect on motor speed in exposed EUR (β = -0.70; P= $2.9x10^{-6}$) compared to unexposed EUR (β = -0.35; P= 0.039). In AFR, rs1309269486 was only associated with motor speed in unexposed survivors (β = -1.33; P= $2.9x10^{-3}$), with a 3.8-times greater effect size compared to unexposed EUR. *ERG* has been shown to play a role in neurogenesis. Another intronic variant in *P2RY12*, rs1755678683, also showed a 1.8-times larger effect on attention span in exposed EUR (β = -0.68; P= $5.9x10^{-4}$) than unexposed EUR (β = -0.38; P= 0.035). However, it was associated with attention span in only unexposed AFR (β = -1.28; P= $2.1x10^{-3}$), showing 3.4-times greater effect than in unexposed EUR. *P2RY12* plays a role in microglia function, neuroinflammation, and neurodegeneration. An intronic variant in *COL15A1*, rs1837227843, was associated with working memory in exposed EUR (β = -0.47; P= $5.3x10^{-7}$) and unexposed AFR (β = -0.58; P= $4.9x10^{-3}$). While *COL15A1* is highly expressed in many brain tissues, previous associations with neurocognition have not been established. **Conclusions:** These findings highlight the independent and combined role (with treatment) of genetics and genetic ancestry in adverse neurocognitive impairment among survivors of childhood cancer. Research Sponsor: National Cancer Institute; National Cancer Institute; the American Lebanese Syrian Associated Charities.

10064 Poster Session

Accelerated aging among long-term survivors of childhood cancer: A report from the Childhood Cancer Survivor Study (CCSS). First Author: AnnaLynn Williams, University of Rochester School of Medicine and Dentistry, Rochester, NY

Background: Cross-sectional studies have suggested childhood cancer survivors demonstrate a pattern of functional limitations and morbidity consistent with premature aging, but cannot confirm if aging is accelerated relative to peers without cancer. We used longitudinal data to characterize aging using a Deficit Accumulation Index (DAI) which examines the accumulation of multiple aging-related deficits. **Methods:** We included 5+ year survivors of childhood cancer (N=21,856; at entry mean age 26.7 [SD 6.1], 18.7 [4.7] years post diagnosis) and siblings (N=4,628, mean age 29.1 [7.1]) from the CCSS, a longitudinal prospective cohort study. Participants completed questionnaires at up to four timepoints (mean[SD] follow-up 9.5[8.9] years), with DAI scores generated as the proportion of deficits out of 30 items related to aging, including chronic conditions (e.g. hearing loss, hypertension), psychosocial and physical function, and activities of daily living. The total score range is 0 to 1; and a moderate clinically meaningful difference is 0.02. As survivors completed multiple surveys at varying intervals, attained age was used as the time scale. Linear mixed models compared DAI in survivors to siblings with an attained age*survivor interaction term to determine if DAI was increasing faster in survivors, adjusted for the first DAI score, age at first DAI and sex. Similar models examined DAI changes associated with treatments among survivors. **Results:** The overall adjusted mean [95%CI] DAI was 0.195[0.194, 0.196] for survivors and 0.179[0.177,0.180] for siblings ($p<0.001$). Survivors experienced more rapid increase in DAI over time compared to siblings ($p<0.001$). For example, at age 20 there was no difference in DAI between survivors and siblings, however the mean difference [95%CI] in DAI between survivors and siblings steadily increased with age to 0.011[0.009, 0.013] at 30 years, 0.024[0.022, 0.026] at 40 years, and 0.038[0.035, 0.040] at 50 years; p's<0.001 (Table). Survivors who received abdominal, cranial or chest radiation experienced more rapid increase in DAI over time compared to those who did not (p's<0.001). Survivors who received platinum agents or neurosurgery also experienced a more rapid increase in DAI over time (p's<0.001). **Conclusions:** Our data confirm survivors of childhood cancer experience significant age acceleration relative to peers. Given the ease of measuring DAI using self-reported data, this tool may be used to routinely monitor survivors and identify those at risk for adverse aging-related outcomes so that we may intervene and mitigate their accelerated aging trajectory. Research Sponsor: National Cancer Institute/U.S. National Institutes of Health; U24CA55727; National Cancer Institute/U.S. National Institutes of Health; R00256356.

Mean difference in DAI in survivors vs. siblings.

	Mean difference (95% CI)	P-value
Age at DAI		
20	-0.003(-0.006, 0.000)	0.0541
30	0.011(0.009, 0.013)	<.0001
40	0.024(0.022, 0.026)	<.0001
50	0.038(0.035, 0.040)	<.0001
60	0.051(0.047, 0.055)	<.0001
70	0.064(0.059, 0.070)	<.0001

10065 Poster Session

Cardiovascular risk factor control and risk of future cardiovascular events in survivors of childhood cancer: A report from the St. Jude Lifetime cohort. First Author: Stephanie B. Dixon, St. Jude Children's Research Hospital, Memphis, TN

Background: Modifiable cardiovascular risk factors (CVRFs; hypertension, diabetes, dyslipidemia) contribute to the excess health-related death in long-term survivors of childhood cancer. However, whether control of CVRFs reduces the risk of major adverse cardiovascular events (MACE) in survivors is not known. **Methods:** Prevalence of hypertension (HTN), diabetes (DM) and LDL cholesterol elevation (LDL) was assessed via in-person assessments in 5+ year survivors ≥18 years old in the St. Jude Lifetime Cohort. Based on ACC/AHA primary prevention guideline recommendations, sub-optimal CVRF control was defined as blood pressure ≥140/90 mmHg, hemoglobin A1c ≥7.0%, and LDL ≥130 mg/dl. MACE was defined as new onset cardiomyopathy, myocardial infarction, stroke and/or cardiovascular death. Piecewise exponential models estimated the multivariable adjusted relative risk (RR) with 95% confidence intervals (CI) for MACE among survivors according to degree of CVRF control. Models were adjusted for sociodemographic factors, physical activity, smoking status, chronic kidney disease, and cancer treatment exposures (anthracycline chemotherapy, chest and/or brain irradiation). **Results:** Among 4876 adult survivors of childhood cancer, 36.1% had HTN, 8.4% DM and 56.5% elevated LDL at first assessment (mean age 28.6 years, standard deviation 9.1). One-third of survivors (33.5%) had at least one sub-optimally controlled CVRF. Among those with HTN, DM or LDL, 30%, 33% and 52% were sub-optimally controlled, respectively. In multivariable models, sub-optimal LDL control was associated with a > 8-fold higher risk of MACE compared to those with no LDL elevation (RR 8.4, CI 4.2 – 19.3; Table). This was more than twice the risk observed in those with well-controlled LDL compared to no LDL elevation (RR 4.0, CI 1.9 – 9.4; p-value <0.001). Similarly, sub-optimal DM control vs never having DM was associated with increased MACE risk (RR 3.4, CI 1.8 – 6.1) with twice the risk in those with sub-optimal control compared to well-controlled DM (p = 0.05; RR well-controlled DM vs no DM 1.6, CI 0.9 – 2.8). HTN, compared to no HTN, was associated with a 3 to 4-fold increase in risk of subsequent MACE, regardless of degree of control. **Conclusions:** Survivors of childhood cancer had a high prevalence of sub-optimally controlled CVRFs that was associated with an increased MACE risk. Optimal control of CVRFs among adult survivors of childhood cancer may reduce the risk of MACE. These findings motivate an intervention trial in intensive CVRF control. Research Sponsor: U.S. National Cancer Institute; U01 CA195547; U.S. National Cancer Institute; P30 CA21765; American Lebanese-Syrian Associated Charities (ALSAC).

CVRF Control	RR of MACE (95% CI)	P-value comparing RR
LDL elevation		
Sub-optimal LDL vs no LDL elevation	**8.4 (4.2 – 19.3)**	**<0.001**
Controlled LDL vs no LDL elevation	**4.0 (1.9 – 9.4)**	
Diabetes		
Sub-optimal DM vs no DM	**3.4 (1.8 – 6.1)**	**0.05**
Controlled DM vs no DM	1.6 (0.9 – 2.8)	
Hypertension		
Sub-optimal HTN vs no HTN	**3.9 (2.2 – 7.0)**	0.28
Controlled HTN vs no HTN	**3.0 (1.9 – 4.8)**	

10066 Poster Session

Breast cancer recurrence and mortality among survivors of childhood cancer: A report from the Childhood Cancer Survivor Study (CCSS). First Author: Lucie Marie Turcotte, University of Minnesota Medical School, Minneapolis, MN

Background: Survivors of childhood cancer are at high risk for developing subsequent breast cancer (BC). However, BC recurrence risk and survival after BC recurrence has not been evaluated in survivors of childhood cancer. **Methods:** Analyses included female 5-year survivors participating in CCSS with pathology-ascertained breast carcinomas (in situ or invasive) diagnosed from 1981-2016 at age ≥18y. BC treatment was evaluated against chronological period-specific National Comprehensive Cancer Network guidelines for primary BC. Recurrent BC cumulative incidence was estimated treating death as a competing risk among survivors and females with first primary BC (controls) matched one-to-one by demographics and first BC clinical characteristics including diagnosis age/year, histology and race/ethnicity (206 pairs with complete data). Among survivors and controls with recurrent BC, all-cause mortality was evaluated with cumulative incidence with time at risk starting at relapse and hazard ratios from multivariable Cox regression models adjusted for age and calendar year of recurrence and race/ethnicity. **Results:** Among the 431 childhood cancer survivors with subsequent BC (median diagnosis age: 40 years, IQR: 35-44), 68 developed recurrent BC. Compared with matched controls, survivors had similar 10-year BC recurrence risk (survivors: 14%, 95% CI: 9-20% versus controls: 12%, 95% CI: 9-18%; P=0.52). Among survivors with BC recurrence, Hodgkin lymphoma was the predominant primary cancer diagnosis (63%) and first subsequent BCs were largely early stage (stage 0: 8%; stage I/II: 69%) and estrogen (71%) or progesterone (80%) receptor positive. Most (84%) received first BC treatment following national guidelines for primary BC. However, nearly half (47%) underwent bilateral mastectomies (81% occurring before recurrence) and most received chest radiotherapy (86%) or anthracycline chemotherapy (69%) for either their primary childhood cancer or first subsequent BC. A total of 48 survivors died after BC recurrence, mostly related to BC (83%) or cardiovascular causes (11%). Following recurrence, the 10-year overall mortality probability was significantly higher among survivors (89%, 95% CI: 61-97%) than controls (42%, 95% CI: 18-58%; P=0.0025) and survivors had an adjusted 2.6-fold (95% CI: 1.05-6.49) greater risk of death. **Conclusions:** Although the risk for BC recurrence among childhood cancer survivors with subsequent BC is similar to females with primary BC, this vulnerable population faces substantially greater mortality risk after recurrence. Future studies to identify early predictors of subsequent BC and BC recurrence among survivors are needed to reduce mortality risk. Research Sponsor: National Cancer Institute/U.S. National Institutes of Health; K08 CA234232, LM Turcotte, principal investigator; U24 CA55727, GT Armstrong, principal investigator.

10068 Poster Session

Financial hardship and non-adherence to lifestyle and surveillance recommendations in adult survivors of childhood cancer: A report from the Childhood Cancer Survivor Study (CCSS). First Author: Neel S. Bhatt, Fred Hutchinson Cancer Center, Seattle, WA

Background: The association between different aspects of medical financial hardship and non-adherence to healthy lifestyle recommendations and surveillance for subsequent neoplasms (SN) and cardiomyopathy in long-term survivors of childhood cancer is unknown. **Methods:** A randomly selected subset of participants in the CCSS completed a financial hardship survey and a follow-up survey assessing lifestyle behaviors and adherence to recommended surveillance. Presence of financial hardship was determined by affirmative response to ≥1 item in material (e.g., high out-of-pocket costs), behavioral (e.g., delaying care due to cost), or psychological (e.g., worry about financial situation) hardship domains. Outcomes included "not meeting physical activity guidelines" (< 9 metabolic-equivalent-of-task-hour/week moderate to vigorous activity), "problematic drinking" (> 7 drinks/week or > 3 drinks/day [women], > 14 drinks/week or > 4 drinks/day [men]), current smoker, unhealthy BMI (< 18.5 or ≥30 kg/m^2), and non-adherence to surveillance for breast, colorectal, and/or skin cancer, and cardiomyopathy screening according to the Children's Oncology Group guidelines. Logistic regression models, adjusted for age at the most recent survey, sex, race/ethnicity, education, and chronic health conditions, examined the association of material, behavioral, and psychological hardship with healthy lifestyle and surveillance outcomes. **Results:** A total of 3,322 survivors, at a median of 34.4 (range:19.7-51.4) years from diagnosis and 41 (20-69) years of age at the most recent survey were included. Presence of material hardship alone was associated with higher risk of not meeting physical activity guidelines (odds ratio 1.6, 95% CI 1.2-2.1) and unhealthy BMI (1.4, 1.1-1.8). Presence of both material and behavioral (1.8, 1.2-2.6) or material and psychological (1.8, 1.4-2.4) hardships further increased the risk for unhealthy BMI. Presence of all 3 hardship domains was associated with higher risk of unhealthy BMI (2.2, 1.8-2.7). Behavioral hardship (2.2, 1.1-4.6) and psychological hardship (3.9, 2.4-6.4) alone were associated with higher risk of being a current smoker at time of follow-up, with presence of both further increasing the risk for smoking (4.1, 2.3-7.3). Presence of psychological hardship alone was associated with higher non-adherence to cardiomyopathy screening (1.3, 1.0-1.8) among those at high risk. Associations between hardship and SN surveillance were not significant. **Conclusions:** Financial hardship is associated with non-adherence to healthy lifestyle and recommended screening for cardiomyopathy among adult survivors of childhood cancer. Findings underscore the need for strategies to identify and mitigate financial hardship and improve adherence to recommended lifestyle and surveillance. Research Sponsor: National Cancer Institute; U24 CA55727.

10069 Poster Session

Assessment of smartwatch-based electrocardiogram (ECG) abnormality detection among childhood cancer survivors. First Author: Ibrahim Karabayir, Wake Forest School of Medicine, Winston-Salem, NC

Background: Childhood cancer survivors (CCS), exposed to cardiotoxic cancer therapies, are at lifelong risk for premature cardiovascular disease. However, adherence to guideline recommended screening is low later in life, long after cancer treatment. Novel wearable technologies offer a potential low-cost, easy screening method for arrythmias in CCS, including AF, bradycardia, and tachycardia. However, their utility in population level screening for CCS is unknown. **Methods:** We collected paired single lead smartwatch with FDA cleared ECG functionality and 12-lead 10 second ECGs from adult participants in the St. Jude Lifetime Cohort Study (SJLIFE) who were treated for their primary cancer 1962-2012 and survived ≥5 years. Participants completed an in-person comprehensive examination including a standard 10 second 12-lead ECG recording as well as single lead rhythms were collected using a smartwatch. The smartwatch provided automated annotations including sinus rhythm, AF, bradycardia (HR<60 bpm), tachycardia (HR>100 bpm), and inconclusive rhythm. We compared the smartwatch generated statements to reference diagnostic statements generated by GE MUSE system. **Results:** There were 598 same day ECG pairs in 580 participants (83% White, 14% Black, 50% male, and mean age(SD) 37(10) years). The mean(SD) times between smartwatch and reference ECG recordings were 32(50) minutes. The heart rate from reference ECG and smartwatch ECG had a Pearson Correlation of r=0.85 (p<0.001). The smartwatch ECGs presented statistically significantly (p<0.001) higher heart rates compared to reference ECGs with mean heart rate difference (95% confidence interval) of 1.2 (0.5-1.8) beats per minute. Standard 12-lead ECGs processed by GE MUSE annotations included 478 (80%) sinus rhythm and 120 (20%) as 'no sinus rhythm' with 1 (0.2%) AF, 57 (9.5%) sinus bradycardia, 18 (3.2%) sinus tachycardia and 28 (6.4%) other rhythms. The smartwatch assigned sinus rhythm to 590 (98.7%) of these ECGs. The detailed rhythm annotations between reference ECG and smartwatch ECGs are summarized in Table 1. The smartwatch detected only 3.5% (2 of 57) of reference bradycardia, none of the 18 reference tachycardia and 1 AF event. Overall, among 120 ECGs labelled as 'no sinus rhythm' by the reference device, only 3 (2.6%) of them were also labeled as 'no sinus rhythm' by the smartwatch. **Conclusions:** The smartwatch considered in this study produces heart rate that is not clinically different than heart rate calculated by a reference 12-lead ECG. However, the ECG abnormalities identified by reference ECGs were typically missed by the smartwatch. Research Sponsor: National Cancer Institute; R01CA261834.

Comparison of GE MUSE and smartwatch ECG statements.

		Smartwatch Statements					
		Sinus Rhythm	Atrial Fibrillation	Low Heart Rate	High Heart Rate	Inconclusive/ Poor	
GE MUSE Statements	Sinus Rhythm	478	0	3	0	2	483
	Atrial Fibrillation	1	0	0	0	0	1
	Bradycardia	55	0	2	0	0	57
	Tachicardia	18	0	0	0	1	19
	Other Rhythm	38	0	0	0	0	38
	Total	590	0	6	0	3	598

10070 Poster Session

Predicting valvular heart disease in adult survivors of childhood cancer: A report from the Childhood Cancer Survivor Study (CCSS) and St. Jude Lifetime Cohort (SJLIFE). First Author: Daniel A. Mulrooney, St. Jude Children's Research Hospital, Memphis, TN

Background: Radiotherapy (RT)-related valvular heart disease (VHD) is an understudied late toxicity of childhood cancer therapy. We aimed to define the risk of VHD with clinical data available at 5 and 20 years from cancer diagnosis. **Methods:** Mean heart RT doses were estimated for participants of the CCSS and SJLIFE cohorts treated with RT. Two piecewise exponential regression prediction models were developed in the CCSS, from entry into survivorship (5 years post cancer diagnosis) and 20 years post diagnosis (inclusive of age- and lifestyle-acquired risk factors), to assess subsequent risk of developing severe/life-threatening/fatal VHD (≥ grade 3 Common Terminology Criteria for Adverse Events [CTCAE]) by age 50 years. Models were validated among clinically assessed SJLIFE survivors. **Results:** Among 18,807 CCSS participants [mean age (±standard deviation) at diagnosis = 8.1 (5.8) years and 40 (11.1) at assessment] including 9,998 treated with RT, 164 (0.9%) reported VHD after cohort entry. Of those ≥20 years post diagnosis (n = 16,618) [7.9 (5.8) years at diagnosis; 42.5 (9.6) at assessment] 138 (0.8%) reported VHD. In SJLIFE, 44 (1.0%) of 4,388 survivors, including 2,103 treated with RT, and 35 (1.4%) of 2,423 ≥20-year survivors had VHD (mean ages at diagnosis and assessment: 7.8 [5.7] and 32 [12] years; 7.6 (5.5) and 38.7 (9.2) years, respectively). Prediction performance at age 50 years was good for both models [areas under the receiver operating characteristic curves 0.84 (95% CI 0.79-0.89) and 0.87 (95% CI 0.81-0.91)]. For each 10 Gy of heart RT, the rate of VHD increased approximately 2.5-fold (Table). Acquired risk factors, except glucose intolerance, further increased the risk, marginally for hypertension, significantly (p < 0.05) for obesity (RR 1.7 95% CI 1.0-2.8) and dyslipidemia (RR 2.3 95% CI 1.3-4.0). **Conclusions:** In the first study to develop validated risk prediction models for VHD in survivors of childhood cancer, mean heart RT dose and acquired factors significantly increased the risk, suggesting opportunities for intervention. Research Sponsor: U.S. National Institutes of Health; R01CA261750; U.S. National Institutes of Health; U24 CA55727; U.S. National Institutes of Health; U01 CA195547; American Lebanese Syrian Associated Charities (ALSAC).

Rate ratios (RR) of VHD.

	From entry into survivorship		From 20-year post diagnosis	
	RR	(95% CI)	RR	(95% CI)
Mean heart RT dose (per 10 Gy)	2.4	(2.2-2.7)	2.5	(2.2-2.9)
Age at diagnosis (years)				
<5	referent		referent	
5-9	1.1	(0.6-2.1)	1.2	(0.6-2.5)
10-15	1.1	(0.6-2.1)	1.3	(0.6-2.6)
≥15	1.1	(0.6-2.1)	1.2	(0.6-2.6)
Female sex	1.1	(0.8-1.5)	1.3	(0.9-1.9)
Race/Ethnicity				
non-Hispanic White	referent		referent	
non-Hispanic Black	1.3	(0.5-2.8)	0.8	(0.2-2.3)
Other	1.1	(0.6-1.6)	1.0	(0.6-1.7)
Anthracycline dose (mg/m^2)				
None	referent		referent	
<100	0.6	0.1-1.6	0.8	(0.2-2.2)
100-249	0.9	0.5-1.4	0.9	(0.5-1.5)
≥250	1.5	1.0-2.2	1.3	(0.8-2.1)
Acquired risk factors*				
Glucose intolerance	N/A		0.3	(0.02-1.3)
Smoking (Y/N)			1.1	(0.8-1.5)
Hypertension			1.6	(0.9-2.7)
Obesity			1.7	(1.0-2.8)
Dyslipidemia			2.3	(1.3-4.0)

*≥grade 2 CTCAE.

10071 Poster Session

Characteristics and concomitant congenital abnormalities among newborns with cancer: A population level analysis. First Author: Sergio Hernandez-Llamas, DHR Health Internal Medicine, Edinburg, TX

Background: Congenital cancers are rare, occurring in 223 per million infants annually. Neuroblastoma, leukemia, and CNS tumors are most common. Up to one-third of cases involve genetic predispositions, emphasizing the need to understand developmental abnormalities for improved surveillance, prognosis, and targeted therapies. **Methods:** A retrospective population-based cohort study was conducted utilizing the Texas Inpatient Public Use Data File (TIPUDF) from 2016 to 2023. The target population consisted of all hospitalizations with Newborn in the source of admission column of the TIPUDF. Hospitalizations discharged more than one year after birth were excluded from the study. The primary exposure was a diagnosis of cancer identified using International Classification of Diseases, Tenth Revisions, Clinical Modification (ICD-10-CM) codes selected from diagnosis chapter NEO: Neoplasms and beginning with C. Outcome variables were selected from diagnosis chapters MAL: Congenital Malformations, Deformations and Chromosomal Abnormalities and PNL: Certain Conditions Originating in the Perinatal Period. Continuous variables are summarized as mean and standard deviation (SD) categorical variables are summarized as counts and percentages. Fisher's exact test and t-tests assessed group differences, with the standardized mean difference (SMD) used as an effect size. **Results:** Out of the 2,906,295 newborn admissions in the TIPUDF from 2016-2023, 136 had a diagnosis of cancer. Compared to newborn admission without cancer, newborn admissions with cancer were more often male (62.5% vs 51.0%). Compared to newborns without cancer, newborns with cancer were associated with higher rates of congenital malformations, deformations and chromosomal abnormalities including atrial septal defects (38.2% vs 1.7%, SMD = 1.0256, p < 0.0001), anomalies of the aorta (1.6% vs 39.7%, p < 0.0001), undescended testicles (0.5% vs 2.9%, SMD = 0.1932, p < 0.0037), ventricular septal defects (15.4% vs 0.7%, SMD = 0.5647, p < 0.0001), Atresia and stenosis of urethra and bladder neck (2.2% vs 0.0%, SMD = 0.2119, p < 0.0001), Cleft lip/palate (2.2% vs 0.1%, SMD = 0.1935, p = 0.0009), anomalies of ureter (1.5% vs 0.0%, SMD = 0.1695, p < 0.0003). Newborns with cancer were more frequently affected by maternal conditions and complications including polyhydramnios (2.9% vs 0.2 %, SMD = 0.2260, p < 0.0001) and maternal infectious and parasitic diseases (7.4% vs 2.6%, SMD = 0.2193, p = 0.0032). **Conclusions:** Congenital cancers are rare but closely linked to congenital abnormalities and maternal complications, emphasizing the importance of early detection and tailored care. Future studies should explore underlying mechanisms and design effective surveillance strategies to enhance early diagnosis and outcomes. Research Sponsor: None.

10072 Poster Session

Evaluating survivorship-related communication gaps to develop a community health worker-led intervention for Hispanic/Latino young adult childhood cancer survivors and their families. First Author: Stephanie M. Smith, Division of Hematology, Oncology, Stem Cell Transplantation & Regenerative Medicine, Department of Pediatrics, Stanford University School of Medicine, Palo Alto, CA

Background: Open communication among young adult childhood cancer survivors (YA-CCS), parents, and clinicians helps YA-CCS understand their cancer history, health risks, and survivorship care needs. However, Hispanic/Latino (H/L) YA-CCS families who prefer a language other than English face significant communication barriers during clinical encounters with English speaking clinicians. As part of an ongoing study aimed at developing an intervention to facilitate family-centered communication, we report here on interviews conducted with H/L YA-CCS and their parents. **Methods:** We held small group and individual interviews in English and Spanish with H/L YA-CCS (ages 18-25, ≥5 years post-diagnosis) and separately with parents of H/L YA-CCS. Transcripts were analyzed qualitatively using thematic analysis in Dedoose software. Participants were recruited through our collaboration with a community-based organization (CBO) and in a pediatric oncology clinic. Using a structured human-centered design process, we assembled a design team of community partners to ideate and prototype an intervention. **Results:** Ten YA-CCS (5 female, 5 male; all bilingual) and 10 parents (all female; Spanish-language preferred) participated, representing 13 families. YA-CCS were median age (min-max) 20.5 (18-25) years and 9 (6-15) years post-diagnosis. YA-CCS described knowledge gaps due to being excluded from parent-clinician conversations during treatment and ongoing avoidance of cancer discussions within families due to emotional burden. Many YA-CCS and parents shared that yearly survivorship clinic visits evoke stress, nervousness, and a sense of being unprepared, often leaving them overwhelmed. Some linked hesitancy to discuss cancer or ask questions during visits to their cultural norms. Guided by these insights, we leveraged our community-clinic partnership to co-develop an intervention to facilitate family-centered communication. In 3 design workshop sessions, CBO staff designed an early prototype for a "pre- and post-visit preparation" communication intervention, in which a community health worker meets with each YA-CCS-parent dyad before and after a survivorship clinic visit to help elicit questions, clarify topics, and debrief action items. **Conclusions:** Effective triadic communication is essential to bridge gaps in cancer survivorship care among H/L YA-CCS. Listening directly to H/L YA-CCS and parents identified communication barriers that are being addressed in the development of a culturally and linguistically tailored intervention to support families affected by cancer. Interviews and the intervention design process are ongoing and updated data will be presented at the meeting. Research Sponsor: Conquer Cancer, the ASCO Foundation; National Institutes of Health, National Cancer Institute; 1K08CA285829-01.

10073 **Poster Session**

Development of a pediatric oncology financial toxicity outcome measure with content and face validity: The Parent-Reported Instrument of Costs and Experiences with financial toxicity (PRICE) measure. First Author: Timothy James Daeeun Ohlsen, Department of Pediatrics, Seattle Children's Hospital, University of Washington, Seattle, WA

Background: Cancer treatment often leads to adverse financial consequences for patients and families (i.e., financial toxicity, FT). There is no validated measure to quantify FT in pediatric cancer settings, limiting research in this area. **Methods:** We applied a stepwise approach to measure development consistent with ISPOR guidelines. First, we conducted qualitative concept elicitation interviews with family caregivers of children treated for cancer, 3-24 months following diagnosis. Second, we drafted de novo survey items guided by salient domains and aspects of FT from the interviews. Items were reviewed by a multi-institutional panel of experts in oncology and/or FT-related research, who provided numeric ratings of item relevance for aggregation into content validity index (CVI) scores. Experts also provided free text feedback on clarity and content. Items with CVI $<$ 0.75 were removed or revised by a consensus-based process. The revised item list was organized into a preliminary measure and forward and back translated into Spanish. Finally, we pretested items with a new cohort of caregivers in English and Spanish, through iterative rounds of language-concordant cognitive interviews (3-4 per round). Between each round, we reviewed and revised the survey to optimize comprehension, decision and response processes, and flow. **Results:** Concept elicitation with 21 caregivers (86% mothers, 47% college-educated, 14% in Spanish) led to the creation of 56 initial survey items across 5 domains of FT: increased household spending, diminished income, household material hardship, psychological distress related to finances, and behaviors in response to FT. The expert panel (n = 11) consisted of 5 providers, 2 clinical social workers, 2 nurse researchers, and 2 non-clinician researchers, with 6 members external to the study institution. CVI was $<$ 0.75 for 13 items; 11 of these were removed and 2 were revised based on free text feedback. Of 43 items with CVI $\geq$0.75, 9 were removed based on feedback and/or overlap with more highly rated items. Cognitive interviews were held with 19 caregivers (15 in English, 4 in Spanish; 74% mothers, 53% college educated) over 5 iterative rounds. The 36 remaining items were revised and/or removed, and ultimately organized into 16 questions, one of which was added during this phase based on caregiver feedback. In the final round of interviews, participants reported no concerns with content, clarity, or organization in either language. **Conclusions:** We developed a novel outcome measure with content and face validity to assess FT specifically in pediatric oncology settings. Next steps consist of field testing to evaluate the measure's psychometric properties and other dimensions of validity. Potential future applications include use as a study endpoint and/or clinical screening tool. Research Sponsor: Conquer Cancer, the ASCO Foundation.

TPS10074 **Poster Session**

A phase 1/2, open-label study evaluating the efficacy, safety, and pharmacokinetics of luveltamab tazevibulin in infants and children < 12 years of age with *CBFA2T3::GLIS2* acute myeloid leukemia. First Author: Sarah K Tasian, Children's Hospital of Philadelphia, Philadelphia, PA

Background: *CBFA2T3::GLIS2*-rearranged acute myeloid leukemia (AML) is a rare subtype of AML occurring exclusively in very young children and is associated with poor prognosis ($<$ 15% 5-year event-free survival [EFS]) with best-available multi-agent chemotherapy. Luveltamab tazevibulin (luvelta) is an anti–FRα-targeting antibody-drug conjugate with a stable cleavable linker and a 3-aminophenyl hemiasterlin warhead (DAR = 4), which induces cytotoxic and immunologic cell death. *CBFA2T3::GLIS2* AML uniquely expresses high cell surface levels of the FRα, suggesting that FRα-targeted therapies may be effective. Preclinical studies have demonstrated that treatment with luvelta can result in leukemia clearance. Preliminary safety and efficacy data from 25 children with relapsed/refractory *CBFA2T3::GLIS2* AML treated with luvelta via compassionate use are promising [Williams, et al, BLOOD 2023, 142 (1): 4295]. **Methods:** This registration-enabling phase 1/2 study (clinicaltrials.gov NCT06679582) will investigate the pharmacokinetics, safety and preliminary efficacy of Luvelta in relapsed or refractory children with *CBFA2T3::GLIS2* AML and $\geq$5% bone marrow (BM) involvement by morphology. The *CBFA2T3::GLIS2* fusion will be confirmed at Foundation Medicine by next generation sequencing (NGS). The trial will open in up to 35 centers across US, Europe, Canada and Australia and is actively enrolling. The initial part of the trial will test luvelta monotherapy at 3.5 mg/kg or 4.3 mg/kg administered IV every 2 weeks in a 28-day cycle. Bayesian sequential monitoring is used for safety monitoring. The study committees will review the data to identify the recommended phase 2 dose of luvelta which will then be tested in the second part of the trial. Children who achieve BM morphological complete response (CR) may proceed to allogeneic hematopoietic stem cell transplantation (HSCT) or continue single-agent luvelta for up to 2 years at the investigators' discretion. Patients without CR after 2 cycles of luvelta monotherapy may add chemotherapy (cytarabine +/- fludarabine or azacytidine) in cycle 3 and beyond. Post-HSCT maintenance therapy with luvelta monotherapy is also allowed for up to 2 years. The primary endpoint is morphologic CR defined as $<$ 5% AML blasts in BM with absolute neutrophil recovery to $>$ 1000 and platelets $>$ 100,000 and absence of extramedullary disease. Secondary endpoints include PK levels and assessment of anti-drug antibody formation, safety, EFS and overall survival. Rates of measurable residual disease-negative CR and FRα antigen levels pre- and post-luvelta will also be explored. Clinical trial information: NCT06679582. Research Sponsor: None.

TPS10075 **Poster Session**

Phase 1/2 study of zilovertamab vedotin in pediatric and young adult hematologic malignancies or solid tumors (LIGHTBEAM-U01A). First Author: Hyoung Jin Kang, Seoul National University College of Medicine, Seoul National University Cancer Research Institute, Seoul National University Children's Hospital, Seoul, South Korea

Background: ROR1 is an oncofetal protein expressed in various blood and solid cancers. Zilovertamab vedotin (ZV) is an antibody-drug conjugate comprising a monoclonal antibody against ROR1, a proteolytically cleavable linker, and monomethyl auristatin E. LIGHTBEAM-U01A (NCT06395103) is a single-arm, open-label, phase 1/2 basket study designed to evaluate ZV in 4 disease cohorts: pediatric B-cell acute lymphoblastic leukemia (B-ALL), pediatric diffuse large B-cell lymphoma (DLBCL)/Burkitt lymphoma, pediatric neuroblastoma, and pediatric or young adult Ewing sarcoma. **Methods:** Pediatric participants (pts) are aged 0 to $<$ 18 years; young adults are aged 18-25 years. Pts must have a confirmed diagnosis of B-ALL or DLBCL/Burkitt lymphoma per WHO criteria that has relapsed after $\geq$2 prior lines of therapy, or histologically confirmed neuroblastoma or Ewing Sarcoma that is refractory to frontline therapy. Pts with B-ALL must have $\geq$5% bone marrow blasts (M2 or M3), pts with DLBCL/Burkitt lymphoma must have radiographically measurable disease per IPNHL response criteria, and pts with neuroblastoma or Ewing sarcoma must have measurable disease per RECIST v1.1 (or MIBG-avid evaluable neuroblastoma). Pts aged $\leq$16 years must have a Lansky play-performance scale $\geq$50, pts aged $>$ 16 to $<$ 18 years must have a Karnofsky performance status of $\geq$50, and pts aged $\geq$18 years must have an ECOG performance status of 0 or 1. The study consists of 2 parts: dose escalation and confirmation (part 1) and efficacy expansion (part 2). Part 1 will enroll 3-12 pts per dose level. Also, $\geq$3 pts will be enrolled in 2 age groups: 1 to $<$ 6 years and 6 to $<$ 18 years. Pts will receive ZV at a starting dose of 2 mg/kg IV Q3W, escalating to 2.25 and 2.5 mg/kg or de-escalating to 1.75 mg/kg per a modified toxicity probability interval design-2. In part 2, eligibility will be expanded to $\geq$6 months for all cohorts and $\leq$25 years for Ewing sarcoma (if adequate safety and tolerability are shown, eligibility will expand to age 0 to $<$ 6 months). In part 2, 10 pts will be enrolled in each cohort and will receive ZV at the preliminary RP2D determined in part 1. Disease assessments for pts with DLBCL/Burkitt lymphoma, neuroblastoma, or Ewing sarcoma will be performed Q8W for 6 months, then Q12W through 24 months, then Q24W through 5 years, then annually. Disease assessments for B-ALL will be performed at the end of each treatment cycle, at 6 months, at 1 year, then annually. Adverse events (AEs) will be monitored $\leq$30 days after last dose of study treatment (90 days for serious AEs; 30 days if new anticancer therapy is initiated) and will be graded per NCI CTCAE v5.0. Primary end points are safety and objective response rate. Secondary end points are pharmacokinetics, immunogenicity, duration of response, and eligibility for transplant/CAR-T therapy for pts with B-ALL or DLBCL/Burkitt lymphoma. Approximately 50-90 pts will be enrolled. Recruitment is underway. Clinical trial information: NCT06395103. Research Sponsor: Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA.

10500 Oral Abstract Session

Sensitivity of age and family history (FH) criteria for determining pancreatic cancer (PC) surveillance (PCS) eligibility among individuals with hereditary PC risk. First Author: Asaf Maoz, Dana-Farber Cancer Institute/Mass General Brigham/Harvard Medical School, Boston, MA

Background: PCS for individuals with pathogenic/likely pathogenic germline variants (PGVs) predisposing to PC is associated with earlier stage at diagnosis (dx) and improved survival, compared to historical controls. For those with such PGVs, PCS eligibility is determined based on FH of PC and age (age ≥30 years for those with *STK11* PGVs; age ≥40 for *CDKN2A*; age ≥50 for other PC risk genes [Table 1]; or 10 years before the youngest PC in the family). For PGV carriers (apart from *CDKN2A/STK11*), guidelines have required a FH of PC in ≥1 first-/second-degree relatives (FDR/SDR) for PCS eligibility. Limited data have evaluated the sensitivity of these criteria in determining which high-risk individuals benefit from PCS. **Methods:** We evaluated the sensitivity of age and FH criteria for PCS in the Myriad Collaborative Research Registry (MCRR). Individuals who were diagnosed with PC and underwent germline genetic testing were included. To determine the number of PGV carriers who would have been eligible for PCS at the time of their PC dx, FH of cancer and personal cancer history were ascertained from data contained in MCRR at the time of germline testing. **Results:** Among 11,248 PC patients who underwent germline testing, 55.5% were female and 59.2% were non-Hispanic White/European. The mean age at PC dx was 64.6 years. PGVs predisposing to PC were detected in 969 (8.6%) individuals [Table 1], of whom 224 (23.1%) met gene-specific PCS criteria. Of the 969, 829 (85.6%) met gene-specific *age criteria* for PCS. Of the 931 individuals with PGVs in genes requiring FH, only 208 (22.2%) fulfilled *FH criteria* for PCS. **Conclusions:** Most individuals with PC who harbor PGVs in PC susceptibility genes would not have met gene-specific age/FH criteria for PCS. FH of PC has particularly poor sensitivity in identifying PGV carriers who go on to develop PC, supporting recent removal of this criterion from NCCN guidelines for *BRCA2/ATM*. Validation in a clinic-based cohort is ongoing. These data suggest that FH of PC should not be used to determine which PGV carriers are eligible for PCS. Research Sponsor: Betsy Rowe and Family.

Gene (n)	Met FH criterion of PC in FDR/SDR - n (%)	Met age# criterion - n (%)	Met age and FH criteria (%)
***ATM* (186)**	47 (25.3)	170 (91.4)	44 (23.7)
***BRCA1* (137)**	28 (20.4)	114 (83.2)	26 (19.0)
***BRCA2* (428)**	101 (23.6)	363 (84.8)	88 (20.6)
***PALB2* (61)**	11 (18.0)	50 (82.0)	10 (16.4)
***MLH1* (11) /**	4 (36.4) /	9 (81.8) /	4 (36.4) /
***MSH2* (40) /**	4 (10.0) /	27 (67.5) /	3 (7.5) /
***MSH6* (32)**	4 (12.5)	27 (84.4)	4 (12.5)
TP53* **(25)**	4 (16.0)	23 (92.0)	4 (16.0)
***CDKN2A* (34) /**	NA	33 (97.1) /	33 (97.1) /
***STK11* (2)**		2/2 (100)	2/2 (100)
> 1 PGV (13)	5/11 (45.5)	11/13 (84.6)	6/13 (46.2)

NA: Not applicable.
#Age ≥30 years for *STK11*; age ≥40 for *CDKN2A*; age ≥50 for other PC risk genes; or 10 years before the youngest PC in the family.
*Ancillary testing to confirm germline status vs clonal hematopoiesis/mosaicism is not available.

10501 Oral Abstract Session

A prospective study of whole-body MRI (WBMRI) as part of a multimodality screening program for individuals with Li-Fraumeni syndrome (LFS). First Author: Asaf Maoz, Dana-Farber Cancer Institute/Mass General Brigham/Harvard Medical School, Boston, MA

Background: Individuals with LFS are at risk for developing cancer in multiple organs and therefore require a multimodal cancer screening program. We assessed the performance of annual WBMRI in early cancer detection for individuals with LFS. **Methods:** Individuals with a germline pathogenic or likely pathogenic variant in the *TP53* gene (defined as LFS) and without cancer diagnosed or treated in the preceding 6 months were eligible to undergo annual non-contrast WBMRI. Clinical findings on WBMRI, follow-up studies, and biopsies were prospectively assessed. Cancer incidence during the study period and up to 18 months after WBMRI was evaluated. **Results:** 162 eligible participants (pts) with LFS (127 adult, 35 pediatric) underwent a total of 477 WBMRIs; 119 (73%) underwent 3 or more. Median age at enrollment was 37 years; 75% of pts were female. Classic or Chompret diagnostic criteria for LFS were met for 66% (84/127) of adult and 77% (27/35) of pediatric pts. Follow-up studies for findings on WBMRI were pursued for 61.4% (78/127) of adult and 34.3% (12/35) of pediatric pts. Biopsies were performed without complication in 18% (29/162) of pts with 39.5% of 38 biopsies confirming a cancer diagnosis. The percentage of pts requiring follow-up studies or biopsies decreased with consecutive WBMRIs (Table 1). During the study period, 37 cancers were diagnosed in 33 pts (27 adults, 6 children); 26 of these pts were alive at the time of data cut off. Fifteen of 37 cancers (40.5%) were asymptomatic cancers diagnosed by WBMRI; 86% (13/15) of these (in 12 patients) were localized and treated with curative intent, including 3 lung cancers and 4 pelvic/abdominal sarcomas. Ten of these 12 pts remain alive at the time of last follow-up. The 22 cancers not diagnosed on WBMRI included five sarcomas, and one each of adrenocortical, lung, thyroid and renal cell carcinoma as well as cancers not likely to be detected on WBMRI (4 breast/chest wall, 3 endoluminal, 3 hematologic, and 3 metastatic recurrences). **Conclusions:** Annual WBMRI contributes substantially to detection of asymptomatic localized cancers among individuals with LFS but interval cancers remain common. Our study highlights limitations of WBMRI and the need for further research to enhance early detection and interception of cancer in LFS. Research Sponsor: Li-Fraumeni Syndrome Association (LFSA); The Cantor Foundation; National Cancer Institute; P30 CA008748 (PI: Vickers); Breast Cancer Research Foundation.

Sequence of WB-MRI scans and timing of follow-up studies, biopsies, and cancer diagnoses.

WB-MRI scan number	# pts evaluated	# pts with follow-up studies n (%)	# pts with biopsies n (%)	# pts dx with ca by WBMRI n (%)	# ca dx based on WBMRI n	# pts with interval ca dx n (%)	# interval ca dx by other means or symptoms (not detected on WBMRI) n
1	162	60 (37.0)	20 (12.3)	6 (3.7)	7	8 (4.9)	8
2	143	38 (26.6)	12 (8.4)	6 (4.2)	6	7 (4.9)	9
3	119	21 (17.6)	3 (2.5)	0 (0)	0	3 (2.5)	3
4	33	5 (15.2)	1 (3.0)	1 (3.0)	1	2 (6.1)	2
5	11	1 (9.1)	0 (0)	1 (9.1)	1	0 (0)	0
6	5	1 (20)	0 (0)	0 (0)	0	0 (0)	0
7	3	1 (33.3)	0 (0)	0 (0)	0	0 (0)	0

pts: participants, ca: cancer, dx: diagnosed.

10502 Oral Abstract Session

The eREACH study: A randomized study of an eHEALTH delivery alternative for cancer genetic testing for hereditary predisposition in patients with metastatic cancers. First Author: Angela R. Bradbury, University of Pennsylvania, Philadelphia, PA

Background: With FDA approval of targeted therapies in patients with germline *BRCA1/2*-related advanced cancers there is a need to evaluate efficient and effective delivery models for germline cancer genetic testing. **Methods:** eREACH is a 4 arm non-inferiority study where traditional standard-of-care pre-test (visit 1) and post-test (visit 2) counseling delivered by a genetic counselor (GC) are replaced with a patient-centered eHealth (digital) intervention in patients with advanced or metastatic cancer. GC visits were offered by telehealth in the home. Arms include: A (GC/GC), B (GC/digital), C (digital/GC) and D (digital/digital). Those assigned to a digital visit could request a visit with a GC if preferred. Surveys were completed at baseline (T0), after visit 1 (T1), visit 2 (T2) and 6 months (T3). Primary non-inferiority outcomes are change in knowledge and anxiety (T0-T1, T0-T2). Secondary outcomes include uptake of testing, depression, cancer specific distress, responses to testing and satisfaction. We used an intention-to-treat approach (ITT) and as-treated approach (secondary). We used ANOVAs and chi-squared tests for hypothesis testing. For non-inferiority testing, we had additional rules based on the magnitude and sign of effects. **Results:** 229 participants were recruited from 14 states through Penn Medicine, community sites and social media, with 56-60 per arm.Participants were 35-91 YO (mean 67 YO),and37% were male, 17% were non-white and 43% had less than a college education. 70% were from academic sites, 21% from community sites and 9% from social media. Cancer types were: 52% breast, 26% prostate, 18% pancreatic, and 5% ovary. 173 (76%) of patients completed testing (12% had a positive result, 12% had a VUS). In our primary ITT analyses, we met the non-inferiority threshold for all primary and secondary outcomes except for knowledge (T0-T2) and uptake of testing. Increases in knowledge (T0-T2) were greater in Arms A-C as compared to Arm D, although differences were small (averages +2.03-2.54 v +1.23). Uptake of visit 1 was lower in the digital arms (A: 94.7%, B: 92.7% v. C: 76.7%, D: 82.5%), although uptake of testing after visit 1 met non-inferiority. 20% assigned to Arm C and 11% assigned to Arm D requested a GC. As-treated non-inferiority analyses were similar to the ITT results. **Conclusions:** Offering patient-centered digital delivery models with one digital visit and one visit with a genetic counselor is non-inferior to two visits with a genetic counselor for patients with metastatic cancer. Reminders, outreach or completion of digital platforms in clinic could address differences in uptake. The fully digital model may be associated with small differences in knowledge gain, although the clinical significance may be small., and longitudinal data could help inform the appropriateness of the fully digital model. Research Sponsor: None.

10503 Oral Abstract Session

Feasibility of Pap-derived ctDNA for detection of sporadic and Lynch-associated endometrial cancer. First Author: Alicia Latham, Memorial Sloan Kettering Cancer Center, New York, NY

Background: Patients (pts) with Lynch Syndrome (LS) have high risk of endometrial cancer (EC) and are recommended risk-reducing hysterectomy (RR-Hys/BSO) due to lack of effective screening. As plasma-derived circulating tumor DNA (plasma-ctDNA) lacks adequate sensitivity in EC, we sought to evaluate Pap-derived ctDNA (Pap-ctDNA) as a novel, non-invasive assay for EC detection. **Methods:** Plasma-ctDNA and Pap-ctDNA were obtained from pts with EC undergoing surgery or LS undergoing RR-Hys/BSO under an IRB-approved protocol. Paired tumor/normal sequencing of ECs was compared to genomic findings from plasma-ctDNA and Pap-ctDNA. Somatic variants in plasma and Pap samples were genotyped using matched tumor tissue, with average allele frequency (VAF) calculated. Tumors were assessed for MSI and/or MMRD via MSISensor or IHC. In LS pts, pathology for precursor lesions was assessed. **Results:** 19 pts (16 EC, 3 LS) underwent prospective collection of 42 samples (20 plasma, 22 Pap). 56% of ECs were low-grade endometrioid and 81% early-stage (I/II) (Table). 12.5% of ECs were MMRD due to MLH1 hypermethylation. Median yield of Pap-ctDNA was higher than plasma-ctDNA (91ng vs. 19.5ng; p=0.0004). 94% of ECs had mutations covered within target regions of both assays, with mutations detected in 93% of Pap-ctDNA, but only 33% of plasma-ctDNA. In pts with mutations detected in both assays, median VAF was higher in Pap-ctDNA vs. plasma-ctDNA in all 5 cases (Table; p=0.012). Among the 13 pts with early-stage EC, 92% of Pap-ctDNA vs 23% of plasma-ctDNA were positive. Of 3 LS pts, one had a focus of MMRD atypical hyperplasia concordant with germline MMR mutation; plasma and Pap-ctDNA were negative. **Conclusions:** Pap-ctDNA from EC pts results in higher ctDNA yield than plasma-based testing. Tumor mutations were detected in >90% of Pap-ctDNA even in early-stage EC, versus only 23% of plasma-ctDNA samples. Pap-ctDNA for early-detection of EC is feasible and is a promising tool for average and high-risk individuals with potential applicability in other neoplasms. Research Sponsor: Society of Memorial Sloan Kettering Cancer Center.

EC characteristics.

ID	Histology	Stage	MSS/ MMRD	Plasma ctDNA yield (ng)	Pap ctDNA Yield (ng)	Avg VAF mutations-Plasma	Avg VAF mutations-Pap
1	G2 Endometrioid	IA	MSS	19.49	36.83	-	-
2	G1 Endometrioid	IA	MSS	57.27	144.97	-	0.00014
3	G1 Endometrioid	IA	MSS	44.3	179.2	-	0.006
4	Carcinosarcoma	IIIC	MSS	23.78	28.21	0.0062	0.279
5	Serous	IV	MSS	38.45	17.03	0.0046	0.403
6	G1 Endometrioid	IA	MSS	13.76	21.38	-	0.004
7	Mesonephric-like	II	MSS	21.34	31.3	-	0.123
8	G2 Endometrioid	IA	MMRD- MLH1 hypermeth	10.67	185.5	0.0092	0.119
9	G1 Endometrioid	IA	MSS	23.92	27.35	-	0.049
10	Serous	IA	MSS	15.61	110	-	0.277
11	G2 Endometrioid	IA	MMRD-MLH1 hypermeth	8.44	222.65	-	0.066
12	Carcinosarcoma	IA	MSS	14.54	104.19	-	0.433
13	Mixed endometrioid, serous	IVB	MSS	22.96	102.85	-	0.166
14	G2 Endometrioid	IA	MSS	7.46	145.68	0.0007	0.125
15	G2 Endometrioid	IA	MSS	19.45	141.34	-	0.156
16	Serous	IB	MSS	19.38	79.2	0.0005	0.473

10504 Oral Abstract Session

Gene-specific outcomes in patients with Lynch syndrome treated by immune checkpoint blockade for advanced cancer. First Author: Violaine Randrian, Memorial Sloan Kettering Cancer Center, New York, NY

Background: Lynch syndrome (LS), caused by germline pathogenic variants (gPVs) in DNA mismatch repair genes (*MLH1, MSH2, MSH6, PMS2*), is characterized by microsatellite instability (MSI)/mismatch repair deficiency (MMRd) of associated tumors. The impact of the underlying gPV on the prognosis of LS patients with advanced cancer receiving ICB has not been elucidated. **Methods:** Consecutive cancer-affected LS pts consented to tumor-normal DNA sequencing via MSK-IMPACT (NCT01775072), from 01/2014-01/2024 with advanced solid tumors and receiving ≥1 ICB dose were identified. In cases of multiple cancers, only the first one was considered. MSI and MMRd was assessed via NGS-derived MSISensor score or IHC staining, respectively. Radiological response rates and survival were assessed. **Results:** Among 186 LS patients, 132 had an ICB treated advanced tumor with the following prevalence of gPV: *MSH2* 41% (N=54), *MLH1* 28% (N=37), *PMS2* 17% (N=23), and *MSH6* 14% (N=18). The most represented tumor types were colorectal (35%, N=46), urothelial (14%, N=18), pancreatic/biliary (13%, N=17), upper gastro-intestinal (11%, N=15), endometrial (11%, N=15). Objective response rate was 58%, including 35% with radiological complete response (CR) with higher CR rates in g*MLH1* and g*MSH2* patients (Table). Median follow-up was 53 months [range:0.3-116.3]. Median overall survival (mOS) / Progression free survival (mPFS) were significantly prolonged in *non-gPMS2* patients vs. g*PMS2* patients (Table). MMR IHC was available for 107 (80%) tumors identifying 88% (n=94) as MMRd and 12% (n=13) as MMRp tumors. 69% (9/13) of MMRp tumors were in *PMS2* patients with 8 being both MMRp and MSS suggesting a sporadic origin rather than LS-related cancer. Stratifying by MMRd and MSI status, mOS was similar in patients with MMRd/MSI and MMRd/MSS tumors (109 months vs not reached (NR); HR=0.86; 95%CI [0.35-2.13]), but significantly diminished in in pts with MMRp as compared to MMRd tumors (20 vs 109 months, HR=0.27; 95%CI [0.77-0.96]). In g*PMS2* patients with MMRd tumors, median OS was 27.7 months. **Conclusions:** ICB treatment results in high CR rates in LS patients. The shorter mOS amongst LS patients with *gPMS2* compared to other LS genes is partially explained by the higher prevalence of sporadic MMRp tumors. Even in the context of an MMRd tumor, patients with g*PMS2* have worse outcomes than LS patients with other gPVs. Research Sponsor: MSKCC; T32-CA009512; U.S. National Institutes of Health; P30 CA008748; Swim Across America; Servier Foundation; Cycle for survival; Romeo Milio Lynch Syndrome Foundation; Nuovo Soldati; Tournut SNFGE; Ligue contre le Cancer; Philippe Foundation.

Treatment	Total	Complete Response % (n)	Objective Response Rate % (n)	Disease Control rate % (n)	mPFS (months)	mOS (months)
MSH2	54	46% (25)	65% (35)	89% (48)	45	109
MLH1	37	41% (15)	65% (24)	81% (30)	50	NR
PMS2	23	9% (2)	30% (7)	74% (17)	11	20
MSH6	18	22% (4)	61% (11)	78% (14)	109	NR
MLH1/MSH2/MSH6	109	40% (44)	64% (70)	84% (92)	52	109
Non-PMS2 vs PMS2	-	OR=7.1 95%CI [1.7-31.6] P=0.003	OR=4.1 95%CI [1.5-10.3] P=0.005	OR=1.9 95%CI [0.64-5.6] P=0.24	HR=0.21 95%CI [0.13-0.35], P<0.0001	HR=0.19 95%CI [0.10-0.35] P=0.0005

10505 Oral Abstract Session

Phase Ib study of a plasmid DNA–based immunotherapy encoding the hTERT, PSMA, and WT1 (INO-5401) +/- IL12 (INO-9012) followed by electroporation in cancer patients and healthy individuals with *BRCA1/2* mutations. First Author: Susan M. Domchek, Abramson Cancer Center, Penn Medicine, Philadelphia, PA

Background: Pathogenic variants in *BRCA1/2* increase the risk of breast, ovarian, pancreatic and prostate cancer. Non-surgical risk-reduction strategies are needed. We evaluated an immunological approach for cancer interception via a DNA plasmid vaccine. INO-5401 is a recombinant plasmid-derived DNA based immunotherapy encoding 3 tumor-associated antigens: human telomerase reverse transcriptase (hTERT), prostate specific membrane antigen (PSMA), and Wilms Tumor-1 (WT1). INO-9012 is a DNA plasmid encoding IL-12 deployed as an immune adjuvant. Previous studies have shown that INO-5401 in combination with INO-9012 administered via intramuscular (IM) injection followed by electroporation (EP) with CELLECTRA is both immunogenic and tolerable in cancer patients and may lead to efficacy. **Methods:** The primary objective of NCT04367675 is to evaluate the safety of INO-5401 +/- INO-9012 followed by EP in individuals with *BRCA1/2*. Cohort A included adults with prior localized cancer, no evidence of disease (N = 16); Cohort B, healthy individuals with no prior cancer (goal N = 28). Eligibility: ECOG performance status 0-1, normal ECG, and adequate bone marrow, hepatic, and renal function. Treatment: INO-5401 9 mg IM followed by EP (Arm 1) and INO-5401 9 mg in combination with INO-9012 1 mg IM. followed by EP (Arm 2) on Day 1, and weeks 4, 8, 12. Subjects are assessed at the time of therapy, 2 weeks after each therapy and then every 16 weeks for 2 years. Secondary endpoints (not reported here) include evaluation of immune response. **Results:** 42 of 44 planned subjects are enrolled and have received >1 vaccine (N = 24 *BRCA2*; N = 15 *BRCA1*, N = 3 *BRCA1* and *BRCA2*). All doses will be administered by June 2025 and safety data during administration will be complete. In Cohort A, 17 women, 1 man were treated (median age of 52 [range 39-75]). In Cohort B (healthy individuals), 14 women, 12 men were treated (median age of 48 [range 31-69]). 148 doses have been given. One patient received only 1 vaccine due to treatment-related Grade 1 hematoma. Treatment-related AEs were seen in 95% of subjects, largely grade 1 injection site reactions. AEs seen in > 25% are as below. Grade 3 AEs were seen in 6 (15%), including urticaria (N = 1), vasovagal reaction (N = 1), and hypertension (N = 4), none of which were treatment-related. **Conclusions:** Administration ofa recombinant plasmid-derived DNA based immunotherapy encoding hTERT, PSMA and WT1, +/- IL12, followed by electroporation is feasible and safe in individuals with *BRCA1/2*, including healthy individuals with no prior cancer. The most common AEs are injection site reactions, all of which were Grade 1/2. Clinical trial information: NCT04367675. Research Sponsor: Inovio Pharmaceuticals.

CTCAE Term	Grade 1	Grade 2	Frequency
Pain	N=26	N=3	72.5% (N=29)
Bruising	N=26	N=0	65.0% (N=26)
Swelling	N=19	N=0	47.5% (N=19)
Redness	N=14	N=0	35.0% (N=14)
Injection Site Reaction	N=11	N=2	32.5% (N=13)

10506 Oral Abstract Session

Menopausal hormone therapy after a diagnosis of breast cancer in women with a *BRCA* pathogenic variant and risk of death. First Author: Joanne Kotsopoulos, Women's College Hospital, Toronto, ON, Canada

Background: Use of menopausal hormone therapy (MHT) is contraindicated for women with a personal history of breast cancer. This topic is of importance among women with a pathogenic or likely pathogenic variant (mutation) in *BRCA1* or *BRCA2* given their tendency to develop early onset disease as well as the recommendation to undergo oophorectomy prior to natural menopause. **Methods:** We conducted a prospective analysis of MHT use following breast cancer in *BRCA* carriers and the risk of death. The study included *BRCA* carriers with a diagnosis of breast cancer, no history of another cancer, no prior MHT use, and who were enrolled in a longitudinal study. Women who initiated MHT after their diagnosis were matched to women who did not use MHT on year of birth, age of diagnosis, and treatments received – resulting in 183 matched pairs. We followed women from the date of first MHT use in the exposed and the matched date in the unexposed. Cox proportional hazards was used to estimate the hazard ratio (HR) and 95% confidence intervals (CI) for the risk of death associated with MHT use. **Results:** Among the 183 MHT users, 53 (29%) used a local MHT and 130 (71%) used a systemic MHT. After 6.0 years of follow-up (range 0.01-22.7); there were 9 (4.9%) deaths in the MHT group vs. 22 deaths (12%) in the no MHT group (P = 0.01). The corresponding number of breast cancer deaths were 6 (3.3%) vs. 16 (8.7%) (P = 0.03). The HR for all-cause mortality was 0.31 (95%CI 0.14-0.69; P = 0.004) and for breast cancer-specific mortality was 0.27 (95%CI 0.10-0.70; P = 0.007). The corresponding risk estimates for all-cause death by invasiveness were 0.25 (95%CI 0.11-0.61; P = 0.002) and 0.54 (95%CI 0.07-4.02; P = 0.54) for invasive disease and DCIS, respectively. All-cause mortality with use of systemic MHT was 0.27 (95%CI 0.11-0.67; P = 0.005) and was 0.19 (95%CI 0.03-1.45; P = 0.11) for local MHT. Compared to never HRT use, the HR for E-alone was 0.35 (0.12-1.02; P = 0.05) and was 0.58 (95%CI 0.08-4.29; P = 0.59) for E+P. Subgroup analyses by formulation, gene mutation and tumour pathology are on-going. **Conclusions:** Although based on small strata, the preliminary findings are suggestive of no increased risk of death with MHT use after *BRCA*-breast cancer and may offer an opportunity to improve quality of life in this unique population. Replication in larger datasets are needed. Research Sponsor: Breast Cancer Canada.

10507 Oral Abstract Session

Glucagon-like peptide-1 receptor agonists and incidence of obesity-related cancer in adults with diabetes: A target-trial emulation study. First Author: Lucas A. Mavromatis, NYU Grossman School of Medicine, New York, NY

Background: Obesity is a major risk factor for cancer development. However, whether glucagon-like peptide-1 receptor agonists (GLP-1RAs), a class of diabetes medication which causes weight loss, reduce cancer incidence is unknown. This study investigated whether GLP-1RAs reduce the risk of obesity-related cancer in adults with diabetes and obesity compared to dipeptidyl peptidase-4 inhibitors (DPP-4is), a weight-neutral class of diabetes medication. **Methods:** 85,015 adult patients from 43 U.S. health systems with a body mass index ≥ 30 kg/m2 and a diagnosis of diabetes, who newly initiated a GLP-1RA or DPP-4i between 2013 and 2023 were included. Patients prescribed GLP-1RAs (mean age, 56.8 years) were matched 1:1 on propensity score for GLP-1RA prescription and prescription year with patients prescribed DPP-4is (mean age, 56.8 years). Obesity-related cancer incidence was compared between groups. **Results:** Over a mean follow-up of 3.9 years, there was a lower risk of obesity-related cancers (adjusted HR, 0.93; 95% CI, 0.88-0.98; P=0.005) and all-cause death (adjusted HR, 0.92; 95% CI 0.87-0.97; P=0.001) associated with GLP-1RA use versus DPP-4i use. Assessments of cancer subtypes showed protective associations between GLP-1RA use and colon and rectal cancers. **Conclusions:** GLP-1RAs were associated with a lower risk of obesity-related cancer compared with DPP-4is in a large, real-world cohort of patients with diabetes and obesity. Future studies should prospectively assess the role of GLP-1RAs in cancer prevention. Research Sponsor: National Institute of Diabetes and Digestive and Kidney Diseases of the National Institutes of Health; R01 DK115534 to MEG; National Institute of Diabetes and Digestive and Kidney Diseases of the National Institutes of Health; K24 HL155861 to MEG; National Institute of Diabetes and Digestive and Kidney Diseases of the National Institutes of Health; K01 DK121825 to JS.

Adjusted hazard ratios of incidence of composite obesity-related cancer and all-cause death in propensity-matched patients prescribed GLP-1RAs versus DPP-4is (n=85,015 pairs).

Outcome	Sex	Events/$N_{at\ risk}$ (GLP-1RA)	Events/$N_{at\ risk}$ (DPP-4i)	HR (GLP-1RA/DPP-4i)	P	$P_{interaction}$
Obesity-related cancer (composite)	Overall	2,501/85,015 (2.9%)	2,671/85,015 (3.1%)	0.93; 95% CI, 0.88-0.98	0.005	NA
Obesity-related cancer (composite)	Female	1,754/44,762 (3.9%)	1,898/45,182 (4.2%)	0.92; 95% CI, 0.86-0.98	0.01	0.63
Obesity-related cancer (composite)	Male	747/40,253 (1.9%)	773/39,833 (1.9%)	0.95; 95% CI, 0.86-1.05	0.29	0.63
All-cause death	Overall	2,783/85,015 (3.3%)	2,961/85,015 (3.5%)	0.92; 95% CI, 0.87-0.97	0.001	NA
All-cause death	Female	1,219/44,762 (2.7%)	1,514/45,182 (3.4%)	0.80; 95% CI, 0.74-0.86	<0.001	<0.001
All-cause death	Male	1,564/40,253 (3.9%)	1,447/39,833 (3.6%)	1.04, 95% CI, 0.96-1.11	0.34	<0.001

Adjusted hazards ratios calculated using Cox regression represent ratios of the incidence of composite obesity-related cancer and all-cause death in matched pairs of patients prescribed GLP-1RA versus DPP-4i over average follow-up durations of 3.8 years (GLP-1RA) and 3.9 years (DPP-4i). Results of sex-stratified and sex interaction analyses are also displayed. The threshold for statistical significance is P<0.05.

10508 Oral Abstract Session

Association of glucagon-like peptide 1 receptor agonists with cancer risk in obesity adults with and without diabetes: A target trial emulation study. First Author: Hao Dai, Department of Health Outcomes and Biomedical Informatics, University of Florida, Gainesville, FL

Background: The use of glucagon-like peptide 1 receptor agonists (GLP-1RAs) has substantially expended given their remarkable benefits in managing obesity. Yet, their impact on long-term cancer risk remains unclear, with existing real-world evidence being limited and yielding conflicting results. **Methods:** This retrospective cohort study followed a target trial emulation design using 2014–2024 OneFlorida+ electronic health records (EHR) data. Adults (≥18 years) eligible for anti-obesity medications (AOMs) and without a cancer history were included. We compared GLP-RA users vs. non-users, with 1:1 propensity score matching applied to balance baseline factors between the two groups. The primary outcomes include the incidence of 16 obesity-associated cancers (liver, thyroid, pancreatic, bladder, colorectal, lung, kidney, breast, endometrial, meningioma, esophageal adenocarcinoma, gallbladder, upper stomach, ovarian, multiple myeloma, and prostate), assessed over a follow-up period of up to 10 years. Cox proportional hazards models were used to calculate hazard ratios (HRs) and 95% confidence intervals (CIs), and cumulative incidences were estimated using Kaplan-Meier analyses. **Results:** After matching, 43,317 GLP-1RA users were compared with 43,315 non-users. The incidence rates of the 16 cancers were 20.5 versus 23.6 per 1,000 person-years, respectively, indicating a significantly lower overall cancer risk among GLP-1RA users (HR, 0.83 [95% CI, 0.76–0.91]) compared to non-users. In particular, GLP-1RA use was associated with a reduced risk of endometrial cancer (HR, 0.75 [95% CI, 0.57–0.99]), ovarian cancer (HR, 0.53 [95% CI, 0.29–0.96]), meningioma (HR, 0.69 [95% CI, 0.48–0.97]), and esophageal adenocarcinoma (HR, 0.34 [95% CI, 0.12–0.94]). However, GLP-1RA users showed a trend toward an increased risk of kidney cancer (HR, 1.38 [95% CI, 0.99–1.93]), particularly among the younger adults (≤65 years) and overweight patients (BMI 27–29.9). **Conclusions:** In this large cohort of real-world obesity population with and without diabetes, GLP-1RA use was associated with an overall reduction in obesity-related cancer risk, as well as lower risks of several specific cancers. However, a potential elevated risk of kidney cancer, especially in younger or moderately obese individuals, highlights the need for targeted surveillance and longer-term follow-up to clarify the underlying mechanisms and clinical implications of these findings. Research Sponsor: None.

10509 Clinical Science Symposium

Association between type of BRCA1/2 pathogenic/likely pathogenic variants and outcome in young patients with breast cancer: Results from an international cohort study. First Author: Angela Toss, University of Modena and Reggio Emilia, Modena, Italy

Background: Pathogenic/likely pathogenic variants (P/LPVs) in the *BRCA1 or BRCA2* genes significantly increase the risk of developing breast cancer (BC) and other malignancies, with distinct clinicopathologic features depending on the gene involved. However, the clinical implications of the type of P/LPVs within *BRCA1* or *BRCA2* genes remain to be elucidated. **Methods:** The BRCA BCY Collaboration (NCT03673306) is an international, multicenter, hospital-based, retrospective cohort study that included *BRCA* carriers diagnosed with invasive BC at the age of ≤40 years between January 2000 and December 2020. In this analysis, only patients with detailed available information on P/LPVs in the BRCA genes were included. Clinicopathologic features and survival outcomes (disease-free survival [DFS] and overall survival [OS]) were investigated according to P/LPV types (insertion-deletion mutations [INDEL] *vs* single nucleotide variants [SNV] *vs* copy number variations [CNV]; truncating *vs* non-truncating P/LPVs; frameshift *vs* nonsense *vs* splicing *vs* missense P/LPVs). **Results:** Out of 5660 patients from 109 centers worldwide, 3294 were eligible for the present analysis (2080 *BRCA1* and 1214 *BRCA2*). Overall, 61.3% of patients carried INDEL, 32.7% SNV and 6.0% CNV; 76.5% of patients exhibited truncating P/LPVs and 8.4% non-truncating P/LPVs (15.1% not classifiable). Frameshift mutations were the most common (60.3%), followed by nonsense (21.2%), splicing (9.6%), and missense (8.4%) P/LPVs. In both *BRCA1* and *BRCA2* carriers, no statistically significant differences in baseline clinicopathologic variables and P/LPV types were observed except for fewer patients with nodal involvement among CNV of BRCA2. Median follow-up was 7.9 (IQR 4.5-12.9) years. No association between the type of P/LPV in both *BRCA1* and *BRCA2* carriers and DFS was observed, except for better DFS in patients with missense variants of *BRCA2* gene. Compared to patients with non-truncating variants, patients with truncating variants in *BRCA1* had a shorter OS (HR 2.00; 95%CI 1.17-3.41). Albeit not statistically significant, a numerically worse OS was observed among *BRCA2* patients with truncating P/LPVs (HR 6.27 95% CI 0.86-45.87). In *BRCA1* carriers, compared to patients with frameshift P/LPVs, those with missense variants were associated with better OS (HR 0.48 95%CI 0.28-0.84 for missense). In *BRCA2* carriers, similar results were observed. **Conclusions:** In this global cohort of young BRCA carriers with BC, truncating P/LPVs were associated with poorer prognosis, and missense P/LPVs with improved prognosis. This study advances our understanding of the influence of specific types of *BRCA1/2* P/LPVs on BC characteristics and outcomes, potentially suggesting more personalized prevention strategies and treatment approaches. Clinical trial information: NCT03673306. Research Sponsor: None.

10510 Clinical Science Symposium

Germline pathogenic variants in cancer predisposition genes and overall survival of women with breast cancer. First Author: Siddhartha Yadav, Mayo Clinic, Rochester, MN

Background: The impact of germline pathogenic or likely pathogenic variants (PVs) in cancer predisposition genes on overall survival (OS) after breast cancer diagnosis is not well defined. In particular, unbiased OS estimates from population-based studies accounting for clinical subtypes of breast cancer (based on ER, PR, and HER2 status) and for genes other than *BRCA1/2* are lacking. **Methods:** The study included 25,168 prospectively followed women with locoregional invasive breast cancer within the population-based CARRIERS study. Germline sequencing using a custom multigene amplicon-based panel was performed to identify PVs. OS was compared between germline PV carriers in *ATM, BRCA1, BRCA2, CHEK2* and *PALB2* and non-carriers (negative for germline PVs in 13 known breast cancer predisposition genes) for each clinical subtype of breast cancer from the time of breast cancer diagnosis to death or last follow up in a multivariable Cox proportional hazard regression analysis adjusting for age at diagnosis, race/ethnicity, histology, TNM stage, type of surgery, use of adjuvant radiation, chemotherapy and endocrine agents. **Results:** Among 25,168 women with breast cancer, germline PVs in one of the five breast cancer predisposition genes were detected in 5.8% of the women [*ATM*: 0.8%, *BRCA1*: 1.3%, *BRCA2:* 1.6%, *CHEK2*: 1.5%, and *PALB2*: 0.6%]. Among women with ER+ breast cancer, compared to non-carriers, a significantly worse OS was noted for *BRCA1* (Hazard Ratio (HR): 1.8, 95% Confidence Interval (CI): 1.1 – 3.0, p=0.02) and *BRCA2* (HR: 1.8, 95%CI: 1.4 – 2.4, p<0.001), but not for *ATM* (HR: 1.2, 95%CI: 0.8 – 1.7, p=0.40) or *CHEK2* (HR:1.0, 95%CI: 0.8 – 1.3, p=1.0) PV carriers. Worse OS was noted in *PALB2* PV carriers with ER+ breast cancer (HR:1.5, 95%CI: 0.9 – 2.2, p=0.09), although it did not reach statistical significance. Similar HR estimates for OS as with ER+ breast cancer were observed in women with ER+/HER2- breast cancer for *BRCA1*, *BRCA2* and *PALB2* PV carriers, but only *BRCA2* results were statistically significant. Among women with ER-negative breast cancer, compared to non-carriers, a significant difference in OS was not observed for PV carriers in *ATM* (HR: 0.8, 95%CI: 0.4 – 1.8, p=0.63), *BRCA1* (HR:1.2, 95%CI: 0.8 – 1.7, p=0.35), *BRCA2* (HR: 0.8, 95%CI: 0.5 – 1.2, p=0.29), *CHEK2* (HR: 0.7, 95%CI: 0.3 – 1.4), or *PALB2* (HR: 0.9, 95%CI: 0.5 -1.7, p=0.78). **Conclusions:** The suggestive differences in OS by ER status of the tumor in *BRCA1* and *BRCA2* PV carriers warrant further investigation of underlying tumor biology and assessment of endocrine sensitivity of breast cancer in germline PV carriers. Research Sponsor: None.

10511 Clinical Science Symposium

Cancer risk of pathogenic germline variants among 164,774 adult cancers. First Author: Jie Liu, Washington University School of Medicine, St. Louis, MO

Background: Pathogenic germline variants (PGV) in cancer-predisposition genes influence the development of many cancer types but our understanding of cancer risks in PGV carriers remains underexplored. This study aims to further characterize the spectrum of cancers associated with PGVs and factors contributing to the development of multiple primary cancers among PGV carriers. **Methods:** A case-control analysis of 61,453 cancer cases and 366,709 controls in the UK Biobank (UKBB) was performed to test for the associations between risks of 43 solid tumor types and PGVs in 237 cancer predisposition genes. We evaluated each association according to the ClinGen Gene-Disease Validity framework and categorized those with moderate or less evidence as novel. An independent validation cohort of 103,321 cases 340,786 controls from All of Us, Mass General Brigham Biobank, TCGA, Memorial Sloan Kettering IMPACT, and a case-control study of ovarian cancer was used to replicate novel associations. **Results:** We identified 51 novel associations between solid tumor development and PGVs in the UKBB. Out of these, 32 were also significantly associated (p<0.05) in our validation cohorts (Table 1). Among PGV carriers in the UKBB, 16% had one primary malignancy and 2% had two or more. Across most PGV carriers, we observed higher risks of multiple primary cancers compared to single primary cancers. Using cox proportional hazards models, we found that PGV carriers with a personal history of cancer showed a higher hazard ratio of second cancer compared to healthy controls, particularly among those diagnosed with the first cancer earlier in life. The association between PGVs and second cancer remained significant in case-only analysis limited to cancer survivors and adjusted for primary tumor type suggesting this was not explained by shared risk factors. **Conclusions:** These findings expand our understanding of spectrum of cancer risks associated with predisposition genes and highlight that PGV carriers are at high risk of developing multiple primary cancers. In addition to family history, personal history of cancer should be considered for tailored cancer screening in genetically predisposed individuals. Research Sponsor: None.

Novel associations between PGV genes and selected cancers. Shown are the odds ratio estimates from the meta-analysis of replication cohorts.

Cancer	Genes Odds ratio (95% CI)				
Breast	*BAP1* 4.68 (2.13-10.25)	*BRIP1* 1.63 (1.18-2.26)	*LZTR1* 2.01 (1.56-2.6)		
Colorectal	*ATM* 1.43 (1.07-1.93)	*BARD1* 2.33 (1.28-4.26)	*BRCA1* 1.69 (1.2-2.37)	*BRCA2* 1.69 (1.27-2.25)	*FLCN* 2.6 (1.17-5.74)
Melanoma	*BLM* 1.68 (1.05-2.71)	*BRCA1* 2.15 (1.29-3.58)			
Lung	*BRCA2* 3.16 (2.36-4.23)	*NBN* 1.94 (1.07-3.53)			
Endometrial	*BRCA1* 8.05 (4.83-13.4)	*BRCA2* 2.32 (1.19-4.54)	*MSH3* 2.25 (1.07-4.72)		
Urinary	*ATM* 1.71 (1.21-2.44)				
Renal	*MITF p.E318K* 1.85 (1.16-2.97)	*WRN* 2.71 (1.39-5.29)			
Head and neck	*CDKN2A* 6.22 (3.31-11.7)	*FANCM* 2.2 (1.38-3.52)			
Ovary	*DDX41* 4.56 (1.56-13.36)	*PALB2* 3.33 (1.98-5.61)			

10512 Rapid Oral Abstract Session

Interactions between polygenic variants and clinical factors as predictors of breast cancer risk in the UK Biobank. First Author: Timothy Simmons, Myriad Genetics, Inc., Salt Lake City, UT

Background: Polygenic risk scores (PRSs) combine information from single-nucleotide polymorphisms (SNPs) across the genome to explain substantial genetic breast cancer (BC) susceptibility. Previous studies have demonstrated that a multiple-ancestry PRS (MA-385) based on 56 ancestry-informative and 329 BC-associated SNPs is accurate for diverse populations and ranks among the most important known factors affecting the risk of BC development. However, medical guidelines call for more evidence before endorsing the clinical use of PRS, including studies to evaluate possible interactions of SNPs with environmental and hormonal risk factors. Here, we use longitudinal outcomes from the UK Biobank (UKB) to explore interactions of MA-385 and the five most informative individual BC-associated SNPs with the widely used Tyrer-Cuzick (TC) risk model and individual TC risk factors. **Methods:** The study cohort included 197,509 female UKB participants with no history of cancer at the time of study enrollment. We used Cox proportional hazards models to test associations of MA-385, individual BC SNPs, TC, and individual TC risk factors with BC outcomes. Effect modification of MA-385 and individual SNPs by clinical risk factors was evaluated by including interaction terms in the models. All models were adjusted for age at UKB enrollment and 10 principal components. Hazard ratios (HRs) and 95% confidence intervals (CIs) are reported per standard deviation, and significance tests were performed using two-sided p-values based on likelihood-ratio test statistics. **Results:** After a median follow-up of 11.8 years, 7,419 (3.8%) participants were diagnosed with BC.In a model including both MA-385 and TC, MA-385 was a significantly better predictor of BC development (HR = 1.56; 95% CI 1.53-1.60, p= 3.2 x 10^{-329}) over the TC model (HR = 1.21; 95% CI 1.18-1.23; p= 5.4 x 10^{-69}). We found no evidence of interaction between MA-385 and TC (p= 0.31), nor between individual SNPs and TC. After Bonferroni adjustment for multiple testing (102 tests), we found no evidence of interaction between MA-385 or individual SNPs with clinical TC factors. The strongest evidence for interaction was found between a BC SNP on chromosome 2 (rs13387042) and age at UKB enrollment (unadjusted p= 0.002; Bonferroni adjusted p= 0.23). **Conclusions:** In a longitudinal analysis of UKB, MA-385 was a highly significant predictor of BC risk and substantially improved prediction over TC. In contrast, interactions of MA-385, and individual BC SNPs, with TC and individual clinical factors in the TC model were not statistically significant. Clinical TC factors have minimal, if any, impact on the strength of the association between MA-385 and BC. These results may help to alleviate concerns expressed in guidelines that SNPs interact with environmental or hormonal risk factors. Research Sponsor: Myriad Genetics.

10513 Rapid Oral Abstract Session

Association of an ancestry-specific variant near the *ESR1* gene with cancer risk and breast density in women of self-reported Hispanic ancestry. First Author: Elisha Hughes, Myriad Genetics, Inc., Salt Lake City, UT

Background: A single-nucleotide polymorphism (SNP), rs140068132, located in the 6q25 region near the *ESR1* gene, is common in self-reported Hispanic women but rare or absent in other populations. Previous studies have shown that rs140068132 is associated with a significantly reduced risk of breast cancer (BC) and may be particularly protective against triple-negative BC (TNBC). Further research suggests that rs140068132 may be linked to lower breast density. However, existing studies have been small, yielding imprecise estimates, and potential associations with cancers beyond BC remain unknown. **Methods:** We examined associations of rs140068132 with BC, TNBC, ovarian cancer (OC), endometrial cancer (EC), and BI-RADS breast density in a consecutive cohort of self-reported Hispanic women referred for hereditary cancer testing with a multigene panel. Cancer associations of rs140068132 were estimated as odds ratios (ORs), with 95% confidence intervals (CIs), from multivariable logistic regression models adjusted for personal/family cancer history, genetic ancestry, and age. We used Fisher's Exact Test to determine whether homozygous rs140068132 carriers had lower BI-RADS breast density than heterozygous or non-carriers. P-values are reported as two-sided. **Results:** Among 55,463 Hispanic women, 9,304 (16.8%) were affected by BC, 998 (1.8%) by TNBC, 1,520 (2.7%) by OC, and 1,616 (2.9%) by EC. 2,053 women were unaffected and had breast density assessment. 9,665 (17.4%) women were heterozygous for rs140068132, and 629 (1.1%) were homozygous. Consistent with previous studies, we found a highly significant protective effect per allele of rs140068132 for overall BC (OR 0.64; 95% CI 0.60-0.69; p= 6.1 x 10^{-37}) and TNBC (OR 0.53; 95% CI 0.44-0.64; p= 7.4 x 10^{-11}). This finding translates to an overall BC risk reduction of 1.6-fold for heterozygous and 2.4-fold for homozygous carriers compared to non-carriers. TNBC risk was reduced by 1.9-fold for heterozygous and 3.6-fold for homozygous carriers compared to non-carriers. Homozygous rs140068132 carriers were more than 3 times less likely to have high (heterogeneously or extremely dense) breast density compared to heterozygous or non-carriers (OR 3.30; 95% CI 1.22-10.35; p= 0.0095). rs140068132 was not associated with risk of OC (OR 0.98; 95% CI 0.86-1.11; p= 0.77) or EC (OR 1.08; 95% CI 0.96-1.21; p= 0.23). **Conclusions:** We present findings from the largest study to date on cancer risks associated with rs140068132. Our research indicates that rs140068132 does not substantially affect the risk of OC or EC. We confirmed previous reports of significantly reduced risk of BC, particularly TNBC, among carriers of rs140068132, and we provided precise estimates of the ORs per allele. These findings have important implications for genetic risk assessment and may guide personalized BC prevention and treatment strategies. Research Sponsor: Myriad Genetics.

10514 Rapid Oral Abstract Session

Association between allostatic load and breast radiomic features among diverse women undergoing screening mammography. First Author: Sara Wallam, Columbia University Irving Medical Center, New York, NY

Background: Allostatic load (AL), an indicator of chronic physiologic stress, is associated with increased breast cancer incidence and all-cause mortality in patients diagnosed with breast cancer. Mammographic density (MD) is a well-established breast cancer risk factor. We developed a deep learning, specifically convolutional neural network (CNN)-based, mammographic evaluation, which is a more accurate predictor of breast cancer risk than MD, particularly among Black and Hispanic women. We evaluated the relationship between AL and CNN risk score in a cohort of racially/ethnically diverse women undergoing breast cancer screening. **Methods:** We conducted a retrospective cohort study of women aged 35-74 years, without a personal history of breast cancer, with available clinical data to calculate AL score and mammograms for CNN analysis (output = risk score from 0-1), who underwent screening mammography at Columbia University Irving Medical Center (CUIMC) in New York, NY from 2014-2018. We extracted data on demographics, MD (BIRADS A-D), laboratory values, vital signs, and body mass index (BMI) from the electronic health record (EHR). We calculated AL score using biometrics from 4 physiologic systems: cardiovascular (heart rate, systolic and diastolic blood pressure), metabolic (BMI, blood glucose, albumin, alkaline phosphatase), renal (creatinine, blood urea nitrogen), and immune (white blood cell count). AL scores ranged from 0 to 10, and patients received one point for each lab value out of the reference range. High AL was defined as an AL score above the median for the overall cohort. Multivariable logistic regression analyses were conducted to evaluate the association between high AL and demographic factors, breast cancer risk factors, and CNN risk score. **Results:** Among 9,798 evaluable women, mean age was 57.0 (standard deviation [SD], 9.5), including 24.7% non-Hispanic White, 9.6% non-Hispanic Black, 36.1% Hispanic, and 4.0% Asian women. Median AL score was 3. In multivariable analyses, high AL was associated with older age (odds ratio [OR] =1.03, 95% confidence interval [CI]=1.02-1.03). Compared to non-Hispanic White women, Black and Hispanic women had increased odds of having high AL (OR= 2.62, 95% CI = 2.23-3.08 and OR = 2.12, 95% CI =1.90-2.37, respectively). MD was inversely associated with high AL, and there was no significant association between CNN risk score and AL. **Conclusions:** In this cohort of diverse women undergoing screening mammography, we observed a significant association between high AL and older age and Black and Hispanic race/ethnicity. However, MD was inversely associated with high AL, likely due to higher BMI, and CNN risk score was not associated with AL. Future studies should evaluate the association between novel breast radiomic features and genetic and hormonal biomarkers of breast cancer risk. Research Sponsor: National Cancer Institute; R01CA293927; National Cancer Institute; P30CA013696; National Center for Advancing Translational Sciences; KL2TR001874; Susan G. Komen Foundation; Susan G. Komen Career Catalyst Research Award.

10515 Rapid Oral Abstract Session

Disparities in cancer screening and preventive care access among LGBTQ+ populations: A cross-sectional analysis. First Author: Manas Pustake, Texas Tech University Health Science Center, El Paso, TX

Background: The incidence and outcomes of certain health conditions, particularly cancers, can vary significantly across different sexual orientation groups, often influenced by disparities in healthcare access and preventive service utilization. Previous research indicates that sexual minorities may face barriers to appropriate healthcare, increasing the importance of understanding how these disparities manifest in preventive health behaviors, such as cancer screenings. This study aims to identify these differences in preventive care among different sexual orientation groups. **Methods:** The study utilized the Behavioral Risk Factor Surveillance System (BRFSS), an annual nationwide survey collecting health-related data from approximately 400,000 U.S. adults, as the primary data source. The data was cleaned for missing cases. The study population included respondents who completed the optional Sexual Orientation and Gender Identity (SOGI) module, while excluding those with missing data on key variables such as sexual orientation, gender identity, and cancer screening. Descriptive statistics were generated from the database to characterize the study population and examine distributions across different demographic and health behavior variables. Statistical analyses were performed to assess associations between sexual orientation and various cancer screening behaviors. **Results:** The final analysis included 278,519 cases, with demographic characteristics presented in Table. Disparities in educational attainment were observed across sexual orientation groups, with straight individuals representing the largest group across all education levels. A significant association was found between sexual orientation and mammogram screening (p=0.001; Fisher's Exact Test), with higher screening rates among straight respondents (851 yes vs. 144 no) compared to gay, bisexual, and other groups. No significant associations were found for cervical cancer screening (p=0.818) or sigmoidoscopy utilization (p=0.818). Mammogram screening varies by sexual orientation, while other preventive practices show uniform utilization across groups. **Conclusions:** The findings highlight significant disparities in mammogram screening among LGBTQ+ individuals, with no such gaps in cervical cancer screening or sigmoidoscopy. These results call for targeted interventions to enhance mammogram uptake in LGBTQ+ communities. Research Sponsor: None.

Distribution of sexual orientation groups among different races.

Race/Ethnicity	Gay	Straight (Not Gay)	Bisexual	Something Else	Total
White only, Non-Hispanic	4026	191801	6340	3020	205187
Black only, Non-Hispanic	358	19582	571	358	20869
Other race only, Non-Hispanic	337	15483	530	394	16744
Multiracial, Non-Hispanic	175	5978	458	204	6815
Hispanic	604	22044	1028	829	24505
Don't know/Not sure/Refused	78	4054	98	169	4399
Total	5578	258942	9025	4974	278519

10516 **Rapid Oral Abstract Session**

Risk patterns for second primary malignancies among human papillomavirus (HPV)–associated first primary cancer survivors in the United States. First Author: Pragati Gole Advani, Roswell Park Cancer Institute, Buffalo, NY

Background: Previous studies have shown an increased risk of second primary malignancies (SPMs) among human papillomavirus (HPV)-associated first primary cancer (FPC) survivors; however, this has not been comprehensively examined by cancer site and patient's sex. We utilized a large population-based database to examine disparities in SPM risk by site of HPV-associated first and second cancers. **Methods:** From 17 United States population-based Surveillance, Epidemiology and End Results (SEER) program cancer registry areas, we identified 124,802 ≥12-month survivors of HPV-associated invasive FPCs (including oropharynx, anus, vulva, vagina, cervix and penis) diagnosed between 2000-2021. Standardized incidence ratios (SIRs) and accompanying 95% confidence intervals (CIs) quantified SPM risk by cancer site compared with the general population. Excess SPM risks were calculated based on SIRs and excess absolute risks (EARs) per 10,000 person-years at risk (PYR). **Results:** Overall, we observed 13,431 SPMs after HPV-associated FPCs representing a 1.6-fold significantly increased risk (95% Confidence Interval [CI] = 1.61-1.67) compared to the general population and an excess of 68 cases per 10,000 PYR. All index HPV-associated FPCs showed statistically significant increased SPM risk compared to the general population. SIRs varied significantly by FPC site with female survivors of vulvar, oropharyngeal and vaginal cancers resulting in higher SPM risk (SIR_{vulva}= 2.46; CI = 2.33-2.58; EAR = 166, $SIR_{oropharynx\text{-}female}$= 2.02; CI = 1.90-2.14; EAR = 121 and SIR_{vagina}= 1.81; CI = 1.56-2.08; EAR = 96) compared to other sites ($p < 0.001$). Analyses by patient's sex revealed significantly increased SPM risk among female survivors of oropharyngeal cancer compared to the males ($SIR_{oropharynx\text{-}male}$= 1.66; CI = 1.61-1.70; $p < 0.01$) but not after anal cancer ($p > 0.05$). Results from SPM site specific analyses revealed significantly higher SIRs for second solid cancers compared to hematological malignancies ($SIR_{solidSPM}$= 1.69; CI = 1.66-1.72; $SIR_{hematSPM}$= 1.03; CI = 0.96-1.11; $p < 0.001$). Among the solid SPMs, the risk of developing a HPV-associated SPM was significantly higher than that of developing a non-HPV-associated SPM ($SIR_{HPV\text{-}SPM}$= 8.89; CI = 8.59-9.21 versus $SIR_{non\text{-}HPV\text{-}SPM}$= 1.33; CI = 1.30-1.35; p-heterogeneity < 0.001); and the difference was more pronounced in females than the males. Strikingly increased SIRs were observed for penile (SIR = 17.61), vulvar (SIR = 27.83) and vaginal (SIR = 32.09) SPMs. **Conclusions:** Using a large-scale population-based data, we observed remarkable similarity in SPM risk by FPC site suggesting a potential role of shared HPV-associated etiology between the two malignancies. SPMs have emerged as an important challenge for cancer survivors, therefore, further research to understand drivers of the observed patterns is warranted. Research Sponsor: None.

10517 **Rapid Oral Abstract Session**

The development and validation of a simulation model–based calculation engine to support individualized physical activity prescriptions for breast cancer survivors. First Author: Jinani C. Jayasekera, NIH/NIMHD, Washington, MD

Background: Current cancer physical activity guidelines recommend clinicians offer individualized 'physical activity prescriptions' to cancer survivors. However, there are limited data to support individualized physical activity prescriptions for breast cancer survivors in clinical settings. We aimed to develop a simulation model-based 'calculation engine' for a clinical decision tool that could generate individualized breast cancer outcomes associated with physical activity considering the individual characteristics of breast cancer survivors. **Methods:** We adapted an established and validated simulation model developed within the Cancer Intervention and Surveillance Modeling Network (CISNET) to estimate breast cancer-specific mortality, all-cause mortality, and life-years gained with post-treatment physical activity for women aged 50-75 years at diagnosis with stage I-III breast cancer. Model inputs were derived from clinical trials, cohort studies, national survey, and registry data. Breast outcomes were generated for 41,472 unique subgroups based on all possible combinations of age, hormone status, HER2 status, stage, tumor size, grade, body mass index, surgery, and treatment. External validation was conducted using an independent data source. We summarized 10-year breast cancer and all-cause mortality rates for varying combinations of weekly aerobic (e.g., 2.5-5.0 hours/week) and muscle-strengthening (e.g., ≥2 days/week) activity. **Results:** Overall, the 10-year breast cancer-specific and all-cause survival rates for stages I-III were 89.1% and 83.2%. These results varied by individual characteristics and physical activity levels. For example, in a 65-69-year-old-woman diagnosed with stage I, hormone receptor-positive, HER2-negative breast cancer, and a body mass index of ≥30kg/m2, the 10-year breast cancer-specific and all-cause survival rates for 0-0.5 hours/week of physical activity were 87.1% and 80.1%, respectively. If the woman was to increase aerobic activity to 0.5-2.5 hours/week, 10-year breast cancer survival increased to 88.5%, and all-cause survival increased to 81.1%. Meeting physical activity guidelines (i.e., 2.5-5.0 hours/week of moderate-intensity aerobic activity; and ≥2-days/week of muscle strengthening activity) was associated with increases in 10-year breast cancer and all-cause survival rates to 93.0% and 82.9%, respectively. The model closely replicated observed rates in independent data. **Conclusions:** These data provide a calculation engine for a clinical decision tool to support individualized physical activity prescriptions and discussions for breast cancer survivors. Research Sponsor: U.S. National Institutes of Health.

10518 **Rapid Oral Abstract Session**

Dietary polyphenols and the risk of prostate cancer in the prospective Southern Community Cohort Study. First Author: Grace Xu, Vanderbilt University, Nashville, TN

Background: In the US, prostate cancer incidence is highest among underrepresented and underserved populations, including Black and low-income populations. Polyphenols, common in plant-based foods, are biologically active compounds previously associated with decreased risk of prostate cancer. **Objectives:** We examined intake of total polyphenols, classes, and subclasses with risk of prostate cancer in the Southern Community Cohort Study (SCCS), a large prospective cohort study established in 2002-2009 to study the causes of racial and income cancer disparities in 12 southern states. **Methods:** Polyphenol intakes (mg/day) derived from food frequency questionnaires were grouped into quintiles. Prostate cancer diagnosis was obtained from state cancer registries and death records. Cox proportional hazard models were used to estimate hazard ratios and 95% confidence intervals to determine associations between polyphenol intakes and prostate cancer risk. Analyses included 29,325 participants, including 1,145 incident prostate cancer cases. **Results:** Higher total polyphenol intake was associated with a modestly decreased risk of prostate cancer compared to the lowest intake except in the highest quintile. 8 subclasses of polyphenols derived primarily from tea, fruit juices, and red wine were associated with a statistically significant decreased risk of prostate cancer comparing the highest to lowest quintiles (e.g. HR 0.58; 0.47-0.72, $p_{trend} < 0.001$ for flavanols). Most associations were similar between Black and White individuals, but flavonoids (HR 0.42; 0.28-0.63, p = 0.0005) and hydroxybenzoic acids (HR 0.45; 0.30-0.67, p = 0.0001) were statistically significant only among White participants. In stratified analyses by smoking status and household income, only flavones were associated with a statistically decreased risk of prostate cancer, specifically among current smokers and participants with an income < $15000. **Conclusions:** Polyphenol intakes were associated with decreased prostate cancer risk among both Black and White participants. Further studies should evaluate whether polyphenol intake is associated with decreased risk for later stages of prostate cancers. Research Sponsor: Meharry Vanderbilt Tennessee Cancer Partnership; 54CA163072; National Cancer Institute; U01CA202979.

10519 **Rapid Oral Abstract Session**

Escalating impact of alcohol-related cancer mortality in the US: A call for action. First Author: Chinmay Jani, University of Miami Sylvester Comprehensive Cancer Center, Miami, FL

Background: Alcohol consumption is known to be a significant risk factor for cancer. This year, the US Surgeon General recommended adding cancer risk warning labels to alcoholic beverages, emphasizing the need for increased awareness. However, data on its impact on individual cancer mortality remains limited. This study aims to evaluate trends in alcohol-associated cancer mortality in the US utilizing Global Burden of Disease (GBD) database. **Methods:** We utilized data from the GBD to analyze absolute and proportional Age-Standardized Mortality Rates (ASMR) attributable to heavy alcohol use—defined as consumption exceeding the theoretical minimum risk exposure level—in the US from 1990 to 2021. We evaluated ASMR for all cancers combined, followed by specific cancers, including esophageal, liver, laryngeal, breast, colorectal, lip-oral cavity, nasopharyngeal, and other (oro/hypo) pharyngeal. Results were reported per 100,000 population and stratified by gender, state, and age groups (20–54, 55+). Estimated Annual Percentage Change (EAPC) was calculated using JoinPoint regression analysis. **Results:** Alcohol-associated cancer deaths in the U.S. doubled from 1990 (11,896) to 2021 (23,207). The 55+ age group showed a significantly higher ASMR than the 20-54 age group (Table 1). Proportional alcohol-associated ASMR increased for all cancers and individual cancers across both age groups and genders, except for liver cancer in 55+ age group. In 2021, for 55+ age, liver cancer had the highest alcohol-associated proportional ASMR in males (38.5%), followed by nasopharyngeal cancer (31.8%), while in females, nasopharyngeal (18.9%) and oro/hypopharyngeal cancers (18.4%) ranked highest. In 20-54 age, lip-oral cavity cancer had the highest alcohol-associated proportional ASMR for both genders (m:41.8%; f:26.9%). In 2021, the District of Columbia had the highest alcohol-associated all-cancer ASMR (m:10.0; f:3.6) followed by Texas (7.5) for males and New Hampshire for females (2.9). In contrast, Utah had the lowest (m:3.5; f:1.4). On evaluating trends, a constant increase was observed in alcohol-associated ASMR for 55+ age group for males (EAPC 0.5, 2008-2021) and females (EAPC 1.1, 2006-2021). **Conclusions:** Alcohol-associated cancer mortality has significantly increased in the U.S. over the past three decades, with a disproportionate burden observed in males and individuals aged 55 and older. Our findings highlight the critical need for targeted prevention efforts, public health policies, and increased awareness to address the rising impact of alcohol consumption on cancer-related mortality across different demographic groups and regions. Research Sponsor: None.

Alcohol associated-all cancer ASMR.

Age (n=Absolute, %= Proportional)	Male - 1990	Male - 2021	Female - 1990	Female -2021
Overall	5.7 (0.03%)	6.2 (0.04%)	2.6 (0.02%)	2.2 (0.02%)
20-54	2.2 (4.3%)	2.4 (6.8%)	1.8 (3.3%)	1.4 (3.6%)
55+	27.3 (2.4%)	31.7 (4.3%)	10.7 (1.5%)	10.4 (1.9%)

10520 **Rapid Oral Abstract Session**

Association between wildfire-dominated $PM_{2.5}$ exposure and non-small cell lung cancer survival in California. First Author: Surbhi Singhal, University of California Davis Comprehensive Cancer Center, Sacramento, CA

Background: Wildfire emissions include hazardous constituents, including fine particulate matter $\leq$2.5 μm in diameter ($PM_{2.5}$). $PM_{2.5}$ exposure is associated with increased risk of lung cancer. However, the impact of wildfire-dominated $PM_{2.5}$ exposure on survival after non-small cell lung cancer (NSCLC) diagnosis is unknown. **Methods:** We identified all patients diagnosed with NSCLC in the California Cancer Registry between 2017-2020. Daily $PM_{2.5}$ was estimated over the same period by random forest regression fusing official air quality monitoring, satellite observations, meteorological modeling, predictive smoke modeling, and low-cost sensors, producing a consensus estimate of $PM_{2.5}$ over a 1-square kilometer grid across California. We quantified $PM_{2.5}$ exposure by averaging daily $PM_{2.5}$ in the 12 months after NSCLC diagnosis based on home address at time of diagnosis. Adjusted cox-proportional hazards regression was used to estimate the hazard ratio (HR) for cancer-related death associated with $PM_{2.5}$ exposure following NSCLC diagnosis overall and stratified by smoking status and stage at diagnosis. We adjusted for patient demographics, comorbidity, body mass index, rural residence, and COVID-19 time-period. **Results:** Among 18,585 patients with NSCLC, the mean age was 70.4 years (standard deviation [SD] 10.5) and the mean $PM_{2.5}$ concentration was 9.8 $\mu g/m^3$ (SD 2.0). Higher mean daily $PM_{2.5}$ in the 12 months after NSCLC diagnosis was associated with 20% increased hazard of cancer-related death (Table). There was a 55% increase in hazard of cancer-related death associated with $PM_{2.5}$ among patients with stage IV disease and no prior smoking use (Table). Notably, patients with Stage IV disease with former or current tobacco use who received immunotherapy had improved cancer-specific survival with more days of high $PM_{2.5}$ concentration (i.e., days with $PM_{2.5}$ $\geq$55 $\mu g/m^3$), HR=0.79, 95% confidence interval 0.66-0.94. **Conclusions:** In this large population-based NSCLC cohort, wildfire-dominated $PM_{2.5}$ exposure after diagnosis was independently associated with increased risk of cancer-related death. The improved survival among patients with Stage IV disease with a smoking history treated with immunotherapy warrants additional investigation. As the size and frequency of wildfires increases, our findings have important public health and clinical implications for patients with NSCLC. Research Sponsor: National Cancer Institute; 5K12CA138464; National Cancer Institute; P30CA093373; California Department of Public Health; Centers for Disease Control and Prevention's (CDC) National Program of Cancer Registries; 1NU58DP007156.

Hazard ratio (HR) for cancer-related death associated with $PM_{2.5}$ concentration after NSCLC diagnosis.

	Number of Patients	Number of Cancer-Related Deaths	Cancer-Related Death HR (95% confidence interval)
Total cohort	18,585	6,097	1.20 (1.05-1.37)
No prior tobacco use	5,059	1,565	1.36 (1.04-1.78)
Former or current tobacco use	13,526	4,532	1.17 (1.01-1.36)
Stage IV, no prior tobacco use	2,198	1,079	1.55 (1.12-2.16)
Stage IV, former or current tobacco use	3,783	2,097	1.09 (0.87-1.36)

10521 **Poster Session**

Large-scale clinical validation of a blood-based, multi-cancer, early detection test across different sample types, platforms, and populations. First Author: Mao Mao, Research & Development, SeekIn Inc., San Diego, CA

Background: Many established cancer screening or diagnostic methods often face challenges in low- and middle-income countries due to high cost, complexity, and reliance on extensive medical infrastructure. OncoSeek, a multi-cancer early detection (MCED) test developed with a panel of protein tumor markers (PTMs), is both affordable (reagent cost ~$20) and accessible, requiring only a blood draw. We evaluated its performance of multi-cancer detection and diagnosis in large-scale clinical studies. **Methods:** 15,122 participants (3,029 cancer vs 12,093 non-cancer) were divided into one training and six validation cohorts according to the different sites in three countries (Brazil, China, and United States). One tube of blood (plasma or serum) from each participant was collected and quantified using a panel of 7 PTMs (AFP, CA125, CA15-3, CA19-9, CA72-4, CEA, and CYFRA 21-1) through four common immunoassay platforms (Roche, Abbott, Luminex, and ELISA) in both retrospective and prospective settings. OncoSeek, utilizing artificial intelligence (AI) algorithm, was developed to differentiate cancer cases from non-cancer cases based on 7 PTM concentrations and clinical information including age and sex. It also predicted the potential affected tissue of origin (TOO). Furthermore, the fifth validation cohort, comprising 1849 patients (1031 cancer vs 818 non-cancer), was leveraged to broaden OncoSeek's application for cancer diagnosis. This cohort specifically targeted symptomatic patients, requiring further confirmation through biopsy or surgery. **Results:** The conventional clinical method, using a single threshold for each PTM, lead to accumulate the false positive rate with the growing number of PTMs. However, OncoSeek, empowered by AI, significantly reduced the false positive rate, elevating specificity from 54.3% to 93.0% and achieving an overall sensitivity of 51.7% in the training cohort. Performance remained robust (58.4% sensitivity and 92.0% specificity) across all seven cohorts, with area under the curve (AUC) values ranging from 0.744 to 0.912. The overall accuracy of TOO prediction was 65.4%. In the fifth cohort with symptomatic patients, OncoSeek achieved a 0.845 AUC for cancer diagnosis at 73.1% sensitivity and 90.6% specificity. **Conclusions:** OncoSeek significantly outperforms the conventional clinical method, showcasing its robust performance across various races, sample types, and platforms. The extensive retrospective assessment of OncoSeek in a symptomatic population demonstrates the feasibility of this MECD test in aiding clinicians for decision-making. Its accuracy of TOO facilitates the diagnostic workup. Research Sponsor: None.

10522 **Poster Session**

Multi-cancer risk prediction in asymptomatic adults using urinary glycosaminoglycan profiling. First Author: Francesco Gatto, Elypta AB, Stockholm, Sweden

Background: Current screening guidelines are based on established risk factors such as age and tobacco use. Currently, no biomarker is routinely used to predict cancer risk. We investigated urinary glycosaminoglycan profiles - aggregated in a "GAGome score" - for multi-cancer risk prediction. **Methods:** In this population-based case-cohort study, we included adults from the Lifelines Cohort Study, Netherlands presumed healthy at baseline. All cases who self-reported any-type cancer or died by the 5-year study visit were confirmed in the Dutch Cancer Registry and matched 1:5 to randomly selected controls. We developed a multivariable Cox proportional hazard regression to estimate the hazard ratio (HR) for incident cancer given the GAGome score and adjusted for established risk factors. Model improvement was assessed using the likelihood ratio test. Then, we used 5-year risk predictions to stratify subjects in four groups: "Low" ($<$0.15%), "High" ($>$2%), and "Very high" ($>$8.5%) risk, or "Intermediate" if otherwise (reference group). Using sampling weights, we estimated the 5-year observed risk in each group, as well as the potentially screen-detectable rate and false positive rate across population and cancer subsets. **Results:** We included 5436 adults (median age = 49 years, 58% females) of whom 827 were diagnosed with incident cancer within 5 years. A standard deviation increase in the GAGome score had an HR = 1.66 (95% CI: 1.62–1.70) for incident cancer – ranging 1.27 for endometrial cancer to 3.4 for cancer of unknown primary - explaining 36% of the variance ($p < 0.0001$). The observed 5-year risk for "Low", "Intermediate", "High", and "Very high GAGome risk" were 0.18%, 2.3%, 7.6%, and 32%, respectively. A "High GAGome risk" or higher prediction would detect 54% of incident cancers (including 54% of in situ carcinomas) with a 17% false positive rate. **Conclusions:** Implementing urine GAGomes as a strategy for risk-stratified targeted screening could pave the way for personalized surveillance approaches and potentially identify a broader range of adults with increased risk of cancer that are not being captured by current screening programs. Research Sponsor: Elypta AB.

10523 **Poster Session**

The effect of metformin exposure on colorectal cancer incidence according to tumor sidedness. First Author: Yehudit Peerless, The Jusidman Cancer Center, Ramat Gan, Israel

Background: Colorectal cancer (CRC) is a leading cause of cancer-related morbidity and mortality. Tumor sidedness influences treatment decisions due to differences in tumor biology and response to therapies. Metformin, a widely used anti-diabetic medication, has been suggested to reduce CRC risk. This study aims to evaluate the relationship between metformin exposure and CRC risk based on tumor-sidedness. **Methods:** A nested case-control study was conducted using the Veterans Administration (VA) database (1999–2020). CRC cases were identified and classified by tumor sidedness. Controls were selected via incidence-density sampling and matched on age, sex, index date, and first VA encounter. Exposure of interest was cumulative metformin use prior to the index-date. Conditional logistic regression was used to estimate adjusted odds-ratios (ORs) and 95% confidence intervals (CIs), adjusted for race, BMI, smoking, aspirin, statins, and other anti-diabetic medications. **Results:** The study included 31,078 patients treated with metformin and 310,621 matched controls. Metformin exposure did not influence the incidence of right-sided CRC with an adjusted OR of 1.03 (95%CI 0.92 – 1.16) and 0.96 (95%CI 0.83 – 1.12) with metformin exposure of 1-3 years and 3-5 years, respectively. In contrast, in patients with left-sided CRC metformin use was associated with a decrease in CRC incidence, with an adjusted OR of 0.90 (95%CI 0.82 – 0.98) and 0.87 (95%CI 0.77 – 0.98) with metformin exposure of 1-3 years and 3-5 years, respectively. **Conclusions:** Metformin was associated with a decrease in the incidence of left-sided CRC incidence. These results suggest the influence of tumor sidedness, not only on treatment effect, but on prevention strategies as well. Research Sponsor: None.

10524 **Poster Session**

Development and validation of a model to predict future breast cancer risk after ER-positive and HER2-negative breast cancer. First Author: Kelly-Anne Phillips, Department of Medical Oncology, Peter MacCallum Cancer Centre, Melbourne, VIC, Australia

Background: Request for bilateral mastectomy after a unilateral breast cancer (BC) diagnosis is increasing. In many cases the benefit of bilateral mastectomy is likely to be small and offset by substantial risks of morbidity, financial toxicity and overburdening of healthcare systems. It is difficult to accurately determine personal risk of developing a future BC. Existing risk prediction models only predict risk for contralateral BC. Australian consumers identified an unmet need for a model that estimates risk of developing BC in any residual breast tissue (ipsi- or contra-laterally); to help women diagnosed with unilateral BC make informed decisions about bilateral mastectomy. **Methods:** Data from 1,162 female BC cases participating in two Australian cohort studies were used to develop a model to predict risk of BC for women who developed a 1st invasive ER positive, HER2 negative BC after cohort entry or within 2 years prior to cohort entry. Women with a germline pathogenic variant in a BC predisposition gene, and those who received neoadjuvant systemic therapy were excluded. 187 (88 ipsilateral, 96 contralateral, 3 unknown laterality) BC events (161 invasive and 26 DCIS) occurred over a median follow-up of 13.8 years. Flexible parametric survival analysis was used, with time since diagnosis as the time scale, and death due to any cause considered as a competing event. Potential predictors of future BC risk were investigated, including age at 1st BC, age at 1st birth, parity, breastfeeding duration, menopausal hormone therapy use, BMI, number of 1st-degree relatives with BC, BC polygenic risk score (PRS-313), contralateral mammographic density, surgery (breast conservation vs unilateral mastectomy), tumor grade and size, number of positive axillary nodes, associated LCIS, and use of adjuvant chemotherapy or radiation. Retained in the final risk prediction algorithm (all $P < 0.05$) were age at diagnosis of 1st BC, surgery type, radiation therapy, family history, and PRS-313. For external validation of the model, data from 3,136 cases (eligibility criteria as per the training set) with 181 subsequent BC events participating in the international Breast Cancer Association Consortium were used. Calibration and a time-dependent area under the curve (AUC) at 10 years were assessed to determine model performance. Sensitivity analysis excluding PRS-313 was also performed (as it is usually not available in clinical practice). **Results:** Discriminatory ability at 10 years was AUC = 0.66 (95% CI 0.62-0.70) or 0.65 (95% CI 0.61-0.69) if PRS-313 was excluded. The model was well calibrated; expected (176 cases) to observed (181 cases) ratio = 0.97 (95% CI 0.84-1.13). **Conclusions:** This model provides valid estimates of 10-year BC risk after a 1st ER-positive HER2-negative BC and may be useful in collaborative decision-making between patients and their surgeons when considering bilateral mastectomy. Research Sponsor: National Breast Cancer Foundation (Australia); IIRS-20-029; National Health and Medical Research Council (Australia); 1195294.

10525 **Poster Session**

Colonoscopy quality indicators for colorectal cancer precursors: Sessile serrated lesion and adenoma detection rates from a large clinical study of a blood-based test for CRC screening. First Author: Man Yee Wong, Freenome Inc, South San Francisco, CA

Background: Colorectal cancer (CRC) is the second leading cause of cancer-related deaths globally. Colonoscopy can reduce mortality by removing precancerous lesions or detecting cancer at an earlier, more treatable stage, with the adenoma detection rate (ADR) as the standard colonoscopy quality indicator. In 2024, the sessile serrated lesion detection rate (SSLDR) was introduced as a new multisociety colonoscopy quality indicator. Both quality indicators have associated performance targets, primarily based on benchmarking to colonoscopy registry data. Serrated lesions, which are precursors to 10-30% of CRC, are often missed due to their flat appearance, indistinct borders, and proximal locations. Published SSLDR data is limited, and to our knowledge, this is the first analysis of SSLDRs and ADRs in a large prospective, multicenter clinical study in an average-risk population. **Methods:** PREEMPT CRC, a clinical validation study of a blood-based test for CRC screening in adults aged 45-85, included 200 diverse U.S. sites. Based on thorough medical review of colonoscopy and pathology reports, SSLDRs and ADRs were calculated across 27,010 subjects that completed screening colonoscopy in the clinical validation. SSLDR and ADR were defined as the percentage of colonoscopies in which at least one SSL or adenoma was detected, respectively. Results were stratified by age and sex, and compared to established performance targets from colonoscopy quality guidelines. **Results:** The overall SSLDR in PREEMPT CRC was 7.2%, surpassing the newly recommended performance target of $\geq$ 6%. The overall ADR was 34.9%, aligning with the latest target of 35% overall (40% in males, 30% in females). The ADR increased significantly with age, from 26.9% in the 45-49 age group to 40.8% in the 75+ age group ($p < 0.001$). In contrast, the SSLDR remained consistent across age groups, with the 45-49 year age group (7.1%) similar to the overall SSLDR (7.2%) (p = 0.789). The ADR demonstrated a clear sex-dependence (41.9% in males, 29.4% in females, $p < 0.001$), while the SSLDR did not (7.4% in males, 7.1% in females, p = 0.433). **Conclusions:** The overall SSLDR and ADR in PREEMPT CRC were consistent with the updated colonoscopy quality guidelines, with the SSLDR exceeding the target, suggesting that the target could be updated from 6% to 7%. Our results underscore the age- and sex-independent risk of serrated lesions. Notably, even the SSLDR in the 45-49 year age group (7.1%, 6.2%-8.0%) exceeded the 6% performance target. Given the relatively high ADR of 26.9% observed among 45 to 49-year-olds, and the age-independence of the SSLDR, our findings highlight the importance of advocating for early CRC screening, especially in younger populations where screening adherence is generally poor. Clinical trial information: NCT04369053. Research Sponsor: None.

10526 **Poster Session**

Machine learning for cancer risk stratification: A bi-directional approach to screening. First Author: Erez Hasnis, Rambam Health Care Campus, Haifa, Israel

Background: Cancer screening programs are often limited by high costs, invasiveness, and potential false results. Machine learning (ML) applied to routine medical data could enable risk-stratified screening approaches. We developed ML models to predict 10-year cancer risk using data from routine periodic health examinations, aiming to identify both high and low-risk populations. **Methods:** We analyzed data from individuals who underwent routine health examinations at Rambam Medical Center (2002-2021), matched with the Israeli National Cancer Registry. After quality control, including removal of cases with previous tumors, we excluded cancers diagnosed less than 183 days after the visit to avoid prevalent cases. Using data from the initial visit only, we developed two XGBoost models for 10-year cancer risk: Model 1 (baseline) using only age and gender, and Model 2 incorporating 53 features including demographics, lifestyle factors (smoking, alcohol, physical activity), laboratory results (26 parameters including complete blood count, biochemistry, and lipids), medication categories (9 groups including statins, antihypertensives, antidiabetics), and medical history (7 disease categories). Models were trained on 75% of the data with cross-validation and evaluated on a 25% hold-out set. **Results:** Our cohort included 27,901 individuals (61% male, mean age 47$\pm$10 years), with 1,960 future incidents of cancer diagnosed at median follow-up of 8 years. Most common malignancies were prostate (21%), breast (19%), skin (15%), and colorectal (12%) cancers. For model development, we reduced the dataset to include only individuals with 10-year follow-up or cancer event within the 10-year window (N = 16,859, cancer cases = 1,268). Model 2 significantly outperformed Model 1 (AUC 0.799 vs 0.706, $p < 0.0001$) and demonstrated remarkable risk stratification. Against a population baseline risk of 7.3%, Model 2 identified: 1) a low-risk group (bottom 50%) with only 1.9% 10-year cancer risk; 2) an high risk group (90-99th percentile) with 25.1% risk (3.5-fold increase); and 3) a very high-risk group (top 1%) with 74.4% risk (10-fold increase). In comparison, the highest-risk group in Model 1 (top 1%) achieved only 20.0% risk. The most important predictive features were age, monocyte count, albumin, total bilirubin, and LDL cholesterol. **Conclusions:** ML analysis of routine health examination data can effectively stratify cancer risk, identifying both very low and exceptionally high-risk groups. This bi-directional stratification could enable more efficient screening strategies: reduce screening intervals or invasiveness in the large low-risk population, while intensifying screening in high-risk groups. Future studies should evaluate and validate these findings in different populations and study whether this approach can improve the efficiency and cost-effectiveness of cancer screening programs. Research Sponsor: ICRF - Israel Cancer Research Fund.

10527 **Poster Session**

Efficacy and toxicity of low-doses versus standard-dose enzalutamide in advanced prostate cancer: A real-world study with implications for cancer prevention/interception. First Author: Martino Oliva, E.O. Ospedali Galliera, Genova, Italy

Background: Prostate cancer (PCa) is the most frequent cancer in males in the US and EU. Enzalutamide is effective in biochemically recurrent and advanced PCa but is associated with considerable adverse events (AEs) at standard doses (160 mg/day). In the ENACT trial, enzalutamide monotherapy reduced the risk of PCa progression compared to active surveillance (AS) in patients with intermediate/low-risk, but AEs were frequent (eg, 55% fatigue). Preliminary case reports suggest that low/intermediate doses ($\leq$80 mg/day) retain efficacy while reducing toxicity. This study evaluates the efficacy and safety of low/intermediate dose vs standard-dose enzalutamide in advanced PCa in a real-world Italian cohort. **Methods:** This single-center, retrospective observational study included 140 assessable metastatic PCa patients treated with enzalutamide for castration resistant (80%) or sensitive (20%) PCa between August 1, 2014 and December 31, 2023. Patients were categorized based on the total dose (actual vs predicted) taken: low (L, $\leq$50%, n = 11), intermediate (I, $>$ 50% and $\leq$80%, n = 16), and high (H, $>$ 80%, n = 113). The primary endpoint was the 12 month progression-free survival (PFS) by restricted mean survival time to account for violation of proportional hazards assumption. Secondary endpoints included PSA response (decline $\geq$50% at 3 months), overall survival (OS) at 36 months and worsening of AEs of special interest (fatigue, neurological disorders, hypertension). PFS and OS were adjusted for ECOG performance status at baseline. **Results:** The three dose groups were not different at baseline on PSA, BMI, Gleason Score, age and castration resistance. The choice of L dose treatment at baseline was due to clinical judgment in 82% of cases (PS $>$ 0 or age $>$ 80), whereas the I dose was due to toxicity reduction after initial high dose in 63%. The median follow-up time was 13.6 months [IQR, 7.2 – 23.1]. There were no significant differences in PFS at 12 months on H vs I dose (10.4 vs 11.4 mo, p = 0.09) and H vs L dose (10.4 vs 9.2 mo, p = 0.37). There was no difference among dose groups in PSA response (70% vs 75% vs 60% on H, I, L, respectively). The use of I or L doses showed no evidence of adverse effects on OS at 36 months. The rate of fatigue worsening on H vs I vs L dose was 61.1%, 63.0% and 27.3% (p = 0.03 for H vs L). Worsening of neurological disorders and hypertension was 19.5%, 18.8% and 0% and 18.6%, 18.8% and 9.1% on H vs I vs L, respectively. **Conclusions:** In our real-life observational cohort, low/intermediate doses of enzalutamide show comparable efficacy relative to high dose while improving tolerability, indicating the need for further search of the optimal dose of this expensive drug. Moreover, our findings prompt a study of low-intermediate dose enzalutamide in the prevention/interception setting in patients with low/intermediate risk prostate cancer under AS. Research Sponsor: None.

10528 **Poster Session**

Growing burden of cancer and high body mass index in the United States from 1990-2021: A benchmarking cross-state analysis. First Author: Adit Dharia, HCA Healthcare/USF Morsani College of Medicine, Oak Hill Hospital, Brooksville, FL

Background: Cancer (CA) remains a major public health challenge and is the second leading cause of death and disability in the United States. Among the various modifiable risk factors, a high body mass index (h-BMI) significantly contributes to the burden of non-communicable diseases, including CA. **Methods:** This study is the first to estimate deaths and disability attributable to h-BMI for 12 different CA types across the USA, disaggregated by age, sex, year, and location, using the standardized Global Burden of Disease Study 2021 methodology from 1990–2021. **Results:** From 1990-2021, the annual percentage change (APC) in age-standardized mortality rates (ASMR) due to CA attributable to h-BMI increased by 0.22%, disability-adjusted life years rates (ASDALR) by 0.19%, and years lived with disability rates (ASYLDR) by 0.78%. Among all CA, the highest increase in APC for ASMR was observed for liver CA at 3.81%, followed by pancreatic CA at 2.66%, uterine CA at 1.16%, thyroid CA at 0.84%, multiple myeloma at 0.50%, and kidney CA at 0.35%. Conversely, APC decreased for leukemia by 0.16%, ovarian CA by 0.37%, non-Hodgkin lymphoma by 0.44%, and gall bladder and biliary tract CA by 0.45%, as well as for colon and rectum CA by 0.49%, and breast CA by 0.85%. Among states, Mississippi observed the highest increase in APC for ASMR at 1.21%, followed by Oklahoma at 1.39%, West Virginia at 1.20%, and New Mexico at 1.19%. In terms of ASYLDR, the largest increases were seen in New Mexico at 1.83%, California at 1.77%, Mississippi at 1.74%, West Virginia at 1.60%, and Tennessee at 1.47%. Age-wise, individuals aged 20-54 recorded 3,833 deaths (95% uncertainty interval: 1,727-5,876), while those 55 and older recorded 43,371 deaths (16,854-71,488) in 2021. Similarly, DALYs for ages 20-54 were 173,448 (82,011-258,288), and for those 55 and older were 930,410 (366,885-1,528,824). In terms of gender, males observed higher increases in ASMR and ASDALR compared to females, with 0.58% vs 0.06% and 0.46% vs 0.05%, respectively, while females saw higher increases in ASYLDR at 1.02% compared to 0.86% from 1990-2021. **Conclusions:** Deaths due to CA attributable to h-BMI accounted for 14.95% of all CA attributable risk factors in 2021. Notably, liver, pancreatic, and uterine CA have shown the most significant rises in ASMR, highlighting an urgent need for targeted public health strategies and research to address these alarming trends. Conversely, decreases in APC for CA like leukemia, ovarian, and breast CA suggest that some progress is being made, possibly attributed to advancements in treatments and early detection programs. Age and gender analyses further illuminate the disproportionate burden of CA on older adults and males, though females exhibit a higher increase in YLDs. Research Sponsor: None.

10529 **Poster Session**

Sex-based disparities in HPV-related cancer outcomes: Insights into social determinants of health. First Author: Xiangren Wang, University of Florida, Gainesville, FL

Background: Human papillomavirus (HPV) is the most common sexually transmitted infection and a leading cause of several cancers. Research suggests that males are more likely to be infected with HPV compared with females and, as a result, have a higher incidence of HPV-related cancers, attributable to multiple social determinants of health (SDoH) factors. This study was to examine these sex-based disparities, with a focus on SDoH. **Methods:** The US nationally representative sample of HPV related cancer adults were analyzed from the 2011-2023 National Health and Nutrition Examination Survey (NHANES). Participants who reported having diagnosis of HPV-related cancers were included in our study. Descriptive analyses were performed, and weighted logistic regression models were used to examine associations between HPV-related cancers(Oropharyngeal Cancer, Esophageal Cancer, Prostate Cancer, Cervical Cancer, Anal Cancer, and Uterine Cancer) and key SDoH variables, including HPV vaccination, mental health issue, education level, smoking, poverty level, and health insurance coverage. Analyses were stratified by sex and adjusted for survey weights. Results are reported as adjusted odds ratios (aORs) with 95% confidence intervals (CIs). **Results:** A total of 692 participants (equating to 22,115,631) with HPV-related cancer were identified from NHANSE 2011-2023, with 60.3% males and 39.7% females. Compared with females, the prevalence of HPV-related cancer was significantly higher among males (34% vs. 20%). Notably, none of the males with HPV-related cancer had received HPV vaccination. Men aged 65 years and older had more than 16 times greater odds of having HPV-related cancers compared to those under 65. In contrast, older women were only 1.5 times more likely to report HPV-related cancers, highlighting a striking disparity between older males and females. Males without a high school degree have significantly lower odds of HPV-related cancer (OR: 0.38, 95% CI: 0.27–0.56). This may be attributed to a lack of HPV awareness and knowledge among males, leading to underreporting. Furthermore, non-Hispanic Black (NHB) males (OR: 1.92, 95% CI: 1.43–2.57) had greater odds of HPV-related cancer compared to non-Hispanic White (NHW) males. In comparison, NHW females had higher odds of HPV-related cancers compared with other racial and ethnic groups. These findings highlight the distinct SDoH risk factors contributing to HPV-related cancers across males and females, resulting in disparities in HPV-related cancer outcomes. **Conclusions:** These findings underscore the disparities faced by males regarding HPV-related cancer. Addressing these inequities requires targeted interventions focusing on men who are particularly vulnerable to HPV-related cancers, including increasing vaccination rates and reducing behavioral risks for males. Research Sponsor: None.

10530 **Poster Session**

Do health care providers offer advice to adolescents about nicotine-containing product use? First Author: Michael T. Halpern, University of Texas School of Public Health at San Antonio, San Antonio, TX

Background: Use of tobacco and other nicotine-containing products is a major preventable cause of cancer. Most individuals initiate nicotine product use during adolescence. Advice from health care providers is important to decrease nicotine product initiation and encourage cessation among individuals using these products. It is unclear how frequently providers offer this advice to adolescent patients. We analyzed national survey data to better understand provider interactions with adolescents about nicotine product use. **Methods:** We analyzed data from 16,120 U.S. middle- and high-school students (weighted to represent a population of 21,836,206) who saw a health care provider (doctor, dentist, or nurse) in the past 12 months and had non-missing data on nicotine product use, family affluence level, and receipt of provider advice regarding nicotine product use from the 2021 National Youth Tobacco Survey (NYTS), a school-based, self-administered survey. Nicotine product use was determined from responses to 13 NYTS questions on use of tobacco or nicotine-containing products; those who indicated use of any products in the past 30 days were classified as "current users". Receipt of advice was assessed from 3 questions on advice to not use cigarettes, e-cigarettes, or other nicotine-containing products during health care provider visits. Family affluence was based on 4 questions on family vacations, cars, computers, and bedrooms. Multivariable logistic regression analyses examined associations of receipt of advice with socio-demographic characteristics separately for current and non-current users, controlling for whether providers asked about nicotine product use adjusting for the complex survey design of the NYTS. **Results:** Of the sample, 1262 (weighted 7.9%) currently used nicotine products. Current users were significantly ($p < 0.05$) more likely to be older, female, and non-Hispanic White (vs. non-Hispanic Asian or Hispanic); 51.3% of current users vs. 44.0% of non-current users received health care provider advice. Among current users, older students were less likely to receive advice (odds ratio [OR] 0.85 per year of age, 95% confidence interval [CI] 0.77-0.93) while males (vs. females) were more likely to receive advice (OR 2.51, 95% CI 1.64-3.86). Among non-current users, older students were less likely to receive advice (OR 0.91, 95% CI 0.89-0.94). Males vs. females (OR 1.54, 95% CI 1.42-1.68); non-Hispanic Blacks vs. non-Hispanic Whites (OR 1.18, 95% CI 1.03-1.36); and those from highly affluent families (OR 1.20, 95% CI 1.06-1.36) were more likely to receive advice. **Conclusions:** Only half of adolescents received nicotine product use advice from health care providers. Those more likely to use nicotine products (older, female, non-Hispanic White students) were less likely to receive advice. Increased provider advice targeting at-risk populations may help decrease adolescent nicotine product use. Research Sponsor: None.

10531 **Poster Session**

Awareness, knowledge, and attitudes toward breast cancer polygenic risk scores for precision prevention in a multiethnic cohort of high-risk women. First Author: Jincong Q. Freeman, Department of Public Health Sciences, The University of Chicago, Chicago, IL

Background: Polygenic risk scores (PRS) have been shown to improve the risk assessment of breast cancer. Though commercially available in the US, PRS testing remains controversial clinically. Recent qualitative research suggests that PRS is understood and accepted by women. However, quantitative research on PRS awareness, knowledge, and attitudes in the US population is scarce. **Methods:** Between July-September 2024, we surveyed high-risk women without breast cancer enrolled in the Chicago Multiethnic Epidemiologic Breast Cancer Cohort and Cancer Prone Registry. PRS awareness was assessed by asking whether participants had ever read/heard about PRS prior to the survey and discussed PRS with a provider. PRS knowledge was measured using an 11-item "true/false" assessment. The total score ranges from 0-11, with higher scores indicating better knowledge. Participants were also asked to what extent they agreed that PRS testing should be offered to the general population and a routine part of breast cancer risk assessment; and how likely receiving a PRS influences their behaviors toward risk management, using a 4-point Likert scale. We performed linear regression, controlling for demographic and socioeconomic factors. **Results:** Of 828 women (mean age 56.8 years), 69.5% identified as White, 20.8% as Black, and 9.7% as Other. Overall, 18.5% and 13.2% had ever read/heard about PRS and discussed it with a provider, respectively. Further, 32.9% reported having learned about PRS from a genetic counselor, followed by 23.1% from their own research/reading, 11.2% from a primary care provider, and 6.3% from an oncologist. There were no significant racial/ethnic differences in PRS awareness (Black 13.0%, Other 19.2%, White 20.7%; $p = .082$) and discussion (Black 11.8%, Other 11.3%, White 14.1%; $p = .874$). The overall mean score on PRS knowledge was 9.7 (SD 1.4). Black (β −0.47, *se* 0.14; $p = .001$) or Other (β −0.50, *se* 0.17; $p = .003$) women were less likely than White women to score higher on PRS knowledge. Higher education (p-trend $< .001$) and income (p-trend = .002) levels were highly associated with increased knowledge scores. 95.4% and 96.2% agreed or strongly agreed that PRS testing should be offered to the general population and a routine part of breast cancer risk assessment, respectively; 93.9% reported receiving a PRS likely or very likely influences their behaviors toward risk management. Attitudes toward PRS were also high across racial/ethnic and socioeconomic groups. **Conclusions:** In this diverse cohort of women, PRS awareness and discussion were low, and there were notable gaps in PRS knowledge. Our findings underscore the need to improve patient-provider communication of breast cancer risk and address gaps in PRS knowledge/health literacy when implementing genetic testing including PRS to increase the uptake of risk-stratified, personalized breast cancer screening. Research Sponsor: National Institute on Aging; T32AG000243; Susan G. Komen Breast Cancer Foundation; TREND21675016; Breast Cancer Research Foundation; BCRF-23-071; National Cancer Institute; R01CA228198; National Cancer Institute; P20CA233307; Susan G. Komen Breast Cancer Foundation; SAC210203.

10532 **Poster Session**

Evaluating the impact of long-term glucocorticoid use on cancer risk in patients with rheumatologic diseases: A retrospective cohort study. First Author: Farigol Hakem Zadeh, HCA North Florida Division, Gainesville, FL

Background: Long-term glucocorticoid (GC) therapy is widely used in the management of rheumatologic diseases, but its immunosuppressive effects have raised concerns about a potential increased risk of cancer. The association between long-term steroid use in patients with rheumatologic diseases and the development of cancer remains unclear. This study aims to evaluate cancer prevalence in patients with rheumatologic conditions who are on long-term steroids compared to those who are not. **Methods:** A retrospective cohort study was conducted involving 35,272 patients with rheumatologic diseases between 2011 and 2024. Patients with rheumatoid diseases were categorized into two groups: those receiving long-term GC therapy (≥30 days; n=5521) and those not on GC therapy (n= 29,751). Cancer prevalence was assessed in both groups as well as their subgroups based on sex, and age. Prevalence rates and odds ratios (OR) were calculated to determine the association between steroid use and cancer. **Results:** Cancer prevalence was significantly higher among GC users (34.2%) compared to non-GC users (20.8%). The odds ratio for cancer in GC users was 1.97 (95% CI: 1.95–2.02), indicating 97% increased odds of cancer for GC users. Stratified by sex, female GC users had a cancer prevalence of 32.6%, compared to 19.9% in non-GC users, with an odds ratio of 1.96 (95% CI: 1.48–2.59), suggesting a nearly two-fold increase in cancer risk. In male patients, cancer prevalence in GC users was 38.2%, compared to 23.4% in non-GC users, with an odds ratio of 2.02 (95% CI: 1.72–2.41), indicating a 102% increase in cancer risk. In those aged over 18 years, cancer prevalence in GC users was 34.5%, compared to 21.3% in non-GC users, with an odds ratio of 1.94 (95% CI: 1.75–2.14), suggesting a significantly higher cancer risk for those on long-term steroid therapy. **Conclusions:** Long-term steroid use in patients with rheumatologic diseases is associated with a higher prevalence of cancer. This association was observed across both sexes and age groups. The substantial cancer risk observed in patients without a personal history of cancer underscores the need for cautious GC prescribing and regular cancer screening. Further investigations should focus on additional factors, including race and comorbidities, to better understand the modulating factors behind this association and refine clinical decision-making. Research Sponsor: None.

10533 **Poster Session**

The Selfie study: Cervical precancer detection using novel human papillomavirus biomarkers. First Author: Sarah Phillips, National Cancer Institute, Rockville, MD

Background: Human papillomavirus (HPV) causes the majority of cervical cancers worldwide. Dual stain cytology can detect HPV oncogenic activity through biomarkers p16/Ki-67 in cervical samples. Dual stain is an acceptable triage strategy for HPV-positive results from clinician-collected samples, reducing the number of low-risk individuals sent for colposcopy or treatment. However, the ability of dual stain to triage self-collected vaginal specimen is poorly understood. The Selfie Study is an observational study to assess the diagnostic accuracy of different biomarkers for cervical precancer on self-collected samples. Here, we evaluated dual stain cytology in clinician and self-collected specimens for detection of cervical precancer. **Methods:** Individuals with a cervix ages 25-69 years undergoing cervical cancer screening, colposcopy, or treatment at George Washington University (GWU) and Sarasota Memorial Hospital (SMH) were included in this study (August 2020-August 2024). Participants were instructed to perform self-collection prior to clinician-collection during the clinic visit. Demographics and clinical outcomes of dual stain on paired cervicovaginal samples and presence of cervical intraepithelial neoplasia 2 or worse (CIN2+) were recorded and assessed using descriptive statistics. Differences in sensitivity and specificity of dual stain to detect CIN2+ between the two collection methods were assessed using McNemar's test. **Results:** A total of 548 participants enrolled in Selfie. Paired dual stain results were available for 411 participants (411/548, 75%), of which 24 participants were CIN2+ (24/411, 5.8%). Missing results were due to inadequate/absent staining for one or both collection methods. Dual stain was positive in 63 clinician-collected samples (63/411, 15.3%) and in 39 (39/411, 9.5%) self-collected samples. Overall percent agreement between collection methods was 89.3% (367/411). Percent positive agreement was 39.7% (29/73). Dual stain was 83.3% (20/24) sensitive to detect CIN2+ in clinician-collected samples and 45.8% (11/24) sensitive in self-collected samples (83.3% versus 45.8%, p = 0.003). **Conclusions:** Dual stain on self-collected samples had significantly lower sensitivity for detection of CIN2+ compared to clinician-collected samples. Additional research is needed to evaluate whether the performance is more comparable for CIN3+ endpoints. Our study highlights the challenges of conducting triage assays from self-collected specimens. Clinical trial information: NCT04423679. Research Sponsor: U.S. National Institutes of Health.

10534 **Poster Session**

Analyzing trends in multimorbidity-related mortality among patients with cancer and myocardial infarction: A decadal analysis. First Author: Abdul Ahad, Northwest General Hospital and Research Centre, Peshawar, Pakistan

Background: Multimorbidity, defined as the coexistence of two or more chronic conditions, poses major challenges to healthcare systems globally. Cancer and myocardial infarction (MI) are leading causes of mortality, yet their combined impact remains underexplored. This study investigates trends in multimorbidity-related mortality among U.S. patients with cancer and MI over two decades, aiming to identify patterns and correlations to guide healthcare interventions and policies. **Methods:** Data were extracted from the Centers for Disease Control and Prevention Wide-Ranging Online Data for Epidemiologic Research (CDC WONDER) database from 1999 to 2020. Death certificates were analyzed for adults aged 25 years and older, with cancer and MI deaths identified using ICD-10 codes (I20 and C00–C97). Variables such as age, sex, race/ethnicity, geographical region, urban-rural classification, and location of death were extracted. Crude and age-adjusted mortality rates (AAMR) per 100,000 population were calculated and Join point regression analysis was employed to assess mortality trends and annual percent changes (APC). Statistical significance was defined at $p < 0.05$. **Results:** A total of 200,884 deaths were analyzed, with 59.9% occurring in medical facilities, followed by deaths at home (25.09%), nursing homes (12.85%), and hospice facilities (2.10%). The overall AAMR declined significantly from 6.83 in 1999 to 3.33 in 2020.Males consistently had higher mortality, with AAMR dropping from 10.85 to 4.79, compared to females (4.30 to 2.22). The highest mortality was observed in individuals aged 85 and above (CMR: 41.42). Mortality trends declined across all age groups until stabilization in recent years. Racial disparities persisted, with NH Black/African Americans experiencing higher mortality rates (8.91 in 1999 to 3.92 in 2020). Geographic analysis showed the highest mortality rates in the Midwest and Northeast regions. Metropolitan and non-metropolitan areas showed declining mortality trends until 2015, followed by stabilization or slight increases in recent years. **Conclusions:** A significant decline in multimorbidity-related mortality has been observed in patients with cancer and MI over the past two decades, with notable disparities across gender, age, race, and geography. Targeted healthcare strategies are essential to address the specific needs of high-risk populations and ensure equitable access to healthcare resources. Research Sponsor: None.

10535 **Poster Session**

Can we determine the mechanism behind cancer risk reduction with glucagon-like peptide-1 receptor agonists (GLP-1RAs)? First Author: Junmin Song, Department of Medicine, Jacobi Medical Center, Albert Einstein College of Medicine, Bronx, NY

Background: Growing evidence suggests that GLP-1RAs may reduce cancer risk in patients with type 2 diabetes (T2D). Most studies have focused on obesity-related cancers (ORCs), with weight loss proposed as a key mechanism. Additional potential mechanisms include the anti-inflammatory effects of GLP-1RAs on various pathways. We evaluated the impact of GLP-1RAs on weight loss and ORC incidence, as well as their effects on lung cancer, which is considered a non-ORC. **Methods:** We utilized the TriNetX database to analyze patients with T2D prescribed a single GLP-1RA from 2010 to 2021. Patients with prior cancer diagnoses were excluded. Semaglutide, dulaglutide, and liraglutide were individually compared to exenatide due to their greater weight loss potential. Propensity score matching (1:1) was used to adjust for demographics, comorbidities, HbA1c, BMI, and medications. Patients were followed for 3 and 5 years, and Cox proportional hazards analyses assessed the risk of 13 ORCs and lung cancer. **Results:** We identified 726,846 patients prescribed GLP-1RAs and conducted multiple comparisons, which were well-matched across analyses. Among the agents, semaglutide demonstrated the greatest weight-loss effect, while exenatide had the least. However, the differences in weight loss did not translate to significant changes in the risk of ORCs. The hazard ratios for semaglutide were 1.11 (95% CI: 0.95–1.29) at 3 years and 1.08 (95% CI: 0.95–1.24) at 5 years. For liraglutide, the hazard ratios were 1.02 (95% CI: 0.88–1.19) at 3 years and 1.05 (95% CI: 0.93–1.20) at 5 years. Dulaglutide had hazard ratios of 1.03 (95% CI: 0.89–1.20) at 3 years and 1.01 (95% CI: 0.89–1.14) at 5 years. None of these differences were statistically significant compared to exenatide. Similarly, no significant differences were observed in the risk for lung cancer. For semaglutide, the hazard ratios were 0.88 (95% CI: 0.59–1.30) at 3 years and 0.88 (95% CI: 0.62–1.25) at 5 years. Liraglutide had hazard ratios of 0.91 (95% CI: 0.62–1.34) at 3 years and 0.90 (95% CI: 0.65–1.24) at 5 years, and dulaglutide had hazard ratios of 1.02 (95% CI: 0.71–1.49) at 3 years and 1.10 (95% CI: 0.81–1.49) at 5 years. These findings indicate no significant differences in cancer risks, whether for obesity-related cancers or non-ORC, lung cancer, among the four GLP-1RAs. **Conclusions:** All four GLP-1RAs demonstrated similar cancer risks for obesity-related cancers despite differences in weight loss among the agents. Similarly, no differences were observed in the risk of non-obesity-related cancer, specifically lung cancer. This suggests that weight loss does not clearly explain a link between GLP-1RAs and reduced cancer risk, as the results were consistent for both obesity-related and non-obesity-related cancers. Research Sponsor: None.

10536 **Poster Session**

Estimation of population attributable fractions based on integrated global cancer incidence data, 1990-2021. First Author: Yongjie Xu, Office of Cancer Screening, National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China

Background: The global cancer burden is increasing, yet emerging risk factors for cancer incidence have not been comprehensively summarized in terms of the population attributable fraction (PAF) from a global perspective. **Methods:** We first searched and screened cancer risk factors from 435,977 studies in the Embase, PubMed, and Cochrane databases. Cancer risk effect sizes, such as RR (relative risk), HR (hazard ratio), and IRR (incidence rate ratio) values, were then obtained from meta-analyses. We further estimated population attributable fractions (PAFs) for each risk factor, cancer type, gender, SDI (Socio-demographic Index), modifiability, and trends from 1990 to 2021, using 94 pre-defined risk factors and 39 cancer types. These risk factors include lifestyle factors, environmental exposures, occupational risks, metabolic factors, comorbidities, and family or cancer history. **Results:** A total of 811 cancer risk effect sizes were obtained covering 75 countries or regions, including 18,084 cancer RR/HR/IRR values. In 2021, 64.1% (56.7% - 71.4%) of global cancer incidences were attributable to the evaluated risk factors, with modifiable risk factors accounting for 57.6%. Among the evaluated cancers, the proportion of incidence cases attributed to risk factors exceeded 50% in 26 types of cancer, with the leading cancers being cervical cancer (97.1%), Kaposi's sarcoma (91.2%), vaginal cancer (87.0%), lung cancer (84.6%), and laryngeal cancer (83.2%). In terms of individual risk factors, tobacco use (17.9%), infection (16.1%), and overweight or obesity (10.2%) contributed the highest PAFs, followed by family and genetic history (6.9%), alcohol consumption (5.7%), cardiovascular diseases (5.0%). The high SDI region shows a higher PAF (68.2% [61.5%–75.0%]) compared to the non-high SDI region (59.6% [52.2%–67.0%]). From 1990 to 2021, the global cancer incidences attributable to risk factors increased from 61.8% to 64.1%. Overweight or obesity, neurological and psychological disorders, and dietary factors were the top three leading increasing risk factors. **Conclusions:** The global cancer burden is significantly influenced by a wide range of modifiable and non-modifiable risk factors, with over 64% of cancer incidence in 2021 attributable to these factors. The rising trends in overweight or obesity, neurological and psychological disorders, and diabetes factors between 1990 and 2021 highlight the urgent need for targeted interventions to address these rapidly growing risks and reduction of the cancer burden. Research Sponsor: Shanghai Xiaohe Medical Laboratory Co., Ltd.

10537 **Poster Session**

Development and clinical validation of a cell-free DNA methylation sequencing test for multi-cancer early detection. First Author: Xiaosheng He, The Sixth Affiliated Hospital, Sun Yat-sen University, Guangzhou, China

Background: Achieving robust early-stage sensitivity in multi-cancer early detection (MCED) poses challenges, relying on large cohorts of early-stage samples and reliable prediction frameworks. Particularly for gastrointestinal cancers (GICs) with poor compliance of screening, early-stage sensitivity in MCED remains insufficient. Moreover, accurate tumor localization is crucial for choosing subsequent diagnostic procedures but remains suboptimal. We evaluate the performance of Genie-seq within the ProFuture study (NCT05874648), focusing on its capacity to detect five high-mortality cancers: lung, colorectal, liver, stomach, and esophageal cancers. **Methods:** The ProFuture study is a prospective multicenter case-control study that initially enrolled 3,515 participants. Following evaluations and a minimum of a half-year follow-up, 3,036 participants remained analyzable. Participants were divided into training (920 cancer; 629 non-cancer), validation (300 cancer; 215 non-cancer), and independent validation (605 cancer; 367 non-cancer) sets. Plasma cfDNA underwent a 1000X target enzymatic methyl sequencing assay (Genie-seq) targeting cancer-specific methylation patterns identified from 2,420 tumor and plasma samples. The assay normalizes abnormal fragment reads within blocks to minimize interference, using a maximization model to select sensitive and robust features. A gradient-boosted tree model was developed to integrate these features for cancer prediction, utilizing a one-vs-rest strategy to determine the tissue-of-origin (TOO). **Results:** Specificity remained consistently high across all phases: 99.0% (95% CI: 97.7-99.6%) in training, 99.1% (96.7-99.9%) in validation, and 99.2% (97.6-99.8%) in independent validation. Sensitivity was 68.6% (65.5-71.6%) in training, 71.0% (65.5-76.1%) in validation and 69.6% (65.8-73.2%) in independent validation. In independent validation set, stages I-III (account for 85.5% of cases) sensitivity reached 65.8% (61.5-69.9%) for all cancer types and 72.1% (66.9-76.9%) for three GICs. The TOO classifier assigned the origin in all screen-positive cases, achieving an accuracy of 87.4% (83.9-90.4%) in independent validation, including reducing misclassification from lung to esophageal cancer due to squamous similarity to 4.5%. **Conclusions:** This MCED test accurately identified signals from five tumor types especially in the early stages. Precise TOO localization minimizes the healthcare burden of subsequent diagnoses. The consistency of performance from training to clinical validation underscores the robustness of feature selection strategy, mitigating the risk of overfitting. Notably, this study demonstrated exceptional sensitive detection of early-stage GICs, indicating the potential efficacy of Genie-seq in MCED within the ongoing interventional Prosight study (NCT06790355). Clinical trial information: NCT05874648. Research Sponsor: None.

10538 **Poster Session**

Utilizing cancer community outreach and engagement to explain impact of age, income, residence, knowledge, and survivorship on cancer fatalism in urban and rural/marginalized areas. First Author: Runcie C.W. Chidebe, Project Pink Blue- Health and Psychological Trust Centre, Abuja, FCT, Nigeria

Background: Nigeria has the highest cancer burden in sub-Saharan Africa, with 124,815 incidences and 78,899 deaths. Popular fatalistic beliefs such as *"cancer is a death sentence"* and *"cancer is not my portion"* exist in this population, which potentially affects cancer prevention, early detection and increases poor treatment outcomes. Yet, factors responsible for these fatalistic cancer beliefs remain largely unknown. This study utilized cancer community outreach and engagement (COE) to understand cancer health disparities among Nigerians. Specifically, we assessed the association of age, income, residence, cancer knowledge, screening, survivorship, and current health on cancer fatalism (i.e., the view that cancer is a death sentence) in Nigeria. **Methods:** A cross-sectional study was used to collect data from participants (n = 1457, 18-68 years old), in two COE events and two marginalized communities. Participants completed questionnaires via self-assessment. Multiple linear regression was used to analyze the data. **Results:** Our findings showed that individuals who had not previously participated in cancer COE events reported higher cancer fatalism ($\beta = 1.21$, $p < 0.001$) compared to those who had previously participated. More cancer knowledge was related to lower cancer fatalism among participants ($\beta = -0.21$, $p = 0.002$). Participants who reported lower monthly income ($\beta = 1.05$, $p = 0.002$) and those who reported mid-low monthly income ($\beta = 1.28$, $p < 0.001$) had higher cancer fatalism. Participants aged 30-49 ($\beta = 0.46$, $p = 0.049$), residing in rural communities ($\beta = 0.62$, $p = 0.006$), and those who were married ($\beta = 0.51$, $p = 0.029$) reported higher cancer fatalism. **Conclusions:** Our study showed that participating in cancer COE events may lower cancer fatalism. The global cancer control communities, donor agencies, and Nigeria's National Institute on Cancer Research and Treatment need to encourage more COE events as a crucial strategy for early detection and closing the cancer disparity gaps. There is a need for more cancer awareness and policy advocacy on cancer in this population. Research Sponsor: None.

10539 **Poster Session**

Machine learning–informed navigation of patients in persistent poverty zip codes to improve colorectal cancer screening: A prospective controlled study. First Author: Ravi Bharat Parikh, Emory University, Atlanta, GA

Background: Colorectal cancer (CRC) screening remains suboptimal, particularly in racially diverse and low-income populations. Machine learning (ML) algorithms trained on routine electronic health record (EHR) data may accurately predict CRC risk. Further, patient navigation programs can address screening barriers such as lack of transportation access and low health literacy around colonoscopy preparation. We tested the impact of an intervention combining ML-based risk stratification and an evidence-based CRC screening navigation program on CRC screening rates and outcomes. **Methods:** This prospective nonrandomized controlled study (NCT05383976) was conducted at a large academic health system, enrolling adults over 50 years of age and at average-risk of CRC. All adults resided in Persistent Poverty zip codes (defined by the US Census Bureau) in the Philadelphia metro area, were attributed to a primary care physician (PCP), and had a colonoscopy order that had not been completed within the past 6 months. We adapted a validated ML algorithm that was previously trained on 22 variables – including age, sex, and longitudinal complete blood counts – to predict CRC risk. Patients enrolled in the intervention arm were prioritized by the ML algorithm for a structured navigation program, including risk-targeted phone-based education, appointment facilitation, transportation support, and mailed FIT tests. A concurrent control cohort received navigation but was not prioritized by the ML algorithm. Adjusted logistic regression models assessed the intervention's impact on the co-primary outcomes of (1) CRC screening completion (colonoscopy or FIT), and (2) positive screening result, defined as precancerous adenoma (sessile serrated, inflammatory, villous, malignant) and/or positive FIT. **Results:** 382 patients were enrolled (199 intervention, 183 control). Among intervention patients, 71.4% were reached via phone and 66.4% scheduled screening, with 26.2% and 17.6% completing colonoscopy and FIT, respectively (see Table). Screening completion was similar for intervention vs. control (46.2% vs. 43.2%; adjusted OR 1.02, 95% CI 0.67-1.56, p=0.93). For intervention vs. control, precancerous adenoma detection was 8.5% vs. 5.2% (aOR 2.43, 95% CI 0.48–12.3, p=0.57) and tubular adenoma detection was 35.6% vs. 25.0%. **Conclusions:** ML-informed navigation was feasible, did not increase screening engagement, and marginally increased rates of precancerous and tubular adenoma detection. Refinements in ML risk stratification and enhanced navigator outreach may maximize impact. Clinical trial information: NCT05383976. Research Sponsor: National Cancer Institute.

Navigator services provided in intervention group.

Number of telephone calls to outreach	
1	81 (40.7%)
2	34 (17.1%)
3+	27 (13.5%)
Prep letter sent	11 (7.7%)
Prep kit sent	24 (16.9%)
Colonoscopy/FIT education	27 (19.0%)
Transportation arrangement	8 (5.6%)

10540 Poster Session

Clinical and radiological characteristics of intermediate and high-risk cases in the Brazilian early lung cancer screening trial (BRELT3): Insights into Lung-RADS categories 3 and 4 and biopsy decision-making factors. First Author: Audrey Cabral Ferreira de Oliveira, Postgraduate Program in Clinical and Translational Research (PgPCT), Gonçalo Moniz Institute (IGM), Fiocruz Bahia, Salvador, Brazil

Background: Lung cancer is the leading cause of cancer death worldwide, and low-dose computed tomography (LDCT) effectively reduces mortality through early detection. BRELT1 and BRELT2, from the Propulmão initiative, highlighted the feasibility of lung cancer screening (LCS) programs in Brazil. This report examines demographic and radiological characteristics of patients with Lung-RADS (LR) 3 and 4 nodules in BRELT3, a mobile LDCT-based LCS initiative, and factors influencing biopsy indication. **Methods:** This prospective cohort study included current or former smokers (cessation ≤15 years), with a smoking history of ≥20 pack-years, aged 50–80 years. Those with LDCT classified as LR 3 or 4 were analyzed, and clinical and tomographic data were collected. The Brock malignancy probability model (PMB, 10% threshold) was applied retrospectively to assess its association with biopsy indication. Statistical methods included logistic regression, t-test, Mann-Whitney, chi-square, and Fisher's exact test. Ethical Committee approval was obtained (SENAI-CIMATEC / Santa Izabel Hospital; n° 67431523.6.0000.9287 / 67431523.6.3001.5520). **Results:** Among 2018 screened patients, 223 (11.1%) had findings for lung cancer risk, Of these, 44.4% classified as LR3 and 55.6% as LR4. Median age was 64 years, with 87.4% self-identified as Black, 63.2% as current smokers, and 75.8% reported no family history of lung cancer. Nodules were predominantly single (82.5%) and solid (77.1%), with a mean size of 13.12 mm. LR3 nodules were smaller (9.53 mm) and exhibited lower PMB (7.43%) compared to LR 4 (15.99 mm; PMB: 18.93%). Biopsy was indicated for 45 participants (98% LR4). Nodules requiring biopsy were larger (22.97 vs 10.63 mm) and had higher PMB (26.44 vs 10.64%). Predictors for biopsy included irregular or spiculated contours (OR 5.83; $p < 0.05$), LR4B/4X vs.4A classification (OR 5.00; $p < 0.05$), PMB > 10% (OR 5.36; $p < 0.05$) and nodule size (OR 1.10; $p < 0.05$). Of the 45 nodules indicated for biopsy, 24 underwent the procedure, and 5 progressed to surgery. **Conclusions:** Mobile LDCT-based screening programs showed potential in identifying high-risk nodules among underserved populations. Factors influencing biopsy decisions included nodule size, irregular or spiculated contours, LR 4B/4X classification, and PMB > 10%. Integrating PMB into LCS may improve diagnostic accuracy and biopsy decision-making, enhancing early lung cancer detection. Research Sponsor: Bristol-Myers Squibb Foundation; Boehringer Ingelheim Brazil; Diagnósticos da América S.A. (DASA); AstraZeneca Brazil; Lung Ambition Alliance; Ethicon Brazil; Panther Brazil.

Association between nodules' characteristics and biopsy indication.

Characteristic (n = 45)	OR (CI 95%; p-value)*
Irregular or spiculated contours	5.83 (2.86 - 11.88; $p < 0.05$)
Lung-RADS 4B/4X vs.4A	5.00 (1.61 - 15.54; $p < 0.05$)
PMB - %	1.05 (1.03 - 1.07; $p < 0.05$)
Nodule size - mm	1.10 (1.06 - 1.13; $p < 0.05$)

*Univariate logistic regression. OR = Odds Ratio; CI = Confidence Interval.

10541 Poster Session

Cost-effectiveness analysis of population-based screening for 6-gene panel testing for hereditary breast and ovarian cancer. First Author: Giovanni Galvis Rojas, Department of Health, Medicine and Caring Sciences (HMV), Linköping University, Linköping, Sweden

Background: Genetic testing for hereditary breast and ovarian cancer (HBOC) has relied on clinical and family history criteria. This approach, has been shown to overlook a significant number of mutation carriers who could benefit from preventative measures. Increasing evidence supports genetic testing in an unselected population, which facilitates the identification of more carriers and allows for the implementation of risk reduction strategies. The aim of this study is to evaluate the cost-effectiveness of utilising an expanded gene-panel in an unselected female population. **Methods:** A Microsoft Excel-based simulation model of a hypothetical cohort of unselected and previously untested 30 years old women was devised to assess three strategies. Strategy 1: genetic testing of unselected women for mutations of a 6-gene panel *BRCA1*, *BRCA2*, *PALB2*, *ATM*, *CHEK2* and *TP53*, Strategy 2: screening to individuals fulfilling family history (FH) criteria for HBOC testing and Strategy 3: no genetic screening. New Generation sequencing (NGS) using TrueSight hereditary cancer panel from Illumina was used as testing platform. The analysis includes quality adjusted life year (QALY) as a health outcome. The incremental cost-effectives ratio (ICER) is calculated using health-care costs and QALYs per treatment strategy, illustrating the additional cost in relation to the additional health benefit (QALYs) associated with the 6 gene-panel strategy compared to the FH-based strategy. One-way sensitivity analyses expressed as ICER, evaluates the uncertainty and the impact of specific parameters on the results. **Results:** A cohort of100 000 unselected women was simulated through the model over 80 cycles as well as women meeting criteria for HBOC investigation. The mutation carriers detected were 1307 and 191 for the unselected population group and FH respectively. As direct effect, 339 risk reducing surgeries (mastectomy or/and salpingo-oophorectomy) were performed in the strategy 1 compared with 50 in the strategy 2. The probabilistic analysis shows that if the willingness to pay is €100.000 per QALY, the unselected population-based testing has 75% probability of being cost-effective. **Conclusions:** Population-based screening with a six-gene panel has 75% probability to be cost-effective if the willingness to pay is over €100 000. This strategy reduces the number of (HBOC) cases and cancer specific mortality which strengthens the benefits of this screening strategy in cancer prevention. Research Sponsor: None.

Outcomes.

Outcomes	Scenario: Population-based	FH-based	Difference
Life years	2 713 534	2 713 369	165
QALY	2 147 507	2 147 312	196
Cost per life years gained (€)			98 079
ICER (cost per QALY gained) (€)			82 642
Costs (€)			
Screening	13 311 720	163 417	13 148 304
Risk reducing Surgery	4 557 420	666 608	3 890 812
Surveillance	45 330 899	43 413 884	1 917 015
Cancer	180 119 575	182 884 672	-2 765 098
Total Cost	243 319 615	227 128 581	16 191 034

10542 Poster Session

The potential of multi-cancer early detection screening in reducing cancer incidence and mortality in high-risk groups: A modeling study. First Author: Jagpreet Chhatwal, Massachusetts General Hospital Institute for Technology Assessment, Harvard Medical School, Boston, MA

Background: Emerging liquid biopsy multi-cancer early detection (MCED) tests have the potential to revolutionize early cancer detection. Using a simulation model, we estimated their impact on cancer incidence and mortality in high-risk groups. **Methods:** We developed Simulation Model for MCED(SiMCED), a microsimulation model of 14 solid tumor cancer types. MCED test sensitivities were derived from the ASCEND-2 case-control study. Using a 10-year horizon, we simulated the life course of 100,000 adults aged 50-84 years, representing the US general population. In addition, we simulated screening in three high-risk groups: smokers (former and current), heavy alcohol users, and individuals with a family history of cancer in ≥1 first-degree relatives (FDRs). Cancer diagnosis could arise from usual care or annual MCED screening. After a cancer diagnosis, individuals followed SEER survival curves to determine the time and cause of death (cancer- or non-cancer-related). **Results:** The table presents overall 10-year reductions in stage IV cancer incidence and mortality per 100,000. Among smokers, MCED screening had the greatest impact (in absolute reduction terms) on lung cancer, which accounted for more than 50% of late-stage incidence. Compared to usual care only, MCED screening reduced stage IV lung cancer incidence by 43% (2,028 vs 1,146) and cancer mortality by 16% (2,589 vs 2,247). Among heavy alcohol users, MCED screening had the greatest impact on lung, colorectal, and head and neck cancer. The stage IV incidence reduction in these three cancer types were, respectively, 44% (805 vs 454), 57% (286 vs 122), and 33% (398 vs 265). The cancer mortality reduction in these three cancer types were, respectively, 14% (1,014 vs 876), 33% (371 vs 248), and 16% (265 vs 223). In the familial cancer cohort, MCED screening had the greatest impact on lung, colorectal, and pancreatic cancer. The stage IV incidence reduction in these three cancer types were, respectively, 44% (821 vs 461), 57% (257 vs 111), and 58% (233 vs 98). The cancer mortality reduction in these three cancer types were, respectively, 14% (1,030 vs 888), 33% (328 vs 220), and 14% (326 vs 279). **Conclusions:** MCED screening demonstrates potential to reduce late-stage cancer incidence and mortality in both the general population and high-risk groups. These findings highlight the value of MCED tests in advancing early detection and improving cancer outcomes. Research Sponsor: Exact Sciences Corporation.

Cohort	Usual care: Stage IV cancer incidence	Usual care + MCED: Stage IV cancer incidence	Reduction: Stage IV cancer incidence	Usual care: Cancer mortality	Usual care + MCED: Cancer mortality	Reduction: Cancer mortality
General population	2,117	1,229	888 (42%)	2,612	2,149	463 (18%)
Smokers	3,523	2,034	1,489 (42%)	4,392	3,691	701 (16%)
Heavy alcohol users	2,619	1,548	1,071 (41%)	3,099	2,552	547 (18%)
Family history of cancer in ≥1 FDRs	2,365	1,360	1,005 (42%)	2,899	2,374	525 (18%)

10543 Poster Session

One-year impact of a large-scale pilot multimodal personalized early cancer detection and prevention program for individuals at high risk of cancers. First Author: Tarek Ben Ahmed, Department of Cancer Medicine, Gustave Roussy, Villejuif, France

Background: The Interception program (IP) is a unique initiative aiming to assess the value of a dedicated personalized care pathway for individuals at high risk (HR) of different cancers. IP includes identification of HR individuals in primary care, a One-Day-Clinic (ODC) (including individual care and workshops aimed at information, education, awareness; informed prevention decisions on an evidence-based shared personalized early detection and prevention plan), implementing and monitoring this plan with community professionals and MyIntercception digital follow-up. **Methods:** This prospective, cohort study analysed data from participants who entered IP between Jan 2021 and May 2023. Eligible participants were adults at high risk of breast (> 2.5% at 5 yrs), lung (> 1.6% at 5 yrs), prostate, pancreatic cancer, or Lynch syndrome. Data cut-off was June 2024. Primary endpoint was the 1-yr adherence rate to planned screening and risk-reduction measures (RRM), (the latter defined by full smoking cessation for smokers, or >1 point improvement of WCRF score for others (or stable if was >5 out of 7). Secondary endpoints were awareness of risk, screening and prevention measures, and cancer incidence. We assessed factors associated with 1-yr adherence to screening and RRM. **Results:** 719 participants were eligible for the present assessment, median age 50 (range 21-81), 80% female. 83% tertiary education, 38% active smokers, at HR of breast (360), lung (281), other (78) cancers. Median baseline WCRF score was 4 (range 0.5-7), 65% had a score < 5. At 1 yr, global adherence to both screening and RMM was 57%. Adherence to screening measures was between 82 and 100% overall. The 1-yr median WCRF score (N = 290) was 4.5 (range 1.25–7) (p = < 7.8e-07 vs baseline), 41% had improved (> = 1 point) their score while 7.4% had remained stable >5. However, only 18% smokers succeeded in fully quitting smoking. The crude incidence of new cancer cases was 1.5%. We found major improvements in perceived knowledge and in the accuracy of self-estimated cancer risk scores 8 days after the ODC (p = < 2.2 e-16). In the multivariable logistic regression analysis, increasing age was associated with higher odds of global adherence (OR = 1.02 per year, 95% CI [1.001, 1.046], p = 0.03). Male sex was associated with a trend toward increased adherence (OR = 1.7, 95% CI [0.97, 3.15], p = 0.06). Smokers had significantly lower odds of adherence compared to other risk categories (OR = 0.17, 95% CI [0.09, 0.3], $p < 0.0001$). Among smokers, male sex was significantly associated with higher odds of adherence compared to female sex (OR = 2, 95% CI [1.1, 3.6], p = 0.01). **Conclusions:** IP demonstrated promising results in promoting cancer risk reduction and achieving satisfactory adherence to screening among HR individuals. However, challenges remain, particularly in enhancing adherence to RRM and reaching less educated populations. Research Sponsor: Odyssea, Fondation Philanthropia,; Fondation Gustave Roussy, Banque des Territoires; France 2030 Tiers Lieux Numériques en santé.

10544 **Poster Session**

Clinical impact of integrating polygenic risk scores with breast cancer risk assessment models: Results from the prospective multisite GENRE-2 clinical trial. First Author: Siddhartha Yadav, Mayo Clinic, Rochester, MN

Background: Incorporation of Polygenic Risk Scores (PRS) can refine traditional breast cancer risk assessment models to provide precise estimates of breast cancer risk. However, the impact of such an integrated model on clinical decision-making related to breast cancer surveillance and preventive strategies is not fully understood. **Methods:** The GENRE-2 is a prospective single-arm multisite clinical trial (NCT04474834) incorporating PRS into standard breast cancer risk assessment models to determine the impact of PRS on clinical decisions on breast cancer prevention and surveillance. Women at high risk of breast cancer due to NCI-BCRAT 5-year risk of $\geq$ 3%, or IBIS (Tyrer-Cuzik) 10-year breast cancer risk of $\geq$5%, biopsy-proven high-risk breast lesion, or a pathogenic variant (PV) in *ATM*, *BRCA1, BRCA2, CHEK2* or *PALB2*, were enrolled from five sites in the United States. All women were invited to complete surveys on their breast surveillance and cancer prevention decisions based on pre-PRS standard risk models and post-PRS risk estimation, and further annual surveys are planned for 10 years. **Results:** Among 902 women enrolled in the study, 605 (median age: 52 years) received PRS results and completed a survey to date. Of those who received PRS results,195 (32.2%) were PV carriers. Among non-carriers, the median 10-year and lifetime pre-PRS IBIS-based risk was 10.0% and 28.7%, respectively. Among PV carriers, the CanRisk-based 10-year and lifetime pre-PRS risk estimates were 6.3% and 25.2% for *ATM*, 22.3% and 77.6% for *BRCA1*, 18.5% and 77.7% for *BRCA2*, 7.1% and 25.7% for *CHEK2*, and 16.8% and 38.0% for *PALB2* PV carriers, respectively. After the incorporation of PRS, the lifetime risk of breast cancer increased by at least 10% in 31% of non-carriers and 7.7% of PV carriers and decreased by at least 10% in 10.7% of non-carriers and 7.7% of PV carriers. The proportion of non-carriers with lifetime risk $<$ 20% or $>$ 40% changed from 17.3% and 22.0%, respectively, in the pre-PRS evaluation to 24.4% and 32.9%, in the post-PRS evaluation. A higher lifetime post-PRS score was associated with intent to take preventive action (surgery or endocrine agents). In non-carriers, the proportion of women with a lifetime risk $<$ 20% with intent to take preventive action was 11%, compared to 36.8% of those with a lifetime risk $>$ 40% ($p < 0.001$). Similarly, in PV carriers, the proportion of women with lifetime risk $<$ 20% with intent to take preventive action was 20.8% compared to 41.1% of those with lifetime risk $>$ 40% ($p = 0.015$). **Conclusions:** The GENRE-2 trial demonstrates that the incorporation of PRS into breast cancer risk assessment models in high-risk women is feasible and leads to clinically meaningful changes in breast cancer risk estimates and decision-making regarding preventive strategies. Evaluation of the implementation of breast cancer risk management strategies in study participants is ongoing and will be reported. Clinical trial information: NCT04474834. Research Sponsor: J. Christopher and Anne N. Reyes Foundation.

10545 **Poster Session**

Genetic predictors of 16,000 multi-omic traits and associations with breast cancer survival outcomes in the Pathways Study. First Author: Arya Mariam Roy, The Ohio State University, Columbus, OH

Background: Polygenic scores (PGS) enable the computation of a genetic predictor for any trait where a well-developed algorithm is available. This is appealing when such trait is not directly measured in the study population for association testing. Based on a large prospective breast cancer cohort, we calculated and investigated the prognostic value of $>$16,000 PGS of multi-omic traits, including plasma proteomics, plasma metabolomics, and whole-blood transcriptomics. **Methods:** The Pathways Study is a prospective cohort study of women with breast cancer who were enrolled soon after diagnosis in 2006-2013 at Kaiser Permanente Northern California, with ongoing follow-up. Using genome-wide genotypes from 3,995 study participants, we calculated 16,020 multi-omic PGS from the INTERVAL study (https://www.omicspred.org/). We analyzed three outcomes: overall survival (OS), breast cancer specific survival (BCSS), and disease-free survival (DFS), with a median (range) follow-up time of 10.5 (0.2-14.2) years. We derived hazard ratios (HRs) and 95% confidence intervals (CIs) for one standard deviation (sd) increment in PGS from multivariable hazards models in the total study population, among those self-reported as non-Hispanic White (NHW), and by tumor estrogen receptor (ER) status in NHW women, with multiple testing corrected by a false discovery rate (FDR) of $q<0.10$. **Results:** The median age at diagnosis was 60 (23.6-94.8) years, with the majority of the study population (68%) self-identifying as NHW. Most women had ER+ tumors (83.4%), diagnosis at stages I and II (89%), and 13.3% had HER2+ tumors. The majority (60%) had lumpectomy and adjuvant therapy (44.3% radiotherapy, 47.0% chemotherapy, 74.6% hormonal therapy). Four PGS-survival outcome tests reached statistical significance with an FDR $q<0.10$, notably all between gene expression PGS and OS, including OPGS013029 for *TINCR* in NHW patients, and OPGS011920 for *TTLL7*, OPGS009036 for *RNF4*, and OPGS011365 for *GGT7* in NHW ER- patients (Table). None of the PGS for proteomic or metabolomic traits reached this level of significance after controlling for multi-testing. **Conclusions:** By leveraging a large catalog of PGS of multi-omic molecular traits, we identified PGS for whole-blood RNA expression for four genes in significant associations with overall survival. Pending on validation in future studies, these genes may have prognostic value for breast cancer. Research Sponsor: None.

PGS of multi-omics traits and associations with OS in the pathways study.

Study population (race, ER status)	PGS	Outcome	Multi-omic trait	HR (95%CI) per sd increment of PGS	p	FDR q
NHW	OPGS013029	OS	RNA_TINCR	0.82 (0.76, 0.89)	3.01E-06	0.05
NHW ER-	OPGS011920	OS	RNA_TTLL7	1.40 (1.22, 1.60)	8.45E-07	0.01
NHW ER-	OPGS009036	OS	RNA_RNF4	1.54 (1.28, 1.85)	4.07E-06	0.03
NHW ER-	OPGS011365	OS	RNA_GGT7	1.54 (1.27, 1.88)	1.60E-05	0.09

10546 **Poster Session**

Impact of 2021 United States cancer screening guideline changes on racial and ethnic differences in patient-reported adherence to age-appropriate colorectal cancer screening. First Author: Nishwant Swami, Hospital of the University of Pennsylvania, Philadelphia, PA

Background: In 2021, the US Preventive Services Task Force and the US Multi-Society Task Force on Colorectal Cancer updated screening guidelines to recommend that average-risk colorectal cancer (CRC) screening should begin at age 45. We used nationally representative survey data to assess CRC screening among patients across racial/ethnic groups ages 45-49 and 50+ before and after the 2021 guideline changes. **Methods:** 2019-2023 biannual data from the National Health Interview Survey (NHIS) was used to select individuals aged $\geq$45 years old who responded regarding receipt of appropriate CRC screening. Patients with prior history of CRC or missing data were excluded. Survey-adjusted percentages were used to characterize differences in CRC screening adherence by racial/ethnic group. Multivariable logistic regression models adjusting for age, gender, year, marital status, and geography generated adjusted odds ratios (aORs) with 95% CI to examine associations of race/ethnicity and CRC screening adherence. **Results:** 188,620 patients met inclusion criteria. Overall, patients aged $\geq$50 had similar CRC screening prevalence before and after guideline changes (58% vs. 61% pre- and post-change) while patients aged 45-49 years had a 10% increase in appropriate screening (21% vs 31% pre- and post-change); largest screening increase was in Non-Hispanic Black (13.92% increase) and Non-Hispanic Asian patients (12.76%) while smallest increase was noted in Hispanic patients (7.05% increase). Prior to guideline changes, among patients 45-49 years old, Asian patients (aOR: 0.45 95%CI: 0.24-0.86) were less likely to report cancer screening compared to non-Hispanic White patients. After guideline changes, among patients 45-49 years old, patients identifying as Asian (aOR: 0.56 95% CI 0.34-0.92) and Hispanic (aOR: 0.62 95% CI 0.41-0.94) were less likely to report age-appropriate cancer screening compared to non-Hispanic White patients, while there was no difference for non-Hispanic Black patients (aOR: 1.31 95% CI 0.91-1.89). Year-age interaction was significant ($p <$ 0.001), while year-race interaction was not significant. **Conclusions:** Our study highlights that while patient-reported adherence to CRC screening increased among patients 45-49 years old after updated screening guidelines, screening disparities were observed among Asian and Hispanic patients. Guidelines had a distinct impact on pts aged 45-49 in relation to pts $\geq$50 who were not impacted by the changes. The time-race interaction was not significant, suggesting no evidence of improvement in the degree of disparity. Patient reported CRC screening rates after guideline changes among pts 45-49 is lagging compared to pts $\geq$50; further work is needed to implement the updated guideline recommendations and improve screening adherence. Research Sponsor: None.

10547 **Poster Session**

Bariatric surgery and risk of gastrointestinal and hormone-sensitive cancers in patients with metabolic-associated steatotic liver disease and obesity: A multicenter matched cohort study. First Author: Diptasree Mukherjee, Apex Institute of Medical Science, Kolkata, India

Background: Metabolic-associated steatotic liver disease (MASLD) is strongly associated with an increased risk of hormone-sensitive and gastrointestinal (GI) malignancies due to obesity-related pro-inflammatory states and altered hormone metabolism. Bariatric surgery (BS) has shown promise in ameliorating MASLD and obesity-related comorbidities; however, data on its potential to reduce cancer risk in this population remain scarce. Hence, we aimed to assess the impact of BS on the risk of hormone-sensitive and GI cancers in patients with MASLD and obesity using a multicenter, matched cohort design. **Methods:** We conducted a retrospective cohort study utilizing the TriNetX. Patients who underwent BS (including Roux-en-Y Gastric Bypass and Sleeve Gastrectomy) were included in the BS cohort and matched controls who are standard of care without a history of BS. We performed 1:1 propensity score matching (PSM) to reduce confounder factors, including demographics, comorbidities, BMI, nicotine dependence, and family history of malignancy. A 1-year lag time was applied to minimize protopathic bias. Cox proportional hazard analysis was performed to calculate hazard ratios (HR) for overall cancer risk, hormone-sensitive cancers (endometrial, breast, prostate, kidney, and ovarian), and GI cancers (colon, rectal, pancreatic, biliary, and hepatocellular). **Results:** A total of 9848 patients with MASLD underwent BS, while 183837 MASLD patients had no history of BS. After PSM, 9791 patients were included in each cohort. The mean follow-up was 4.8 years for BS and 5.1 years for controls. BS was associated with a significantly lower overall cancer risk (HR: 0.72 (0.65-0.80)). Among hormone-sensitive cancers, BS patients demonstrated reduced risks of endometrial (HR 0.50) and breast cancer (HR 0.62), with no significant differences for prostate, ovarian, lung, or thyroid cancer. A lower risk of kidney cancer was noted (HR 0.91). For GI malignancies, BS patients had a reduced risk of HCC (HR 0.32), malignant neoplasms of the cholangiocarcinoma (HR 0.29), pancreatic cancer (HR 0.18), and colon cancer (HR 0.53). No differences were observed for esophageal or gastric cancers. **Conclusions:** In this large multicenter analysis, BS was associated with a significantly lower risk of hormone-sensitive and GI cancers in patients with MASLD and obesity. These findings suggest that weight loss and improved metabolic profiles following surgery may mitigate the pro-inflammatory and pro-neoplastic effects of obesity and MASLD. Further research is needed to explore BS's underlying mechanisms and long-term cancer prevention benefits. Research Sponsor: None.

10548 Poster Session

Escalating burden and trend of cancer attributable to smoking in Southeast Asia, east Asia and Oceania from 1990-2021: A benchmarking systematic analysis. First Author: Abdullah Jamal, Baptist Hospitals of Southeast Texas, Beaumont, TX

Background: Cancer (CA) is a leading cause of death and disability in Southeast Asia (SEA), East Asia (EA), and Oceania. Among the various risk factors, smoking is notably the most preventable. Its strong association with various CA types underscores the urgent need for effective tobacco control measures as a cornerstone of CA prevention strategies. **Methods:** This study utilized the standardized methodology of the Global Burden of Disease Study 2021 to estimate deaths, disability-adjusted life years (DALYs), and years lived with disability (YLDs) attributable to smoking for 16 types of CA in SEA, EA and Oceania, stratified by age, sex, year, and location from 1990-2021. The results are presented in absolute counts and age-standardized rate. **Results:** The annual percentage change (APC) in the total number of deaths due to CA attributable to smoking increased by +2.64%, DALYs by +2.16%, and YLDs by +3.57% from 1990-2021. Regionally, the highest increase in APC was observed in EA, with deaths at +2.67% and DALYs at +2.14%. For age-standardized mortality rates (ASMR), highest increases in APC were observed in Indonesia (+0.81%), Kiribati (+0.02%), Marshall Islands (+0.56%), and Niue (+0.16%), while declines were observed in most other regions. By cancer type, the highest increases in APC in deaths were observed due to kidney CA (+4.43%), pancreatic CA (+3.54%), tracheal, bronchus, and lung CA (+3.45%), lip and oral cavity CA (+3.29%), and prostate CA (+3.23%). Moderate increases were observed due to colon and rectum CA (+2.87%), leukemia (+2.76%), bladder CA (+2.13%), liver CA (+1.81%), breast CA (+1.76%), larynx CA (+1.59%), esophageal CA (+1.50%), other pharynx CA (+1.35%), stomach CA (+0.83%), and cervical CA (+0.62%). Nasopharynx CA was the only type to show a slight decline (-0.03%). By age, an APC of +0.90% was observed in deaths among individuals aged 20-54 years and +2.97% among those aged 55+ years. By gender, APC for deaths were +2.69% in males and +2.18% in females, DALYs were +2.19% in males and +1.80% in females, and YLDs were +3.63% in males and +3.04% in females. **Conclusions:** Deaths due to CA attributable to Smoking accounted for 60.31% of all attributable risk factors in 2021. The observed increases in the APC in deaths, DALYs, and YLDs due to smoking-attributable cancers highlight a significant and growing public health burden, particularly in EA and among males and older age groups. These trends emphasize the need for strengthened tobacco control policies, early CA detection programs, and targeted public health interventions to address regional and demographic disparities. For clinicians, these findings underscore the importance of prioritizing smoking cessation counseling, routine CA screenings, and personalized treatment strategies to mitigate the impact of smoking-related CA. Research Sponsor: None.

10549 Poster Session

Global burden and trend of pancreatic cancer in high-income countries: A 30-year analysis of disease dynamics. First Author: Anmol Singh, Internal Medicine, John H Stroger Hospital of Cook County, Chicago, IL

Background: Pancreatic cancer (PC) has a disproportionately high impact in high-income countries (HIC), where it ranks as the 3rd leading cause of cancer-related deaths, compared to 6th globally. **Methods:** This study is the first ever systematic analysis estimating the incidence, prevalence, mortality, disability, and associated risk factors of PC across the HIC and its territories from 1990-2021. Using a standardized approach, this analysis examines data by age, sex, year, and location, using insights from the Global Burden of Disease Study 2021. The results are presented in absolute count and age-standardized rate (per 100,000). **Results:** From 1990-2021, the total prevalence counts increased from 89,475 (95% UI: 85,159–92,609) to 214,254 (95% UI: 192,172–227,351), while deaths rose from 105,828 (95% UI: 99,853–109,660) to 216,444 (95% UI: 193,299–230,784). Concurrently, disability-adjusted life years (DALYs) increased from 2.3 million (95% UI: 2.2–2.3) to 4.1 million (95% UI: 3.8–4.3). Western Europe exhibited the highest regional burden throughout the study period. Nationally, Denmark demonstrated the highest annual percentage change (APC) in the age-standardized incidence rate (ASIR) at 1.34%, followed by France (1.18%), Switzerland (0.85%), Germany (0.82%), and the United States (0.33%). Similarly, the highest APC in the age-standardized mortality rate (ASMR) was observed in Denmark (1.25%), followed by Switzerland (0.78%), France (0.73%), and the United States (0.20%). In 2021, the age group 70–74 years recorded the highest incidence (36,968; 95% UI: 34,001–38,744), mortality (34,990; 95% UI: 32,218–36,771), and DALYs (703,300; 95% UI: 646,488–738,141). Gender-specific analyses revealed that females exhibited a greater burden increase, with APCs of 0.52% in ASIR and 0.30% in ASMR, compared to 0.28% and 0.10%, respectively, in males. Notably, the age-standardized DALY rate (ASDALR) increased by 0.20% in females but decreased by 0.05% in males. **Conclusions:** Deaths due to PC accounted for 7.77% of all cancer related casualties in 2021 in HIC. The concentration of disease burden in older populations (70–74 years) and the greater increase observed in females compared to males highlight critical demographic and gender-specific disparities. Furthermore, the increase in DALYs, even in regions with stabilizing or declining mortality, calls for enhanced strategies to address long-term disability and improve quality of life. Research Sponsor: None.

Annual percentage of change in pancreatic cancer from 1990-2021 in high income region, age-standardized rate (per 100,000).

High Income Region	AAPC (%), 1990-2021, ASIR	AAPC (%), 1990-2021, ASMR	AAPC (%), 1990-2021, ASDALR
Australasia	0.38	0.15	0.01
High-income Asia Pacific	0.42	0.22	-0.01
High-income North America	0.29	0.14	0.04
Southern Latin America	-0.08	-0.14	-0.18
Western Europe	0.46	0.27	0.14

10550 Poster Session

Evaluation of a plasma cell-free DNA methylation-based multi-cancer detection test. First Author: Yupeng He, Guardant Health, Palo Alto, CA

Background: Blood-based multi-cancer detection (MCD) tests hold promise for early cancer detection. MCD tests should demonstrate high specificity, clinically meaningful sensitivity, and provide information to guide clinical diagnostic evaluation. **Methods:** We developed an MCD test that leverages a next-generation sequencing epigenomics hybrid capture assay (Shield) to measure DNA methylation in regions differentially methylated across solid tumor cancers. We then implemented a two-step classification algorithm. First, a regression model (multi-cancer classifier) was trained to distinguish cancer from non-cancer samples at 98% target specificity. Next, a cancer signal of origin (CSO) model was trained to categorize 10 solid tumors (Table 1) in samples predicted to be cancer. The test was evaluated in a blinded case-control cohort of plasma samples (3mL; Streck) from adults with treatment naïve cancer, or who were self-reported cancer free with 1 year of follow-up (NCT05334069). **Results:** Final evaluable dataset was 962 participants (excludes 31 (3.1%) that failed quality control). Median age was 62 years (range: 40-78). 55% were female. Self-reported race was 81% White. Observed specificity was 98.6% (436/442). Sensitivity for the 10 cancer types included in the CSO model was 59.7% (224/375) and was 55.7% (263/472) overall when incorporating 4 solid tumor types not included in the CSO model. Primary or secondary CSO prediction was 92% accurate for the cancer types included (Table 1). **Conclusions:** In this cohort, this MCD test shows 59.7% sensitivity, 98.6% specificity, and 92% primary or secondary CSO accuracy for the cancer types included. Integrating an MCD test with an FDA approved blood-based CRC screening test may increase the MCD clinical value in the intended use population, which should be studied further. A version of this MCD test is being studied in a prospective, interventional study evaluating MCD testing feasibility. Research Sponsor: None.

Overall and per cancer sensitivity and CSO accuracy results.

	Overall Sensitivity %	Sensitivity Stage I/II, %	Sensitivity Stage III/IV, %	Primary or Secondary CSO Accuracy, %
All Samples, 472	**56%**	**31%**	**81%**	-
Cancers included in CSO caller, 375	**60%**	**35%**	**84%**	**92%**
Bladder, 13	62%	44%	100%	75%
Breast, 86	45%	17%	88%	97%
Colorectal, 41	83%	53%	100%	91%
Esophageal-Stomach, 25	96%	100%	95%	96%
Hepatocellular, 16	94%	100%	92%	67%
Lung, 57	67%	41%	93%	97%
Ovarian, 20	70%	80%	67%	100%
Pancreas, 59	68%	50%	96%	93%
Prostate, 59	21%	3%	41%	92%
Cancers not included in CSO caller, 97	**40%**	**18%**	**65%**	
Endometrial, 29	38%	12%	75%	
Head & Neck, 15	80%	100%	63%	
Kidney, 44	34%	0%	71%	
Melanoma, 9	11%	0%	20%	

10551 Poster Session

Incidence of viral and non-viral etiologies of hepatocellular carcinoma (HCC) in the US over time by race and ethnicity. First Author: Mona Cai, AbbVie, Inc., North Chicago, IL

Background: HCC has an incidence of 5–6 cases per person-yr in the US, with varying rates among different racial and ethnic groups. While viral HCC accounts for ~50% of all HCC cases in North America, recently, a shift from viral to non-viral HCC was observed in the US. Here, we investigate the incidence of viral and non-viral HCC over time across different racial and ethnic groups in the US. **Methods:** This is a cross-sectional study using data from the TARGET-HCC registry, a longitudinal observational cohort study enrolling adult patients (pts) with newly diagnosed HCC across 43 academic and community centers in the US. Pts were enrolled from 1 Jan 2017 to 30 Sep 2023, and consented to share medical records 36 mo retrospectively and prospectively for up to 60 mo. **Results:** Among 2,924 enrolled pts, etiology was available for 2,139 (73%). Median (IQR) age was 64 (59, 68) yr and 77% were male. At HCC diagnosis, 66% of pts had BCLC stage 0/A, 16% BCLC B, 13% BCLC C, and 6% BCLC D; 69% of pts had Child-Pugh class A, 26% class B, and 5% class C. 1,727 (81%) pts had underlying cirrhosis. 1,484 (72%) pts were White, 414 (20%) Black/African American (Black/AA), 86 (4%) Asian/Native Hawaiian or Pacific Islander (Asian/NH/PI), and 68 (3%) American Indian/Alaskan Native. 1,786 (87%) pts were of non-Hispanic ethnicity and 257 (13%) of Hispanic ethnicity. The incidence of viral and non-viral HCC over time by race and ethnicity is shown in the Table. In the overall population, although the incidence of viral HCC decreased over time, it remained higher than that of non-viral HCC across all periods. The proportion of pts diagnosed with viral vs non-viral HCC was 75% vs 59% in 2014–2016, 69% vs 55% in 2017–2019, and 65% vs 57% in 2020–2023. **Conclusions:** Despite variations in the number of pts enrolled in each period, there is an overall trend of decreasing incidence of viral HCC over time across all racial groups. The incidence of viral HCC has declined among non-Hispanics but increased among Hispanics. Nevertheless, non-viral liver disease remains the most common cause of HCC in Hispanics. Research Sponsor: AbbVie Inc.; n/a.

	2014–2016			2017–2019			2020–2023		
Race (R)/Ethnicity (E)[a]	Total, N	Viral, n (%)	Non-Viral, n (%)	Total, N	Viral, n (%)	Non-Viral, n (%)	Total, N	Viral, n (%)	Non-Viral, n (%)
Overall, N=2138[b]	545	411 (75)	324 (59)	1441	994 (69)	793 (55)	152	99 (65)	87 (57)
R: White	371	253 (68)	241 (65)	1003	631 (63)	608 (61)	110	66 (60)	71 (65)
R: Black/AA	114	111 (97)	53 (46)	268	243 (91)	97 (36)	32	29 (91)	9 (28)
R: Asian/NH/PI	25	23 (92)	9 (36)	61	46 (75)	26 (43)	0	0	0
R: American Indian/ Alaska Native	12	9 (75)	5 (42)	55	37 (67)	32 (58)	1	0	1 (100)
E: Non-Hispanic	454	352 (78)	263 (58)	1210	842 (70)	658 (54)	121	78 (64)	66 (55)
E: Hispanic	62	35 (56)	43 (69)	174	107 (61)	109 (63)	21	14 (67)	16 (76)

The percentage may add to more than 100 because pts have mixed etiologies.
[a]Etiology for 7 pts of "Other" ethnicities: 2 viral in 2014–2016; 4 viral and 3 non-viral in 2017–2020.
[b]1 pt diagnosed ≤2013 not included.

10552 **Poster Session**

Early-onset (EO) cancer trends in Brazil: A comprehensive analysis of hospital-based cancer registry data (2000–2019). First Author: Wesley Rocha Grippa Sr., Universidade Federal do Espírito Santo, Vitoria, Brazil

Background: The rising incidence of early-onset (EO) cancers (< 45 years) since the 1990s presents a global public health challenge. In Brazil, Hospital-Based Cancer Registries (HCR) provide essential data for understanding cancer epidemiology, encompassing diagnosis, treatment, and outcomes. This study analyzes temporal trends in EO cancer incidence rates (IR) and clinical data in Brazil from 2000 to 2019. **Methods:** A retrospective cohort study was conducted using data from the Brazilian HCR system (SIS-RHC). Individuals aged 19–44 years, diagnosed with malignant neoplasms (ICD-10) and treated within Brazil's oncology network, were included. Temporal trends in cancer incidence (2000–2019) were evaluated using the Mann-Kendall test, and bivariate analyses explored associations between demographic and clinical variables. **Results:** A total of 701,115 individuals were included (mean age: 35 years, SD: 6.62); the cohort was predominantly female (71.9%), non-white (54%), with basic education (49%), and residing in the southeast region (44%). Family history of cancer was reported by 47%, alcohol use by 28%, and smoking by 29%. The Unified Health System (SUS) referred to 79% of cases. Breast (21%) and cervical (21%) cancers were the most prevalent malignancies, followed by non-melanoma skin cancers (8.8%) and thyroid cancer (7.3%). Colon cancer ranked seventh (2.8%). Most cases were diagnosed at localized stages (51.7%), with 28.3% regional and 19.8% metastatic. Localized diagnoses increased significantly over time. Sex differences were observed across age groups and cancer stages ($p < 0.001$). Annual cancer cases rose significantly from 93,714 cases (2000 to 2004) to 222,301 cases (2015 to 2019) ($p < 0.001$). Incidence rates (IR) increased with age and over time, rising from 5.65 (ages 19–24) and 46.80 (ages 40–44) in 2000 to 12.28 and 77.11 in 2019. Peaks in IR were observed in 2014 and 2016, reaching 17.41 (ages 19–24) and 111.42 (ages 40–44). Overall, reported cases increased by 219% during the study period. **Conclusions:** The incidence of EO cancers in Brazil rose by 219% between 2000 and 2019, with breast cancer as the leading malignancy. These findings emphasize the growing cancer burden among younger populations and the need for enhanced cancer registries to guide targeted EO interventions. Future population-based studies are critical to validate and expand upon these results. Research Sponsor: Fundação de Amparo à Pesquisa e Inovação do Espírito Santo (FAPES); 155/2021.

10553 **Poster Session**

Evaluation of a polygenic risk score for breast cancer in Chinese women: A three-stage case-control study of 13,715 subjects. First Author: Yuxiang Lin, Fujian Medical University Union Hospital, Fuzhou, Fujian, China

Background: Polygenic risk score (PRS) is a valuable tool for predicting the risk of breast cancer (BC). However, limited studies have been conducted in Chinese women. This study aimed to develop and validate a PRS which could be used to identify individuals with high risk of breast cancer. The associations between the PRS and patients' clinicopathological characteristics or survival outcomes were also evaluated. **Methods:** The PRS was developed based on findings from genome-wide association studies (GWAS) and validated in four independent cohorts with a three-stage design. A total of 7,056 patients and 6,659 controls were enrolled from Fujian Medical University Union Hospital (FJMUUH) and Shanghai Breast Cancer Genetics Study (SBCGS). Five approaches were utilized to calculate the PRS, including repeated logistic regression (RLR), logistic ridge regression (LRR), artificial neural network (ANN), random forest (RF) and support vector machine (SVM). Logistic regression analyses were performed to assess the association between established PRS and clinicopathological characteristics. The correlation between PRS and patients' survival outcomes was evaluated by cox regression models. **Results:** The LRR-based PRS was indicated to have the best predictive accuracy among five approaches (AUC = 0.601, OR per 1 SD increase = 1.39, Table 1). Women in the top 5% and 80-95% percentiles of PRS had a 1.43-fold and a 1.34-fold elevated risk of developing breast cancer compared with those at average risk (PRS in 40-60th percentiles). The predictive performance of PRS for patients with HER-2 positive tumors was demonstrated to be higher than that of HER-2 negative tumors (AUC = 0.612 vs 0.585, OR = 1.47 vs 1.35). It was also identified that the PRS was not correlated with age at diagnosis nor tumor characteristics. In survival analyses, an increase in PRS was associated with unfavorable disease-free survival (DFS) for ER negative patients (HR = 1.48, 95% CI = 1.08-2.03, p= 0.016). However, this association diminished after adjusting for clinicopathological characteristics. Regarding overall survival (OS), we observed significant correlations between increased PRS and overall survival (adjusted HR = 1.35, 95% CI = 1.05-1.75, p= 0.021), especially among ER negative patients (adjusted HR = 1.57, 95% CI = 1.07-2.30, p= 0.021) in the multivariate model. **Conclusions:** The PRS could provide additional information for Chinese women at high risk of breast cancer and holds significant value for BC screening. An increase in PRS also indicates an unfavorable prognosis and could play a crucial role in the clinical management of breast cancer patients at the time of diagnosis. Research Sponsor: None.

10554 **Poster Session**

Trends in cancer incidence in Singapore over the last two decades. First Author: Hui Miao, National University of Singapore, Singapore, Singapore

Background: Singapore has witnessed a significant rise in cancer incidence over recent decades. The most rapid increase in age-specific incidence of cancer was observed among younger age group in recent years. Gaining insight into the factors driving this trend is essential for developing prevention strategies. **Methods:** This population-based study analysed 268,189 cancer cases diagnosed between 2000 and 2021 from the Singapore Cancer Registry via the TRUST platform (https://trustplatform.sg/). Cases diagnosed in 2020 and 2021 were subsequently excluded from the trend analysis due to potential COVID-19 effects. We first examined the temporal trend of age-standardized incidence rate and estimated average annual percentage changes (AAPC) using Joinpoint regression analysis. Decomposition analysis was performed to assess the increase in cancer cases attributable to changes in population age structure, population size, and cancer risk due to epidemiological factors. We conducted an Age-Period-Cohort analysis to estimate the net drift, local drift, and the cohort- and period-specific incidence rate ratio (IRR). These analyses were repeated for the four most common cancers in Singapore: breast, colorectal, lung and prostate cancer. **Results:** Over the 22-year period, the number of cancer cases nearly doubled for both men and women. The age-standardized incidence rate rose from 200.77 per 100,000 to 246.43 per 100,000 for women and remained stable at 235.30 per 100,000 for men. The AAPC was 0.92% (0.73%-1.15%) for women and 0.13% (-0.01%-0.30%) for men, and was the largest for female breast and prostate cancer. Decomposition analysis showed that aging population was the primary driver for an overall increase in cancer cases, whereas change in cancer risk had the highest impact for breast cancer, prostate cancer and lung cancer in men. The Age-Period-Cohort analysis revealed significant period and birth cohort effects with a net drift of 1.17% (0.90% - 1.43%) for women and 0.78% (0.54% - 1.05%) for men. For breast cancer, both birth cohort and period effects showed an increasing trend [IRRcohort1990vs1950 = 1.47 (0.98-2.22), IRRperiod2015vs2000 = 1.24 (1.17-1.31)]. A similar trend was observed for prostate cancer [IRRcohort1970vs1935 = 3.42(1.83-6.38), IRRperiod2015vs2000 = 1.74(1.59-1.92)]. In contrast, a decreasing trend was noted for lung cancer in men [IRRcohort1970vs1945= 0.65(0.48-0.87), IRRperiod2015vs2000 = 0.76 (0.70-0.82)]. **Conclusions:** The rising cancer incidence in Singapore is multifactorial, with demographic factors, particularly an ageing population, playing a significant role. Our analysis revealed important temporal patterns and a notable rise in cancer risk for breast and prostate cancers, likely influenced by shifts in environmental and lifestyle factors, and cancer screening. These insights should be used to inform and guide future public health policies aimed at addressing modifiable risk factors. Research Sponsor: Singapore Translational Cancer Consortium.

10555 **Poster Session**

Racial differences in the association between agent orange exposure and the progression of monoclonal gammopathy of undetermined significance to multiple myeloma in US Veterans. First Author: Lawrence W. Liu, St. Louis Veterans Affairs Medical Center, St. Louis, MO

Background: Agent Orange (AO), an herbicide used during the Vietnam War Era (1/9/1962-5/7/1975), is implicated in myelomagenesis due to 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD). TCDD has a long half-life (3.2 years) and many occupations (e.g. pest control, agricultural, etc) are exposed. Work from our group (Liu L, et al., *JHO* 2024) demonstrated that AO exposure during the high TCDD period of 1/9/1962-11/30/1965 was associated with increased risk of monoclonal gammopathy of undetermined significance (MGUS) to myeloma (MM) progression. Given the higher incidence of MM in Black patients, we assessed whether there are racial differences in this association. **Methods:** We identified patients diagnosed with MGUS from 10/1/1999-12/31/2021 in the Veterans Health Administration. a published natural language processing-based algorithm was used to confirm diagnoses of MGUS and MM. We excluded: progression<1y, non-IgG/IgA subtype, race other than Black or White due to low numbers, no service during 1/9/1962-5/7/1975, and birth years outside of 1924-1953 so that the groups with and without exposures both have the same birth year range. Patients were stratified by race (Black or White). AO exposure was stratified by three TCDD levels: high (1/9/1962–11/30/1965), medium (12/1/1965–12/31/1970), or low (1/1/1971–5/7/1975). The association between AO exposure levels and progression were estimated using multivariable Fine-Gray subdistribution hazard model with death as a competing event and presented by multivariable-adjusted hazard ratio (aHR). The covariates included age, sex, body mass index (BMI), monoclonal protein (M-protein) level, MGUS subtype, and Charlson Comorbidity Index (CCI). **Results:** We identified 3,960 Black patients (AO exposed: n=865 [21.8%]) and 6,887 White patients (AO exposed: n=1,986 [28.8%]) with MGUS. Compared to no exposure: Black patients had aHR 1.03 (95% CI 0.51-2.06) for high, aHR 0.88 (95% CI 0.65-1.17) for medium, and aHR 0.3 (0.08-1.18) for low exposure, and White patients had aHR 1.80 (95% CI 1.14-2.83) for high, aHR 1.18 (95% CI 0.95-1.46) for medium, and aHR 1.17 (95% CI 0.66-2.05) for low exposure. **Conclusions:** White patients had an 80% increased risk of progression with AO exposure during the high TCDD period. No association was observed in Black patients. Research Sponsor: National Cancer Institute; R01 CA253475; National Cancer Institute; CA265735.

Multivariable analysis of the association between AO exposure and risk of progression to MM by race.

Variable	Black (N=3,960) aHR (95% CI)	P-value	White (N=6,887) aHR (95% CI)	P-value
AO Exposure				
No exposure	**ref.**		**ref.**	
Low TCDD Level	0.30 (0.08-1.18)	0.08	1.17 (0.66-2.05)	0.59
Medium TCDD Level	0.88 (0.65-1.17)	0.37	1.18 (0.95-1.46)	0.14
High TCDD Level	1.03 (0.51-2.06)	0.94	1.80 (1.14-2.83)	0.01

The covariates included age, sex, MGUS subtype, BMI, m-protein, and CCI at MGUS diagnosis.

10556 **Poster Session**

Lung cancer combined with interstitial lung disease: Controversial role of preexisting hypertension and emphysema observed in a fully followed 20-year patient cohort. First Author: Zhichao Wang, Affiliated Hospital of Nanjing University of Chinese Medicine, Nanjing, China

Background: The coexistence of interstitial lung diseases (ILD) and lung cancer (LC) presents a clinical challenge. ILD, including idiopathic pulmonary fibrosis (IPF) and non-IPF entities, is associated with an elevated risk of LC. However, the clinical features, treatment patterns, and survival outcomes of ILD-LC, especially IPF-LC, remain underexplored. We aimed to comprehensively evaluate survival outcomes and risk factors for mortality of ILD-LC patients based on a real-world long-term clinical cohort. **Methods:** A total of 1,341 eligible patients for this study were drawn from the Epidemiology and Genetics of Lung Cancer research program database (Mayo Clinic) including 96 IPF-LC, 111 Non-IPF ILD-LC, 99 ILD-only, and 1,035 propensity-matched LC-only patients (Controls). Data were collected on demographics, comorbidities, tumor features, treatment, and patient outcomes. Survival analyses used Kaplan-Meier methods; risk factors were assessed via Cox Proportional Hazards models. All comparisons reported below were statistically significant with p-values≤0.001 unless specified. **Results:** Among the 20,470 primary LC patients who were diagnosed from 1997 through 2016 and followed to 2021, 207 (1.0%) had ILD-LC, of which 96 (46.4%) had IPF. Comparing to Controls, ILD-LC patients were 4 years older at the time of LC diagnosis, 63.8% (vs. 52.8%) male, had a higher rate of former smokers (60.4% vs. 47.3%), a lower proportion of adenocarcinoma (37.7% vs. 57.5%), and a higher proportion of squamous cell (28.0% vs. 20.3%) and small cell carcinoma (13.5% vs. 8.4%). Although no significant differences in either LC stage or grade, ILD-LC patients had a significantly higher mortality rate (90.3% vs. 78.8%), particularly among IPF-LC patients (97.9% vs. 83.8%). ILD-LC patients were less likely to undergo surgery or receiving pharmacological treatments (73.9% vs. 93.5%). The median 5-year overall survival rate (OS, months) were 49.5 for Controls, 35.2 for Non-IPF ILD-LC patients, and 15.9 for IPF-LC patients. Analysis of six most common comorbidities revealed that pulmonary hypertension was associated with worse OS in ILD-LC patients compared to those without it (11.9% vs. 20.1%, $P < 0.05$); however unexpectedly, hypertension in ILD-LC patients was associated with better OS (21.3% vs. 14.4%) and emphysema in IPF-LC patients with better OS (7.9% vs. 3.4%, $P < 0.05$) when compared to those without the two comorbidities, respectively. **Conclusions:** This study highlights the poorer survival outcomes in ILD-LC patients, particularly IPF-LC patients, emphasizing the need for further investigation into optimized therapies and comorbidity management. Our findings also call for attention to two unexpected associations of hypertension and emphysema, warranting in-depth research on the possible biological and physiological mechanisms. Research Sponsor: U.S. National Institutes of Health; R03 CA77118, R01 CA80127, R01 CA84354; National Institute on Aging; R01 AG034676, R01 AG052425; Mayo Clinic Foundation.

10557 **Poster Session**

GLP-1 receptor agonists and breast cancer risk in type 2 diabetes. First Author: Guo Cheng, Greater Baltimore Medical Center, Baltimore, MD

Background: Type 2 diabetes mellitus (T2DM) is associated with an increased risk of breast cancer. Glucagon-like peptide 1 receptor agonists (GLP-1RAs), which improve glucose metabolism and promote weight loss, are widely used to treat T2DM. However, the trophic activity of GLP-1RAs is concerning. In diabetic patients, GLP-1 receptors are highly expressed in breast cancer tissues and their activation can lead to breast cancer cell proliferation. Combining GLP-1RAs and dipeptidyl-peptidase IV inhibitors (DPP4i), which also enhance GLP-1 pathway, was associated with more cases of breast cancer in the FDA Adverse Event Reporting system. We investigated the relationship of GLP-1RAs with breast cancer in T2DM patients using Epic Cosmos, a HIPPA law-compliant dataset with longitudinal records of 289 million de-identified patients. **Methods:** A retrospective cohort study was performed on patients with T2DM but without breast cancer. Patients treated with GLP1-1RAs between 1/1/2010 and 12/31/2020 were compared to those treated with metformin, sodium-glucose cotransporter-2 inhibitor (SGLT2i), sulfonylurea (SU), DPP4i, thiazolidinediones (TZD) or insulin. The incidence of breast cancer was tracked from 1/1/2021 to 12/12/2024. Subgroup analysis was conducted on White patients, African American patients, and five subgroups with different BMI ranges. Risk ratio (RR) and 95% confidence interval (CI) were calculated via RStudio (version 2024.09.1). **Results:** Patients with T2DM and treated with GLP-1RAs had a higher incidence of breast cancer compared to patients treated with each of the other antidiabetics (Table). Results of subgroup analysis were consistent with the overall effect; except that in the obese subgroups, GLP-1RA exposure was not associated with breast cancer compared with DPP4i. Weight and age were not significantly different between each pair of cohorts. **Conclusions:** GLP-1RAs was associated with an increased incidence of breast cancer compared to other antidiabetic regimens in patients with T2DM in a long-term observation. Acting on identical pathway, GLP-1RAs may show a blunt effect versus DPP4i in obese patients. The study is empowered by an enormous sample size in Epic Cosmos. Future improvements include stratifying exposure levels and stringently matching confounders. Research Sponsor: None.

GLP-1RAs cohorts	Non-GLP-1RAs cohorts	GLP-1RAs cohorts cancer cases (%)	Non-GLP-1RAs cohorts cancer cases (%)	RR (95% CI)
(-) Metformin (N=209090)	(+) Metformin (N=4989038)	1406 (0.67%)	25037 (0.50%)	1.34 (1.27-1.41)
(-) SGLT2i (N=639303)	(+) SGLT2i (N=826786)	4014 (0.63%)	4380 (0.53%)	1.19 (1.14-1.24)
(-)SU (N=497603)	(+) SU (N=2465377)	3109 (0.63%)	11271 (0.46%)	1.37 (1.31-1.42)
(-)DPP4i (N=716984)	(+) DPP4i (N=1123264)	4220 (0.59%)	5966 (0.53%)	1.11 (1.07-1.15)
(-)TZD (N=838249)	(+) TZD (N=464680)	5212 (0.62%)	2141 (0.46%)	1.35 (1.28-1.42)
(-) Insulin (N=467130)	(+) Insulin (N=2757742)	2921 (0.63%)	9895 (0.36%)	1.74 (1.67-1.82)

10558 **Poster Session**

Unmasking the link between sleep apnea and lung cancer risk: A retrospective propensity-matched cohort study. First Author: Mohammed Al-Nusair, MedStar Washington Hospital Center, Washington, DC

Background: Obstructive sleep apnea (OSA) is a prevalent disorder characterized by intermittent hypoxia, systemic inflammation, hypercapnia, and oxidative stress. These factors pose a risk for carcinogenesis and potential tumor formation. The association between OSA and lung cancer remains unclear. This study evaluates the impact of OSA on lung cancer incidence using a large-scale retrospective cohort analysis. **Methods:** A comparative outcomes analysis was conducted using the TriNetX database. Data were extracted from the Johns Hopkins Medicine healthcare organization. Two cohorts were defined: patients with OSA (Cohort 1, n = 124,100) and those without OSA (Cohort 2, n = 2,330,110). Propensity score matching (PSM) was employed to balance baseline characteristics, including age, gender, race, and comorbid conditions, resulting in 62,750 in each cohort. The primary outcome was lung cancer incidence (ICD-10: C34), with risk difference (RD), risk ratio (RR), and odds ratio (OR) calculated to compare the cohorts. Statistical significance was set at $p < 0.05$. **Results:** Before propensity score matching, the OSA cohort had a higher mean age (60.8 $\pm$ 16.6 vs. 51.8 $\pm$ 20.3 years) and a higher prevalence of comorbid conditions such as obesity, hypertension, and diabetes compared to the non-OSA cohort (all $p < 0.001$). After PSM, demographic and clinical characteristics were well-balanced between cohorts. In the matched analysis, the incidence of lung cancer was slightly higher in the OSA cohort at 0.8% (n = 530) compared to 0.7% (n = 440) in the non-OSA cohort. The RD was 0.1% (95% CI: 0.0%-0.2%, p = 0.004 via T-Test), and the RR was 1.205 (95% CI: 1.062-1.366). The OR for lung cancer in OSA patients relative to non-OSA patients was 1.206 (95% CI: 1.063-1.369). Kaplan-Meier survival analysis showed a modestly reduced time to lung cancer diagnosis in the OSA cohort, although the difference was not clinically significant. **Conclusions:** This study reveals a statistically significant association between OSA and lung cancer risk. Subsequent studies are needed to investigate the degree of clinical significance between OSA and lung cancer. OSA patients may benefit from screening and/or early intervention strategies. Additionally, further research is needed to elucidate the potential mechanism and pathogenesis of lung cancer formation in OSA patients. Research Sponsor: None.

Lung cancer incidence and associated risk estimates in patients with and without OSA.

Cohort	Lung cancer incidence	RD	RR	OR
OSA (n=62,750)	0.8% (n=530)	0.1% (95% CI: 0.0%-0.2%, p = 0.004	1.205 (95% CI: 1.062-1.366)	1.206 (95% CI: 1.063-1.369)
Non-OSA (n=62,750)	0.7% (n=440)			

10559 **Poster Session**

Exposure to Di-2-ethylhexyl phthalate and hormone receptor-positive breast cancer incidence. First Author: Lijuan Tang, Department of Head and Neck Surgery, Sichuan Clinical Research Center for Cancer, Sichuan Cancer Hospital & Institute, Sichuan Cancer Center, School of Medicine, University of Electronic Science and Technology of China, Chengdu,China, China

Background: Phthalates are ubiquitous environmental endocrine disruptors. As the predominant phthalate, di-2-ethylhexyl phthalate (DEHP) has been considered possibly carcinogenic to humans but large-scale longitudinal evidence is needed to further clarify its carcinogenicity. Up to date, no study have examined the in-situ DEHP exposure in breast cancer, in comparison with normal breast tissue or benign breast tumor.The present study aims to examine the association between DEHP exposure and incidence of hormone receptor-positive breast cancer (HR+BC) , both in a large cohort and in a group of patients whose in-situ DEHP exposure was analyzed. **Methods:** In 116,885 women of UK Biobank cohort, diagnosis of HR+BC was ascertained using general practitioner prescription records and information from National Health Service Cancer Registry and National Death Index. Baseline and yearly-average level of external DEHP exposure via water were estimated for each individual by linking chemical monitoring record of European Environment Agency with home address of the participants by Kriging interpolation model. We used Cox proportional hazards regression to estimate the association between DEHP exposure by water and risk of breast cancer. Furthermore, in-situ internal exposure level of DEHP in tumor tissue and normal breast tissue in 67 Chinese women with HR+BC or benign tumors was quantified using high performance liquid chromatography-tandem mass spectrometry (HPLC-MS/MS), then binary Logistic regression was used to explore whether the in-situ DEHP level was higher in HR+BC compared to benign tumor or normal breast tissues. **Results:** In the UKB cohort women, during a median of 13.5 years follow up, the fourth quartile of baseline DEHP was associated with 1.20 fold risk of HR+BC (95% CI, 1.1 to1.4, $P < 0.001$). As for yearly-average exposure, each quartile of DEHP was positively associated with higher risk of HR+BC (HR, 1.12; 95% CI, 1.1 to 1.17, $P_{trend} < 0.001$). The fourth quartile of yearly-average DEHP was associated with 1.52 fold risk of HR+BC (95% CI, 1.31 to 1.78, $P < 0.001$). No significant association was found between DEHP exposure and hormone receptor-negative breast cancer (P = 0.294). In the Chinese women, the overall detection rate of DEHP (detected in any tissue type) in HR+BC women was significantly higher than in women with benign tumors (96.2% V.S. 7.1%, $P < 0.001$), and the detection rate of DEHP in breast cancer tissues was higher than in benign tumor tissue (55.7% V.S. 4.5%, $P < 0.001$). Logistic regression showed that breast cancer tissue was associated with a higher risk of DEHP contamination compared with benign tumor tissue (OR,11.77; 95% CI, 1.20 to 115.25, P = 0.034). **Conclusions:** Real-world level of DEHP exposure was associated with higher risk of HR+BC. The results may be crucial for effective and precise prevention of breast cancer. Research Sponsor: Chongqing Science and Technology Commission; 2024NSCQ-KJFZMSX0314; Daping hospital; ZXAIYB014.

10560 Poster Session

Burden and trend of breast cancer attributable to high red meat consumption in the United States from 1990-2021: An insight from the Global Burden of Disease study 2021. First Author: Shivani Modi, Albert Einstein Healthcare Network, Philadelphia, PA

Background: Breast Cancer (BC) 4th most common cause of cancer in the United States (USA). In the USA, dietary factors, particularly high red meat consumption, have been implicated in the increased risk of breast cancer among women. Studies suggest that red meat intake is associated with a higher incidence of breast cancer, possibly due to carcinogens formed during cooking at high temperatures. **Methods:** We estimated incidence, deaths and disability-adjusted life years (DALYs), Years lived with disability (YLDs) due to BC attributable to diet high in red meat by age, year, location across the USA from 1990-2021 using global burden of disease study 2021. **Results:** The total percentage change (TPC) in deaths increased by 9% (range: -59% to 54%), while DALYs rose by 1% (range: -47% to 51%) from 1990 to 2021. At the sub-national level, the highest TPC in deaths was observed in Nevada, with a 148% increase, followed by Utah (80%), Alaska (69%), and Arizona (68%) over the same period. In contrast, the District of Columbia experienced the largest decrease, with a 39% reduction in deaths. Age-wise, the highest number of deaths in 2021 occurred in the 70–74-year age group, with 968 cases, while the 60–64-year age group recorded the highest number of DALYs at 26,627. Among individuals aged 55 years and older, there were 6,253 deaths (range: -2,860 to 13,435), while those aged 20–54 years recorded 1,056 deaths (range: 400 to 2,267). Regarding DALYs, the 20–54-year age group accounted for 52,503 (range: -19,790 to 114,305), and the 55+ age group contributed 142,073 (range: -70,770 to 303,577) in 2021. **Conclusions:** The results underscore the importance of widespread education campaigns promoting healthier dietary patterns, policy interventions to encourage reduced red meat consumption, and targeted prevention strategies for at-risk populations. Clinically, these findings emphasize the critical role of healthcare providers in integrating dietary risk assessments and personalized nutritional counseling into routine care. By addressing this modifiable risk factor, both public health initiatives and clinical practices can work synergistically to reduce the burden of BC, improve patient outcomes, and advance preventive care strategies. Research Sponsor: None.

10561 Poster Session

Recent trends in cancer distribution and survival outcomes among adolescent and young adult patients: A national data analysis. First Author: Fatma Nihan Akkoc Mustafayev, Miami Cancer Institute, Baptist Health South Florida, Miami, FL

Background: Cancer distribution varies significantly among adolescents and young adults (AYAs) aged 15 to 39. Understanding these trends is essential for developing strategies to enhance early detection and improve survival outcomes. This study analyzes national data to assess time-bound changes in new cases and survival outcomes within the AYA population. **Methods:** A retrospective cohort study was performed using the National Cancer Database to analyze AYA patients diagnosed with the 20 most common cancer types by mortality from 2004 to 2021. Patients with confirmed malignant neoplasms, ≥6 months of follow-up, and known survival status were included. Descriptive statistical methods were used to evaluate demographic characteristics, while survival outcomes were analyzed using Kaplan-Meier estimates and multivariable Cox proportional hazard models. Linear regression models were used to analyze changes in new cases over time for each cancer group. **Results:** A total of 637,460 AYA cancer patients were included in the analysis. The median age was 33 years (IQR: 27-37). Most were female (61.5%) and White (79.6%). Breast cancer was the most common malignancy (21.3%), followed by central nervous system (CNS) tumors (11.6%), melanoma (9.3%), testicular cancer (8.5%) and colorectal cancer (CRC, 6.9%). Between 2004 and 2021, CRC, leukemia, liver, pancreatic, renal, stomach, and uterine cancers showed significant increases in new cases ($P < 0.001$), with CRC having the highest increase (annual rate change [β]:1.7, $P < 0.001$). Bladder, Hodgkin lymphoma (HL), melanoma, cervical and lung cancer significantly decreased ($P < 0.001$), with melanoma showing the largest decline (β: -1.83, $P < 0.001$). Breast, CNS, and ovarian cancers showed no significant trends. Among AYA cancer patients, the survival rate at 3 and 6 years were 89.2% and 83.9%, respectively. The overall survival rate at 12 years was 78.1%, with the highest survival rates observed in testicular cancer (93.1%), HL (91.4%) and melanoma (90.8%), and the lowest in liver (38.6%) and stomach cancer (41.3%). AYA cancer patients aged 35–39 (HR: 1.28, 95% CI:1.25-1.30, $P < 0.001$), Black (HR: 1.47, 95% CI: 1.45-1.5, $P < 0.001$), and Hispanic individuals (HR: 1.03, 95% CI: 1.01-1.05, P= 0.003) had worse survival outcomes. **Conclusions:** Our findings indicate that the proportion of AYAs diagnosed with certain cancers, such as colorectal, liver, renal and stomach cancers, has significantly increased over the past two decades. Prioritizing early detection and tailored treatment strategies are crucial to addressing this growing challenge. Further research is needed to understand the underlying factors contributing to these trends. Research Sponsor: None.

Annual rate changes in cancer distribution.

Cancer group	β	P
↑Trends		
CRC	1.7	<0.001
Renal	0.63	<0.001
Uterus	0.53	<0.001
↓Trends		
Melanoma	-1.83	<0.001
HL	-0.84	<0.001
Cervical	-0.66	<0.001

10562 Poster Session

Epidemiology of *MET* gene mRNA expression in metastatic colorectal cancer: Analyses of a real-world clinicogenomic database. First Author: Gregory Sampang Calip, University of Southern California, Los Angeles, CA

Background: The *MET* proto-oncogene encodes the c-Met protein and is associated with promotion of tumor growth, angiogenesis, metastasis, and drug resistance. Our objective was to describe the prevalence of increased corresponding to c-Met protein expression and its associations with demographic and clinical characteristics among patients with metastatic colorectal cancer (mCRC) in a US-based clinicogenomic database. **Methods:** We conducted a retrospective cohort study of patients diagnosed with mCRC between 2014 and 2023 using the ConcertAI Patient360 electronic health record database with linkage to Caris Life Sciences genomic data. Patients were followed from first-line therapy (index time) until death or end of study follow up (Jan 2024). A 5-fold cross-validated and cross-cohort tested machine learning classifier trained on c-Met protein immunohistochemistry (IHC) labels (defined as 3+, ≥10% staining) was applied to derive prevalence of increased MET gene mRNA expression from whole transcriptome sequencing. Prevalence rate ratios (RR) with 95% confidence intervals (CI) were calculated using modified Poisson regression. **Results:** From an overall cohort of 1,020 patients with mCRC with a median age of 63 at metastatic diagnosis, 46% were female and 70% were non-Hispanic White, 20% non-Hispanic Black, 1% non-Hispanic Asian, and 5% Hispanic. At mCRC diagnosis, 81% had an ECOG performance status of 0-1 and 71% were diagnosed with de novo metastatic disease. The overall prevalence of increased MET gene mRNA expression corresponding to 3+, ≥10% c-Met IHC staining in the cohort was 35% (95% CI 32-38) and most samples (84%) were collected prior to treatment initiation. Patients with and without increased expression at this cutoff were broadly similar with respect to demographic and clinical characteristics. However, trends suggested that patients with increased expression had greater representation of individuals that were ages ≥75 years, non-Hispanic Black, had body mass index (BMI) <18.5 kg/m2, ECOG of ≥2, colon as primary tumor site and were microsatellite stable. **Conclusions:** Increased MET gene mRNA expression was observed among 35% of patients with mCRC in our cohort and was correlated with older age, low BMI at metastatic diagnosis, non-Hispanic Black race/ethnicity, poor performance status, colon as primary site, and microsatellite stable tumors. Research Sponsor: AbbVie.

		Prevalence	RR (95% CI)			Prevalence	RR (95% CI)
Age, years	<45	32%	REF	Race/ethnicity	NH White	35%	REF
	45-54	34%	1.06 (0.75, 1.50)		NH Black	40%	1.12 (0.92, 1.36)
	55-64	33%	1.03 (0.73, 1.46)	ECOG	0	34%	REF
	65-74	35%	1.07 (0.77, 1.50)		1	35%	1.03 (0.85, 1.24)
	≥75	42%	1.30 (0.93, 1.83)		≥2	44%	1.29 (1.00, 1.68)
BMI (kg/m^2)	<18.5	53%	1.47 (1.03, 2.10)	Primary site	Rectum	29%	REF
	18.5-24.9	36%	REF		Colon	37%	1.29 (1.03, 1.62)
	25.0-29.9	35%	0.96 (0.78, 1.19)	MSS/MSI	MSI-H	28%	REF
	≥30.0	34%	0.94 (0.77, 1.16)		MSS	36%	1.28 (0.84, 1.96)

10563 Poster Session

Decoding tumour bacterial ecosystems: Topological data analysis of bacterial association with immunogenicity. First Author: Eva Lymberopoulos, BioCorteX Inc., New York, NY

Background: The tumour microbiome is increasingly recognised as a key contributor to cancer progression and clinical outcomes, as highlighted in recent iterations of the Hallmarks of Cancer. Translating microbial signatures into actionable insights is hampered by a reliance on dimensionality reduction and a limited capacity to dissect non-linear relationships, leading to incomplete and inconsistent findings. Topological Data Analysis (TDA) is an unsupervised machine learning method that overcomes these limitations by preserving the complexity of high-dimensional data. Here, we applied TDA to characterise tumoural bacterial ecosystems across cancer types. **Methods:** Analysis was conducted using BioCorteX's knowledge graph and proprietary engines v20250124_015926. The dataset constituted of 551 sequenced primary tumour microbiome samples from six cancer types, as well as associated host age and gender. TDA Mapper was used to generate network graphs of the bacterial data, combined with an enrichment algorithm to analyse host metadata. Clusters in the TDA network represent samples with overlapping microbiome features. **Results:** The resultant network graph shows clear clustering of tumour bacteria along cancer types, suggesting distinct signatures of tumoural bacteria for each cancer. Notably, TNCB and melanoma cluster in the same area, while ovarian, colorectal, and glioblastoma cluster together in a different area of the graph. NSCLC clusters separately to both of the other two major clusters. Host age and gender do not significantly interact with the bacterial signatures or the cancer types. **Conclusions:** This strengthens the notion of highly cancer-specific tumoural bacteria, while also highlighting the similarities observed across cancer types. Notably, the 2 main clusters could suggest a bacterial association with immunogenicity: TNBC and melanoma tumours are both immune-responsive, while ovarian, colorectal, and glioblastoma tumours are generally not. Previous studies have suggested a major role of tumoural bacteria in immune responses, and this study suggests that tumoural bacteria can distinguish cancer immunogenicity. Further, it demonstrates the potential of TDA to extract novel insights from large, high-dimensional datasets, surpassing traditional approaches. Capturing non-linear associations is crucial for understanding complex host-bacteria interactions, paving the way for more precise characterisation of cancer-specific microbial signatures, with implications for oncology and therapeutic development. Research Sponsor: BioCorteX Inc.

10564 **Poster Session**

Environmental PFAS exposure as an understudied social determinant of health for endometrial cancer disparities: A geospatial study in Florida. First Author: Ming Sheng Lee, University of Miami Sylvester Comprehensive Cancer Center, Miami, FL

Background: Endometrial cancer (EC) is the most common gynecological malignancy in the U.S. Although overall survival rate for EC in the US is 81%, non-Hispanic Black (NHB) women die from EC at higher rates than non-Hispanic White (NHW) women. Currently, population-based research on social determinants of health associated with EC disparities is limited. PFAS exposure has been linked to increased risk for EC, but the potential impacts of environmental PFAS exposure on EC disparities are largely understudied. This research examined how EC incidence rates and mortality odds by census tracts vary with respect to proximity to industrial PFAS facilities as well as drinking water PFAS contamination in Florida. **Methods:** Florida cancer registry data from 2011 to 2020 was used to calculate age-adjusted incidence rates and mortality odds (number of mortalities divided by number of cases diagnosed) of both Type I and Type II EC by race/ethnicity for all census tracts in Florida. Data on the locations of industrial facilities handling PFAS as well as ZIP codes with public drinking water tested positive for PFAS were obtained from US EPA. A geographic information system was used to calculate indicators of proximity to PFAS facilities within 5 km of a census tract. Statistical tests including two-way ANOVA and two-sample t-test were used to compare mean incidence rates and mortality odds for three levels of PFAS proximity and drinking water PFAS status. **Results:** A total of 11,796 cases (8,931 in NHW, 1,821 in Hispanics, and 1,044 in NHB) of Type I EC and 9,715 cases (6,088 in NHWs, 1,450 in Hispanics, and 2,177 in NHB) of Type II EC were diagnosed and geocoded to 3,095 census tracts in Florida from 2011 to 2020. ANOVA showed that higher proximity to PFAS facilities is associated with higher rates of poverty as well as higher likelihood of drinking water PFAS contamination. Census tracts with higher proximity to PFAS show higher age-adjusted incidence and mortality odds for both Types I and II EC in NHW. NHB living in areas with higher PFAS proximity show higher mortality odds, while no statistically significant associations were found for Hispanic. T-tests showed that positive drinking water PFAS status is associated with higher aged-adjusted incidence and mortality odds for Type I EC in NHW as well as higher type II EC mortality odds in NHB and Hispanic. **Conclusions:** Results of this study demonstrate environmental PFAS exposure as a critical yet underexplored social determinant of health for EC epidemiology. Further research is needed to unearth the effect mechanism and to firmly establish PFAS exposure as a risk factor for EC disparities in the population. Such efforts can help develop public health policies to protect vulnerable populations from PFAS exposure and subsequent EC development as well as to accelerate the regulation process for environmental PFAS contamination. Research Sponsor: None.

10565 **Poster Session**

Nationwide analysis and trend of liver cancer mortality attributable to drug use in United States from 1991 to 2021. First Author: Adit Patel, Saint Vincent Hospital, L.L.C., Worcester, MA

Background: Liver cancer attributable to drug use represents an escalating public health concern in the United States (US). This study analyzes mortality, and related metrics for liver cancer attributed to drug use from 1991 to 2021, focusing on national and state-level trends and examining gender disparities and geographic variations with projections of Age-standardized mortality rates (ASMR) extending to 2040. **Methods:** The Global Burden of Disease (GBD) 2021 database was used to extract age-standardized mortality rate (ASMR) and disability-adjusted life years (DALY) for liver cancer mortality attributable to drug use in the United States from 1991 to 2021. Mortality data were stratified by gender, year, and region. Joinpoint regression analysis was performed to further evaluate trends and Annual Percent Change (APC) was calculated. Time series regression was used to calculate projected ASMR in 2040. **Results:** From 1991 - 2021, the ASMR for liver cancer attributable to drug use in the U.S. increased nearly threefold, from 0.54 per 100,000 (95% CI: 0.44–0.65) to 1.60 per 100,000 (APC:6.51%, 95% CI: 1.35–1.84). The DALY rate rose significantly from 15.22 per 100,000 to 39.36 per 100,000, highlighting the growing burden. Gender analysis revealed higher ASMRs in males, increasing from 0.74 to 2.12 per 100,000, compared to 0.38 to 1.14 per 100,000 in females, with APC of 6.25% and 6.55%, respectively. A state-level analysis of ASMR in 2021 showed the highest ASMR in California (2.27), followed by the District of Columbia (2.11), and Michigan (1.93). Meanwhile, Nebraska (0.73) had the lowest ASMR in 2021, followed by Iowa (0.91) and New York (1.15). The highest annual percent change (APC) was 11.47% in Nebraska, while the lowest was 3.58% in the District of Columbia. The Joinpoint regression analysis identifies five distinct periods of varying Annual Percent Changes (APC) in liver cancer mortality attributable to drug use. From 1991 to 2001, there was a sharp increase in mortality (APC = 5.75%), followed by slow growth between 2001-2007 (APC = 2.86%). However, from 2007-2010, there was a reacceleration (APC = 4.63%). Between 2010 - 2016, the growth rate decreased further (APC = 2.67%), after which 2016 - 2021, mortality rates stabilized (APC = 0.58%). The forecasted national ASMR for 2040 is estimated to be approximately 2.38 per 100,000. **Conclusions:** This study underscores a substantial rise in liver cancer mortality attributable to drug use in the United States from 1991 to 2021, with notable gender and geographic disparities. Projected increases in ASMR, coupled with observed trend shifts, emphasize the urgent need for targeted prevention and intervention strategies to mitigate the growing burden of drug use-related liver cancer. Research Sponsor: None.

10567 **Poster Session**

Germline pathogenic variants in *BRCA1-, BRCA2-*, and *PALB2*- genes among Ethiopian young women and men diagnosed with breast cancer. First Author: Tove Ekdahl Hjelm, Department of Molecular Medicine and Surgery, Karolinska Institute, Stockholm, Sweden

Background: Breast cancer incidence is rapidly increasing in low-and-middle-income countries (LMICs), where access to care is limited and survival outcome is poor. Young women and men are overrepresented among breast cancer (BC) patients diagnosed in LMICs in Sub-Saharan Africa (SSA), for reasons not yet fully understood. As hereditary cancer is more common in young women and men with BC, genetic factors may play a significant role. Even though carriers of germline pathogenic variants (PV) in the genes *BRCA1*, *BRCA2*, and *PALB2* have a very high risk of BC, studies of PV in these genes are very limited in SSA. In order to increase knowledge, this study investigated the prevalence of PV in high-risk BC susceptibility genes in young women and men diagnosed with BC in Ethiopia. **Methods:** This is a descriptive cross-sectional study. One-hundred young women (age 18-39) and men (all ages) diagnosed with invasive BC were included from Departments of Oncology and Surgery at Tikur Anbessa Specialized Hospital, Addis Ababa, Ethiopia. Potential participants were given oral and written information by a trained physician, and those consenting were included in the study. Basic patient- and tumor characteristic as well as information about family history was collected. DNA was extracted from blood samples, before shipment to BRCAlab, Lund University, Sweden for genetic analysis of genes *BRCA1*, *BRCA2* and *PALB2*, using a gene panel and next generation sequencing on an Illumina platform. **Results:** Genetic analysis results were available for 89 study patients. There was a high proportion (21.3%) of PV in tested genes. In total, 19 PV were found in *BRCA1* (n = 7), *BRCA2* (n = 8) and *PALB2* (n = 4). One of the PV was in a male. There were five individuals with an identical PV in *BRCA1* (c.4524G $>$ A, NM_007294.3), three individuals with identical PV in *BRCA2* (c.5159C $>$ A, NM_000059.3), and two individuals with identical PV in *PALB2* (c.1216delG, NM_024675.4). Two novel PV not previously reported in literature were found, *BRCA1* c.5278-864_5332+621del, NM_007294.3 and *PALB2* c.1169_1170del, NM_024675.4. **Conclusions:** This study demonstrates that germline PV in *BRCA1*, *BRCA2* and *PALB2* are common among young women and men diagnosed with BC in Ethiopia, with over 1 out of 5 patients carrying a PV. Genetic predisposition appears to play an important role in the tumor genesis in the studied group. Multiple patients carried identical PV, which could indicate that the detected PV are founder variants. Since the majority of the patients in Ethiopia are young, and male BC seem more prevalent compared to in western countries, efforts directed to these groups and development of services for genetic testing and follow-up programs for carriers of PV should be further emphasized. This approach has the potential to reduce BC incidence, morbidity and mortality through increased awareness, risk-reducing procedures and earlier cancer detection. Research Sponsor: Swedish Research Council.

10568 **Poster Session**

Discrepancies between germline and somatic laboratories in the reporting of germline cancer predisposition variants. First Author: Brittany Cooper, Rutgers University, Department of Genetics, Piscataway, NJ

Background: Individuals with a cancer diagnosis may not qualify for germline testing to identify cancer predisposition variants due to restrictive testing guidelines. However, many have somatic Next Generation Sequencing (NGS) to guide treatment. Somatic NGS may offer a less restrictive approach to identify germline variant carriers. However, the rate of germline variant reporting via somatic NGS is unclear. We investigated what percentage of known germline variants were reported by matched somatic testing laboratories. **Methods:** Cancer patients seen at Rutgers Cancer Institute who had a positive germline report between 1/1/18 and 1/31/23 and at least one matched somatic NGS report on file were eligible for the study. We compared each germline-somatic report pair to analyze if the pathogenic/ likely pathogenic (P/ LP) germline variant was reported by the somatic NGS laboratory. We also assessed factors impacting germline variant reporting. **Results:** A total of 65 cases were included. Of matched somatic reports, 52.9% reported the corresponding germline variant, while 47.1% of germline variants were not reported by the matched somatic laboratory. The most frequent reasons germline variants were not reported included: (1) the gene was not included on the somatic NGS panel (60%), (2) the germline variant was filtered out of reporting by the somatic NGS laboratory as a suspected incidental germline finding of limited treatment relevance (10%), (3) the variant was intronic (7.5%), and (4) the variant was a copy number variant (7.5%). Less common reasons germline variants were not reported included differences in variant interpretation, limited coverage in the region containing the variant, and suspected mosaicism and/or clonal hematopoiesis. **Conclusions:** Almost 50% of germline variants in this cohort were not reported by the corresponding somatic laboratory. So, our findings suggest that clinical providers cannot rely on somatic NGS for germline variant reporting. We also expanded on reasons certain germline variants were not reported by somatic laboratories beyond reasons previously reported. In our cohort, the second most common reason germline variants were not reported was because the variant was detected and then intentionally filtered out of reporting. In these cases, the somatic lab interpreted the variant as an incidental finding of probable germline origin with limited treatment relevance. This highlights the different goals of germline vs somatic testing labs and how these varying goals impact what is reported to ordering clinicians. We hope our findings will contribute to the growing literature surrounding the overlap between germline and somatic testing methodologies and assist clinicians in their interpretation of genomic results. Research Sponsor: None.

10569 **Poster Session**

Implementation of pan-cancer universal germline testing in an ethnically diverse and rural community oncology practice. First Author: Sarah Nielsen Young, Labcorp (formerly Invitae Corp.), San Francisco, CA

Background: Universal germline genetic testing (GGT) is increasingly utilized in precision cancer care. There is limited data on this approach in patients (pts) from historically underrepresented and underserved populations receiving care at community practices. Herein, we present an interim analysis of ~500 unselected pts who underwent standard of care GGT at a rural community oncology practice. **Methods:** The UNITY (UNIversal germline Testing in the communitY) trial (NCT05416710) is a prospective, observational study of pts with newly or previously diagnosed cancer from July 1, 2022-August 1, 2024 (censor date). GGT was performed largely via an 80+ gene panel and insurance-billed. Patient demographic and clinical features were collected by clinicians. NCCN criteria for the pt's primary cancer at the time of GGT determined if the pt was in-criteria (IC) or out-of-criteria (OOC). Differences among groups were determined by two-tailed Fisher's exact, one-way ANOVA and Tukey's HSD tests with significance set at $p < 0.05$. **Results:** 462 pts had complete data: 73% were female; most common cancers: breast (54%), colorectal (14.5%), lung (9%), head & neck (6%), prostate (4%); mean age at diagnosis and testing: 63.2 and 67.6; 21% stage IV/metastatic; 66% Non-Hispanic white, 30% Black/African-American; 17% > 1 cancer diagnosis; 77% family history of cancer; 48% met NCCN criteria; 61% commercial insurance; 27% annual income < $25,000. 47 pathogenic germline variants (PGV) were identified in 41 pts (8.9%). 12 pts (3%) carried a single PGV in a gene associated with autosomal recessive cancer risk (e.g. *MUTYH*) and were excluded from further analyses, resulting in 6.3% (29/462) pts with a PGV. There was no significant difference in the rate of PGVs in IC vs. OOC pts (5.9% vs. 6.7%, p = 0.85). 16/29 (55%) pts with PGVs were OOC, with *CHEK2, ATM, BRCA2* being the most frequently mutated genes. Additionally, the majority of PGVs were potentially clinically actionable (25/29, 86%) and most (14/25, 56%) were OOC. 190 (41%) pts had a variant of uncertain significance (VUS) in the absence of a PGV, with Black/African-American pts having significantly higher rates of VUS-only findings compared to non-Hispanic White pts (50% vs. 36%, p = 0.04). Conversely, PGV rate showed the opposite pattern (0.7% Black/African-American; 8.5% non-Hispanic White, p = 0.01). **Conclusions:** Universal GGT in this diverse cohort identified PGVs in nearly 1 in 15 pts, most of which were potentially clinically actionable, but > 50% would have been missed by NCCN criteria. As Black pts had significantly lower odds of carrying a PGV and higher odds of a VUS result, broader GGT testing criteria would help mitigate racial disparities by increasing the number of (diverse) individuals tested resulting in better representation of genetic variation. Clinical trial information: NCT05416710. Research Sponsor: Labcorp Genetics (formerly Invitae Corp.).

10570 **Poster Session**

Preventative intervention uptake among women with breast cancer and pathogenic germline variants. First Author: Sarah Nielsen Young, Labcorp (formerly Invitae Corp.), San Francisco, CA

Background: Risk-reducing (RR) interventions in patients (pts) with pathogenic germline variants (PGV) in breast cancer (BC) risk genes include RR mastectomy (RRM), RR salpingo-oophorectomy (RRSO) and pancreatic cancer surveillance (endoscopic ultrasound [EUS] and/or MR cholangiopancreatography [MRCP]). Gene-specific intervention uptake was stratified by family history (FHx) of cancer in 1903 BC pts with PGV in high/moderate BC risk genes (*ATM, BARD1, BRCA1/2, CDH1, CHEK2, NF1, PALB2, PTEN, RAD51C/D, SK11, TP53*). **Methods:** Germline genetic testing (GGT) and insurance claims data were analyzed female DCIS/BC pts diagnosed 2015-24, GGT <120 days after diagnosis and ≥1 year of claims pre/post-GGT (uptake measured within 1 year of GGT). Inclusion/exclusion criteria followed prior work (PMID 32027353). Following NCCN (Genetic/Familial High-Risk Assessment: Breast, Ovarian, Pancreatic and Prostate v2.2025) guidelines, PGV were in genes in the following categories: 1) gene-specific criteria (GSC): eligible for intervention +/- FHx; 2) gene and FHx-specific criteria (GFHxSC): consider (RRM, RSSO) or eligible (EUS/MRCP) for intervention if pt has relevant FHx or 3) Other: no specific intervention eligibility. Multivariable logistic regression models compared odds of intervention uptake for pts stratified by the categories above and by relevant cancer FHx (RRM: breast, RRSO: ovarian, EUS/MRCP: pancreatic). **Results:** 1903 pts with BC had ≥ 1 PGV. Clinico-demographics included were: 70% White, 74% BC FHx, 16% ovarian FHx, 35% pancreatic FHx, and mean (range) age at GGT, 50 (21-90). RRM had the highest uptake (56% overall, 75% in those with GSC PGV). RRSO uptake: 23% overall, 37% in pts with GSC PGV. EUS/MRCP uptake was 9% in pts with GSC PGV or GFHxSC PGV (+) FHx. Pts with GSC PGV (+) FHx had 5x higher odds of RRM vs. pts with GFHxSC PGV (-) FHx. Compared to pts with Other PGV (-) FHx, pts with GSC PGV (+) FHx had 18x higher odds of RRSO and 6x higher odds of MRCP/EUS (Table). **Conclusions:** In this retrospective analysis, intervention uptake generally followed NCCN guidelines, with uptake consistently higher in pts with PGV in GSC genes and positive FHx. Other factors in the shared decision-making process should be studied to identify gaps in quality of care. Research Sponsor: None.

Association of model variables with intervention uptake.

	RRM OR (CI)	RRSO OR (CI)	MRCP/EUS OR (CI)
PGV/FHx	ref: GFHxSC PGV (-) FHx	ref: Other PGV (-) FHx	
GSC PGV (+) FHx	5 (3-8)	18 (11-30)	6 (3-13)
GSC PGV (-) FHx	3 (2-6)	16 (10-24)	3 (1-6)
GFHxSC PGV (+) FHx	NS	7 (2-22)	6 (2-13)
GFHxSC (-) FHx	NA	3 (2-5)	NS
Other PGV (+) FHx	NA	NS	NS
Age	NS	1.5 (1-2)	1.2 (1.0-1.4)
Ethnicity (ref: White)	Hispanic: 2 (1-5)	Ashkenazi Jewish: 0.2 (0-0.7) Asian: 0.4 (0.2-0.9)	Multiracial: 2 (1-4)
Lymph node disease	1.6 (1-2)	0.7 (0.5-1)	NS

OR, odds ratio; CI, 95% confidence interval; NS, not significant (p≥0.05); NA, not applicable; other variables not shown: insurance, DCIS, age2, days from diagnosis to GGT.

10571 **Poster Session**

Better together: Synergy of germline and somatic testing in HRR pathway-driven cancers. First Author: Michelle Green, Labcorp, Durham, NC

Background: Germline and somatic pathogenic variants inform eligibility for poly (ADP-ribose) polymerase inhibitors (PARPi) in breast, ovarian, prostate and pancreatic (BOPP) cancers. The role of BRCA1/BRCA2 in BOPP cancers is well-established, but the significance of other homologous recombination repair (HRR) genes is evolving. Integrating germline and somatic data provides a comprehensive understanding of oncogenesis and informs therapeutic decisions and risk assessment. For example, patients with "two hits" (germline and somatic alteration in the same HRR gene) often exhibit exceptional responses to PARPi. **Methods:** Patients with BOPP cancers receiving standard of care germline genetic testing (GGT) (Labcorp Genetics, formerly Invitae) and comprehensive genomic profiling (CGP) (Omniseq Insight, Labcorp) between 2021-2024 were analyzed. CGP data was queried to determine if the germline pathogenic variant (PGV) 1) was detected in the tumor, 2) had suggestive loss-of-heterozygosity (LOH) with a variant allele fraction (VAF) of ≥ 0.6, 3) had a second hit in the same gene, or 4) had somatic mutation(s) in other HRR gene(s). These were compared between BRCA1/BRCA2 and other HRR PGVs using Fisher's exact test with significance set at <0.05. **Results:** 607 patients with BOPP cancers underwent GGT and CGP; 57 (9.4%) had ≥ 1 PGV in an HRR gene. The PGV+ cohort was 51% White; mean age at GGT was 62 years (26-88). Breast cancer was the most common cancer (27), followed by ovarian (15), pancreatic (12) and prostate (4); 20 (35%) patients had a BRCA1/BRCA2 PGV and 37 (65%) patients had other HRR PGV, primarily CHEK2, ATM, PALB2 (Table). Most (88%) PGV were detected by CGP, with 100% of BRCA2 PGV identified. However, 8 (12%) of PGV+ patients would have been missed by CGP testing alone. VAF ≥ 0.6 and/or 2nd hits in the same gene were significantly more likely in those with BRCA1/2 PGV vs. other HRR. Rates of additional mutations in other HRR genes were not significantly different (p>0.05) between the groups (Table). **Conclusions:** BRCA1/2 PGV were frequently identified as suspected drivers of BOPP cancers compared to other HRR genes. However, one-third of patients with other HRR variants exhibited features suggestive of driving cancer pathogenesis. These findings may qualify indicated patients for targeted therapies or trials and highlight the synergistic value of combined germline and somatic testing. Research Sponsor: None.

Tumor characteristics of patients with HRR PGV.

Genes	Total PGV+ patients	N (%) PGV detected by CGP	N (%) VAF ≥ 0.6	N (%) 2nd hit, same gene	N (%) VAF ≥ 0.6 OR 2nd hit	N (%) 2nd mutation, different HRR gene
BRCA1/2	20	17 (85)	**12 (71)**[a]	2 (12)	**14 (82)**[b]	6 (35)
BRCA1	11	8 (73)	7 (88)	0 (0)	7 (88)	2 (25)
BRCA2	9	9 (100)	5 (56)	2 (22)	7 (78)	4 (44)
Other HRR[c]	37	33 (89)	**9 (27)**[a]	4 (12)	**11 (33)**[b]	9 (27)

[a]p=0.011; [b]p=0.005; [c]*CHEK2* (14), *ATM* (7), *PALB2* (5), *BRIP1* (2), *RAD51C* (2); *BARD1*, *BLM*, *FANCA*, *FANCA/CHEK2*, *FANCM*, *NBN*, *RAD50* (1 each).

10572 **Poster Session**

Polygenic risk score for breast cancer in the Thai population: Addressing genetic disparities in underrepresented populations. First Author: Phuwanat Sakornsakolpat, Division of Medical Oncology, Department of Medicine, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand

Background: Effective breast cancer prevention and management require accurate risk prediction tools. Polygenic risk scores (PRS) have shown promise but are often less effective in non-European populations due to differences in genetic architecture. This study evaluates PRS performance and adaptation for breast cancer in the Thai population, addressing disparities in underrepresented groups. **Methods:** We retrospectively analyzed breast cancer cases from the Genomics Thailand project at Siriraj Hospital and general population controls from the National Health Examination Survey (NHES) in Thailand. Whole-genome sequencing was performed for cases, and genotyping with imputation was done for controls using the TOPMed r2 reference panel. Clinical data were extracted from electronic medical records. PRS were constructed using SBayesRC, incorporating variants from publicly available genome-wide association study (GWAS) summary statistics and variant functional annotations. Logistic regression and area under the receiver operating characteristic curve (AUC) analyses were conducted using R. **Results:** The discovery cohort included 975 cases and 1,502 controls, with 230 cases and 265 controls in the validation cohort. Of the 330 previously reported GWAS loci, only 231 lead variants were identified in our dataset. We further analyzed variants near these lead variants within the 330 loci, identifying nominal associations with breast cancer for 329 loci ($p<0.05$). Four PRS models were tested: (1) 231 variants, (2) ~7 million functional variants based on European (EUR) data, (3) East Asian (EAS) models, and (4) combined EUR and EAS models. The EUR-based model (AUC 0.66) outperformed the 231-variant model (AUC 0.59) and the population-specific EAS model (AUC 0.58) at $p<0.05$. The combined EUR and EAS models showed no significant improvement over the EUR model alone (AUC 0.66 for both, p=0.69). Individuals in the highest PRS risk group (above the 90th percentile) had an odds ratio (OR) of 3.34 for breast cancer compared to the rest of the population (95% confidence interval: 2.54–4.42, $p<0.05$). Among 249 patients with pathology data, PRS was not associated with tumor size, estrogen receptor status, or nodal metastasis. **Conclusions:** In the Thai population, PRS derived from large-scale European GWAS provided the highest prediction accuracy for breast cancer risk. The limited transferability of a top-variant PRS (e.g., 330-variant model) underscores the challenge posed by variant availability in this population. Validation in prospective studies is essential to optimize PRS utility and address disparities in genetic risk prediction. Research Sponsor: None.

10573 **Poster Session**

Histopathologic and demographic features of non-small cell lung cancer in patients with *BRCA* pathogenic germline variants. First Author: Benjamin Aaron Bleiberg, University of Pennsylvania, Philadelphia, PA

Background: Patients with pathogenic germline variants (PGVs) in *BRCA1* and *BRCA2* (*BRCA1/2*) have a known increased risk of breast, pancreatic, and prostate cancers. Limited data also suggest a potential increase in lung cancer risk. It is not known if the features of non-small cell lung cancer (NSCLC) in individuals with *BRCA1/2* PGVs differ from those in PGV negative patients. **Methods:** Patients with *BRCA1/2* PGVs were identified using a single-institution registry of PGV patients. Using electronic health records, NSCLC cases were identified via ICD codes. Demographic and histopathologic data were manually abstracted. A PGV negative cohort was derived from NSCLC patient cases detailed in the Penn Medicine Cancer Registry. Categorical variables were compared between the *BRCA1/2* PGV and PGV negative groups using Pearson's chi-squared test. Continuous variables were compared using the Wilcoxon rank-sum test. **Results:** 25 NSCLC patients with PGVs (10 *BRCA1* and 15 *BRCA2*), and 623 PGV negative NSCLC patients were identified. Median age at diagnosis was similar (68, IQR=14 vs 67, IQR=13 years for *BRCA1/2* PGV and PGV negative patients, respectively); sex (64% vs 51% female) and race (80% vs 74% White) were also similar between groups. Never smokers comprised a significantly larger proportion of the *BRCA1/2* PGV cohort (44%) than the PGV negative cohort (16%; $p<0.01$). Stage at diagnosis was similar between groups, with the majority diagnosed with stage I or II disease (56% in *BRCA1/2* PGV vs 66% in PGV negative patients). Histologic findings were also similar, with the most common being adenocarcinoma and squamous cell (68% and 20% in *BRCA1/2* PGV vs 71% and 19% in PGV negative patients, respectively). All 14 BRCA1/2 PGV patients with stage I-II disease received curative intent local therapy; there were 3 recurrences within 5 years. Among 11 *BRCA1/2* PGV patients with advanced stage III-IV disease, 6 had actionable genetic alterations, most commonly in EGFR (3/11). PD-L1 status in these patients was evenly distributed, 3 $<$1%, 5 1-49%, and 3 $>$50% expression. **Conclusions:** The histopathologic and demographic features of NSCLC including age and stage at diagnosis and distribution of histology were largely similar for *BRCA1/2* PGV patients and PGV negative patients. However, never smokers represented a significantly larger proportion of the *BRCA1/2* PGV cohort. The presence of actionable genetic alterations and PD-L1 expression in BRCA1/2 PGV patients with NSCLC was comparable to those reported in the general NSCLC population. Research Sponsor: None.

Features of NSCLC in patients with *BRCA1/2* PGVs compared to PGV negative patient.

	BRCA1/2 PGV (N=25)	PGV Negative (N=623)	*p*-value
Median age of onset, years, ± IQR	68±14	67±13	0.68
Female Sex	16 (64%)	319 (51%)	0.21
Never Smoker	11 (44%)	99 (16%)	<0.01
Stage I or II at diagnosis	14 (56%)	370/561 (66%)	0.20
Histology			
Adenocarcinoma	17 (68%)	445 (71%)	0.71
Squamous cell	5 (20%)	120 (19%)	0.92

10574 **Poster Session**

Profiling DNA damage response in ATM/BRCA2 carriers to inform hereditary cancer risk. First Author: Demitrios Dedousis, Fox Chase Cancer Center/Temple University Hospitals, Philadelphia, PA

Background: Approximately 10% of cancers stem from inherited germline pathogenic variants (gPV), predominantly in DNA repair genes including *ATM* and *BRCA1* or *BRCA2*. Identification of a gPV in high-risk families can guide management, however the clinical implications of variants of uncertain significance (VUS) identified by genetic testing remain unclear. Our aim is to develop a DNA damage response (DDR) activity profile of high-risk populations with/without cancer with *ATM or BRCA2* gPV to assist in determining the relevance of *ATM or BRCA2* gPV/VUS. **Methods:** We profiled several key proteins that play a role in DDR using a Luminex-based Multianalyte immunoassay (hereafter referred to as DDR xMAP) in peripheral blood monocytes (PBMCs) derived from whole blood. The standardized DDR xMAP assay was first applied to PBMC specimens from sporadic colorectal cancer (CRC, n = 95) patients and cancer-free age-matched controls (n = 47) at baseline. The DDR xMAP was used to profile seven DDR proteins, phosphorylated $Chk1^{S345}$, $Chk2^{T68}$, $\gamma H2AX^{S139}$, $p53^{S15}$ and total ATR, MDM2, p21. Univariate classification and regression tree analysis was used to identify statistically significant cut points in DDR analyte levels. We then measured the DDR analyte levels in individuals with *BRCA2* gPVs with (n = 11) and without a diagnosis of cancer (n = 11) as well as in cancer-free non-carrier controls (n = 15) at baseline. We compared these values using the two-sided Mann-Whitney test and the Benjamini-Hochberg false discovery rate method to account for multiple markers. **Results:** Using the initial set of CRC cases and healthy controls, we identified statistically significant cut points in multiple DDR analyte levels including total ATR ($>$ 81.8), $Chk1^{S345}$ ($>$ 28.0) and $\gamma H2AX^{S139}$ ($>$ 51.3) that can individually distinguish between CRC cases and cancer-free controls ($P < 0.001$). Next, in preliminary analysis of patients with *BRCA2* gPV with and without cancer had increased levels of all DDR analytes ($P < 0.05$) compared to non-carrier cancer-free controls, except for $\gamma H2AX^{S139}$. Levels of proteins involved in replication stress response, ATR and downstream $Chk1^{S345}$, were elevated. Total MDM2 levels, negative regulator of p53, were highly elevated in *BRCA2* gPV carriers. There was not a significant difference between DDR analytes for those with *BRCA2* gPV with and without cancer. **Conclusions:** Profiling key DDR markers can significantly distinguish between CRC patients and cancer-free controls. DDR analytes are significantly increased in PBMC specimens from individuals with *BRCA2* gPV (with or without a diagnosis of cancer) compared to non-carrier cancer-free controls. Ongoing research in high-risk groups will establish cut points for this assay, improving our understanding of DDR activity in individuals with *ATM/BRCA2* gPV and clarifying the clinical significance of gPV/VUS. Research Sponsor: National Cancer Institute; U.S. Department of Defense; W81XWH-18–1-0148; National Institute of Health/National Cancer Institute; 1UH2CA271230-01; Fox Chase Cancer Center.

10575 **Poster Session**

Age-related germline landscape of endometrial cancer: Focus on early-onset cases. First Author: Judy J. Wang, Weill Cornell Medical Center, New York, NY

Background: Endometrial cancer (EC) has traditionally been associated with older age; however, recent trends indicate more cases in younger women. There is also a growing appreciation for germline drivers of EC, and these may be enriched in younger patients (pts). Given this, we sought to define germline pathogenic variants (gPV) in pts with EC by age. **Methods:** Pts with EC treated at our institution who underwent clinical tumor-normal sequencing from 12/2024-6/2021, inclusive of germline analysis of ≥76 genes, were identified. Clinical variables including age at diagnosis were collected. Logistic regression models evaluated associations between age at EC diagnosis and presence of gPV, biallelic loss, and Lynch syndrome (LS). Age categories were defined as early-onset (EC$<$50 years) and later-onset (EC ≥70 years) and were compared to those diagnosed ages 50-69 years. Appropriate statistical analysis had been performed. **Results:** Among 1625 pts with EC, median age at diagnosis was 63 (range 24-96) years. We observed differences in gPV rate across age groups, with 28/170 (16%) in early-onset EC, 152/1066 (14%) in EC diagnosed 50-69 years, and 36/389 (9%) in later-onset EC (p=0.016). Biallelic loss also exhibited differences by age groups with enrichment in early-onset EC (8.2% vs. 4.5% vs. 2.1% respectively, p=0.004). LS was enriched in early-onset EC, with 6.5% of patients diagnosed age $<$50 years having LS. Age was associated with gPV in univariate and multivariable (MV) logistic models, even after adjusting for ancestry and molecular subtype. Compared to those with EC diagnosed 50-69 years, early-onset EC was more likely to be exhibit biallelic loss (OR 3.34 95% CI 1.44-7.35) and be associated with LS (HR 3.49 95% CI 1.63-7.01) in MV models. In contrast, later-onset EC was less likely to be associated with gPV (OR 0.56 95% CI 0.37-0.83) and biallelic loss (OR 0.37 95% CI 0.15-0.82) in MV models. Among early-onset EC, 14/28 (50%) gPV were high penetrance and 14/28 (50%) exhibited biallelic loss. For late-onset EC, only 5/36 (14%) gPV had high penetrance with 8/36 (22%) showing biallelic loss. While the most common high-penetrant gPVs were *MSH2* (n=5), *MSH6* (n=3), and *MLH1(n*=3) for the early-onset cohort, the later-onset cohort had gPV in *BRCA2* (n=3), *BRCA1* (n=1), and *PALB2* (n=1). Among the 39 pts with LS and EC, the youngest pt (*MLH1* gPV) was diagnosed at 31 years, and the oldest pt (*PMS2* gPV) was diagnosed at 69 years. Heterogeneity was observed in the early-onset EC cohort. Rates of gPV were 8.9% and 19%, biallelic loss was 0% and 11%, and LS was 2.2% and 8% in those diagnosed $<$40 years and 40-49 years respectively, suggesting potentially different drivers of very early-onset EC. **Conclusions:** Rates of gPV, biallelic loss and LS differ across age groups for EC, with higher rates of highly penetrant genes that drive tumorigenesis enriched in younger pts. However, very early-onset EC may have different drivers and necessitates more research. Research Sponsor: National Cancer Institute/U.S. National Institutes of Health; P30 CA008748.

10576 **Poster Session**

Leveraging high variant allele frequencies (VAF) of DNA damage repair (DDR) mutations (muts) in liquid biopsy (LBx) as a surrogate for germline testing: Implications for precision medicine. First Author: Sagal Pannu, Stephenson Cancer Center at The University of Oklahoma Health Sciences Center, Oklahoma City, OK

Background: LBx based next-generation sequencing (NGS) provides a minimally invasive means to detect true DDR muts as well as DDR muts that represent clonal hematopoiesis of indeterminate potential (CHIP), and in certain cases identifying high VAF DDR muts of suspected germline origin. Herein, we aim to address the knowledge gap in interpreting these findings to guide germline testing. **Methods:** We retrospectively collected data on patients (pts) with cancer who underwent LBx with FoundationOneLiquid CDx (311 gene panel) from 2022-2024 and tissue biopsy (TBx) based NGS using either Caris Life Sciences or FoundationOne CDx. A panel of 22 muts directly involved in the DDR pathway were designated as DDR muts. Findings from LBx and TBx were reported using descriptive statistics. Best objective clinical responses were evaluated using RECIST v1.1. **Results:** The study cohort consisted of 637 pts tested using LBx, with the majority being male (62.6%; n=399) and white (81%; n=517). On LBx, 203 pts (31.8%; n=203/637) were identified to have one or more DDR muts. Paired testing with LBx and Tbx was available for 221 pts of which 28 pts (12.6%) had 'true CHIP' (identified on LBx but not on TBx), all contributed by ATM and CHEK2 (50% each; n=14/28). Of pts who had paired LBx and TBx (n=221), 24 pts (10.8%) had the same DDR mut on both, suggesting likely somatic origin (True DDRs), the most common being ATM (25%; n=6/24), PALB2 (12.5%; n=3/24) and CDK12 (12.5%; n=3/24). Using a linear mixed-effects model to account for patient- and gene-level variability in VAF, true DDRs had a significantly ($p < 0.001$) higher VAF (median: 46.8, IQR: 49.6, n = 26) compared to true CHIP DDRs (median: 0.24, IQR: 0.29, n = 31). LBx revealed potential germline implications based on high VAF in 7.9% pts (n=50/637) of which 45 pts had DDR muts. Genetic referrals were initiated in 48% (n=24/50) with subsequent confirmatory germline testing done for 66.6% (n=16/24), all confirming germline muts (table 1). Notably, for the 52% (n=26/50) without genetic referrals, 73% (n=19/26) lacked documentation of a referral discussion. Out of the 50 pts with muts likely of germline origin, 19 were enrolled in phase-1 clinical trials, with 6 receiving matched therapies targeting DDR muts (PARP and ATR inhibitors). Of these, 1 had a partial response (CHEK2) and 3 had stable disease (1-MUTYH, 2-PALB2). **Conclusions:** LBx can be used as a potential surrogate indicator of likely germline muts as evidenced by high VAFs. Our findings underscore the need for improved interpretation of LBx reports to guide timely genetic referrals and confirmatory germline testing. Research Sponsor: None.

Gene	Median VAF (IQR)
BAP1 (n=1)	52.4% (52.4-52.4)
MUTYH (n=2)	51.3% (50.7–51.9)
CHEK2 (n=2)	51.0% (50–52)
ATM (n=2)	50.2% (49.8–50.6)
BRCA2 (n=4)	50.0% (48.5–52.2)
PALB2 (n=2)	48.4% (46.7–50.2)
MSH6 (n=1)	46.6% (46.6-46.6)

10577 **Poster Session**

Estimated prevalence of pathogenic variants in patients with breast, colon, and/or endometrial cancer who do not meet guidelines for genetic testing. First Author: Ryan Bernhisel, Myriad Genetics, Inc., Salt Lake City, UT

Background: Patients with cancer who carry pathogenic variants (PVs) in hereditary cancer genes often have improved outcomes when their treatment is guided by their germline genetics. Identifying germline PVs also allows cascade testing of family members to pursue cancer prevention interventions. Guidelines recommend genetic testing for patients with female breast (BC), colorectal (CRC), or endometrial cancer (EC) who meet specific criteria, including early age at diagnosis and/or family history (FH). However, many patients with cancer who do not meet these guidelines may unknowingly carry PVs and may, therefore, receive suboptimal care. **Methods:** Multivariable logistic regression models were constructed to analyze trends in the prevalence of PVs based on age and FH in a consecutive cohort of patients referred for hereditary cancer testing (MyRisk, Myriad Genetics). We report model-based prevalence estimates for patients without FH diagnosed with BC, CRC, or EC at various ages. Prevalence is summarized overall for 25-48 hereditary cancer genes and for genes most frequently implicated in each cancer type. **Results:** Estimates of prevalence of PVs among patients with BC and CRC decreased substantially with age of diagnosis (Table 1). For patients with BC/CRC (respectively) without FH, overall prevalence estimates were 13.0%/11.8% among those diagnosed at age 30, 6.9%/7.1% at age 50 and 2.5%/3.2% at age 80. Among BC patients, PVs were most frequently identified in the *BRCA1, BRCA2, CHEK2, ATM,* and *PALB2* genes. Among CRC patients, PVs were most prevalent in the Lynch syndrome genes *MLH1, MSH2, MSH6, PMS2*. Prevalence was not significantly associated with age at EC diagnosis. Women with no FH had overall prevalence estimates of 7.5% if diagnosed with EC at age 30, 7.3% at age 50 and 7.1% at age 80 (Table 1). PVs were most common in the aforementioned Lynch syndrome genes. **Conclusions:** These results support existing literature that a substantial fraction of patients who do not meet guidelines for genetic testing may carry PVs, including a high prevalence of PVs among EC patients without FH, regardless of age at diagnosis. Elimination of age-based restrictions on genetic testing could improve the survival of cancer patients and their family members. Research Sponsor: Myriad Genetics.

Estimated prevalence (%) according to age of diagnosis among patients with no family history of cancer.

Age at dx	30	40	50	60	70	80
BC	13.0%	9.5%	6.9%	5.0%	3.5%	2.5%
CRC	11.8%	9.2%	7.1%	5.5%	4.2%	3.2%
EC	7.5%	7.4%	7.3%	7.2%	7.2%	7.1%
BC[a]	12.3%	8.3%	5.6%	3.7%	2.4%	1.6%
CRC[b]	7.3%	5.1%	3.5%	2.4%	1.7%	1.1%
EC[b]	4.4%	4.3%	4.3%	4.2%	4.1%	4.1%

BC=breast cancer; CRC=colorectal cancer; dx=diagnosis; EC=endometrial cancer.
[a]*BRCA1, BRCA2, CHEK2, ATM, or PALB2.*
[b]*MLH1, MSH2, MSH6, or PMS2.*

10578 **Poster Session**

Performance of previously described polygenic risk scores for prostate cancer in a population with mixed ancestry. First Author: Vinícius Marques Rocha, Faculdade de Medicina da Universidade de São Paulo, São Paulo, Brazil

Background: It is unclear whether polygenic risk scores (PRS) for prostate cancer (PrCa), developed using data from European populations, are applicable to individuals of mixed ancestry, such as the Brazilian population. We are conducting a case-control study to evaluate the performance of existing PrCa PRSs in Brazilian people. **Methods:** We prospectively included unselected PrCa patients (pt). The control group consisted of 347 elderly community men from Sao Paulo city (SABE cohort) included from 2000 to 2010, with whole genome sequencing (WGS 30x depth) data previously reported in the ABRAOM study. Men who developed cancer in the follow-up were excluded. The mean age at admission to the study was 72 years. DNA was extracted from blood samples for performing WGS at 15x depth (PrCa pt), using Illumina technology. VCF quality filtering and pre-processing were performed according to best practices of GATK, BCFtools and Plink. Ancestry composition was calculated using ancestry-informative markers derived from global populations. AUCs were calculated using the results from the total PRS value obtained with PGSCalc for cases and controls, without filters. We calculated PRS scores for 11 different PRSs for PrCa, described in 7 studies, derived from people with different ancestries and available in The Polygenic Score (PGS) Catalog or the literature (BARCODE1). **Results:** A total of 588 PrCa patients were included. The median age at diagnosis was 64.6 years. Most patients were diagnosed with clinical stages II (32.8%) and III (43.1%), and ISUP grades 2 (40.2%) and 3 (22.9%). Twenty PrCa pt, who were carriers of pathogenic or likely pathogenic germline variants on high and moderate penetrance prostate cancer predisposition genes, were excluded. The mean ancestry genetic composition for PrCa pt was 61.4% European and 24.6% African. We calculated the AUC for the Brazilian cohort (BZL) for 11 PRSs available in PGS Catalog. 1) PGS000030 - Schumacher et al. 2018; 147 SNPs - AUC BZL: 0.666; 2) PGS000751 - Du et al. 2019; 178 SNPs - AUC BZL: 0.694; 3) PGS000662 - Conti et al. 2021, 269 SNPs - AUC BZL: 0.705; 4) PGS002796, PGS002797, PGS002798, PGS002799 - Shi Z, et al. 2022; 232, 67, 128, 138 SNPs - AUC BZL, respectively: 0.684; 0.663; 0.670; 0.627; 5) PGS002240, PGS002241 - Mars et al. 2022; 1,092,093 (AUC BZL: -) and 6,497,734 SNP (AUC BZL: -) PRS for risk prediction of common diseases. 6) PGS003460 - Chen F et al. 2023; 278 SNPs - AUC BZL: 0.702; 7) Barcode1 - 130 SNPs - AUC BZL:0.674. **Conclusions:** We used WGS 15x to improve SNP capture associated with population genetic differences. PRS 269 (Conti et al., 2021) and PRS 278 (Chen F et al. 2023) yielded the best results, suggesting that a multiancestry-derived PRS may be applicable to the admixed Brazilian population. We continue including participants to confirm these results. Research Sponsor: None.

10579 **Poster Session**

Frequency and spectrum of BRCA pathogenic/likely pathogenic variants in the Hispanic population of south Florida: A retrospective analysis. First Author: Srika Amin, Miami Cancer Institute, Baptist Health South Florida, Miami, FL

Background: The genetic landscape of hereditary breast and ovarian cancer in diverse populations remains underexplored, particularly within Hispanic/Latino communities. While *BRCA1* and *BRCA2* pathogenic and likely pathogenic (P/LP) variants are well-studied in some ethnic groups, data on Hispanic populations with varied ancestries is limited. South Florida's unique demographic, characterized by a large Hispanic population with ancestries from the Caribbean, Central, and South America, provides an opportunity to examine the prevalence and spectrum of *BRCA1* and *BRCA2* variants in this group. **Methods:** Data was extracted from Progeny and Cerner PowerChart and de-identified in MS Excel. The cohort consists of individuals who underwent germline genetic testing (ranging from single site to multigene panels) at Miami Cancer Institute's Clinical Genetics clinic from 01/01/2017 to 07/08/2022 with a personal/family history of breast and/or ovarian cancer. The sample was categorized by self-reported race, ethnicity, and ancestry, with a focus on White, Black, and Hispanic/Latino categories. We compared *BRCA1* and *BRCA2* P/LP variants across race/ethnicity. **Results:** A total of 3,784 cases were reviewed, predominantly female (97.6%), with 73.6% (n = 2786) affected by breast cancer. The median age was 54 years (range: 20-92). Most of the population identified as Hispanic/Latino (65%, n = 2,460), with Cuban ancestry reported most frequently on both maternal (38.4%) and paternal (37.3%) sides. The prevalence of *BRCA1* and *BRCA2* P/LP variants in Hispanic/Latino individuals was 5.1% (126 of 2460), with the majority having a BRCA2 variant (n = 86; 68.2%). Variants of uncertain significance were observed in 3.4% of the Hispanic population. The most frequent P/LP variants in *BRCA1* included c.211A > G (n = 5, 12.5%) and c.3331_3334delCAAG (n = 3, 7.5%). In *BRCA2*, common P/LP variants were c.771_775del (n = 8, 9.3%), c.2808_2811del (n = 6, 7%), c.5799_5802del and c.9235delG (each n = 5, 5.8%), and c.5073dupA (n = 4; 4.6%). **Conclusions:** This cohort revealed a variety of unique P/LP variants in *BRCA1* (n = 31) and *BRCA2* (n = 56), reflecting the genetic diversity in this population. Other cancer susceptibility gene P/LP variants were noted but were not the focus of the study. Notably, *BRCA2* c.771_775del (n = 8), an established Icelandic founder variant not reported to be recurrent in Hispanics, was only observed in those of Cuban/Spaniard ancestry in this cohort. Other variants, such as c.9235delG and c.5073dupA in *BRCA2*, were identified in Nicaraguan and Cuban populations for the first time. The study also highlighted common founder and recurrent variants in European, Caribbean, Central, and South American populations. South Florida's Hispanic population, including individuals from underrepresented regions, offers a rich and unique dataset of *BRCA1* and *BRCA2* P/LP variants. Research Sponsor: None.

10580 **Poster Session**

Mainstreaming the diagnosis of Lynch syndrome (LS) in colorectal cancer (CRC) patients: The ItaLynch study. First Author: Alberto Puccini, Humanitas University, Pieve Emanuele, IRCCS Humanitas Research Hospital, Humanitas Cancer Center, Pieve Emanuele, Milano, Italy

Background: International guidelines recommend universal screening for LS through somatic DNA mismatch repair deficiency (dMMR) testing in CRC. However, LS remains largely underdiagnosed, often due to inconsistent referrals from oncologists to genetic counseling and germline testing. We report preliminary results of the ItaLynch study, proposing a mainstream, oncologist-led diagnostic pathway for LS. **Methods:** ItaLynch is a prospective, observational, multicenter, multidisciplinary Italian study on pts with dMMR CRC. It started in May 2021, and is ongoing in 23 high-volume centers. The ItaLynch diagnostic pathway is based on three key steps. The first step is universal screening through dMMR testing by immunohistochemistry (IHC) in all CRC pts. The second step consists of reflex testing and a Lynch alert: MLH1-deficient (dMLH1) pts undergo reflex testing for $BRAF^{V600E}$ and, if wild-type, for MLH1 promoter methylation. A Lynch alert is added to the pathology report of all dMMR CRC pts. The alert is positive for pts with a high risk of LS as per reflex testing results or loss of non-MLH1 proteins; it is negative for pts not likely to have a hereditary predisposition (i.e. $BRAF^{V600E}$ mut or *MLH1* promoter hypermethylated dMLH1). The third and most innovative step is the oncologist-led mainstreaming germline testing for pts with a positive Lynch alert. Carriers of a germline pathogenic variant (PV) as well as those who have non-informative test results but are clinically suspicious are then referred to post-test genetic counselling. **Results:** Up to Dec. 19 2024, we enrolled 1,146 pts with dMMR CRC. Among the 937 pts eligible for the current analysis, 714 (76%) were dMLH1, and 223 (24%) displayed loss of non-MLH1 proteins. Reflex testing was carried out in 653 (91%) of the dMLH1 pts and 271 (41%) were *BRAF* wt. Of these, 219 (80%) subsequently underwent *MLH1* promoter methylation testing, and 98 (45%) were not hypermethylated. Of these, 60 (61%) underwent oncologist-led germline genetic testing, and 11 (18%) were carriers of an LS-associated PV. Among the 223 cases with loss of non-MLH1 proteins, 157 (70%) underwent genetic testing, and 86 (55%) were diagnosed with LS. At the time of writing, the overall proportion of LS cases is 10% (97/937 pts with data available for the current analysis). These 97 LS cases represent 45% of the 217 pts who were flagged with a positive Lynch alert and underwent oncologist-led genetic testing (60 of which with dMLH1 and 157 with non-MLH1 loss). **Conclusions:** Overall, our large cohort is representative of the population of pts with dMMR CRC. Our novel diagnostic algorithm, through the implementation of the Lynch Alert flagging system that identifies dMMR CRC pts with a high likelihood of LS and of an oncologist-led germline genetic testing, obtained a high diagnostic yield. Further analyses are ongoing on the entire cohort to evaluate the feasibility of the proposed diagnostic pathway. Research Sponsor: None.

10581 Poster Session

Identification of germline hereditary cancer syndrome variants and associated cancers in a healthcare biobank population. First Author: Juliann Savatt, Department of Genomic Health, Geisinger, Danville, PA

Background: Identification of pathogenic/likely pathogenic variants (P/LPV) in hereditary cancer syndrome (HCS) genes enables surveillance and prevention. Population genomic screening can complement traditional ascertainment of at-risk individuals based on personal or family history. But lack of data on cancer risks in unselected individuals with a HCS P/LPV challenges clinical decision making in these cohorts. We summarize a biobank's population screening for HCS variants and a case-control assessment of reported relevant cancers. **Methods:** MyCode is a health system biobank with >357,000 patients consented to research leveraging exome and electronic health record (EHR) data and to the receipt of medically relevant P/LPV. Available exomes were evaluated for P/LPV in 27 HCS genes based on predicted molecular consequence and ClinVar status. Clinically confirmed P/LPV were disclosed to eligible patients (cases). Patients' prior knowledge of their result was determined using EHR data and patient report. Relevant cancer diagnoses were extracted from the EHR using validated methods in cases and variant-negative controls (n=169,099) with available EHR data. Associations between P/LPV and relevant cancers were assessed using a Firth logistic regression in 9 genes with >30 cases. Ages of diagnoses were compared using Wilcoxon rank sum test. **Results:** 183,822 patients' exomes have been evaluated; 2,035 P/LPV in 27 HCS have been disclosed to 2,027 patients. 80% (n=1,625) of patients were previously unaware of their result. Increased odds and earlier ages of diagnosis for a subset of relevant cancers were observed in patients with P/LPV (Table). **Conclusions:** HCS P/LPV were disclosed to 1.1% of biobank patients, most of whom were unaware of their result. P/LPV were associated with a higher odds and earlier age of diagnosis of some relevant cancers compared to controls, indicating that genomic screening facilitates ascertainment of at-risk individuals. To guide clinical recommendations, research on cumulative cancer risks in broader populations will be needed. Research Sponsor: Geisinger; Goldsmith Foundation; Regeneron Genetics Center.

Associations (OR and 95% CI) between P/LPV and relevant cancers.

Gene	Breast	Ovarian	Pancreatic	Prostate	Colorectal	Endometrial	Thyroid (Medullary)	Renal
APC n=61					15.8 (6.5-33.5)*,a			
BRCA1 n=308	13.4 (9.6-18.5)*,a	28.6 (18.5-42.8)*,a	2.4 (0.5-6.7)	1.5 (0.8-2.6)				
BRCA2 n=599	6.0 (4.6-7.7)*,a	7.6 (4.6-11.9)*	2.1 (0.7-4.7)	2.4 (1.6-3.5)*				
PALB2 n=133	2.5 (1.2-4.7)*	2.5 (0.3-9.2)	6.0 (1.2-17.3)*	2.7 (1.0-6.4)*				
MLH1 n=48		2.2 (0.02-15.5)	3.4 (0.02-24.2)	0.5 (0.03-4.1)	59.6 (31.0-111.8)*,a	26.5 (11.6-56.3)*,a		
MSH6 n=212		0.6 (0.01-4.3)	2.1 (0.2-7.6)	1.7 (0.8-3.2)	5.2 (2.8-8.8)*,a	14.0 (8.3-22.5)*,a		
PMS2 n=194		1.9 (0.2-7.0)	0.7 (0.01-5.1)	1.0 (0.4-2.3)a	4.7 (2.4-8.2)*	4.3 (1.8-8.5)*		
RET n=105							2690.6 (1593.8-4580.1)*	
SDHB n=45								11.4 (3.1-30.5)*

*denotes significant OR α = 0.05, [a]age of diagnosis significantly lower in cases.

10582 Poster Session

Clinical characteristics of young-onset breast cancer and the role of germline pathogenic variants. First Author: Nara Tashjian, Mayo Clinic, Rochester, MN

Background: Breast cancer is the most common cancer in young women, with an increasing incidence over the past two decades. This study aims to evaluate the characteristics of young-onset breast cancers among patients aged ≤50 and compare tumor characteristics by germline mutation carrier status. **Methods:** Patients with breast cancer diagnosis ≤50 years old and evaluated across the Mayo Clinic enterprise between 2000 and 2024 were identified through the prospective Mayo Clinic Breast Cancer Study and the institutional tumor registry. Demographics, tumor characteristics, and clinical outcomes were obtained and described using summary statistics. Germline pathogenic or likely pathogenic variant (PV) carrier status for 5 established breast cancer predisposition genes (BRCA1, BRCA2, ATM, CHEK2 and PALB2) was available in a subset of unselected patients who consented to participation in sequencing studies at Mayo Clinic. Clinical characteristics were compared between PV carriers in each gene and non-carriers utilizing Chi-square test. All tests were two-sided and p-value less than 0.05 was considered statistically significant. **Results:** Among 8,462 patients (8435 women, 27 men) with breast cancer diagnosis at age ≤50 in the study, the median age of diagnosis of breast cancer was 44 years (range 18 – 49). At diagnosis, 84% had invasive disease, 43% of the tumors were high-grade, 15.8% had triple-negative breast cancer (TNBC), more than two-thirds (67.5%) presented with stage I or II breast cancer, and 3.7% had bilateral breast cancer. Among the 2,527 patients who consented to germline sequencing, 10.1% were found to be carriers of PVs; these included BRCA1 (3.3%), BRCA2 (2.7%), CHEK2 (2.3%), ATM (1.3%), and PALB2 (0.6%). Compared to non-carriers, a significant enrichment ($p<0.05$) of invasive breast cancer (92.6% vs. 83.3%) and high grade tumors (61.7% vs. 31.4%) were noted in BRCA1 PV carriers, and of bilateral breast cancer (13.4% vs. 3.8%) and high grade tumors (46.4% vs. 31.4%) in BRCA2 PV carriers. After exclusion of in-situ disease, proportion of TNBC was observed to be significantly higher in BRCA1 (61.3%), BRCA2 (15.5%) and PALB2 (30.7%) PV carriers compared to non-carriers (11.2%), whereas >90% of ATM or CHEK2 PV carriers had ER+ breast cancer and none had TNBC. A significant difference in stage at presentation was not observed by germline PV carrier status. **Conclusions:** The high frequency (>10%) of PVs in young-onset breast cancer underscores the importance for genetic testing in this population. The observed differences in breast cancer phenotypes based on germline PV carrier status among young-women may have significant implications for clinical outcomes and needs to be further explored. Research Sponsor: None.

10583 Poster Session

NuGenA (Nurse Led Genetic Counselling and Awareness): A proof-of-concept to implementation of genetic counseling for HBOC in LMICs. First Author: Asima Mukhopadhyay, Kolkata Gynecological Oncology Trials and Translational Research Group, Kolkata, West Bengal, India

Background: Poor access to genetic testing and counselling represents a major gap in cancer care in resource-restricted-settings. Our pilot work in Eastern India (2017-2019) demonstrated improved uptake of BRCA genetic testing (89% vs.55%) in ovarian cancer (OC) after training one nurse specialist in genetic counselling. We introduced NuGenA program in 2020 to scale-up this effort as proof-of-concept. **Methods:** Ethical approvals were obtained (KolGo/CTRI/2021/06/034308/HMSC). A nurse-led structured training program combining lectures/modules/live-demonstration-workshops/role-playing using offline and virtual learning methods were administered to sensitize/train all tiers of nurses including train-the-trainers in genetic counselling. A comprehensive NuGenA questionnaire including demographic, family history, CAM, pre/post-test counselling satisfaction-regret scale, QOL and willingness-to-pay (WTP) for genetic testing was administered by trained nurses. Physician and nursing interviews were conducted at 1 year to assess barriers/challenges/success of program. KolGoTrg EASE (Ethical/Acceptable/Affordable/Sustainable/Scalable/Effective/Early-diagnosis-and-treatment of barriers) matrix was used to measure key performance indicators and impact of implementation. **Results:** Through 40 sessions/workshops, 126 nurses were trained across India (8 centres, 34 nurses), Nepal (10 centres,30 nurses), Bangladesh (2 centres,60 nurses) and Africa (2 centres,2 nurses) with significant improvement in post training KAP scores. 7 genetic clinic/set-ups were created. 270 OC patients and 458 family members were counselled by nurses. 159 OC patients had BRCA testing, 48 (30%) being positive. Until now, out of 235 at-risk family members identified, 90 were counselled and 12 tested for BRCA (6 positive);2 opted for risk-reducing surgery. Unique barriers/challenges were identified including cost of BRCA test, provider hesitancy, social stigma, requiring customised solutions. WTP for genetic testing using CoPay model was accepted by 99/158 (62%). Another 100 community-nurses were sensitized through NuGenA camps/sessions approved by government/health authorities resulting in conduct of >150 COBRA (cervix/oral/ovary/breast-cancer awareness) sessions and patient-public-engagement initiatives. NuGenA modules are being included in national/international nursing curriculums. A World Ovarian Cancer Coalition charter-champion award and adoption by IGCS training sites exemplify global recognition/outreach. **Conclusions:** Nurse-led model proved scalable and impactful in resource-restricted settings, facilitating transformative changes in provider/patient-public engagement, attitude and practice towards genetic testing. Research Sponsor: Conquer Cancer, the ASCO Foundation; 2022IIG-7593471658; DST-UKIERI; DST/INT/UK/P-134/2016; OVARCOME, USA; MEDGENOME LABS LIMITED, INDIA; Kolkata Gynecological Oncology Trials and Translational Research Group.

10584 Poster Session

Concordance of somatic whole exome sequencing and germline genotyping of DPYD to screen for DPD deficiency. First Author: Aditya Sharma, Dartmouth Cancer Center, Lebanon, NH

Background: Fluoropyrimidines are amongst the most commonly used chemotherapeutic agents in the treatment of gastrointestinal and breast malignancies. Fluoropyrimidines carry a risk of severe adverse events in the 2-3 % of the population with DPD deficiency caused by decreased function variants of DPYD. As a result, pre-treatment testing to identify patients with decreased function variants including DPYD genotyping is critical. However, pre-treatment DPYD genotyping is not yet broadly used in the United States. We hypothesized that our in-house somatic exome DHCancerSeq assay could serve as an effective tool to screen for DPD deficiency. **Methods:** We identified patients in our health system with somatic whole exome sequencing who had clinical DPYD genotyping using either a limited real time PCR assay (including the *2A, *13, and c.2846A > T alleles) or a dedicated NGS-based PGx panel covering all known clinically relevant mutations in DPYD. HapB3 screening on the somatic whole exome was performed using only the coding sequence variant (c.1236G > A), not the causative deep intronic variant (c.1129-5923C > G), given the known high linkage disequilibrium amongst these variants. We then evaluated concordance of somatic whole exome sequencing and targeted germline genotyping. **Results:** A total of 115 patients had DPYD genotyping results from both somatic and germline testing and were eligible for evaluation of concordance (48 germline PCR tests and 67 NGS based). There was complete (100%) concordance of genotypes across germline and somatic assays, with genotypes of DPYD *1/*1 (106/106 samples), *1/*2A (3/3), *1/*13 (2/2) and *1/HapB3 (4/4). **Conclusions:** There was 100% concordance of somatic whole exome sequencing with traditional germline testing for DPYD deficiency. While germline testing remains the standard of care given the nuances of somatic copy number changes, our results suggest that somatic whole exome sequencing is a viable and efficient screening tool for DPD deficiency. Research Sponsor: None.

10585 **Poster Session**

Clinical features and occurrence of other cancers in patients with chronic lymphocytic leukemia and their families with *POT1* tumor predisposition syndrome. First Author: Jennifer Croden, The University of Texas MD Anderson Cancer Center, Houston, TX

Background: *Protection of telomere 1 (POT1)* tumor predisposition syndrome (POT1-TPD) is a hereditary leukemia predisposition syndrome that is identified in up to 5% of patients with chronic lymphocytic leukemia (CLL) and is characterized by a predisposition to other cancers such as gliomas, melanomas, angiosarcomas, and cardiac myxomas. Herein, we report clinical features and cancer diagnoses of the largest cohort of patients with CLL and members of families with POT1-TPD published to date. **Methods:** Patients and family members with pathogenic or likely pathogenic germline *POT1* variants evaluated in the Hereditary Hematologic Malignancy Clinic (HHMC) at MD Anderson Cancer Center were included. Individuals with a variant of uncertain significance (VUS) in the *POT1* gene were also included if found to have telomeres $>90^{th}$ percentile of age predicted length. **Results:** A total of 24 individuals in 17 families were identified. At the time of referral, 11 (46%) had a diagnosis of CLL, and 1 (4%) had monoclonal B-cell lymphocytosis (MBL). The remaining 12 individuals had no history CLL or MBL and were referred based on family history; however, 4 were found to have MBL at the time of referral (4/12, 17%). Among the 24 individuals, additional malignancies included: 6 melanoma, 3 hematologic cancers (1 CML, 2 NHL), and 1 papillary thyroid cancer. Among the 17 families, we documented a high reported prevalence of melanoma (8/17, 47%), CLL (6/17, 25%), glioblastoma (3/17, 18%) and sarcoma (2/17, 12%). Details of the *POT1* variants were available for 16 families. Variants were classified as pathogenic in 7 (44%), likely pathogenic in 7 (44%), and as VUS in 2 (19%). Additional pathogenic germline variants in *CHEK2*,*BRCA2*, and *MITF* were observed in 3 (19%) families, respectively. Five families had telomere length testing performed (31%), and lymphocyte telomere lengths were above the 99^{th} percentile in 60% and above the 90^{th}percentile in 100%. The patients with CLL (n=11) had a median age at diagnosis of 55 years (range 29-68). 82% of patients had diploid karyotype, 64% had del13q by FISH, and 60% had mutated IGHV. Of the 7 patients with NGS testing performed, additional somatic mutations were present in 6 (86%) and *NOTCH1* was the most common (43%). Five patients (45%) have received treatment for CLL with a median time to treatment of 4.5 years from diagnosis (95% CI 4.3, 4.6). Median overall survival of all patients was 13.8 years (95% CI 9.4, 18.3). **Conclusions:** This analysis provides insights into familial patterns of malignancy and the natural history of CLL in individuals with POT1-TPD. Patients with germline POT1 variants appear to develop CLL and MBL at an early age. Evaluation from a genetic counselor and augmented cancer screening due to the high risk of solid tumors and other hematological malignancies is paramount. Research Sponsor: None.

10586 **Poster Session**

Incidence of concurrent pathogenic variants in *BRCA1* breast cancer patients. First Author: Angel Lok Yiu Lee, Lenox Hill Hospital/Northwell Health, New York, NY

Background: Over the years, advancements in genetic testing have led to an expansion in the number of detectable mutations. This progress has enabled the identification of patients with pathogenic genetic variants, allowing for the implementation of tailored cancer screening strategies. For patients with breast cancer or high risk of breast cancer, there are advocates for comprehensive expanded genetic testing panels while others prefer to only perform selective testing for genes associated with breast cancer. The goal of this study was to determine how often patients with *BRCA1* pathogenic variants have additional mutations picked up on panel tests and whether they are clinically significant. **Methods:** We used the Myriad Collaborative Research Registry to access de-identified information on breast cancer patients with *BRCA1* variants. We looked at the data collected from individuals that were tested for mutations in 26 or more genes. We identified the most commonly mutated genes that are found in patients with *BRCA1* mutations. For this study, the term deleterious is equivalent to pathogenic/likely pathogenic. **Results:** Among breast cancer patients who underwent expanded panel testing for at least 26 genes, 10,250 individuals were identified to carry deleterious mutations. Of these, 400 patients had deleterious mutations in two or more genes. Within this subgroup, 184 individuals had deleterious *BRCA1* mutations along with at least one additional pathogenic mutation. Table 1 lists the most frequently mutated additional genes in patients with *BRCA1* mutations in our dataset. The most common pathogenic mutations that co-occur with *BRCA1* mutations were found in *MUTYH* (31.5%), *CHEK2* (12.5%), *BRCA2* (12.5%), and *ATM* (11.4%). One patient had deleterious mutations in *BRCA1* and two additional genes (*MUTYH* and *BRIP1*). **Conclusions:** Our data underscores the importance of evaluating patients for additional gene mutations. Extensive evidence demonstrates that certain pathogenic genes increase the risk of specific cancers. Restricting genetic testing to a targeted panel of breast cancer-associated genes may overlook other pathogenic genes that could predispose these individuals to additional malignancies. For instance, identifying pathogenic mutations in *PMS2*, in addition to *BRCA1*, could lead to meaningful alterations in clinical management. Further research is essential to investigate the clinical significance of co-occurring genetic variants, particularly those involving *BRCA1* and other high-risk genes. Research Sponsor: None.

Most commonly identified concurrent pathogenic genes in *BRCA1* breast cancer.

Concurrent pathogenic gene	Count
MUTYH	58 (31.5%)
CHEK2	23 (12.5%)
BRCA2	23 (12.5%)
ATM	21 (11.4%)
BRIP1	16 (8.7%)
PALB2	8 (4.3%)
PMS2	8 (4.3%)
NTHL1	6 (3.3%)
BARD1	4 (2.2%)

Genes in bold are known to be associated with breast cancer.

10587 **Poster Session**

Exploring the prevalence of germline mutations in young-onset biliary tract cancer (BTC). First Author: Osama M. MoSalem, Mayo Clinic Florida, Jacksonville, FL

Background: The American Society of Clinical Oncology (ASCO) and NCCN recommend germline testing for patients (pts) with biliary tract cancers (BTC), particularly those diagnosed at a young age. Prior studies estimate that approximately 15% of pts with BTC harbor pathogenic germline alterations. Germline testing can identify hereditary cancer syndromes, guide targeted therapy, and inform family counseling. This study aimed to further characterize and describe the prevalence of pathogenic germline variants (PGVs) in patients with young-onset BTC (YO-BTC). **Methods:** We conducted a retrospective review of medical records for pts diagnosed with YO-BTC (ages 18–55) across all Mayo Clinic tri-sites from January 2014 to October 2024. Data collected included results from germline DNA sequencing, tumor genetic testing, demographics, history of other malignancies, and family history of cancer. The primary outcome was the identification of pathogenic germline mutations associated with cancer predisposition. **Results:** Among 239 pts with YO-BTC, the median age at diagnosis was 43 years (range 19–55), with 62% female and 65.2% identifying as white. Clinical germline testing (e.g., Invitae, Ambry, Myriad) was performed in 123 pts (51.5%), revealing PGVs in 15 pts (12.1%), variants of uncertain significance (VUS) in 30 pts (24.3%), and likely benign variants in 4 pts (3.2%). Among those with PGVs, DNA repair mutations were the most common findings (10/15), including ATM (4), CHEK2 (2), BRCA2 (2), BAP1 (1), and PALB2 (1). One pt had a Lynch syndrome-associated mutation (MSH6), and four had mutations in other cancer-related genes (MUTYH, HOXB13, RMRP, and PIK3CA). Tumor genomic profiling (via CARIS, TEMPUS, or FoundationOne) was performed in 9 pts with PGVs, detecting the variant in 4 (44%), while liquid biopsy (Guardant) identified the PGV in 4 of 6 cases (66.6%).The majority of PGV carriers had advanced BTC (14/15), with intrahepatic cholangiocarcinoma being the most prevalent (11/15), while 4 had extrahepatic cholangiocarcinoma. Additionally, most PGV carriers had a first- or second-degree relative with a prior history of malignancy (14/15), and 3 pts had a second malignancy. Of the 15 pts with PGVs, 4 had BTC associated with primary sclerosing cholangitis. **Conclusions:** In this large institutional series of YO-BTC, PGVs were identified in 12.1% of pts, demonstrating a significant yield from germline testing in this population. Notably, tissue and liquid biopsies demonstrated different detection rates for PGVs, underscoring the variability in PGVs reporting across platforms. Germline testing through CLIA-approved methods should remain the standard of care. DNA repair pathway mutations, particularly ATM, CHEK2, and BRCA2, were the most frequently identified PGVs, highlighting their role in the pathogenesis of YO-BTC and their potential to guide treatment decisions. Research Sponsor: None.

10588 **Poster Session**

Limited versus expanded multigene germline genetic testing among adolescents and young adults (AYA) with breast cancer. First Author: Baha' Sharaf, King Hussein Cancer Center, Amman, Jordan

Background: In low- and middle-income countries, like ours, breast cancer is diagnosed mostly in younger women. With a median age of 50-52 years, breast cancer is diagnosed at least 10 years younger than in Western societies. Though most breast cancer cases are sporadic, 5-10% of cases are hereditary and mostly related to *BRCA1* or *BRCA2* variants. However, the widespread use of genetic testing, mutations other than BRCA1/2 are currently detected, the clinical importance of which is questionable. In this paper, we aim to study the prevalence and pattern of pathogenic/likely pathogenic (P/LP) variants among adolescents and young adults (AYA). **Methods:** Blood samples of patients with breast cancer diagnosed at age 39 years or younger were obtained for DNA extraction and sequencing. Mutations were classified as benign/likely benign (non-carrier), P/LP (carrier), and variant of uncertain significance (VUS). At the initial phases of testing, patients were tested for only *BRCA1* and *BRCA2* (n = 415), then *PALB2* was added (n = 145). With availability and affordability of germline genetic testing, 267 patients were tested utilizing an 84-gene panel before we settled on a 21-gene panel (n = 897). Testing was done at reference referral labs. All patients were counselled by a genetic counsellor before and after testing. **Results:** During the study period, a total of 1,724 patients with breast cancer diagnosed at age 18-39 had germline genetic testing and were included in the analysis. Majority (n = 1,530, 88.8%) were Jordanian, while the rest were non-Jordanian Arab. Median (range) age was 35 (15-39) years, and except for 6 patients, all were female. Among the whole group, 262 (15.2%) had pathogenic or likely pathogenic (P/LP) variants and were mostly *BRCA2* (n = 121, 46.2%) and *BRCA1* (n = 76, 29.0%). Other variants include *TP53* (n = 15, 5.7%), *ATM* (n = 12, 4.6%), *CHEK2* (n = 11, 4.2 %) and *PALB2* (n = 8, 3.1%). Rate of P/LP variants was significantly higher among patients younger than 30 years (23.6%) compared to a rate of 13.8% among older ones aged 30-39 years, p = 0.0001. Rates of P/LP variants were higher in patients tested with the 84-multigene panel (17.9%) compared to those who were tested with the 21-MGP (15.5%) or BRCA1/2 with or without *PALB2* (13.6%). VUS rates were significantly higher with expanded gene testing; 54.7% with 84-gene, 22.5% with 21-gene and less than 10% with limited gene testing, $p < 0.0001$. Limiting testing to *BRCA1, BRCA2, PALB2, CHEK2, TP53* and *ATM* would include 92.7% (n = 243) of all P/L variants. The remaining 19 (7.3%) are variants of low penetrance. **Conclusions:** The rate of P/LP variants in AYA patients, particularly those under 30 years, with breast cancer is higher than what has been previously observed in older patients. Expanding genetic testing beyond *BRCA1, BRCA2, PALB2, CHEK2, ATM*, and *TP53* in this age group leads to a lower yield and a significantly higher proportion of VUS. Research Sponsor: None.

10589 **Poster Session**

Sequential EHR interventions to increase genetic testing for breast and ovarian cancer predisposition across diverse patient populations in gynecology practices at Penn Medicine. First Author: Heather Heather Symecko, Basser Center for BRCA, Philadelphia, PA

Background: Genetic testing (GT) identifies individuals who may benefit from increased surveillance and risk reduction strategies. GT is under-utilized, especially in those without a personal history of cancer and in minority populations. **Methods:** We identified a patient cohort meeting NCCN criteria for genetic testing utilizing electronic health record (EHR) phenotyping in 2 diverse gynecological practices. NCCN criteria included individuals with a personal history of ovarian cancer, early-onset (<50) breast cancer diagnosed before 2021, or a family history (FH) of ovarian cancer or male breast cancer. Participants with prior genetics visits were excluded. Patient nudges and provider messaging strategies were introduced to boost genetic counseling consultation. Nudges included patient portal messaging (PP) followed by texts using the Way To Health platform (WH) in those that did not respond to PP. For non-responders to patient directed nudges, genetic counseling consult orders were placed using Epic's Pend & Send tool and sent to their gynecologist. Endpoints included the open rate for PP, response rate for the WH text, and the number of genetic counseling appointments completed. Differences between the clinics were calculated by Chi Square. **Results:** Of 1055 patients identified and who received a PP message regarding genetic counseling, 81% had a FH of ovarian cancer. Characteristics of the patient populations differed across clinics: Clinic D (n=505): 71.3% Black, 18% White and 67% < 45 years. Clinic R (n=550):10% Black, 83.5% White and 63% > 60 years.79% opened PP and 22.1% replied to PP, more in Clinic R (26.7% vs 17.0%, p<0.001). Patient engagement by PP or WH was 59.8% (631/1055), more in Clinic R (67.1% vs 51.9%, p<0.001). Of those that connected by patient nudges, 62.8% (396/631) declined additional follow-up (more in Clinic R, 41.5% then Clinic D, 33.3%, p=0.014), either due to incorrect family history in EHR, prior genetic testing, or, in the majority of cases, because they were not interested (296/631) (46.9%). Provider nudges added little to patient nudges with regard to GT uptake. 25% (266/1055) scheduled and 14.9% (157/1055) of the cohort completed GT appointments with no difference between the two (Clinic D 13.9% vs Clinic R 15.8%, p=NS). **Conclusions:** Patient directed nudges led to engagement of nearly 60% of patients in two diverse gynecology practices. 25% of individuals scheduled and 14.9% completed appointments, with continued follow-up. Although engagement in PP and WH differed between the two clinics, the number of visits did not. An EHR-based approach to identifying patients and encouraging genetic testing is a relatively low effort, scalable strategy to increase reach and encourage engagement in genetic counseling. However, a majority of patients either did not respond or did not wish to be tested. Clinical trial information: NCT05721326. Research Sponsor: National Cancer Institute; P50 CA244690; Basser Center for BRCA.

10590 **Poster Session**

Clinical utility of germline genetic testing in diverse cancer types. First Author: Diane Renee Koeller, Dana-Farber Cancer Institute, Boston, MA

Background: Germline genetic testing (GGT) is often recommended for cancer patients with an estimated ≥10% risk of carrying a clinically actionable pathogenic germline variant (PGV). Clinical utility of GGT is understudied for many cancer types, making assessing risk challenging. Herein we describe interim results from a GGT study of diverse cancer types. **Methods:** The PROACTIVE (Profile And Cancer gene Testing for IndiVidual Evaluation) Study is an ongoing institute-wide study at Dana-Farber Cancer Institute through which participants may opt-in to blood- or saliva-based clinical GGT of 133-156 genes, with results returned. Participants were identified by their clinical program, mainly consisting of those who did not meet clinical criteria for GGT based on having cancers that are considered low-risk for hereditary cancer predisposition syndromes. Clinically actionable PGV were defined as those that conferred potential eligibility for clinical management guidelines, targeted therapies and/or clinical trials. **Results:** Between 03/15/2019 and 11/30/2024, 1569 participants completed GGT. PGV were identified in 437/1569 (27.9%) participants, however 285 (18.2%) had PGV associated only with autosomal recessive cancer risk or low penetrance. Clinically actionable PGV were identified in 152/1569 (9.7%) participants and made up one-third (152/437) of PGV results. Clinically actionable PGV were identified most frequently in *ATM*, *CHEK2*, *APC*, *BRCA2*, and *TP53*, with the highest rates in gastric, central nervous system (CNS), and thyroid cancer (Table). High risk PGV were identified in 67/1569 (4.3%) participants, and were most frequent in the gastric, thyroid, and CNS cohorts (Table). Only 47/1569 (3.0%) participants had a PGV that was concordant with their cancer type. **Conclusions:** GGT identified clinically actionable findings in nearly 1 in 10 participants, most of whom were considered low-risk for hereditary cancer predisposition based on their personal cancer types. Most clinically actionable results were secondary findings unrelated to the presenting cancer type, but still impact cascade testing and screening for second primary cancers. This demonstrates the clinical utility of offering universal pan-cancer GGT to a broader range of cancer patients. Research Sponsor: None.

Largest cohorts by cancer type.

Cancer Type^	N	Any PGV (%)	Clinically Actionable PGV (%)	High Risk PGV (%)	PGV Concordance with Cancer Type (%)
Lung	409	130 (32)	41 (10)	16 (4)	8 (2)
Sarcoma*	229	59 (26)	19 (8)	9 (4)	6 (3)
Endometrial (normal IHC)	206	52 (25)	13 (6)	6 (3)	5 (2)
CNS*	125	37 (30)	15 (12)	6 (5)	3 (2)
Renal*	121	27 (22)	8 (7)	5 (4)	2 (2)
Bladder	77	13 (17)	5 (7)	2 (3)	0 (0)
Thyroid*	56	14 (25)	6 (11)	4 (7)	2 (4)
Cholangiocarcinoma	53	10 (19)	4 (8)	2 (4)	0 (0)
Gastric	40	13 (33)	7 (18)	3 (8)	1 (3)

*Includes adult and pediatric participants.

^Additional enrolled cancer types with fewer participants (N) include: melanoma, mesothelioma, multiple myeloma, therapy-associated polyposis, tongue, colon, breast.

10591 **Poster Session**

Clinical significance of germline CFTR mutations in pancreatic cancer. First Author: Nicholas Liguori, Cedars Sinai Medical Center, Los Angeles, CA

Background: Pancreatic ductal adenocarcinoma (PDAC) remains a malignancy with high cancer-related mortality. The majority of PDAC is sporadic, but approximately 10% are implicated by germline mutations. We recently reported that CFTR was one of the most mutated germline genes occurring in 11.9% of 1203 patients with PDAC. However, the clinical implications of germline CFTR mutations remain unknown. This study sought to evaluate the differences in clinical outcomes in PDAC patients with and without germline CFTR mutations. **Methods:** Eligible patients were ≥18 years who consented for BioBank specimen collection and Invitae genetic testing (n = 66). Patients were separated into two groups: patients with a known CFTR mutation (pathogenic variant or variant of uncertain significance (VUS)) (n = 35), and an age- and stage-matched cohort with no known CFTR mutation (n = 31). Subgroups were further stratified by stage at diagnosis: Stage I-III (early stage) vs Stage IV. Survival analysis was performed using Kaplan-Meier method and log-rank testing. A P-value < 0.05 was considered significant. Multiple linear regression was performed to investigate any associations between clinical variables (age at diagnosis, pathogenic variant vs VUS, history of smoking, alcohol use, pancreatitis) and survival. **Results:** A total of 35 patients with germline CFTR mutations and 31 age- and stage-matched patients were analyzed. Across all stages, the CFTR group had a median OS of 868 days vs 462 days (95% CI 1.014-3.48, P = 0.0390) in the non-mutated group. There was no difference in median OS between CFTR-mutant and non-mutant groups when stratified by early stage (I-III) disease: 929 days vs 765 days (95% CI 0.5950-2.478, P = 0.8543), respectively. Notably, CFTR mutated patients with stage IV disease derived greater OS benefit compared to the non-mutated group (572 days vs 182 days, 95% CI 1.025-9.639, P = 0.0140). Within the pathogenic (n = 25) and VUS (n = 10) subgroups of the germline CFTR mutant group, there was no difference in survival between those with pathogenic variants vs VUS (868 days vs 535 days, 95% CI 0.5233-5.031, P = 0.3573). Within the CFTR group, there was no difference in outcomes when analyzing for exposure to risk factors including smokers and non-smokers (868 days vs 572 days, 95% CI 0.2290-1.897, P = 0.5137), history of pancreatitis and no pancreatitis (929 vs 868 days (95% CI 0.3719-3.080, P = 0.5877), and alcohol use (chronic and social) and no alcohol use (939 days vs 622 days, 95% CI 0.5245-4.345, P = 0.0612). Multiple linear regression did not show any significant associations between pre-specified clinical variables and survival. **Conclusions:** This study suggests there is an association between germline CFTR mutation and improved survival in patients with advanced PDAC. CFTR may be a potential prognostic biomarker, which underscores the need for further studies focusing on the implications of CFTR mutations and PDAC. Research Sponsor: None.

10592 **Poster Session**

Germline genetic testing for hereditary cancer syndromes among newly diagnosed patients with solid tumors: A report of 10,000 patients from the Jordanian Exploratory Cancer Genetics study. First Author: Hikmat Abdel-Razeq, King Hussein Cancer Center, Amman, Jordan

Background: Hereditary factors play a key role in the risk of developing several cancers. Identification of germline cancer predisposing genes can have important implications for cancer screening, risk-reduction, risk-reducing interventions, and treatment decisions. **Methods:** In this study, patients with various cancers diagnosed and treated at King Hussein Cancer Center (KHCC) between January 2014 and December 2024 who had germline genetic testing (GGT) were retrospectively reviewed. Most patients were tested as per the National Comprehensive Cancer Network (NCCN) guidelines for GGT, while 3,319 patients were tested as part of a study for universal testing of all newly diagnosed cancer patients. Genetic testing was performed at reference commercial laboratories, or at academic centers. **Results:** The study involved 9,872 patients, the mean age at diagnosis was 49.7 (range: 18-90) years. Breast cancer was the most prevalent cancer type, comprising 67.3% of all cases, followed by colorectal cancer at 11.5%. Pathogenic/likely pathogenic (P/LP) variants were detected in 1,007 (10.2%) of the patients, while variants of uncertain significance (VUS) accounted for 33.6% of all genetic test results, highlighting the challenges of expanded panel testing. The most frequently identified pathogenic genes were BRCA1 and BRCA2, with 197 (2.0%) and 333 (3.4%) P/LP variants detected, respectively. Other notable genes included CHEK2 (n=28), PALB2 (n=38) and TP53 (n=47). Breast and colorectal cancers showed the highest number of pathogenic variant detections, with breast cancer accounting for 66.3% of all P/LP cases. Among less common cancers, ovarian cancer demonstrated a relatively high pathogenic variant rate (21.9%) despite its lower overall prevalence. Testing eligibility played a significant role in outcomes, with the majority of patients undergoing guideline-based testing (60%) and 26% undergoing universal testing. Expanded testing panels increased the detection of VUS significantly but did not improve pathogenic variant detection rates compared to guideline-based testing (p<0.001). There was also a significant association between cancer type and genetic testing results (p<0.001), underscoring the importance of cancer-specific testing strategies. **Conclusions:** These findings highlight the high prevalence of pathogenic variants in breast and colorectal cancers, the clinical relevance of BRCA1/2 and other high-risk genes, and the trade-offs of expanded genetic testing panels in balancing broader detection capabilities with interpretive challenges due to increased VUS rates. This emphasizes the need for targeted genetic counseling and strategic use of comprehensive testing panels for optimal clinical impact. Research Sponsor: None.

10593 **Poster Session**

Results of a program addressing multi-level barriers to completion of hereditary cancer genetic testing (GT) among underserved and minority individuals in Texas. First Author: Darya Aleksandrovna Kizub, The University of Texas MD Anderson Cancer Center, Houston, TX

Background: 5-10% of breast and colorectal cancers are hereditary, but uptake of GT among eligible individuals remains low. Our previous study showed that only 10 % of the 150 underserved and minority women deemed eligible for GT based on our validated Cancer Genetic Risk Assessment (CGRA) completed GT. Based on lessons learned, we implemented a multi-level program including: 1) genetic services education; 2) one-stop CGRA screening, scoring, and GT, 3) financial navigation, 4) telegenetics, and evaluated its impact. **Methods:** This prospective 12-months two-part program was implemented in Harris County, Texas, in 2023-2024. The primary outcome was GT completion. Both participants and providers received education about hereditary cancers. In the first part of the program, women who presented for mammography screening at clinics in underserved communities filled out the CGRA. In the second part, participants who identified as Black filled out the CGRA during events organized by trusted community organizations. The CGRA was scored and, if warranted, a saliva-based GT kit was offered during the visit or mailed later. Our study coordinator assisted with all financial paperwork. When a pathogenic variant (PV) or variant of uncertain significance (VUS) was found, participants received telegenetic counseling; others were notified of negative results. Sociodemographic characteristics and genetic services participation were analyzed via descriptive statistics and standard tests of association. Program implementation was assessed via in-depth interviews with a purposeful sample of participants and providers, which were audio-recorded, transcribed, double-coded, and analyzed via thematic analysis. **Results:** In the first part of the program, out of 870 women who presented for mammography screening and were approached, 590 (87%) agreed to be screened via CGRA (median age 52), including 537 (91.0%) who identified as Hispanic, 427 (72.4%) with preferred language Spanish. Median annual salary was 19,200. 99 (16.8%) were eligible for GT and 54 (54.5%) completed it, with 35 (64.8%) negative, 14 (25.9%) VUS, 5 (9.2%) PV in MUTYH , NF1, CHEK2, MSH3. In the second part of the program, out of 4,192 people who attended 20 community events, 390 (9.3%) individuals were screened via the CGRA (median age 54); all identified as Black. Median annual salary was 65,000. 187 (47.9%) were eligible for GT and 97 (51.8%) completed it, with 74.2% (72) testing negative, 22.7% (22) VUS, 3.09% (3) PV in RAD51C, CHEK2, BRCA1. GT completion was not associated with race, ethnicity, or salary ($p > 0.05$). Based on interviews with 56 participants and 16 providers, main GT facilitators included program convenience, while main barriers included cost and fear of results. **Conclusions:** Our program was successful in improving GT completion among underserved and minority participants. Clinical trial information: NCT05649072, NCT05694559. Research Sponsor: Susan G. Komen; CH22GCT001; The Community Outreach and Engagement Fund for Underserved Texans (COEFUT) sponsored by the Quasi Endowment Committee (QEC); RCTS number: 2022-00060886-Y1.

10594 **Poster Session**

Germline genetic testing among patients with pancreatic cancer (PC): A Pancreatic Cancer Action Network (PanCAN) patient survey. First Author: Udhayvir Singh Grewal, University of Iowa Hospitals and Clinics, Iowa City, IA

Background: Universal germline genetic testing for PC is endorsed by multiple professional organizations like the National Comprehensive Cancer Network (NCCN), yet implementation remains limited. We sought to investigate practices related to germline testing in PC and identify potential causes of under-testing through a large patient survey. **Methods:** We used the PanCAN patient registry to administer this HIPAA-compliant survey electronically to patients and caregivers. Logistic regression was used to determine the association between patient-reported demographic and clinical characteristics and the odds of undergoing germline genetic testing. A multivariate model was built to include all characteristics that were significant on univariate analysis. The association between receipt of genetic counseling and cascade germline genetic testing among first degree relatives (FDR) of patients with germline mutations was assessed via a chi-square test. **Results:** A total of 1,046 patients with PC were included, of which, 724 (69.2%) reported undergoing germline genetic testing. On multivariate analysis, race ($p = 0.01$), insurance type ($p < 0.01$), stage ($p < 0.01$), and treatment facility type ($p < 0.01$) were significantly associated with the odds of undergoing germline genetic testing after PC diagnosis. Black patients (compared to White) [OR = 0.42 (95% CI 0.23-0.78)], uninsured patients (compared to Medicare) [OR = 0.11 (95% CI 0.03-0.44)], patients insured through Veterans Health Administration (compared to Medicare) [OR = 0.26 (95% CI 0.08-0.92)] and patients receiving care at large [OR = 0.62 (95% CI 0.46-0.84)] and small community practices (compared to academic/teaching hospitals) [OR = 0.51 (95% CI 0.29-0.88)] were at significantly decreased odds of undergoing germline genetic testing. Patients with stage IV (compared to stage I) [OR = 2.23 (95% CI 1.46-3.40), stage II/III PC (compared to stage I) [OR = 1.58 (95% CI 1.11-2.23)] and those with private insurance (compared to Medicare) [OR = 1.51 (95% CI 1.11-2.05)] were at significantly increased odds of undergoing germline genetic testing. Of 724, 167 (23.2%) patients reported testing positive for germline mutations. Only 103 of 167 (61.7%) of these patients reported cascade testing among FDR. Patients undergoing genetic counselling had higher rates of cascade germline genetic testing among FDR (67.7% v 38.2%, $p < 0.01$). **Conclusions:** This is one of the largest patient-reported surveys from recent times suggesting sub-optimal implementation of guideline-based germline genetic testing in PC. This study highlights key inequities in testing based on race, insurance and practice setting. Our findings also underscore the critical role of genetic counselling in facilitating cascade testing among FDR of patients with PC and germline genetic mutations. Research Sponsor: None.

10595 **Poster Session**

Concordance of parent-of-origin predictions for hereditary cancer variants using proband-only analysis. First Author: Lilian Cordova, Department of Medical Genetics, University of British Columbia, Vancouver, BC, Canada

Background: Determining the parental origin of germline variants is a critical gap in clinical genetics, essential for risk management, variant classification, and cascade genetic testing. Traditional methods rely on testing family members, which can be time-consuming and impractical when relatives are unavailable, deceased, or unwilling to participate. Parent-of-Origin-Aware Genomic Analysis (POAga) offers a transformative solution by enabling accurate assignment of any autosomal variant to either parent with 99% accuracy using only a blood sample from the proband. This method integrates methylation and sequence data from Oxford Nanopore long-read sequencing with chromosome-length haplotypes generated from Strand-seq, leveraging the accurate phasing of imprinted differentially methylated regions (iDMRs) that occur on each autosome to infer the parent of origin (PofO) of variants across the genome. This study aims to validate POAga across multiple hereditary cancer syndromes, including high-penetrance conditions such as hereditary breast and ovarian cancer (HBOC) and Lynch syndrome, as well as rarer syndromes with PofO effects and other genes associated with breast and gastrointestinal malignancies. **Methods:** Blood samples from carriers of pathogenic variants in *ATM*, *BRCA1*, *BRCA2*, *CDH1*, *MLH1*, *MSH2*, *MSH6*, *PMS2*, *EPCAM*, *PALB2*, *SDHD*, *SDHAF2* and *TP53* with known parental segregation, are currently being ascertained and undergoing whole-genome analysis to determine the analytic validity of POAga. These samples span diverse demographics, including variations in age, sex, ethnicity, and cancer status. PofO predictions are made according to previously described methods (Akbari V, Hanlon VCT, *et al*. Cell Genom. 2022 Dec 21;3(1):100233) under an REB-approved protocol. **Results:** To date, 188 individuals carrying 189 pathogenic variants with known parental segregation have been analyzed. The distribution of variants includes *BRCA2* (n=31), *MLH1* (n=23), *MSH2* (n=22), *BRCA1* (n=22), *SDHD* (n=21), *MSH6* (n=20), *PALB2* (n=14), *PMS2* (n=13), *ATM* (n=9), *CDH1* (n=9), *SDHAF2* (n=2), *EPCAM* (n=2) and *TP53* (n=1). PofO assignment was successful for 172 of 189 (91%) variants. Only one sample with an *MLH1* variant was misassigned, while all other cases demonstrated concordance between the predicted and known parental origin (188 of 189, 99.5% accuracy). **Conclusions:** These results support the ability of POAga to accurately infer the parental origin of pathogenic variants in diverse hereditary cancer syndromes using only blood sample from the proband. Ongoing validation will further assess its feasibility in real-world clinical settings and refine its clinical translation. POAga represents a powerful advancement in hereditary cancer genetics, with the potential transform how we conduct genetic cancer risk assessments for patients and families. Research Sponsor: BC Cancer Foundation; Canadian Institutes of Health Research; Genome Canada Genomic Applications Partnership Program; University of British Columbia; Canadian Foundation for Innovation; Canada Research Chairs Program; BC Cancer.

10596 **Poster Session**

Clinical decision support system based on artificial intelligence and the patient's subjective intention treatment model: A randomized controlled clinical trial. First Author: Lu Wang, Department of Oncology, Tongji Hospital of Tongji Medical College, Huazhong University of Science & Technology, Wuhan, China

Background: To achieve intelligent diagnosis and treatment of tumors through the application of artificial intelligence and to meet the needs of areas lacking medical resources, a new treatment model based on the patient's subjective intention (PSI) was proposed, and a clinical decision support system (CDSS) called Doctors In Hands (DIH) was designed. Here, we report the DIH trial with the PSI treatment model to evaluate its efficiency. **Methods:** In this randomized controlled open-label trial (ChiCTR2400094469), patients from the departments of oncology, internal medicine, and surgery signed informed consent forms and were randomly divided into the clinician group, the CDSS plus clinician group and the CDSS group. The PSI treatment model was applied in the CDSS group. The primary endpoint was the sensitivity of alternative diagnoses and treatment options. The secondary endpoints were patient satisfaction and the specificity of alternative diagnoses and treatment options in different departments and groups. A multimodal large model based on the novel PSI treatment model was used as the intelligent platform for diagnosis and treatment data analysis and human–computer interaction. **Results:** A total of 120 patients and 9 doctors were enrolled and randomly divided into three groups. In the clinician group, the sensitivity and specificity of diagnosis were 0.82 and 0.76, the Youden index was 0.58. In the CDSS group, the sensitivity and specificity were 0.85 and 0.80, the Youden index was 0.65. For the CDSS plus clinician group, the sensitivity and specificity were 0.90 and 0.87, the Youden index was 0.77. Subgroup analysis of patients according to treatment strategy revealed that the satisfaction of patients in the PSI-based CDSS group was significantly greater than that of patients in the clinician group (92% vs. 86%, $P < 0.01$), but there was no significant difference between the CDSS group and the CDSS plus clinician group (92% vs. 93%, $P = 0.37$). Subgroup analysis of the PSI-based CDSS group according to diagnostic strategy revealed that the diagnostic accuracy for patients from the department of oncology was significantly greater than that for patients from the department of internal medicine (0.88 vs. 0.81, $P < 0.05$) but was not significantly different from that for patients from the department of surgery (0.88 vs. 0.87, $P = 0.14$). **Conclusions:** DIH has good performance in the diagnosis of tumors and development of treatment plans. In the PSI model, patients can make independent choices regarding disease treatment plans according to the objective clinical or basic research evidence provided by DIH to reduce the duration of consultation and save medical resources. The clinical significance of this trial is that the CDSS can promote the sharing of medical resources and improve the efficiency and quality of clinical work in areas lacking medical institutions. Clinical trial information: ChiCTR2400094469. Research Sponsor: None.

10598 **Poster Session**

Impact of incretin mimetic therapy on weight change in patients with cancer: A pan-cancer analysis from a single institutional cohort. First Author: Yan Leyfman, Icahn School of Medicine at Mount Sinai South Nassau, Oceanside, NY

Background: An elevated body mass index (BMI) is a frequent comorbidity in patients with cancer. Chemotherapy can exacerbate metabolic dysfunction and weight gain, further complicating cancer management. Glucagon-like peptide-1 receptor agonists (GLP-1RA) are indicated for the treatment of diabetes (DM) and obesity, promoting weight loss through mechanisms such as insulin secretion, delayed gastric emptying, and reduced appetite. However, their effect after a cancer diagnosis, particularly during chemotherapy, remains underexplored. **Methods:** This was a single-institution retrospective study evaluating cancer patients prescribed GLP-1 receptor agonists (GLP-1RA). Patient demographics, cancer type (solid vs. hematologic), and treatment details were extracted from the medical records. The overlap between GLP-1RA therapy and chemotherapy administration was recorded. Changes in BMI were analyzed using descriptive statistics, including percentiles and median values. A one-sample t-test assessed the overall significance of BMI changes, while subgroup analyses using Welch two-sample t-tests evaluated the impact of chemotherapy, sex, and cancer type on BMI reduction. R software was used to perform statistical analyses. **Results:** Between 2015 and 2024, 339 cancer patients were treated with GLP-1RAs, mainly semaglutide (48%) and liraglutide (28%). DM was the primary indication in 92% patients (Table 1). The median age at initiation was 60.8 years (range: 19.0–88.2), for a median duration of 11.8 months (range: 2.6–94.1). Median BMI decreased from 32.5 kg/m² (range: 18.9–58.9) pre-treatment to 31.5 kg/m² (range: 16.6–60.2) on/post-treatment, with a median change of -1.0 kg/m² (95%CI: -1.64, -1.01) and a median percentage reduction of -3.71% (95%CI: -4.59%, -2.83%). Subgroup analyses showed significant BMI reductions in patients receiving chemotherapy (median: -4.18%, 95%CI: -6.38%, -2.82%) and those not receiving chemotherapy (median: -2.32%, 95%CI: -4.32%, -2.31%), with no significant difference between the groups (95%CI: -0.22, 1.28). Additionally, BMI reductions were consistent across sex (95%CI: -0.91, 0.36) and cancer type (solid vs. hematologic, 95%CI: -0.77, 0.64). **Conclusions:** GLP-1RA use resulted in weight loss in cancer patients independent of chemotherapy exposure, sex, or cancer type. Although the degree of weight loss was modest, findings were consistent with GLP1-RA treatment dosed for a diabetes indication. These findings support the need for clinical trials evaluating incretin mimetics for weight management and their potential impact on cancer-specific outcomes. Research Sponsor: None.

Patient demographics.

Variable:	# of Patients (*n*):	%:
Sex: F / M	180 / 156	54 / 46
White	171	61
Black	56	20
Asian	20	7
Other Race or Unknown	34	12
Solid Tumor	249	74
Hematological Cancer	87	26
Chemotherapy During GLP-1RA	103	30
GLP-1RA Use for DM Indication	313	92

10599 **Poster Session**

Assessing the association between cycles of fertility treatments with gonadotropins and cancer risk. First Author: Amichay Meirovitz, Soroka - Clalit and Ben Gurion University Medical Center, Be'er Sheva, Israel

Background: Fertility treatments such as in vitro fertilization (IVF) and controlled ovarian hyperstimulation relies on exogenous hormones known as gonadotropins that directly stimulate ovarian activity. Concerns have arisen regarding the increased risk of hormone-sensitive cancer development due to repeated hormonal stimulation. The literature regarding this risk is ambiguous. We aimed to assess the association between the number of fertility treatments with gonadotropins (FT-GT) cycles and cancer risk in a large national HMO database. **Methods:** The Clalit Health Services database was analyzed between 2003-2013 to identify females who underwent FT-GT along with matched controls by age, ethnicity and socioeconomic status. FT-GT cycles were identified through the use of gonadotropins. Controls were matched 4:1 with untreated females. Patients were grouped based on number of FT-GT cycles being 1–4, 5–7, or $\geq$8. Cancer risk analysis focused on breast, colon, thyroid, stomach and pancreas, as well as any detectable cancer. We performed a separate sub-analysis of women who received $\geq$10 FT-GT cycles. **Results:** A total of 178, 637 patients were analyzed- 39,068 received FT-GT; 24,716 underwent 1–4 cycles; 7,774 underwent 5–7 cycles; and 6,578 received $\geq$8 cycles. For the separate sub-analysis, 3,949 women received $\geq$ 10 cycles. The median follow-up was 12.6 years. The risk of breast cancer increased with the number of FT-GT cycles, with the highest risk observed in patients receiving $\geq$8 cycles (HR = 1.67, 95% CI: 1.22-2.27), followed by 5-7 cycles (HR = 1.42, 95% CI: 1.07-1.89), and 1-4 cycles (HR = 1.34, 95% CI: 1.15-1.56), when adjusting for hypothyroidism. When analyzing the $\geq$ 10 cycle sub-group, the hazard ratio for breast cancer reaches 1.79 (95% CI: 1.19-2.70). There was no correlation between FT-GT cycle number and colon, stomach or pancreatic cancer, or any other detected cancer. **Conclusions:** It appears that females receiving FT-GT are at a higher risk for breast cancer from the first cycle. The risk of breast cancer increases with the number of FT-GT cycles. None of the other cancers analyzed showed any significant cancer risk associated with FT-GT. Research Sponsor: None.

10600 **Poster Session**

Decoding oncology terminology: Using large language models for patient education. First Author: Yuqing Wang, Montefiore Medical Center - Albert Einstein College of Medicine, Bronx, NY

Background: Large language models (LLMs), such as OpenAI's ChatGPT-4, are designed to process natural language and generate responses to text-based prompts. While these models have shown promise in addressing clinical and patient-related inquiries, they lack integration with dedicated medical knowledge databases, leading to potential inaccuracies. Meanwhile, healthcare professionals and models explicitly trained in medical texts frequently rely on specialized terminology, which can create significant barriers to clear and patient-friendly communication. This study aims to utilize LLMs to translate complex medical terminology into easy-to-understand explanations, focusing on hematology and oncology fields where communicating medical concepts to the public is particularly challenging. Our objective is to develop a solution that ensures explanations are both accurate and accessible, bridging the gap between technical medical knowledge and patient comprehension. **Methods:** We curated a dataset of cancer-related terms and their explanations from two sources: the National Cancer Institute (NCI) Dictionary, which provides detailed medical definitions, and simplified explanations based on National Comprehensive Cancer Network (NCCN) guidelines for patients. Using Meta's LLaMA 7 B-based chat model, we implemented retrieval-augmented generation (RAG) to enable the model to access the NCI Dictionary as needed. To fine-tune the model to generate patient-friendly explanations, we applied LoRA-based supervised fine-tuning (SFT). The model was evaluated on a holdout set of terms. Readability was measured using the Flesch Reading Ease Score (FRES) and Dale-Chall Readability Formula (DCRF). Improvements in accessibility were quantified through a two-sample t-test, comparing the mean readability scores of the model's outputs against the baseline. **Results:** The fine-tuned model demonstrated significant improvements in both accessibility and readability, achieving a 5% and 4% increase in the FRES (baseline: 69.25; output: 72.60, $P < 0.01$) and DCRF (baseline: 9.50; output: 9.15, $P < 0.01$), respectively. Preliminary results also indicate the model's capability to translate entire paragraphs of dense medical text into patient-friendly explanations. Expert validation on a larger scale is currently underway, further solidifying the model's potential to revolutionize patient communication in oncology. This innovative approach sets a new standard for leveraging advanced language models in healthcare education. **Conclusions:** We successfully trained a LLM specifically designed to simplify complex oncology medical terms into patient-friendly language. By serving as a reliable tool for delivering precise and accessible medical information, it holds the potential to reduce the workload of healthcare providers and enhance patient understanding in clinical settings. Research Sponsor: None.

10601 **Poster Session**

Recruitment strategies and enrollment for a virtually supervised exercise intervention for Hispanic/Latinx breast cancer survivors. First Author: Christina Marie Dieli-Conwright, Dana-Farber Cancer Institute, Boston, MA

Background: Hispanic and/or Latinx cancer survivors remain underrepresented in clinical trials, particularly in exercise oncology and energy balance research, with less than 1% of exercise oncology trials focused on this population. The purpose of this analysis was to describe recruitment strategies and enrollment rates among Hispanic and/or Latinx breast cancer survivors screened for and enrolled in an exercise intervention. **Methods:** The ROSA Trial was a culturally tailored, virtually supervised exercise intervention designed to mitigate metabolic dysregulation in sedentary, overweight/obese Hispanic and/or Latinx breast cancer survivors. Trial recruitment strategies at the Dana-Farber Cancer Institute (DFCI) involved screening pre-determined electronic medical records of breast cancer patient lists for the DFCI Boston location, direct referral from the DFCI Merrimack Valley satellite which is comprised of $>$ 70% Hispanic patient population, recruitment letter mail outs the Massachusetts Department of Public Health (MDPH) cancer registry, American Cancer Society (ACS) Making Strides for Breast Cancer Boston events (2022-23), and media outlets. Descriptive statistics were used to determine frequency of recruitment strategies used and screening variables. **Results:** Trial recruitment occurred from September 2021-August 2024. The majority of women screened were identified at the DFCI Boston location (70%) followed by the MDPH (23%), DFCI Merrimack Valley (5%), and ACS events (2%). Out of 710 women screened, 396 were ineligible. Main reasons for ineligibility included did not identify as Hispanic/Latinx (n = 78; 19.7%), not sedentary (n = 60; 15.2%), and lived out of country/state (n = 56; 14.1%). Of the 314 women deemed eligible, 240 declined participation, with primary reasons including no communication response (i.e., never responded to voicemails or emails; n = 84; 35%), not interested (n = 46; 19.2%), and no time/scheduling issues (n = 42; 17.5%). There were 74 women who consented for the trial from the 314 deemed eligible, resulting in a 23.6% success rate. A total of 64 women were successfully randomized with 10 women unable to proceed to randomization due to no time (n = 4) or did not provide a specific reason/stopped responding to study staff (n = 6). Randomized participants were 55.47 $\pm$ 9.5 years old, overweight or obese (BMI = 30.33$\pm$ 5.6), postmenopausal (71%), diagnosed primarily with stage I (37.1%) or stage II (37.1%) breast cancer. **Conclusions:** Multiple recruitment strategies with specific attention to consistent points of contact are necessary to recruit Hispanic and/or Latinx breast cancer survivors in the Greater Boston area. Unique situations such as residency out of the country is important to consider in the planning of future trials among said population. Clinical trial information: NCT04717050. Research Sponsor: American Cancer Society.

10602 **Poster Session**

Women's breast cancer mortality trends: The impact of lifestyle factors from the 2021 Global Burden of Disease (GBD) study. First Author: Samantha El Warrak, University of Miami, Miami, FL

Background: Breast cancer (BC) remains a leading cause of death among women globally. Understanding the role of modifiable risk factors is critical for designing targeted prevention strategies. The 2021 GBD study offers a comprehensive analysis of global health, quantifying the impact of diseases and risk factors on morbidity and mortality worldwide. This study provides an updated risk factor analysis in relation to women's BC mortality over the past three decades. **Methods:** Data from the study were used to examine trends in BC mortality in the United States from 1990 to 2021, stratified by age group representing younger pre-menopausal (ages 20-54) and older post-menopausal women (ages ≥55), associated with five key risk factors: tobacco use, red meat consumption, alcohol consumption, high body mass index (BMI), and high fasting plasma glucose (FPG). Age-standardized mortality rates (ASMR) were calculated for each factor, and differences between age groups were analyzed. All rates were reported per 100,000 population. Joinpoint regression analysis was conducted to evaluate trends. **Results:** In 2021, a high red meat diet (consuming >70 g/day of red meat), was the leading risk factor for BC-ASMR overall (2.3), both in older (11.4) and younger (1.4) women, contributing 14% to ASMR across all age groups. Older women had significantly higher ASMR for all risk factors (Table 1). From 1990 to 2021, tobacco-associated BC-ASMR exhibited the greatest decline, with a global reduction of 55.06%, more pronounced in younger (58.39%) than older (46.58%) women. Alcohol-related mortality also decreased significantly, more evident in younger (37.69%) than older (13.09%) women. While the absolute increase in risk factor-associated ASMR was observed with high FPG (+4.4%), a proportional ASMR increase was observed for all three metabolism-related risk factors, including high FPG (+75%), high BMI (+32%), and alcohol use (+14%). High FPG was associated with increased BC-ASMR in both age groups, while younger women experienced a significant rise due to high BMI (+689%). **Conclusions:** These findings highlight the impact of modifiable risk factors on BC mortality. There is a notable reduction in tobacco and alcohol-related deaths, particularly among younger women, likely due to public health campaigns and smoking cessation programs. Moreover, the rising prevalence of alcohol intake in older women, the growing impact of metabolic-related morbidity in younger women, and the hormonal changes amplifying BMI-related risks in post-menopausal women, stress the need for targeted health interventions that could markedly reduce the burden of BC mortality globally. Research Sponsor: None.

Risk factors	Overall trend (1990-2021)	Ages 20-54	Ages ≥55
Tobacco	1.4→0.6	1.1→0.5	5.2→2.8
Alcohol use	1.4→1	1.3→0.8	4.6→4
High FPG	1.1→1.1	0.36→0.39	5.7→6.2
High BMI	2→1.6	0.02→0.1	12.5→10.4
Diet high in red meat	3.9→2.3	2.3→1.4	17.4→1.5

10603 **Poster Session**

Are indulgent lifestyle practices the driving determinants behind the rising cancer rates in young adult men? First Author: Nathan Tran, California Pacific Medical Center Research Institute, San Francisco, CA

Background: This study aims to determine trends and incidences of cancers associated with social behaviors including tobacco use, excess body fat, alcohol consumption, insufficient physical activity, and human papillomavirus infection among male adults in the U.S. over a 20 year study period. **Methods:** Cancer incidence was extracted from the United States Cancer Statistics Public Use Database (USCS). Tobacco associated cancers were defined as: oropharyngeal, esophageal, stomach, colorectal, liver, pancreas, larynx, lung, kidney, bladder, and acute myeloid leukemia cancers. Obesity associated cancers were defined as: colorectal, liver, kidney, and thyroid cancers. Alcohol associated cancers were defined as: oropharyngeal, esophageal, colorectal, liver, and larynx cancers. Physical-inactivity associated cancers were defined as colorectal cancers. HPV associated cancers were defined as: oropharyngeal, penile, and anorectal cancers. SEER*Stat 8.4.1.2 and Joinpoint regression program 5.0.2 were employed to calculate estimated and actual incidence rates per 100,000 women. **Results:** Based on USCS data, the 2021 incidence of tobacco, obesity, alcohol, physical-inactivity, and HPV associated cancers for males was 217.4, 111.9, 80.9, 27.2, and 9.5 per 100,000, respectively. Moreover, besides HPV associated cancers which had an average annual percent change (AAPC) from 2001-2021 of 0.9% ($p<0.001$) among males, physical-inactivity, alcohol, tobacco and obesity associated cancers decreased at -2.63% ($p<0.001$), -1.29% ($p<0.001$), -1.28% ($p<0.001$), and -0.41% ($p<0.001$), respectively. Evaluating cancer trends among young adult males, physical-inactivity, obesity, alcohol, and tobacco associated cancers have been increasing for males aged 20-49, each with the sharpest rise among those aged 20-24 at 4.15% (p=0.037), 3.43% ($p<0.001$), 2.09% ($p<0.001$), and 1.22% ($p<0.001$), respectively. In contrast, incidence for these cancers has been decreasing among all older age groups of men (≥50). Among 20-24 year old males in 2021, the incidence of tobacco, obesity, alcohol, and physical-inactivity associated cancers was 6.46, 4.8, 2.13, and 1.16 per 100,000 men, respectively. Lastly, HPV associated cancers decreased among all males younger than 55 and increased for older male age groups (≥55) - particularly for the 65-69 age group (AAPC: 2.17%, $p<0.001$). **Conclusions:** Of cancer-related sociobehavioral lifestyle risk factors, young men were most impacted by cancers associated with tobacco use. However, younger males observed the highest annual increases in cancer incidence for these modifiable risk factors, particularly in physical-inactivity in obesity and physical-inactivity associated and obesity associated cancers. Further research is warranted to investigate whether diet, physical inactivity, alcohol, tobacco, or HPV among younger adults play a larger role in these trends. Research Sponsor: None.

10604 **Poster Session**

Skewed offspring distribution of *TP53* pathogenic variants in Israeli Li-Fraumeni syndrome families. First Author: Naama Halpern, The Jusidman Cancer Center, Ramat Gan, Israel

Background: Li-Fraumeni Syndrome (LFS) [OMIM #151623] is an autosomal dominant cancer predisposition syndrome caused primarily by germline pathogenic (PV) or likely pathogenic variants (LPV) in the TP53 gene. Classical autosomal dominant (AD) inheritance predicts a 50% risk of inheritance for offspring of TP53 PV/LPV carriers. However, clinical observations in Israeli LFS families suggest a higher-than-expected prevalence of TP53 PV/LPV carriers among offspring. This study aims to further investigate this phenomenon. **Methods:** Relevant clinical data from 36 LFS families followed at Sheba Medical Center's high-risk clinic (2015–2024) were reviewed under an IRB-approved protocol. Twenty families met inclusion criteria after excluding those with incomplete clinical data or carriers without offspring. Detailed pedigree analyses were conducted to determine the carrier status of all offspring of confirmed and obligate TP53 mutation carriers. Probable carriers were defined as individuals who fulfilled two criteria: (1) a diagnosis of an LFS-associated malignancy, and (2) being a first-degree relative of a confirmed carrier. Deceased parents with LFS-associated malignancies, whose partners had normal TP53 sequencing and whose offspring tested positive for TP53 PV/LPV, were also considered obligate carriers. A t-test was used to compare the observed proportion of TP53 PV/LPV carriers among offspring with the expected 50% inheritance rate for AD conditions. **Results:** A total of 174 individuals met the study criteria and were either genotyped for the family-specific TP53 PV/LPV or assigned obligatory or probable carrier status. Of these, 115 (66.1%) were identified as TP53 PV/LPV carriers, either through genotyping (n= 87), obligatory (n= 13) or probable carrier designation (n= 15). This observed proportion was significantly higher than the expected 50% based on AD inheritance ($p<0.0001$). Out of the TP53 PV/LPV carriers, 67 (58.3%) individuals were healthy at the time of genotyping, and 62 (53.9%) were male. **Conclusions:** Our findings reveal a significant skewing of TP53 variant inheritance in Israeli LFS families, with a higher-than-expected prevalence of carriers among offspring. To our knowledge, this phenomenon has not been previously reported in LFS. A potential mechanism for this skewing may involve TP53's role in cell cycle regulation and apoptosis. Reduced TP53 protein levels could confer a selective advantage during early embryonic development by enhancing cell proliferation, potentially improving embryonic survival and implantation success. If corroborated in larger and ethnically diverse LFS cohorts, this finding could have implications for genetic counseling, particularly in reproductive decision-making for LFS families. Further research is needed to validate these findings and explore the underlying biological mechanisms driving this skewing. Research Sponsor: None.

10605 **Poster Session**

Long-term safety of belzutifan in von Hippel-Lindau syndrome: A single-center experience. First Author: Paulo Siqueira do Amaral, Vandebilt University Medical Center, Nashville, TN

Background: Belzutifan has improved control in Von Hippel-Lindau (VHL) syndrome, reducing the need for interventions. However, its long-term safety and side effect burden remain incompletely understood. This study evaluates long-term safety, tolerability and the impact of dose modifications in VHL patients (pts) treated with belzutifan. **Methods:** A single-center retrospective study of VHL pts ≥ 18 years treated with belzutifan at Vanderbilt (Nov 2018 - Dec 2024). Demographic and clinical data were collected. The primary endpoint was treatment discontinuation. Secondary endpoints included incidence of adverse events (AEs) (any-grade and grade ≥ 3 per CTCAE 5.0), dose reductions, time to dose reduction, treatment interruptions, subsequent procedures, and treatment failure (defined as radiological progression per RECIST 1.1 or physician assessment) while on treatment. Follow-up duration was defined as the time from the belzutifan initiation to last follow-up or discontinuation. **Results:** Twenty-five pts were identified, with a median age of 42 years, 64% female and 88% white, with a baseline hemoglobin of 13.7 (range: 11.0 – 19.0). As of January 2025, the median follow-up was 32.5 months (mo) (range: 2.5 – 75). Most common VHL-associated neoplasms included CNS hemangioblastomas (88%), renal cell carcinoma (72%), and pNET (32%). All pts started belzutifan at 120 mg. AEs occurred in 92% of pts (detailed in Table 1). Anemia was observed in 64% of pts (no grade ≥ 3), with a median onset of 3.4 mo (range: 1.1 – 17.7). Treatment interruptions were required by 68% of pts. At the last follow-up, 32% remained on 120 mg, 52% were on 80 mg, and 16% discontinued. The median time to discontinuation was 33 mo (range: 24.5 – 34); due to symptomatic anemia (1 pt), grade 3 hypoxia (1pt), disease progression (1pt) and a non-related death (1pt). Dose reductions were needed by 60% of pts, primarily due to anemia, with a median time to dose reduction of 6.8 mo (range: 1 – 17). Among the 15 pts with dose reductions, none experienced treatment failure during a median follow-up of 21.3 mo (range: 1 – 31), although one pt had persistent grade 3 hypoxia. No pts required transfusions and 8% received erythropoietin stimulating agents. Before belzutifan, 92% of pts had undergone procedures related to VHL manifestations. Following treatment initiation, 8% required additional procedures. **Conclusions:** These findings provide long-term safety data on belzutifan in VHL. While AE were common, dose reductions were effective in maintaining tolerability without compromising disease control. Research Sponsor: None.

Adverse events in at least 5% of the safety population (25 pts).

	Any-grade	Grade ≥ 3	Leading to dose reduction	Leading to discontinuation
Fatigue	20 (80)	1 (4)	4 (16)	0
Anemia	16 (64)	0	9 (36)	1 (4)
Nausea	8 (32)	0	2 (8)	0
Dizziness	8 (32)	0	0	0
Headache	7 (28)	0	1 (4)	0
Hypoxia	2 (8)	1 (4)	1 (4)	1 (4)
AST or ALT elevation	2 (8)	0	1 (4)	0
Cognitive impairment	2 (8)	0	0	0
Pericardial Effusion	2 (8)	1 (4)	2 (8)	0

LBA10606 **Poster Session**

The Genetic Information and Family Testing (GIFT) trial. First Author: Steven J. Katz, University of Michigan Medical School, Ann Arbor, MI

The full, final text of this abstract will be available at meetings.asco.org on the day of presentation and in the online supplement to the June 10, 2025, issue of the *Journal of Clinical Oncology*.

10607 **Poster Session**

Breast cancer post-ovarian cancer in germline non-BRCA homologous recombination (HR) gene pathogenic variant carriers. First Author: Ariadna Roque-Lloveras, Hereditary Cancer Program, Genetic Counseling Unit, Catalan Institute of Oncology (ICO), IDIBGI, Girona, Spain

Background: Ovarian cancer (OC) is characterized by deficiencies in homologous recombination (HR). Although germline and somatic *BRCA1/2* pathogenic variants (PVs) play a critical role in HR and OC, germline PVs in other genes associated with HR, such as *RAD51C, RAD51D, BRIP1*, and *PALB2*, have also been linked to an increased risk of OC development. Most of these genes are also associated with increased risk of certain types of breast cancer (BC). However, little is known about risks of secondary BC after OC in this germline non-BRCA HR population. **Methods:** We identified patients with OC treated at a single institution undergoing tumor-normal sequencing (MSK-IMPACT) from 07/01/2015 to 12/31/2020. Germline assessment of ≥76 genes was performed, including HR genes *ATM*, *BARD1*, *BRIP1*, *FANCA*, *FANCC*, *NBN*, *PALB2*, *RAD50*, *RAD51B*, *RAD51C*, and *RAD51D*. Biallelic inactivation was assessed within tumors at the germline variant locus using the FACETS (fraction and allele-specific copy number estimates from tumor sequencing) algorithm. In this study, genes with high rates of biallelic inactivation (≥60%) were included based on role in OC tumorigenesis. Thus, we focused on patients with *BRIP1*, *PALB2*, and *RAD51B/C/D* PVs and further extracted clinical data including secondary BC screening patterns and rates. **Results:** Of the 882 patients with OC and germline assessment, 56 (6%) had germline PV in non-BRCA HR genes, and 35 (4%) patients had germline PV in *BRIP1* (n = 13), *PALB2* (n = 4), *RAD51B* (n = 4), *RAD51C* (n = 4), or *RAD51D* (n = 10). With a median follow-up after OC diagnosis of 55.82 months, no metachronous BC diagnosis occurred in these 35 patients. Among this cohort, 23 (66%) patients received PARP inhibitor therapy for OC, and 17 (49%) patients died from OC. Three patients (9%) were diagnosed with BC before OC diagnosis (germline *PALB2*, *RAD51B,* and *RAD51D* PV carriers). All 3 patients were BC disease-free at the time of data cutoff, and 2 died of their OC. Twenty-five patients (71%) underwent BC screening during OC treatment/follow-up with annual mammography, and 4 (16%) underwent additional annual magnetic resonance imaging. Only two patients were more intensively followed due to abnormal breast findings that were resolved during the follow-up. No patients underwent risk-reducing breast surgery. Interestingly, 30 patients (86%) had a family history of cancer: 12 (40%) with breast cancer, 6 (20%) with ovarian cancer, 8 (27%) with both breast and ovarian cancer, and 4 (13 %) with other cancers. **Conclusions:** BC incidence after OC diagnosis and treatment in non-BRCA HR germline PV carriers remains low, probably due to the poor prognosis of OC and the potential preventive effects of PARP inhibitor treatments on BC development. Further prospective studies are needed to address this question. Research Sponsor: MSK Cancer Center Support Grant by the NIH/NCI (P30 CA008748); International Mobility Grants IDIBGI 2023; SEOM Visiting Fellowship for short-term visits to reference centers 2024.

10608 **Poster Session**

Codon 167 missense mutations in von Hippel-Lindau syndrome: Genotype-phenotype correlations in a population-based study. First Author: Jianhui Qiu, Department of Urology, Peking University First Hospital, Beijing, China

Background: Von Hippel-Lindau (VHL) disease is caused by germline mutations of the *VHL* gene, resulting in multi-centric and multiorgan tumors. Codon 167 is most commonly affected by pathogenic missense mutations (MMs). The objective of this study is to elucidate the clinical features of individuals with germline pathogenic MMs at codon 167 of *VHL*. **Methods:** 674 patients from 282 unrelated families were enrolled. Their clinical features and prognosis were reviewed. **Results:** 86 patients from 41 unrelated families were identified with codon 167 MMs, indicating codon 167 MMs account for the largest number of patients and families. Codon 167 MMs were associated with a significantly higher risk of pheochromocytoma (HR=7.384, 95%CI 4.496-12.126, P<0.001), lower risks of central nervous system hemangioblastoma/CHB (HR=0.568, 95%CI 0.412-0.781, P=0.001) and renal cell carcinoma/RCC (HR=0.693, 95%CI 0.483-0.993, P=0.046). And codon 167 MMs correlated with better overall survival (HR=0.408, 95%CI 0.210-0.790, P=0.008) and CHB-specific survival (HR=0.201, 95%CI 0.062-0.645, P=0.007) compared with other mutations. The most dominant types of codon 167 MMs are c.499C>T p.Arg167Trp (45.3%) and c.500G>A p.Arg167Gln (48.8%). Multivariate Cox regression analyses discover that the mutation type was not an independent factor for VHL-associated tumors. **Conclusions:** In the VHL disease population, codon 167 MMs account for more than 10% of patients and unrelated families. Individuals with codon 167 MMs had unique clinical features and should be described as a separate subtype of VHL syndrome. The results of this study were important for genetic counseling and clinical decision-making. Research Sponsor: Peking University First Hospital; 2023SF40.

Cox regression analyses of age-related tumor risks between codon 167 MMs, oMMs and TR.

Tumor	Variables	Univariate analysis			Multivariate analysis		
		HR	95%CI	P value	HR	95%CI	P value
Overall	**Sex** (Male vs. Female)	0.974	0.829-1.144	0.744	0.971	0.827-1.141	0.772
	Mutational type			0.510			0.505
	Codon 167 MMs	0.928	0.724-1.188	0.552	0.928	0.724-1.189	0.556
	oMMs	0.905	0.762-1.076	0.258	0.905	0.761-1.075	0.254
	TR	**Reference**			**Reference**		
CHB	**Sex** (Male vs. Female)	1.157	0.956-1.401	0.135	1.149	0.949-1.391	0.154
	Mutational type			**0.001**			**0.001**
	Codon 167 MMs	0.566	0.411-0.778	**<0.001**	0.568	0.412-0.781	**0.001**
	oMMs	0.772	0.631-0.946	**0.013**	0.774	0.632-0.947	**0.013**
	TR	**Reference**			**Reference**		
RA	**Sex** (Male vs. Female)	1.160	0.823-1.634	0.397	1.170	0.831-1.649	0.368
	Mutational type			**0.010**			**0.010**
	Codon 167 MMs	0.651	0.381-1.113	0.117	0.653	0.382-1.117	0.120
	oMMs	0.571	0.390-0.836	**0.004**	0.569	0.388-0.833	**0.004**
	TR	**Reference**			**Reference**		
RCC	**Sex** (Male vs. Female)	1.070	0.858-1.335	0.547	1.069	0.857-1.334	0.552
	Mutational type			0.092			0.092
	Codon 167 MMs	0.693	0.483-0.993	**0.046**	0.693	0.483-0.993	**0.046**
	oMMs	0.848	0.670-1.071	0.167	0.848	0.671-1.072	0.167
	TR	**Reference**			**Reference**		
PCT	**Sex** (Male vs. Female)	0.792	0.637-0.985	**0.036**	0.789	0.634-0.981	**0.033**
	Mutational type			0.356			0.330
	Codon 167 MMs	0.772	0.542-1.099	0.151	0.765	0.537-1.089	0.136
	oMMs	0.945	0.748-1.195	0.638	0.947	0.749-1.196	0.646
	TR	**Reference**			**Reference**		
PHEO	**Sex** (Male vs. Female)	1.145	0.788-1.663	0.478	1.153	0.793-1.676	0.455
	Mutational type			**<0.001**			**<0.001**
	Codon 167 MMs	7.374	4.491-12.110	**<0.001**	7.384	4.496-12.126	**<0.001**
	oMMs	2.603	1.592-4.257	**<0.001**	2.597	1.588-4.247	**<0.001**
	TR	**Reference**			**Reference**		

10609 **Poster Session**

Clinical characteristics and cancer spectrum among breast cancer patients with TP53 germline mutation from a single institution. First Author: Ashley Woodson, University of Texas MD Anderson Cancer Center, Houston, TX

Background: Li-Fraumeni syndrome (LFS), due to germline TP53 mutations, is associated with elevated risks of multiple cancers including early onset breast cancer (BC). Due to multi-disciplinary cancer screening and treatment access, The UT MD Anderson Cancer Center (MDACC) follows a large cohort of individuals diagnosed with LFS. We aimed to describe women with BC diagnosed with LFS and the spectrum of their additional cancer history before and after BC. **Methods:** Patients with BC and LFS were identified from a prospective BC database between 2001-2024. Patients with a pathogenic variant in TP53, and in two cases a variant of uncertain significance with special clinical consideration for LFS-management, were included for review. We evaluated the cancer histories and described the breast cancer characteristics of these women. We identified the incidence of secondary cancers post radiation therapy and secondary leukemia in patients who received alkylating agents given known secondary malignancy risks with such exposures. Summary statistics were generated for the population along with statistical methods for associations between factors of interest including, Chi-squared test and Fisher's exact test. **Results:** Ninety-six women were identified with a history of BC and clinically followed for a diagnosis of LFS. A total of 127 breast tumors diagnosed among 96 women with mean age 35.8 (range 20-69 years). Of these, 68 patients had one primary BC, 26 had two BCs, one had three BCs, and one had four BCs. Individuals ranged from having a diagnosis of 1 to 7 individual cancers; 54 individuals had BC as well as at least one other type of cancer besides BC. Among individuals with more than one cancer, excluding individuals with only BCs, BC was the first cancer diagnosis in 67% (36/54). Other than BC, the other most common cancers were 40 sarcomas, 14 leukemia/other hematologic malignancy, 9 thyroid cancers, 7 brain cancers, and 29 other cancers. Fifty-six percent (54/96) of women received radiation treatment with 14 (26%) individuals developing a subsequent radiation-induced malignancy (RIM). Fourteen percent developed a hematologic malignancy following anthracycline exposure (8/56). **Conclusions:** This study describes the LFS population followed in a high-risk, multi-disciplinary clinic to further understand the spectrum of cancers among women with BC. Our study found that 29% of patients have at least a second BC. More than half of the patients also had a non-BC primary and, in the majority, BC was their first cancer. We also found a high rate of RIM as well as high rate of hematologic malignancies. Understanding multiple cancer histories in LFS could lead to better screening for other cancers. Summarizing the natural history of cancer frequency helps clinicians better predict when genetic testing may be warranted and aim to increase early detection of subsequent cancers. Research Sponsor: None.

10610 **Poster Session**

Characterization of hereditary tumor risk in individuals with SDHA germline variants. First Author: Kelsey Ellis, Huntsman Cancer Institute at the University of Utah, Salt Lake City, UT

Background: Paragangliomas (PGLs) are rare neuroendocrine tumors with a high degree of heritability; up to 30% of individuals diagnosed with a PGL are estimated to have a germline pathogenic variant (GPV) related to hereditary PGL risk. GPVs in the *SDHA* gene have been associated with a PGL and gastrointestinal stromal tumor (GIST) risk lower than that of other hereditary PGL predisposition genes (van der Tuin *et al.* 2018). However, data about penetrance, tumor characteristics, and other aspects of *SDHA* carriers is limited. Further characterization of *SDHA* GPV is important to better understand tumor risks and develop *SDHA*-specific screening recommendations. **Methods:** Participants were identified from the Family Cancer Assessment Clinic at the University of Utah Huntsman Cancer Institute and had an *SDHA* pathogenic/likely pathogenic variant. Cancer diagnoses and diagnostic modalities were confirmed by medical records. **Results:** Out of 93 identified *SDHA*+ individuals, 14 (15%) had a personal history of an *SDHA*-associated tumor (10 PGL and 4 GIST). None of these individuals also had a known family history of an *SDHA*-associated tumor. Average age at diagnosis was 37 (range = 17-69) with two diagnoses under age 18. There were no cases of multiple PGL/GIST in a single individual. Head and neck PGLs were the most common *SDHA*-associated tumor (7/14, 50%). They appeared to have lower malignancy risk (0/7, 0%) compared to extra-adrenal PGL (3/3, 100%) and GIST diagnoses (3/4, 75%). Secreting PGLs were rare (1/10, 10%). SDHB immunohistochemistry staining was completed for 8/14 PGL/GIST and was deficient in 5/8 (63%). Fifty-four (58%) *SDHA*+ individuals were seen by HCI's hereditary paraganglioma clinic and 39 (42%) had undergone some type of high-risk PGL screening as of January 2025. The most common reasons for not undergoing screening or being seen by the clinic included age $<$10 years old or $>$70 (8/93), deceased status (4/93), and current active cancer treatment (16/93). Fifty-eight of 93 (63%) *SDHA* variants were an incidental finding or a known familial variant without a family history of PGL/GIST. Zero (0/79) asymptomatic individuals have had a documented PGL/GIST diagnosis after *SDHA*+ genetic testing. **Conclusions:** As work continues to develop gene-specific hereditary PGL screening recommendations, our analysis adds to the body of research affirming lower penetrance of *SDHA* variants compared to other hereditary PGL genes. Additionally, the lack of individuals with a personal and family history of *SDHA*-associated tumors or with multiple tumors indicates that a more nuanced approach to screening recommendations in this patient population is likely warranted. However, the younger age of onset and increased malignancy risk seen in the affected individuals in our study compared to sporadic PGL indicates that in certain contexts, such as in an individual diagnosed with a PGL/GIST, an *SDHA* GPV could impact surgical and treatment decisions. Research Sponsor: None.

10611 **Poster Session**

Famitinib for familial adenomatous polyposis-associated aggressive desmoid tumors: 32-month follow-up from a single-center exploratory study. First Author: Sai Ge, Department of Gastrointestinal Oncology, Key laboratory of Carcinogenesis and Translational Research (Ministry of Education), Peking University Cancer Hospital & Institute, Beijing, China

Background: Desmoid tumors (DTs) associated with familial adenomatous polyposis (FAP) are rare, locally aggressive soft-tissue tumors with high recurrence rates and poor prognosis. Famitinib, an orally administered multi-targeted tyrosine kinase inhibitor targeting VEGFR-2, PDGFR, c-KIT, and FGFR, has shown promising efficacy in a prospective, single-arm study for these patients (pts). This report presents updated efficacy and safety data from a 32-month follow-up. **Methods:** Pts with FAP carrying germline APC mutations and pathologically confirmed DTs that progressed within 6 months according to RECIST v1.1 criteria were enrolled. Famitinib was administered at 20 mg once daily in 3-week cycles. The primary endpoint was the objective response rate (ORR). Secondary endpoints included disease control rate (DCR), progression-free survival (PFS), overall survival (OS), and safety. **Results:** Between November 2021 and March 2023, 12 eligible pts were enrolled, with a median age of 35.5 years (range: 25-53). Of these, 41.7% (5/12) were male. Intra-abdominal (IA) DTs were present in 83.3% (10/12) of pts, while 2 pts had extra-abdominal (EA) DTs. Eight pts presented with stage III-IV DTs characterized by rapid progression and severe symptoms. As of January 20, 2025, the median follow-up duration was 32.2 months (21.8-37.9). Seven pts achieved partial response (PR), and five achieved stable disease (SD), with a median time to response of 7.1 months (4.1-11.7). The confirmed ORR was 50%, with a DCR of 100%. Among pts with IA DTs, the confirmed ORR was 60.0% (6/10). One patient who achieved PR withdrew from the study after being diagnosed with duodenal cancer. The 6-month and 1-year PFS rates were 100% and 91.7%, respectively, while the 1-year OS rate was 100%. At 2 years, the PFS and OS rates were 54.5% and 72.7%, respectively. The median PFS and OS were not reached. Treatment-emergent adverse events (TEAEs) occurred in all pts (100%). The most common TEAEs (all grades) included COVID-19 (91.7%), leukopenia (83.3%), hypertension (83.3%), neutropenia (83.3%), proteinuria (66.7%), and elevated bilirubin levels (50%). Grade 3 TEAEs occurred in six pts, including neutropenia (41.7%), leukopenia (25%), hypertension (16.7%), hand-foot syndrome (8.3%), intestinal obstruction (8.3%), and abdominal hemorrhage (8.3%). One patient experienced a grade 4 adverse event (intestinal perforation), declined surgical intervention, and passed away three months later. All male pts tolerated the 20 mg dose, while 5 female pts (71.4%) reduced to 15 mg. **Conclusions:** Famitinib demonstrated sustained clinical efficacy and meaningful survival benefits in pts with FAP-associated aggressive DTs after a median follow-up of 32 months. Given the unique characteristics, careful monitoring for intestinal perforation and the risk of second primary tumors is crucial during treatment. Clinical trial information: ChiCTR2100051307. Research Sponsor: None.

10612 **Poster Session**

A phase 2 study of lanreotide as a therapy for pheochromocytomas (PCs) and paragangliomas (PGs). First Author: Bahar Laderian, Montefiore Einstein Comprehensive Cancer Center, Bronx, NY

Background: PCs arise from adrenomedullary chromaffin cells, while PGs are derived from extra-adrenal chromaffin cells of the sympathetic paravertebral ganglia of the thorax, abdomen, and pelvis, or the parasympathetic ganglia located along the glossopharyngeal and vagal nerves in the neck and base of skull. Although considered neuroendocrine tumors [NETs] by many, their rarity and often difficult management has meant they're never included in clinical trials of NETs. And while they express somatostatin receptors [SSTRs] comparable to other NETs haven't been managed with SSTR-antagonists. **Methods:** Conducted clinical trial to assess efficacy/toxicity of Somatuline Depot / Lanreotide Autogel every 4 weeks in patients with advanced/metastatic PC/PG. Evidence of recent disease progression while either not receiving any therapy or receiving a therapy deemed ineffective was required. Treatment planned for 52 weeks with option to continue for additional 52 weeks. Endpoints included OS, PFS and response according to RECIST. Additionally given rarity of these cancers, estimates of tumor growth rates were planned to allow comparisons to data in NETs enrolled in CLARINET. **Results:** Eighteen patients median age 42 years enrolled including 11 females and 7 males of whom 13 were white, 2 black, 3 other. 14/18 had an SDHx mutation. Prior therapies included surgery, RT, chemotherapy, and PRRT. Lanreotide was well tolerated with 68%G1, 26%G2, 6.5%G3 and $<$ 1% G4 adverse events (AEs) and no unexpected toxicities. No patient discontinued treatment for AEs. Blood pressure control uneventful. Ten patients completed two years of lanreotide, three ongoing, two discontinued at one year due to burden of traveling for participation and three had PD. RECIST response at one year was 15 SD, and 3 PD. One additional patient had PD at the two-year assessment. Serum chromogranin was elevated in only 4/18 and was not helpful in assessing response. With a median follow up of 40 months, median PFS exceeds 2 years with only three deaths to date 14, 18 and 52 months after enrollment. Rates of tumor growth and regression could be assessed in 16/18 patients. Growth was not detected in 5/16 but estimable in 11/16 with a median growth rate of 0.00067/day [tumor doubling time, 1034 days] compared to rate of 0.00046 for 83 patients treated with lanreotide in CLARINET. **Conclusions:** These data demonstrate efficacy for lanreotide in the treatment of PC/PG comparable to that previously found in NETs with prolonged disease stability the primary outcome. Given emerging data with PC and PG reports limited efficacy for Lutathera with meaningful toxicity, these data with lanreotide achieving a longer median PFS support a management strategy for PC/PG similar to that employed with NETs. Begin with a SSTR antagonist, extract its benefit and delay Lutathera administration until meaningful, consistent disease progression is documented. Clinical trial information: NCT03946527. Research Sponsor: Ipsen Biopharmaceuticals.

10613 **Poster Session**

Genetics and family history in a diverse cohort of females with early-onset breast cancer. First Author: Tanaya Shroff, Yale New Haven Health - Smilow Cancer Hospital, New Haven, CT

Background: Genetic testing for breast cancer susceptibility genes is a crucial component of clinical care for patients with early-onset breast cancer (EOBC) diagnosed $<$ age 50 with implications for treatment and surgical decision-making, future surveillance, and cascade genetic testing for family. Limited data exist regarding prevalence of pathogenic/likely pathogenic variants (P/LPV) and patterns of family history (FH) of cancer across diverse patient populations and merit further research given the rise in EOBC rates. This study examines a cohort of EOBC patients from a cancer genetics program at a comprehensive cancer center to derive insights into the genetic and FH spectrum for a diverse cohort of patients with EOBC in hopes of informing clinical care and public awareness strategies. **Methods:** A retrospective analysis of women seen in the Smilow Cancer Genetics and Prevention program at Yale-New Haven Hospital from 2015-2023 was conducted. Women diagnosed with EOBC who underwent germline genetic testing were included. Data on demographics, age at diagnosis, genetic test results, and FH of breast, ovarian, pancreatic, and prostate cancer in 1st/2nd/3rd degree relatives was obtained from the electronic medical record and Progeny family history software using manual and automated querying and natural language processing. The dataset was assessed for frequency of P/LPVs in cancer predisposition genes, variants of uncertain significance (VUS), and FH of cancer. Fisher's exact test was used to assess the association between categorical variables, and ANOVA to assess the difference in continuous variables among groups. **Results:** 1676 women with available race and ethnicity data were analyzed. Patients identified as White (83.3%), Black (11.5%), Asian (5.3%). 5% of all patients identified as Latinx. Mean age at diagnosis was 42.4 years (SD 5.48 years). P/LPVs were identified in 15.1% and VUS in 22.6%. The most common genes with P/LPVs were *ATM* (4.8%), *BRCA2* (4.1%), *CHEK2* (4.1%), and *BRCA1* (3.0%). Rates of Ashkenazi Jewish ancestry were higher for Whites (7.5%) compared to Blacks (1.0%) and Asians (1.0%) ($p<0.001$). Family history of breast cancer was higher among Black (80.2%) and White patients (80.9%) than Asians (53.4%) ($p<0.001$), as was history of prostate cancer (Black, 29.7%; White, 29%; Asian, 11.4%, p=0.017). P/LPV rates were highest among Whites (15.8%), followed by Blacks (11.5%) and Asians (10.2%) while VUS rates were highest for Asians (34.1%) and Blacks (28.6%) than Whites (21.0%) ($p<0.001$). **Conclusions:** Our results from a diverse EOBC population underscore the higher rates of P/LPVs among White patients while non-White populations have higher rates of VUS. Given the rise in EOBC rates, greater genetic insights as well as additional factors impacting EOBC risk need to be identified and studied particularly across diverse racial/ethnic populations. Research Sponsor: None.

10614 **Poster Session**

Post-mastectomy surveillance: A patient-reported survey of 110 women with Li-Fraumeni syndrome. First Author: Renata Lazari Sandoval, Dana-Farber Cancer Institute, Boston, MA

Background: Li-Fraumeni syndrome (LFS) is a highly penetrant autosomal dominant hereditary disorder associated with young onset breast cancer (BC). Therapeutic mastectomy is preferred to enable avoidance of radiation at BC diagnosis (dx), and bilateral mastectomy (BM) for risk reduction as a preventive strategy. After a BM, current guidelines do not recommend post-mastectomy breast screening beyond clinical breast examination (CBE) for LFS carriers. During a patient-focused discussion at the 6th Li-Fraumeni Syndrome Association (LFSA) Symposium in 2022, women expressed concern about not being offered imaging after the surgery. We therefore conducted a survey study to investigate BC screening practices and new breast events following BM in women with LFS. **Methods:** Recruitment was performed through electronic invitation sent to members of the LFSA. Respondents 18 years or older who self-identified as having an LFS dx and a personal history of BM, were invited to answer a survey about their cancer history, breast screening, breast surgery and breast events after mastectomy. Post-BM BC event was defined as the first BC event after BM. Questionnaires were administered from August 13th to September 3rd, 2024. Bivariate associations between BC history and clinical characteristics were assessed using Fisher's exact test for nominal categorical variables and two-sample Wilcoxon tests for continuous variables. **Results:** Among 148 respondents, 110 were eligible; 30 (27.3%) had BM for risk reduction and 80 (72.7%) for BC treatment (60 unilateral BC and 20 for bilateral BC). Median age at first mastectomy was 35.5 years (IQR 28.2,43.0). Most patients (n=82; 74.5%) underwent breast reconstruction with implants only. Periodic CBE performed by a health provider was reported by 70 respondents (63.6%). Patients with BC prior to mastectomies received more clinical surveillance (71.2% vs 43.3%, $p<0.01$). Follow-up imaging with any modality in regular intervals was reported by 52 respondents (47.3%), and there were no differences between groups regarding BC history and imaging modalities used for surveillance. At a median follow-up of 6 years (IQR 3.0-9.8), a total of 10 post-BM BC events (10/110, 9%) were reported, 50% were identified due to symptoms. Among patients who were receiving imaging surveillance (n=52), only 1 BC event was identified through breast MRI screening. was not significantly associated with a new BC event after BM (p=0.28). All BC events in patients with a BC prior to mastectomies were in the ipsilateral breast of the first BC. Patients with a prior BC had a longer follow-up (7.0 vs 3.0 years, p=0.003). **Conclusions:** Breast cancer events after mastectomies in this cohort were identified by symptoms rather than surveillance. Further studies are needed to distinguish these subsequent BC events as recurrences or new primaries, and to confirm the clinical value of breast imaging in this setting. Research Sponsor: None.

10615 **Poster Session**

Clinicopathologic and allele-specific analysis of germline *ATM* alterations in a pan-cancer cohort. First Author: Matteo Repetto, Memorial Sloan Kettering Cancer Center, New York, NY

Background: *ATM* is a tumor suppressor gene involved in DNA repair and telomere maintenance. *ATM* biallelic pathogenic or likely pathogenic germline variants (gPV) are associated with ataxia-telangiectasia syndrome. Monoallelic ATM gPV are associated with increased cancer risk; however, their contribution to carcinogenesis has not been elucidated. We sought to characterize the genomic landscape of gPV *ATM*-associated cancers in a pan-cancer cohort. **Methods:** *ATM* alterations (germline and somatic) were identified in patients (Pts) with a solid tumor diagnosis sequenced with MSK-IMPACT, an FDA-approved, tumor-normal paired targeted NGS. Genetic-imputed ancestry clinicopathologic characteristics and FACETS estimated allele-specific copy number profiles were evaluated. Samples with purity <0.2 or with undetermined copy number profiles were excluded. HRD score was evaluated using FACETS profiles. Both somatic and germline sequencing data were analyzed within protocol NCT01775072. **Results:** Among 40,136 Pts with cancer who underwent germline testing, 1.1% (n=442) harbored an *ATM* gPV, inclusive of 2 Pts with biallelic *ATM* gPVs. The most frequent mutations were: R2547_S2549del (n=17), K2756* (n=14) and V1268* (n=11). Among these, R2547_S2549del and K2756* were identified exclusively in Pts with European ancestry, while E343Ifs*2 (n= 9/10) and c.1065+1G>T (n= 6/7) were most prevalent in Pts with Ashkenazi Jewish (AJ) ancestry. Concomitant gPVs in other genes were observed in 10% (n=47), with the most frequent ones being *APC* (I1307K), *MUTYH*, *BRCA2, CHEK2*, and *BRCA1*. 63,270 out of 86,039 tumor samples had usable FACETS profiles. *ATM* somatic allele-specific information was available for 67% (297/442) of Pts. 62% (197/317) of tumor samples from Pts with monoallelic *ATM* gPVs exhibited somatic biallelic (Bi) *ATM* inactivation, while 38% (120/317) retained monoallelic (Mono) ATM status. The underlying mechanism of Bi-ATM inactivation was loss of heterozygosity in 75% (149/197) and additional somatic *ATM* mutations in 25% (48/197). Samples from Pts with tumors known to be associated with ATM gPVs (Breast, Pancreatic and Prostate cancers) had significant enrichment in Bi-ATM inactivation compared to tumors without strong association with ATM gPVs (88% Vs 58%; $p<0.01$). Although samples with Bi-*ATM* had higher overall HRD-scores compared to Mono-*ATM* (median = 34 Vs 20; $p<0.01$), no significant enrichment in HRD-High phenotype was seen in Bi-*ATM* (23 Vs 18; p=0.49). **Conclusions:** Evaluation of a pan-cancer Pt population with *ATM* gPVs demonstrated a high prevalence of biallelic somatic inactivation. Most Pts with *ATM* gPVs who had malignancies implicated in *ATM*-associated cancer risk, had biallelic somatic inactivation in their tumors suggestive of their contribution to tumorigenesis. While biallelic ATM inactivation is associated with higher genomic instability, no enrichment in HRD phenotype was observed. Research Sponsor: National Cancer Institute/National Institutes of Health Cancer Center Support grant to Memorial Sloan Kettering Cancer Center; (P30 CA008748).

10616 **Poster Session**

Cancer genetics evaluation among individuals at risk for Lynch syndrome across all qualifying indications. First Author: Vinit Singh, Roswell Park Comprehensive Cancer Center, Buffalo, NY

Background: < 20% of individuals suspicious for Lynch syndrome (LS) and other inherited cancer syndromes undergo genetic testing in the US. Undiagnosed individuals will not benefit from enhanced screening and prophylactic interventions. Thus, to dramatically increase the identification of at-risk individuals and respective indications, we set up the At-Risk Cancer Genetic Syndrome Identification Registry (ACAGEN-ID). **Methods:** NCCN/ACMG criteria for genetic testing were translated into three distinct rule-based conditional logic statements in the EHR. A total of 218 rules that serially evaluate each aspect of individual criteria and roll into a logic statement of "at-risk" for inherited cancer syndromes. The rules assess personal history (PH) and/or family history (FH) of cancers, determine age at onset, and categorize family relationships. Patient's genetic evaluation status, sociodemographic, and clinical data were extracted. Descriptive statistics used for summary. Pearson chi-square used for comparison of categorical variables. **Results:** Out of 1.34 million individuals in Yale New Haven Health System, ARCAGEN-ID identified 5,190 at risk individuals for LS. Of those, 3,581 (69%) had not been previously evaluated. Accuracy was assessed through a manual review of 130 randomly selected individuals among the identified, which showed appropriate identification in 129 cases. Among the already evaluated, 509/1609 (31.6%) had a pathogenic variant (PV): 124 (24.6%) MSH2, 112 (22.2%) MSH6, 55 (10.9%) MLH1, 118 (23.4%) PMS2, 3 (0.6%) EPCAM, 141(28%) other PV. Newly identified individuals through ARCAGEN-ID more often had only a PH of cancer (39.99% vs 21.01%) or only FH of cancer (41.02% vs 38.41%), and less often both, PH and FH (18.99% vs 40.58%) ($p<0.01$). The great majority of individuals with only qualifying FH or PH had not been identified before (80.90% and 70.39% respectively), while half (51.01%) with both, PH and FH, had already been identified. Having an early onset (EO) LS-associated cancer was the most common reason for prior identification (22.30%), though EO endometrial cancer (EC) (107/1135, 9.42%) was much less recognized than EO Colorectal Cancer (CRC) (284/775, 36.64%, $p < 0.01$). The highest missed identification before ARCAGEN-ID implementation was individuals with ≥2 LS-related cancers: 69.85% (190/272); FH of EO-CRC: 66.67% (298/449); ≥3 FH of CRC. Even 29.73% (121/407) of individuals with FH of diagnosed LS had been missed. 263/385 (68.31%) Patients with Non-EC/CRC related LS cancers were not evaluated. **Conclusions:** Current practice misses most individuals at-risk for LS across all qualifying indications.A system that can leverage currently existing information in the EHR can dramatically improve the identification without any other added resources. An automated outreach pilot project is underway to assess feasibility and outcomes. Research Sponsor: None.

10617 **Poster Session**

Familial lung cancer: A thirteen-year prospective analysis of participants with germline EGFR T790M pathologic variant. First Author: Elizabeth R. Francis, Thoracic and Gastrointestinal Malignancies Branch, Center for Cancer Research, Division of Cancer Prevention, Division of Cancer Epidemiology and Genetics, National Cancer Institute, National Institutes of Health, Bethesda, MD

Background: Lung cancer in never-smokers is the eighth leading cause of cancer-related mortality in the United States. Familial lung cancer, a rare syndrome associated with germline *EGFR* pathologic variants (PV) such as T790M (accounting for 0.3-0.9% of lung adenocarcinomas), is a recently identified cause of non-tobacco-related lung cancer. Data on this population is limited. We describe a 13-year prospective analysis, the longest thus far to study the natural history. **Methods:** From2011 to 2024, 19 participants enrolled in a National Cancer Institute study of *EGFR* germline PV (NCT01306045).Eligibility included: (1) lung cancer diagnosis (invasive or pre-invasive) with two affected family members, (2) first-degree relative of someone with a germline *EGFR* PV, (3) T790M detected in lung cancer tumor before tyrosine kinase inhibitor, (4) significant family history of lung cancer, or (5) *EGFR* germline PV detected externally. Participants with germline *EGFR* PV were followed prospectively. Germline *EGFR* PV carriers completed risk-based screening computed tomography. Germline *EGFR* PV participants with lung cancer were followed while completing guideline-directed treatment and surveillance. Lung nodules were examined using standard radiologic assessment. **Results:** Of 19 enrolled participants, seven (37%) had germline *EGFR* T790M. Demographics of *EGFR* germline T790M versus not include mean age at enrollment (46, 56), gender (female 4, 9), white/African American/Asian race (6/1/0, 10/0/2), and current/former/never smoker (0/6/1, 0/4/7). Of the seven participants with *EGFR* T790M, three (43%) had lung adenocarcinoma diagnosed on average at age 63 (range, 53-80), two as stage I and one as stage IV. The other four (57%) did not have lung cancer during the study period. At diagnosis with germline *EGFR* T790M (average age 31, range 26-36), all four participants without cancer had multiple bilateral pulmonary nodules and/ or ground glass opacities (GGO) which, over 6-10 years, remained stable to slightly larger, with increased numbers. One germline *EGFR* T790M participant developed multiple primary lung adenocarcinomas (invasive, minimally invasive, in situ) over 26 months and metastasis 14 months later. One primary started with ground glass components and became solid and larger over 26 months. The two participants with stage IV lung adenocarcinoma survived 15 and 67 months. **Conclusions:** Our study confirms that germline *EGFR* T790M carriers present as early as the third decade of life with multiple bilateral GGOs that can remain dormant for years before exhibiting malignant behavior. Long-term surveillance imaging is necessary, and volumetric changes can potentially be automatically quantified using artificial tools. However, further studies are needed to define a risk-based schedule and examine the role of prophylactic therapy, such as osimertinib. Clinical trial information: NCT01306045. Research Sponsor: None.

10618 **Poster Session**

Mammography results in male *BRCA* carriers. First Author: Maliha Tayeb, University of Pennsylvania, Philadelphia, PA

Background: Patients assigned male at birth (AMAB) with pathogenic germline variants (PGVs) in *BRCA1* or *BRCA2* (*BRCA+*) have a 1-10% lifetime risk of developing breast cancer (BC). NCCN guidelines currently recommend that male *BRCA1/2* carriers consider annual mammograms. However, there is minimal data on the mammography among male *BRCA1/2* carriers. **Methods:** We identified a cohort of 489 *BRCA+* male patients with male gender identity from the electronic health record (EHR) at Penn Medicine who had no prior BC diagnosis. Charts were reviewed to determine indication for and results of mammography episodes between 2008-2024. A mammography episode was defined as all breast imaging studies obtained for a specific reason, i.e. asymptomatic screening or for symptoms within six months. An independent cohort of 1808 *BRCA* negative AMAB patients with male gender identity and no prior BC diagnosis from the Penn Medicine EHR was analyzed for the true positive rate of BI-RADS 4/5 findings. **Results:** Of 489 *BRCA+* individuals, 85 (17%) patients completed at least one mammography episode and 46 (9%) had at least one subsequent mammography episode during the study period. Of 85 *BRCA+* patients, 71% had *BRCA2* PGVs. Of 404 patients who did not complete a mammogram, 270 were at least 50 years old at the time of data abstraction. Of these 270 patients, 50% had no discussion of mammograms in their charts, 8% of patients had a physician ordered mammogram that was not completed by the patient, and 42% had a shared decision-making discussion between the physician and patient indicating a decision against mammography. The first observed and subsequent mammography episodes were ordered for asymptomatic screening in 65% and 83% of 85 *BRCA+* individuals, respectively. In *BRCA*neg individuals, 92% of mammography episodes were for symptoms. Nine (11%) and one (2%) *BRCA+* individuals were diagnosed with BC after the first observed or subsequent mammography episode, respectively. No breast cancers were identified on mammography episodes among asymptomatic patients. Combining all mammography data, the true positive rate of BI-RADS 4 mammograms was significantly higher in *BRCA+* vs *BRCA*neg individuals (71% vs 11%, p=0.0007); whereas the true positive rate of BI-RADS 5 mammograms was similar in *BRCA+* vs *BRCA*-neg individuals (100% vs 82%, p=0.54). Hormone receptor status and clinical stage of identified BC were similar between *BRCA+* and *BRCA*neg individuals. **Conclusions:** The majority of male *BRCA1/2* carriers in our cohort did not complete mammography. All BC diagnosed in *BRCA+* individuals were identified on mammography episodes obtained for symptoms. The true positive rate of a BI-RADS 4 mammogram was significantly higher in *BRCA+* compared to *BRCA*neg individuals. Additional data is needed regarding whether mammography identifies asymptomatic BC in male *BRCA1/2* carriers and whether mammograms improve clinical outcomes. Research Sponsor: None.

10619 **Poster Session**

The evolution of breast cancer genetic testing: Comparative outcomes of NCCN, ASCO, and universal guidelines in 6,000+ patients. First Author: Hikmat Abdel-Razeq, King Hussein Cancer Center, Amman, Jordan

Background: Germline genetic testing for breast cancer has significantly advanced over the past decade. At King Hussein Cancer Center, 6,336 breast cancer patients underwent genetic testing between 2012 and 2024, transitioning from limited BRCA1/2/PALB2 panels to comprehensive 20-gene and 84-gene panels. Eligibility criteria evolved from strict criteria for testing to broader NCCN and ASCO guidelines by 2024. Universal genetic testing was implemented for all breast cancer cases between April 2021 and September 2022. ASCO guidelines have simpler eligibility criteria, whereas NCCN guidelines are more complex and regularly updated. **Methods:** This study analyzed genetic testing trends, categorized results by panel type, and compared detection rates of pathogenic/likely pathogenic (P/LP) variants and variants of uncertain significance (VUS). Detection rates were assessed using Chi-square tests, and linear regression calculated annual changes in positive rates. Outcomes were compared between guideline-based (ASCO/NCCN) and universal testing. **Results:** Of 6,336 patients, 1,731 (27.3%) underwent testing with the 84-gene panel, 3,759 (59.3%) with the 20-gene panel, and 846 (13.4%) with limited testing. Testing volumes increased from 248 cases between 2012-2017 to ~1,000 annually after 2021. Overall, 686 (10.8%) patients had P/LP variants, with higher rates in patients under 30 years (24.4%) and triple-negative breast cancer (20.6%). Among 5490 patients tested with multigene panels, P/LP detection rates were similar: 10.5% (306/2917) for NCCN, 9.4% (87/924) for ASCO, and 9.1% (150/1649) for Universal; p-value was 0.276. No significant difference in P/LP rates was observed between the 84-gene panel 9.2% (160/1,731), and the 20-gene panel 10.2% (383/3,759, p=0.297), but the VUS rate was significantly higher in the 84-gene panel (66.2% vs. 26.2%; p<0.001). **Conclusions:** Expanded panels (84-gene) did not improve detection of P/LP but significantly increased VUS rates. Universal testing did not lower P/LP detection rates compared to guideline-based testing, and no significant difference was observed between ASCO and NCCN guidelines. ASCO guidelines, offering simpler eligibility criteria, or even universal testing, may be more practical compared to the periodically updated NCCN guidelines and should improve compliance and referral rates. Research Sponsor: None.

Genetic testing.

Genetic testing		Number 6,336	P/LP	p-value	VUS	p-value
Limited test (BRCA1/2, PALB2)		846	143.0 (16.9%)		73.0 (8.6%)	
Multigene panel (5490)	84-gene panel	1,731	160/1731 (9.2%)	0.297	1146/1731 (66.2%)	<0.001^
	20-gene panel	3,759	383/3759 (10.2%)		986/3759 (26.2%)	
Guidelines*	Universal testing	1649	150 (9.1%)	0.276	1131 (68.6%)	<0.001^
	NCCN Guideline	2917	306 (10.5%)		784 (26.9%)	
	ASCO Guidelines	924	87 (9.4%)		217 (23.5%)	

*Excluding patients with limited genetic testing.
^Pearson's chi-squared test.

10620 **Poster Session**

Rurality and screening colonoscopy participation in patients with Lynch syndrome. First Author: Isabel Thomas, University of Vermont Larner College of Medicine, Burlington, VT

Background: Lynch Syndrome (LS) is a hereditary condition that increases risk for colorectal and other primary cancers. LS arises from pathogenic variants (PVs) in *MLH1*, *MSH2*, *MSH6*, and *PMS2*. Gene-specific prevention and surveillance strategies exist, and screening colonoscopy reduces overall mortality. Several barriers to screening colonoscopy are known, however the impact of rurality is not well characterized. **Methods:** We enumerated a cohort of LS patients residing in Vermont or upstate New York who were seen by the Cancer Genetics Program at the University of Vermont, and for whom regular screening colonoscopies were recommended based on current PV- and age-based NCCN guidelines. We reviewed electronic medical records and abstracted patient characteristics and colonoscopy procedures performed between 2021-2024, capturing most recent practices while avoiding the impact of COVID-19 restrictions. We defined screening compliance as having >1 colonoscopy in the 3-year period, concordant with the minimum expected number of procedures over this time period for all PV groups. We assigned rurality status (metropolitan/micropolitan vs. small town/rural) based on residential ZIP code using Rural-Urban Commuting Area codes. We fit log-binomial and proportional odds regression models to estimate the impact of rurality and recency of a genetics focused clinic visits on colonoscopy adherence and on the number of colonoscopies received, adjusting for age, sex, and PVs. **Results:** We enrolled 201 LS patients for whom annual, bi- or triennial colonoscopies were recommended. Median age at baseline was 60 years (range: 28-98), 131 (65%) were female, and 58 (29%) resided in a small town/rural setting. Compared with metropolitan/micropolitan, small town/rural residence was associated with a lower probability of having ≥1 screening colonoscopy in the 3-year follow-up period (43% vs. 64%; RR=0.67, 95% CI: 0.49, 0.92). This association did not change substantially upon adjustment for age, sex, and pathogenic variants. Small town/rural residence was also associated with undergoing fewer colonoscopies in the 3-year period (cumulative OR=0.46, 95% CI: 0.25, 0.84). Furthermore, recency of Cancer Genetics Program clinic visit was associated with a higher probability of receiving at least one colonoscopy, independent of rurality (*e.g.*, RR for last visit ≤3 years ago, compared with last visit >10 years ago = 1.8, 95% CI: 1.1, 2.8). **Conclusions:** In a cohort of patients with LS, residing in a rural area was associated with a reduced probability of compliance with screening colonoscopy. Resources should be invested in studies aimed at understanding and ameliorating the mechanisms underlying this association. Shorter time since last clinic visit in the genetics program was associated with a higher likelihood of having a screening colonoscopy, suggesting the importance of genetics longitudinal follow-up for hereditary cancer patients. Research Sponsor: None.

10621 **Poster Session**

Retrospective review of hereditary leiomyomatosis and renal cell cancer at a single institution. First Author: Michael N. Trinh, Massachusetts General Hospital, Boston, MA

Background: Hereditary Leiomyomatosis and Renal Cell Carcinoma (HLRCC) is an autosomal dominant syndrome caused by loss-of-function mutations in the Fumarate Hydratase (*FH*) gene. HLRCC poses an elevated risk for skin leiomyomas, uterine fibroids, pheochromocytomas, paragangliomas, and renal cell cancer (RCC), particularly FH-deficient RCC and potentially clear cell RCC. It is recommended that patients with personal and/or family history of a single skin leiomyoma, multiple FH-deficient (by immunohistochemistry (IHC)) uterine fibroids, pheochromocytoma, paraganglioma, or FH-deficient RCC be tested for, among other genes, germline *FH* mutations, with yearly surveillance with abdominal imaging being the recommendation if positive. To better describe this patient population, we present our experience with high-volume referrals for HLRCC testing at a single institution. **Methods:** We performed retrospective chart review (2017-present) of all patients referred for HLRCC testing at the Hereditary Renal Cell Carcinoma & VHL Disease Clinic and the Hemangioblastoma Center at the Massachusetts General Cancer Center. The study was approved by the Massachusetts General Brigham IRB. **Results:** We herein describe the largest, to our knowledge, series of HLRCC patients (67) at a single institution. While the majority (30, 45%) of cases were referred due to an incidental genetic finding either on prenatal screening or through a comprehensive multi-cancer gene panel sent for hereditary cancer screening, 31% (21) of patients were referred after being found to have an HLRCC-related lesion. Of this subset, the most common first HLRCC-related lesion was a uterine fibroid that was FH-deficient by IHC (13), followed by an equal number of skin leiomyomas (4) and RCCs (4). Importantly, we calculate the rate of patients later confirmed to have an HLRCC diagnosis (pathogenic variant by genetic sequencing) based on referral reason: patients referred for uterine fibroids deficient in FH by IHC, 59.1% (13 of 21); patients referred for RCC either with loss of FH by IHC or papillary RCC, 80% (4 of 5); patients referred with cutaneous leiomyomas deficient in FH by IHC, 66.7% (4 of 6); and patients with family members with known diagnosis of HLRCC, 83.3% (15 of 18). Mutations in positive HLRCC cases either caused premature termination by nonsense or frameshift (18, 26.9%), point mutations by missense (22, 32.8%), or had an AAA duplication at c.1431_1433, causing a lysine duplication at amino acid residue 477 of the fumarate hydratase protein (20, 22.9%), the last of which has ongoing discussion of true association with HLRCC. One patient was indeed seen to have papillary RCC with this mutation, supporting the association of c.1431_1433dupAAA with HLRCC. **Conclusions:** In sum, we describe populations characteristics, common reasons for referral, and likelihood of genetic testing confirmation for patients with concern for HLRCC. Research Sponsor: None.

10622 **Poster Session**

Characteristics and outcome of breast cancers diagnosed in patients with germline ATM mutations. First Author: Amanda Lanier, The University of Texas MD Anderson Cancer Center, Houston, TX

Background: The purpose of this study is to investigate clinicopathologic characteristics of invasive breast cancers diagnosed in individuals carrying germline mutations in ATM. Individuals with germline pathogenic variants (PV) in ATM have an elevated lifetime risk of breast cancer (17-52%). Clinical characteristics and outcomes of breast cancer amongst patients with ATM PV are not well described. Our aim was to describe a cohort and clinical outcome of patients with breast cancer and ATM PVs. **Methods:** Patients receiving care at MD Anderson Cancer Center with at least one invasive breast cancer diagnosis and who underwent germline testing and were found to have a germline ATM PV were included in the study. Individuals with co-occurring germline mutations in BRCA2 and CHEK2 were excluded. Germline positive and tested negative patients were identified using our prospective Breast Cancer and Clinical Cancer Genetics research database. **Results:** 86 patients with ATM PV were identified. Overall ER positivity was 94.19%. 72.09% were ER+/HER2- and 22.09% were ER+/HER2+. HER2+/ER- and TNBC occurred at lower rates in this cohort (2.33% each). When compared to ATM PV negative, patients with ATM PVs were more likely to have ER+ tumors (HR 1.26). Most individuals with ATM PVs were diagnosed with Stage I (40.7%) or II (34.9%) disease. However, they were more likely to be diagnosed at Stage IV than the control cohort (10.47% vs 1.99%, HR 5.25). Amongst patients receiving neoadjuvant chemotherapy, the pathologic Complete Response (pCR) rate in the ATM positive cohort was 15.63% (5/32), compared to 46.09% in the control group. Locoregional recurrence rates were similar in the ATM and control cohorts (8.14% and 5.85%), but those with germline ATM PVs were more likely to have distant recurrence (23.26% vs 10.96%, HR 2.12).Individuals with germline ATM PVs were also more likely to be diagnosed with a second or third invasive breast cancer than those in the control group (9.3% vs 2.79%, HR 3.33). Overall survival was not significantly different between the two cohorts. In addition to invasive breast cancers, we collected data on secondary malignancies and found that in the ATM PV cohort, 34.88% were diagnosed with at least one additional invasive cancer, including breast, gynecologic, colorectal, pancreatic, melanoma, and other tumor types. **Conclusions:** Patients with hereditary ATM PVs diagnosed with breast cancer have distinct characteristics and outcomes. In our cohort patients with ATM PVs had a higher risk of distant metastasis suggesting a more aggressive disease course that may require tailored treatment strategies. In addition, they also have an increased risk of developing second and third primary breast cancers, therefore risk reducing mastectomy should be considered. Finally, because of increased risk of non-breast malignancies, screening for potential new malignancies is warranted in this patient population. Research Sponsor: None.

TPS10623 **Poster Session**

A process evaluation trial of a telehealth service intervention to support uptake of breast cancer prevention medications. First Author: Kelly-Anne Phillips, Department of Medical Oncology, Peter MacCallum Cancer Centre, Melbourne, VIC, Australia

Background: Breast cancer prevention medications (BCPrevMeds), such as tamoxifen and anastrozole, halve breast cancer (BC) risk. Our prior research has shown that only 2% of Australian women who know they are at increased risk of BC have ever used BCPrevMeds, and that this evidence-implementation gap is driven by lack of awareness of BCPrevMeds by patients and their primary care physicians (PCPs). In addition, few PCPs report feeling confident to discuss BCPrevMeds, most would not initiate prescribing, but 98% would provide ongoing prescriptions if initiated by a specialist. The Preventing Cancer with Medications (PCMed) Specialist Telehealth Service intervention was developed, based on the Knowledge to Action Implementation Framework, to respond to these findings. The PCMed intervention delivers personalised information to patients to facilitate their informed decision-making, initiates BCPrevMeds prescriptions, and supports PCPs to manage patients during their treatment course. **Methods:** A mixed methods process evaluation trial is evaluating the effectiveness, adoption, acceptability, feasibility, fidelity, and cost of the PCMed intervention. Women aged 20-70 years with no history of invasive BC or DCIS are eligible if they have a remaining lifetime BC risk $>$ 20% or 10-year risk of $>$ 5%. The intervention includes 1 to 2 telehealth sessions with a medical oncologist or nurse practitioner in which patients receive tailored education about the BCPrevMeds relevant to them, a personalised discussion of the absolute risk reduction they could achieve with BCPrevMeds and tailored discussion of other benefits and side-effects of BCPrevMeds applicable to them. Those who desire BCPrevMeds receive a prescription and are reviewed in 8 to 10 weeks to manage any side-effects. Care is then transferred to the PCP who receives educational information and detailed instructions to continue management. A telephone hotline is available for clinicians and patients to address any concerns relating to side effects during the treatment course. Effectiveness of the PCMed Service intervention will be determined by comparing uptake of BCPrevMeds before and after the intervention, using a chi-square, Fisher's exact test, and/or mixed effects regression (as appropriate based on the number of uptake events). Secondary outcomes include adoption of the intervention (the proportion of eligible women who attend the PCMed Service), acceptability for patients and referring clinicians (survey and semi-structured interviews based on the Theoretical Framework of Acceptability), feasibility and fidelity (adherence to the planned intervention processes), and cost (using a micro-costing approach). Currently 33 of a planned 63 participants have been recruited - sample size is based on 80% power to detect a change in uptake from 2% to 20%. Clinical Trial Information: ISRCTN 15718519. Clinical trial information: 15718519. Research Sponsor: Tour de Cure; RSP-307-2024; National Health and Medical Research Council (Australia); 1195294.

TPS10625 **Poster Session**

A phase II biomarker RCT in women at high risk for breast cancer: Low dose tamoxifen and lifestyle changes for breast cancer prevention (TOLERANT study). First Author: Sara Gandini, IEO, European Institute of Oncology IRCCS, Milan, Italy

Background: Breast cancer (BC) prevention in high-risk women is crucial. Tamoxifen, despite its efficacy, has limited use due to its side effects. Low-dose tamoxifen (LDT) has shown much better balance between BC risk reduction and adverse effects. Additionally, lifestyle interventions (LI) like intermittent caloric restriction (ICR) and physical activity may further reduce BC risk by modulating factors such as mammographic density (MD) and sex hormone-binding globulin (SHBG) levels, which we showed is correlated with reduced breast cancer risk. This study evaluates whether LDT increases circulating SHBG more effectively than LI with or without ICR after six months. **Methods:** The TOLERANT study is a randomized, four-arm, phase II trial involving 200 high-risk women recruited from four Italian hospitals. Participants will be randomly assigned to one of four intervention arms: (1) LDT, (2) LDT + ICR, (3) LI with step counter, (4) LI with step counter + ICR. Interventions will last six months, and participants' adherence will be monitored through visits, telephone calls and diaries. Eligible women are aged 18-70 with a high risk for BC due to genetic predisposition or a history of intraepithelial neoplasia. Key exclusion criteria include history of invasive BC, BMI $<$18.5, and certain medical conditions. LDT involves 10 mg tamoxifen every other day. ICR follows a "5:2 diet" model, with five days of normal intake and two days at 25% of regular caloric intake. LI includes personalized advice and step counters targeting 10,000 steps per day. Primary outcome is the change in SHBG levels. Secondary outcomes include changes in metabolic and inflammatory markers, QoL, body composition, microbiome diversity, and MD. Blood and stool samples will be collected at baseline (B), three (3M), and six months (6M) to analyze biomarkers. Body composition will be assessed using bioelectrical impedance analysis, at B, 3M and 6M and MD will be measured in a subset of participants using digital mammography. As of January 20, 2025, a total of 43 participants have been enrolled, including 18 with DCIS and 25 high-risk women. The study, which has received approval from relevant ethics committees, will provide insights into the effectiveness of LDT and LI in reducing BC risk among high-risk women. The results could inform personalized prevention strategies, balancing efficacy with QoL. Trial registration: EuCT number:2023-503994-39-00; Clinical trials.gov NCT06033092 Funding: This work is funded by European Union – Next Generation EU – PNRR M6C2 – Investimento 2.1 Valorizzazione e potenziamento della ricerca biomedica del SSN – Project Code: PNRR-MAD-2022-12376567 - PI Bernardo Bonanni. Co-PI Sara Gandini. The funders had no role in study design, data collection and analysis, or abstract preparation. Reference*: Guerrieri-Gonzaga A et al. PLoS One. 2024 doi journal.pone.0309511. Clinical trial information: NCT06033092. Research Sponsor: European Union – Next Generation EU – PNRR M6C2.

TPS10626 **Poster Session**

The Hercules study: A prospective real-world evaluation of screening whole-body MRI (sWB-MRI) for multi-cancer detection and general preventive healthcare. First Author: Yosef Chodakiewitz, Prenuvo, Vancouver, BC, Canada

Background: Cancer remains a leading cause of mortality, with major gaps in early detection contributing to later-stage diagnoses and poorer outcomes. While single cancer screening methods are effective for specific populations, they leave most cancers undiagnosed such that only 14% of cancers are detected through screening. Multi-cancer detection technologies, such as screening whole-body MRI (sWB-MRI), address this gap by enabling simultaneous systemic cancer risk stratification. Advances in sWB-MRI protocols, including whole-body diffusion-weighted imaging, improve tumor detection without the use of ionizing radiation or contrast agents. This positions sWB-MRI as a non-invasive, radiation-free tool for preventive care suitable for longitudinal monitoring. The need for prospective studies using standardized image acquisition and reporting frameworks, larger cohorts, and long-term follow-up data motivated this study. **Methods:** The Hercules Project is a prospective real-world data study evaluating the predictive accuracy and utility of sWB-MRI for detecting cancer and other clinically significant diagnoses (CSD). Radiological scoring frameworks used include: ONCO-RADS: A validated 5-point scale stratifying cancer risk, from no oncological relevance (ONCO-1) to highly suspicious (ONCO-5). CSD Framework: A novel 5-point scale categorizing pathologies (not limited to cancer) from no clinical relevance (CSD-1) to findings requiring expedited follow-up (CSD-5). Radiologists assign ONCO-RADS and CSD scores during scan interpretation, applied to structured reports by body region and organ system. These frameworks support sensitivity, specificity, PPV and NPV analyses by type of diagnosis. Follow-up at 12–18 months compares findings with diagnostic confirmation and clinical outcomes, enabling analysis of diagnostic pathways and long-term patient impact. Participants are enrolled via one of two arms: Pragmatic: Self-funded participants paying participation-fees reflecting typical U.S. out-of-pocket costs for sWB-MRI. Health Equity: Subsidized access (10–50% of cohort) reduces financial barriers for underserved populations, with sliding-scale subsidies (50–100%) based on socioeconomic factors. Endpoints: Primary endpoints include diagnostic accuracy (sensitivity, specificity, ROC AUC, PPV, NPV), time-to-diagnosis, stage at detection, healthcare utilization (e.g. TCOC), and cost-effectiveness (e.g., QALY). Exploratory endpoints assess the impact of socioeconomic and biological factors on disparities, and the utility of sWB-MRI enabled multi-dimensional diagnostics structured by ONCO-RADS and CSD frameworks. Trial Info: The study is active at a research-dedicated MRI center in Boston, with IRB approval for multi-center expansion to 20 locations. Clinical trial information: NCT06212479. Research Sponsor: None.

TPS10627 **Poster Session**

HERA-TEST: A novel precision oncology tool using breast milk for early detection of postpartum breast cancer. First Author: Alejandra Díaz, Instituto Maimónides de Investigación Biomédica de Cordoba (IMIBIC)-Hospital Universitario Reina Sofia, Universidad de Cordoba, Córdoba, Spain

Background: The incidence of breast cancer (BC) in women under the age of 45 has risen in recent decades, partly due to delayed childbearing. More specifically, postpartum breast cancer (PPBC), defined as BC diagnosed within 10 years of childbirth, accounts for 5 to 7% of these cases and it is recognized as a distinct clinical and molecular entity. PPBC is associated with increased aggressiveness, a higher risk of metastasis, and worse survival outcomes. Previous research has identified observed distinct signature gene expression associated with DNA repair and cell proliferation pathways, as well as T-cell immunity. However, the key molecular drivers of PPBC remain unclear. Currently, invasive procedures such as breast biopsy or ductal lavage are the primary methods to access tumour biomarkers. In this regard, breast milk represents a promising, unique and accessible source of biomarkers —including exfoliated epithelial cells and miRNAs— that directly reflects the breast microenvironment and could provide valuable insights into early molecular changes associated with cancer development. Ultimately, it holds significant potential for identify biomarkers in breast milk for early identification of women at high risk of developing PPBC. **Methods:** This study aims to recruit 2,000 lactating women, requiring a large-scale awareness campaign and collaboration with eight Andalusian hospitals to facilitate donor recruitment and sample collection. To date, breast milk samples (10–30 mL from each breast) have been collected from 3,000 women, exceeding initial recruitment goals. Samples are preserved in two formats: whole milk stored at -80°C and fractionated components (cells, serum, and lipids). This initiative has led to the establishment of the world's largest breast milk biobank. Simultaneously, dried breast milk samples are being collected parallel to the fresh milk. Additionally, comprehensive clinical, gynaecological and lactation-related data are collected via participant questionnaire, including family history of BC, breastfeeding duration, number of births, weaning patterns, prior breast conditions, and medication history. A multi-omics analysis—including genomic, epigenomic, proteomic, and viromic profiling—will be conducted to identify molecular differences between women who develop PPBC and those who do not. Integrating these findings with clinical and epidemiological data to enhance the understanding of PPBC pathogenesis and improve early detection strategies. Upon identification of robust predictive biomarkers, efforts will focus on adapting the test for use with dried milk samples, facilitating large-scale implementation. This approach aims to address critical gaps in current screening methods for young women, with the ultimate goals of enhancing clinical outcomes, reducing healthcare costs, and advancing precision medicine. Research Sponsor: Instituto de Salud Carlos III; Sociedad Andaluza de Oncología Médica (SAOM).

TPS10628 **Poster Session**

Acolbifene vs tamoxifen for breast cancer prevention in premenopausal women at high risk for breast cancer. First Author: Carol J. Fabian, Department of Medicine Medical Oncology and Precision Prevention, University of Kansas Medical Center, Westwood, KS

Background: The TAM01 trial of low dose (5 mg) tamoxifen (LDTAM) vs placebo was associated with significant improvement in risk for breast cancer in postmenopausal women with a hazard ratio of 0.30 along with a favorable side effect profile. Risk reduction in premenopausal women was less clear, with a non-significant hazard ratio of 0.73. Tamoxifen in premenopausal women can induce substantial increases in systemic estradiol and in preclinical studies upregulate endocrine resistance gene *AGR2*. Both phenomena may impact LDTAM efficacy in premenopausal women. A pilot study (NCT00853996) of 20 mg/d of the SERM acolbifene in premenopausal women was associated with reduction in mammographic density, benign breast tissue Ki-67, and estrogen response gene expression (Fabian et al; Cancer Prev Res 2015) with no increase in *AGR2* or vasomotor symptoms. Further studies of LDTAM and acolbifene in premenopausal women are warranted assessing change in imaging and benign breast tissue risk biomarkers with change in systemic hormones, ovarian reserve, and drug metabolites. **Methods:** NCT05941520 is a randomized, double-blind Phase II trial performed as part of the University of Michigan Early Phase Clinical Cancer Prevention (ClinCaP) Consortium part of the Cancer Prevention Clinical Trials Network (CP-CTNet) comparing 6 months of tamoxifen 5 mg and acolbifene 20 mg. Eligible participants are premenopausal women $\geq$35 without prior invasive breast cancer, but with $\geq$ 2-fold increased risk for the disease. The primary endpoint is difference in change in levels of *AGR2* mRNA between the two arms. Secondary endpoints are within-arm change in an endocrine response gene index (ERGI), mammographic density, and MENQOL. Exploratory endpoints include within-arm change in benign breast Ki-67, ER, PR and AGR2 protein, association of baseline Anti-Mullerian Hormone (a measure of ovarian reserve) with 6-month serum estradiol and change in tissue estrogen responsive gene expression and *AGR2*. Based on the preliminary data, mean log base2 (fold change, FC) of *AGR2* in the acolbifene arm is assumed to be -1, which is tantamount to a 50% reduction. The estimated SD of the log2(FC) is 2.25. Assuming a log2(FC) of +0.6 in the low dose tamoxifen arm (50% increase), and the same SD as in the acolbifene arm, 36 evaluable subjects per arm are required to detect, with 80% power at an alpha = 0.03 (two-sided), a difference in FC of this magnitude between the two arms. Secondary endpoints are assessed via paired samples t-test or Wilcoxon signed-rank test. Target enrollment in this 4-site trial is 80 over 2.5 years. The protocol opened for accrual at the University of Kansas Medical Center in October 2024 and as of January 2025 is pending activation at the other sites. Clinical trial information: NCT05941520. Research Sponsor: National Cancer Institute.

11000 Oral Abstract Session

Psychosocial digital application for caregivers of patients undergoing hematopoietic stem cell transplantation (HSCT): A randomized controlled trial. First Author: Jamie M. Jacobs, Department of Psychiatry, Mass General Brigham, Harvard Medical School, Boston, MA

Background: Caregivers (i.e., relatives and friends) of patients undergoing HSCT struggle with considerable quality of life (QOL) impairments and psychological strain before, during, and after HSCT. However, few interventions address the supportive care needs of these caregivers while prioritizing accessibility and scalability. We assessed the efficacy of a self-guided digital application, called BMT-CARE App, for improving HSCT caregivers' QOL, burden, mood symptoms, coping skills, and self-efficacy. **Methods:** We conducted a single-center randomized trial of the BMT-CARE App for HSCT caregivers, compared with usual care (UC). Eligible individuals were adults caring for patients with hematologic malignancies undergoing autologous or allogeneic HSCT at a tertiary care center and were randomly assigned 1:1 to the BMT-CARE App or UC, stratified by transplant type. Intervention participants engaged with the app before transplant and up to 60 days post-HSCT. The app comprises five modules integrating psychoeducation, evidence-based behavior change, and stress management, delivered through interactive features, educational games, and videos. Participants completed self-report measures at baseline and day 60 post-HSCT. The primary endpoint was QOL at day 60 post-HSCT assessed by the CareGiver Oncology QOL (CarGOQOL) questionnaire. We also assessed caregiving burden (Caregiver Reaction Assessment [CRA]), anxiety and depression symptoms (Hospital Anxiety and Depression Scale [HADS]), posttraumatic stress disorder (PTSD) symptoms (PTSD Checklist [PCL-5]), coping skills (Measure of Current Status-A [MOCS-A]), and self-efficacy (Cancer Self-Efficacy Scale-transplant [CASE-t]). We used analysis of covariance controlling for baseline criterion values to assess the effect of the intervention on study outcomes. **Results:** From 2/2023 - 7/2024, we enrolled 125 of 174 approached (71.8%) caregivers (BMT-CARE App n = 62, UC n = 63; median age = 58.7 years [range, 27.8-78.6]). Most participants were spouses (71.2% [89/125]). Participants assigned to BMT-CARE App used the app for a mean of 133.2 minutes (SD = 101.9). At 60 days post-HSCT, intervention participants reported better QOL compared to those assigned to UC (76.2 vs 69.9, p = 0.006]), exceeding the 5-point clinically meaningful difference on the CarGOQOL. BMT-CARE App participants also reported lower caregiving burden (11.2 vs 12.3, p = 0.024), depression (3.8 vs 5.6, p = 0.002), and PTSD symptoms (26.0 vs 31.3, p = 0.011), and better coping skills (33.9 vs 28.2, p = 0.003). The two groups did not differ significantly in anxiety symptoms or self-efficacy at day 60 post-HSCT. **Conclusions:** The BMT-CARE App, a psychosocial digital health intervention, led to substantial improvements in QOL, caregiving burden, depression and PTSD symptoms, and coping skills in caregivers of HSCT recipients. Clinical trial information: NCT05709912. Research Sponsor: Leukemia and Lymphoma Society.

11001 Oral Abstract Session

Outcomes of an electronic patient-reported outcomes (ePRO)—based symptom management program (eSyM): A cluster randomized trial. First Author: Michael J. Hassett, Dana-Farber Cancer Institute, Boston, MA

Background: Although ePROs have been shown to reduce resource utilization and improve outcomes among people with cancer, they have not been widely adopted. We conducted a pragmatic type II hybrid effectiveness-implementation cluster randomized stepped-wedge trial of an ePRO-based, EHR-integrated symptom management program (eSyM) across 6 health systems. Here, we report the primary effectiveness outcome comparing patients treated before (control/not exposed) versus after (intervention/exposed) eSyM deployment. **Methods:** Eligible patients were adults who started chemotherapy (CHEMO) or were discharged after surgery (SURG) for a suspected or confirmed GI, GYN, or thoracic cancer. The intervention included ePRO questionnaires based on PRO-CTCAE items, severe symptom alerts, self-management tip sheets, and communication support. Outcomes included having an emergency department (ED) visit or inpatient admission (INPT) within 30 and 90-days. Logistic regression models accounted for socio-demographic, clinical, calendar time, health system, and other factors. Secondary analyses stratified results by treatment and health system to assess for effect modification. **Results:** From Jan. 2018 to Feb. 2023, the control and intervention conditions accrued 21,112 and 18,830 patients, respectively (median age 62 vs. 65; female 68% vs. 63%). Patient enrollment by health system ranged from 3,961 to 14,560. In the intervention cohort, 51% of patients used eSyM to report symptoms. Crude 30-day event rates for the control and intervention cohorts were 5.4% vs. 6.2% for ED, and 8.5% vs. 9.1% for INPT. Accounting for other factors, there were no significant differences in ED or INPT at 30 (Table) or 90 days. Among SURG patients, there was significantly greater odds of ED, but not INPT, for the intervention vs. control cohort. Results varied by health system, with evidence of higher, similar, and lower odds for the intervention vs. control cohort. **Conclusions:** eSyM deployment did not significantly reduce ED or INPT events. Only half of exposed patients used eSyM to report symptoms. Since prior analyses found lower odds of acute care utilization among patients who reported symptoms via eSyM, implementation and engagement barriers may have substantially impacted effectiveness outcomes. Heterogeneity of effect by health system and treatment suggest that healthcare structures, processes, and baseline performance may influence the uptake and impact of ePRO-based symptom management systems. Clinical trial information: NCT03850912. Research Sponsor: National Cancer Instiute; 1UM1CA233080-01.

Events at 30 days		OR for ED	95%CI	OR for INPT	95% CI
Overall		1.10	0.94-1.29	1.00	0.88-1.14
Stratified by treatment	Chemo	0.93	0.72-1.20	0.85	0.70-1.05
	Surg	1.23	1.01-1.49	1.10	0.93-1.30
Stratified by health system	A	1.26	1.07-1.50	1.59	1.37-1.85
	B	1.47	1.15-1.88	1.25	0.98-1.58
	C	0.74	0.61- 0.90	0.71	0.61-0.82
	D	0.90	0.68-1.20	0.92	0.75-1.12
	E	0.92	0.70-1.23	1.09	0.87-1.38
	F	1.19	0.96-1.47	0.80	0.68-0.95

11002 Oral Abstract Session

Improving care of older adults with cancer: A randomized trial. First Author: Manali I. Patel, Division of Oncology, Veterans Affairs Palo Alto Health Care System, Palo Alto, CA

Background: Undertreated symptoms are common among older adults with cancer. Previously, a lay health worker (LHW)-led proactive symptom assessment intervention was associated with reduced symptoms in one community clinic. Yet, the effect on acute care use, total costs, and end-of-life (EOL) care at scale remains unknown. **Methods:** Adults ages 75 years or older who were Medicare Advantage beneficiaries with newly diagnosed cancer were eligible to participate in this randomized trial across 43 clinics in Southern California and Arizona. Participants were randomized 1:1 into a control group (usual care alone) or an intervention group (usual care and LHW-led proactive, telephone-based weekly symptom assessments for 12 months using the validated Edmonton Symptom Assessment System) with a planned enrollment of at least 200 in both groups. The LHW reviewed assessments with a physician assistant who conducted follow-up for symptoms that changed by 2 points from a prior assessment or were rated 4 or greater. We used generalized regression models to compare acute care use and total costs (obtained from payer claims data) for 12-months follow-up or death, whichever was first, offset for length of follow-up, and, among those who died, compared EOL acute care use, costs, and acute care facility deaths. **Results:** 416 patients participated (216 control; 200 intervention) with median age of 82 years (range 75-99); 205 (49.28%) were Hispanic or Latino, 10 (2.4%) African American or Black, 12 (2.88%) Asian, 2 (0.48%) Native Hawaiian, 1 (0.24%) Pacific Islander, 180 (43.3%) Non-Hispanic White, 6 (1%) other; 219 (52.6%) were male; 118 (28.3%) had gastrointestinal, 92 (22%) had genitourinary, 62 (14.9%) had breast, and 48 (11.5%) had thoracic cancer; 171 (41%) had stage 4 disease. The intervention group had 53% lower odds of emergency department use (OR: 0.47, 95% CI 0.37-0.62) and 68% lower odds of hospital use (OR: 0.32, 95% CI 0.20-0.51) than the control group. Among deceased participants (71 (32.9%) control; 71 (35.5%) intervention), the intervention group had 68% lower odds of acute care (OR: 0.32, 95% CI 0.12-0.88), lower total costs of care by $12,000 USD per participant (p = 0.01), and 75% lower odds of an acute care facility death (OR 0.25; 95% CI 0.08-0.77). **Conclusions:** This proactive symptom assessment intervention may be one sustainable, scalable, efficient, and effective approach to improve care for older adults with cancer. Clinical trial information: NCT04463992. Research Sponsor: None.

11003 Oral Abstract Session

Randomized trial of a supportive oncology care at home intervention for patients with cancer receiving curative treatment. First Author: Ryan David Nipp, The University of Oklahoma, Oklahoma City, OK

Background: Patients with cancer receiving curative treatment often endure substantial symptoms and utilize significant healthcare resources. Symptom monitoring interventions and hospital at home care models represent a promising approach for improving these patients' outcomes. **Methods:** We conducted a randomized trial of a Supportive Oncology Care at Home intervention versus usual care in adult patients receiving treatment with curative intent (chemotherapy and/or chemoradiation) for pancreatic, rectal, gastroesophageal, and head and neck (H&N) cancer, as well as non-Hodgkin lymphoma, who resided in-state, within 50 miles of our hospital. Patients were randomized to receive the Supportive Oncology Care at Home intervention or usual care within two weeks of initiating therapy and remained on trial for up to 6 months. The intervention entailed: 1) remote monitoring of daily patient-reported symptoms, vital signs, and body weight; 2) a hospital at home care model for symptom assessment and management; and 3) structured communication with the oncology team. The primary outcome was the proportion of patients requiring inpatient hospital admission or emergency department (ED) visits during the study period. Secondary outcomes included urgent visits to the clinic, treatment delays, and longitudinal changes in monthly assessments of quality of life (QOL; Functional Assessment of Cancer Therapy-General), symptoms (Edmonton Symptom Assessment System [ESAS] and Hospital Anxiety and Depression Scale [HADS]), and activities of daily living (ADLs). **Results:** We enrolled 50.8% (199/392) of potentially eligible patients. One patient withdrew consent and 2 became ineligible following consent, resulting in 196 participants (median age=65.8 [range: 21.1-92.0], 39.8% female, cancer types: 34.2% pancreatic, 27.0% H&N, 16.3% lymphoma, 12.8% rectal, 9.7% gastroesophageal). The proportion of patients requiring hospital admission or ED visit did not differ significantly between the intervention and usual care groups (37.1% v 35.7%, p=.87). Intervention participants were less likely to require an urgent visit (7.2% v 24.5%, $p<.01$), but there were no differences in rates of treatment delays >7 days (29.9% v 33.0%, p=.62). Compared to baseline assessments, intervention participants had greater improvement in ESAS symptoms ($p<.01$) and ADLs (p=.04) over time. QOL and HADS depression/anxiety symptoms did not differ longitudinally between groups. **Conclusions:** Although this Supportive Oncology Care at Home intervention did not have a significant impact on rates of hospital admissions or ED visits, we found encouraging results for reducing urgent visits to the clinic and substantial improvement in symptom burden and ADLs, underscoring the potential utility of this novel care model for enhancing care delivery and outcomes for patients with cancer receiving curative treatment. Clinical trial information: NCT04544046. Research Sponsor: The Medically Home Group.

11004 **Oral Abstract Session**

Empowering young-onset colorectal cancer patients with an accessible, self-navigable online platform for universal germline testing. First Author: Julie B. Moskowitz, The University of Texas MD Anderson Cancer Center, Houston, TX

Background: Since 2022, the National Comprehensive Cancer Network (NCCN) has recommended universal germline testing (UGT) for all individuals diagnosed with colorectal cancer (CRC) under age 50. Up to 20% harbor a germline cancer predisposition, and identifying this high-risk cohort is critical for personalized care. Realizing UGT has been hampered by access to and delivery of cancer genetics care, highlighting the need for novel strategies. We report the impact of an accessible, self-navigable online platform for UGT. **Methods:** Consecutive YOCRC patients were offered a standardized care pathway including UGT. A prospective quality improvement trial aimed at UGT launched an interactive online platform designed to enable self-eligibility screening, self-navigation to video-based pretest education and counseling, consent submission, and blood or saliva collection arrangements. Patients could self-opt for genetic counseling (GC, in-person or virtual) at any time, and those who did not engage with the online platform after 3 invitations were reflexively referred to GC. The trial was designed with a 3-month run-in pilot followed by a 12-month study period. The primary outcome was UGT completion rate; secondary outcomes were process feasibility and GC resource preserved. **Results:** Among 377 YOCRC patients, 158 had GT prior to referral, 7 were international, 3 declined all contact, and 209 patients were invited to the online UGT platform. Another 49 reported prior GT, leaving 160 patients of interest. Active platform engagement was observed in the majority (100 of 160 patients, 63%), where 89 (89%) completed UGT, including 79 (96%) of the 82 who self-navigated the entire online platform and 10 (71%) of the 14 who had opted for GC. Lack of platform engagement led to reflex GC referral for 60 patients, and 19 (32%) have completed GT to date. Taken together, among 160 patients of interest, pre-test GC workforce involvement was spared in 79 (49%) patients through the online platform. **Conclusions:** The rising incidence of YOCRC, increasing patient demand and limited GC resources are barriers to executing UGT. We successfully implemented an online platform achieving 96% GT completion rate among those who self-navigated the entire process, and eliminating the need for pre-test GC resource utilization in nearly half of the cases. Our experience supports online care delivery platforms that highlight accessibility and autonomy. Research Sponsor: None.

11005 **Oral Abstract Session**

Real-world social determinants of health (SDOH) and outcomes of early-onset colorectal cancer (EO-CRC): An analysis of a large, nationally representative US community oncology network. First Author: Lisa Herms, Ontada, Boston, MA

Background: The rise of EO-CRC in individuals under the age of 50 presents a major public health challenge, as these patients may encounter unique barriers to both screening and treatment. Understanding the drivers and implications of EO-CRC is crucial, and real-world data (RWD) can serve as a valuable tool by offering insights into evolving diagnostic, utilization, and practice landscapes, with robust information on social determinants of disease burden. Building on existing disparity concerns, this study leveraged RWD from a large, nationally diverse network of US community oncology practices to describe the SDOH and outcomes of patients with EO-CRC. **Methods:** This retrospective observational cohort study examined adult CRC patients within The US Oncology Network and non-Network practices, encompassing over 2,500 community-based providers treating more than 1.4 million patients annually. All patients diagnosed with CRC between 2000 and 2024 were included; patients were categorized as EO-CRC if they were $<$ 50 years at first diagnosis and average-onset (AO)-CRC otherwise. Patient characteristics were sourced from iKnowMed, an oncology-specific electronic health record system, and descriptively summarized. Overall survival (OS) was assessed from diagnosis using Kaplan-Meier methods. **Results:** A total of 104,281 patients were identified, including 14,611 (14%; median age: 44 years) with EO-CRC and 89,670 (86%; median age: 67 years) with AO-CRC. Patients in the EO-CRC cohort were more likely to be Black (11% vs. 8%), American Indian or Alaska Native race (1.3% vs. 0.9%), of a documented race other than White (20% vs. 15%), and of Hispanic/Latino ethnicity (11% vs. 8%) versus the AO-CRC cohort. Few of EO-CRC (11%) and AO-CRC (10%) patients were current smokers at time of diagnosis. More than one-third of EO-CRC group was obese (36%), slightly higher than in AO-CRC (31%). EO patients were more commonly located in urban areas (69% vs. 63% of AO patients). Among 2,810 patients with Distress Thermometer data, EO-CRC patients were more likely to report high or moderate distress (29% vs. 22%) and less likely to report low distress (71% vs. 78%). 5-year OS probability was 72% (95% CI: 71-73) for EO-CRC and 64% (95% CI: 63-64) for AO-CRC. **Conclusions:** In one of the largest cohorts of patients with EO-CRC to date, this study confirmed that EO-CRC is an emerging concern within the US community oncology setting, particularly regarding heightened disparities in race, ethnicity, and lifestyle factors. EO patients may face unique burdens related to timely screening and diagnosis, necessitating tailored and cross-disciplinary approaches to their care, and warranting additional investigation into social and clinical drivers of survival outcomes to improve long-term prognosis. Research Sponsor: Ontada.

11006 **Oral Abstract Session**

Association of Medicaid expansion with five-year survival after cancer diagnosis. First Author: Elizabeth Schafer, American Cancer Society, Atlanta, GA

Background: Medicaid expansion is associated with improvements in early detection, access to treatment, and increased 2-year cancer survival. However, the association between Medicaid expansion and longer-term survival outcomes in newly diagnosed cancer patients remains understudied. **Methods:** Patients aged 18-59 years newly diagnosed with first primary cancers in 2007-2008 and 2014-2015 living in 25 states (AZ, AR, CA, CO, CT, DE, HI, IL, IA, KY, MD, MI, MN, NV, NH, NJ, NM, NY, ND, OH, OR, RI, WA, WV) that expanded Medicaid in 2014 and 12 states (AL, FL, GA, MS, MO, NC, OK, SC, TN, TX, WI, WY) that had not expanded Medicaid by the end of 2020 were obtained from the Cancer Incidence in North America (CiNA) Survival dataset compiled by the North American Association of Central Cancer Registries. Cases were stratified by cancer type, race and ethnicity, census-tract poverty level, and rurality. Difference-in-differences analysis was used to examine the association of Medicaid expansion with changes in 5-year observed overall and cause-specific survival (CSS) based on multivariable flexible parametric survival models adjusted for age group, sex, race and ethnicity, census tract–level poverty, rurality, state, and year of diagnosis. **Results:** A total of 1,256,349 individuals were diagnosed with cancer in Medicaid expansion (N = 698,870) and non-expansion states (N = 557,479) during the study period. The 5-year overall survival increased from 65.0% to 73.4% in expansion states and from 61.0% to 70.0 in non-expansion states, leading to a non-significant net increase of 0.21 percentage points (95%CI: -0.11,0.53) in expansion states after adjusting for sociodemographic factors. Increases in observed and cause-specific survival were greatest in expansion states for cancers of the pancreas (observed: 1.86ppt, 95%CI: 0.33ppt – 3.39ppt; CSS: 2.33ppt, 95%CI: 0.51ppt – 4.14ppt), colon and rectum (observed: 1.55ppt, 95%CI: 0.45ppt – 2.65ppt; CSS: 1.64ppt, 95%CI: 0.53ppt – 2.76 ppt), and lung (observed: 1.19ppt, 95%CI: 0.32ppt – 2.07ppt; CSS: 1.16ppt, 95%CI: 0.09ppt – 2.24ppt). The net increase associated with Medicaid expansion was also prominent among non-Hispanic Black patients (observed: 1.25ppt, 95%CI: 0.30ppt – 2.19ppt; CSS:0.80ppt, 95%CI: -0.10ppt – 1.70ppt), people living in the most deprived area (observed: 1.21ppt, 95%CI: -0.14ppt – 2.56ppt; CSS:1.45ppt, 95%CI: 0.16ppt – 2.75ppt), and rural communities (observed: 2.30ppt, 95% CI: -0.30ppt – 4.88ppt; CSS:2.40ppt, 95%CI: -0.03ppt – 4.83ppt). **Conclusions:** Medicaid expansion was associated with greater increases in 5-year observed and cause-specific survival for Non-Hispanic Black individuals, individuals living in the most deprived area, and rural communities. These findings reinforce the importance of Medicaid expansion in reducing disparities in cancer survival outcomes. Research Sponsor: None.

11008 **Oral Abstract Session**

A randomized controlled trial comparing pragmatic interventions to improve mammogram uptake in a non-compliant population. First Author: Sasidharan Swarnalatha Lucky, Cancer Science Institute, Singapore, National University of Singapore, Singapore, Singapore

Background: Despite over 20 years of a national breast cancer screening program, mammogram uptake in Singapore, a highly developed Asian country, remains under 40%. Limited large-scale prospective data exist on effective pragmatic interventions to boost screening participation. **Methods:** 9000 Singaporean women aged 50-69, eligible for free biennial screening, non-compliant (at least 1 prior mammogram but overdue by $>$ 2 years from last screen), with no breast cancer history and registered on hospital's mobile health app, were randomly selected from a tertiary hospital's electronic medical records and allocated to one of the 5 arms in a 2:1:1:1:1 ratio. Arm 1 (control; n = 3000) received physical mailer reminders (MR). Four intervention arms (n = 1500 each) received MR plus- Arm 2: US$7.4 voucher on screening completion, Arm 3: US$3700 lottery chance, Arm 4: video health message, and Arm 5: health concierge for appointment scheduling. Arms 1–5 also received the reminders via 3 push notifications (PN), spaced 3 weeks apart, through the app. A non-interventional (NI) cohort (n = 3000) fulfilling similar criteria served as comparison. Primary outcome was mammogram uptake rate within 4 months of reminder in Arm 1 vs Arms 2-5. Secondary outcomes included participation rate in Arm 1 vs NI group. Exploratory analysis included cost-effectiveness of intervention and app utility in shaping health behaviour. **Results:** 74% of the 12000 participants were Chinese, followed by Malay (13%) and Indian (7%), reflecting Singapore's demographics. Median age was 62 years (67% aged 60-69). 89% lived in public and 11% in private housing. 99% lived within 5 km of a mammogram facility. Median interval from last mammogram was 5.2 years (range: 2.0–21.5); longer in women aged 60-69 vs 50-59 (6.1 vs 3.9 years, $p < 0.0001$). Mammogram uptake in the NI group was 3.3% and increased to 11.2% with MR alone (Arm 1; RR 3.28, 95% CI 2.60–3.96, $p < 0.01$). Uptake in Arm 5 was slightly higher than in Arm 1 (13.8% vs 11.2%, RR 1.23, 95% CI 1.07-1.38, p = 0.01), but not significant after adjusting for multiple comparisons (p-adj = 0.11). Arms 2-4 (12.1%, 11.3%, 10.8%) showed no difference vs Arm 1. Intervention cost per compliant subject was US$7 in Arm 1, increasing to $13, $28, $32 and $40 in Arms 2-5 respectively. Only 4.1% (3.1–4.6%) in the 5 intervention arms accessed the webpage via PN and $<$ 1% clicked the self-help booking link. **Conclusions:** A physical MR significantly improved mammogram participation in a non-compliant population, but additional monetary incentives or health message offered no further benefit. A concierge service slightly improved uptake but at a 6-fold higher cost. PNs had limited utility in this older population. A low-cost MR program is scalable and piloting concierge services for targeted groups may enhance cost-effectiveness. Further research should explore barriers to digital intervention engagement in this age group. Clinical trial information: NCT06733155. Research Sponsor: National University Cancer Institute, Singapore (NCIS).

11009 Rapid Oral Abstract Session

Association between environmental burden and cancer incidence rates across population subgroups in the United States (US). First Author: Azar Mohammad Abadi Kamarei, University of Alabama at Birmingham, Birmingham, AL

Background: With more than 2 million projected new cancer diagnoses in 2025 in the US alone, many studies have linked environmental pollutants to carcinogenesis. However, they often examine exposures in isolation, overlooking the complexity of real-world multi-exposure conditions. In this study, we investigate the impact of multiple simultaneous environmental exposures on cancer incidence rates at the county level. **Methods:** Data on environmental burden (for e.g. air and water pollution, toxic sites, built environment), measured using the Environmental Burden Module (EBM), were obtained from the CDC Environmental Justice Index. County-level cancer incidence rates for breast, pancreas, prostate, lung, colon, and all cancers combined were obtained from the CDC State Cancer Profiles. Multivariable linear regression models estimated the effects of EBM quartiles (Q1 as the reference, representing the lowest burden, and Q4 noting highest) on cancer incidence rates for the total population and stratified by urbanicity, sex, and age. Interaction terms between EBM quartiles and demographic variables (sex and age) were significant ($p < 0.05$). All results are presented as cases per 100,000 population. **Results:** Higher environmental burden was associated with increasing incidence rates for all cancers in Q3 (15.61 [9.45, 21.78]) and Q4 (7.87 [1.59, 14.15]) across all US counties. Breast (4.45; 95% CI [2.10, 6.80]) and prostate cancer (2.57 [1.00, 4.78]) noted strongest association in Q4. Similarly, rural counties too showed increased rates of all cancers with increasing environmental burden (Q3: 18.22 [10.56, 25.88]); Q4: 21.15 [7.41, 34.89]). In urban counties, prostate cancer incidence was higher in Q4 (4.65; [0.08, 9.22]). Among males, lung cancer incidence increased significantly in the most environmentally burdened counties (Q4: 0.45 [0.21, 0.89]). For colon cancer, while incidence rate for males decreased significantly (Q4: -0.45 [-0.91, -0.01]), it increased among females in the most environmentally burdened counties (Q4: 21.15 [14.21, 28.18]). For older individuals ($>$ 65y), Higher rates of all cancers combined were found in Q3 (125.70 [76.95, 174.44]) and Q4 (117.15 [68.04, 166.26]). Lung cancer incidence was especially sensitive to environmental burden – higher rates were observed in Q2 (3.99 [0.12, 7.87]), Q3 (4.88 [1.49, 8.28]), and Q4 (4.73 [1.56, 7.91]). **Conclusions:** Greater environmental burden was associated with increased cancer incidence rates across several cancer types with sociodemographic variation. These results indicate the need for regulatory policy and infrastructural investment aimed at mitigating these risks in targeted communities. Further research with higher-resolution data is needed to elucidate these associations and underlying etiologic mechanisms. Research Sponsor: None.

11010 Rapid Oral Abstract Session

Complex interplay between housing insecurity and forgone care among U.S. cancer survivors. First Author: Shreya Kondle, Texas Health Presbyterian Hospital Dallas, Dallas, TX

Background: One-sixth of U.S. cancer survivors experience housing insecurity, and one-fifth report delaying or forgoing care due to costs. The role of social determinants of health (SDoH) among cancer survivors is complex and poorly understood. We sought to examine the prevalence of housing insecurity and forgone care, and their effects in conjunction with SDoH among cancer survivors. **Methods:** The Medication Expenditure Panel Survey (MEPS) is an annual survey representative of the civilian, non-institutionalized United States population. The 2022 MEPS survey included a Preventative Care Self-Administered Questionnaire measuring late rent/mortgage payments indicative of housing insecurity in the past year. We considered adult cancer survivors (excluding non-melanoma skin cancer) who reported an inability to afford or had to delay any medical/dental care or prescription medications, as forgoing care. We extracted sociodemographic and clinical characteristics. Survey-adjusted Wilcoxon rank-sum tests and chi-square tests assessed differences in continuous and categorical variables, respectively, for individuals with and without housing insecurity, cancer, and forgone care. A multivariate regression analysis adjusting for age, sex, race, and poverty status identified predictors of forgoing medical care. We conducted weighted analyses to account for the complex survey design and considered $p < 0.05$ as statistically significant. **Results:** A total of 1,776 cancer survivors (weighted (w): 21,088,176) and 20,655 individuals with no cancer (w: 311,965,067) were identified. Among cancer survivors, 13% (w: 1,315,879) reported housing insecurity while 19% (w: 4,063,946) were forgoing care. Housing insecurity was reported in 8% of female survivors compared to 4% of male survivors, while 22% of women forwent care compared to 16% of men. Black Americans were less likely to report forgone care (13%) compared to White (19%) and Hispanic cancer survivors (25%), while housing insecurity was higher among all minorities (~10%) compared to White survivors (5%). Younger cancer survivors aged 18-45 years reported four-fold rates of housing insecurity and 1.5 times the rate of forgone care compared to survivors over 65. Multivariate logistic regression revealed forgoing medical care was more prevalent in individuals aged 45–64 (aOR = 1.6), women (aOR = 1.5), the near poor (aOR = 2.9), and those experiencing housing insecurity (aOR = 4.1), but less prevalent in Black Americans (aOR = 0.5) (all $p < 0.05$). **Conclusions:** This is the first nationally representative study to report the complex interplay between housing insecurity and forgone care among cancer survivors. The interactions highlight some unexpected high-risk groups like women, near-poor individuals, and middle-aged individuals, who are more likely to forgo care when forced to choose or prioritize care. Future policies need to target these high-risk groups. Research Sponsor: None.

11011 Rapid Oral Abstract Session

Beyond the clinic: Comprehensive assessment of time burdens in cancer care. First Author: Rachel I. Vogel, University of Minnesota, Minneapolis, MN

Background: Managing cancer care can be highly demanding, consuming time and energy. Measuring this time has been limited to date. We sought to comprehensively measure the time spent on cancer-related care by leveraging a mobile application, Daynamica, which collects spatiotemporal sensing data in real-time while limiting intrusiveness to capture both objective and subjective dimensions of time use. **Methods:** As a proof-of-concept, we recruited individuals with metastatic breast or advanced stage ovarian cancer receiving treatment at the University of Minnesota and University of Alabama-Birmingham. Participants utilized the Daynamica app for 28 days, reporting healthcare encounters (location and type), along with completing end-of-day (EOD) surveys regarding at-home cancer-care related activities. We summarized the number and type of healthcare encounters and quantified time spent traveling to/from, waiting for, and receiving care. Utilizing the EOD survey data, we also quantified time spent on cancer-care related tasks at home. **Results:** A total of 58 individuals provided data for this analysis: 31 (53%) with metastatic breast cancer and 27 (47%) with advanced stage ovarian cancer; 29% were $<$ 50 years old, 72% non-Hispanic (NH) White and 17% NH Black. Participants reported a median of 6 out-of-home healthcare episodes during the study, representing a median of 108 min/week. These episodes were most frequently labeled as including treatment (33%), clinic visit (27%) and/or labs (28%); imaging (12%), pharmacy (11%) and research (3%) were less frequent. Participants reported varying wait times during their healthcare episodes, with most involving $<$ 15 min wait (37%), though both no wait (19%) and $>$ 60 min of waiting (19%) were frequent. We observed variation in time individuals spent traveling to/from their healthcare visit, with a median travel time per episode of 31 min (5th-95th percentile range 4-125). The proportion of time spent receiving care relative to wait and travel time was often less than 50% of the total time, particularly when the time spent receiving direct care was $<$ 60 min. Participants reported spending a significant amount of time on telehealth visits, taking medications, scheduling appointments, and managing insurance and medical bills (median 120 min/week); of these 4 tasks, taking medicines or injections was the most frequently reported and time-consuming category. This estimate jumped to 325 min/week when also including time spent on symptom management, arranging help/transportation, and seeking information about cancer. **Conclusions:** The time spent on cancer related-care is vastly underestimated when capturing healthcare encounters only. Comprehensive measurement of time spent on cancer related tasks is an important first step towards developing and testing interventions to improve healthcare efficiencies and reduce patient burden. Research Sponsor: National Institutes of Health, National Cancer Institute; 1R01CA277714-01.

11012 Rapid Oral Abstract Session

Association of medical debt with cancer incidence rates in the US. First Author: Jiazhang Xing, Sinai Hospital of Baltimore, Baltimore, MD

Background: Medical debt is a growing challenge for U.S. patients and has been associated with higher cancer mortality. However, whether medical debt is associated with advanced-stage cancer diagnoses – a strong predictor of worse prognosis – remains unclear. This study investigated the association between medical debt in collections and overall and advanced stage cancer incidence rates in the U.S. **Methods:** We conducted an ecological study using 2019 county-level medical debt in collections data from the Urban Institute Debt in America project and age-adjusted cancer incidence rates (2017-2021) from the CDC State Cancer Profiles dataset. Outcomes were age-adjusted cancer incidence and age-adjusted late-stage (i.e., regional or distant) incidence rates for ten common cancers with screening tests or early signs. We used generalized linear mixed models, adjusting for urban-rural status, county-level Social Vulnerability Index, county population size, primary care physician density, median population age and state. **Results:** We included data from all 3,143 counties. The county-level percentage of medical debt in collections ranged from 0.0% to 23.5%. One percentage increase in medical debt was associated with a 74.80 (95% CI=43.45-106.19) increase in overall cancer incidence rate per 100,000 person-years. Regarding late-stage cancer incidence, one percentage increase in medical debt was associated with a 5.16 (95% CI=1.05-9.28) increase in late-stage incidence rate for colorectal, a 2.11 increase (95% CI=1.04-3.18) for bladder, a 2.73 (95% CI=1.08-4.39) increase for kidney and renal pelvis, a 28.69 (95% CI=22.22-35.17) for lung and bronchus, and a 0.14 (95% CI=0.01-0.26) increase for oral cavity and pharynx cancers, and a 2.99 (95% CI=1.53-4.44) increase for melanoma of the skin. No significant association was noticed in other cancer types. **Conclusions:** Medical debt in collections is associated with higher overall incidence and late-stage rates for multiple cancer types, suggesting financial barriers may impede both cancer screening and timely symptom evaluation. Research Sponsor: None.

Adjusted association of percent of population with medical debt in collections with cancer incidence rate at the county level (per 100,000).

	Incidence	Late stage incidence
All cancers	74.80 (43.45-106.19)	-
Colorectal	9.48 (3.68-15.28)	5.16 (1.05-9.28)
Kidney and renal pelvis	9.84 (6.48-13.22)	2.73 (1.08-4.39)
Lung and bronchus	41.02 (32.46-49.58)	28.69 (22.22-35.17)
Cervix	0.64(0.40-0.88)	0.17(0.00-0.34)
Melanoma	-5.73(-11.52-0.05)	2.99 (1.53-4.44)
Bladder	-0.73(-4.01-2.51)	2.11 (1.04-3.18)
Prostate	-13.70(-29.67-2.29)	-5.28(-11.10-0.42)
Breast	-1.43(-13.83-10.89)	4.57(-1.71-10.88)
Oral Cavity and Pharynx	0.16(0.01-0.31)	0.14(0.01-0.26)

Data for late-stage incidence of all cancer sites combined not available from CDC.

11013 Rapid Oral Abstract Session

Treatment preferences between survival and quality of life and their association with clinical outcomes in older adults with advanced cancer. First Author: Daniel R. Richardson, UNC Lineberger Comprehensive Cancer Center, Chapel Hill, NC

Background: Preference-concordant care improves quality of life (QoL) and reduces healthcare utilization. However, limited research exists on how preferences impact clinical outcomes in older adults with advanced cancer. Our study explores differences in outcomes between patients (pts) prioritizing extending survival versus maintaining QoL. We hypothesized that patients prioritizing survival would live longer, while those prioritizing QoL would have fewer treatment-related toxicities and hospitalizations. **Methods:** We analyzed data from pts aged $\geq$ 70 with incurable solid tumors or lymphoma and $\geq$ 1 impaired geriatric assessment domain starting a new systemic cancer treatment within NCI's Community Oncology Research Program as part of a cluster randomized trial (NCT02054741, PI: Mohile). Pts reported their preference for prioritizing extending survival versus maintaining QoL at baseline: agree, neutral, disagree. We used generalized linear mixed models and generalized estimating equations to assess the association of treatment preference with hospitalization and treatment-related toxicities, and Cox shared frailty models for survival. Analyses were adjusted for study arm, age, sex, race, education, and practice. **Results:** We included 706 pts. Mean age was 77.2 years (SD 5.4, range 70-96); 43% were female; and 89% were non-Hispanic white. Gastrointestinal (34.6%), lung (24.8%), and genitourinary (15.4%) cancers were most common. Fewer pts preferred to prioritize extending survival (n = 59, 8.4%) versus maintaining QoL (n = 506, 71.7%) versus no preference/neutral (n = 141, 20.0%). Choice of initial therapy (single agent, multiple agent, or combined chemotherapy plus another agent) did not differ by preference. Most pts (61.7%) had grade 3-5 treatment-related toxicity; 25.2% were hospitalized in the first 3 months; 26.3% died within 6 months; 47.3% died within one year. No significant associations were found between preference for prioritizing survival v. QoL and grade 3-5 toxicity (Risk ratio [RR] 0.90, 95% Confidence Interval [CI] 0.70–1.16), hospitalization (RR 0.81, 95% CI 0.48–1.36), nor survival (Hazard ratio 0.75, 95% CI 0.42–1.33 at 6 months; 1.18, 95% CI 0.82–1.71 at 1 year). **Conclusions:** Over two-thirds of older adults with advanced cancer prioritize maintaining QoL over extending survival. Prioritizing QoL was not associated with shorter survival. However, it was also not associated with reductions in hospitalization nor treatment-related toxicities. While these findings may suggest a lack of responsiveness of the healthcare system to patient preferences, additional studies are necessary to better evaluate this relationship. More research is needed to develop treatment modifications and interventions so that older adults with advanced cancer achieve those outcomes that matter most to them. Funding: UG1CA189961, R01CA177592. Research Sponsor: None.

11014 Rapid Oral Abstract Session

Utilization and timing of first tumor next-generation sequencing testing (NGS) in patients (pts) with five most common cancers in the USA. First Author: Chadi Hage Chehade, Huntsman Cancer Institute at the University of Utah, Salt Lake City, UT

Background: In the USA, the 5 most common advanced/metastatic solid tumors are advanced non-small cell lung cancer (aNSCLC), metastatic breast cancer (mBC), metastatic prostate cancer (mPC), advanced colorectal cancer (aCRC), metastatic pancreatic cancer (mPanC). Life-prolonging targeted therapies are approved for pts with tumor-susceptible alterations, and guidelines recommend NGS to identify these alterations. Herein, we assessed the overall utilization of NGS and the timing of NGS in relation to the time of death in real-world pts with these cancers. **Methods:** This retrospective study utilized the nationwide Flatiron Health electronic health record (EHR) derived de-identified database. Eligibility: diagnosis of aNSCLC, mBC, mPC, aCRC, mPanC with information on receipt of NGS (blood/tissue) and recorded date of death. The time between each pt's first NGS result and date of death was measured and pts were categorized into 3 groups: NGS results delivered $>$ 3 months (mo) before death, within 3 mo of death, and delivered/reported after death. Frequencies and percentages of the 3 categories were reported, also by the year of death and practice type. **Results:** Of 86,536 pts with aNSCLC, 31,375 received NGS (36.3%), of whom 19,958 had a date of death recorded. Of 36,000 pts with mBC, 11,550 were tested (32.1%), of whom 5,689 had a date of death recorded. Of 24,105 pts with mPC, 7,439 were tested (30.9%), of whom 3,397 had a date of death recorded. Of 35,702 pts with aCRC, 14,642 were tested (41%), of whom 8,553 had a recorded date of death. Of 14,964 pts with mPanC, 5,298 were tested (35.4%), of whom 3,957 had a recorded date of death. The timing of NGS relative to the time of death by cancer type is shown in Table. Across all cancers, the rate of pts receiving NGS results $>$ 3 mo before death increased over time, while the rate of those receiving results within 3 mo of death or after death decreased. Baseline characteristics (race-ethnicity, insurance plan, practice type) and NGS rates by year of death in the 3 categories will be presented in the meeting. **Conclusions:** Despite the availability of life-prolonging targeted therapies based on NGS results, a sizeable number of pts either do not undergo NGS or have their first NGS very late in the course of disease (i.e. within 3 mo of death). These results warrant better utilization of tumor NGS in a timely fashion in pts with cancer to optimize survival outcomes. Research Sponsor: None.

Rates of first NGS relative to the time of death (in pts who underwent NGS and had a date of death recorded).

Timing of first NGS results	aNSCLC N = 19,958	mBC N = 5,689	mPC N = 3,397	aCRC N = 8,553	mPanC N = 3,957
> 3 mo before death, n (%)	14,431 (72.3%)	4,643 (81.6%)	2,901 (85.4%)	7,271 (85%)	2,815 (71.1%)
Within 3 mo of death, n (%)	5,109 (25.6%)	959 (16.9%)	457 (13.5%)	1,173 (13.7%)	1,047 (26.5%)
After death (NGS result reported after death), n (%)	418 (2.1%)	87 (1.5%)	39 (1.1%)	109 (1.3%)	95 (2.4%)

11015 Rapid Oral Abstract Session

Overall survival and quality of life superiority in modern phase III oncology trials. First Author: Alexander Dean Sherry, The University of Texas MD Anderson Cancer Center, Houston, TX

Background: The use of alternative endpoints, such as progression-free survival, has increased over time in phase III randomized clinical trials (RCTs). However, PFS and other alternative endpoints are often not valid surrogates for overall survival (OS) and quality of life (QOL), and may be less relevant to patients. We sought to determine the proportion of phase III oncology RCTs with OS or QOL superiority. A secondary goal was to evaluate the approach of QOL analyses, since "change-from-baseline" approaches may bias results (Bland and Altman. *Trials.* 2011;12:264). **Methods:** We performed a meta-epidemiological study of two-arm, superiority-design, interventional phase III oncology RCTs screened from ClinicalTrials.gov. RCT publications were reviewed for alternative endpoint, OS, and QOL results by at least two investigators. Alternative endpoint and OS superiority were defined for the experimental arm vs control arm according to the pre-specified statistical criteria for each RCT. QOL superiority was defined by either statistically significant or minimal clinically important differences (MCID). QOL was sub-classified as global QOL, defined by the composite summary measure obtained using the patient-reported outcome instrument, or domain QOL, referring to measures obtained from instrument subscales. **Results:** We included 791 RCTs published between 2002 and 2024, representing 555,580 enrolled patients. Primary RCT results were published between 2002 and 2024. Alternative primary endpoints were most common (n = 495, 63%). The primary endpoint was met in 53% of the RCTs (n = 420). Alternative endpoint superiority was shown in 55% of the RCTs (n = 434). OS was reported by 705 RCTs (89%), and OS superiority was shown in 28% of the RCTs (n = 221). Patient-reported outcomes were collected in 61% of the RCTs (n = 482), and 34% of the RCTs published global QOL results (n = 271). Most global QOL analyses were change-from-baseline (55%, n = 148). Global QOL superiority was shown in 11% of the RCTs (n = 84). In a sensitivity analysis of QOL subscale outcomes, 80 trials (10%) showed superiority in at least one QOL domain. Collectively, in 32% of the RCTs (n = 257), superiority of either OS or global QOL was demonstrated. In 6% of all RCTs (n = 48), both OS and global QOL superiority was shown. **Conclusions:** Phase III, superiority design oncology RCTs are commonly interpreted as "positive." However, this is usually based on improvements in unvalidated alternative endpoints. Gains in either OS or QOL are uncommon, and exceedingly rare in combination. QOL appears both under-evaluated and under-reported. Furthermore, the majority of phase III QOL analyses, which are based on change-from-baseline comparisons, may be misleading. To increase the meaningfulness of late-phase research, future trial designs and regulatory processes should be re-focused towards OS and methodologically rigorous QOL improvements. Research Sponsor: National Cancer Institute; P30CA016672; Andrew Sabin Family Foundation.

11016 Rapid Oral Abstract Session

SWOG S2302, PRAGMATICA-LUNG: A pragmatic trial designed to increase participant representation. First Author: Karen L. Reckamp, Department of Medicine, Cedars Sinai Cancer Center, Los Angeles, CA

Background: Effective therapy following frontline immune checkpoint inhibitor (ICI)-based treatment for advanced non-small cell lung cancer (NSCLC) is needed as limited options are available. Lung-MAP S1800A was a Phase II randomized study of ramucirumab plus pembrolizumab versus standard of care (SOC) for patients with NSCLC previously treated with immunotherapy that demonstrated benefit in overall survival (OS) with an improved toxicity profile over SOC. S2302 Pragmatica-Lung trial was pragmatically designed to evaluate the impact on OS while reducing barriers to participation and decreasing clinical trial staff burden. We assessed reduction in barriers to participation and clinical staff burden in S2302 in relationship to S1800A. **Methods:** S2302 (NCT05633602) is a registration-intent randomized phase III trial for patients with advanced NSCLC who previously received PD-(L)1 inhibitor therapy for at least 84 days and platinum-based therapy, stratified by immediate prior line of therapy including PD-(L)1 inhibition (yes/no) and PS (0/1 v. 2). The pragmatic design has limited eligibility criteria, which are focused on stage, prior therapy and safety to enroll patients as would occur in real world practice. Laboratory assessment and imaging with RECIST reads are not required due to the OS endpoint. Data collection was developed to minimize the burden with fewer time points for data submitted, number of forms and number of data elements. Concomitant medications are not collected. Given the known safety profile of both study drugs, only related and unexpected grade 3/4 and all grade 5 adverse events are collected. **Results:** Accrual to S2302 was robust with 838 patients enrolled from March 2023 to December 2024 (21 months), averaging $>$ 50 patients/month in the final 6 months. The trial enrolled 77% White and 13% Black patients. versus 87% and 8%, respectively on S1800A. Over 65% were $\geq$ 65 years of age. Reduced data collection on S2302 relative to S1800A results in an estimated decrease in the number of forms and data elements submitted within the first year on study by 45% and 66%, respectively. **Conclusions:** Incorporating pragmatic elements into S2302 resulted in robust accrual, increased participant representativeness and access for patients. The reduced burden on staff due to decreased data forms and elements is substantial. Pragmatic design elements should be considered as we develop trials to generalize to a broad and representative population. Clinical trial information: NCT05633602. Research Sponsor: NIH/NCI/NCTN grants U10CA180888 and U10CA180819; Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA, and Eli Lilly and Company.

11017 **Rapid Oral Abstract Session**

Benefit of adding Cureety remote patient monitoring (RPM) to usual care during injectable anticancer treatment: The OPTIMACURE multicentric French prospective randomized study. First Author: Audrey Faveyrial, Centre François Baclesse, Medical Oncology Department, Caen, France

Background: In routine care, assessing whether a patient can safely be administered an injectable anticancer treatment requires the review of blood tests, risk factors and relevant adverse events (AEs). Thus, some French centers use coordinated phone calls and blood tests to improve chemotherapy prescription accuracy and reduce wait times for patients. For example, as part of usual care, the François Baclesse center uses the OPTIMA program. Digital RPM could further streamline this process by efficiently collecting and evaluating patient data without needing systematic phone calls. The OPTIMACURE study aimed to assess whether integrating Cureety RPM into usual care (with OPTIMA or equivalent) can increase the quality of care and decrease the hospital staff workload. **Methods:** The prospective, randomized, multicenter, open-label OPTIMACURE study was designed to assess whether adding Cureety RPM to usual care would reduce the number of phone calls during the first two months after randomization. Outpatients with solid tumor initiating injectable anticancer treatment were randomly assigned (2:1) to either usual care with Cureety RPM or usual care alone (with OPTIMA or equivalent). The numbers of phone calls were compared between arms using an analysis of covariance (ANCOVA) model adjusted for study arm, treatment type, infusion frequency, performance status, and center. **Results:** From April to August 2024, 192 patients (127 in RPM arm, 65 in control arm) were enrolled in 3 centers: women (73%), mean age 61 $\pm$ 13 yrs. The cancers were breast in 40%, non-small cell lung in 14%, colorectal in 9.5%, and prostate in 7.4%. The infusion frequency was once every 1-2 weeks in 37% and $\geq$3 weeks in 63%. Nine patients were excluded due to protocol deviations. Calls, for any reasons, were significantly reduced in the RPM arm (3.80 versus 2.61, relative change of -1.20, 95% CI [-1.89 to -0.53], $p < 0.001$, ANCOVA model). Those results were further analyzed by differentiating outgoing calls to prepare the outpatient visits and those to follow-up on toxicity reports. Preparation calls were less frequent for patients in the RPM arm than those in the control arm (no preparation call for 73.2% of patients vs 12.3%; $\geq$3 calls for 3.2% of patients vs 69.2%), corresponding to a higher reduction of preparation calls (-2.7 [-3.12;-2.3], $p < 0.001$, ANCOVA model). As for calls for toxicity follow-up, they were more frequent in the digital RPM arm (1.6 [1.14;2.05], $p < 0.01$), associated with earlier report of grade 3-4 non hematological AEs (Hazard ratio for first report of severe AE: 4.06, $p < 0.001$) and better care management for patients in the RPM arm compared to the control arm. **Conclusions:** Adding digital RPM to routine cancer care was beneficial, with a significant gain in time to prepare cancer treatment in day unit and with improved detection and management of toxicities. Clinical trial information: NCT06371911. Research Sponsor: Cureety.

11018 **Poster Session**

Improving clinical trial interpretability and efficiency: A Bayesian re-analysis of individual patient outcomes from 230 phase III oncology trials. First Author: Alexander Dean Sherry, The University of Texas MD Anderson Cancer Center, Houston, TX

Background: The conventional interpretation of superiority oncology trials relies on statistical significance defined by *P* values, which are frequently misinterpreted and oversimplified. On the other hand, Bayesian analysis, which incorporates prior knowledge, directly estimates the probability of a hypothesis, with greater flexibility to examine clinically relevant effect sizes. Here, we studied the effects of Bayesian models on phase III trial interpretation. We further hypothesized that Bayesian approaches, using differential priors for efficacy and futility, would improve trial efficiency. **Methods:** Phase III superiority-design, two-arm oncology trials were screened from ClinicalTrials.gov for this meta-epidemiological study. Individual patient-level data were manually reconstructed from the Kaplan-Meir curves of the primary endpoint. First, Bayesian Cox regressions of reconstructed data applied skeptical *N* (0, 0.355), enthusiastic *N* (-0.41, 0.4), and neutral priors N (0, 10^6), where *N* (mean, standard deviation) denotes a normal distribution, to estimate posterior probabilities of the primary endpoint effects with Markov chain Monte Carlo sampling. Minimum clinically important differences (MCID) in the experimental arm were defined by HR < 0.8 per ASCO criteria (Ellis et al, *J Clin Oncol* 2014). Second, a single event or enrollment-driven interim analysis with Bayesian stopping rules was simulated 100 times for each trial using *in silico* models of randomly varying accrual kinetics with published patient outcomes. Interim efficacy and futility were defined per simulation by probabilities $\geq$ 85% for achieving effect sizes larger than the MCID/3 using a skeptical or enthusiastic prior, respectively. Early trial closure was recommended if $\geq$ 75% of simulations met efficacy or futility criteria. **Results:** After screening,194,129 patient outcomes from 230 trials were reconstructed. Overall survival was the primary endpoint in 90 trials (39%). All trials interpreted as positive had $>$ 90% probabilities of marginal benefits (HR < 1). However, 38% of trials interpreted as positive had $\leq$ 90% probabilities of achieving the MCID (HR < 0.8), even under an enthusiastic prior. Conversely, 24% of trials interpreted as negative had $>$ 90% probability of achieving marginal benefits, even under a skeptical prior. In the interim analysis simulations, early closure was recommended for 82 trials (36%). Bayesian interim analysis was associated with $>$99% probability of reducing enrollment sizes. The trial and its simulated interim analysis remained concordant (Bayesian Cohen's κ, 0.95). **Conclusions:** Bayesian models add unique interpretative value for clinically relevant effects, and may improve trial efficiency without compromising trial interpretation. Bayesian models should be increasingly incorporated in phase III trials. Research Sponsor: National Cancer Institute; P30CA016672; Andrew Sabin Family Foundation.

11019 **Poster Session**

Adherence of published randomized phase 3 cancer trials to principles proposed by common-sense oncology. First Author: Omar Abdihamid, Garissa County Hospital, Garissa Cancer Center, Garissa, Kenya

Background: Randomized clinical trials (RCTs) remain the gold standard for evaluating the efficacy and safety of novel cancer therapies. Some RCTs are well-designed and show meaningful improvements in patient outcomes while others are confounded by various types of bias, or do not reflect outcomes that matter to patients. Published RCTs should be designed, analyzed and reported to provide optimal, unbiased information for clinicians to enhance treatment decision-making Common-Sense Oncology (CSO) is an initiative of clinicians, patient advocates, researchers, and policymakers with the mission of ensuring that cancer care and research are focused on outcomes that matter to patients. CSO has published a checklist for the design, analysis and reporting of RCTs evaluating systemic treatments for cancer. In the present study, we have applied the checklists to a cohort of cancer drug trials to assess the extent to which CSO principles were incorporated in reports of RCTs published in 2023 in high-impact journals. **Methods:** We reviewed retrospectively phase 3 RCTs evaluating systemic therapies for adult solid tumors published in 2023 in *The New England Journal of Medicine, Lancet, Lancet Oncology, JAMA, JAMA Oncology, Journal of Clinical Oncology,* and *Annals of Oncology*. These journals were selected based on their high impact. For each trial we evaluated the trial design in the methodology, how the results were reported and the discussion section using the CSO RCT Checklist. **Results:** 50 RCTs evaluating systemic therapies for solid tumors were published in 2023. The most common tumor types were lung, liver, and prostate cancer. Progression-free survival and overall survival were the primary endpoints in 44% (22) and 42% (21) of trials, respectively. Only 36/50 trials justified the control arm, 25/50 justified the primary endpoint, and 18 included Quality-of-Life as a secondary endpoint. Only two trials addressed strategies to limit censoring and dropout; numbers of censored patients (with numbers at risk) were shown under Kaplan-Meier curves in only 21/50 trials, and sensitivity analysis to determine the potential effects of censoring was done in only 5 trials. Chronic toxicities were reported in only one trial, only 7 trials included patient-reported outcomes and only 3/50 trials mentioned cost of the drug. **Conclusions:** Our findings underscore the need for standardized methodologies, comprehensive design, and reporting in oncology RCTs. By identifying gaps in RCT design and reporting, CSO aims to improve the quality and consistency of future trials. Research Sponsor: None.

11020 **Poster Session**

Kaleido registry: A multi-center registry platform with site staff and automation to enable accelerated clinical research and drug development at scale in community practices. First Author: Luis T. Campos, Oncology Consultants, Medical Center, Houston, TX

Background: The number of candidate drugs and clinical trials in oncology is rapidly increasing, necessitating innovative approaches to streamline patient identification, enrollment, and trial execution. However, data collection for patient eligibility assessments remains highly manual, placing significant burden on clinical teams. Technology solutions leveraging Electronic Health Records (EHR) data are emerging, but missing or inaccurate data often impede high-fidelity and low-latency prescreening. In 2022, the Kaleido registry was initiated to address these challenges by implementing on-site staff, abstraction prior to each visit, and draft notes for medical oncologists in the registry. **Methods:** The Kaleido registry enrolls patients with oncological/hematological diagnoses at four community practice sites. Real-time data abstraction is performed in all patients prior to each visit in an expanding set of indications (NSCLC, CRC, prostate cancer, and myeloproliferative neoplasms) to provide systematic and unbiased trial prescreening. An automated prescreening tool has been developed and validated in 394 pts to identify potential trial candidates. Standardized note drafts free up staff time. A questionnaire addressing social determinants of health (SDOH) and self-reported performance status was introduced to further reduce missing data in the EHR. **Results:** To date, over 10,000 patients (61% female, 39% male) have been enrolled. 6% of approached patients declined to consent. The most common diagnoses include breast, prostate, lung, and colorectal cancer. The automated prescreening tool was validated with 90% sensitivity and 97% specificity. The patient questionnaire has a completeness rate of 99%. Real-time abstraction was demonstrated to be feasible, with completeness above 90% for key variables. Among patients with metastatic NSCLC, the genomic testing rates exceeded 80% supporting the sites' suitability for clinical trials. **Conclusions:** With high consent rates, data completeness, and a validated automation tool, the Kaleido registry offers a scalable model for systematic, unbiased patient recruitment and comprehensive data collection across oncology/hematology. This approach has the potential to accelerate clinical research and drug development in oncology and hematology, ultimately enhancing trial efficiency and improving patient outcomes. Research Sponsor: N-Power Medicine.

11021 **Poster Session**

Are patients satisfied with the information in an informed consent form? Questionnaire-based study examining patients' viewpoints. First Author: Bhagyashree Pathak, Tata Memorial Hospital, Mumbai, India

Background: Ensuring that patients understand the information in an Informed Consent Form (ICF) is key to shared decision-making and ethical conduct of a trial. Data regarding patients' views on the ICF are limited. **Methods:** Descriptive questionnaire-based survey study conducted in patients with malignancy aged 18 years and over who had earlier been enrolled in an interventional clinical trial at the Tata Memorial Center (Mumbai, India) and had filled an ICF for that trial. Patients were asked to provide their basic demographic information and fill in a 14-item questionnaire regarding their views/suggestions about the information in the ICF. Primary end point was patients' satisfaction with the information provided in the ICF. Satisfaction was scored on a Visual Analog Scale of 0-10; 0 indicated "least satisfied" and 10 meant "most satisfied". Level of satisfaction was categorized as low (0 – 4), moderate (5 – 7), and high (8 – 10). The study was approved by the ethics committee and registered with CTRI. **Results:** Between Jan 2023 – Jun 2024, we recruited 426 patients. Median age was 47 (IQR, 39-56) years; 234 (54.9%) were male, and 43 (10%) were illiterate. Malignancies included head and neck (202 [47.4%]), breast (108 [25.4%]), gastrointestinal (45 [10.6%]), thoracic (44 [10.3%]), and hematolymphoid (27 [6.3%]). Intent of therapy was curative in 375 (88%). There were 31 (7.3%) patients who did not know that they had participated in a clinical trial. The ICF was not completely read by 68 (16%) patients, due to the following reasons: excessive technical terms (38 [8.9%]), lengthy ICF (18 [4.2%]) and insufficient time provided (17 [4%]). Fifty-two (12.2%) patients did not understand the language of the ICF. Majority of patients (360 [84.5%]) suggested that ICF length be limited to 1-4 pages. Over half the patients wanted the ICF to include more information on standard treatments (230, 54%), side-effects (223, 52.3%), reason for study participation (214, 50%), and risks and benefits (249, 58.5%). Twenty-two (8%) patients felt over-burdened with the information provided in the ICF. Median satisfaction score was 8 (IQR 6 – 10); but only 56.6% patients were highly satisfied with the information in the ICF. Low satisfaction was reported by 167 (39.2%) patients with the information in the reimbursement/compensation section and 164 (38.%) with the alternative treatment options section. Age, sex, education, type of cancer, intent of cancer-directed therapy, and socioeconomic status did not significantly impact the level of satisfaction with the information in the ICF. **Conclusions:** The information in the ICF for interventional clinical trials needs to be concise, and in simple language. Addressing patient preferences and providing clear information in each section would enhance patient understanding and satisfaction, fostering a more effective and ethical informed consent process. Clinical trial information: CTRI/2023/01/048999. Research Sponsor: None.

11022 **Poster Session**

Why the duration of cancer treatment requires a closer look: An empirical analysis of recent FDA approvals. First Author: Jeremy Birkmire, Baylor College of Medicine, Houston, TX

Background: The duration of cancer treatment directly impacts its efficacy, toxicity, and cost. Yet, its systematic evaluation is missing in most clinical trials. In July 2024, the FDA critiqued trial designs for failing to assess the contribution of perioperative (adjuvant and/or neoadjuvant) components but did not address the broader question of optimal treatment duration. **Methods:** We conducted a comprehensive, retrospective review of FDA anti-tumor drug approvals issued between January 2019, and August 2024. Landmark publications supporting each approval were identified through Google Scholar, PubMed, and DailyMed. Each trial's duration of treatment design was classified as either indefinite or fixed, with subgroups of fixed perioperative, fixed non-perioperative, and single-dose. We also recorded the planned duration (PDOT) and median duration of treatment patients received (MeDOT). After excluding n=48 trials with altered initial approvals, 216 remained for overall analysis; 35 lacked MeDOT data and were excluded from MeDOT-specific analyses, leaving 169 for those analyses. We performed non-parametric comparisons and LASSO-selected multivariable regression of duration variables to explore predictors such as trial phase, treatment intent, drug class, and cancer type. As this research used publicly available, aggregate data, our protocol was reviewed by a senior team and did not require IRB submission per 45 CFR §46.102(f). **Results:** 70% of the included trials requiring >1 dose were indefinite. Among fixed, the PDOT – MeDOT difference gap was significantly larger in non-perioperative (median 16.3 months) than in perioperative (0.8 months). The MeDOT distributions for non-perioperative and indefinite trials were right-skewed with medians of 6.4 and 7.6 months respectively. In regression analyses, non-perioperative trials had significantly shorter MeDOTs, often treated hematologic malignancies, used checkpoint inhibitors, or involved front-line palliative intent. Indefinite trials were more frequent for small-molecule and tyrosine kinase inhibitors (TKIs), and fixed TKI trials had notably longer PDOTs (17.6 months). Importantly, none of the 216 approvals were based on trials comparing different treatment durations. **Conclusions:** While our findings suggest current oncology likely errs toward overtreatment, it is clear that researchers and regulators are not adequately assessing optimal treatment duration. Indefinite duration dominates current trial designs, while non-perioperative shows wide PDOT–MeDOT discrepancies, reflecting uncertainty about when therapeutic benefits plateau and harms increase. Future trials and regulatory directives should prioritize randomized duration comparisons to reduce toxicity and costs while optimizing patient outcomes. Research Sponsor: None.

11023 **Poster Session**

Publication and data sharing of completed NCI cooperative group trials. First Author: Lauren N. Cueto, Yale School of Public Health, New Haven, CT

Background: Concerns about timely publication of NIH trial results, as well as sharing of clinical trial data, have led to important initiatives. The NCI developed an online archive of individual patient data (IPD) for cooperative group trials published after 2014, and ClinicalTrials.gov has required data sharing plans for all trials that began enrollment after 2018. We examined the dissemination of NCI cooperative group trial results via published manuscripts as well as availability of IPD from completed trials. **Methods:** We queried the Access to Aggregate Content of ClinicalTrials.gov database for phase II or III interventional trials for which NCI cooperative groups were listed as the sponsor, responsible party, or principal investigator. We included trials that were initiated between 2011 and 2022 and reached actual primary completion status (i.e. completion of data collection to fulfill the primary outcome measurement) by 2022. Primary manuscripts that reported the study primary outcome data were identified by searching NCT ID numbers on ClinicalTrials.gov, PubMed, and Google Scholar through a dual review. We restricted our 2 and 5-year assessments of study publication status to studies that had reached their primary completion date before 2022 and 2019, respectively. Individual patient data (IPD) sharing was assessed by reviewing the data-sharing statements on ClinicalTrials.gov for trials that began enrollment after the ClinicalTrials.gov mandate in January 2019. Next, we searched the NCT trial number in the NCTN/NCORP data archive to look for the availability of IPD among trials that published their primary outcome after January 2015. We also conducted a subgroup analysis of phase III trials. **Results:** Of 232 eligible studies, 159 (68.5%) were phase II, 11 (4.7%) were phase II/III, and 62 (26.7%) were phase III. NRG Oncology (n=58), Eastern Cooperative Oncology Group (n=47), and Alliance for Clinical Trials in Oncology (n=42) were the most represented cooperative groups. Overall, 33 (14.2% of the total) trials published their primary outcome results within one year of their primary completion, compared to 67 (31.6%) within 2 years, and 69 (63.3%) in 5 years. Among phase III trials, 26 (44.8%) had published their primary outcome findings within 2 years of study completion, and 22 (78.6%) published within 5 years. Among the 138 trials that published their primary outcome since January 2015, 36 (26.1%) had their IPD stored in the NCI online archive (76.1% of the 46 phase III trials). Among the 9 trials initiated since January 2019, 3 indicated on ClinicalTrials.gov that they had a plan to share their IPD. **Conclusions:** A substantial proportion of NCI cooperative group trials have not published manuscripts reporting their primary results in a peer-reviewed journal within 5 years of study completion. Approximately three quarters of phase III group trials completed during the study period had their IPD available within the NCI archive. Research Sponsor: None.

11024 **Poster Session**

Predictors of withdrawal for FDA accelerated approvals of anticancer drugs, 1992-2022. First Author: Alejandra Romano, Oncology Department, Hospital De La Santa Creu I Sant Pau, Institut d'Investigació Biomèdica Sant Pau. Departament of Medicine, Universitat Autònoma De Barcelona, Barcelona, Spain

Background: The US Food and Drug Administration's (FDA) accelerated approval pathway facilitates timely access to novel therapies based on surrogate measures that are supposed to be reasonably likely to predict clinical benefit. Post-approval, confirmatory studies are required to verify safety and efficacy, with approved indications subject to withdrawal from the labeling if these studies fail. While this pathway has been useful in some cases, concerns about delayed and an increasing number of withdrawals of anticancer indications highlight its associated risks to patients. This study identifies factors at the time of initial accelerated approval associated with subsequent withdrawal. **Methods:** In this retrospective cohort study, we analyzed FDA-approved drugs for solid and hematologic cancers receiving AA from 1992 to 2022. The analysis focused on key factors present at the time of accelerated approval, including the indication and pivotal trial characteristics, mechanisms of action and clinical outcomes. Clinical benefit was assessed using the European Society of Medical Oncology-Magnitude of Clinical Benefit Scale (ESMO-MCBS), categorizing benefits as high (A-B/4-5) or low (C/$\leq$2). Multivariable logistic regression was used to identify associations between these factors and indication withdrawal. **Results:** Among 167 accelerated approvals for 113 anticancer drugs, by August 2024, 102 (61%) had been converted to regular approval, 31 (19%) were withdrawn, and 34 (20%) were still in the accelerated approval phase. Of the 133 indications either converted or withdrawn, 52 (39%) were approvals for hematologic cancer drugs, and 41 (31%) supported genome-targeted drug approvals. Among 83 eligible indications, 46 (55%) were granted Breakthrough Therapy designation. Of 133 indications analyzed, 106 (80%) were based on single-arm pivotal trials, and 112 (84%) used response rate as the primary endpoint. Most trials (66%) showed low clinical benefit (86/130) per the ESMO-MCBS framework. In multivariable analysis, indications associated with lower withdrawal risk were more likely to have Breakthrough Therapy designation (OR 0.26; 95% CI, 0.10-0.75; p = 0.01) and be genome-targeted (OR 0.26; 95% CI, 0.08-0.80; p = 0.02). Low ESMO-MCBS scores conversely increased the likelihood of withdrawal (OR, 4.63; 95% CI, 1.50-14.33; p = 0.008). **Conclusions:** Accelerated approvals based on pivotal trials demonstrating low clinical benefit have been at higher risk of subsequent withdrawal, whereas indications with Breakthrough Therapy designation or supporting genome-targeted therapies were more likely to achieve full approval. Patients and health care providers should consider these factors when evaluating therapies newly granted accelerated approval. Research Sponsor: Alfonso Martín Escudero Foundation and Arnold Ventures.

11025 Poster Session

Disparities in NIH and federal cancer research funding across different cancer types. First Author: Suneel Deepak Kamath, Cleveland Clinic Cancer Center, Cleveland, OH

Background: National Institutes of Health (NIH) and other federal funding resources are critical for research and advocacy, but may not be equitably allocated across cancers. **Methods:** This study evaluated funding from the NIH and Congressionally Directed Medical Research Programs (CDMRP) supporting lung, breast, colorectal, pancreatic, hepatobiliary, ovarian, cervical, endometrial and prostate cancers, leukemia, lymphoma and melanoma, from 2013-2022. The primary objectives were to assess for funding disparities across different cancers compared to their incidence and mortality and across racial groups. We also determined if underfunding correlates with fewer clinical trials. Correlations between funding for each cancer and its incidence, mortality and number of clinical trials were analyzed using descriptive statistics and Pearson correlation coefficients (PCCs). **Results:** Diseases with the largest combined NIH and CDMRP funding from 2013 - 2022 were breast ($8.36 billion), lung ($3.83 billion) and prostate ($3.61 billion) cancers. Those with the least funding were uterine ($435 million), cervical ($1.12 billion) and hepatobiliary ($1.13 billion) cancers. Cancer-specific NIH and CDMRP funding correlated well with incidence (PCC: 0.85) but was poorly aligned with mortality (PCC: 0.36). Cervical, ovarian, breast, leukemia and lymphoma were consistently well funded compared to their incidence and mortality rates while lung, colorectal, liver and uterine cancers were consistently underfunded. These data are summarized in the Table. Cancers with higher incidence among Black people were disproportionately underfunded. The amount of combined NIH and CDMRP funding for a particular cancer correlated well with the number of clinical trials in that disease (PCC: 0.76). **Conclusions:** Federal cancer research funding aligns well with incidence but significantly underfunds cancers with higher mortality rates. Underfunding strongly correlates with fewer clinical trials, which impedes future advances in underfunded cancers that already have worse outcomes. Research Sponsor: None.

	Lung	Breast	Colorectal	Pancreas	Liver	Prostate	Uterine	Ovary	Cervix	Melanoma	Leukemia	Lymphoma
NIH+CDMRP Funding 2013-2022 (millions)	$3,831	$8,360	$3,074	$2,020	$1,132	$3,610	$435	$1,803	$1,124	$3,371	$2,585	$2,850
Funding/ Incidence	$1,711	$3,148	$2,175	$3,874	$2,033	$1,766	$732	$7,915	$8,601	$1,852	$4,180	$3,451
Funding/ Deaths	$2,520	$19,998	$6,067	$4,835	$3,224	$12,314	$4,050	$12,456	$26,850	$17,571	$10,502	$13,446

11026 Poster Session

Communication of uncertainties about recent cancer drugs in large language models. First Author: Avi Cherla, Harvard Medical School, Boston, MA

Background: Increasingly more people use large language models (LLMs) to find information about medical treatments. However, there are notable concerns about the accuracy and completeness of information generated by these models. We assessed whether LLMs accurately summarized uncertainties about the benefits and harms of new cancer drugs. **Methods:** We identified the 10 cancer drugs approved by the US Food and Drug Administration (FDA) between 2019 and 2022 with the highest Medicare spending in 2022 (5 in Part B and 5 in Part D). We then searched FDA review documents to extract information about the uncertainties with each drug's clinical trial evidence that were identified by FDA reviewers at the time of approval. Uncertainties with clinical trial evidence were assigned to mutually exclusive categories. We evaluated the extent to which 4 state-of-the-art LLMs (OpenAI's ChatGPT-4, Google's Gemini 1.5 Pro, Meta's Llama 3.1, and Anthropic's Claude 3.5 Sonnet) provided information about FDA-identified uncertainties when queried for information about the drugs using two prompts: (1) *how well does [drug] work for [condition]?*; (2) *is there anything uncertain about how well [drug] works for [condition]?*. **Results:** For the 10 recently approved cancer drugs with the highest Medicare spending in 2022, FDA reviewers identified a total of 38 uncertainties with the clinical trial evidence. For 9 of 10 drugs, FDA reviewers identified uncertainties related to the generalizability of the evidence. Other common uncertainties included bias related to the measurement of the outcome and the use of single arm trial designs. When the LLMs were prompted about how well these 10 cancer drugs worked, the models rarely provided information about the uncertainties identified by FDA reviewers: GPT-4 (4/38, 11%), Gemini 1.5 Pro (3/38, 8%), Llama 3.1 (3/38, 8%), and Claude Sonnet (2/38, 5%). The proportion of FDA-identified uncertainties reported by the models improved marginally when specifically prompted for uncertainties about the drugs. Qualitative assessment of the information generated by the LLMs showed that most of the models tended to report similar, non-specific uncertainties for every drug with little variation. **Conclusions:** LLMs do not provide adequate information about uncertainties related to the benefits and harms of recently approved cancer drugs, despite the availability of this information in the public domain. There is a need to improve LLMs to accurately report such information, so that patients can make informed decisions about cancer treatments. Research Sponsor: None.

Performance of LLMs compared to uncertainties identified by the FDA.

Prompt	GPT-4	Gemini 1.5 Pro	Llama 3.1	Claude 3.5 Sonnet	Average
How well does [drug] work for [condition]?	4/38 (11%)	3/38 (8%)	3/38 (8%)	2/38 (5%)	3/38 (8%)
Is there anything uncertain about how well [drug] works for [condition]?	8/38 (21%)	5/38 (13%)	6/38 (16%)	5/38 (13%)	6/38 (16%)

11027 Poster Session

Achieving equity in genomic testing for breast cancer through partner-led strategies and policies. First Author: Mary Umahi Obasi, Stanford University School of Medicine, Division of Oncology, Stanford, CA

Background: Genomic testing is recommended for individuals with estrogen/progesterone receptor-positive, HER2-negative early-stage breast cancer to determine the need for chemotherapy alongside endocrine therapy. However, access disparities persist by race, ethnicity, and income. This study aims to identify modifiable barriers and co-design policy recommendations for equitable genomic testing for low-income, and racial and ethnic minoritized people with breast cancer in Northern California. **Methods:** Using community-based participatory research and expert panel methods, we collaborated with an 18-member expert panel of patients, caregivers, oncology clinicians, community organizations, advocates, and policymakers to identify modifiable barriers and propose solutions. Phase 1 involved an 85-question survey and semi-structured interviews with patients, caregivers, clinicians, navigators, policymakers, and payers, administered by bilingual community health workers in Spanish, Tagalog, and Chinese, to assess genomic testing barriers and solutions. Phase 2 used Delphi consensus methods with the expert panel to finalize policy recommendations. **Results:** Of 912 invited, 831 participated in surveys (90% response rate), and all 30 purposively sampled individuals participated in interviews (100% response rate). Survey participants included 514 patients, 101 caregivers, 94 clinicians, 74 navigators, 25 policymakers, and 23 payers. Among patients, 102 (19.8%) were Asian, 132 (25.7%) Black, 138 (26.9%) Hispanic White, 28 (5.5%) Non-Hispanic White, and the remainder preferred not to answer. Racial and ethnic minoritized patients had significantly lower odds of genomic testing compared to Non-Hispanic Whites: Black patients 86% lower (OR: 0.15; 95% CI: 0.07-0.31), Asian patients 71% lower (OR: 0.29; 95% CI: 0.14-0.59), and Hispanic White patients 79% lower (OR: 0.21; 95% CI: 0.11-0.43). Four themes emerged from interviews: 1) limited awareness/resources, 2) inequitable care, 3) financial/cultural barriers, and 4) insufficient social support. The expert panel reached consensus on policy recommendations, including mandating reflexive, fully reimbursed genomic testing (mean rating $\pm$ SD: 8.3 $\pm$ 0.9), eliminating prior authorization (8.2 $\pm$ 0.8), removing co-pays/out-of-pocket costs (8.1 $\pm$ 0.8), and providing educational materials in preferred languages with lay terminology (7.9 $\pm$ 1.2). **Conclusions:** Disparities in genomic testing persist, highlighting the need for targeted interventions. Policy recommendations co-designed with communities and other interested groups can be implemented to improve equitable care. Research Sponsor: California Breast Cancer Research Program.

11028 Poster Session

Pain in cancer survivors in the US after federal and state opioid prescribing guidelines and laws. First Author: Justin Michael Barnes, Washington University School of Medicine in St. Louis, St. Louis, MO

Background: Cancer-associated pain is common among survivors and may require opioid medications for effective management. In 2016, the Centers for Disease Control and Prevention (CDC) published guidelines to limit opioid prescribing, leading to a subsequent decline in prescriptions in the US. Many states also enacted opioid prescribing laws after 2016. Cancer-associated pain is explicitly exempted by the CDC and from some state opioid laws. As state laws and exemptions are heterogeneous and sometimes unclear, this study was designed to assess whether cancer survivors were impacted by post-2016 opioid prescribing patterns and legislation. **Methods:** The 2011-2023 Behavioral Risk Factor Surveillance System (BRFSS), an annual, national survey, was queried for cancer survivors. Quality of life (QoL)-limiting pain (included in 2011-17) was defined as having $\geq$1 days where pain made it hard to participate in usual activities. A sensitivity analysis utilized a $\geq$7 day cutoff. Cancer-associated pain (included in 2016-23) was defined as currently having pain caused by cancer or cancer treatment. Linear probability models examined whether there were nationwide changes in QoL-limiting pain after the 2016 CDC guidelines. State-level difference-in-differences (DiD) analyses compared changes in cancer-associated pain over time between states with and without opioid prescribing laws. State opioid laws included (A) any opioid prescribing legislation and (B) explicit cancer-associated pain exemptions. States that enacted opioid policies prior to the 2nd quarter of 2016 were excluded due to lack of cancer-associated pain data before 2016. Analyses accounted for the complex survey design and BRFSS weights and utilized robust SEs, and models were adjusted for sociodemographic, Medicaid expansion, and cancer site factors. DiD analyses also accounted for state and year-quarter fixed effects. **Results:** 2,725 cancer survivors were included in the 2011-17 QoL-limiting pain analyses and 31,955 in the 2016-23 cancer-associated pain analyses. QoL-limiting pain was present for 40.3% ($\geq$1 days affected) and 27.0% ($\geq$7 days affected) and cancer-associated pain was present in 11.9%. There was no significant change in QoL-limiting pain after 2016 in our primary (-9.6 percentage points [95% CI -30.9, 11.7]) or sensitivity analysis ($\geq$7 day affected, 4.32 [-14.24, 22.89]). In adjusted DiD analyses, there were no significant associations between cancer-associated pain and state opioid laws (-2.17 [-6.32, 1.98]) or explicit cancer exemptions in state opioid laws (4.16 [-1.75, 10.07]). **Conclusions:** Among this nationally representative sample of cancer survivors, cancer-associated pain affected $>$1 in 10 survivors and $>$1 in 4 had QoL-limiting pain. However, federal and state opioid prescribing guidelines and laws had minimal impact on the prevalence of pain among cancer survivors, perhaps due to effective exemptions for cancer. Research Sponsor: None.

11029 Poster Session

Industry promotion of oncology drugs with accelerated approval that failed confirmatory trials. First Author: Maryam Mooghali, Yale School of Medicine, New Haven, CT

Background: Oncology drugs are commonly granted accelerated approval by FDA based on pivotal trials using surrogate markers as primary endpoints, while requiring sponsors to complete postapproval studies that confirm clinical benefit. Industry payments to physicians may influence treatment recommendations, which is particularly concerning for accelerated approval drugs, where clinical benefit remains uncertain. We investigated industry payments to physicians before and after results of confirmatory studies for oncology drugs with accelerated approval whose confirmatory studies failed to confirm clinical benefit. **Methods:** In this cross-sectional study, using Drugs@FDA database, we identified oncology drugs granted FDA's accelerated approval, their required postapproval confirmatory studies, and FDA status changes (withdrawn or converted to traditional approval). We searched ClinicalTrials.gov, publications, and company press releases to identify drugs with confirmatory studies failing to confirm clinical benefit. We searched OpenPayments database to record industry payments made to physicians associated with these drugs. **Results:** From 2009-2021, of 73 drugs granted accelerated approval by U.S. FDA, 7 (9.6%) had indications for which all confirmatory studies were negative. Among these, 6 were voluntarily withdrawn following FDA's recommendation, while for Pepaxto (melphalan flufenamide), the sponsor appealed FDA's proposed withdrawal; it was ultimately withdrawn by FDA. Pepaxto was excluded from our analysis as it had no reported payments on OpenPayments. The results of postapproval confirmatory trials for the remaining 6 indications were announced after a median time of 4.2 (2.2-6.6) years. All 6 drugs were withdrawn from the market, with a median duration of 4.9 (IQR, 2.7-6.9) years from approval to withdrawal. Following announcement of negative postapproval confirmatory study results, average monthly payments received by all physicians increased for Marqibo (vinCRIStine sulfate) from $138 in the year preceding announcement to $164 during the period between announcement of negative results and market withdrawal, but decreased for Farydak (panobinostat) ($12,317 to $4,916), Blenrep (belantamab mafodotin) ($152,417 to $119,394), and Ukoniq (umbralisib) ($23,139 to $14,130). Lartruvo (olaratumab) and Aliqopa (copanlisib) had almost no payments after announcement of negative confirmatory study results. **Conclusions:** Industry payments for oncology drugs with accelerated approvals mostly decreased after announcement of negative confirmatory trial results; however, there was evidence of continued promotion for certain drugs until a request for voluntary withdrawal was made by FDA. This suggests that regulatory oversight and enforcement might be necessary to mitigate ongoing promotion of such drugs after confirmatory trials fail to confirm clinical benefits. Research Sponsor: Arnold Ventures.

11030 Poster Session

Unpacking the relationship between cancer survival and political environment in the United States (US). First Author: John E. Dobbs, Johns Hopkins Hospital, Baltimore, MD

Background: Several studies have reported on how health outcomes may differ by the political majority of a county. It is unclear the extent to which this discrepancy is due to a broader political landscape compared to underlying sociodemographic and structural determinants. Using county level presidential voting patterns and a national cancer registry, we present a rigorous analytic approach to assessing survival trends. **Methods:** We linked SEER-Medicare's (100% sample) database on the 4 most common cancers (lung, breast, prostate and colorectal) from 2007-2019 to county-level data on US presidential elections over the same period. Using the total number of votes in each party, county political environment was classified as either Democratic or Republican for the four years following a presidential election. Cox proportional hazards estimated changes in survival over time according to political party. Models were sequentially fit adjusting for age, sex, diagnosis year (Model 1), race/ethnicity (M2), rural/urban continuum code (RUCC) (M3), cancer type (M4), Medicaid/Medicare Advantage enrollment and original reason for entitlement (M5), and primary care doctors and oncologists per 100,000 people (M6). Analyses were performed separately by cancer type and for the entire cohort. **Results:** Of the 1,899,334 individuals, 1,222,228 (64%) resided in Democratic counties and 677,106 (36%) in Republican counties. Democratic counties were majority urban (90% vs 55% for Republican). Adjusting for factors generally associated with worse survival (older age, male gender, earlier diagnosis year), Republican counties had worse survival (HR 1.14, 95% CI [1.14, 1.15], $p < 0.001$) compared to Democratic counties. However, following sequential adjustment of aforementioned variables (M1-M6), this difference disappeared (HR 1.00, 95% CI [1.00, 1.01], p = 0.56, Table). In stratified analyses, similar results were noted for colorectal, lung, breast, and prostate cancer. Among all cancer types, Republican counties had 2% higher risk of diagnosis of later stage cancer, but no difference in overall survival. Finally, limiting our dataset to rural counties only, a 12% higher risk of death in Republican counties reduced to no difference following adjustment. **Conclusions:** Survival differences between counties by presidential voting status disappeared following adjustment of sociodemographic and structural determinants. In a charged political climate, our study cautions against oversimplified claims and underscores the importance of careful methodological approaches in identifying key confounders in aggregate-level studies when identifying meaningful trends. Research Sponsor: None.

Hazard Risk of Death: Whole Cohort	Hazard Ratio	95% CI
M1	1.14	[1.14, 1.15]*
M2	1.14	[1.13, 1.14]*
M3	1.08	[1.08, 1.09]*
M4	1.02	[1.02, 1.03]*
M5	1.02	[1.01,1.02]*
M6	1.00	[1.00, 1.01]

M1-M6 note sequentially adjusted models (see Methods).
*$p < 0.001$.

11031 Poster Session

Progression-free survival in control arms of clinical trials: Analysis of FDA cancer drug approvals between 2014 and 2023. First Author: Angela Viggiano, Department of Clinical Medicine and Surgery, University of Naples Federico II, Naples, Italy

Background: FDA regularly approves new cancer drugs based on the results of surrogate endpoints, often using expedited programs. When assessing the efficacy of new anticancer treatments, the choice of the control arm plays a crucial role. Herein, we evaluated the progression-free survival (PFS) performance of control arms in trials that led to FDA approvals for oncology treatments. **Methods:** We investigated FDA drug approvals issued between January 2014 and December 2023 for the treatment of advanced cancers, available on the FDA.gov website. We analysed publications of phase III or double-arm phase II trials that prompted approvals. For each clinical trial, we collected: i) The assumed median PFS (amPFS) value of the control arm, generally indicated in the study protocol for the sample size calculation; ii) The control arm's recorded median PFS (rmPFS) and its confidence interval (CI). Control arms of each trial were considered under- or out-performing if amPFS exceeded the highest CI of rmPFS or was inferior than the lowest CI of rmPFS, respectively. All other cases were defined as "within the range". **Results:** We found 72 trials leading to new cancer drug approvals. Immune checkpoint inhibitors (ICIs) and small molecules were investigated in the majority of cases, in 27 (37.5%) and 19 (26.4%) trials, respectively. Control arms under- or out-performed in 24/72 (33.3%) and 8/72 (11.1%) cases, respectively. In the remaining 40/72 (55.5%) trials, control arms performances were "within the range". Interestingly, in 12/27 (44.4%) trials leading to ICIs approval, control arms underperformed. We found that in 6/14 (42.9%), 5/16 (31.3%) and 5/16 (31.3%) trials leading to new approvals in lung, breast and genitourinary cancers, respectively, the control arms underperformed. In 18/24 (75.0%) underperforming control arms, the discrepancy between amPFS and rmPFS was larger than 20%. Among the 19 trials with underperforming control arm and leading to expedited approval, in 7 (36.8%) cases a final overall survival (OS) advantage was not observed. **Conclusions:** The PFS benefit observed in several trials leading to FDA approval of new anticancer drugs may have been influenced by shorter-than-expected PFS in the control arms. Accurate analysis of control arms outcomes in clinical trials is essential for a comprehensive assessment of the efficacy of experimental drugs. Research Sponsor: None.

11032 Poster Session

Early signals of Inflation Reduction Act impact on small-molecule versus biologic post-approval oncology trials. First Author: Hanke Zheng, National Pharmaceutical Council, Washington, DC

Background: The Inflation Reduction Act's Drug Price Negotiation Program (DPNP) has shifted the financial incentives for post-approval clinical development, which is particularly relevant to oncology given the role of subsequent indications in expanding treatment options in cancer patients. The law may disproportionately disincentivize post-approval development in small molecules, which faces a shorter timeline towards DPNP eligibility than biologic (7 vs. 11 years post first approval). We aimed to explore the impact of IRA's passage on industry-sponsored small-molecule versus biologic post-approval clinical trials in oncology. **Methods:** Using the Citeline's TrialTrove database, we identified industry-funded Phase I-III trials initiated between 7/2014 and 8/2024 for approved oncology drugs, excluding vaccines and COVID-19-related trials. Trials were categorized into subgroups based on whether they primarily tested small molecules or biologic, excluding trials testing both (e.g., combination therapies) from the subgroup analysis. We used Wilcoxon rank-sum tests to compare the monthly average of trials pre- and post-IRA for all post-approval oncology trials and in the subgroups. The pre/post-IRA comparison was conducted (1) across the full period (7/2014-7/2022 vs. 8/2022-8/2024), and (2) between the year before IRA's passage and the most recent available year (shorter-time: 8/2021-7/2022 vs. 9/2023-8/2024). We performed a difference-in-difference (DiD) analysis to assess the marginal impact ("dosage effect") of IRA on small molecule trials, using biologic trials as the counterfactual. The assumption was that trials would have followed a similar trajectory in both groups in the absence of IRA's differential DPNP eligibility timelines. **Results:** Across the full period, monthly average of post-approval oncology trials decreased by 38.4% ($p<0.01$) following the IRA' passage, and small molecule and biologic trials dropped by 48.6% ($p < 0.01$) and 27.4% ($p < 0.01$) post-IRA, respectively. In the shorter-time comparison, there was a 29.6% ($p<0.01$) reduction overall, and the monthly average of small molecule trials decreased by 43.9% ($p < 0.01$), with no statistically significant change in biologic trials (p = 0.48). Across the full period, the DiD model suggested that the IRA was associated with 7.7 fewer trials per month for oncology small molecule drugs, compared to the biologic drugs (-7.7, 95% C.I.: -9.9 to -5.5, $p < 0.01$). **Conclusions:** The IRA's passage was associated with fewer industry-funded post-approval oncology trials and larger reductions for small molecule trials than biologic trials. These findings support concerns about IRA's disincentivizing effect on post-approval development in oncology, particularly for small molecule drugs, which are subject to a shorter DPNP eligibility timeline. Research Sponsor: None.

11033 Poster Session

Cost-effective cancer care: The role of oncology biosimilars in generating cost savings. First Author: James W. Gilmore, American Oncology Network, Fort Myers, FL

Background: Biosimilar versions of biologic drugs (reference drugs) present a promising opportunity to reduce healthcare costs. Although not labeled as directly interchangeable, biosimilars are considered reasonable alternatives to their reference drugs by experts. We evaluated the adoption, costs, and savings of key biosimilars used primarily in oncology practice. **Methods:** We used publicly available, specialty agnostic, HCPCS level utilization and cost data from the Medicare Part B Spending by Drug dataset published by the Centers for Medicare and Medicaid Services to study the use of biosimilars for five reference drugs (Bevacizumab, Trastuzumab, Rituximab, Peg-filgrastim, Filgrastim) between 2015 and 2022. We then modeled two spending scenarios for 2022: one where only the reference drugs were used, and one where the lowest cost option (reference or biosimilar) was used for eligible indications. We calculated the savings and incremental savings opportunity to Medicare by comparing these scenarios to the actual 2022 spending. **Results:** Over the 8-year evaluation period, each reference drug received multiple biosimilar approvals, and biosimilar use increased from 0% to 56.4%. Lower biosimilar use of Bevacizumab may have been due to the lack of approval for ophthalmic use. The introduction of biosimilars caused price reductions for the reference drugs and the biosimilars. Biosimilar prices in 2022 were lower than their reference drugs for all except Peg-filgrastim, whose price fell below that of its biosimilars. In 2022, biosimilar adoption resulted in a 23% spending reduction for Medicare, with an additional 14% savings opportunity. Table 1 shows biosimilar adoption rates by reference drug and savings vs savings opportunity. **Conclusions:** The adoption of Oncology biosimilars has resulted in significant cost savings for Medicare, but there are still opportunities for further savings. The complex relationship between biosimilar prices and their utilization warrants additional evaluation. Additionally, the effects of biosimilar payment policies, such as those introduced by the Inflation Reduction Act, and the impact of payer specific product mandates on overall biosimilar adoption need to be explored further. Research Sponsor: None.

Biosimilar adoption & 2022 spending, savings & opportunity with biosimilar adoption.

	Biosimilar Adoption							
Reference Drug	**2015**	**2016**	**2017**	**2018**	**2019**	**2020**	**2021**	**2022**
Bevacizumab	-	-	-	0.0%	0.6%	10.5%	18.4%	22.6%
Trastuzumab	-	-	-	0.0%	2.7%	37.2%	64.2%	74.5%
Rituximab	-	-	-	-	0.0%	20.5%	49.9%	59.7%
Peg-filgrastim	-	-	0.0%	1.2%	16.9%	25.5%	34.6%	41.9%
Filgrastim	0.8%	27.8%	54.6%	65.5%	72.3%	77.0%	81.5%	83.2%
Total	**0.2%**	**5.6%**	**10.9%**	**13.3%**	**18.5%**	**34.1%**	**49.7%**	**56.4%**

	2022 Spending, Savings and Opportunity		
($ in Millions)	**Total Spend**	**Savings**	**Savings Opportunity**
Bevacizumab	$698	$324	$60
Trastuzumab	$380	$182	$111
Rituximab	$1,044	$310	$276
Peg-filgrastim	$628	-$37	$37
Filgrastim	$37	$49	$13
Total	**$2,787**	**$827**	**$498**

11034 Poster Session

Access to cancer care for undocumented immigrants in the United States. First Author: Patricia Mae Garcia Santos, Division of Health Services, Outcomes, and Policy, Department of Radiation Oncology, Winship Cancer Institute, Emory University, Atlanta, GA

Background: Undocumented immigrants represent a disproportionate share of uninsured individuals in the United States, owing to federal restrictions on Medicaid eligibility. Emergency Medicaid (EM) and other state programs offer avenues for healthcare coverage, but their impact on access to cancer care remains poorly understood. **Methods:** Between January-July 2024, information on the availability and breadth of cancer coverage for undocumented immigrants under EM and other insurance mechanisms were reviewed for all 50 states and the District of Columbia (D.C.). For each state, ≥4 authors reviewed publicly available data compiled from multiple, independent sources including Medicaid policy handbooks, provider manuals, legislative documents, and other state government website resources. Abstracted data included state-specific information on extent of coverage, specifically as it pertains to cancer diagnosis, treatment, and follow-up care. Discrepancies in policy findings were discussed during consensus meetings to ensure accurate interpretation. In cases where policies remained unclear, state Medicaid agencies were directly contacted for further clarification. **Results:** Undocumented immigrants receive cancer care coverage via (1) expansions to EM (*n*=3), (2) Medicaid-equivalent programs (*n*=7), or (3) other non-Medicaid mechanisms (*n*=5; Table). Of the 6 states and D.C. with Medicaid-equivalent plans, 4 states and D.C. cover all adults, while 2 states only cover some adults (IL: limited to adults age ≥42; NY: limited to adults age ≥65, but adults age <65 can receive cancer coverage via EM). Of the 5 states with non-Medicaid mechanisms, 2 states (CO, WA) allow purchase of commercial plans on the ACA Marketplace or Marketplace-like platform; other strategies include Iowa's Breast and Cervical Cancer Treatment Program (BCCTP), Massachusetts' Health Safety Net program, or New Mexico's high-risk insurance pool. The remaining 35 states had no documented cancer coverage mechanism. **Conclusions:** In this national analysis of EM and other policies supporting healthcare coverage for undocumented immigrants, access to cancer care remains fragmented, intermittent, and largely limited to the emergency setting. Although Medicaid-equivalent plans and Marketplace-based offer promising avenues for comprehensive coverage, budgetary constraints and political challenges pose threats to viability. Absent federal support, sustainable policy solutions are needed to ensure continued progress towards a more equitable model of care. Research Sponsor: None.

	Emergency Medicaid	**Medicaid-Equivalent Plan**	**Other Mechanism**
California		All adults	
Colorado			Marketplace-like
D.C.		All adults	
Illinois		Adults (age ≥42)	
Iowa			BCCTP
Maryland	All adults		
Massachusetts			Health Safety Net Program
Minnesota		All adults	
New Mexico			High-risk insurance pool
New York	Adults (age <65)	Adults (age ≥65)	
Oregon		All adults	
Pennsylvania	All adults		
Washington		All adults	Marketplace

11035 Poster Session

Likelihood of unplanned readmission among oncology patients with a completed post-discharge follow-up encounter. First Author: Emma Hannan, Sidney Kimmel Comprehensive Cancer Center, Jefferson Health, Philadelphia, PA

Background: Literature suggests that oncology patients are more likely to be admitted from the emergency department to the hospital than patients without a cancer diagnosis[1]. Avoiding unplanned readmissions (UR) becomes a joint responsibility of the patient and the oncology care team. The premise of one ASCO Certified standard is that patients who receive post-discharge follow-up (PDFU) may avoid a readmission if their needs are addressed promptly in the outpatient setting. We evaluated the impact of completion of a PDFU after an index admission on URs. **Methods:** We performed a retrospective analysis of patients with an index admission to a system hospital between January and November 2024. Included were patients with a discharge (d/c) to home and an encounter with an oncology provider within the past year. We compared the overall proportion of patients with any UR in the measurement period between those patients who did and did not complete a PDFU, as well as that of patients who completed an early PDFU (within 3 days of d/c) and a later PDFU (between 4-7 days of d/c). PDFUs are defined as a telemedicine or clinic encounter within 7 days of the d/c date. Chi Squared analysis was utilized to evaluate if PDFU reduced UR. **Results:** 2,533 d/cs occurred within the measurement period. 542 (21%) of encounters resulted in a UR. 1,057 (42%) encounters had a PDFU. Of the 1,057 encounters where a PDFU was completed, 240 (23%) resulted in a UR. Of the 1,476 encounters where a PDFU was not completed, 302 (20%) resulted in a UR. The findings were not clinically significant. Chi-squared p-value: .17 **Conclusions:** Completion of a PDFU is not a factor in predicting an oncology patient's potential unplanned readmission. In addition, excluding some high risk patients such as those with hematologic malignancies did not change the overall analysis. We found no difference in rate of UR among patients who completed a PDFU within 3 days or 4-7 days. Further investigation is needed to better understand if modifiable factors contributed to UR in this cohort. Other factors need to be considered, such as patient risk for unplanned re-admission, in evaluating the impact of PDFU on UR, as expected in the ASCO Certified standard. [1] Waters TM; Kaplan CM, Graetz I, et al. (2019) Patient-Centered Medical Homes in Community Oncology Practices: Changes in Spending and Care Quality Associated with the COME HOME Experience. Journal of Oncology Practice, 15(1), e56-e64. Research Sponsor: None.

Proportion of d/cs with UR by PDFU completion.

	No UR # d/c (%)	**Yes UR # d/c (%)**
Yes PDFU	817 (77%)	240 (23%)
No PDFU	1174 (80%)	302 (20%)

11036 Poster Session

Molecular testing and targeted therapy use in lung cancer across state Medicaid programs. First Author: Thomas J. Roberts, Massachusetts General Hospital, Harvard Medical School, Boston, MA

Background: Comprehensive molecular testing is the standard of care for patients with metastatic non-small cell lung cancer (NSCLC) and is essential to identify patients with tumors harboring *EGFR*, *ALK* alterations that can be treated with efficacious targeted therapies. Prior work has shown that use of targeted therapies for NSCLC is lower than expected among Medicaid beneficiaries and rates of use may vary across state Medicaid programs. We used Medicaid claims and encounter data to estimate the rates of molecular testing and targeted therapy use across state Medicaid programs. **Methods:** Using Transformed Medicaid Statistical Information System Analytic Files (TAF) data from 2017 and 2018, we identified beneficiaries with new diagnoses of metastatic NSCLC who were continuously enrolled in Medicaid during the period of analysis. Among these patients, we identified claims for molecular tests that could identify *EGFR* or *ALK* alterations and claims for FDA-approved targeted therapies during a 120-day window around the first claim for antineoplastic therapy. We tabulated rates of molecular testing and targeted therapy use by state. We ran logistic regressions for molecular testing and targeted therapy use with patient characteristics, and then we used the regression coefficients to estimate adjusted rates of molecular testing and targeted therapy use for each state. **Results:** We included 41 states with complete TAF data in the study years. In these states there were 5,432 beneficiaries who initiated antineoplastic therapy for new diagnoses of metastatic NSCLC. The number of incident cases within each state Medicaid program ranged from 11 in Utah to 824 in California. In logistic regression, the characteristics associated with lower rates of molecular testing were male sex, high Charlson comorbidity indices, and lower income. The characteristics associated with low rates of targeted therapy use were older age, male sex, and lower education levels. The adjusted rate of molecular testing among patients with incident metastatic NSCLC across all state Medicaid programs was 55.9% with rates ranging from 39.2% in Texas to 69.3% in Washington state. The mean adjusted rate of targeted therapy use across state Medicaid programs was 8.6% with rates ranging from 3.4% in Michigan to 24.8% in New York. **Conclusions:** After adjusting for patient characteristics, there was substantial state-by-state variation in the rate of molecular testing and targeted therapy use among Medicaid beneficiaries with NSCLC. More work is needed to understand whether specific Medicaid policies such as prior authorizations or restrictions on access to diagnostic testing may contribute to the observed disparities. Research Sponsor: None.

11037 Poster Session

Comprehensive analysis on reactive cutaneous capillary endothelial proliferation following camrelizumab-based therapy in patients with solid tumors: A large-scale pooled analysis of nine phase 2 or phase 3 registration trials. First Author: Shukui Qin, Nanjing Tianyinshan Hospital of China Pharmaceutical University, Nanjing, China

Background: Previous studies demonstrated the positive association between cutaneous immune-related adverse events and long-term survival in advanced cancer patients treated with immunotherapy. As a unique adverse event related to camrelizumab, the association of reactive cutaneous capillary endothelial proliferation (RCCEP) with patient prognosis may also exist. Here we comprehensively analyzed the characteristics of RCCEP and this association. **Methods:** This was a pooled analysis based on individual patient-level data derived from seven phase 3 and two phase 2 registration trials for new drug application in China. Patients with advanced non-small cell lung cancer, hepatocellular carcinoma, esophageal squamous cell carcinoma, nasopharyngeal carcinoma, and gastric cancer treated with camrelizumab monotherapy (Camre), camrelizumab plus apatinib (Camre-Apa), or camrelizumab plus chemotherapy (Camre-Chemo) were included. Landmark analyses taking the median time to the first RCCEP onset as cutoff reference were performed for survival. **Results:** RCCEP occurred in 74.5% (251/337) of patients with Camre, 30.6% (120/392) with Camre-Apa, and 73.2% (737/1007) with Camre-Chemo. The severity was grade 1 or 2 in almost all patients with RCCEP (97.9%; 1085/1108), and the median frequency of RCCEP events was 1 (IQR, 1-2). Median time to the first RCCEP onset was 1.0 months [IQR, 0.7-1.2] with Camre, 4.7 months (IQR, 2.8-7.8) with Camre-Apa, and 1.5 months (IQR, 1.0-2.6) with Camre-Chemo; 1-month, 5-month, and 2-month landmark analyses of survival were performed for the three treatment groups, respectively. Patients with RCCEP showed better clinical outcomes than those without (objective response rate: 22.7% vs 2.3% with Camre, 42.5% vs 18.0% with Camre-Apa, and 73.7% vs 45.9% with Camre-Chemo; median progression-free survival [landmark analysis]: 3.0 vs 1.9 months [HR = 0.51, 95% CI, 0.38-0.69], 13.8 vs 12.6 months [HR = 0.88, 95% CI, 0.61-1.26], and 9.7 vs 6.9 months [HR = 0.58, 95% CI, 0.47-0.71]; median overall survival [landmark analysis]: 11.8 vs 3.9 months [HR = 0.44, 95% CI, 0.33-0.59], 35.2 vs 23.7 months [HR = 0.66, 95% CI, 0.49-0.90], and 23.4 vs 12.0 months [HR = 0.45, 95% CI, 0.37-0.54]). Discontinuation of camrelizumab treatment due to RCCEP barely occurred (0.3%; 5/1736). **Conclusions:** Although RCCEP occurred commonly, most events were mild without impact on camrelizumab treatment. RCCEP occurred early with 1-2 events mainly in each patient. The occurrence of RCCEP was positively associated with both short-term response and long-term survival, regardless of camrelizumab monotherapy or combination therapy. These findings can enhance patient confidence in continuing camrelizumab treatment. Research Sponsor: Jiangsu Hengrui Pharmaceuticals Co., Ltd.

11038 Poster Session

Demographic and clinical factors associated with young-onset rectal cancer: Is the Latinx population at higher risk? First Author: Antoine Jeri-Yabar, Icahn School of Medicine at Mount Sinai Morningside/West, New York, NY

Background: The incidence of colorectal cancer is rising among younger adults, with some studies indicating a disproportionate increase in the Hispanic population. As one of the fastest-growing demographics in the United States, Hispanic individuals face unique barriers to cancer prevention and care. However, data specifically addressing disparities in rectal cancer within this group remain limited. The aim of our study is to elucidate demographic and clinical factors associated with young-onset rectal cancer (YO-RC) and evaluate if the Latinx population is at higher risk compared to other races. **Methods:** We evaluated patients ≥18 years of age with rectal cancer from the Surveillance, Epidemiology, and End Results (SEER) database, with a study period from 2018 to 2021. The study population included adult patients diagnosed with RC as first primary, histologically confirmed diagnoses, complete data on race, MSI status, stage, and known cause of death. A retrospective cohort study was done. Individuals were divided into two groups: young onset (diagnosed <50 years old) and average-onset (diagnosed at ≥50 years old). Univariate and multivariate logistic regression was done, adjusted logistic regression to race, sex, area of living, MSI status and stage. **Results:** A total of 13,768 individuals were analyzed, with 2,661 (19.33%) classified as YO-RC and 11,107 (80.67%) as AO-RC. In the YO-RC group, 60.28% were Non-Hispanic White (NHW), 21.20% Hispanic (H), 7.22% Non-Hispanic Black (NHB), 10.54% Non-Hispanic Asian or Pacific Islander (NHAPI), and 0.76% Non-Hispanic American Indian (NHAI). Most were male (58.51%) and diagnosed at advanced stages (43.03% stage III and 27.58% stage IV), with 93.24% having MSI-stable tumors. In the AO-RC group, NHW accounted for 68.46%, followed by H (12.52%), NHB (7.70%), NHAPI (10.46%), and NHAI (0.86%). Stage III (32.86%) and stage I (24.45%) were the most common stages, and 94.97% had MSI-stable tumors. H individuals were nearly twice as likely to have YO-RC compared to NHW (aOR 1.87, 95% CI 1.67–2.10, p<0.001). Females had a higher likelihood of YO-RC than males (aOR 1.14, 95% CI 1.04–1.24, p=0.002). MSI-high tumors were associated with YO-RC (aOR 1.57, 95% CI 1.27–1.94, p<0.001). Patients diagnosed at later stages were also more likely to have YO-RC (stage III aOR 1.99, 95% CI 1.76–2.25, p<0.001; stage IV aOR 1.98, 95% CI 1.73–2.26, p<0.001). **Conclusions:** Hispanic individuals are more likely to have YO-RC, which suggests the critical need for targeted outreach and earlier screening efforts within the young Latinx population. Female patients and those with MSI-high tumors were also more likely to have YO-RC suggesting possible biological and genetic influences, including Lynch syndrome. The strong correlation of advanced-stage diagnoses and YO-RC demonstrates the need to improve early detection efforts. Research Sponsor: None.

Demographic and clinical factors associated with young-onset rectal cancer.

Variable	Unadjusted OR (95% CI)	p value	Adjusted OR (95% CI)	p value
Race				
Non-Hispanic White		Ref.		
Hispanic	1.92 (1.71-2.14)	**<0.001**	1.87 (1.67-2.10)	**<0.001**
Non-Hispanic Black	1.07 (0.91-1.26)	0.386	1.03 (0.89-1.24)	0.658
Non-Hispanic Asian/PI	1.17 (1.02-1.35)	0.021	1.14 (0.99-1.32)	0.055
Non-Hispanic AI	0.49 (0.25-0.95)	0.037	0.48 (0.24-0.92)	**0.029**
Sex				
Male		Ref.		
Female	1.12 (1.03-1.22)	**0.007**	1.14 (1.04-1.24)	**0.002**
Area of Living				
Non-Metropolitan		Ref.		
Metropolitan	1.23 (1.08-1.41)	0.002	1.10 (0.95-1.26)	0.177
Socioeconomic Status				
<$40,000-79,999	Ref.		*Not included due to collinearity	
$40,000-$79,999	0.89 (0.61-1.31)	0.576		
$80,000-$100,000	0.95 (0.65-1.40)	0.818		
>$100,000	0.93 (0.63-1.37)	0.738		
MSI status				
MSI stable		Ref.		
MSI low	1.15 (0.85-1.55)	0.357	1.08 (0.79-1.47)	0.604
MSI high	1.49 (1.21-1.83)	**<0.001**	1.57 (1.27-1.94)	**<0.001**
Stage				
I		Ref.		
II	0.94 (0.85-1.10)	0.495	0.94 (0.81-1.10)	0.483
III	1.99 (1.76-2.25)	<0.001	1.99 (1.76-2.25)	**<0.001**
IV	1.97 (1.73-2.25)	<0.001	1.98 (1.73-2.26)	**<0.001**

Multivariate logistic regression, adjusted logistic regression is adjusted to race, sex, area of living, MSI status and stage. Income was not included due to a VIF >10, suggesting collinearity. †: p value <0.05, statistically significant.

11039 Poster Session

Pharmacotherapy as an adjunct to behavioral weight loss treatment in survivors of breast cancer. First Author: Jennifer Y. Sheng, Johns Hopkins University, Baltimore, MD

Background: Approximately half of breast cancer (BC) survivors attain 5% weight loss with 6 months of behavioral intervention alone. We conducted a single-arm, phase II study evaluating the addition of FDA-approved anti-obesity pharmacotherapy Contrave (Naltrexone +Buproprion) to a behavioral weight loss (BWL) intervention in BC survivors who did not attain 5% weight loss after 8 weeks. **Methods:** Women with stage 0-III BC and BMI > 27 kg/m^2 who completed local therapy and chemotherapy were enrolled in a 6-month, remotely-delivered BWL program. Patients completed demographic and psychosocial surveys, lab draws (Hba1c and lipid panel) and were weighed in clinic at baseline, 2 and 6 months. An adaptive design utilizing weight loss at 2 months identified those with greater likelihood of weight loss at 6 months with BWL alone. Patients with and without ≥5% weight loss at 2 months were stratified as FAST-BWL and SLOW-BWL, respectively. FAST-BWL continued BWL alone for 4 months, while SLOW-BWL received Contrave plus BWL. Within the SLOW-BWL arm, the trial continued with a Simon two-stage minimax design with the proportion of SLOW-BWL attaining ≥5% weight loss at 6-months as the primary endpoint. The planned sample size of 30 had 80% power at a type I error rate of 5% if the true rate of attaining the primary endpoint by 6 months was 29%, compared to 10.9% under the null. Secondary endpoints included measures of physical function, endocrine function, pain, fatigue, depression, anxiety, sleep disturbance, and sexual problems. **Results:** Of 53 enrolled patients, 15 (28%) were FAST-BWL and 38 (72%) were SLOW-BWL responders. Compared to FAST-BWL, SLOW-BWL included more participants who were Black (32% v 7%), premenopausal (21% v 7%), and had an ECOG 1 (26% v 13%). At 6-months, mean % weight change was -5.1±2.9 and -10.8±3.5 for SLOW-BWL and FAST-BWL, respectively. In the intent-to-treat population of SLOW-BWL (n = 38), 42% had 5% weight loss by 6-months. SLOW-BWL had significant improvement in Hba1c between 2 and 6 months. Among SLOW-BWL patients, every two pounds over the two-month average change, patients were one third as likely to be successful at 6 months, OR = 0.3 (95% CI: 0.1, 0.88), p = 0.03. Of 21 in SLOW-BWL with PROs evaluable for minimally important differences at 6-months, 29% had less anxiety, 24% had improved physical function, and 19% had less pain, fatigue, sleep disturbance, and sexual dysfunction. Regardless of arm, physical function and pain improved in those with >5% weight loss (p = 0.03 and p = 0.02, respectively). The change in pain was primarily in those with > 5% weight loss in SLOW-BWL. **Conclusions:** Contrave can enhance weight loss outcomes in BC survivors who do not attain significant weight loss with diet and exercise modification alone. Further research is needed to understand individuals who benefit most from pharmacotherapy. Clinical trial information: NCT04499950. Research Sponsor: NCCN Foundation; American Institute of Cancer Research; Breast Cancer Research Foundation; Maryland Cigarette Restitution Fund; National Capital Cancer Research Fund.

11040 Poster Session

Association between frailty and clinical outcomes in older adults with early breast cancer: Results from the Hurria Older Patients (HOPE) study. First Author: Yuliya Zektser, UCLA Medical Center, Los Angeles, CA

Background: Older adults with early breast cancer are a heterogenous population with varying physiologic and functional age. Pretreatment frailty may help better characterize this heterogenous population compared to chronological age. We investigated the association between pretreatment frailty and clinical outcomes in older adults with early breast cancer treated with chemo. **Methods:** We leveraged a prospective cohort of 499 adults age ≥65 with stage I-III breast cancer undergoing treatment with neo/adjuvant chemo (R01AG037037). Pretreatment frailty status was determined using a Deficit Accumulation Index, which categorized patients as robust vs. prefrail/frail. Clinical outcomes included grade 3+ toxicity, dose reduction, treatment delay, early chemo discontinuation, hospitalization, and survival (overall, breast cancer related, and non-breast cancer related). We conducted a multivariable analysis evaluating the association between baseline frailty status (robust vs. prefrail/frail) and these outcomes, adjusting for age, race/ethnicity, stage, and regimen. **Results:** The median (range) age was 70 (65-86) years, 65% had stage II/III disease, and 38% received anthracycline. At baseline, 21% were prefrail/frail and 79% were robust. In total, 46% had a grade 3+ toxicity, 24% had a dose reduction, 26% had a treatment delay, 22% had early chemo discontinuation, and 23% were hospitalized. After multivariable analysis, prefrail/frail participants had greater odds of having grade 3+ toxicity (odds ratio [OR]=2.70, 95% CI, 1.66-4.40), dose reduction (OR=1.87, 95% CI 1.12-3.15), treatment delay (OR=1.85, 95% CI 1.10-3.13), and early chemo discontinuation (OR=1.76, 95% CI 1.05-2.95) compared to robust participants. Prefrail/frail participants had a higher likelihood of non-breast cancer related death (hazard ratio=2.56, 95% CI 1.08-6.05) compared to robust participants. There were no associations between frailty and hospitalizations, overall survival, and breast cancer related mortality. **Conclusions:** In this cohort of older adults with early breast cancer, participants who were prefrail/frail pretreatment had an increased risk of grade 3+ toxicity, dose reduction, treatment delay, early chemo discontinuation, and non-breast cancer related death. Pretreatment frailty assessments may improve risk stratification of older adults with early breast cancer and guide treatment decision-making. Clinical trial information: NCT01472094. Research Sponsor: U.S. National Institutes of Health; R01AG037037.

Clinical outcomes in older adults with early breast cancer, odds ratio (95% CI).*

Frailty Status	Grade 3+ Tox (n=229)	Dose Reduction (n=120)	Treatment Delay (n=132)	Early Discontinuation (n=111)	Hospitalization (n=115)
Robust	1.00	1.00	1.00	1.00	1.00
Prefrail/ Frail	2.70 (1.66-4.40)	1.87 (1.12-3.15)	1.85 (1.10-3.13)	1.76 (1.05-2.95)	1.61 (0.96-2.69)

*Adjusted for age, race/ethnicity, stage, and regimen.

11041 Poster Session

The impact of iron deficiency anemia on long-term cardiovascular outcomes in breast cancer patients hospitalized with heart failure preserved ejection fraction: A propensity score–matched retrospective cohort study. First Author: Colton Jones, Jefferson Einstein Hospital, Philadelphia, PA

Background: Breast cancer (BC) patients are at risk for iron deficiency anemia (IDA) due to the effects of chemotherapy on the bone marrow and because of potential malignant infiltration of the bone marrow. Additionally, BC patients are at increased risk for heart failure either from the effects of chemoradiation on the myocardium or because of direct tumor invasion of the heart. Studies have shown that IDA is associated with worse functional outcomes, hospitalization, and mortality in heart failure preserved ejection fraction (HFpEF). There is limited data on the impact of IDA on long-term cardiovascular outcomes in BC patients with HFpEF, and our study aims to assess these outcomes. **Methods:** We utilized data from the Global Collaborative Network-TriNetX. Patients aged 18 to 85 were divided into two cohorts: those with BC, HFpEF, and IDA, and those with BC, HFpEF but without IDA. Using ICD-10 codes, we evaluated the following outcomes: risk of myocardial infarction (MI), arrhythmia, cardiogenic shock, mortality, and hospitalization. Generalized linear models were used to measure the association, and estimates were presented as risk ratios and 95% confidence intervals. **Results:** After propensity score matching, each cohort consisted of 9,204 patients. The IDA cohort had a mean age of 74.4 $\pm$ 8.6 years and 94% were female. Caucasians accounted for 65% of patients and blacks 21%. Our study found that over a 5-year period (Table 1), BC patients with HFpEF and concomitant IDA had a statistically significant higher risk of MI (RR: 1.576, 95% CI 1.408-1.765), arrhythmia (RR: 1.589, 95% CI 1.300-1.942), cardiogenic shock (RR: 1.660, 95% CI 1.347-2.045), and mortality (RR: 1.052, 95% CI 1.002-1.104). There was an increased risk of hospitalization (RR: 1.256, 95% CI 0.871-1.813) but the results were statistically insignificant. **Conclusions:** Our study demonstrated that IDA is associated with long-term adverse cardiovascular outcomes in BC patients with HFpEF. More prospective studies are needed to assess the impact of iron therapy on cardiovascular outcomes, specifically in the BC population with HFpEF. Research Sponsor: None.

Long term cardiovascular outcomes in breast cancer patients with heart failure preserved ejection fraction.

	1 year follow up		5 year follow up	
Outcome	**RR and 95% CI**	**p value**	**RR and 95% CI**	**p value**
Myocardial Infarction	1.481 (1.261-1.738)	<0.001	1.576 (1.408-1.765)	<0.001
Arrhythmia	1.631 (1.206-2.207)	0.001	1.589 (1.300-1.942)	<0.001
Cardiogenic Shock	1.592 (1.194-2.123)	0.001	1.660 (1.347-2.045)	<0.001
Mortality	0.899 (0.840-0.963)	<0.002	1.052 (1.002-1.104)	0.04
Hospitalization	1.335 (0.684-2.606)	0.40	1.256 (0.871-1.813)	0.2

RR: risk ratio, CI: confidence interval.

11042 Poster Session

Sex-based differences in clinical outcomes for solid tumours: A pooled IPD meta-analysis of contemporary anticancer drug trials. First Author: Rakchha Chhetri, Flinders University, College of Medicine and Public Health, Bedford Park, Australia

Background: Sex-based differences in outcomes with contemporary oncology treatments remain underexplored, creating a gap in the evidence required for personalised care. To address this, our objective was to systematically evaluate whether sex differences exist in survival and adverse event outcomes with modern anticancer therapies. **Methods:** Individual patient data (IPD) was accessed via the Vivli platform from 60 clinical trials supporting US Food and Drug Administration approvals of anticancer medicines for the treatment of solid tumours from 2012 to 2022. Of these, 39 trials were included in analysing sex-based differences in clinical outcomes (i.e. breast, prostate, and ovarian cancer were excluded) Two-stage IPD meta-analysis approaches were employed. First, Cox proportional hazards models were applied to estimate hazard ratios (HRs) with confidence intervals for overall survival (OS), progression-free survival (PFS), and grade $\geq$3 adverse events (AEs) outcomes by sex within each clinical trial. Complete case analyses were conducted, with adjustments for covariates including age, race, ECOG performance status, and weight, as well as study-level factors, such as randomisation arm stratification. The results for each clinical trial were then pooled using random-effects meta-analysis. Subgroup analyses were performed to evaluate findings by cancer and treatment types. **Results:** Data from 39 trials for solid tumours (n=20,806; females=8,367) were analysed, including non-small cell lung (n=19), melanoma (n=6), colorectal (n=3), urothelial (n=2), gastric (n=2), and other (n=7) cancers. Treatment regimens evaluated included immunotherapies (n=9 trials), chemotherapies (n=18), and targeted therapies (n=32). In adjusted analyses, females demonstrated favourable OS (HR 0.78, 95% CI: 0.72–0.84; I^2 = 60%, p <0.001) and PFS (HR 0.84, 95% CI: 0.80–0.89; I^2 = 47%, p <0.001) compared to males. However, females had a higher risk of grade $\geq$3 AEs (HR 1.12, 95% CI: 1.05–1.18; I^2 = 40%, p <0.001). Subgroup analyses by cancer type and treatment regimen showed consistent trends in survival and AE outcomes according to sex. **Conclusions:** This meta-analysis, highlights consistency in females experiencing improved survival but higher toxicity compared to males with contemporary oncology treatments. These findings underscore the need to incorporate and prioritise sex as a key biological variable in trial design, dose optimisation, outcome analysis, and clinical decision-making within the oncology setting. Acknowledgement This publication is based on research using data from AstraZeneca, Boehringer Ingelheim, Daiichi Sankyo, Eli Lilly and Company, Hoffmann-La Roche, Janssen, Pfizer, Sanofi, and Takeda that has been made available through Vivli, Inc. Vivli has not contributed to or approved, and is not in any way responsible for, the contents of this publication. Research Sponsor: None.

11043 Poster Session

Race/ethnicity reporting and representation in clinical trials presented at the American Society of Clinical Oncology (ASCO) presidential plenaries from 2014 to 2024. First Author: Bingtao Xiang, University of Illinois Chicago, Chicago, IL

Background: The lack of appropriate racial and ethnic representation in life saving innovative trials has been linked to poor outcomes. To address this, ASCO published an Equity, Diversity, and Inclusion Action Plan in 2021 which aimed to improve clinical trial diversity. This study evaluates the frequency of race reporting and proportional race representation in trials presented at ASCO plenary sessions. **Methods:** We reviewed ASCO plenary sessions from 2014 through 2024 to identify clinical trial presentations. These clinical trials were then identified using the National Institutes of Health trials registry (ClinicalTrials.gov). Trial characteristics and race reporting were abstracted from primary report publications or ClinicalTrials.gov if race reporting was not included in the primary report. When an ASCO plenary session involved multiple trials, each trial was included in the analysis. US population-based cancer estimates were calculated using data from National Cancer Institute-Surveillance, Epidemiology, and End Results and US Census databases. Age-standardized incidence and mortality rates adjusted to the year 2000 standard US population by race were used to calculate estimated 5-year average incidence and mortality rates from 2017 to 2021. **Results:** Between 2014-2024, 46 clinical trials with a total 67496 participants were presented at ASCO plenary sessions. Race was reported in 31 (67%) trials and both race and ethnicity were reported in 15 (33%) trials. Between 2014 and 2019 vs 2021 and 2024, the proportion of trials reporting race or both race and ethnicity increased 57% to 83% and 25% to 44%, respectively. Overall, White, Asian, Black, and Hispanic patients represented 78.8%, 8.3%, 6.8%, and 6.3% of the trial participants, respectively. Between 2014 and 2019 vs 2021 and 2024, Black (19.7% vs. 18.1% of expected) and Hispanic (40.3% vs. 46.6% of expected) patients remained underrepresented compared to White (113.8% vs 76.3% of expected) and Asian (209.7% vs. 719.1% of expected) patients. **Conclusions:** Since the ASCO 2021 Equity Action Plan, there has been an increase in reporting race and ethnicity of clinical trial participants with no significant effect on Black and Hispanic patients enrolled on trials. This study shows a need for policy revision and meaningful intervention to address underrepresented population enrollment in trials to ensure equitable access and consistent outcomes for all patients. Research Sponsor: None.

11044 Poster Session

Prognostic value of time-varying patient-reported symptoms and quality of life in cancer patients receiving chemotherapy. First Author: Roshan Paudel, Dana-Farber Cancer Institute, Boston, MA

Background: Prior research has demonstrated that pre-treatment patient-reported outcomes (PROs) predict post-treatment survival. Symptom burden, physical function and overall wellbeing are time-varying concepts, so making survival predictions using pre-treatment data may have limited clinical actionability. The prognostic value of time-varying patient-reported symptom burden, physical function (PF) and wellbeing (WB) are not well characterized. **Methods:** Six US-based cancer centers collaborated to develop and deploy an EHR-integrated ePRO monitoring system to facilitate active symptom management. Patients receiving chemotherapy for a gastrointestinal (GI), gynecologic (GYN), or thoracic cancer were asked to report on 12 common symptoms using PRO-CTCAE items and 2 quality of life items twice weekly for up to 180 days after starting chemotherapy. Herein, we employed Cox regression to model 180-day survival using time-varying overall symptom burden, calculated as the sum of 12 symptom scores, PF and WB. Multivariable models also included demographics, clinical variables, treatment goal, and comorbidities. **Results:** The cohort included 3,999 patients (45% GI, 23% GYN, 32% thoracic) who submitted 42,254 symptom reports and had 481 deaths within 180 days. Median age was 66 (IQR 15), 59% female, 86% White, 42% Medicare, 5% Medicaid, 50% retired, 10% disabled. The mean symptom burden score was 7.57 (SD 4.66, min 0, max 34); severe deficit in PF and WB were reported in 13.2% and 7.8% of questionnaires, respectively. In bivariate analyses, greater symptom burden, more deficits in PF and WB, increasing age, female sex, and palliative treatment goal predicted inferior survival. After adjusting for other covariates, symptom burden, moderate and severe PF deficits, and severe WB deficits predicted inferior 180-day survival (Table). **Conclusions:** There is a significant inverse linear relationship between time-varying symptom burden and survival for patients receiving chemotherapy. Among chemotherapy patients, assessments that elicit symptom burden as well as PF and WB may augment the prognostic value and usefulness of ePRO tracking systems. Clinical trial information: NCT03850912. Research Sponsor: National Cancer Instiute; 1UM1CA233080-01.

	Unadjusted		Multivariable	
Characteristic	**HR**	**95% CI**	**HR**	**95% CI**
Symptom Burden (Linear)	1.13	1.11, 1.15	1.08	1.06, 1.10
Physical Function Deficit (ref = no deficit)				
Mild	1.65	1.13, 2.41	1.12	0.74, 1.69
Moderate	3.82	2.64, 5.53	1.89	1.23, 2.92
Severe	9.55	6.74, 13.5	3.61	2.35, 5.55
Overall Wellbeing Deficit (ref = no deficit)				
Mild	1.98	1.27, 3.07	1.30	0.81, 2.10
Moderate	4.18	2.74, 6.36	1.51	0.92, 2.48
Severe	9.97	6.49, 15.3	1.75	1.02, 3.00
Age (Linear)	1.02	1.01, 1.03	1.03	1.01, 1.04
Sex (Female, ref = male)	0.57	0.49, 0.68	0.61	0.51, 0.74
Treatment Goal (ref =curative)				
Palliative	4.27	3.22, 5.66	3.66	2.71, 4.95
Control/Other/Unknown	2.66	1.99, 3.55	2.52	1.85, 3.42

11045 Poster Session

Treatment patterns and out-of-pocket cost after CAR-T cell therapy in commercially insured patients with hematologic malignancies: A real-world US study. First Author: Mohammed Zuber, Clinical and Administrative Pharmacy, College of Pharmacy, University of Georgia, Athens, GA

Background: Chimeric Antigen Receptor T (CAR-T) cell therapy has improved outcomes in hematologic malignancies since its FDA approval in 2017. However, real-world data on treatment patterns and out-of-pocket (OOP) costs after CAR-T failure or cancer relapse remain limited. This study evaluated subsequent treatment risk, patterns, and OOP costs post-CAR-T therapy. **Methods:** A retrospective cohort study was conducted using the Merative MarketScan database (2017–2022). Commercially insured patients receiving CAR-T for acute lymphoblastic leukemia (ALL), diffuse large B-cell lymphoma (DLBCL), follicular lymphoma (FL), mantle cell lymphoma (MCL), or primary mediastinal large B-cell lymphoma (PMBCL) were included. Patients had ≥6 months of continuous insurance enrollment before the index date (CAR-T administration date) and were followed until disenrollment or the end of 2022. Initiation of additional therapy >14 days post-index (chemotherapy, immunotherapy, stem cell transplant, or radiotherapy) served as a proxy for CAR-T failure or relapse, with cumulative risk estimated using Kaplan-Meier methods. OOP costs (outpatient, inpatient, and prescription claims) were calculated for patients with ≥6 months of post-index enrollment and adjusted to 2022 USD. **Results:** Of the 246 patients, 22 had ALL, 185 DLBCL, 15 FL, 23 MCL, and 1 PMBCL. The mean age was 53.2 years (SD: 10.7), and 69.9% of patients were male. Overall, 98 patients (39.8%) initiated subsequent therapy. The cumulative risk of CAR-T failure was 21.3% (95% CI: 16.8%-25.8%) at 3 months, 37.0% (95% CI: 30.1%-43.9%) at 6 months, and 51.5% (95% CI: 43.5%-59.4%) at 12 months. After CAR-T failure, the most common first-line therapies were lenalidomide (n=12), ibrutinib (n=7), and pembrolizumab (n=5) for DLBCL, and blinatumomab (n=3) and ruxolitinib (n=2) for ALL. Total OOP costs incurred over six months were $310,246.2, with outpatient services accounting for 66.0%. The mean per-patient OOP cost for six months was $2,248.2. While the median OOP costs were similar between groups, mean per-patient OOP costs were higher for patients who required subsequent therapy ($2,881.0 vs $1,910.7), with some patients facing costs as high as $38,889.2. **Conclusions:** This study highlights a substantial risk of CAR-T failure, with targeted therapies and immunotherapies commonly used post-CAR-T. OOP costs were significant, particularly for patients requiring additional therapy, with considerable variability. These findings emphasize the need for strategies to improve outcomes and reduce financial toxicity in this population. Research Sponsor: None.

11046 Poster Session

Receiving a cancer diagnosis during hospitalization and associations with care outcomes. First Author: Saurav Kadatane, The University of Oklahoma Health Sciences Center, Oklahoma City, OK

Background: Patients often receive their cancer diagnoses during a hospitalization, but little is known about patients who are diagnosed inpatient versus outpatient. We sought to describe associations between patients diagnosed with cancer in the hospital and their clinical outcomes. **Methods:** We conducted a retrospective cohort study of adults with cancer admitted from 1/2017-12/2022 to the University of Oklahoma Medical Center. Using the electronic health record, we extracted patient demographics (age, sex, race, area deprivation index [ADI; categorized into quartiles Q1-Q4; Q4=areas of highest deprivation]) and clinical characteristics (cancer type, Charlson Comorbidity Index [CCI]), including those who received their cancer diagnosis during their respective hospital admission. We used regression models to explore associations of inpatient cancer diagnosis with patients' demographics, clinical characteristics, and clinical outcomes (hospital length of stay [hazard ratio {HR} for time to discharge], time to readmission, and overall survival). **Results:** Among 20,683 hospitalized patients with cancer (mean age 62.2; 51.5% female, 80.0% White, most common cancer types: gastrointestinal [GI; 19.3%], genitourinary [GU; 13.8%], and gynecologic [GYN; 13.7%]), 36.8% of patients received their cancer diagnosis during hospital admission. We found that Black patients (OR=.81, p<.001) and female patients (OR=.91, p=.007) were less likely to receive an inpatient cancer diagnosis. Compared to those with GU cancers, patients with neuroendocrine (OR=1.72, p<.001), thoracic (OR=1.68, p<.001), hematologic (OR=1.38, p<.001), CNS (OR=1.34, p<.001), and GI (OR=1.23, p=.018) cancers were more likely to receive an inpatient diagnosis whereas patients with breast (OR=.48, p<.001), GYN (OR=.67, p<.001), and head/neck (OR=.84, p=.009) cancers were less likely. Patients residing in higher ADI areas (Q2: OR= 1.18, p=.002; Q3: OR=1.55, p<.001; Q4: OR= 1.55, p<.001) were more likely to receive an inpatient cancer diagnosis compared to Q1. Patients with more comorbidities (CCI 1-2: OR=1.41, p<.001; CCI 3+: OR=1.69, p<.001) were more likely to receive an inpatient cancer diagnosis. For clinical outcomes, those who received an inpatient cancer diagnosis had a longer hospital length of stay (HR=.71, p<.001), higher risk of readmission (HR=1.12, p<.001), and worse overall survival (HR=1.28, p<.001) than patients who were not diagnosed in the respective hospitalization. **Conclusions:** In this large cohort of hospitalized patients with cancer, we identified factors associated with receiving an inpatient cancer diagnosis and demonstrated that diagnosis during hospitalization correlated with worse clinical outcomes. These findings highlight the importance of developing targeted interventions to enhance care delivery and outcomes for individuals who receive their cancer diagnosis during a hospital admission. Research Sponsor: U.S. National Institutes of Health; U54GM104938.

11047 Poster Session

Impact of angiotensin-converting enzyme inhibitors (ACEis) or angiotensin II receptor blockers (ARBs) on mortality and kidney function in cancer patients receiving cisplatin. First Author: Saad Javaid, Charleston Area Medical Center, Charleston, WV

Background: Cisplatin is a cornerstone of cancer treatment, but its nephrotoxicity often requires dose reduction or withdrawal, compromising antitumor efficacy. This study aimed to determine if concomitant use of cisplatin with angiotensin-converting enzyme inhibitors (ACEis) or Angiotensin II receptor blockers (ARBs) increases the risk of acute kidney injury (AKI) and impacts mortality. **Methods:** A retrospective analysis using the TriNetX Research Network identified cancer patients ≥18 treated with cisplatin from January 1, 2010, to November 27, 2024. Eligible cancers included head and neck, lung, esophageal, biliary tract, pancreatic, or testicular cancer. Patients were stratified by ACEi/ARB use within 1 week of cisplatin treatment. Groups were compared using 1:1 propensity matching, adjusting for age, type 2 diabetes, hyperlipidemia, CAD, CHF, and hypertensive heart disease. Primary outcomes were AKI risk and overall mortality; secondary outcomes included renal replacement therapy (RRT), hospitalization within 3 months, and proteinuria or hematuria. Outcomes were assessed using risk analysis and Kaplan-Meier log-rank tests. **Results:** A total of 36,779 cancer patients taking cisplatin were identified. Of these, 2,585 patients were taking an ACEi/ARB within 1-week of cisplatin treatment, while 36,194 were not. Patients taking ACEis/ARBs had a significantly increased risk of AKI within 30 days of cisplatin use based on the measures of association (risk difference [RD]: 1.713%, p = 0.0152) and the Kaplan-Meier test (hazard ratio [HR]: 1.372, p = 0.01). Similarly, overall mortality was higher in patients with concomitant use of ACEis/ARBs and cisplatin based on both the risk assessment (RD: 5.228%, p = 0.0002) and the Kaplan-Meier (HR: 1.196, p< 0.0001). Patients on ACEis/ARBs also had higher rates of hospitalization 3-months after treatment with cisplatin (RD: 9.24%, p < 0.0001 and HR: 1.53, p < 0.0001). However no significant difference was noted in the need for RRT or the diagnosis of proteinuria or hematuria up to 3-months after treatment. **Conclusions:** Our study suggests that the use of Cisplatin in patients taking ACEi/ARBs increased the risk of early AKI, mortality, and hospitalizations. Careful consideration should be taken when using Cisplatin in these patient groups, focusing on alternative hypertensive regimens. Research Sponsor: None.

	ACEi/ARB use		Risk Difference/Odds Ratio			Log-Rank Test		
Outcomes	Yes	No	RD	OR (95% CI)	P Value	HR	95% CI	P-Value
AKI Risk	6.82%	5.10%	1.713%	(1.06,1.745)	0.0152	1.372	(1.077,1.747)	0.01
Overall Mortality	49.01%	43.78%	5.228%	(1.105-1.379)	0.0002	1.196	(1.103-1.297)	< 0.0001
Hospitalization	33.44%	24.20%	9.24%	(1.393-1.778)	< 0.0001	1.534	(1.384-1.702)	< 0.0001

11048 Poster Session

Sociodemographic differences in lung cancer mortality trends across the United States (US) rural-urban divide. First Author: Dena Rhinehart, The Sidney Kimmel Comprehensive Cancer Center, Johns Hopkins University School of Medicine, Baltimore, MD

Background: It is known that rural populations face higher lung cancer mortality than urban populations, but it is unknown how trends vary across demographic groups. We investigated rural-urban disparities in age-adjusted mortality rates (AAMRs) from lung cancer across demographic groups over 20 years. **Methods:** We analyzed lung cancer mortality (ICD codes C34.0 - 34.3, 34.8, 34.9) from 1999-2019 using the CDC WONDER database. Populations were classified as urban or rural based on 2013 US census definitions. AAMRs were calculated as deaths per 100,000 using the US Standard Population and stratified by sociodemographic categories. Annual percentage change (APC) and 95% CIs were estimated using linear regression with the log-scale AAMRs as the dependent variable and year as a continuous covariate. **Results:** There were 3,244,056 deaths attributable to lung cancer (79.7% urban, 20.3% rural) with overall AAMR reduction from 86.9 to 53 deaths per 100,000 from 1999-2019. Rural populations had slower mortality improvements compared to urban populations (APC -2.6 [-2.9, -2.4] vs -1.6 [-1.9, -1.3]; p <0.001), with greatest rural-urban differences seen in younger and female populations (Table). Younger adults (<65)in rural areas had nearly 2-fold slower improvement than urban areas (APC -2.1 [-2.3, -1.9] vs -3.7 [-3.9, -3.5]; p<0.001). Females in rural areas had 3-fold slower improvement than females in urban areas (APC -0.6 [-0.9, -0.3] vs -2.0 [-2.3, -1.7], p<0.001). Slower mortality improvements were also seen for non-Hispanic patients in rural than in urban areas. While AAMR remained slightly higher for Hispanic patients in rural than urban areas, it noted faster improvement in rural areas (APC -3.3 [-3.7, -3.9] vs -2.4 [-2.7, -2.2]). **Conclusions:** Patients in rural areas had higher AAMR than urban counterparts across all demographic groups analyzed with slower improvements in almost all subgroups. This study highlights populations in greatest need of health services initiatives such as tobacco cessation efforts, lung cancer screening, and guideline concordant treatment receipt to close the rural-urban gap. Research Sponsor: None.

	Overall	Urban	Rural	P
Overall	-2.5 (-2.7, -2.2)	-2.6 (-2.9, -2.4)	-1.6 (-1.9, -1.3)	<0.001
Age 25-65	-3.4 (-3.6, -3.2)	-3.7 (-3.9, -3.5)	-2.1 (-2.3, -1.9)	<0.001
Age >65	-2.1 (-2.5, -1.8)	-2.3 (-2.6, -2.0)	-1.4 (-1.8, -1.1)	0.006
Female	-1.7 (-2.1, -1.4)	-2.0 (-2.3, -1.7)	-0.6 (-0.9, -0.3)	<0.001
Male	-3.2 (-3.4, -2.9)	-3.3 (-3.6, -3.1)	-2.5 (-2.8, -2.2)	0.002
Hispanic	-2.5 (-2.8, -2.3)	-2.4 (-2.7, -2.2)	-3.3 (-3.7, -2.9)	0.025
Non-Hispanic Black	-3.0 (-3.2, -2.7)	-3.1 (-3.4, -2.8)	-2.1 (-2.4, -1.9)	0.002
Non-Hispanic White	-2.24 (-2.5, -2.0)	-2.4 (-2.7, -2.1)	-1.5 (-1.8, -1.2)	0.002

APC for overall, urban, and rural geographic regions by demographic subgroups. P value for difference in change in AAMR over time between Urban and Rural areas, overall and within subgroups, estimated using interaction tests. All CIs are 95%.

11049 Poster Session

Cost-effectiveness of ribociclib plus endocrine therapy in HR-positive, HER2-negative early breast cancer in the United States. First Author: Kunal C. Potnis, Yale School of Medicine, New Haven, CT

Background: Cyclin-dependent kinase 4 and 6 (CDK4/6) inhibitors are an efficacious treatment for HR-positive (HR+), HER2-negative (HER2-) early breast cancer. The phase 3 NATALEE trial demonstrated that ribociclib ($12,000 monthly) plus a nonsteroidal aromatase inhibitor (endocrine therapy) significantly improved invasive disease-free survival. We performed the first cost-effectiveness analysis of ribociclib plus endocrine therapy in patients with HR+, HER2- early breast cancer in the United States (US). **Methods:** We constructed a partitioned survival model based upon clinical data from the NATALEE trial, employing a health system perspective across all accepted willingness-to-pay (WTP) thresholds in the US. Patients with a median age of 51 years entered the model to receive (1) ribociclib plus endocrine therapy versus (2) endocrine therapy alone. Standard extrapolation techniques were utilized to extend overall and invasive disease-free survival curves to a 10-year time horizon. Costs were informed by the US Centers for Medicare & Medicaid Services. Effectiveness was informed by age-, sex-, and breast cancer-specific utility values and was measured in both quality-adjusted life years (QALYs) and equal value life years (evLYs). The primary outcome was the incremental cost-effectiveness ratio (ICER) in USD per evLY. We concluded with deterministic sensitivity analyses and threshold and probabilistic analyses, with all input parameters informed by relevant probability distributions. **Results:** In the base-case, ribociclib plus endocrine therapy and endocrine therapy alone accrued discounted costs of $442,000 and $186,000, with discounted QALYs/evLYs of 7.76/7.79 and 7.57/7.57, respectively. This resulted in an ICER of $1.2 million/evLY (and $1.3 million/QALY) for the addition of ribociclib (Table 1). Deterministic sensitivity analysis revealed our model was only sensitive to the price of ribociclib: no other parameter changed the conclusion. Threshold analysis demonstrated that a 90% reduction in the price of ribociclib would be necessary for ribociclib plus endocrine therapy to be cost-effective even at the highest WTP threshold. Endocrine therapy alone was favored in 100% of 10,000 Monte Carlo simulations across the entire range of accepted WTP thresholds in the US. **Conclusions:** At current pricing, ribociclib with endocrine therapy is not expected to be a cost-effective strategy compared to endocrine therapy alone for patients with HR+, HER2- early breast cancer in the US. These results align with prior studies in other countries assessing the cost-effectiveness of CDK4/6 inhibitors in HR+, HER2- early breast cancer. Research Sponsor: None.

Base-case analysis results.

Strategy	Cost (USD)	QALY	evLY	ICER (USD/evLY) [95% credible interval]
Endocrine therapy alone	186,000	7.57	7.57	–
Ribociclib with endocrine therapy	442,000	7.76	7.79	1,200,000 [800,000 to 1,700,000]

11050 Poster Session

Cancer-related mortality of incarcerated populations in the United States. First Author: Owen Tolbert, University of Rochester, Rochester, NY

Background: The United States has the largest incarcerated population of any country in the world with 1.2 million prisoners as of 2022, but little research has fully characterized the disease burden in these incarcerated populations. Due to the increasing size and age of the prison population, it is paramount to better understand causes of mortality in inmate populations. **Methods:** Mortality data was collected from 41 states via UCLA's Behind Bars Data Project. 40,922 deaths were were recorded between 1999 and 2021, however, only 16,477 deaths had a specific cause of death. To account for individuals with unknown cause of death, analysis was conducted only on the cohort with a known cause of death. From this cohort, one Medical Student and two General Surgery Residents reviewed the death records and assigned each individual into one of 25 mechanisms of death. Protocol for this manual sorting of data was reviewed by the Surgical Health Outcomes and Reaching for Equity group (SHORE). This multidisciplinary group consists of statisticians, public health researchers, Surgery residents, and attending surgeons. **Results:** Of the 25 mechanisms of death, cancer was the leading cause accounting for 4,351 deaths. Approximately 26 different types of cancer were identified with the incarcerated population. The most common types of malignancies within this population were Lung, Hepatic/Biliary, Colorectal, and Esophageal cancers. The rates of Lung, Hepatic/Biliary, and Esophageal Cancer were significantly higher in the incarcerated population compared to the general population. Both the mean and median age of death in the incarcerated population was 61 years old (IQR 54-68), 37.6% were White, 21.3% were Black, 7.1% were Hispanic, and 35.8% unknown. In contrast, cancer related deaths accounted for a smaller proportion of deaths in the general population at 17.5% and 18.5% in 2021 and 2022 respectively. **Conclusions:** This analysis is the first of its kind to stratify mortality by cancer type within the prison population. Previous research that indicates prisoners have a high incidence of Hepatitis B due to the prevalence of IV drug use which is a major risk factor for Hepatic/Biliary cancer. Furthermore, incarcerated populations have higher rates of tobacco use compared to the general population which may account for some of the difference in Lung cancer rates. Delayed access to care in the prison environment may contribute to later diagnosis and correspondingly higher mortality rates among incarcerated individuals. Our results highlight the importance of access to care for effective cancer treatment, and the importance of understanding risk factors for cancer. Research Sponsor: None.

Type of Cancer	Deaths in Prison	% in Prison	Estimated Deaths in General Population	% in General Population	Difference
Lung	1041	23.9%	125,070	20.4%	3.5%
Hepatic/ Biliary	600	13.8%	29,840	4.9%	8.9%
Colorectal	363	8.3%	53,010	8.7%	-0.4%
Esophageal	325	7.5%	32,240	5.3%	2.2%

11051 Poster Session

Age acceleration among adolescent and young adult patients with Ewing sarcoma and osteosarcoma. First Author: Michael J. Robinson, Vanderbilt University Medical Center, Nashville, TN

Background: Ewing sarcoma (ES) and osteosarcoma (OS) are two common bone malignancies affecting adolescent and young adult (AYA) patients, often requiring intensive and multi-modal therapy. Cancer and its associated treatments may accelerate the aging process, as reflected in phenotypic age acceleration (PAA), leading to increased risk for developing chronic health conditions typically ascribed in older individuals.We conducted a pilot study to evaluate the impact of treatment completion for ES and OS on age acceleration among an AYA cohort using the validated phenotypic age (PheAge) instrument. **Methods:** This pilot study included participants who completed treatment at Vanderbilt University Medical Center from 2012-present for either ES or OS between age 20 and 39 years. Phenotypic age at diagnosis and end of treatment was derived using a modified PheAge equation, which was validated for patients age $\geq$20 years and based on chronological age and eight clinical biochemistry measurements, including albumin, creatinine, glucose, lymphocyte percent, mean cell volume, red cell distribution width, alkaline phosphatase, and white blood cell count. PAA was then calculated as the difference between PheAge and chronologic age. A positive PAA indicates an individual's phenotypic age is older than their chronological age, signifying accelerated aging. A descriptive analysis of PAA across patient demographics and disease strata was then conducted. **Results:** Among 30 AYA participants included in our study, 15 participants were diagnosed with ES and 15 with OS. The mean age at diagnosis was 23.8 (Q1 21.8, Q3 27.5). There was an overall male predominance of 19 participants (63.3%). Among participants with ES, the median PAA was 16.1 years (13.8, 18.1) at diagnosis and 18.4 years (13.6, 25.8) at end of therapy. Among participants with OS, the median PAA was 16.0 years (12.9, 20.7) at diagnosis and 15.9 years (13.9, 19.7) at end of therapy. **Conclusions:** This pilot study suggests that AYA patients with ES and OS had accelerated aging at diagnosis and ES patients may endure further age acceleration following treatment, while patients with OS had shown a nearly unchanged PAA. These results highlight the need for a larger and more comprehensive investigation into the contributing factors of PAA, including an evaluation of genetics, environmental exposures, cancer characteristics, treatment modalities, as well as acute and chronic toxicities of therapy. Such knowledge will contribute to understanding the etiology and cumulative and long-term impact of these common bone malignancies among AYAs. Research Sponsor: National Institutes of Health (NIH)/National Cancer Institute (NCI); Vanderbilt Training Program in Molecular and Genetic Epidemiology of Cancer (MAGEC).

11052 Poster Session

Evaluating the effectiveness of immersive virtual reality in reducing distress in patients with cancer receiving chemotherapy: A prospective randomized trial. First Author: Maria Herran, Department of Hematology and Oncology, Maroone Cancer Center, Cleveland Clinic Florida, Weston, FL

Background: Patients diagnosed with cancer commonly face high levels of distress, anxiety, and depressive symptoms along with discomfort or pain, that can be exacerbated during chemotherapy treatment. Immersive Virtual Reality (VR) has not been evaluated in patients with cancer as an intervention to relieve psychological and physical symptoms. In this randomized trial, we sought to assess the effect of a unique immersive type of VR on reducing distress compared to standard of care (SOC). **Methods:** This is a two-arm, prospective controlled randomized trial. Eligibility criteria included patients diagnosed with any type of cancer at any stage, with an NCCN Distress Thermometer Score $\geq$ 5, and actively receiving chemotherapy. Participants were randomized in a 1:1 ratio to receive either the intervention (VR) or the control group (SOC). Questionnaires, available in English and Spanish, were administered to both groups before and after the intervention. The primary outcome was to evaluate the effectiveness of VR in reducing distress levels while receiving chemotherapy infusion (NCCN Distress Thermometer) compared to SOC. Secondary outcomes included evaluating the effectiveness in reducing anxiety levels (GAD-7); pain (Universal Pain Assessment Tool) and improving overall wellbeing (Cleveland Clinic 4 Visual Analog Scale - CCVAS). Changes in questionnaire scores were assessed using a two-sample t-test for both arms. All data analyses were conducted using SAS version 9.4. **Results:** A total of N=70 participants meeting the eligibility criteria are expected to be enrolled in this study. To date, N=41 participants have been enrolled and were included in this preliminary analysis, with n=19 assigned to the intervention group (VR) and n=22 assigned to the control group (SOC). A significant difference was observed for the primary outcome, where the intervention group (VR) demonstrated a mean score reduction in NCCN distress thermometer of 3.9 points (SD$\pm$ 3.3) compared to 1.0 points (SD$\pm$ 2.0) for the control group (p = 0.0017). In addition, the VR group showed an improvement in overall wellbeing symptoms measured by decreased CCVAS of 1.7 (SD$\pm$2.2) vs. 0.2 (SD$\pm$1.4) points in the control group (p=0.0160). No significant difference was observed for anxiety and pain. **Conclusions:** VR is an innovative immersive experience with the potential to relieve distress and improve wellbeing during chemotherapy sessions in patients diagnosed with cancer.The study is currently ongoing, and final results will be reported upon completion. Research Sponsor: VeloSano.

Comparison of test changes between pre- and post-intervention.

	Virtual Reality (n=19)	SOC (n=22)	p-value
Primary Outcome, mean ±SD			
NCCN Distress Thermometer	3.9 ± 3.3	1.0 ± 2.0	0.0017
Secondary Outcomes, mean ±SD			
GAD-7	0.4 ± 1.6	0.6 ± 1.7	0.7096
CCVAS	1.7 ± 2.2	0.2 ± 1.4	0.0160
Universal Pain Assessment Tool	1.2 ± 3.0	-0.2 ± 2.9	0.1404

11053 Poster Session

How cancer impacts adolescents' and young adults' (AYAs) scholastic experiences: Insight on supportive survivorship care needs from AYAs, parents, and clinicians. First Author: Carla L. Fisher, University of Florida, Gainesville, FL

Background: Cancer disrupts AYAs' educational and vocational trajectories given treatment demands and acute or late effects of treatment on cognitive functioning. This occurs during a developmental phase when scholastic experiences are central to AYAs' socio-emotional and cognitive growth. Despite education being a critical determinant of health-related quality of life, typically families do not receive support for scholastic issues. According to clinical guidelines, key stakeholders in cancer care must have a shared understanding of these concerns to effectively address them. We aimed to identify how cancer impacts scholastic experiences when diagnosed at age 15-29 through the perspectives of diagnosed AYAs, parents caring for AYAs, and AYA oncology clinicians. **Methods:** Drawn from studies funded by The Leukemia & Lymphoma Society and an NCI-Designated Cancer Center, a secondary thematic analysis was conducted on three interview datasets: AYAs (n=10); parents (n=15); clinicians (e.g., oncologists, APPs, LCSWs) (n=7). Analyses were separated by stakeholder group and triangulated to identify shared perspectives. **Results:** AYAs, parents, and clinicians all describe cancer contributing to four challenging scholastic-related impacts: 1) having to advocate for academic accommodations (e.g., virtual option, reduced workload, disability assistance); 2) disrupting school/vocational trajectories (e.g., relocating/changing schools for treatment, stopping school/career pursuits, limitations in performance); 3) losing extracurriculars (e.g., sports, school activities); and 4) losing peer social connection (e.g., feeling isolated/disconnected). They collectively described the impacts as distressful, as a parent expressed: "He was managing all this mental and emotional pain [with cancer], and then [the school] caused so much other stress and pain in our life." One positive impact was identified by AYAs and parents: changing mindsets about school/career (e.g., using school/work as motivator or way to take control, being inspired to change passion/paths). **Conclusions:** Findings illustrate distressful scholastic issues parents and AYAs need support with during cancer care. AYAs and parents described having to advocate on their own with no support. While clinicians recognized the same concerns as patients/caregivers, AYAs and parents described needing to initiate discussions with clinicians, further demonstrating a need to streamline scholastic performance into the standard of care. AYAs and parents recognized cancer could also impact AYAs' mindset about school/work in a positive manner, thus, addressing scholastic concerns may help empower and engage AYAs. Findings can inform resources and support the importance of developing a patient-centered metric that addresses scholastic performance in AYA survivors. Research Sponsor: The Leukemia & Lymphoma Society; HSR9028-24; National Cancer Insitute; University of Florida Health Cancer Center Predoctoral Award; 3P30CA076292.

11054 Poster Session

Demographic and genomic landscape of early mortality in patients with stage IV non–small-cell lung cancer. First Author: Osama Mustafa Younis, The University of Jordan, Amman, Jordan

Background: Early mortality presents an ongoing challenge to oncologists all over the world. Specifically, one-third of patients that present with late-stage lung cancer progress rapidly, succumbing to their disease before treatment is initiated. That is why stratification of high-risk patients is imperative. In this study, we describe the epidemiologic and genomic landscape of early mortality in Stage IV non-small cell lung cancer (NSCLC). **Methods:** We retrospectively analyzed clinical and genetic data from the AACR Genie NSCLC v2.0 cohort via cBioPortal. Patients with Stage IV NSCLC who died within 3 months of their sequencing sample collection were classified as early mortality and compared to patients who survived more than 3 months. The chi-squared test was used to assess statistical association between variables. A p value or a q value of < 0.05 was considered significant. **Results:** A total of 871 patients were retrieved; 66 patients died within the first 3 months of diagnosis. Patients in the early mortality group were older (68.1 vs 64.1, $p < 0.05$). No significant difference in sex, stage, and histology was present. Patients who died earlier had more brain, adrenal, and subcutaneous metastasis ($P < 0.05$). Notably, patients in the early mortality group had a higher prevalence of current smokers as compared to a higher prevalence of never smokers in the other group, with a statistically significant difference in overall smoking rates between both groups ($p < 0.05$). A total of 18/66 (27.3%) patients received any form of treatment in the early mortality group, 3 of whom received PD-1 or CTLA4 ICI's. In terms of genomic alterations, patients who died early had a higher frequency of KRAS (56.1% vs. 27.0%, $q < 0.05$) and STK11 (38.6% vs 11.2%, $q < 0.05$). On the other hand, those who did not die early had a higher frequency of EGFR mutations (32.3% vs 6.10%, $q < 0.05$). KEAP1 alteration was higher in the early mortality group but did not achieve statistical significance (31.8% vs 11.5%, q = 0.095). **Conclusions:** Patients who are older, current smokers, and possess KRAS or STK11 mutations were more likely to die within 3 months of diagnosis. These results are in line with the literature and are known to be strong predictors of mortality in NSCLC patients and should be incorporated in the initial evaluation of Lung cancer patients. Research Sponsor: None.

11055 Poster Session

Development of second primary malignancies (SPMs) in head and neck cancer survivors stratified by receipt of radiation therapy (RT) and chemotherapy (CT). First Author: Kriti Ahuja, University at Buffalo/Roswell Park Comprehensive Cancer Institute, Buffalo, NY

Background: Head and neck cancers (HNC) often require multimodality management for curative intent with surgery, radiation therapy (RT) with or without chemotherapy (CT), resulting in significant impairment of nutrition, speech and quality of life. Survivors are also at risk for future cancers from field cancerization. We aim to study the incidence and characteristics of SPMs in HNC survivors. **Methods:** We performed a retrospective analysis of the Surveillance, Epidemiology and End Results (SEER) 17 registries database to identify the cases diagnosed with cancer of the oral cavity, pharynx or larynx as primary malignancy between the years 2000 to 2021. The data was stratified by receipt of RT and CT. Standardized incidence ratios (SIR) for the development of SPMs were calculated using the SEER Stat software. **Results:** A total of 206144 HNC survivors were identified, of which 78055 received CT + RT (CRT group) while 57898 patients received RT with no/unknown CT (RT group). The CRT group had a lower risk than the RT group for several local SPMs with SIRs ($p<0.05$): lip (5.13, 5.71), salivary gland (4.11, 5.21), floor of mouth (18.47, 19.7), gum/other mouth (20.18, 25.04), tonsil (4.54, 5.47) and larynx (5.18, 6.79). However, the CRT group had higher SIRs ($p<0.05$) than the RT group for tongue SPMs (15.91, 13.03) and all pharyngeal SPMs: nasopharynx (9.65, 8.51), oropharynx (13.21, 12.11), hypopharynx (20.47, 16.44), other oral cavity/pharynx (31.08, 24.69). The CRT group had higher SIRs ($p<0.05$) than RT recipients for most gastrointestinal SPMs: esophagus (6.44, 4.53), stomach (1.49, 1.27), colorectal (1.34, 1.23). The RT group had higher SIRs ($p<0.05$) than CRT recipients for hepatobiliary SPMs (1.48, 1.29) and anus/anal canal /anorectum SPMs (1.87, 1.73). CRT group had higher risk than RT group for nose/nasal cavity/middle ear, lung/ bronchus, bone/joint, soft tissue and kidney SPMs but lower risk for trachea, eye/orbit non - melanoma, and thyroid SPMs (Table). CRT group had a lower risk for nodal Hodgkin Lymphoma (SIR 0.3) and myeloma (SIR 0.76) than the general population ($p<0.05$). Both groups had lower risk for Chronic Lymphocytic Leukemia SPMs, with SIRs: RT 0.71, CRT 0.59 ($p<0.05$). Understandably, CRT recipients had a higher risk for Acute Myeloid Leukemia (SIR 2.24, $p<0.05$). **Conclusions:** HNC survivors demonstrate varying risks for SPMs in RT and CRT recipients. This necessitates close monitoring during survivorship care, with a comprehensive approach to screening and preventive measures to improve long-term outcomes and quality of life. Research Sponsor: None.

SPMs in HNC survivors.

SPM	RT SIR (p<0.05)	CRT SIR (p<0.05)
Nose, nasal cavity, middle ear	6.25	8.33
Lung, bronchus	4.01	4.69
Trachea	55.08	38.19
Bones, joints	4.62	6.15
Soft tissue including heart	1.67	2.21
Urinary bladder	1.27	1.24
Kidney	1.29	1.42
Eye, orbit – Non-melanoma	6.18	5.19
Thyroid	2.93	2.77

11056 Poster Session

A digital intervention to enhance engagement with oral oncolytic treatments and assess patient experiences with novel therapies. First Author: David Michael Waterhouse, OHC (Oncology Hematology Care)/US Oncology Network, Cincinnati, OH

Background: Adherence to oral oncolytic therapy influences treatment efficacy and outcomes. Effectively managing adherence requires a clear understanding of how treatments impact the patient. By directly monitoring adherence through precise dose administration data and electronic patient-reported outcomes (ePROs) using ReX, clinicians can improve outcomes while enhancing overall care quality and experience. We aimed to assess the impact of ReX on oral therapy adherence, dose reductions, and treatment discontinuations in real-world practice. **Methods:** Patients at 1 large community practice and 4 academic health systems were included in this retrospective cohort analysis. Participants all had either: chronic lymphocytic leukemia, and initiated treatment with acalabrutinib on or after September 12, 2023, or hormone receptor-positive, HER2-negative metastatic breast cancer who initiated ribociclib on or after May 22, 2024. Control data was abstracted from charts within the practices from those who did not receive the ReX device. Medication was dispensed as standard of care in ReX (Dosentrx Inc), an FDA approved handheld pocket-sized device. At a programmable time, patients take their medication from ReX and are asked ePROs about side effects via a touch screen on the device. Pill intake data and ePROs were available on the ReX Therapy Manager, a cloud-based platform. **Results:** A total of 35,760 pills were taken and 16,885 ePROs answered; resulting in 95% dosing adherence and 97% ePRO engagement (total questions answered/questions presented) in those using ReX. Ribociclib control (median age 56, all female), ribociclib ReX (median age 53, all female), acalabrutinib control (median age 73, 60 males and 33 females), and acalabrutinib ReX (median age 70, 49 males and 32 females). Patients using ReX had fewer dose reductions and discontinuations compared to the control group (Table 1). **Conclusions:** This data suggests that ReX leads to high adherence and ePRO engagement rates, resulting in fewer dose reductions and significantly greater persistence of both acalabrutinib and ribociclib use in community and University settings. Future studies with a greater sample size will be needed to confirm these endpoints and assess the impact of lower discontinuation rates on health outcomes. Research Sponsor: None.

Endpoint objectives.

	Control Group	ReX	p-value*
Patient sample size	94 acalabrutinib 69 ribociclib	81 acalabrutinib 63 ribociclib	
Dose Reductions	6% acalabrutinib 29% ribociclib	1% acalabrutinib 11% ribociclib	0.083 0.011
Discontinuation ≤ 3 mo	10.6% acalabrutinib 17.9% ribociclib	2.5% acalabrutinib 6% ribociclib	0.033 0.052
Discontinuation ≤ 6 mo	15% acalabrutinib 24.9% ribociclib	8.6% acalabrutinib 11% ribociclib	0.205 0.044
Discontinuation < 12 mo	24.5% acalabrutinib 31.8% ribociclib	13.5% acalabrutinib 11% ribociclib	0.070 0.004

*Two sample Z-test (2-tail, α=0.05).

11057 Poster Session

From chemotherapy allergy to tolerance: Desensitization as a safe alternative in oncology. First Author: Magda Arredondo, Hospital Universitario "Dr. José Eleuterio González", Monterrey, NL, Mexico

Background: Hypersensitivity reactions (HSRs) are a significant challenge in oncology, often leading to treatment modifications or interruptions. Rapid Drug Desensitization (RDD) is a method to reintroduce chemotherapeutic agents and monoclonal antibodies in patients with previous HSRs. This study focuses on safety, comparing the severity of initial HSRs with breakthrough reactions (BTRs) during desensitization. **Methods:** An observational, ambispective study was conducted from August 2020 to August 2024 at the University Hospital in Mexico. Patients with HSRs underwent RDD using a 12-step, 3-bag protocol. HSR severity was classified using Brown's scale. The primary endpoint was BTR severity compared to initial reactions, with secondary endpoints assessing BTR frequency and RDD completion rates. Data were sourced from electronic medical records under a protocol reviewed and approved by the hospital's research ethics committee. Inclusion required documentation of HSRs, the need to continue treatment with the implicated drug, and completion of the RDD protocol. Missing severity data were inferred from clinical notes or excluded. Chi-square tests compared severity grades (mild, moderate, severe) between initial reactions and BTRs, including cases without reactions for comprehensive analysis. Proportional frequencies were applied to address the difference in sample size. **Results:** A total of 927 RDD procedures were performed in 219 patients, with 84% female and a median age of 43 years. The severity of initial reactions was classified as mild in 12.1%, moderate in 43.3%, and severe in 44.6%. During the 927 desensitizations, breakthrough reactions occurred in only 8.6% of cases, distributed as mild (4.5%), moderate (1.8%), and severe (2.3%). Chi-square analysis confirmed a statistically significant difference in severity distribution between initial HSRs and BTRs ($\chi^2 = 834.72$, $p < 0.0001$). This demonstrated a substantial reduction in severity for BTRs compared to initial reactions. Despite the occurrence of BTRs, all patients completed the RDD protocol, received the full therapeutic dose, and no fatalities were reported. **Conclusions:** The comparison between initial HSRs and breakthrough reactions during RDD highlights the distinct nature of these events: initial HSRs represent baseline sensitivity, whereas BTRs occur as controlled outcomes during desensitization. The analysis confirms that desensitization is a safe and effective tool in oncology, significantly reducing both the frequency and severity of breakthrough reactions compared to initial reactions, ensuring treatment continuity and minimizing risks for patients. Research Sponsor: None.

Severity distribution of initial HSRs and BTRs.

Severity	Mild (%)	Moderate (%)	Severe (%)	Total (%)	Reference Population
Initial HSRs	27 (12.3)	95 (43.3)	97 (44.2)	219 (100)	219 patients
BTRs	42 (4.5)	17 (1.8)	21 (2.3)	80 (8.6)	927 desensitizations

11058 Poster Session

Exploring two decades of cancer trends in adolescents and young adults: Insights from a resource-restricted country. First Author: Sarah Abdel-Razeq, King Hussein Cancer Center, Amman, Jordan

Background: Over 40% of the Jordan population are adolescents and young adults (AYA), aged 15-39 years. Cancer diagnoses in this age group have distinct clinical characteristics and patients face unique needs and psychosocial challenges. We present data on local trends in cancer diagnoses among AYA, and their treatment outcomes. **Methods:** We utilized reports from the Jordan Cancer Registry (JCR) and the King Hussein Cancer (KHCC) registry to obtain treatment outcomes. **Results:** During 2022 a total of 8,754 new cancer cases were reported by the JCR; 4,736 (54.1%) were females and the median age at diagnosis was 57 years. Only 312 (3.6%) of the cases were diagnosed in childhood age group (<15 years), while 1,167 (13.3%) cases were diagnosed among AYA (15-39 years) and most of these cases (36.8%) were among the older AYA subgroup (35-39 years). Over the past 22 years, the total number of reported cancer cases among AYA has almost doubled from 654 in 2000 to 1,167 cases in 2022. Hodgkin's lymphoma (13.6%), testicular cancer (12.2%), non-Hodgkin's lymphoma (NHL) (10.9%), colorectal cancer (10.0%) and acute leukemia (9.8%) were the most encountered tumors in males, while breast cancer (31.5%), thyroid cancer (15.4%), Hodgkin's lymphoma (7.2%), colorectal cancer (6.2%) and ovarian cancer (5.5%) were the most common cancers in females in the AYA group. In the childhood age group, acute leukemia (24.4%) and brain tumors (20.2%) were the two most common cancers, accounting for almost half of all tumors in this group. The age-standardized incidence rate (ASIR) was higher among females compared to males across all age subgroups within the AYA. Such difference is more evident within the "older" group (30-34) years (64.3 versus 35.0) and in the (35-39) years age group (116.1 versus 52.3). These differences may be attributed to breast, and to a lesser extent thyroid cancer. Additionally, the ASIR increases with increasing age within the AYA age group; rates increased from 17.3 (15-19 years) up to 84.4 in the (35-39 years) group. Survival data on 7,202 AYA cancer patients treated and followed-up at KHCC were obtained from its hospital-based cancer registry. The 5-year overall survival was 73.0% (95% CI, 71.8-74.1), better than 57.1% (95% CI, 56.4-57.8) among 26,604 older adults (>39 years old), and lower than 75.2% (95% CI, 73.6%-76.9%) among 3,031 pediatric patients (<15 years) treated during the same period, p<0.0001. **Conclusions:** Over 40% of the Jordanian population is within the AYA age group. Though the cancer incidence is lower, and overall survival is better in this age group compared to older adults, a comprehensive plan that values the special physical and psychosocial needs of this group of patients should be addressed. Establishing a specialized AYA program with specialized ancillary services addressing these issues, especially those related to late treatment effects, is a national health care priority. Research Sponsor: None.

11059 Poster Session

Treatment patterns, use of healthcare resources, and clinical characteristics of patients with castration-resistant prostate cancer (mCRPC) in Colombia: Preliminary analysis from ProColombia RC study. First Author: Ray Manneh, Sociedad de Oncología y Hematología del Cesar, Valledupar, Colombia

Background: The clinical characteristics of metastatic castration-resistant prostate cancer (mCRPC) patients in Colombia remain poorly understood, particularly regarding their clinical profiles, stage at diagnosis, treatment options, and healthcare resource utilization (HRU). This study aims to describe real-world treatment patterns and HRU in mCRPC patients. **Methods:** This is a non-interventional, multicentre, retrospective study in mCRPC patients treated at reference centers across Colombia from Jan/2017 to Jun/2023. Data on demographic and clinical characteristics, treatment history, and (HRU) were extracted from electronic medical records. Progression-free survival (PFS) and overall survival (OS) were analyzed using the Kaplan-Meier method. **Results:** We present the Interim findings from the first 130 of the 380 patients we plan to enroll. The median follow-up was 70.0 months (IQR 46.8–136.1). The median age was 68y (IQR 61–73), with 86.2% residing in urban areas. Comorbidities were hypertension (64.6%) and type 2 diabetes (22.3%); 10.8% reported a family history of PC. Upon diagnosis, 54.6% had a Gleason grade of 4 or 5, and 82.7% passed through a metastatic hormone-sensitive prostate cancer (mHSPC) scenario and 47.7% of those mHSPC patients had high-volume disease. In the mCRPC setting, 14.6% had visceral metastases, while 78.4% had bone-predominant disease. In the first-line treatment, 73.8% received androgen receptor pathway inhibitors (ARPI) and 25.4% underwent taxane-based chemotherapy. Among the 81 patients (62.3%) who received second-line therapy, 27.1% received ARPI, 59.3% received taxane-based chemotherapy, 9.9% were treated with Radium-223, and 3.7% received PSMA-Lutetium. The median PFS in the first-line setting was 16.8 months (95%CI: 13.0–20.7), with a median OS of 39.2 months (95%CI:32.6–45.9). Only 31% of patients were tested for HRR and MSI, with median OS from mCRPC diagnosis being 59.2 months (95%CI:34.6–83.7) for those tested versus 39.5 months (95%CI:32.8–46.1) for those not tested, a statistically significant difference (p=0.016). In terms of healthcare utilization, 60.0% required palliative radiation therapy, and 52.3% consulted with a palliative care specialist; 20.8% required at least one emergency consultation due to cancer-related issues. **Conclusions:** This study represents the first comprehensive report on the demographic, clinical, treatment patterns, and HRU of mCRPC patients in Colombia. The significant survival differences based on biomarker testing highlight quality of care that patients received. Standardized PC management protocols, developed collaboratively by multidisciplinary teams and multiple institutions in Colombia, could enhance patient outcomes and healthcare efficiency across the country. Research Sponsor: MSD Colombia.

11060 Poster Session

Differential and cumulative impact of metabolic syndrome traits on cardiovascular, renal, and mortality outcomes in cancer patients. First Author: Arunkumar Krishnan, Department of Supportive Oncology, Atrium Health Levine Cancer, Charlotte, NC

Background: Metabolic syndrome (MetS) is a known risk factor for developing at least 13 cancer types and adverse outcomes. However, the effects of MetS on their differential and cumulative impact on cardiovascular, renal, and mortality outcomes in cancer patients remains uncertain. We aimed to determine whether MetS components increase cancer patients' risk of adverse cardiorenal and all-cause mortality. **Methods:** This large retrospective cohort study used the TriNetX database between 2013 to 2024. Adults (>18 years) with new cancer diagnoses and ≥1 MetS trait (obesity, insulin resistance(IR), hypertension (HT), or dyslipidemia (DLD)) were compared with matched controls without MetS. We performed 1:1 propensity score matching to adjust for confounding factors (demographics, comorbidities, cancer type, and medications). The primary outcomes were new adverse cardiovascular events like heart failure (HF), major adverse cardiovascular events (MACE), and cerebrovascular events (CVE). The secondary outcomes were end-stage renal diseases (ESRD), the need for dialysis, and all-cause mortality. We conducted sensitivity analyses to assess the robustness of the findings. Hazard ratios(HR) were calculated using Cox regression models stratified by MetS traits. **Results:** In total, 204,297 patients were identified (median age 54 years) with a median follow-up of 7.8 years. Patients with ≥1 MetS trait had significantly increased risks of adverse cardiorenal events. HR for HF was 1.76; this risk increased to 2.54 with ≥3 MetS traits. The risk of MACE was HR of 2.34 in those with ≥1 trait and HR of 2.47 in those with 4 traits. CVE had an HR of 1.56, increasing to 2.38 with ≥3 traits. For secondary outcomes, the risk of ESRD was HR of 1.76 in patients with ≥1 MetS trait, rising to HR of 2.29 in those with ≥3 traits. The need for dialysis was significantly elevated (HR 1.86), and all-cause mortality was HR of 2.15 in patients with ≥1 trait, increasing to 3.10 with 4 traits. Stratified analyses revealed obesity increased HF risk (HR 1.58) and mortality (HR 1.75). IR was linked to higher risks of MACE (HR 1.88) and ESRD (HR 2.59). HT increased the risk of CVE (HR 2.16) and dialysis (HR 2.11). DLD moderately elevated the risk of IHD (HR 1.47) and mortality (HR 1.59). Sensitivity analyses confirmed these findings across cancer types and treatments. A cumulative relationship was observed, with the number of MetS traits correlating to higher risks of outcomes. **Conclusions:** Our study showed a differential effect of MetS components on cardiovascular, renal, and all-cause mortality outcomes in cancer patients, with a cumulative impact of multiple MetS on overall risk. Early intervention targeting MetS traits may reduce these risks and improve outcomes. Comprehensive metabolic management should be integrated into oncology care to mitigate these risks and improve patient outcomes. Research Sponsor: None.

11061 Poster Session

Transfusion-related cost and time burden offsets in patients with myelofibrosis treated with pacritinib compared to best available therapy based on PERSIST-2 trial. First Author: Abiola Oladapo, Sobi Inc., Waltham, MA

Background: Anemia in patients (pts) with myelofibrosis (MF) is associated with a significant disease burden, especially in pts who require red blood cell (RBC) transfusions, as it negatively impacts quality of life and disease prognosis. In the PERSIST-2 trial, treatment with pacritinib (PAC), a JAK1 sparing inhibitor of JAK2/IRAK1/ACVR1, was associated with anemia benefit. A significant proportion of non-transfusion independent (non-TI) pts at baseline on PAC compared to best available treatment (BAT) achieved transfusion independence (TI) (37% vs 7%) in any 12 weeks over a 24-week interval and significantly more had a $\geq$50% reduction in transfusion burden (49% vs 9%) (Oh ST, et al. 2023) with lower RBC transfusion rates (Mean [2.45 vs 3.54/30-day]) (Data on file). This study aimed at estimating the projected differences in transfusion-related cost and time burden with PAC vs BAT. **Methods:** An economic evaluation based on transfusion-related data in pts treated with PAC or BAT (including ruxolitinib [RUX] and erythroid support [ES]) from the PERSIST-2 trial (NCT02055781). Transfusion status (TI and non-TI) at baseline and over any 12-week interval within the 24-week study period was defined based on the Gale criteria (i.e. presence or absence of RBC transfusions). RBC transfusion rates over 30-day periods, including all reported transfusions within the initial 24-week study period, were annualized and used as proxy for transfusion-related visits. Annual transfusion-related cost estimates by transfusion status were based on a previous MF burden of illness study which utilized IBM MarketScan data (Gerds AT, et al. 2022) and was adjusted to 2024 US dollars using the medical component of the Consumer Price Index. Transfusion-related time burden estimates were based on previously reported RBC transfusion visits in transfusion dependent pts with β-thalassemia (Knoth RL, et al. 2022). **Results:** Annual transfusion-related cost with PAC was projected to be 19.5% lower, with a cost saving of ~$61K compared to BAT (~$252K vs ~$313K). Annual transfusion-related time burden with PAC vs BAT was lower by 25.3% with a time saving of ~172 hrs (~508 vs ~680 hrs). Among pts who were non-TI at baseline, projected annual cost and time savings for PAC vs BAT were ~$73K and ~204 hrs, respectively. Results remained robust regardless of type of BAT (i.e. RUX or ES therapies). **Conclusions:** The reduction in transfusion rates associated with PAC treatment relative to BAT is projected to result in decreased transfusion-related medical cost and time burden for pts with MF and anemia. Research Sponsor: None.

11062 Poster Session

Trends and disparities in sepsis-related mortality among patients with malignancies: A 25-year nationwide analysis. First Author: Malik WZ Khan, Khyber Medical University, Peshawar, Pakistan

Background: Sepsis is a leading cause of mortality worldwide, with cancer patients at higher risk due to immune suppression from the disease and its treatments. Despite advancements in sepsis care, their impact on sepsis-related mortality among cancer patients remains unclear. Understanding these trends is crucial for developing targeted interventions to improve sepsis outcomes in patients with malignancies. **Methods:** We conducted a retrospective cohort analysis using the CDC WONDER database from 1999 to 2023, focusing on adults aged >25 years with malignancies. Deaths were identified using international classification of disease 10 (ICD-10) codes for instances where both sepsis and malignant neoplasms were listed as causes of death. Age-adjusted mortality rates (AAMR) per 100,000 population were extracted, and temporal trends were analyzed using Joinpoint regression to calculate the annual percentage change (APC) and its weighted average, the average annual percentage change (AAPC). Results were stratified to evaluate temporal, gender-based, racial, and geographic disparities in mortality. **Results:** From 1999 to 2023, a total of 684,930 sepsis-related deaths were recorded among adults with malignancies. Over this period, the AAMR increased significantly from 12.06 to 14.21, with an AAPC of 0.86 (95% CI: 0.74 to 1.06). Males had a higher overall AAMR (15.09) compared to females (9.91), but females experienced a sharper increase over time (23.77% vs. 9.56%). Non-Hispanic (NH) Black or African Americans had the highest AAMR (18.98), followed by NH American Indian or Alaska Natives (11.59) and NH Whites (11.35), while NH Asians/Pacific Islanders exhibited the lowest rate (10.24). Geographic disparities were significant, with state-specific AAMRs ranging from 24.62 in the District of Columbia to 7.50 in Montana. States in the top 90th percentile included Mississippi, Rhode Island, West Virginia, New Jersey, and the District of Columbia, while those in the bottom 10th percentile included Montana, Oregon, Idaho, and Wisconsin. Regionally, the Northeast had the highest AAMR (12.65), followed by the South (12.49) and West (11.69), with the Midwest exhibiting the lowest rate (11.08). **Conclusions:** This nationwide analysis highlights a concerning rise in sepsis-related mortality among patients with malignancies over the past 25 years, with females, NH Blacks and residents of the Northeastern region emerging as the most vulnerable populations. These findings underscore the need for prompt implementation of targeted strategies designed to overcome these disparities. Research Sponsor: None.

11063 Poster Session

Impact of a novel oral medication delivery device on patient engagement and discontinuation in individuals receiving oral oncolytic medications. First Author: Melissa Taylor, Yale New Haven Hospital, New Haven, CT

Background: Patient-reported outcomes (PROs) are essential for monitoring patient status and improving outcomes. ReX by Dosentrx physically administers oral medications and collects PROs at the time of dosing, allowing healthcare teams to track patient adherence, medication tolerance, and side effects. ReX aims to identify early toxicities between clinic visits, reduce acute care utilization, and improve adherence and overall outcomes. This study evaluates the impact of ReX on treatment adjustments and discontinuations in individuals taking either ribociclib or acalabrutinib. **Methods:** The study focused on a cohort of individuals prescribed either ribociclib or acalabrutinib. Patients using ReX were tracked for at least 6 months. The primary objective was to evaluate discontinuation rates at 3, 6, and 12 months. Secondary objectives included evaluating dose reductions and reasons for discontinuation. Outcomes from individuals using the ReX device were compared to a historical control group drawn from the same clinics prior to ReX implementation. **Results:** In the ribociclib group, 69 patients were in the historical control cohort and 63 in the ReX cohort, with median ages of 56 and 53, respectively. For acalabrutinib, the historical control had 94 patients and the ReX cohort 81, both with a median age of 70. Table 1 presents the discontinuation at 3, 6, and 12 months, along with the clinical reasons for discontinuation. Dose reductions were lower in the ReX group, with 11% for ribociclib at 10 months and 1% for acalabrutinib at 15 months, compared to 29% and 6% in the control group. **Conclusions:** ReX demonstrated a lower percentage of medication discontinuation at 3, 6, and 12 months for patients taking ribociclib or acalabrutinib, with fewer adverse event-related discontinuations and dose reductions compared to a historical control group. Additional studies investigating the impact of this novel medication delivery device on longer term medication adherence and clinical outcomes is currently underway. Research Sponsor: None.

Discontinuation at 3, 6, and 12 months and reason for discontinuation.

Discontinuation						
	3-months		6-months		12-months	
	Control	ReX	Control	ReX	Control	ReX
Ribociclib	17.8%	6%	24.9%	11%	31.8%	11%
Acalabrutinib	10.6%	2.5%	15%	8.6%	24.5%	13.5%
Clinical Discontinuation Reason						
	Disease Progression		Adverse Events		Medication Change	
	Control	ReX	Control	ReX	Control	ReX
Ribociclib	55%	0%	27%	0%	18%	100%
Acalabrutinib	55%	50%	27%	25%	18%	25%

11064 Poster Session

Impact of protein-energy malnutrition on inpatient mortality, healthcare cost and clinical outcomes among patients with head and neck cancer. First Author: Vaishali Deenadayalan, Roswell Park Comprehensive Cancer Institute, Buffalo, NY

Background: Protein-energy malnutrition (PEM) is a critical issue among patients diagnosed with head and neck cancers (HNC), primarily due to the tumor's anatomical location, and treatment-related side effects. Here, we examine the impact of PEM on the clinical outcomes and healthcare costs among hospitalized patients with HNC. **Methods:** This retrospective cohort study was conducted using data from the National Inpatient Sample database. Data of adult patients admitted with a diagnosis of HNC from 2016 to 2020 were analyzed and stratified based on the presence of PEM. The primary outcome was inpatient mortality rate, secondary outcomes included length of hospitalization, total hospital charges and other medical outcomes. **Results:** A total of 729,095 patients with HNC were identified, of whom 174,000 (23.8%) had PEM, with a mean age of 65.5 years and whites (77%) being the predominant race. Among the 32,075 patients who died, 11,715 (4.4%) had PEM. PEM was associated with a higher risk of mortality (6.74% vs 3.67%; OR:1.84, 95%CI 1.73-1.95; $P < 0.001$). Patients with PEM had an increased length of hospitalization (8.9 vs 5.2 days; adjusted difference of 3.3 days; 95% CI 3.21-3.45; $P < 0.001$), and higher total hospital charges ($98,959 vs $71,449; adjusted difference of $27,715, 95% CI $23,864-27,565; $P < 0.001$). Additionally, the presence of PEM was associated with increased risk of several secondary outcomes including septic shock, intubation, acute kidney injury, pneumonia, blood transfusion, neutropenia and urinary tract infections compared to the non-PEM cohort. **Conclusions:** This study demonstrated a two-fold increased risk of mortality and a prolonged length of stay, with approximately $27,000 more total charges in malnourished patients with HNC compared to those without PEM. Prospective trials evaluating strategies to improve PEM, and provide adequate nutritional support are essential to enhance clinical outcomes, reduce mortality and decrease healthcare costs. Research Sponsor: None.

Effect of PEM on clinical and healthcare outcomes among hospitalized patients with HNC.

Outcomes	HNC with PEM	HNC without PEM	Adjusted Odds Ratio	95% Confidence Interval	P value
Mortality	6.74%	3.67%	1.84	1.73-1.95	<0.001
Length of stay	8.9	5.2	3.33	3.21-3.45	<0.001
Total hospital charge	98,959	71,449	25,715	23,864-27,565	<0.001
Sepsis	10.89	5.08	2.20	2.09-2.30	<0.001
Intubation	15.87	10.01	1.61	1.54-1.68	<0.001
Pressors	1.68	1.03	1.61	1.40-1.86	<0.001
Acute kidney injury	16.89	11.82	1.42	137-1.48	<0.001
Pneumonia	13.97	8.84	01.65	1.58-1.72	<0.001
Neutropenia	4.67	2.5	1.86	1.73-2.00	<0.001
Urinary tract infection	5.70	4.15	1.42	1.34-1.51	<0.001
Blood transfusion	10.19	6.09	1.71	1.63-1.8	<0.001

11065 **Poster Session**

Efficacy of immune checkpoint inhibitors in smokers vs non-smokers: A large real-world retrospective cohort analysis. First Author: Nanda Siva, West Virginia University, School of Medicine, Morgantown, WV

Background: Immune checkpoint inhibitors (ICIs) play a critical role in strengthening the immune response against tumors. Prior literature has shown higher objective response rates of ICIs in lung cancer patients who are smokers vs. non-smokers, thought to be due to increased expression of PD-1/PD-L1 in smokers. This study aims to assess the clinical impact of smoking on the efficacy of ICIs across multiple cancer types. **Methods:** This multicenter retrospective study utilized the TriNetX Network, a database containing over 130 million deidentified patient records to identify patients diagnosed with lung, breast, melanoma, colorectal, head and neck, bladder, hepatocellular, and renal cell carcinomas, who underwent subsequent treatment with ICIs (PD-1, PD-L1, and CTLA-4 inhibitors). Kaplan-Meier survival analysis was performed to assess three-year survivability. Propensity-score matching (PSM) was performed based on demographics, lab work, and pertinent comorbidities between smokers and non-smokers in each cancer type. The analysis included patients who had documented smoking status (ICD 10: Z72.0) prior to ICI therapy. **Results:** A total of 95,178 cancer patients receiving ICI met the inclusion criteria, of whom 15.5% were tobacco users. After PSM, 12,203 patients were in the smoking group and 12,203 were in the non-smoker group. For lung cancer patients, there was statistically significant superior survivability in the smoker group compared to the nonsmoker group, (HR: 0.894, 95% CI [0.854, 0.935]). A similar trend was identified in the colon, hepatocellular, and breast cancer groups, however, this was not statistically significant. There was no significant difference in mortality seen in the smoker versus non-smoker groups in melanoma, bladder, head and neck, and renal cell cancers. **Conclusions:** Our findings reaffirm previous studies demonstrating superior efficacy of ICIs in smokers with lung cancer. Additionally, this study highlights other cancer types, such as colon, hepatocellular, and breast cancers, that may exhibit improved outcomes in smokers, while also identifying cancers such as melanoma, bladder, head and neck, and renal cell carcinomas where smoking status appears to have no apparent effect on survivability. To our knowledge, this is the largest retrospective cohort study examining the impact of smoking status on ICI therapy outcomes across multiple cancer types. Research Sponsor: None.

Survivability in smokers compared to non-smokers treated with ICIs.

Cancer type (ICD 10)	N (smoker)	N (non-smoker)	3-year HR	95% CI
Colon (C18)	292	292	0.808	(0.622,1.048)
Liver (C22.0)	559	559	0.884	(0.748,1.045)
Lung (C34)	8130	8130	0.894	(0.854,0.935)
Breast (C50)	540	540	0.934	(0.756,1.154)
Bladder (C67)	713	713	1.001	(0.856,1.169)
Renal cell (C64)	706	706	1.016	(0.859,1.202)
Head & neck (C76.0)	583	583	1.042	(0.888,1.224)
Melanoma (C43)	680	680	1.087	(0.889,1.328)

11066 **Poster Session**

Identifying multi-level social determinants for disparities in survival and patient-reported outcomes in national head and neck cancer trials. First Author: Jinbing Bai, Emory University Winship Cancer Institute, Atlanta, GA

Background: This study aimed to determine to what extent area-level social determinants of health (SDOH) interact with individual, institutional, and biological factors to predict outcomes in head and neck cancer (HNC) trials. **Methods:** Five NRG Oncology HNC trials (2635 patients receiving chemoradiation) were analyzed. Area-level SDOH coded by patient ZIP codes included rurality (rural-urban commuting area code), neighborhood socioeconomic deprivation (Area Deprivation Index [ADI] categorized as upper vs. lower quartile), and travel burden (distance and time to treatment site). Individual (demographic, cancer and treatment-related factors), institutional (accrual volume), biological (HPV+/-) factors, and outcomes (overall survival [OS], progression free survival [PFS], quality of life [QOL], and symptoms) were analyzed. Multivariable Cox proportional hazards regression and mediation analysis using logistic regression assessed associations using hazard ratio (HR) or odds ratios (OR) and 95% confidence intervals (CI). **Results:** Most patients were White (88%), non-Hispanic (92.7%), of mean age of 57 years, HPV+ (64.6%), and received intensity-modulated radiotherapy (95.9%) and cisplatin (94.2%). ADI and rurality were not associated with OS and PFS. OS and PFS were higher in patients with travel time $<$1 hour (HR=0.85, 95% CI [0.75, 0.98]; HR=0.85, 95% CI [0.73, 0.98]) and travel distance $<$50 miles (HR=0.84, 95% CI [0.72, 0.96]; HR=0.85, 95% CI [0.73, 0.98]). ADI, travel time, and travel distance were not associated with QOL decline. Patients treated at institutions with high rural accrual volume had worse QOL decline from baseline (OR=0.36, 95% CI [0.15, 0.85]). The impact of travel distance but not time varied by race to influence QOL decline (OR=0.38, 95% CI [0.16, 0.93]). ADI was not associated with symptoms, but patients from institutions with high rural accrual volume had worse symptoms (OR=7.83, 95% CI [1.98, 31.01]). HPV status had a significant indirect effect on the relationship between travel distance and survival at 1 year (estimate [β]=0.03, 95% CI [0.01, 0.05]) and 5 years (β=0.03, 95% CI [0.004, 0.05]), as well as a direct and total mediation effect of travel distance on QOL decline at 1 year (direct β=-0.08, 95% CI [-0.16, -0.004]; total β=-0.89, 95% CI [-0.17, -0.01]). **Conclusions:** This study showed the impact of area-level SDOH and their interactions with race and institutional accrual volume, which are associated with survival, QOL, and symptom changes. HPV status potentially mediated the effects of travel distance on outcomes. Our findings provide novel approaches to identify patients at risk for poor outcomes, such as those with travel burden at institutions with high rural accrual, to design community-based interventions to improve cancer outcomes. Research Sponsor: None.

11067 **Poster Session**

Impact of protein energy malnutrition on hospitalized patients with breast cancer: A United States population-based cohort study. First Author: Arshi Syal, Jefferson Einstein Philadelphia Hospital, Philadelphia, PA

Background: Advances in chemotherapeutics and surgical options have improved survival in patients with breast cancer. With prolonged survival, these patients are often predisposed to comorbidities affecting their quality of life. Patients with breast cancer suffer from varying degrees of protein-energy malnutrition (PEM) due to multiple factors, including cachexia, sarcopenia, and adverse effects of chemotherapeutics. However, the impact of PEM on outcomes among patients with breast cancer needs further exploration. **Methods:** We utilized the 2020 National Inpatient Sample (NIS) Database in conducting this retrospective cohort study. We identified patients with breast cancer and PEM using appropriate ICD-10 diagnostic codes. We stratified patients with breast cancer based on the presence or absence of PEM. A survey multivariable logistic and linear regression analysis was used to calculate adjusted odds ratios (ORs) for the primary and secondary outcomes. A p value of $<$0.05 was considered statistically significant. The aim of this study was to investigate the impact of PEM on in-hospital mortality, hospital length of stay (LOS), and total hospitalization charge among hospitalized patients with breast cancer. **Results:** We identified a total of 24770 hospitalized patients with breast cancer, of which 6.17% (1530/24770) had comorbid PEM. The overall in-hospital mortality among patients with breast cancer was 3.37% (835/24770). Among those with concomitant PEM, the mortality rate was significantly higher at 12.74% (195/1530, p$<$0.001). Utilizing a stepwise survey multivariable logistic regression model that adjusted for patient and hospital level confounders, PEM was found to be an independent predictor of increased in-hospital mortality (adjusted OR 2.74; 95% (confidence interval [CI] 1.74-4.30; p$<$0.001), longer LOS (coefficient 3.56 days; CI 2.67-4.45; p$<$0.001), but not higher total hospitalization charge ($4400; CI -$9818-$18620; p=0.544) or increased need for mechanical ventilation (adjusted OR 2.26; CI 0.89-5.69; p=0.084). **Conclusions:** Our analysis demonstrated that PEM was widely prevalent in hospitalized patients with breast cancer and was associated with significantly worsened in-hospital mortality and longer LOS. Efforts should be made to promote nutritional assessment and screening mechanisms to include early nutritional support as indicated. Further prospective studies with larger sample sizes are warranted to understand these associations better. Research Sponsor: None.

11068 **Poster Session**

Incidence and outcomes of rejection in solid organ transplant recipients treated with immune checkpoint inhibitors: A systematic review and meta-analysis. First Author: Muhammad Awidi, Roswell Park Comprehensive Cancer Center, Buffalo, NY

Background: Immune checkpoint inhibitors (ICIs) are a cornerstone in the treatment of many solid tumors; however, their use in cancer patients with solid organ transplants (SOTs) poses unique challenges due to the risk of allograft rejection. We conducted a systematic review and meta-analysis of retrospective studies to determine the incidence of rejection and associated outcomes in SOT patients treated with ICIs. **Methods:** We searched PubMed, Embase, and Scopus to identify retrospective studies examining ICI therapy in SOT patients with cancer. Primary endpoints were the incidence of rejection and its clinical outcomes. Statistical analyses were performed using the "meta" package in R. **Results:** Seventeen studies encompassing 587 patients were included. The most frequent malignancies were hepatocellular carcinoma (HCC), melanoma, and cutaneous squamous cell carcinoma (cSCC). The overall rejection incidence was 16% (95% CI: 9%-24%), with variation across cancer types: multiple cancers (18%, 95% CI: 5%-36%), HCC (22%, 95% CI: 15%-29%), and cSCC (4%, 95% CI: 0%-21%). Rejection incidence was higher among liver transplant recipients (18%, 95% CI: 10%-26%) compared to kidney recipients (16%, 95% CI: 5%-32%). Geographic differences were observed, with rejection rates of 15% (95% CI: 1%-37%) in U.S.-based studies, 25% (95% CI: 18%-33%) in China, and 9% (95% CI: 0%-25%) in Korea. Pre-transplant ICI exposure was associated with a higher rejection rate (18%, 95% CI: 9%-28%) compared to post-transplant exposure (15%, 95% CI: 7%-26%). Outcomes of rejection varied, with 44% (95% CI: 24%-65%) achieving stabilization or resolution. Liver transplant recipients demonstrated higher resolution rates (67%, 95% CI: 46%-85%) compared to kidney recipients (27%, 95% CI: 7%-52%). Regional differences in resolution were notable, with higher rates reported in China (65%, 95% CI: 45%-83%) compared to the U.S. (26%, 95% CI: 13%-42%). **Conclusions:** This meta-analysis reveals a 16% overall rejection rate in SOT recipients treated with ICIs, higher in liver allografts and HCC, with regional disparities. Nearly half of patients who experienced rejection improved or stabilized, especially liver recipients. These findings underscore the need for personalized approaches to balance oncologic efficacy and graft survival in this complex population. Research Sponsor: None.

Category	Rate (% [95% CI])
Overall Rejection Rate	16 [9-24]
Rejection by Cancer Type	Multiple: 18 [5-36], HCC: 22 [15-29], cSCC: 4 [0-21]
Rejection by Transplant Type	Liver: 18 [10-26], Kidney: 16 [5-32]
Rejection by Geography	USA: 15 [1-37], China: 25 [18-33], Korea: 9 [0-25]
Rejection by Timing	Pre-Transplant: 18 [9-28], Post-Transplant: 15 [7-26]
Overall Reversibility	44 [24-65]
Reversibility by Transplant Type	Liver: 67 [46-85], Kidney: 27 [7-52]
Reversibility by Geography	China: 65 [45-83], USA: 26 [13-42]

11069 **Poster Session**

Evaluating the impact of Medicaid expansion on outcomes for patients with gastric cancer in Louisiana. First Author: Donnell White III, School of Medicine, Louisiana State University Health Sciences Center, New Orleans, LA

Background: Prior to June 2016, Louisiana's Medicaid program did not extend coverage to adults, regardless of income. With the expansion, up to 138% of the Federal Poverty Level (FPL) became eligible for enrollment, allowing 784,310 adults to enroll in the state's Medicaid program as of June 2023. Medicaid expansion (ME) effects on gastric cancer treatments and outcomes have not been fully understood. This study seeks to investigate the impact of Medicaid expansion (ME) on gastric cancer outcomes, such as changes in presentation, treatment patterns, time-to-treatment, and survival in Louisiana patients. **Methods:** Patients with primary invasive gastric cancer were identified using the Louisiana Tumor Registry. Patients diagnosed with gastric cancer were stratified into pre-expansion (2012–2015) and post-expansion (2017–2020) periods. Patients under 18 years old, unknown gastrectomy status, and those with unknown insurance or socioeconomic data were excluded from the study. **Results:** A total of 2,554 patients diagnosed with primary invasive gastric cancer were analyzed, predominantly male (63.7%) and urban residents (85.3%). Post-ME, the uninsured rate decreased significantly from 5.5% to 2.2% ($p<0.001$), with the largest reductions observed in younger adults (12.4% to 4.1%; $p<0.001$), Black patients (7.2% to 1.7%; $p<0.001$), rural residents (5.7% to 2.3%; $p<0.001$), and individuals from high-poverty neighborhoods (3rd quartile: 5.6% to 2.6%; p=0.028; 4th quartile: 6.1% to 2.6%; p=0.004). For treatment patterns, chemotherapy use increased for local/regional disease (50.4% post-expansion vs. 47.6% pre-expansion; p=0.038), while gastrectomy rates remained stable (60.3% vs. 56.4%; p=0.119). The median time to treatment increased significantly for local/regional disease (38 days post-expansion vs. 29 days pre-expansion; p=0.031) and metastatic disease (33 days post-expansion vs. 30 days pre-expansion; p=0.184). Survival outcomes showed significant improvement for local/regional disease post-expansion, with 12-month survival increasing from 67.2% to 76.2% ($p<0.001$) and 24-month survival improving from 52.8% to 59.7% (p=0.008). For metastatic disease, 12-month survival improved modestly (30.5% vs. 25.9%; p=0.111), while 24-month survival remained unchanged (12.6% vs. 12.7%; p=0.968). **Conclusions:** Overall, Medicaid expansion reduced uninsured rates and improved access to chemotherapy and survival for local/regional gastric cancer. However, it had a limited impact on late-stage presentation and survival disparities across racial groups. Addressing systemic barriers and optimizing healthcare delivery remains critical to achieving equitable outcomes for gastric cancer patients. Research Sponsor: None.

11070 **Poster Session**

Racial disparities in major adverse cardiovascular and cerebrovascular events outcomes among gastric cancer patients. First Author: Amanda Lussier, New York Medical College/Landmark Medical Center, Woonsocket, RI

Background: Racial disparities in healthcare outcomes represent a critical challenge in achieving equity in gastric cancer care. Gastric cancer, often associated with high morbidity and mortality, also places patients at risk for major adverse cardiovascular and cerebrovascular events (MACCE). This study explores racial disparities in MACCE outcomes among gastric cancer patients using data from the National Inpatient Sample (2016–2021), focusing on differences in mortality, myocardial infarction (MI), arrhythmias, and healthcare resource utilization. **Methods:** A retrospective cohort analysis of the NIS database from 2016 to 2021, identifying adult gastric cancer patients using ICD-10 codes. Demographic and clinical variables, including race/ethnicity, age, sex, income, and hospital characteristics, were analyzed. MACCE outcomes, including mortality, myocardial infarction (MI), atrial fibrillation (A-fib), arrhythmias, and other cardiovascular events, were compared across racial groups. Multivariable logistic regression adjusted for confounders to evaluate the odds of MACCE outcomes and healthcare utilization disparities. **Results:** Among 243,544 gastric cancer patients, the racial distribution included White (53.2%), Black (16.5%), Hispanic (17.3%), Asian or Pacific Islander (7.8%), Native American (0.7%), and Other (4.1%). Significant disparities were noted in MACCE outcomes: Black patients had higher odds of mortality (OR 1.196, $p < 0.001$) and sudden cardiac arrest (OR 2.206, $p < 0.001$) compared to Whites. Hispanic and Asian patients had significantly lower odds of myocardial infarction (OR 0.768, p = 0.011; OR 0.998, p = 0.991, respectively). Atrial fibrillation was significantly less frequent among Black (OR 0.486, $p < 0.001$), Hispanic (OR 0.4, $p < 0.001$), Asian (OR 0.466, $p < 0.001$), and Native American (OR 0.568, p = 0.009) populations compared to Whites. Notably, Hispanic and Asian or Pacific Islander patients had significantly higher total charges (TOTCHG) compared to Whites ($7,945.6 and $13,467.1 higher, respectively, $p < 0.001$). Length of stay (LOS) was significantly longer for Black patients (0.707 days, $p < 0.001$) compared to Whites. **Conclusions:** This study highlights significant racial disparities in MACCE outcomes, mortality, and healthcare resource utilization among gastric cancer patients. Black and Other racial groups demonstrated higher odds of mortality and sudden cardiac arrest, while Hispanic and Asian patients showed a protective effect against myocardial infarction and atrial fibrillation. Disparities in healthcare charges and LOS further emphasize systemic inequities. Addressing these disparities requires targeted interventions to reduce cardiovascular risks and improve healthcare access and equity for minority populations with gastric cancer. Research Sponsor: None.

11071 **Poster Session**

Patient-reported communication and satisfaction in breast cancer: Does doctor-patient identity concordance matter? First Author: Kamaria L. Lee, The University of Texas MD Anderson Cancer Center, Houston, TX

Background: Effective communication is a key element in patient engagement, adherence, and satisfaction. Prior research has shown that doctor-patient race and/or gender concordance may improve both health outcomes and patient satisfaction, however the effects of identity concordance in oncology and specifically within breast cancer are less studied. **Methods:** Between 7/2023-8/2023, cancer survivors were recruited from Breastcancer.org and consented to participate in an anonymous online survey in English or Spanish. Eligibility included: US resident, age $\geq$18, and diagnosed within the past 10 years. Survey assessed patient-reported aspects of communication as well as patient-identified provider race/ethnicity and gender. Chi-square and Fisher's exact tests tested associations between patient and/or provider identity and patient-reported satisfaction with communication. **Results:** Of 997 who completed the survey, 759 reported provider race/ethnicity and gender and were included in this analysis. Patients were median age 63 (range, 32-97), mostly White race (91%) and non-Hispanic (99%); almost all were women (98%). Patients were a median of 3.3 years (1.4-10) post diagnosis. Overall, 60% had concordant gender with their provider. 64% had concordant race; White patients had higher racial concordance 68% (n=470/690) than Black (14%, n=5/35) or Asian/Pacific Islander patients (50%, n=9/18) ($p<0.0001$). 0% of Hispanic patients (n=0/11) had ethnic concordance with their provider. Patients reported high levels (94-97% "usually" or "always") of being treated with courtesy/respect, with no significant differences by identity concordance (either racial, ethnic, or gender concordance). Similarly, they reported their doctors listened carefully (89-98% usually/always) and explained things in a way they could understand (89-98% usually/always), with no differences by concordance. Most patients reported no one talked to them about possible clinical trial options (75% White, 51% Black, 56% Asian patients, p=0.003 comparison), but there were no differences by concordance. There were no significant differences by patient-reported race for questions regarding courtesy/respect, listening, explanations, or discussing clinical trials. Similarly, there were no significant differences by patient-reported provider race or gender. **Conclusions:** In this study of breast cancer survivors, patient-provider identity concordance did not have effects on patient-reported communication. There were no identified differences in communication by race, ethnicity, or gender of patient or provider, although overall satisfaction was very high with limited sample diversity which may stymie capacity for identifying differences. Very few Black and zero Hispanic patients had racial or ethnic concordance with their provider, reflecting known gaps in the oncology workforce. Research Sponsor: AstraZeneca; Pfizer; Biotheranostics Inc. (A Hologic Company); Lilly; MacroGenics; Exact Sciences; Seagen; The University of Texas MD Anderson Cancer Center (Biostatistics Resource Group); National Cancer Institute/U.S. National Institutes of Health.

11072 **Poster Session**

Patient-reported health experiences among US immigrant patients with cancer. First Author: Anh B. Lam, The University of Oklahoma Health Sciences Center, Oklahoma City, OK

Background: Patients often experience complex, multifaceted challenges while navigating cancer care, including many interactions with the health system and care teams. For immigrant patients, language barriers may further complicate their cancer care experience. **Methods:** We used the Medical Expenditure Panel Survey database from 2019-2022 to study patient-reported differences in cancer care experiences based upon immigrant status and speaking another language at home. We extracted data about patient factors (age, sex, race, marital status, poverty levels from reported income, immigrant status [born in the US or not], speaking another non-English language at home) and cancer type for all adults > 18 years with self-reported history of cancer. We compared health experiences (i.e., if provider asks about treatments/medications from other providers, if provider explains all treatment options, includes patient in medical decision-making, delays in medical care) by immigrant status and speaking another language at home using Rao-Scott Chi-square test with person-level survey weight. **Results:** We identified 7,771 patients with cancer (63.4% age 65+, 59.4% female, 82.5% White, 50.6% married). Most common cancers were breast (21.6%) and prostate (15.3%). Overall, 10.3% were immigrants and 11.4% reported speaking another language at home; these patients were more commonly younger, female, Hispanic, less educated, living below the poverty line, and had non-private insurance (table). Immigrant patients were less likely to report a provider asked about other treatments (58.5% v 64.6%, p = .022), explained all treatment options (71.6% v 78.2%, p = .032), and included patient in making medical decisions (38.8% v 45.7%, p = .007). Immigrant patients were less likely to report delays in medical care due to cost (6.1% v 6.9%, p = .022) than patients born in the US. Patients who reported speaking another language at home were less likely to report a provider asked about other treatments (58.6% v 64.6%, p = .015), explained all treatment options (71.7% v 78.2%, p = .017), and included patient in making medical decisions (36.5% v 46.0%, $p < .001$). We found no differences in reporting delays in medical care due to cost (6.6% v 6.9%, p = .059). **Conclusions:** In this national survey study, we found patient-reported health experiences (i.e., discussions about treatment and shared decision-making) differed for immigrants and those speaking another language at home. Findings should inform future work to enhance the cancer care experience in culturally and language appropriate ways for all patients. Research Sponsor: None.

	Immigrant			Speak another language at home		
Patient Factor	**Yes**	**No**	**P**	**Yes**	**No**	**P**
Age 65+	55.7%	64.3%	.004	50.2%	65.1%	<.001
Female	69.3%	58.2%	<.001	67.3%	58.3%	.014
Hispanic	49.3%	5.0%	<.001	66.0%	2.4%	<.001
< Bachelor's Degree	58.2%	55.8%	.001	65.0%	54.8%	<.001
Below Poverty Level	22.8%	14.0%	.001	25.8%	13.5%	<.001
Privately Insured	45.3%	54.6%	<.001	38.1%	55.6%	<.001

11073 **Poster Session**

Factors associated with readmission to index vs. non-index hospitals after major cancer surgery: Does centralization play a role? First Author: Avanish Madhavaram, University of Pittsburgh School of Medicine, Pittsburgh, PA

Background: While centralization of complex cancer surgery at regional referral centers improves perioperative outcomes, many vulnerable patients face barriers in accessing these hospitals. When these patients do manage to undergo surgery at referral centers, it remains unclear where they are readmitted to receive postoperative care when unplanned complications arise. Patients with cancer surgery who are readmitted to the hospital where the surgery was performed (index readmission) often have improved outcomes compared with those readmitted to a different hospital (non-index readmission). This study examined whether factors associated with readmission to index versus non-index hospitals differ for patients undergoing surgery at referral versus non-referral centers. **Methods:** We used data from the Pennsylvania Cancer Registry linked to all-payer statewide inpatient discharge records to identify patients who had surgery for bladder, brain, esophageal, liver, lung and pancreatic cancers between 2013-2019 and were subsequently readmitted within 90 days. We fit a multivariable logistic regression model to identify factors associated with 90-day readmission to an index versus non-index hospital. We included an interaction term between referral center status and cancer type in this model. We defined referral centers as National Cancer Institute-designated cancer centers or American College of Surgeons Commission on Cancer-accredited academic comprehensive cancer programs. **Results:** Of the 28,951 patients with major cancer surgery, 28% (N=8215) were readmitted within 90 days of cancer surgery. Of all patients readmitted, 57% (N=4671) were originally treated at referral centers and 78% (N=6388) were readmitted to the index hospital. On multivariable analysis, factors associated with lower odds of index versus non-index readmission included older age ($\geq$70 years: odds ratio (OR)=0.61; 95% confidence interval (CI), 0.49-0.77, relative to $<$55 years), high Elixhauser comorbidity scores ($>$16: OR=0.74; 95% CI, 0.63-0.88; relative to $<$8), longer travel times ($>$60 minutes: OR=0.12; 95% CI, 0.10-0.15; relative to $<$15 minutes), and Medicaid insurance (OR=0.68; 95% CI, 0.54-0.86; relative to commercial insurance). There was no significant difference in odds of index readmission when patients were treated at referral versus non-referral centers (OR=0.77; 95% CI, 0.50-1.20). When assessing interactions, patients with lung cancer had lower odds of index readmission when treated at referral versus non-referral centers, relative to other cancers (OR=0.59; 95% CI, 0.40-0.89). **Conclusions:** Ongoing centralization may be significantly increasing care fragmentation for patients with lung cancer surgery. Future interventions to improve care coordination after surgery should target patients with higher clinical complexity and greater travel burdens. Research Sponsor: National Cancer Institute; R37CA262366.

11074 **Poster Session**

The association between profitability, clinical benefit, and physicians' selection of cancer drugs. First Author: Aaron Philip Mitchell, Department of Epidemiology and Biostatistics, Memorial Sloan Kettering Cancer Center, New York, NY

Background: Compensation for provider-administered cancer drugs (such as intravenous chemotherapy and immunotherapy) is volume-based and proportional to drug price. Providers receive greater compensation for more expensive drugs. If providers respond to this incentive by selecting more-profitable but clinically less-beneficial treatments, cancer care spending may be increased unnecessarily and care quality may be impacted. The goal of this study was to estimate the association between the billing (profit) margin of cancer treatments and use by oncologists. **Methods:** This was a population-based cohort study using fee-for-service Medicare claims. We included beneficiaries with an incident cancer diagnosis (a new occurrence of a cancer diagnosis code after a >= 1 year washout period) from 2014-2020. The primary outcome was which cancer treatment, among available options, each patient received. The treatment-level characteristics of interest were provider billing margin (using Medicare reimbursement rates) and clinical benefit (using the National Comprehensive Cancer Network Evidence Blocks scores), both measured coincident with each patient's diagnosis date. We included cancer treatment "indications" (e.g., metastatic melanoma, adjuvant therapy for stage III colon) that had variation in both the clinical benefit and billing margin of available treatment options. We modeled the association between treatment received, billing margin, and clinical benefit, including inverse probability-of-treatment weights to control for patient (age, comorbidity, frailty, low income subsidy, regional income and poverty prevalence, rurality) and provider (years in practice, academic setting, patient volume) characteristics. Models were estimated within individual cancer indications, and results were then aggregated via meta-analysis. **Results:** We included 12 cancer indications comprising 19,397 individual patients. Across all treatments for the 12 cancer indications, provider billing margin ranged from $0-$12,692 per course of treatment. There was no association between a $100 increase in provider billing margin and likelihood of treatment use (OR 0.97, 95%CI: 0.91-1.03). Higher clinical benefit was associated with greater treatment use (OR 1.62, 95%CI: 1.15-2.29). These findings were unchanged in sensitivity analyses applying different methods for billing margin calculation, measurement of clinical benefit, and weighting. **Conclusions:** In this observational study of Medicare beneficiaries, selection of cancer treatments was associated with treatment clinical benefit but not billing margin. Restated, oncologists preferred more beneficial treatments but not more profitable ones. These results suggest that changes in the billing margin of cancer treatments may be unlikely to shift utilization patterns. Research Sponsor: The Commonwealth Fund; Arnold Ventures; The National Cancer Institute.

11075 **Poster Session**

Use of low-value cancer treatments in Medicare Advantage versus traditional Medicare. First Author: Aaron Philip Mitchell, Department of Epidemiology and Biostatistics, Memorial Sloan Kettering Cancer Center, New York, NY

Background: Medicare Advantage (MA) has steadily grown during the past decade, covering over half of Medicare beneficiaries in 2024. Because MA plans receive capitated payments for Medicare beneficiaries, they have the financial incentives to reduce service utilization and costs. MA plans may discourage enrollees from using low-value services, such as medically unnecessary care and expensive treatments for which low-cost alternatives are available. No prior study examining the use of low-value services between MA and TM has evaluated the use of low-value cancer treatments specifically. We compared use of low-value cancer treatments between MA and TM. **Methods:** Using national Medicare data, we performed retrospective analyses of beneficiaries who had a new cancer diagnosis between 2016 and 2021, and who were at risk of receiving one of the following low-value treatments: growth factors (GCSF) for patients receiving low-risk chemotherapy; denosumab for castration sensitive prostate cancer (CSPC); nab-paclitaxel instead of paclitaxel for breast or lung cancers; adding bevacizumab to carboplatin + paclitaxel for ovarian cancer; and branded drugs or biologics for which generic or biosimilar versions existed. We estimated linear regression models for each cohort/outcome separately. The key explanatory variable was MA enrollment (vs. TM). We used inverse probability of treatment weights to balance characteristics between MA and TM: patient age, sex, race, Medicare and Medicaid dual-eligibility status, cancer metastasis, a frailty index, and summary health-risk scores, area-level socio-economic and health care environment variables. We included year indicators to adjust for temporal trends and oncology practice indicators to control for practice-specific prescribing patterns. **Results:** Receipt of any low-value cancer treatment was 1.7 percentage points lower in MA than in TM (34.2% versus 35.9%; $p<0.001$). MA enrollees had lower utilization than TM for GCSF (7.3% versus 8.9%; $p<0.001$), denosumab (26.4% versus 33.1%; $p<0.001$), nab-paclitaxel (7.9% versus 8.7%; $p<0.05$), addition of bevacizumab for ovarian cancer (8.3% versus 10.5%, p=0.001), and biologics with biosimilar alternatives (66.8% vs. 68.5%; $p<0.001$). Receipt of branded drugs did not significantly differ between MA and TM. **Conclusions:** For Medicare beneficiaries at risk of receiving a low-value cancer treatment, MA enrollees were less likely to receive low-value cancer treatments than TM beneficiaries. These reductions in low value services may prevent avoidable toxicity and lower treatment cost to the patient and health care system. Increased efforts are needed to identify approaches that MA plans use to reduce low-value cancer treatments, and explore ways to promote those approaches in both MA and TM. Research Sponsor: National Institute of Aging; The Commonwealth Fund; Arnold Ventures; The National Cancer Institute.

11076 **Poster Session**

Longitudinal changes in credit status for newly diagnosed metastatic colorectal cancer patients (SWOG S1417). First Author: C. Natasha Kwendakwema, Fred Hutchinson Cancer Center, Seattle, WA

Background: We previously reported that 71% of insured patients with newly diagnosed metastatic colorectal cancer (mCRC) self-reported major financial hardship (MFH), defined as one or more of increased debt, new loans from family and/or friends, selling or refinancing a home, or 20% or more income decline, within 12 months of diagnosis. In this secondary analysis using credit data, we examined if enrolled patients experienced changes in credit status over time. **Methods:** Depersonalized credit data were obtained from TransUnion, one of the largest credit agencies in the United States, at enrollment, 6, and 12 months. Patients with a baseline and at least one follow-up credit record were analyzed. Demographic data were obtained from questionnaires at enrollment. We determined the mean number or proportion of patients with adverse credit events (defined as past due or delinquent credit cards or mortgage payments, third-party collections, tax liens, charge-offs, bankruptcies, foreclosures, or repossessions) and the mean past due credit card amount, if applicable, at baseline and follow-up. We used paired t-tests to compare credit characteristics between baseline and follow-up in the entire cohort and in subgroups with and without MFH. Multivariate logistic regression was used to identify factors associated with adverse credit events. **Results:** 318 patients were analyzed (median age 59.1, 41% female, 80% white, 59% married, 42% with private health insurance). Approximately 3.4% of patients experienced a new adverse credit event during the study period, 143 (45.0%) patients at baseline and 154 (48.4%) at follow-up (p=0.07). Overall, new adverse credit events were uncommon and only third-party collections significantly worsened over time (mean 3.20 (SD 3.17) at baseline and mean 4.11 (SD 3.85) at follow-up; $p < 0.001$). Charge-offs numerically increased over time, but the value did not reach significance. On average, past due amounts on open credit cards increased over time ($100.60 at baseline and $291.33 at follow-up), with the increase largely seen among patients self-reporting MFH. Adverse credit events were more likely to worsen in patients who were younger (OR 2.51, CI 1.08-5.84), had lower household income (OR 3.09, CI 1.07-8.92), lower educational status (OR 2.07, CI 1.10-3.88), and fewer assets, defined as less than $100,000 (OR 4.15, CI 1.58-10.91). **Conclusions:** Despite high levels of self-reported MFH in this cohort, credit data showed no significant increase in adverse credit events between baseline and follow-up, except for increased third-party collections and total past due credit card balances. This may be due to credit reports capturing only more severe financial impacts or because the impacts of financial hardship take longer to be reflected in credit reports. A future study will examine how patients leverage credit, such as applying for new credit cards or reaching credit limits. Research Sponsor: ASCO Career Development Award (2013); Hope Foundation Charles A. Coltman Jr. Award (2012).

11077 Poster Session

Association of county-level medical debt and timely treatment initiation among individuals newly diagnosed with cancer. First Author: Jingxuan Zhao, American Cancer Society, Atlanta, GA

Background: Medical debt is associated with adverse cancer outcomes, including poor survival. However, it is unknown if living in a county with high medical debt is associated with treatment initiation. We examined the association of county-level medical debt and timely treatment initiation among individuals newly diagnosed with cancer. **Methods:** We identified adults aged ≥19 newly diagnosed with cancer from the 2012-2021 Colorado Central Cancer Registry linked to the Colorado All-Payer Claims Database, which were combined with data on county-level share of adults with medical debt in collections. We used Cox proportional hazard models to examine the associations of county-level medical debt and receipt of any treatment within 90 days after cancer diagnosis overall and by selected cancer sites (acute leukemias, lymphomas, breast, colorectal, and lung cancers) and health insurance coverage, adjusting for individual sociodemographic characteristics. P-trend was calculated using medical debt quartile as a continuous variable in the models to examine dose-response associations. **Results:** Among 35,789 individuals newly diagnosed with cancer, individuals living in counties with the highest share of adults with medical debt in collections (Quartile 4 (Q4)) had lower likelihood of initiating treatment within 90 days after diagnosis compared to those living in counties with the lowest share of adults with medical debt (Q1), adjusting for covariates (HR: Q4 vs Q1: 0.93, 95% confidence interval: 0.90-0.97, P-trend < 0.001). When stratified by cancer site, higher county-level medical debt was associated with lower likelihood of timely treatment initiation among individuals diagnosed with lymphoma (HR: Q4 vs Q1: 0.82 (0.69-0.98), P-trend = 0.022) and female breast cancer (HR: Q4 vs Q1: 0.90 (0.85-0.94), P-trend < 0.001). When stratified by insurance, higher county-level medical debt was associated with lower likelihood of timely treatment initiation among individuals aged 19-64 years with private fee-for-service (FFS) plans (HR: Q4 vs Q1: 0.88 (0.78-0.98), P-trend = 0.011) and individuals aged ≥65 years with Medicare FFS plans (HR: Q4 vs Q1: 0.90 (0.82-0.98), P-trend = 0.007). **Conclusions:** County-level medical debt in collections was associated with delays in treatment initiation among individuals newly diagnosed with cancer. Policies aimed at preventing and alleviating medical debt could be effective strategies for improving access to timely cancer treatment. Research Sponsor: Leukemia and Lymphoma Society; HSR9027-24.

11078 Poster Session

Association between cost and insurance on receipt of guideline-concordant mammography. First Author: Nicole E. Caston, The University of North Carolina at Chapel Hill, Chapel Hill, NC

Background: Many organizations offer mammography guidelines with slight differences, which can serve as a barrier to receiving a mammogram. Furthermore, it is unknown how both cost and insurance serve as a barrier to receiving a mammogram. Therefore, our study explored the associations between cost and insurance on guideline-concordant mammography. **Methods:** This cross-sectional study used 2023 National Health Interview Survey data. Inclusion criteria included women eligible for a mammogram. The outcome was receipt of guideline-concordant mammography and was based on women following 2016 US Preventive Services Task Force or current American Cancer Society guidelines for age and frequency requirements. The exposures of interest included report of at least one healthcare-related cost issue (yes, no) and insurance status (uninsured, insured). Questions for healthcare-related cost issue included: in the past 12 months did you, 1) have problems paying or were unable to pay medical bills, 2) delayed medical care due to cost, & 3) did not get necessary medical care due to cost. We estimated odds ratios (OR) and 95% confidence intervals (CI) using logistic regression to assess the interaction between cost issues and insurance status on receipt of guideline-concordant mammography. The model controlled for age at survey completion, race and ethnicity, Rural-Urban Classification Scheme, income to poverty ratio, and personal & family history of breast cancer. **Results:** A total of 13,529 women were included. Mean age was 55 years, 63% were non-Hispanic White, 10% were in poverty. About 1 in 4 had not received guideline concordant mammography. When compared to those who had received a guideline-concordant mammogram, individuals who did not have a mammogram were younger (p-value: <.0001), uninsured (<.0001), and had reported at least one cost issue (<.0001). In our adjusted analysis, we found that the uninsured, regardless of cost issue, had lower odds of receipt of guideline-concordant mammography (Table). Among insured individuals, those who did vs did not report a cost issue had 0.68 (95% CI 0.59-0.77) times the odds of receipt of a guideline-concordant mammogram. **Conclusions:** By interacting cost issues and insurance status, we found that individuals with health insurance and issues paying for care had low prevalence of guideline-concordant mammography. This is important when determining how best we can provide screening for those in need. We recommend that screening services that offer free or low-cost mammograms include women who have health insurance and report healthcare-related cost issues. Research Sponsor: None.

Model results (N=13529).

	OR (95% CI)
Healthcare-related cost issue	
Uninsured vs insured	**0.59 (0.43-0.81)**
No healthcare-related cost issue	
Uninsured vs insured	**0.46 (0.35-0.60)**
Uninsured	
Healthcare-related cost issue vs none	0.87 (0.60-1.27)
Insured	
Healthcare-related cost issue vs none	**0.68 (0.59-0.77)**

11079 Poster Session

Shifts in Medicare spending for patients with cancer undergoing chemotherapy following implementation of the Maryland Global Budget Revenue program. First Author: Yu-Li Lin, University of Texas MD Anderson Cancer Center, Houston, TX

Background: In January 2014, the statewide Maryland Global Budget Revenue (GBR) model was implemented to control the growth in total hospital spending and improve the quality of care. Specific impacts of GBR on cancer-related spending are not fully understood. This study aimed to 1) quantify the impact of GBR on Medicare spending for beneficiaries undergoing chemotherapy for cancer and 2) investigate any shift in such spending during GBR to non-hospital settings. **Methods:** Using 2011-2018 Medicare claims from Maryland and a control set of 11 comparable states, we constructed 6-month chemotherapy episodes. Propensity matching was used to identify appropriate comparison episodes based on treatment year, patient demographic, clinical, and area-level characteristics. Using a difference-in-differences (DiD) approach, we evaluated the impact of GBR on standardized total Medicare payments and non-hospital professional payments during the episode, after confirming the parallel trends assumption during GBR's pre-period (2011-2013). **Results:** Among 42,206 and 708,486 chemotherapy episodes in Maryland and control states, respectively, we studied 42,199 episodes in Maryland matched to 42,199 episodes in control states. Our analysis showed that GBR's implementation led to smaller increases in total episode payments over time relative to control states and larger increases in non-hospital professional payments (Table); these impacts notably varied with time. **Conclusions:** Our finding of smaller increases in total Medicare payment for a 6-month chemotherapy episode in Maryland versus control states indicates that GBR's intended reductions on the spending growth in the context of cancer patients undergoing chemotherapy were actualized. Importantly, larger increases in non-hospital professional payments suggest these savings may have been attained via shifts in sites-of-care following GBR's implementation. Further studies evaluating the effects of these shifts on cancer care quality are warranted. Research Sponsor: U.S. National Institutes of Health.

Adjusted mean standardized payments in 2018 dollars during 6-month chemotherapy episodes and DiD estimates versus 2013.

	Total payments			Non-hospital professional payments		
Year	Adjusted Mean, Maryland	Adjusted Mean, Control states	DiD	Adjusted Mean, Maryland	Adjusted Mean, Control states	DiD
2013	$54,213	$52,659	Ref	$22,876	$14,844	Ref
2014	$54,522	$53,476	-$759	$21,261	$14,327	$828
2015	$55,355	$55,426	-$2,001	$22,249	$14,186	$1,433*
2016	$58,599	$59,331	-$2,940*	$24,314	$14,922	$1,286
2017	$61,141	$60,462	-$1,561	$27,954	$15,330	$3,612*
2018	$62,329	$64,756	-$4,853*	$27,969	$15,356	$2,753*

*p<0.05. The adjustment methodology accounted for patient demographic, clinical and area-level characteristics, and time-varying Hospital Service Area (HSA) level variables. For the DiD analysis, HSA fixed effects were also included.

11080 Poster Session

Insurance coverage of germline genetic testing for ovarian, pancreatic, and early-onset colorectal, endometrial, and breast cancers, stratified by self-reported race and ethnicity. First Author: Erica M. Vaccari, Labcorp, San Francisco, CA

Background: Universal germline genetic testing (GGT) for patients with ovarian (OV), pancreatic (PANC), and early-onset colorectal, endometrial cancer, and breast cancer (CRC <50, ENDO <50, and BR ≤50) is the medically necessary standard of care per clinical guidelines and many payer medical policies. Individuals with multiple cancers, diagnosed at any age (MULTI), also commonly meet these guidelines for GGT. We report a single national laboratory experience with GGT coverage for these indications. **Methods:** Patients with GGT between 6/1-12/31/2023 from a commercial laboratory were stratified by cancer type (using ICD-10s), age at testing, and self-reported race and ethnicity. We assessed differences in coverage rates, frequency and types of denial codes (technical and clinical denials), and appeal success across cancer types. Reported p-values are from G-Tests of independence, only groups containing at least 100 individuals were retained in statistical tests. **Results:** We reviewed 12,304 patients with cancer, 19% with OV, 29% with PANC, 13% with CRC <50, 2% with ENDO <50, 26% with BR ≤50, and 9% with MULTI. Of all patients, GGT was not covered for 31%, including 29% of OV, 27% of PANC, 35% of CRC <50, 39% of ENDO <50, 35% of BR ≤50, and 27% of MULTI. Of all cases with no coverage for clinically indicated GGT, 30% had clinical denial codes (e.g. medical necessity, non-covered services, experimental), 68% had only technical denial codes, and 2% had no denial codes. Overall, appeals were successful in 32% of cases, including 27% of OV, 25% of PANC, 44% of CRC <50, 39% of ENDO <50, 33% of BR <50, and 22% of MULTI. The proportion of cases with coverage differed significantly by self-reported race and ethnicity (58%-81%, p <0.00001), with Black and Hispanic individuals being less likely to be covered in comparison to Ashkenazi Jewish, Asian, and White individuals. Whereas the proportion of those receiving denial codes differed between self-reported race and ethnicity groups (p <0.00001), the percentages of technical vs. clinical denial codes received did not (p = 0.56). **Conclusions:** Despite clinical guidelines and payer medical policy affirming the medical necessity of universal GGT in these cancer types, these data demonstrate that 30% of patients did not receive coverage for standard of care GGT, and was lower in traditionally under-represented groups. Denials overturned on appeal suggest those cases should not have been denied initially. These data suggest that coverage denials are a substantial obstacle to medically necessary GGT for patients with cancer despite clinical practice guidelines. Research Sponsor: None.

11081 **Poster Session**

Longitudinal risk of physical functional impairment and health care utilization in cancer survivors within 3 years of diagnosis. First Author: Ann Marie Flores, Northwestern University Feinberg School of Medicine, Chicago, IL

Background: Despite known physical functional (PF) impairment in cancer survivors, patterns of its development and relationships to healthcare utilization remain poorly characterized. We examined PF impairment trajectories among outpatient cancer survivors in a large Midwestern academic health care system during the first three years after a new cancer diagnosis. We hypothesized that PF impairment would be common, vary by extent of disease, cancer care phase, with differing patterns of rehabilitation services (RS) referral, emergency department (ED) and cancer center urgent care (CCUC) visits. **Methods:** We included 2,254 adults with a cancer diagnosis, treated in medical oncology clinics, and completed 2 or more Patient Reported Outcome Measurement Information System – Physical Function (PROMIS-PF) surveys within a 3-year period. A PROMIS-PF T-score $<$ 40 represents moderate – severe impairment. We used group-based trajectory modeling (GBTM) to identify patterns of impairment likelihood (0.7 threshold for accurate fit) in the 3 years after cancer diagnosis. Trajectory models identified the demographic profile, cancer type, stage, and treatment intent (intent to cure, non-intent to cure, other) most associated with each trajectory. We assessed trajectory associations with rates of RS referrals, and visits to ED and CCUC during the study period with multiple logistic regression ($p<.05$). **Results:** On average, participants were newly diagnosed within 11 months (s.d. 10.92) before enrollment in the study. We determined 4 PF impairment trajectory patterns during the first 3 years after a cancer diagnosis: (1) low probability of impairment which remained steady over time ("Low Steady", 64% participants); (2) decreasing probability ("Decreasing", 13%); (3) increasing probability ("Increasing", 9%); (4) high probability of PF impairment that remained high ("High Steady", 14%). Patients in trajectories 2, 3, and 4 were significantly more likely to have ED and/or CCUC visits and receive RS referrals than those in trajectory 1, although differences by cancer type, stage, and Beacon module between groups 2 – 4 were mixed. **Conclusions:** Over one-third of cancer survivors experienced substantial impairment and 14% had persistent, severe impairment with higher rates of RS referrals, ED and CCUC visits. These patterns had few variations by tumor type and cancer care phase. Our data suggest that patients in Trajectories 2 – 4 should be targeted for early and frequent monitoring with PROMIS-PF and referral for rehabilitation services to address impairments –ideally within the first six months after cancer diagnosis. PROMIS-PF effectively identified impairment variation across patients and time. Future studies will explore whether screening and triaging for appropriate cancer rehabilitation referral and intervention improve impairment trajectories. Research Sponsor: National Cancer Institute/U.S. National Institutes of Health; UM1CA233035; National Cancer Institute/U.S. National Institutes of Health; 3UM1CA233035-01S1.

11082 **Poster Session**

Addressing disparities by implementing a supportive care program in oncology. First Author: Emily Meichun Ko, Division of Gynecologic Oncology, University of Pennsylvania, Philadelphia, PA

Background: Financial toxicity, transportation needs, and emotional strain are known barriers to receipt of cancer care and cause for disparities in cancer outcomes. We sought to evaluate the implementation of a supportive care program (SCP) on the delivery of cancer care, its associated health care utilization outcomes and cost. **Methods:** From May 2022-Nov 2024, SCP included a standardized social determinant of health (SDOH) screening tool, financial navigation, transportation ridesharing, and peer-support program in the 5 gynecologic oncology practices within a NCI Comprehensive Cancer Center. Patients were referred through the SDOH screener or usual clinical care referrals. We report descriptive statistics on the mechanism for referral for SCP, associated health care utilization, and costs. We assessed differences in SCP financial and transportation sub-groups with bivariable non-parametric testing (p-value$<$ .05 considered statistically significant). **Results:** Of 7159 patients encompassing 22041 encounters, 259 received SCP (41 financial navigation, 177 transportation, 3 transportation + financial navigation, 18 peer-support program). Only 73 (28.7%) were referred through the SDOH screening tool, and the rest through usual clinical care. Most SCP recipients (60.6%) were Black/Asian/Other, in contrast to our general clinical population (63% White). Only 65 (25.6%) of SCP patients were employed, and 72.8% had Medicare or Medicaid. Nearly all SCP patients resided in the MidAtlantic tristate area. Patients receiving financial navigation were younger ($p<0.001$), more likely to be privately insured ($p<0.001$), and less likely to reside in the metropolitan area (43.9% v. 63.8%, p=0.05) compared to those receiving transportation. A total of 1770 rides were completed, costing $51885.20 which included the ride and administrative scheduling fee. A total of 14 SCP participants were clinical trial participants; of these, 78.6% utilized transportation assistance. Following receipt of SCP, the total scheduled visits for SCP patients included 7768 visits. Patients receiving transportation assistance had higher rates of unplanned admission (43.5% v. 22.0%, p=0.011), and no-show rates (4.6% vs 1.2%, $p<0.001$) compared to those receiving financial navigation. **Conclusions:** Our SCP served primarily racial-minority and publicly insured patients. Only 25% were employed during active cancer treatment. Transportation was the most frequently used SCP service, including by our clinical trial participants. Patients with transportation needs had higher rates of unplanned admissions and no-shows than those receiving financial navigation. Financial toxicity affected younger patients including those privately insured. SCP facilitates cancer care delivery, but requires infrastructural development, substantial investment in resources, and further analyses of health care utilization, outcomes and cost. Research Sponsor: Ovarian Cancer Research Alliance; HEG-2024-2-1774.

11083 **Poster Session**

Evaluating a patient ambassador program to improve clinical trial knowledge and intent to discuss gynecologic oncology trials. First Author: Emily Meichun Ko, Division of Gynecologic Oncology, University of Pennsylvania, Philadelphia, PA

Background: To evaluate the implementation of a pilot patient-ambassador program to provide peer-to-peer clinical trial education aimed at increasing awareness, knowledge, and intent to discuss gyn oncology (GYO) trials in trial-naïve patients. **Methods:** We conducted a mixed-methods interventional behavioral study at an urban-metropolitan NCI comprehensive cancer center to evaluate the implementation of a program for initiating "chats" about GYO clinical trials. From Feb-Oct 2024, we recruited patients as "ambassadors" who previously participated in a GYO clinical trial. Ambassadors underwent training via an educational curriculum and then were paired with 5-7 "mentees," who were trial-naïve patients with high-risk or advanced gyn cancer. Outcomes assessments included post-chat quantitative surveys using the acceptability and feasibility of intervention measures (AIM & FIM), net promoter score (NPS), and change in clinical trials knowledge score. Qualitative analyses of open-ended survey responses, dyad "chat" recordings, and feedback from ambassadors at training, mid-program and exit interviews were completed by two coders using a modified content analysis approach. Chi-square test and t-tests were applied with $p<0.05$ considered significant. IRB exemption obtained (IRB #: 854317). **Results:** 3 ambassadors and 20 mentees completed the program, resulting in 20 "chats" from a pool of 266 eligible mentees. On the pre-chat survey, 90% of mentees reported they had previously heard of clinical trials and 75% of mentees reported they perceived trials as somewhat/very positive. Post chat, 90% of mentees reported their perception of trials as somewhat/very positive, 85% felt the chat changed their view of trials, and 95% felt confident to ask their oncology provider about trials. Participants reported high acceptability, feasibility, and program promotion, but no increase in knowledge (table). Qualitative themes of barriers to trial participation included misconceptions of trial types and inability to withdraw, and fear of side effects, and cost. Facilitators included desire to help humanity and hope for new treatments. Implementation concerns included emotional strain on ambassadors, mismatched ambassador-mentee expectations, and ambassadors' variability in discussing recruitment of diverse populations. **Conclusions:** This pilot patient-ambassador program is a feasible, acceptable, and highly promoted intervention to increase patients' confidence in discussing and intent to ask oncology providers about clinical trials. Research Sponsor: Robert A. Winn Diversity in Clinical Trials Award Program; National Cancer Institute; P50CA228991.

Outcomes	Mentee		Ambassador	
(mean, SD)	Pre chat	Post chat	Pre chat	Post chat
Knowledge Survey (%)	74.17 (13.22)	77.08 (16.42)	83.33 (16.67)	83.33 (14.43)
AIM*	-	4.29 (0.74)	-	5.00 (0.00)
FIM*	-	4.18 (0.74)	-	4.92 (0.14)
NPS*	-	8.90 (2.47)	-	10.00 (0.00)

*AIM and FIM (Scale 1-5). NPS (Scale 1-10).

11084 **Poster Session**

The state of the oncologist workforce in America in areas prone to natural disasters. First Author: M. Kelsey Kirkwood, ASCO, Alexandria, VA

Background: Natural disasters are increasingly common in the U.S., causing significant localized disruptions to cancer care. The American Society of Clinical Oncology (ASCO) examines the supply of and demand for cancer services in areas prone to natural disasters to support emergency preparedness planning, response, and recovery. **Methods:** We tabulated the number of U.S. hematologists and medical oncologists by county from Medicare Care Compare (March 2024 data). Demand for cancer services was approximated using 2017-2021 average annual counts of new cancer cases by county from State Cancer Profiles. We extracted US Climate Vulnerability Index county rankings for extreme flooding, storm, and wildfire events, as well as for community resilience (derived from health, social, economic, infrastructure, and environmental measures). We defined "high-risk" counties as those with the highest decile rankings for extreme flooding, storm, and/or wildfire events across all U.S. counties and determined the share of U.S. oncologists and people with incident cancer in those areas. We also identified oncologists and patient populations in counties adjacent to high-risk counties who might be affected. Among high-risk and adjacent counties, we further isolated those ranked in the highest quartile for baseline vulnerability (i.e., low community resiliency). **Results:** Of 1.7M people with newly diagnosed cancer in the U.S., a majority (65%, 1.1M) lived in proximity to counties at high-risk for extreme flooding, storms, and wildfires (642K people from 886 counties designated high-risk and 479K from 716 adjacent counties). Similarly, most oncologists (65%, 9,471 of 14,547) practiced in proximity to high-risk counties (5,501 oncologists in top ranked counties, 3,970 in adjacent counties). When factoring in community resilience, 325 counties at or adjacent to high-risk for extreme weather events also ranked highest for baseline vulnerability: 14% of oncologists (n=2,036) worked in these counties, where 13% of people with incident cancer lived (226K). **Conclusions:** ASCO has recommended that health systems create geographically appropriate plans for natural disasters. Our analysis indicates that most oncologists and most patients in the U.S. are in or adjacent to areas prone to natural disasters, and that many people at risk reside in counties with low community resilience. Practice-level emergency preparedness for response and recovery from natural disasters, including patient referrals and minimization of treatment disruptions, informed by community-specific needs, should be pursued on a broad scale. Additional planning is needed at all levels of the health care system and government to meet this substantial and potentially growing need for crises planning in cancer care. Future research could focus on other types of disasters and on global impacts. Research Sponsor: None.

11085 **Poster Session**

Influenza and COVID-19 vaccination uptake among cancer survivors in the US. First Author: Ted Akhiwu, MedStar Health Georgetown University, Baltimore, MD

Background: Cancer survivors are at increased risk of comorbidity and mortality from respiratory viral infections including influenza (flu) and COVID-19 and therefore, vaccinations against these viruses are important for their health. Little is known about the receipt of these vaccines among cancer survivors in the post-COVID era. This study sought to evaluate the uptake of flu and COVID-19 vaccinations between cancer survivors and the general population in the US. **Methods:** We analyzed cross-sectional data from the 2023 National Health Interview Survey that used multistage probability sampling to interview US adults. Adults with a history of cancer were defined as cancer survivors, and those without a history of cancer were the general population. Flu vaccination receipt was defined as having had a flu shot in the past 12 months. COVID-19 vaccination receipt was defined as having received ≥2 doses of the COVID-19 vaccine. Weighted proportions were compared using Rao-Scott Chi-squared tests. Weighted logistic regression was conducted, adjusting for demographic and socioeconomic factors. Adjusted odds ratio (AOR) and 95% CIs were calculated. All analyses accounted for complex survey design and weights. **Results:** The total sample size was 29,522, representing a weighted sample of 258,237,552 adults in the US. The mean age was 48 years; 61.9% were White, followed by 17.5% Hispanic, 11.8% Black, and 8.8% Asian or Other; and 9.7% were cancer survivors. Overall, 73.7% (95% CI: 72.9-74.5%) received ≥2 doses of COVID-19 vaccinations, and 48.0% (95% CI: 47.1-48.8%) had a flu shot in the past 12 months. Compared to the general population, higher proportions of cancer survivors received COVID-19 vaccinations (84.8% [95% CI: 83.5-86.3%] vs 72.5% [95% CI: 71.6-73.4%], $P<0.001$) and a flu shot (67.3% [95% CI: 65.5-69.1%] vs 45.8% [95% CI: 45.0-46.7%], $P<0.001$). After covariate adjustment, cancer survivors had greater odds of having received COVID-19 vaccinations than the general population (AOR 1.38, 95% CI: 1.22-1.56). Cancer survivors also had greater odds of having had a flu shot than the general population (AOR 1.35, 95% CI: 1.23-1.49). Additionally, we found that male sex, lack of insurance or public insurance, and rural residence were associated with lower odds of having received either vaccine. **Conclusions:** In this US national adult sample, COVID-19 and flu vaccination uptakes were higher among cancer survivors than in the general population. Although this is encouraging, vaccination rates, particularly with the flu vaccine, remain below the 70% Healthy People 2030 goal. To achieve this goal, tailored interventions and policies are necessary to improve vaccine uptake and socioeconomic disparities across cancer survivors and the general population.Future research can explore how the receipt of the vaccines impact the quality of life and health outcomes of the growing population of cancer survivors. Research Sponsor: Susan G. Komen Breast Cancer Foundation; TREND21675016; National Institute on Aging; T32AG000243.

11087 **Poster Session**

The implications of using truncated Medicare definitions of avoidable hospital visits. First Author: Pranathi Pilla, UT Southwestern Medical Center, Dallas, TX

Background: As part of the Outpatient Quality Reporting program, Medicare reports on potentially avoidable, acute hospital visits after chemotherapy, using only fee-for-service (FFS) claims. This measure aggregates emergency department visits, observations, and inpatient admissions for 10 avoidable conditions (e.g. pain, vomiting), within 30 days of a chemotherapy infusion and is known as the OP-35 measure. The literature largely applies the diagnosis codes without reference to chemotherapy: it can be impractical to apply clinic-level changes only to Medicare FFS enrollees, and large, nationally-representative, hospital visit datasets do not contain chemotherapy infusion dates. There has been little scrutiny of the implications of using such truncations of this policy tool. **Methods:** We used a population-based cohort of incident cancers (2015-2023) from two sites: an academic medical center and safety-net health system, identifiably linking patients to their comprehensive hospital use from a regional health information exchange (all non-federal hospitals within a 150-mile radius of Dallas, TX). We tracked the changes in avoidable hospital visits for each measure specification: using diagnosis codes alone; narrowing to within 30 days of chemotherapy; counting only the first visit in a 30-day span; narrowing to Medicare FFS. We used mixed-effects (clustered to patient) multivariate logit to model avoidable visits occurring within or outside of a chemotherapy 30-day window; and avoidable vs. non-avoidable hospital visits across payors, adjusting for clinical and demographic variables. **Results:** We linked 31,305 incident cancer diagnoses (mean age 64; 50.6% female; 57.7% Black or Hispanic; 23.6% advanced stage cancer; 19.2% gastrointestinal cancer, 12.2% breast, 9.2% lung) to 190,967 visits across 76 hospitals. Although 28.0% (n= 54,233) had an avoidable diagnosis coded, only 24.3% (n=13,179) of them were within 30 days of chemotherapy. After excluding multiple visits in the 30-day span, 9.1% (4,917 of the 54,233 avoidable conditions visits) remained, with 14.0% (n=689, or 1.3% of 54,233) under Medicare FFS (1.6% Medicare Advantage, 30.2% commercial, and 54.4% uninsured/Medicaid). In adjusted analyses, avoidable conditions were significantly more likely to occur within 30 days of chemotherapy than outside of it (aOR 1.34, 95% CI: 1.27-1.40, $p < 0.001$); and compared to Medicare FFS, commercially-insured encounters had higher odds of avoidable hospital visit (aOR 1.31, 95% CI: 1.12–1.50, $p < 0.001$). **Conclusions:** Three-quarters of hospital visits for avoidable conditions occurred outside of a 30-day span after chemotherapy, though in adjusted analysis, avoidable visits were more likely to occur after chemotherapy. As little as 1.3% of visits for avoidable conditions were captured by the Medicare definition. Further investigation of the best uses of this measure is warranted. Research Sponsor: U.S. National Institutes of Health; CA282242.

11088 **Poster Session**

United States treatment pattern response to carboplatin and cisplatin shortages. First Author: John Kent Lin, Department of Health Services Research, The University of Texas MD Anderson Cancer Center, Houston, TX

Background: In response to cisplatin (2/10/23) and carboplatin (4/28/23) shortages, national guidelines recommended prioritizing cisplatin and carboplatin for their most important indications to preserve availability while maximizing survival outcomes. We examined the real-world response to recent platinum shortages in lung cancers (LC), for which guidelines recommended preserving platinum chemotherapies when non-metastatic versus allowing substitution to immunotherapy monotherapy when metastatic. **Methods:** Using IQVIA PharMetrics data (9/1/22-10/31/23), we developed claims algorithms to identify intravenous anticancer therapy infusion claims for patients with incident non-metastatic vs. metastatic LC, which we validated against SEER-Medicare. Our outcomes were the fraction of infusions containing either (1) cisplatin, (2) carboplatin, or (3) immunotherapy (IO) without platinum. We performed an interrupted time series (ITS) analysis, using a linear probability model with three time-periods: pre-platinum shortage (9/1/22-1/31/23), post-cisplatin shortage (2/1/23-4/30/23), and post-carboplatin shortage (5/1/23-10/31/23), adjusting for age, gender, region, and comorbidities. **Results:** There were 11,983 infusions (2,411 patients) and 1,650 infusions (428 patients) for incident non-metastatic and metastatic LC, respectively. For non-metastatic LC, between 2/2023 (cisplatin shortage) and 04/2023 (carboplatin shortage), cisplatin use declined by 1.7 percentage point (pp) per month (p=0.03) and a non-significant 1.6 pp monthly increase in carboplatin usage (p=0.24). After carboplatin shortage, there was an immediate 4.5 pp drop in use of carboplatin (p=0.04), as well as an immediate 5.8 pp increase in use of cisplatin ($p<0.0001$). Overall platinum use (receipt of either cisplatin or carboplatin) throughout this entire period did not have any significant change. For metastatic LC, cisplatin was rarely used, so results after the cisplatin shortage were not assessed. After carboplatin shortage, there was a 15.7 pp immediate decline in use of carboplatin (p=0.002), with a concomitant 18.4 pp immediate increase in use of IO without platinum ($p<0.001$). **Conclusions:** The real-world response to platinum shortages in LC appeared to follow guidelines. For non-metastatic LC, for which platinum chemotherapy increases cure rates, declines during either the cisplatin or carboplatin shortages were equally balanced with increases in the other platinum chemotherapy, such that overall platinum chemotherapy usage remain stable. For metastatic LC, declines in carboplatin were balanced with increases in immunotherapy monotherapy. Research Sponsor: None.

11089 **Poster Session**

Medicare plan switching, hospice enrollment, and place of hospice services at the end-of-life among decedent patients diagnosed with distant stage cancers in 2010-2019. First Author: Xin Hu, Emory University School of Medicine, Atlanta, GA

Background: Prior studies showed higher hospice utilization among Medicare Advantages (MA) than among Traditional Medicare (TM) beneficiaries. With more beneficiaries enrolling in MA and switching between TM and MA in recent years, this study examines hospice utilization patterns and associated factors among patients with advanced cancers enrolled in continuous TM, continuous MA, or switching between these plans. **Methods:** We identified Medicare beneficiaries aged ≥66 years diagnosed with distant-stage breast, colorectal, lung, pancreatic, or prostate cancers in 2010-2019 and followed through 2020 from SEER-Medicare data. Patients surviving ≥3 months post-diagnosis were categorized by plan-switching patterns: continuous TM, continuous MA, switching from TM-to-MA, and from MA-to-TM. Outcomes included hospice enrollment in the last year of life, within 14 days of death, and site of last hospice service (e.g., home, nursing home, hospice facility, inpatient facility, or other). Multivariable regression models estimated associations of plan-switching patterns and patient characteristics with study outcomes. **Results:** Among a total of 196,568 patients with advanced cancers, plan switching was relatively infrequent, with 1.5% switching from TM-to-MA and 1.8% from MA-to-TM. Beneficiaries who switched plans were more likely to be racial or ethnic minorities and dual-eligible than those with continuous coverage. Hospice enrollment in the last year of life was highest for continuous MA (74.8%), followed by TM-to-MA (69.0%), continuous TM (68.5%), and MA-to-TM (66.4%). Enrollment within 14 days of death was similar across groups. The last hospice service was received at home by 49% of beneficiaries, followed by 7.6% at hospice facilities, 6.7% at nursing homes, and 5.3% at inpatient facility. Compared to continuous TM, continuous MA and TM-to-MA switching beneficiaries had higher likelihoods of receiving last hospice service at home (6.2 ppts and 3.0 ppts respectively, p-values$<.01$), while MA-to-TM beneficiaries had higher likelihoods of receiving last hospice service at nursing homes (1.7 ppts, $p<.001$). Beneficiaries who gained dual eligibility had increased likelihood of receiving last hospice service at nursing homes (25.8 ppts, $p<.001$) and decreased likelihood of receiving last hospice service at home (-23.5 ppts, $p<.001$) than non-dual-eligible beneficiaries. **Conclusions:** Continuous MA coverage was associated with greater likelihood of hospice utilization, particularly at home. In contrast, switching from MA-to-TM and gaining dual eligibility were associated with greater reliance on nursing homes for hospice care. Future research examining patient-centered outcomes across plan-switching patterns and addressing care coordination gaps to ensure equitable hospice care are warranted. Research Sponsor: None.

11090 Poster Session

Disparate recovery of cancer screenings by demographic in traditional Medicare post-pandemic. First Author: T. Anders Olsen, Beth Israel Deaconess Medical Center, Boston, MA

Background: Cancer screenings are a pillar of public health and early diagnosis of cancer (doi.org/10.1016/j.soncn.2017.02.002) The COVID 19 pandemic impacted access to outpatient services, such as cancer screenings (doi:10.1001/jamaoncol.2022.5481) Our study aims to assess how this impact and the recovery following the 2020 pandemic differed by race and ethnicity in Traditional or Fee-For-Service Medicare (TM). **Methods:** Claims data on a 5% sample of TM included 1.3 million beneficiaries eligible for colorectal (CRC) cancer screenings and 736,000 females eligible for breast cancer (BC) screenings. This sample was followed for a multi-year cross sectional analysis using Medicare Beneficiary Summary Files from 2017 to 2023. Claims were linked to Current Procedural Terminology (CPT) and Healthcare Common Procedure Coding System (HCPCS) codes to monitor annual utilization rates of screenings by demographic for BC and CRC. Utilization proportions were estimated based on the eligible population categorized by race/ethnicity and sex for BC. **Results:** Overall, screenings decreased in 2020 during the first year of the pandemic. BC screenings recovered quickly to pre-pandemic levels, comparing the 2019 pre-pandemic (35%) to 2021 post-pandemic (35%) rates overall in our TM sample. This was mirrored for women of non-Hispanic white (pre/post 36%), African American (pre: 33% post: 33%) and Asian/Pacific Islander (API; pre/post: 27%) groups in TM. These demographics nearly returned to 2019 rates by the 2nd year of the pandemic in 2021. American Indian/Alaska Natives (AIAN; pre: 22% post: 21%) and Hispanic women (pre: 27% post: 25%), however, did not return to pre-pandemic rates until 2022 and 2023 respectively. AIAN and Hispanic women also had the lowest utilization of BC screenings throughout our study period. CRC screenings had a slower recovery below 2019 levels (13%) in 2021 (12%), but recovering by 2023 (13%). This was mirrored across most racial demographics with the slowest recovery amongst AIAN (pre: 8%, post: 7%) and Hispanic (pre: 13%, post: 11%) beneficiaries. AIAN and African American beneficiaries displayed the lowest rates of CRC screenings throughout our study. **Conclusions:** Past research displayed decreased cancer screenings at the outset of the pandemic in 2020.[2,3] While services generally rebounded by 2021, the rate of recovery differed not only by screening type but also by demographic. BC screenings returned overall to 2019 rates by 2021. Hispanic and AIAN women lagged in recovery and utilized the lowest rates of BC screenings annually relative to the average TM beneficiary. CRC screening utilization saw a slower recovery, narrowly meeting 2019 levels by 2023. The lowest rates of CRC screenings were noted amongst African American and AIAN beneficiaries, who also struggled to recover to pre-pandemic (2019) levels by 2023. Our data highlights the disparate effects of the pandemic, especially for CRC screenings and certain racial demographics. Research Sponsor: Department of Health and Human Services.

11091 Poster Session

Workforce, economic, and infrastructural barriers to global oncology clinical trial participation: Focus on sub-Saharan Africa. First Author: Oyepeju Folashade Abioye, Allegheny Health Network, Pittsburgh, PA

Background: Despite Sub-Saharan Africa's (SSA) growing cancer burden, the region remains grossly underrepresented in global oncology clinical trials. With only 109 open trials identified continent-wide in 2019 compared to 7,557 in the United States, this disparity highlights systemic barriers. As well, the unique genetic variations in the African pan-genome makes a strong case for urgent population-specific research. **Methods:** Using the Pan African Clinical Trial Registry, we identified 151 oncology trials across 255 continent-wide recruitment sites. A review of published literature was carried out to assess oncologist distribution and SDI index within highlighted countries hosting clinical trials in SSA. **Results:** Of the 1,759 clinical oncologists identified in SSA, Egypt accounts for 85.2% (n=1,500) and hosts 46.36% of all oncology trials (n=70). Kenya, with only 0.34% oncologists (n=6), contributes 17.88% of clinical trials (n=27). Nigeria, with 3.63% oncologists (n=64), hosts 11.26% of trials (n=17). Ethiopia and Tanzania each house 0.34% oncologists (n=6), yet Ethiopia conducts 7.95% (n=12) and Tanzania 3.97% (n=6) of trials. South Africa, with 2.27% oncologists (n=40), hosts 3.97% of trials (n=6). Other countries, including Ghana and Morocco, collectively contribute to 8.61% of trials (n=13) with varying oncologist representation. The few available trials are mostly concentrated in Egypt, Kenya, and Nigeria. In addition, most trials disproportionately focus on breast and cervical cancer, with the added challenge of limited oncologist distribution. Infrastructure deficits, financial constraints, and cultural barriers further impede trial initiation and participation. **Conclusions:** Access to clinical trials remains a pillar of high-quality cancer care. Oncology research in SSA is hindered by multifaceted barriers, limiting the development of effective, region-specific therapies. Strategies to address these barriers include investing in the training of healthcare professionals, providing adequate infrastructure, increasing funding through public-private partnerships, and enhancing community engagement to build trust and improve trial participation. Research Sponsor: None.

Distribution of clinical oncologists, oncology trials, and SDI index across selected African countries.

African Countries with Oncology Clinical Trials	Number of Clinical Oncologists in Africa N=1759	% of Clinical Oncologists in Africa by Country	Number of Clinical Trials in Africa by Country	% of Clinical Trials in Africa by Country	SDI Index
Egypt	1500	85.2%	70	46.36%	Middle
Kenya	6	0.34%	27	17.88%	Low-Middle
Nigeria	64	3.63%	17	11.26%	Low-Middle
Ethiopia	6	0.34%	12	7.95%	Low
South Africa	40	2.27%	6	3.97%	Middle
Tanzania	6	0.34%	6	3.97%	Low-Middle
Ghana	10	0.57%	5	3.31%	Low-Middle
Morocco	28	1.59%	1	0.66%	Low-Middle
Others	99	5.63%	7	4.64%	
Total	1759	100%	151	100%	

11092 Poster Session

Financial toxicity for cancer patients: Out-of-pocket costs by cancer diagnosis in traditional Medicare. First Author: T. Anders Olsen, Beth Israel Deaconess Medical Center, Boston, MA

Background: Financial toxicity is defined as the fiscal issues that can arise in a patient's life related to the costs of medical care (DOI: 10.1093/tbm/ibab091). These can include financial distress, resource rationing and even medical debt. A patient's spending obligation is measured through out-of-pocket costs (OOP) which are comprised of copayments, co-insurance and/or deductibles (DOI: 10.18553/jmcp.2022.21270). Cancer patients face especially high costs and potentially greater risk of financial distress compared to other illnesses (DOI: 10.1093/tbm/ibab091). An American Cancer Society survey of 1,218 cancer patients/survivors found that over half (51%) of respondents reported medical debt resulting from cancer treatment despite nearly all (98%) having active insurance (https://www.fightcancer.org/policy-resources/costs-cancer-survivorship-2022). Our study aims to qualify and quantify the cancers with the highest out-of-pocket costs for beneficiaries in Traditional, or Fee-for-service, Medicare (TM) to determine cancers that expose patients to the highest financial risk. **Methods:** A 5% sample of TM beneficiaries in 2023 was collected, which included 1.3 million individuals and 261,099 unique beneficiaries with some form of cancer. Beneficiary claims were categorized by International Classification of Disease (ICD-10) coded cancer diagnoses. Patient OOP costs were aggregated across inpatient, outpatient and prescription drug settings using Medicare Beneficiary Summary File (MBSF) and Prescription Drug Event (PDE) claims data across Parts A, B and D Medicare, respectively. Costs per beneficiary were sorted by highest average out-of-pocket cost per beneficiary organized by cancer diagnosis. Comparison groups in our sample included a cohort of TM beneficiaries with any type of cancer and beneficiaries without cancer. **Results:** The 5 cancers with the highest average out-of-pocket costs annually in 2023 were multiple myeloma ($14,400), acute leukemia ($10,498), biliary cancers ($9,725), hepatocellular carcinoma ($9,469) and pulmonary (small and non-small-cell) cancers ($8,572). This is relative to TM beneficiaries with any cancer who spent an average of $4,800 annually OOP in 2023 and $2,364 for beneficiaries without cancer in TM. Prescription drugs are a substantial component of OOP cost for certain cancers. For multiple myeloma and acute leukemia, 19.8% and 21.5% of OOP costs were attributable to prescriptions compared to 8.6%, 8.1% and 10.2% for biliary, hepatocellular and lung cancer, respectively. **Conclusions:** Cancer is expensive for Medicare patients in the United States. These OOP costs can pose severe affordability issues for TM beneficiaries, who had an average income of $36,000 annually in 2023 (https://www.kff.org/medicare/issue-brief/income-and-assets-of-medicare-beneficiaries-in-2023/). Within TM, patients with multiple myeloma, acute leukemia, biliary, hepatocellular and lung cancers experience especially high costs and have an elevated risk of financial toxicity. Multiple myeloma and acute leukemia notably have significantly higher prescription cost-sharing through Part D compared to high-cost solid tumors. Research Sponsor: Department of Health and Human Services.

11093 Poster Session

Climate change and cancer: An ecological evaluation of climate risks for cancer survivors. First Author: Joseph M. Unger, Fred Hutchinson Cancer Center, Seattle, WA

Background: Changes in climate patterns will influence the frequency and severity of extreme weather events, leading to increased disasters (e.g., floods, fires), air pollution levels, and climate-related costs. Cancer survivors may suffer disproportionate effects of climate change-related events on mental health, care disruptions, morbidity, and mortality, yet evaluations of area-level climate risks and cancer survivorship are lacking. We examined future climate change risks faced by communities with high levels of cancer mortality. **Methods:** Data were from the Climate Vulnerability Index, a county-level measure of future climate change risks (45 variables) alongside a baseline vulnerability index (BVI) including health, socioeconomic, and environmental factors (139 variables). Variables ranging from 0 (least vulnerable) to 100 (most vulnerable) were split into high (rank $\geq$50) vs. low (rank $<$50) categories and linked to county-level cancer mortality data from the NCI's SEER registry. We compared the top quartile of the U.S. population living in counties with the highest cancer mortality rates (54.7% of counties) to other areas. Data were randomly split using a 2:1 training/validation ratio. We identified candidate variables in bivariate analyses between climate risk factors (RFs) and area-level cancer mortality. Best-subset selection with logistic regression and K-fold cross-validation was used to derive a parsimonious model of adverse RFs. These were summed, creating a score, and split at the median to test in the validation set. All analyses were adjusted for the BVI. **Results:** Overall, N=3,139 counties were examined. In the training set (n=2,094), a model with 6 RFs was identified including weather-related events (increased hurricane, tornado, and precipitation exposure), air pollution factors (increased ozone/CO2 levels), increased climate-related costs, and future economic/productivity losses. Compared to low cancer mortality counties, high cancer mortality counties were more than threefold more likely to have high exposure to the 6 climate RFs (69.6% vs. 30.4% with 3-5 factors; OR=3.07, 95% CI, 2.52-3.74, p$<$.0001). In the test set (n=1,045), results were similar, validating the model. Overall, the BVI-adjusted model C-statistic was 0.80 (unadjusted, 0.73). The association of high cancer mortality areas and high exposure to climate RFs was evident for both high (OR=3.87, p$<$.0001) and low (OR=2.75, p$<$.0001) BVI counties. **Conclusions:** In this first-of-its-kind ecologic association study, we found that living in counties with high cancer mortality was associated with future climate change risks including extreme weather events, air pollution, climate-related costs, and economic factors. Future work is needed to identify potential mechanisms between climate events and worse cancer outcomes such as decreased treatment tolerability, treatment quality, or treatment access. Research Sponsor: None.

11094 Poster Session

Preliminary efficacy of VOICE, a decision support tool for older adults with advanced cancer: A pilot randomized trial. First Author: Amy C. Cole, The University of North Carolina at Chapel Hill, Chapel Hill, NC

Background: Quality shared decision-making (SDM) requires integrating patient values into treatment decisions. Many older patients (pts) with cancer report that clinicians do not elicit their values when making treatment decisions. We developed a decision support tool for older adults with advanced cancer (called VOICE) with values elicitation, real-time feedback to patients, and tailored question prompt lists. Prior research suggests that variation in clinician behavior may impact the efficacy of SDM tools. **Methods:** We evaluated the preliminary efficacy of VOICE to improve SDM quality in a pilot double-blinded randomized trial. We enrolled pts $\geq$ 60 years with advanced solid cancers. Pts were randomized to receive VOICE or an American Cancer Society (ACS) educational document with general cancer-related question prompts. Pts completed 2 simulated consultations where they made a treatment decision for a fictional secondary cancer diagnosis: one values-based (VB), where clinicians initiated values elicitation, and one non-values-based (NVB), where clinicians did not. Logistic regression, Fisher's exact and Mann-Whitney tests evaluated the relationship of trial arm and clinician behavior to pt reports of SDM quality (CollaboRATE) and perceived usefulness of intervention (PrepDM). Five medical students, trained in VB and NVB consultations, functioned as clinicians during consultations. All consultations were recorded and analyzed for fidelity. **Results:** Forty-four pts (ages 60-88; 50% female; 86% Caucasian, 7% Black, 7% other) with advanced cancer (34% prostate, 23% breast, 18% lung, 11% melanoma, 14% other) were randomized and completed 88 consultations. Pts were more likely to report quality SDM for VB over NVB consultations (Odds ratio [OR] 2.57, 95% Confidence Interval [CI] 1.09-6.25, p=0.03). Pts reported VOICE was more useful to inform SDM than ACS document (mean PrepDM score 65.1 v. 17.4, p$<$0.001). Pts in the VOICE arm were more likely to report quality SDM (OR 1.70, 95% CI 0.73-4.04) but this did not reach statistical significance (p=0.22). The difference in the percentage of patients reporting high-quality SDM between arms was larger for NVB (43% VOICE v. 22% ACS) than for VB consultations (57% VOICE v. 52% ACS) though not statistically significant. **Conclusions:** This study demonstrates the value of using simulated encounters for "early-phase" testing of SDM tools. In this pilot randomized trial using simulated clinical encounters, clinician initiation of a discussion of patient values resulted in the highest quality of SDM regardless of study arm. VOICE improved preparation for SDM and showed encouraging preliminary data for its potential to improve the quality of SDM for older adults with advanced cancer especially when clinicians did not engage in values elicitation. Further research is needed to improve values elicitation as part of treatment decision-making. Research Sponsor: National Cancer Institute/U.S. National Institutes of Health; 1K08CA273684.

11095 Poster Session

The studies industry neglects: Characteristics of cancer clinical trials conducted by federal versus industry sponsors. First Author: Joseph M. Unger, SWOG Statistics and Data Management Center, Fred Hutchinson Cancer Center, Seattle, WA

Background: A defining feature of federally sponsored cancer clinical trials is their mandate to examine clinical research questions not routinely addressed by industry, which is financially incentivized to conduct trials that support new drug applications to the FDA. Yet no evaluation has quantified the types of trials federal versus industry sponsors conduct. These data are vital for policymakers given the need to prioritize federally sponsored trials in a clinical research landscape increasingly dominated by industry sponsorship. **Methods:** We analyzed registry data from ClinicalTrials.gov between 2008-2022. U.S.-based interventional trials for patients with cancer were included. Studies were categorized by lead sponsor (federal versus industry) and by purpose, phase, intervention, de-escalation, rare cancer, and age. Odds ratios were calculated. Chi-square tests were used. **Results:** Overall, N=9,626 federal (n=1498, 15.6%) and industry (n=8128, 84.4%) sponsored studies were examined. Most studies were conducted for treatment (federal, 92.8%; industry, 97.5%). Federally sponsored studies were more commonly prevention (5.3% vs 1.2%, OR=4.69, p$<$.001), screening (1.0% vs 0.4%, OR=2.73, p=.003), and early phase (91.6% vs 81.6%, OR=1.77, p$<$.001) studies (Table). Federally sponsored studies were more commonly multi-modality studies combining drug and biologic agents (24.3% vs. 7.4%, OR=3.28, p$<$.001) or systemic therapy with radiation or surgery. Federally sponsored studies also more commonly tested dose de-escalation strategies (1.5% vs 0.6%, OR=2.68, p$<$.001) and were more often conducted in rare cancers and in children. **Conclusions:** Nontreatment interventions, early phase, multi-modality, dose de-escalation, rare cancer, and child-focused studies were much more likely to be conducted by federally sponsored research groups than by industry. These findings highlight the unique role of federally funded studies in cancer clinical research. Research Sponsor: The Hope Foundation.

Federal- versus industry-sponsored study characteristics.

		Federal		Industry			
Study Characteristic	Category	N=1498	%	N=8128	%	Odds ratio (Fed/Ind)	P-value
Purpose	Prevention	74	5.3	89	1.2	4.69	$<$.001
	Screening	14	1.0	28	0.4	2.73	.003
	Supportive Care	13	0.9	74	1.0	0.95	1.0
	Treatment	1304	92.8	7504	97.5	0.56	$<$.001
Phase	1 or 2	1288	91.6	6307	81.6	1.77	$<$.001
	3	118	8.4	1424	18.4	0.40	$<$.001
Intervention	Biological (B)	97	8.1	668	8.9	0.77	.39
	Drug (D)	654	54.4	6180	82.1	0.24	$<$.001
	D & B	292	24.3	558	7.4	3.28	$<$.001
	D/B & Radiation	120	10.0	104	1.4	6.72	$<$.001
	D/B & Surgery	39	3.2	15	0.2	14.46	$<$.001
Dose de-escalation	Yes	23	1.5	47	0.6	2.68	$<$.001
Rare cancer[1]	Yes	284	19.0	977	12.0	1.71	$<$.001
Age category	Child[2]	192	12.8	451	5.5	2.50	$<$.001

Fed=Federal; Ind=Industry. Percentages and p-values calculated among those in the specified categories. "Other" categories not shown.
[1]Cancers that affect $<$40,000 U.S. persons/year.
[2]Studies that include those $<$18 years.

11096 Poster Session

Early examination of national changes in potentially avoidable hospital visits after chemotherapy, 2018–2022. First Author: Pranathi Pilla, UT Southwestern Medical Center, Dallas, TX

Background: Medicare tallies potentially avoidable hospital visits after chemotherapy and has been publicly reporting this quality measure since 2018. The measure reports absolute visit rates for emergency department (ED) and inpatient admission (ADM), and generates relative comparisons to national rates ("better than", "no different than", "worse than"). We sought to identify changes in avoidable hospital visit rates through 2022. **Methods:** Retrospective analysis of avoidable hospital visit rates from 2018 – 2022, from a longitudinal cohort of hospitals in the Medicare Outpatient Quality Reporting Program. We performed descriptive and trend analysis for absolute visit rates and for relative performance. We stratified hospitals into quartiles of absolute performance in 2018, then applied multivariate generalized linear regression to model change in visit rates by 2022. We estimated the contribution of regression to the mean. **Results:** We analyzed 1,179 hospitals (23% teaching). National avoidable ED visit rates were 6.0% in 2018, 5.4% in 2022; ADM rates were 12.5% in 2018, 10.3% in 2022. Nearly all hospitals were deemed to have performed "no different" than the national rate each year for ED ($\geq$ 95.3%) and ADM ($\geq$ 91.1%). In adjusted analyses, visit rates for hospitals in the lowest 2018 visit rate quartiles declined the least by 2022 (ED: -0.44% 95% CI: -0.58 to -2.94; ADM: -0.91%, 95% CI: -1.14 to -0.69), but declined the most for hospitals in the highest 2018 quartiles (ED: -1.72%, 95% CI: -1.85 to -7.73; ADM: -3.03%, 95% CI: - 3.27 to -2.81). We estimated that regression to the mean accounted for a small proportion of the decline among the highest 2018 quartile of hospitals (ED: 10.6% of rate change, 95% CI: 9.8 to 11.5; ADM: 9.0%, 95% CI: 8.2 to 9.8). **Conclusions:** It appeared that nationally, and within quartiles of hospital performance, hospitals had improved their performance on this outpatient chemotherapy quality measure. Regression to the mean accounted for only a small proportion of this change, but the decline may reflect overall lower hospital visits post-COVID19 pandemic. Research Sponsor: U.S. National Institutes of Health; CA282242.

	Unadjusted Mean 2018 rate (SD)	Unadjusted Mean 2022 rate (SD)	Unadjusted mean absolute difference, 2022 – 2018 (SD)	Adjusted absolute difference, 2022 – 2018 (95% CI)
ED rate 0-25% (lowest rates)	5.00 (0.39)	5.06 (0.80)	0.07 (0.77)	0.18 (-0.14, 0.51)
ED rate 26-50%	5.71 (0.14)	5.41(0.82)	-0.29 (0.83)	-0.44 (-0.58, -0.29)***
ED rate 51-75%	6.28 (0.20)	5.52 (0.89)	-0.76 (0.89)	-0.91 (-1.04, -0.77)***
ED rate 76-100%	7.36 (0.63)	5.85 (0.63)	-1.51 (1.06)	-1.72 (-1.86, -1.57)***
ADM rate 0-25% (lowest rates)	10.79 (0.66)	10.03 (1.35)	-0.76 (1.35)	-1.00 (-1.53, -0.49)***
ADM rate 26-50%	12.08 (0.28)	10.42 (0.29)	-1.66 (1.31)	-0.91 (-1.14, -0.69)***
ADM rate 51-75%	13.12 (0.36)	10.64 (1.38)	-2.48 (1.41)	-1.75 (-1.97, -1.52)***
ADM rate 76-100%	14.94 (1.02)	11.20 (1.52)	-3.74 (1.58)	-3.03 (-3.27, -2.81)***

***p value $<$0.001.

11097 Poster Session

Impact of social determinants of health on mortality in diffuse large B-cell lymphoma (DLBCL) using real-world data. First Author: Maureen Canavan, Yale School of Medicine, New Haven, CT

Background: Treatment advances in DLBCL have led to remarkable improvements in patient outcomes. Social determinants of health (SDOH) can contribute to inequities in outcomes in multiple cancer types, and there is a paucity of studies evaluating their impact in DLBCL. **Methods:** We used the nationwide Flatiron Health electronic health record derived de-identified database and included adults with a confirmed diagnosis of DLBCL from 2011-2024 to evaluate the association between SDOH and real-world overall survival (from time of initial treatment). Area-level SDOH variables were derived from the Census Bureau's American Community Survey and the 2019 AHRQ's SDOH database. These census tract level measures were grouped into US population-weighted quartiles and evaluated across the following domains: economic, social (including racial segregation), neighborhood & physical environment, and healthcare. We estimated adjusted hazard ratios (aHR) for the highest social deprivation quartile (least resourced areas) compared to the lowest quartile using Cox proportional hazard models, adjusting for age, sex, race/ethnicity, LDH, ECOG, presence of extranodal disease, stage, and cell of origin. **Results:** We included 6,855 patients in the analysis. After adjustment, residence in areas with the highest social deprivation was consistently associated with increased mortality across all SDOH domains compared with the lowest deprivation areas. A higher risk of death ($>$ 20%) was found for patients residing in predominantly Black vs. White neighborhoods, those residing in medically underserved areas, and areas with the lowest levels of private insurance. Similarly, residence in areas with the least access to the internet, computing devices, and cellular data plans was associated with increased mortality risk. **Conclusions:** Higher SDOH deprivation was significantly associated with increased mortality among patients with DLBCL, despite controlling for demographic and clinical factors. The SDOH influencing mortality ranged from socioeconomic and technological inequities to limited healthcare access and racial segregation. These factors may aid improved prognostication of DLBCL, and future studies should focus on developing interventions to mitigate SDOH-linked inequities in DLBCL. Research Sponsor: None.

	aHR	95% CI	Domain
Households that received food stamps/SNAP	1.15	1.02, 1.29	Economic
Households with no internet access	1.15	1.02, 1.29	Neighborhood
Households without a computing device	1.12	1.00, 1.26	Physical
Households without cellular data plan	1.13	1.00, 1.26	Environment
Medically underserved area	1.20	1.02, 1.40	Healthcare
Population private health insurance ($\leq$ 64)	1.24	1.10, 1.39	
Population TRICARE/military/ VA insurance only ($\leq$64)	1.17	1.05, 1.30	
Population no health insurance ($\leq$64)	1.18	1.06, 1.33	
Residential Segregation Blacks (reference: Whites)	1.23	1.01, 1.51	Social

11098 **Poster Session**

Integration of a virtual personalized medicine review board integration into a major community oncology phase 1 unit. First Author: Marilyn Elaine Hammer, Sarah Cannon Research Institute, Nashville, TN

Background: Inclusion criteria for participating in oncology clinical trials have grown more complex, often challenging the enrollment process. Our objective was to improve the process of identifying and enrolling patients by incorporating personalized medicine assistance into the initial patient intake and trial selection procedure at a major community-based phase 1 oncology unit. **Methods:** A virtual personalized medicine review board (vPMRB) comprised of two PhD scientists reviewed patients for suitable trial options based on molecular sequencing results and scientific rationale during the intake and screening processes at a phase I oncology clinic. vPMRB reviews leveraged a propriety clinical trial identification software, Genospace, to generate patient-trial matches based on general inclusion/exclusion criteria including disease, histology, staging, and biomarker criteria. Trial options were returned via email and added to patients' charts in the electronic health record for reference by their clinical care team. Trial candidates were screened for trial options and consented for treatment on trial by the enrollment nursing (ERN) team. Data pertaining to vPMRB review, trial screening, trial consent, and trial enrollment were collected by the vPMRB and ERN teams and combined to determine consent and enrollment rates. **Results:** Between 1/1/2024 and 12/31/2024, 953 patient reviews for 815 unique patients were completed by the vPMRB with an average turnaround time of 4 $\pm$ 5 business hours. 900 (94%) of these reviews included potential trial options for the patient. Of 790 reviewed patients with sufficient information for comparison with enrollment team data, 473 (60%) were screened for trial options by the ERN team in 2024. Of these, 343 (73%) consented to a trial and 270 (57%) started trial treatment in 2024. Comparatively, of the 744 patients reviewed for trial options by the ERN team, but not the vPMRB, 431 (58%) were consented to a trial and 313 (42%) started trial treatment in 2024. 167 (35%) patients consented to a trial and 130 (28%) patients started a trial recommended by the vPMRB for that patient in 2024. **Conclusions:** vPMRB review was associated with increased trial enrollment compared to patients without vPMRB review. Upcoming research will explore the effects of further personalized medicine integration techniques, including the involvement of team members in therapeutic strategy meetings held by clinical care teams, along with the use and effectiveness of clinical trial matching software in a phase 1 unit. Research Sponsor: None.

Trial consenting and screening rates in 2024 for patients with and without vPMRB review.

	vPMRB Review	No vPMRB Review
Patients screened for trial by enrollment team	473	744
Consented on Trial	343 (73%)	431 (58%)
Started Trial	270 (57%)	313 (42%)
Consented on trial surfaced in vPMB review	167 (35%)	N/A
Started on trial surfaced in vPMB review	130 (28%)	N/A

11099 **Poster Session**

Temporal trends in opioid prescription fills following cancer-directed surgery. First Author: Andrea Catherine Enzinger, Dana-Farber Cancer Institute, Boston, MA

Background: Postoperative pain is a common complication of cancer surgery. Opioid prescribing has declined dramatically since the early 2010's; however, little is known about trends in opioid prescribing following cancer-directed surgeries. **Methods:** Using administrative data for 100% Medicare fee-for-service beneficiaries enrolled in parts A, B, and D, we identified initial episodes of cancer-directed surgeries from 2012-2021 among adults who survived $>$ 30d after surgery and were discharged home. We used Part D claims to identify early postop opioid fills, defined as prescriptions filled in the 30d after surgery for outpatient surgeries, and in the 30d following hospital discharge for inpatient surgeries. We described opioid fills, median dose, pill counts, and the proportion with subsequent fills overall and annually. **Results:** We identified 981,702 episodes of cancer directed surgeries, most often for breast (38%), colorectal (15%), prostate (13%), and lung (10%) cancers. Patients' mean age was 73(SD,8), 36% were male, 83% White, 8% Black, 4% Hispanic, and 2% Asian. Overall, 66.6% of patient episodes had $\geq$1 postoperative opioid fill, declining from 70.7% in 2012 to 59.3% in 2021. Among episodes with $\geq$1 opioid fill, the median dose of the first opioid fill declined from 225 (IQR:150,300) morphine milligram equivalents (MMEs) to 100 (IQR:75,150) MMEs between 2012-2021, and the total dose of all fills in 30d fell from 250 (IQR: 150,450) MMEs to 112.5 (IQR:75,210) MMEs. Median pill counts for the first short-acting opioid fill declined from 30(IQR:30,40) to 18(IQR:10,25) over the study. Among episodes with $\geq$1 short-acting opioid fill, the proportion with subsequent short-acting opioid fills declined from 30.7% to 17.8%. **Conclusions:** Medicare beneficiaries undergoing cancer-directed surgeries have experienced steep declines in prescription opioid medication fills in the postoperative period. Future work is needed to understand potential impacts of declining postoperative opioid prescribing on outcomes such as uncontrolled pain, pain-related emergency department visits, persistent opioid use, and development of opioid use disorders. Support: R01CA279414. Research Sponsor: None.

11100 **Poster Session**

Integrative oncology interest in persons with a cancer diagnosis. First Author: Julia Witkowski, Thomas Jefferson University, Philadelphia, PA

Background: Integrative oncology (IO) is an evidence-informed field of cancer care that utilizes mind-body practices, natural products, and lifestyle medicine from different traditions alongside conventional therapies. With growing evidence of benefit and inclusion in guideline recommendations, the Sidney Kimmel Comprehensive Cancer Center (SKCCC) at Thomas Jefferson University's integrative oncology program assessed patients' understanding of integrative health, their utilization of integrative medicine approaches, and interest in formal IO consultations. **Methods:** Persons with a history of cancer who presented for care at a SKCCC clinical site received an electronic record invitation to complete a brief survey with binary and free-response questions regarding current knowledge, experiences, and interest in IO. At the end of the survey, patients also had the option to express their interest in IO consultations at SKCCC. **Results:** Demographics for the 1681 responders were: 1116 (67.1%) were female; 1285 (76.4%) were between 45-75 years of age; 313 identified as Black or African American (19.0%) and 1276 as White (77.5%). Breast cancer (494, 29.37%) and hematologic cancers (289, 17.18%) were the most reported malignancies. Overall, 446 (27.4%) and 153 (9.3%) had previously utilized in-person IO services and virtual IO services, respectively. 1,133 (67.36%) reported that IO was never discussed during their care. 1201 (73.9%) expressed interest in an IO consultation. Black or African American participants had 117% higher odds of expressing an interest in IO consultation (OR: 2.17, 95% CI: 1.52 – 3.09, $p<0.001$) compared to all other participants. **Conclusions:** In contrast to the prevalence of IO approaches in literature, only one third of patients who completed the survey had previously used an IO modality. However, nearly 70% expressed interest in a formal IO consultation. Due to the overwhelming interest, an IO information session hosted by a Board-Certified Medical Oncologist and Integrative Oncologist is being offered. 250 (14.9%) participants have requested appointments so far. With the increasing evidence of benefit for IO care and the inclusion of these recommendations in clinical guidelines, expansion of IO services, especially those which focus on Black or African American participants who are usually not reached by these interventions, is indicated. IO consultations can address knowledge gaps, enhance implementation of guideline-based care, and, perhaps, improve clinical outcomes. Research Sponsor: None.

11101 **Poster Session**

Utilization and timeliness of next-generation sequencing testing for patients with resected or metastatic non-small cell lung cancer: A real-world analysis. First Author: Raheem Bell, Northwestern University Feinberg School of Medicine, Chicago, IL

Background: Comprehensive next-generation sequencing (NGS) is an evidence-based molecular testing modality used to identify actionable oncogenic drivers in tumor tissue, guiding therapy selection and improving survival in early-stage and metastatic non-small cell lung cancer (NSCLC). However, uptake of NGS in oncology practices varies. This study aimed to identify hospital-level variation in NGS testing adoption within a statewide quality improvement collaborative. **Methods:** We conducted a cross-sectional analysis of patients with clinical Stage IB-IIIA NSCLC who underwent surgical resection and clinical Stage IV NSCLC sampled in 2023 across 10 academic, community, and integrated network hospitals in a statewide cancer quality improvement collaborative. Rates of NGS testing and turnaround times between biopsy date, NGS order date, NGS result date, and first treatment time were analyzed. Subsets of patients treated at facilities with in-house molecular labs or reflex molecular testing protocols were described. Multivariable logistic regression identified demographic and clinical predictors of NGS use. In a subset of patients with EGFR or ALK mutations, we evaluated tyrosine kinase inhibitor (TKI) use across hospital sites. **Results:** Among 318 patients, 34.9% had clinical Stage IB-IIIA and 65.1% had clinical Stage IV lung adenocarcinoma. NGS testing was performed in 65.1% of patients, with rates ranging from 13.5% to 97.8% across sites. Facilities with in-house NGS capabilities had higher NGS rates (87.8%) compared to facilities relying on send-out testing (50.8%). Similarly, facilities with reflex molecular testing protocols demonstrated higher NGS rates (75.4%) compared to those without reflex protocols (50.4%). Among patients with EGFR or ALK mutations, 77.8% received TKI therapy, with rates ranging from 0% to 100%. Of 113 early-stage patients, 32 (28.3%) had NGS performed pre-resection, 36 (34.0%) post-resection, and 40 (37.7%) did not have NGS performed. Across all sites, the median time from biopsy to NGS order was 29 days (IQR 20–49), from order to results was 13 days (IQR 11–18), and from biopsy to treatment initiation was 42 days (IQR 31–58). Smoking status was an independent predictor of NGS use with OR 0.28 (0.13-0.61, p=0.002). **Conclusions:** Significant variation exists in NGS adoption across hospital sites in a statewide quality improvement collaborative. However, turnaround times were consistent across sites. These benchmarking data, combined with qualitative insights, can inform quality improvement interventions for underperforming sites. Research Sponsor: AstraZeneca Pharmaceuticals LP.

11102 Poster Session

Health-related quality of life and financial toxicity among patients with gynecological cancers in southern Nigeria: A multicenter cross-sectional study. First Author: Chibuzor Franklin Ogamba, Nuffield Department of Population Health, University of Oxford, Oxford, United Kingdom

Background: Gynecological cancer-related morbidity and the financial burden of care impact the quality of life of patients. However, the health-related quality of life (HRQoL) and experience of financial toxicity (FT) of affected women in sub-Saharan Africa have not been sufficiently explored. This study assessed predictors of HRQoL and FT, and the effect of FT on HRQoL among women with gynecological cancers in Nigeria. **Methods:** This hospital-based cross-sectional study investigated consenting women with gynecological cancers receiving care at various stages at five academic hospital centers in southern Nigeria, between June 2022 and September 2024. The main outcomes were HRQoL and FT evaluated using the FACT-G and FACIT-COST tools, respectively. Patients' sociodemographic and clinical characteristics were additionally retrieved using a structured questionnaire. Multivariable linear regression models estimated the associations of patient and disease characteristics with HRQoL and FT, and the effect of FT on HRQoL, adjusting for potential confounders. Ethical approval was obtained from all centers. **Results:** Overall, 574 women were recruited with a mean FACT-G score of 58 (SD $\pm$ 15) and a median FACIT-COST score of 16. Of these, 92.8% experienced FT, with 42.6% having moderate-to-severe FT. After multivariable adjustments, HRQoL was significantly poorer among unemployed women (β = -2.4; 95%CI: -4.8, -0.02; p= .048), women with ovarian (β = -3.4; 95%CI: -6.4, -0.4; p= .028) and uterine cancers (β = -3.8; 95%CI: -7.0, -0.6; p= .021) and choriocarcinoma (β = -7.8; 95%CI: -15, -0.2; p= .045), and women with stages II (β = -4.6; 95%CI: -7.7, -1.6; p =.003), III (β = -5.5, 95%CI: -8.9, -2.2; p= .001), and IV disease (β = -4.6; 95%CI: -8.7, -0.4; p= .031). Conversely, patients in remission had significantly better HRQoL (β = 9.3; 95%CI: 5.0, 14; $p<$ .001). FT was worse with stages III (β = -2.2; 95%CI: -4.0, -0.4; p =.016) and IV disease (β = -5.4; 95%CI: -7.6, -3.2; $p<$.001), and in women on active treatment (β = -2.9; 95%CI: -4.4, -1.3; $p<$ .001). However, older women (β per 10-year increase in age = 0.6; 95%CI: 0.1, 1.1; p= .029), those with health insurance (β = 3.4; 95%CI: 1.4, 5.5; $p<$.001), higher income (β per 1000 Naira = 0.02; 95%CI: 0.01, 0.03; p= .004), ovarian cancer (β = 1.9; 95%CI: 0.3, 3.6; p= .021) and choriocarcinoma (β = 6.7; 95%CI: 2.6, 11; p= .001) had lower FT. FT scores varied linearly with HRQoL after adjustments, with better HRQoL per unit lower FT (β = 0.46; 95% CI: 0.3, 0.6; $p<$ .001). This effect was more pronounced in women with a first tumor (β = 0.53; 95% CI: 0.4, 0.7; $p<$.001), those in pre-treatment (β = 0.69; 95% CI: 0.4, 1.02; $p<$.001) and those in remission (β = 0.69; 95% CI: 0.04, 1.3; p =.037). **Conclusions:** Our findings identify possible predictors of HRQoL and FT, and suggest potential benefits of reducing FT on the HRQoL of women with gynecological cancers in Nigeria. Research Sponsor: None.

11103 Poster Session

Patient preference for first-line treatments of ALK-positive metastatic non-small cell lung cancer: A discrete choice experiment. First Author: Baohui Han, Department of Respiratory and Critical Care Medicine, Chest Hospital Affiliated to Shanghai Jiao Tong University, Shanghai, China

Background: For patients with ALK-positive metastatic NSCLC, targeted therapy with ALK inhibitors is a recommended first-line treatment. The development and approval of ALK-TKIs have resulted in longer survival benefits for patients with ALK-positive mNSCLC. Three generations of ALK-TKIs are now available, varying in efficacy and side effects. Therefore, it is important to identify patients' priorities and the benefit-risk trade-offs patients are willing to make among potential treatment options. This study quantified the preferences of patients for attributes of ALK-positive mNSCLC first-line treatment. **Methods:** An online discrete choice experiment was conducted to elicit the preferences of Patients with ALK-positive mNSCLC and their family members (both decision-makers for the treatment). Respondents completed multiple hypothetical treatment profiles characterized by 7 attributes, including progression-free survival (PFS), reduced risk of brain metastasis, intracranial complete response (iCR), degree of cognitive side effects, risk of liver damage, risk of severe hyperlipidemia and the dose reduction rate. Data were analyzed using a conditional logit model and mixed logit model. **Results:** Respondents (N=115) placed most value on PFS (RI=58.13%), followed by reduced risk of brain metastasis (RI=13.04%). Attributes related to side effects were considered less critical in respondents' decision-making. Respondents exhibited a willingness to accept an increased risk of treatment for improved clinical outcomes. When the degree of side effects was altered from mild to moderate, respondents require a minimum increase of 5.34 months in PFS as compensation to maintain the same utility. Scenario analysis estimated 97.06% of respondents would endorse the new treatment option if the PFS was improved from 36 months to 60 months. Subgroup analysis revealed that the preference patterns of patients and their families are similar. However, respondents' preferences exhibit heterogeneity for patients with different brain metastasis status, age, and annually household income. **Conclusions:** This is currently the first patient preference study for First-Line Treatments of ALK-positive mNSCLC. The results revealed that patients' decision makers place the highest priority on PFS, with comparatively less emphasis on side effects, and they are willing to accept a higher risk of side effects in exchange for prolonged survival. Understanding these preferences can enhance shared decision-making between patients and clinicians, fostering personalized prophylactic treatment plans that may optimize adherence and improve clinical outcomes. Research Sponsor: None.

11104 Poster Session

Characterizing unmet supportive care needs in diverse adolescent and young adult cancer survivors. First Author: Akina Natori, University of Miami, Miami, FL

Background: Research addressing the supportive care needs of diverse adolescent and young adult (AYA) cancer survivors remains underdeveloped relative to younger and older cancer survivor populations. Given their distinct developmental, psychosocial, and healthcare challenges, it is critical to characterize the unmet supportive care needs (USCN) specific to AYAs. This study aimed to compare self-reported USCN between AYA and older (>39 years old) cancer survivors to identify age-specific gaps in care and opportunities to improve outcomes. **Methods:** Between October 2019 and October 2024, 20,520 cancer survivors (n=1,287 AYA and n=19,233 non-AYA) at Sylvester Comprehensive Cancer Center completed the *My Wellness Check* (MWC) questionnaire. *MWC* is fully integrated and scored in real-time in the electronic health record, and evaluates 16 domains of supportive care needs (e.g., stress management, financial concerns, informational resources, transportation) alongside patient-reported outcomes (PROs; PROMIS measures of pain interference, fatigue, physical function, anxiety, and depression) and health-related quality of life (HRQOL; FACT-G7). Sociodemographic and clinical characteristics and the prevalence of USCNs were compared between AYA and other cancer survivors using chi-square and t-tests. **Results:** The AYA group had a higher proportion of females (64% vs. 51%), non-White (20% vs. 14%), Hispanic (56% vs. 44%), uninsured (4% vs. 3%), and unpartnered individuals (59% vs. 34%) compared to non-AYAs (all $ps < 0.01$). Across both groups, the most frequently reported USCNs were general cancer education (11%), coping with a cancer diagnosis (11%), and financial concerns (9%). AYAs were more likely to report at least one USCN compared to non-AYA survivors (33% vs. 28%). AYAs were also more likely to endorse needs related to coping with a cancer diagnosis (14% vs. 11%), financial concerns (12% vs. 9%), work-related issues (6% vs. 3%), oncofertility (10% vs. 1%), and childcare (3% vs. 0.5%) (all $ps <$ 0.001). No significant differences were observed for other USCN, including transportation, housing, family problems, sexual health, spiritual concerns, access to medicines, and advance directives. **Conclusions:** While both AYA and non-AYA cancer survivors face substantial unmet supportive care needs, AYAs exhibit additional challenges, particularly in areas such as financial concerns, work-related issues, fertility preservation, and childcare. These findings align with prior research while uniquely emphasizing the unmet needs of a more ethnically diverse population. This study underscores the urgent need for targeted assessments and interventions to address the unique supportive care needs of AYA cancer survivors, ensuring equitable and age-appropriate survivorship care. Research Sponsor: None.

11105 Poster Session

Understanding psychosocial wellbeing and concern for death and dying: Insights from a psycho-oncology clinic. First Author: Shahrzad A. Zamani, Moffitt Cancer Center, Tampa, FL

Background: Patients with cancer face burden of mental health symptoms and an ongoing concern for death and dying. The psycho-oncology clinic aims to address these concerns by integrating mental health services into cancer care. This study evaluates key domains of psychosocial health and their relationship with mortality salience. **Methods:** Data from 60 patients treated at a psycho-oncology clinic were analyzed. Demographics, cancer site, disease stage (localized vs. metastatic), treatment status, and psychiatric diagnoses were collected. Outcomes were assessed using the Patient-Reported Outcomes Measurement Information System (PROMIS) Short Forms, including measures of Emotional Distress (Anxiety, Depression, Social Isolation), Meaning and Purpose, Psychosocial Illness Impact (Negative and Positive), and Concern for Death and Dying. Descriptive and univariate regression analyses explored cohort trends. **Results:** Among the 60 patients, the mean age was 63 years (SD=14.8), with 52.2% identifying as female, 45.5% as male, and 2.3% as non-binary. The most common primary cancer sites were lung (20.5%), breast (18.2%), and multiple myeloma (9.1%). Of the patients, 61.4% had localized disease, while 38.6% had metastatic disease. A significant proportion (79.6%) were undergoing active treatment. Calculated t-scores demonstrate that concern for death and dying was more than two standard deviations above the population mean while meaning and purpose was lower. Metastatic disease, higher levels of anxiety, depression, negative psychosocial illness impact, and a lower sense of meaning and purpose were all associated with greater concern for death and dying. **Conclusions:** This study highlights the high prevalence of concern for death and dying in patients who are referred to a psychosocial oncology clinic and its association with key psychological variables for which there are standard treatments. PROMIS measures offer valuable insights, underscoring the importance of comprehensive psychosocial assessments. Tailored interventions targeting emotional distress, meaning, and end-of-life concerns may improve patient outcomes. Research Sponsor: None.

Variables	Mean (SD)	Calculated t-score* [SE]	Regression	
Death & Dying Concern	25.2 (8.5)	71 [3.5]	95% CI	p-value
Age	63 (14.8)	-	(-0.1-0.22)	.48
Localized vs Metastatic	-	-	**(2.0-11.3)**	**.006**
Anxiety	20.5 (6.7)	58.4 [2.0]	**(0.31-0.91)**	**<.001**
Depression	17.0 (7.3)	54.5 [3.1]	**(0.31-0.84)**	**<.001**
Meaning & Purpose	27.8 (7.6)	44.6 [2.9]	**(-0.64–0.1)**	**.008**
Negative Illness Impact	16.3 (5.6)	66.4 [2.9]	**(0.21-0.93)**	**.003**
Positive Illness Impact	35.6 (9.0)	50.5 [3.2]	(-0.16-0.06)	.14
Social Isolation	16.5 (6.6)	50.0 [1.8]	(-0.16-0.5)	.3

*Population t-score = 50.0 (10.0).

11106 **Poster Session**

Self-reported adherence to cancer therapy: Development and validation of a cancer-specific DOSE-Nonadherence measure. First Author: Yashasvini Sampathkumar, Memorial Sloan Kettering Cancer Center, New York, NY

Background: Patients with cancer take different types of medication (e.g., enteral, parenteral), with varying treatment schedules, in various settings. They are also sometimes instructed to stop medication in response to toxicity. To measure medication nonadherence in this heterogenous population, we modified and pilot-tested a self-report measure originally developed to assess nonadherence to daily oral medication, the Domains of Subjective Extent of Nonadherence (DOSE-Nonadherence), in adults with cancer. **Methods:** Participants were ≥21 years, on active cancer treatment at Memorial Sloan Kettering, and spoke English and/or Spanish. A branching logic was added to allow participants to select the setting where they take cancer medication: 1) only at home, 2) only in clinic, or 3) partly at home/partly in clinic. Based on administration setting, participants reported nonadherence to medications their clinician expected them to take over a given reference period (1 week for home and 1 month for clinic medications). Participants then reported on setting-relevant reasons for nonadherence. Survey instructions/items were refined in an iterative process using feedback from a patient investigator committee and participant cognitive interviews. During interviews, we asked participants about the interpretation of instructions/items, recall period, and comprehensiveness of reasons for nonadherence, regardless of their own adherence. After initial testing in English, a Spanish version was developed through transcreation. Adherence was dichotomized for analysis (complete adherence vs. any nonadherence). For all participants who received clinic medications, concordance between chart abstracted and self-reported adherence was evaluated. **Results:** Of 55 participants who completed the surveys and interviews (67% in English; 33% in Spanish), 87% were female and 44% identified as Latino. The majority (73%) had breast cancer; 60% had metastatic disease. 12 of 45 who received medication in clinic reported nonadherence as did 8 of 35 who took medication at home. Participants felt able to respond accurately to both recall periods. All reasons for nonadherence were perceived as relevant to themselves or other patients. There was 89% concordance between self-reported and chart abstracted adherence for clinic-administered medication. To improve concordance, changes were made to the formatting and instructions. Of 12 participants who completed the final version of the survey for clinic-administered medication, there was 100% concordance between self-reported and chart abstracted nonadherence. **Conclusions:** Our results support the reliability and validity of modified DOSE-Nonadherence for cancer patients. This instrument can be used to better identify nonadherence to cancer medications in a population of adult patients with cancer receiving various treatment regimens. Research Sponsor: National Cancer Institute; P30CA008748; National Cancer Institute; T32CA275764; Patient-Centered Outcomes Research Institute (PCORI); BPS-2023C1-32172; Department of Veterans Affairs Health Systems Research Service; RCS 14-443; Geoffrey Beene Cancer Research Center at Memorial Sloan Kettering Cancer Center.

11107 **Poster Session**

Employer-sponsored insurance, paid sick leave, and financial toxicity among cancer survivors. First Author: Michael T. Halpern, University of Texas School of Public Health at San Antonio, San Antonio, TX

Background: Financial toxicity (FT), the adverse economic effects resulting from cancer, its treatment, and associated long-term effects, may affect the majority of cancer survivors. FT is associated with multiple factors including employment disruptions; however, the role of workplace policies in mitigating FT is poorly understood. We examined how employer-sponsored health insurance and paid sick leave influence FT among employed U.S. cancer survivors. **Methods:** We analyzed data from 1,122 employed cancer survivors aged 18-64 with non-missing insurance status and a self-reported history of cancer (diagnosed age 18 or older), representing a weighted total of almost 5 million survivors from the 2021/2022 National Health Interview Survey (NHIS), a nationally representative household survey of the civilian noninstitutionalized U.S. population. Multivariable logistic regression analyses examining associations of employer-sponsored health insurance and paid sick leave (separately) with FT items, controlling for sociodemographic characteristics and cancer type, were conducted using PROC SURVEYLOGISITC in SAS 9.4 adjusting for the complex survey design of the NHIS. **Results:** Compared with cancer survivors who had employer-sponsored health insurance (n = 842, weighted 76.6%), those without employer-sponsored insurance were significantly ($p < 0.05$) more likely to experience FT, including worrying about paying medical bills (odds ratio [OR] 1.7, 95% confidence interval [CI] 1.2-2.4), skipping/delaying medical care due to costs (OR 2.4, 95% CI 1.5-3.9), and delaying counseling/therapy due to costs (OR 2.5, 95% CI 1.3-4.6). These associations persisted when restricting the sample to survivors with private insurance only. Similarly, compared to survivors with paid sick leave (n = 807, weighted 72.0%), those without paid sick leave were significantly more likely to worry about paying medical bills (OR 1.4, 95% CI 1.1-1.9) and skip/delay medical care due to costs (OR 2.2, 95% CI 1.4-3.4), with consistent findings in the private insurance only subgroup. Having employer-sponsored insurance and paid sick leave were also associated with decreased food insecurity. **Conclusions:** Workplace policies can mitigate FT and food insecurity among cancer survivors. Employers should consider offering benefits that support health and economic outcomes for employees with cancer and other medical conditions and enhance their ability to contribute to positive workplace environments. Research Sponsor: None.

11108 **Poster Session**

Ethnic disparities in unmet supportive care needs and outcomes among older ambulatory cancer patients. First Author: Frank J. Penedo, University of Miami Sylvester Comprehensive Cancer Center, Miami, FL

Background: Older cancer patients often face unmet supportive care needs (USCNs), leading to adverse clinical outcomes. Existing research largely focuses on non-Hispanic White populations, leaving a gap in understanding the unique determinants and consequences of USCNs in underrepresented groups. This study aimed to identify factors associated with USCNs and evaluate their impact on clinical outcomes, including emergency room (ER) visits and hospitalizations, among ambulatory cancer patients aged 65 and over. **Methods:** A retrospective analysis was performed for older ambulatory cancer patients (aged ≥65) via *My Wellness Check*, an electronic health record (EHR)-based supportive care needs and patient-reported outcomes (PROs) screening and referral program. Patient demographics and clinical characteristics and outcomes were extracted from the EHR. PROs (i.e., PROMIS computerized adaptive tests for anxiety, depression, and physical function), health-related quality of life (HRQOL) using the FACT-G7, and supportive care needs (e.g., stress management, financial concerns, transportation) were also collected. Logistic regression models examined predictors of USCNs. The cumulative incidence of ER visits and hospitalization was assessed using Cox proportional hazards regression models adjusting for covariates. **Results:** A total of 8,996 older cancer patients were analyzed (mean age: 74±6.3 years, 44% female). Among participants, 3,297 (37%) were Hispanics, 4,901 (55%) were non-Hispanic White, and 561 (6%) were non-Hispanic Black. Most patients were partnered (64%) and insured (98%). Hispanics were more likely to experience USCNs (adjusted odds ratio [aOR]=1.79). Other factors associated with USCNs included non-White race (aOR=2.42), being unpartnered (aOR=1.24), uninsured status (aOR=1.80), shorter time since diagnosis (aOR=0.94), anxiety (aOR=1.03), depression (aOR=1.02), lower physical function (aOR=0.99), and poorer HRQOL (aOR=0.95). Hispanic ethnicity was independently associated with an increased risk of ER visits (adjusted hazard ratio [aHR]=1.76). USCNs were independently associated with an increased risk of ER visits (aHR=1.25) and hospitalizations (aHR=1.29) (all p's<0.05). **Conclusions:** Older Hispanic cancer patients are disproportionately burdened by USCNs, leading to higher risk of ER visits compared to their non-Hispanic counterparts. Underrepresented groups, patients lacking social support, and those experiencing greater emotional or physical distress are more likely to report USCNs. Addressing these needs is critical, as USCNs significantly contribute to increased healthcare utilization, including ER visits and hospitalizations. Tailored interventions to meet supportive care needs in historically vulnerable populations are imperative to improving outcomes and reducing healthcare disparities among older cancer patients. Research Sponsor: None.

11109 **Poster Session**

Treatment preferences of patients, caregivers, and physicians in follicular lymphoma (FL): A global discrete-choice experiment (DCE) study. First Author: Mitchell Reed Smith, The Follicular Lymphoma Foundation, Washington, DC

Background: While recent FL therapy advances offer various treatment options, data are limited on FL treatment preferences in the shared decision-making process. A comprehensive survey with a DCE design was conducted to assess preferences of patients, caregivers, and physicians for different attributes that impact treatment choice. **Methods:** A web-based DCE survey available in English and Spanish was administered in Oct-Nov 2024 to patients with FL, caregivers, and physicians recruited in the US, the UK, Spain, Australia, and Canada through the Follicular Lymphoma Foundation (FLF). FL treatment attributes were selected based on targeted literature review, clinical inputs, and review with FLF patient and caregiver advisors. Attributes included efficacy (progression-free survival [PFS]), safety (impact of adverse events [AEs], including fatigue, cytokine release syndrome [CRS], and neurologic events [NE], on quality of life [QOL]), and convenience (mode of administration, treatment duration and frequency of visits, time needed to travel to treatment center). Survey responses were analyzed by patient, caregiver, and physician groups. Preference weights were generated from conditional logistic regression models and used to calculate the relative importance of attributes and willingness to trade off. **Results:** A total of 337 patients, 37 caregivers, and 29 physicians (median age: 59, 45, and 51 y, respectively) from 25 countries (>75% from US, UK, and Spain) responded to the DCE survey. The majority (93.7%) of patients reported having experienced ≥1 AE from previous treatment. Patients preferred treatments with longer PFS; mild or no impact of fatigue, CRS, and NEs on QOL during treatment; oral tablets vs infusions; a 3-mo duration with twice-weekly visits vs continuous duration with visits once every 3 mo; and <30 min of travel time vs >2 h (all P<.05). PFS was ranked as the most important attribute across patients, caregivers, and physicians. Following efficacy, treatment convenience attributes were ranked higher by patients and caregivers while safety attributes were more important to physicians. On average, patients were willing to accept reductions of 1 y of PFS for treatment requiring <30 min of travel vs >2 h, 0.7-1 y to receive treatments with less impact of AEs on QOL, 0.6 y for oral tablets vs blood collection and intravenous infusion, and 0.5 y for 3-mo treatment vs continuous duration. **Conclusions:** Efficacy is the most important attribute in treatment choice for patients, caregivers, and physicians. Following efficacy, patients and caregivers prioritize convenience and reduced impact of AEs, while physicians prioritize safety over convenience. Insights on differences between preferences highlight the importance of informed discussion and a balanced, individualized approach to treatment selection. Research Sponsor: BeOne Medicines Ltd.

11110 **Poster Session**

Patient-reported pain and emergency department utilization in patients with newly diagnosed ovarian cancer: A retrospective cohort study. First Author: Esin Christine Namoglu, Memorial Sloan Kettering Cancer Center, New York, NY

Background: Pain is one of the most common reasons for emergency department (ED) visits among patients with cancer. While patient-reported pain is increasingly captured in routine clinical care, its role in predicting ED utilization remains unclear. This study aimed to evaluate whether baseline patient-reported pain after ovarian cancer diagnosis is associated with subsequent ED visits. **Methods:** We conducted a retrospective cohort study of patients aged 18 years or older treated for ovarian cancer at an urban academic institution between 2019 and 2024. Inclusion criteria required (1) completion of a pain survey within 6 months of diagnosis, (2) all or part of first line treatment at our institution, and (3) at least six months of follow-up after pain survey submission. Patients rated their average pain over the past week on a 0–10 scale as part of routine intake, with mild defined as a score of 1 to 3 and moderate to severe as 4 or higher. The outcome was the occurrence of at least one ED visit within 6 months of the pain survey submission. Multivariable logistic regression was used to assess the relationship between patient-reported pain and ED utilization, adjusting for sociodemographic and clinical variables. **Results:** Among 894 patients who met inclusion criteria, the mean age at diagnosis was 59.7 years, 74.4% (n=665) were white, 7.3% (n=65) Hispanic or Latino, 69.0% (n=617) had advanced stage (III or IV) disease, 83.9% (n=750) received chemotherapy and 66.7% (n=596) had surgery within 6 months of diagnosis. Among the cohort, 331 (37.0%) reported mild pain, 345 (38.6%) reported moderate to severe pain, and 239 (26.7%) experienced at least one ED visit in the 6 months following the survey. A higher proportion of patients with moderate to severe pain had an ED visit compared to 26.0% of those with mild pain and 15.1% of those with no pain (34.8% vs. 26.0% vs. 15.1%, $p<0.001$). After adjusting for covariates, both mild (aOR 1.77, 95% CI 1.09-2.93, p=0.02) and moderate to severe (aOR 2.28, 95% CI 1.42 - 3.73, p=0.001) pain at baseline were associated with higher odds of an ED visit compared to patients without pain. In addition, younger age, non-white race, receipt of chemotherapy or surgery, and advanced stage disease were all significantly ($p<0.05$) associated with higher adjusted odds of an ED visit. **Conclusions:** Three out of four people with newly diagnosed ovarian cancer experience pain, with higher pain levels associated with increased odds of an ED visit. Our findings suggest that routinely collected pain scores could potentially be leveraged to identify at risk population, improve pain management and reduce ED visits for people diagnosed with ovarian cancer. Research Sponsor: None.

11111 **Poster Session**

Patient experiences of diagnosis and treatment of invasive lobular carcinoma: A qualitative study from a prospective registry. First Author: Astrid Quirarte, University of California, San Francisco, San Francisco, CA

Background: Invasive lobular carcinoma (ILC) is the second most common subtype of breast cancer and comprises 10-15% of all cases. ILC is characterized by a diffuse tumor growth pattern due to the absence of E-cadherin, resulting in diagnostic and management challenges including delays in diagnosis. The impact of these unique features on patients with ILC is unknown. To better understand the patient experience, we conducted a qualitative study using thematic analysis. **Methods:** 92 patients diagnosed with ILC and treated at a single institution were recruited to a prospective ILC registry from 2023-2025. We collected data primarily through structured patient interviews regarding screening and surveillance methods, locoregional treatment, systemic therapy, and recurrence. Participants were also asked two open-ended questions regarding how they were diagnosed and about their overall experience. The interviews were conducted through 30 to 60-minute phone calls and transcribed verbatim. Inductive coding was used to develop themes. **Results:** Unique themes were identified corresponding to stages in the diagnosis, treatment, and surveillance of ILC. Participants commonly reported a delay in their diagnosis due to mammographically occult disease and perceived poor sensitivity of breast imaging modalities. This was more pronounced among patients who reported a physical finding related to their breast cancer prior to diagnosis. Additional themes included experiencing a dismissal of symptoms by providers, underestimation of ILC tumor size on preoperative imaging, and concerns over the impact of dense breasts on imaging sensitivity. At the treatment stage of their patient journey, participants reported that providers did not recognize ILC as a distinct tumor subtype and often recommended mastectomy as the initial surgical approach. After treatment of ILC, participants frequently recounted concerns about how they would identify a recurrence and a desire for improved surveillance methods. Reflecting on their journey, many shared that they wished they had been better informed about breast cancer symptoms and breast self-awareness before their diagnosis. **Conclusions:** This study highlights the unique challenges and concerns experienced by patients with ILC, emphasizing the need for more tailored imaging strategies, improved awareness among healthcare providers, and enhanced patient education. Research Sponsor: None.

Selected themes in the patient journey.

Patient Journey Stage	Unique themes
Diagnosis	Mammographically occult disease
	Poor sensitivity of imaging modalities
	Dismissal of symptoms
	Underestimation of ILC tumor size
	Concerns over breast density on imaging sensitivity
Treatment	Providers not recognizing ILC as a distinct tumor-type
	Recommending mastectomy
Surveillance	Concerns about identifying recurrence
	Desire for improved surveillance methods

11112 **Poster Session**

Disparities in glioblastoma care: Insights from a nationwide survey. First Author: Jacob Ellen, Harvard Medical School, Boston, MA

Background: Glioblastoma (GBM) care requires specialized, multidisciplinary management, often creating barriers to healthcare delivery and disparities in care. To identify disparities in how GBM is treated across the United States, we conducted a nationwide survey evaluating healthcare quality and accessibility for GBM patients. **Methods:** OurBrainBank, a patient-led GBM nonprofit, designed and distributed a 36-item HIPAA-compliant survey covering patient experience, quality of life, and demographic data in collaboration with a professional market research company. The survey, available from February to September 2024, targeted current GBM patients, current caregivers, or caregivers who have lost someone within the last year. Recruitment involved newsletters, social media, and communication partnerships with brain cancer organizations. We hypothesized that financial and educational disparities would influence GBM care experiences, assessed through logistic and linear regression using R (version 4.0.5). Only patients with non-missing data were included for each regression analysis. **Results:** Of 525 participants overall (77% caregivers; 23% patients), the median age at diagnosis was 59, with 58% being male, 55% with a college degree, 66% with private insurance and 94% living in urban areas. Education and financial difficulties were associated with disparate GBM care experiences, controlling for age, race, gender, geography (rural, small town, urban), and insurance type (private, public). Participants with no college education (21%) were significantly less likely to be informed about tissue storage (OR = 0.40, 95% CI [0.21, 0.75], p = .004), to undergo MGMT and IDH testing (OR = 0.28, 95% CI [0.11, 0.68], p = .005), to be offered a clinical trial (OR = 0.50, 95% CI [0.29, 0.86], p = .013), and to discuss a second opinion with their doctor (OR = 0.44, 95% CI [0.26, 0.73], p = .002) compared to those with a college degree (55%). They also reported lower satisfaction with care on a 1-10 scale (β = -0.70; 95% CI [-1.26, -0.13], p = .016). These disparities were not observed in participants with some college experience (24%) compared to those with college degrees. Participants reporting financial difficulty in the past year (29%) were also less satisfied with their care (β = -0.58, 95% CI [-1.06, -0.10], p = .018). Financial struggles, however, did not significantly impact mutational testing (OR = 0.57, 95% CI [0.28, 1.18], p = .12), clinical trial offers (OR = 1.25, 95% CI [0.81, 1.92], p = .31), or second opinion discussions (OR = 0.94, 95% CI [0.62, 1.44], p = .79). **Conclusions:** This survey highlights disparities in GBM care, with lower educational attainment linked to reduced access to mutational testing, second opinion discussions and clinical trials, and both lower education and financial difficulties associated with lower care satisfaction. Addressing these disparities is critical to improving GBM care nationwide. Research Sponsor: None.

11113 **Poster Session**

A prospective observational study to compare speech and swallowing outcomes in different types of oral tongue defects and reconstructions in patients undergoing treatment for oral tongue squamous cell carcinoma. First Author: Shivakumar Thiagarajan, Tata Memorial Centre, Mumbai, India

Background: The tongue is an important organ for speech and swallowing functions. Oral tongue squamous cell carcinoma (OTSCC) can per se affect these functions. Surgery followed by adjuvant treatment may further influence these functions. **Methods:** In this prospective study (CTRI/2020/01/023080) we aimed to assess the speech and swallowing outcomes of 100 treatment-naive OTSCC patients receiving the standard care at our center and compare these outcomes with the type of reconstruction done. Speech was assessed using the London speech evaluation scale (LSES), Performance Status Scale for Head & neck (PSSHN) Speech, and Speech Handicap Index (SHI). Swallowing was assessed with Functional Oral Intake Scale (FOIS), Water swallow test (WST), PSSHN diet, videofluoroscopy (VFS) and New Zealand Index for Multidisciplinary Evaluation of Swallowing (NZIMES). These assessments were done at baseline, 1 month, at 6 months and 1 year after surgery. **Results:** Between November 2021 and December 2024, 100 eligible patients were enrolled in the study. The median age of the patients was 45 years. With predominantly male patients. There were 40 T1 & T2 and 60 T3 & T4 OTSCC. Fifty percent of the patients were clinico-radiologically N+ disease. All patients underwent surgery with appropriate reconstruction and adjuvant treatment (n=77,77%). We utilised the tongue defect classification proposed by Bhattacarya S et al, of which 18 patients had type 1 defect, 32 patients had type 2 defect, 9 patients type 3 defect and 41 had type 4 defect. Primary closure was done in 23 patients, Local flaps in 19 patients, free flaps in 28 patients and pectoralis major myocutaneous/myofascial flap (PMMC/PMMF). There were no difference in the baseline functional outcomes except for the restriction in the range of tongue movements in cT3 & cT4 OTSCC. In patients with cT1 & cT2 and cT3 & cT4 OTSCC there was no difference in most of the functional assessment parameters throughout the follow up period with respect to the type of reconstruction done. There was a difference in the SHI from baseline to 1st follow up (p=0.039) and 3rd follow-up (p=0.041) in patients with class 1 & 2 defect. There was a similar difference in patients with class 3 & 4 defects at 1st (p=0.016) and 3rd follow up visit (0.041) compared to baseline. There was no major swallowing differences observed on VFS (NZIMES) in patients with class 1 & 2 defect. However, there was a significant difference in patients with class 3 & 4 defect. **Conclusions:** In this study, we have witnessed no major differences in the functional outcomes with the kind of flap used for various defects. The functional issue seem to be more associated with the defects (reflecting on the extent of resection) more rather than the type of reconstruction done. Clinical trial information: CTRI/2020/01/023080. Research Sponsor: TMC Research Adminstrative Council (TRAC); ICON.

11114 Poster Session

Association between alcohol intake and health-related quality of life in breast cancer survivors. First Author: Sanjna Rajput, Mayo Clinic Hospital, Rochester, MN

Background: Advances in early detection and treatment of breast cancer (BC) have significantly improved survival outcomes. In this growing survivor population, addressing modifiable lifestyle factors such as alcohol intake (AI), a known risk factor for BC and BC recurrence, is critical to improving prognosis and health-related quality of life (HRQoL). This study examines AI patterns and their associations with mental and physical HRQoL in early BC survivorship. **Methods:** Adult patients newly diagnosed (≤1 year) with stage I–III BC at Mayo Clinic Rochester were invited to enroll in the Mayo Clinic Breast Disease Registry. Of the 3252 patients who consented, 1997 completed surveys approximately one-year post-diagnosis, capturing weekly AI, demographic factors, and PROMIS-10 scores. PROMIS-10 (a 10-item measure of health, well-being, and distress) physical and mental health T-scores (mean = 50, SD = 10) are standardized to the U.S. population. Weekly AI was categorized as minimal/none (<1 drink), mild (1–4 drinks), moderate (5–14 drinks), or high (≥15 drinks). Univariate analyses were performed with Monte Carlo-based Fisher exact tests. Multivariate multinomial logistic regression models using a glogit link function assessed AI as the outcome and PROMIS-10 scores as independent variables, adjusting for financial status, smoking, chemotherapy, and moderate exercise because those were associated with AI at year 1 in prior analyses. **Results:** Univariate analyses revealed statistically significant associations between AI and PROMIS-10 scores (Table 1). Adjusted multivariate analyses identified that patients with better physical health were more likely to drink 1–4 or 5–14 drinks/week and less likely to abstain (<1 drink/week) than those with poorer physical health (p=0.027). There was no statistically significant association between AI and mental health QoL after adjustment for covariates. **Conclusions:** Better physical HRQoL during early survivorship was associated with higher AI, suggesting that patients who are feeling physically unwell may be less likely to drink alcohol. Additional public health messaging about the relationship between AI and breast cancer risk and recurrence may be needed, especially for those who are feeling well enough to consume alcohol. Research Sponsor: National Cancer Institute; P30 CA015083.

Univariate analyses of year 1 PROMIS-10 scores with year 1 alcohol consumption using Monte Carlo-based Fisher exact test.

	Alcoholic drinks per week at year 1					
	< 1 (N=1204)	1-4 (N=600)	5-14 (N=175)	15+ (N=18)	Total (N=1997)	P-value
PROMIS global mental health T score, Year 1, n (%)						0.008
< 50	466 (63.8%)	200 (27.4%)	54 (7.4%)	10 (1.4%)	730 (37.1%)	
50+	718 (57.9%)	394 (31.8%)	120 (9.7%)	7 (0.6%)	1239 (62.9%)	
Missing	20	6	1	1	28	
PROMIS global physical health T score, Year 1, n (%)						<0.001
< 50	440 (66.5%)	165 (24.9%)	50 (7.6%)	7 (1.1%)	662 (33.6%)	
50+	740 (56.7%)	432 (33.1%)	124 (9.5%)	10 (0.8%)	1306 (66.4%)	
Missing	24	3	1	1	29	

11115 Poster Session

Caregiver distress: Caring for those who care for our patients. First Author: Abigail Smith Zamorano, UTHealth Houston, Houston, TX

Background: Gynecologic cancers cause high physical and psychosocial strain, worsened by unmet social determinants of health (SDOH) in cancer care. Caregivers help patients access and complete treatment, and increased caregiver distress, especially in vulnerable populations, is linked to worse patient outcomes in chronic illnesses. This study aimed to assess caregiver distress and SDOH in a diverse gynecologic cancer population, understand the relationship between caregiver and patient distress, explore how caregiver distress evolves during chemotherapy, and examine its effect on short-term patient outcomes. **Methods:** A prospective pilot study was conducted of patients starting chemotherapy for gynecologic cancer and their self-identified caregivers at a single academic site after IRB approval. Patient distress was measured with the NCCN Distress Thermometer. Caregivers completed the Modified Caregiver Strain Index (MCSI) and SDOH questionnaires at enrollment (T0) and three months after chemotherapy initiation (T3). Descriptive statistics, χ^2 analyses, and linear regression analyzed differences between high- and low-distress caregivers and changes between time points. **Results:** Between 12/2023 and 06/2024, 60 patients and 38 caregivers enrolled. Patients' mean age was 62, with 27% identifying as Black and 37% as Hispanic. Most (72%) were starting chemotherapy for initial treatment of uterine (47%), ovarian (32%), cervical (20%), and vulvar (1.6%) cancer, and 73% had stage III/IV disease. Caregivers were 63% male, 40% Hispanic, 24% Black, and 26% over age 65. Almost 40% of caregivers did not live with their patient, and 27% cared for others, including 80% for children. Nearly 40% had incomes under $50,000; only 13.2% had paid job-related support. At T0, 77% of patients reported high distress, decreasing to 70% at T3. Caregivers of high-distress patients were younger, working full-time, and had lower incomes. At T0, 42% of caregivers reported high distress, increasing to 66% at T3. MCSI scores rose significantly from 5.84 at T0 to 9.84 at T3 (p<0.001). At T0, 63% of caregivers screened positive for ≥1SDOH domain, rising to 80% by T3. Caregivers with ≥1 SDOH domain at T3 were more likely to experience increased distress (p=0.037). Linear regression showed caregivers with one SDOH domain had MCSI scores 3.69 points higher (p=0.111); those with ≥2 domains scored 5.60 points higher (p=0.024). No differences were found in patient outcomes based on caregiver MCSI scores. **Conclusions:** Caregiver distress and SDOH needs increase significantly during the first months of chemotherapy for gynecologic cancer. Distress is also more pronounced in caregivers with greater SDOH needs. Long-term studies are needed to evaluate caregiver distress and its impact on patient survival. This study highlights the importance of monitoring caregiver well-being and addressing SDOH through targeted interventions. Research Sponsor: UT Center for Clinical and Translational Sciences; UL1TR003167.

11116 Poster Session

Factors associated with patient-reported outcomes in hospitalized patients with cancer. First Author: Noha Soror, The University of Oklahoma Health Sciences Center, Oklahoma City, OK

Background: Utilization of patient reported outcomes (PROs) in the ambulatory setting can help to improve symptom control and clinical outcomes among individuals with cancer. However, little is known about PROs among hospitalized patients with cancer. **Methods:** We conducted a prospective study to examine PROs among hospitalized patients with cancer at the University of Oklahoma Medical Center from 8/2023 to 9/2024. Within 2-5 days of admission, we asked patients to complete surveys assessing physical symptoms (MD Anderson Symptom Inventory [MDASI]; scored 0-10, higher scores = higher severity/interference), psychological symptoms (PHQ-4; scored 0-12, higher scores = higher distress), coping (Brief COPE; scored 2-8 for each of 14 coping domains), and resilience (Brief Resilience Scale [BRS] scored 1-5, higher scores = higher resiliency). We obtained demographic data and clinical characteristics from the electronic health record, including the Charlson Comorbidity Index (CCI). We used regression models to identify factors associated with PROs. **Results:** We enrolled 300 of 441 (68.0%) eligible patients (median age = 64.8 years, 43.0% female, 78.0% White, 73.3% with incurable cancer). The most common cancers were hematologic (29.6%), gastrointestinal (20.0%), and gynecologic (17.0%). The mean MDASI severity and MDASI interference scores were 4.20 and 4.77. Symptoms with the highest mean MDASI severity scores were fatigue (6.56), pain (5.87), disturbed sleep (5.77), and drowsiness (5.27). The mean MDASI interference score was highest for normal work (6.45) and general activity (6.45). The mean PHQ-4 score was 4.41, and the mean BRS score was 2.98. Coping measures with the highest mean Brief COPE scores were use of emotional support (6.66), acceptance (6.55), and religion (6.04) coping. Older age at enrollment was associated with lower MDASI severity (B = -0.02, P < .01), venting (B = -0.02, P = .03), and humor coping scores (B = -.02, P < .01), yet higher use of emotional support (B = 0.02, P = .03) and religion coping scores (B = 0.03, P = .01). Female sex was associated with higher MDASI severity (B = 0.65, P < .01), self-distraction coping (B = 0.63, P < .01), and positive reframing coping (B = 0.77, P < .01). Higher CCI was associated with higher substance use coping (B = 0.11, P < .01) and behavioral disengagement (B = 0.10, P = .03). Patients with hematologic malignancy had higher use of self-distraction coping (B = 0.55, P = .02). We found no differences in PROs for curable versus incurable cancer. **Conclusions:** Hospitalized patients with cancer report high physical and psychological symptoms, with significant associations of PROs with increasing age, female sex, comorbidities, and diagnosis of hematologic malignancy. Our findings highlight the importance of addressing symptom concerns and coping mechanisms in hospitalized patients with cancer, which could inform targeted interventions to enhance PROs and clinical outcomes. Research Sponsor: None.

11117 Poster Session

Perception of postoperative functional status in gastrointestinal and hepatobiliary cancer patients over 80. First Author: Sarah Remer, Loyola University Medical Center, Maywood, IL

Background: Advanced age independently predicts poor surgical outcomes in cancer patients, making octogenarians a particularly high-risk surgical population. Improvement in the delivery of care to these vulnerable patients is critical to improve not only morbidity and mortality outcomes, but also patient-centered outcomes such as functional status. Postoperative functional outcomes can be evaluated by subjective perception and quantified performance. The aims of this study were to 1) identify risks associated with 30-day postoperative perceptions of functional decline in octogenarians undergoing operations for gastrointestinal or hepatobiliary cancers and 2) explore whether these perceptions correlate with quantitative decline measured as a function of decreased ability to perform activities of daily living (ADLs). **Methods:** American College of Surgeons National Surgical Quality Improvement Program Geriatric Surgery data (2015-2017) was used. All postoperative diagnoses related to gastrointestinal or hepatobiliary cancers were included for patients ≥80 years old. Multivariable logistic regression models identified risks associated with perceiving worsened physical function 30-days postoperatively. Chi-square tests were used to examine concordance between 30-day outcomes of perceptions of physical function with measured performance of ADLs. **Results:** 369 patients from 14 hospitals were included. Mean age was 85.4 (SD 4.1 years). The most common diagnosis was "malignant neoplasm of ascending colon" (16%). Preoperatively 62% of patients were living supported at home, 37% were using a mobility aid, and 17% had ≥1 fall in the past year. Overall, 80% did not have a quantified decline in function as measured by ADLs; however, 17% of these reported perceived functional decline (K= 0.47). Significant risk factors for perceived functional decline were major postoperative morbidity (OR 5.5; 95% CI 2.3-13), disseminated cancer (2.2; 1.1-4.4), new postoperative mobility aid use (2.2; 1.1-4.6), and cognitive impairment (4.7; 1.7-12.9). **Conclusions:** There are inconsistencies between patient experience and clinician view of functional outcomes for octogenarians undergoing surgical intervention for gastrointestinal and hepatobiliary cancers. Ability to perform ADLs is frequently used to evaluate patient functional status. This discrepancy in patient perception and quantified measure highlights the need for the development and utilization of patient-centered and patient-reported outcome (PRO) measures to evaluate this vulnerable patient population. PROs may enhance surgeon understanding of the patient experience and allow for more nuanced goals of care discussions and targeted interventions to improve delivery of care to these patients. Research Sponsor: None.

	Quantified Functional Decline		
Patient Reported Functional Decline	No	Yes	Total
No	246	22	268
Yes	49	52	101
Total	295	74	369

11118 **Poster Session**

Prospective assessment of health-related quality of life in early phase clinical trials. First Author: Udit Nindra, Liverpool Hospital, Liverpool, Australia

Background: Early phase clinical trials (EP-CTs) provide patients with access to novel therapeutics once standard of care options are exhausted or not available. Health related quality of life (HRQoL) is not routine in all EP-CTs where key focus may lie on dose limited toxicities and safety analyses. However for clinicians, understanding the impact of such trials on HRQoL is fundamental to consent patients, especially when the benefits on tumour response may be unknown. **Methods:** The PEARLER (Patient Experience in eARLy phasE cancer clinical tRials) study was conducted with a key aim of focusing on assessing HRQoL in participants undergoing EP-CTs using a multi-centre prospective cohort setting. All participants completed a baseline demographic survey on cycle 1 day 1 with EORTC-QLQ-C30 on day 1 of cycles 1 through 6 or end of trial (EoT). Multilevel models were used to analyse trend over time for Global Health Status (GHS), and Physical Function Score (PFS). **Results:** A total of 122 participants were recruited. Median age was 62 years (25 – 83 years) with 63 (52%) participants identifying as female. Of the total participants, 47 (39%) were enrolled in immuno-oncology EP-CTs whilst the remainder participated in EP-CTs focused on targeted therapies. The median number of EP-CT cycles completed by participants was 3. Median GHS) Score was 67 at baseline and remained steady across all participants throughout their EP-CT (p=0.188). GHS deterioration, defined by a 10-point decrease from baseline to EoT, occurred in 29/122 (24%) whilst GHS improvement occurred in 16/122 (13%). Median Physical Function Score (PFS) was 87 at baseline and remained steady across all participants throughout their EP-CT (p=0.104). PFS deterioration, defined by a 10-point decrease from baseline to EoT, occurred in 30/122 (25%) whilst GHS improvement occurred in 6/122 (5%). There was no statistically difference in change in GHS or PFS in younger versus older patients (less than or equal to 60 years versus over 60 years), tumour type, EP-CT type, gender or those from lower versus higher socioeconomic backgrounds. **Conclusions:** PEARLER is the first prospective cohort study investigating change in GHS and PFS over time in patients undergoing EP-CTs. Although almost three-quarters of participants who undertake EP-CTs either sustain or improve their GHS or PFS, one quarter do not. Patients need to be educated not only on the potential response rate of the EP-CT they are enrolling into but also the possibility of reduced HRQoL whilst participating in studies. Further research is needed to identify predictive and protective factors of HRQoL in patients undergoing EP-CTs. Research Sponsor: None.

11119 **Poster Session**

Financial, social and time toxicity in early-phase cancer clinical trials: The PEARLER study. First Author: Udit Nindra, Liverpool Hospital, Liverpool, Australia

Background: Early phase clinical trials (EP-CTs) provide patients with access to novel therapeutics once standard of care options are exhausted or not available. In addition to the drug related potential benefits and risks with participating in such studies, patients are also exposed to hidden toxicities which often go unnoticed. Hidden toxicities have been classed into a number of major categories which include but are not limited to time, financial, and social. Currently there are no prospective studies assessing these hidden toxicities in the EP-CT space. **Methods:** The PEARLER (Patient Experience in eARLy phasE cancer clinical tRials) study was conducted with a key aim of focusing on assessing time toxicity, financial toxicity and social toxicity in a multi-centre prospective cohort setting. All participants completed a baseline demographic survey on cycle 1 day 1 along a time toxicity survey and the EORTC-QLQ-C30 on day 1 of cycles 1 through 6. Multilevel models were used to analyse trend over time for financial toxicity and social toxicity. **Results:** A total of 122 participants were recruited. Median age was 62 years (25 – 83 years) with 63 (52%) participants identifying as female. A total of 47 (39%) participants were enrolled in immuno-oncology EP-CTs whilst the remainder participated in targeted-therapy focused EP-CTs. The median time toxicity was 26%. Of 122 participants, 20 (16%) reported subjective time toxicity with 17 (85%) reporting this occurring at either cycle 1 or 2. Under half (54/122, 44%) reported any degree of financial toxicity whilst participating in their EP-CT; with 9 of this 54 (17%) reporting the maximum score of '4'. Financial toxicity remained largely stable throughout EP-CT participation (p=0.136), with 6/122 (5%) participants reporting higher financial burdens at the end of their clinical trial compared with baseline. Most participants (87/122, 71%) reported any degree of reduced social function, whilst participating in their EP-CT. However, 26/122 (21%) participants reported lower social functional scores at conclusion of their EP-CT compared with baseline whilst 24/122 (20%) reported higher social functional scores. **Conclusions:** PEARLER is the first prospective cohort study investigating financial, social and time toxicity in EP-CTs. Although time toxicity remains a concern of EP-CTs, the majority of subjects did not subjectively note this to be a concern. Financial and social toxicity remained stable during EP-CT participation thereby suggesting that EP-CTs may not negatively affect the majority of participants. However almost half of patients experienced financial toxicity and more than half experienced social toxicity due to cancer related treatment and greater efforts to identify and support patients financially and socially is needed. Research Sponsor: None.

11120 **Poster Session**

Final patient-reported outcomes (PROs) in unselected men receiving talazoparib (TALA) + enzalutamide (ENZA) vs placebo (PBO) + ENZA as initial treatment for metastatic castration-resistant prostate cancer (mCRPC): Results from the phase 3 TALAPRO-2 study. First Author: Nobuaki Matsubara, National Cancer Center Hospital East, Kashiwa, Japan

Background: TALAPRO-2 demonstrated statistically significant improvement with TALA + ENZA vs PBO + ENZA in radiographic progression-free survival (primary endpoint; HR=0.63; 95% CI, 0.51–0.78; $P<0.0001$) in unselected men with mCRPC. Prior PRO analyses (data cutoff: Aug 16, 2022) reported no clinically meaningful between-arm differences in any functioning scales and a longer time to definitive deterioration (TTDD) in global health status (GHS)/quality of life (QoL) for TALA + ENZA (median 30.8 mo) vs PBO + ENZA (25.0 mo; HR=0.780; 95% CI, 0.62–0.99; $P=0.038$). Here we report updated (data cutoff: Sep 3, 2024) final PROs for the unselected cohort. **Methods:** PROs were assessed at day 1 (baseline) and scheduled visits (every 4 weeks until week 53, and then every 8 weeks) until radiographic progression using the EORTC QLQ-C30 and its prostate cancer module, QLQ-PR25, and worst pain by BPI-SF item 3. Prespecified PRO analyses included overall mean change from baseline (per longitudinal repeated measures mixed-effects model), time to deterioration (TTD), and TTDD. The clinically meaningful threshold was ≥10 points for EORTC scales and ≥2 points for BPI-SF. Between-arm comparisons of TTD/TTDD were made using a stratified log-rank test and a Cox proportional hazards model. **Results:** Of the 805 men randomized to treatment, 793 (TALA + ENZA, n=395; PBO + ENZA, n=398) had 1 baseline + ≥1 follow-up PRO score. With extended follow-up, median TTDD for GHS/QoL in the TALA + ENZA arm was 41.5 mo vs 34.1 mo in the PBO + ENZA arm (HR=0.878; 95% CI, 0.704–1.096; $P=0.2487$). Median TTDD for urinary symptoms in the TALA + ENZA arm was 59.8 mo vs 58.0 mo in the PBO + ENZA arm (HR=0.861; 95% CI, 0.622–1.191; $P=0.3655$). No clinically meaningful between-arm differences in QLQ-C30 functioning and symptoms scales were observed (Table). No between-arm difference in TTD for worst pain by BPI-SF was observed. **Conclusions:** With extended follow-up, QoL was maintained with TALA + ENZA. These data confirm that QoL is not compromised when TALA is added to ENZA, for initial treatment of unselected men with mCRPC. Clinical trial information: NCT03395197. Research Sponsor: Pfizer Inc.; Astellas Pharma Inc. provided enzalutamide.

QLQ-C30 Scale		Estimated Mean Difference, TALA + ENZA – PBO + ENZA (95% CI)	*P* Value
Functioning	GHS/QoL	-2.2 (-4.3, -0.1)	0.0382
	Physical	-1.6 (-3.9, 0.7)	0.1663
	Role	-1.7 (-4.2, 0.9)	0.2009
	Emotional	-0.9 (-2.7, 1.0)	0.3620
	Cognitive	-0.9 (-3.0, 1.1)	0.3791
	Social	-0.9 (-2.9, 1.2)	0.4088
Symptoms	Fatigue	2.4 (0.1, 4.7)	0.0437
	Nausea + Vomiting	0.8 (-0.1, 1.6)	0.0723
	Pain	-0.8 (-3.3, 1.7)	0.5270

Positive values favor TALA + ENZA for GHS/QoL and functioning scales; negative values favor TALA + ENZA for symptoms scales.

11121 **Poster Session**

Final patient-reported outcomes (PROs) in men with metastatic castration-resistant prostate cancer (mCRPC) and homologous recombination repair (HRR) gene alterations receiving initial treatment with talazoparib (TALA) + enzalutamide (ENZA) vs placebo (PBO) + ENZA in the TALAPRO-2 study. First Author: Andre P. Fay, PUCRS School of Medicine, Porto Alegre, Brazil

Background: The phase 3 TALAPRO-2 study showed a statistically significant improvement in radiographic progression-free survival for TALA + ENZA vs PBO + ENZA (HR=0.45; 95% CI, 0.33–0.61; $P<0.0001$) in men with HRR-deficient mCRPC. Prior PRO analyses (data cutoff: Oct 3, 2022) reported no clinically meaningful between-arm differences in any functioning scales and a longer time to definitive deterioration (TTDD) in global health status (GHS)/quality of life (QoL) for TALA + ENZA (median 27.1 mo) vs PBO + ENZA (median 19.3 mo; HR=0.69; 95% CI, 0.49–0.97; $P=0.032$). Here we report updated (data cutoff: Sep 3, 2024) final PROs for the HRR-deficient cohort. **Methods:** PROs were assessed at day 1 (baseline) and every 4 wks until wk 53, then every 8 wks until radiographic progression using the EORTC QLQ-C30 and its prostate cancer module, QLQ-PR25, and worst pain by BPI-SF item 3. Prespecified PRO endpoints included overall mean change from baseline (per longitudinal repeated measures mixed-effects model), time to deterioration (TTD), and TTDD. The clinically meaningful threshold was ≥10 points for EORTC scales, ≥2 points for BPI-SF. Between-arm comparisons of TTD/TTDD were made via stratified log-rank test and Cox proportional hazards models. **Results:** At extended follow-up, 394/399 patients in the HRR-deficient cohort (n=197, both arms) had completed baseline + ≥1 follow-up PRO score. TALA + ENZA resulted in a numerically longer TTDD in GHS/QoL vs PBO + ENZA (HR=0.766; 95% CI, 0.555–1.057; $P=0.1063$; median, 34.2 vs 22.1 mo, respectively). HR for TTDD in disease-specific urinary symptoms was 0.684; 95% CI, 0.421–1.113; $P=0.1247$) for TALA + ENZA vs PBO + ENZA. TTD in worst pain by BPI-SF favored TALA + ENZA vs PBO + ENZA (HR=0.552; 95% CI, 0.325–0.937; $P=0.0255$). Differences in physical, role, emotional, cognitive functioning scores and pain favored TALA + ENZA vs PBO + ENZA, but did not meet the clinically meaningful threshold (Table). **Conclusions:** With extended follow-up, treatment differences favoring TALA + ENZA vs PBO + ENZA were observed in some functioning and symptoms scales. Consistent with prior analyses, overall QoL was maintained in patients with HRR-deficient mCRPC receiving initial treatment with TALA + ENZA in TALAPRO-2. Clinical trial information: NCT03395197. Research Sponsor: Pfizer Inc.; Astellas Pharma Inc.

QLQ-C30 Scale		Estimated Mean Difference, TALA + ENZA – PBO + ENZA (95% CI)	*P* Value
Functioning	GHS/QoL	2.7 (-0.8, 6.2)	0.1294
	Physical	5.3 (1.9, 8.7)	0.0022
	Role	4.3 (0.0, 8.6)	0.0524
	Emotional	4.9 (1.6, 8.2)	0.0038
	Cognitive	5.5 (2.0, 9.1)	0.0024
	Social	1.9 (-1.7, 5.4)	0.3005
Symptoms	Fatigue	-1.5 (-5.2, 2.3)	0.4448
	Nausea + Vomiting	0.1 (-1.4, 1.6)	0.8936
	Pain	-8.5 (-12.3, -4.7)	<0.0001

Positive values favor TALA + ENZA for GHS/QoL and functioning scales; negative values favor TALA + ENZA for symptoms scales.

11122 Poster Session

Beyond survival: Prospective longitudinal insights into quality of life after hepatectomy for colorectal liver metastases. First Author: Ankur P. Choubey, Department of Surgery, Memorial Sloan Kettering Cancer Center, New York, NY

Background: The long-term health related quality of life (QoL) after curative intent hepatectomy for high-risk colorectal liver metastases (CRLM) is not well described. **Methods:** This prospective single-center study enrolled patients with resectable CRLM with Clinical Risk Score ≥3. European Organization for Research and Treatment of Cancer QLQ-C30, LMC21, and EuroQol EQ-5D-5L were administered at preoperative and postoperative visits, and at 6, 12, 18, 24, and 36 months from hepatectomy. Patient characteristics at baseline along with colorectal cancer disease state were collected at each timepoint on a scale from no evidence of disease (NED) to progressive disease on best supportive care. Linear mixed models were used to examine the trajectory of QoL scores with disease state modeled as a time-varying variable. **Results:** From 297 consented, 146 were evaluable by completing preoperative and postoperative surveys. Median age was 52 years (IQR: 45, 63), 42% (n=61) were female, 84% (n=122) were Non-Hispanic White, 70% (n=102) had synchronous CRLM, and 80% (n=117) received hepatic artery infusion chemotherapy (HAIC). Overall, QLQ-C30 demonstrated decrease in global health from baseline at post-operative survey ($p<0.05$) with subsequent improvements until returning to pre-operative levels at 12 months. Similarly, self-assessed health state on EQ-VAS— a visual analog scale from 0 to 100 that corresponds to worst and best health possible, respectively— decreased post-operatively ($p<0.05$) with recovery to baseline by 6 months. Among NED patients, QLQ-C30 QoL scores recovered to pre-operative levels 6 months after hepatectomy, whereas those with recurrent cancer reported scores below baseline at every follow-up assessment (all $p<0.05$). On EQ-VAS, NED patients were comparable to baseline at 6 months and reported higher scores than baseline at 24 months (p=0.029). Patients with recurrence had similar EQ-VAS scores as baseline at 12 months but remained lower than NED patients at each timepoint (all $p<0.05$). HAIC did not impact QoL assessed by QLQ-C30 (p=0.725) or EQ-VAS (p=0.559) during follow-up. **Conclusions:** Health related QoL suffers in the immediate post-operative period before returning to pre-operative levels and exceeding it among patients without recurrence. While cancer recurrence significantly influenced patient experience, HAIC did not sway QoL. Research Sponsor: None.

Comparison of self-assessed EQ-VAS scores stratified by cancer recurrence status, where 0 and 100 correspond to worst and best health possible, respectively.

Time Point	No Recurrence, QoL Estimate	Cancer Recurrence, QoL Estimate	P-value
Pre-op		75.28	
Post-op		66.45	
6m	75.37	68.10	<0.05
12m	80.78	70.15	<0.05
18m	80.28	70.48	<0.05
24m	83.38	74.21	<0.05
36m	78.32	57.44	<0.05

11123 Poster Session

Quality of life in a phase III study of prospective radiation therapy (IMRT) +/- cetuximab for locally advanced resected head and neck cancer: NRG/RTOG 0920. First Author: Clement K. Gwede, H. Lee Moffitt Cancer Center and Research Institute, Tampa, FL

Background: We tested the primary question whether the addition of cetuximab to postoperative radiotherapy (IMRT) results in poorer patient reported outcomes (PROs) at 12 months compared to IMRT alone. We also examined changes in PROs over time. **Methods:** Randomized and eligible patients who consented to quality of life (QOL) assessment completed PROs measured by 5 instruments, prior to treatment (baseline) and at 3, 12, and 24 months after IMRT. Instruments included: 1) *Functional Assessment of Cancer Therapy-Head & Neck (FACT-HN),* a multidimensional QOL instrument for use with head and neck cancer patients; 2) *University of Michigan Xerostomia-Related Quality of Life Scale (XeQOLS)* covering mouth/throat dryness and its impact on oral health-related QOL; 3) *Dermatology Life Quality Index (DLQI)* for skin-related changes; 4) *EuroQol (EQ-5D-3L)* covering usual activities and perceived current health state; 5) *Performance Status Scale for Head and Neck Cancer (PSS-HN)* assessing normalcy of diet, public eating, and understandability of speech. Higher scores on XeQOLS and DLQI indicate worse QOL; otherwise higher scores indicate better QOL for other measures. For FACT-HN, XeQOLS, DLQI, and EQ-5D-3L, changes from baseline were compared by Van Elteren test, and for PSS-HN, the % ≤ 50 was compared by Z test. 158 patients per arm provided 80% power to test the difference between IMRT + cetuximab and IMRT alone. Changes in PROs over time were evaluated using mixed models. Two-sided tests were used with α=0.05. **Results:** 499 of 577 eligible patients (86%) consented to QOL. There were no significant differences between treatment arms (IMRT vs. IMRT + cetuximab) for all PRO measures in change from baseline to 3 or 12 months post-IMRT (see table). At 24 months, the change from baseline was significantly different for DLQI (p=0.02), but the difference was not clinically meaningful; other PROs were not significantly different. There were no significant differences between treatment arms for PSS-HN diet, eating, or speech at any time point (see table). Regarding treatment effect over time, in both treatment groups, all PRO measures showed greatest decline at 3 months followed by improvement towards baseline by 24 months. **Conclusions:** Treatment with IMRT + cetuximab was not associated with worse PROs compared to IMRT alone. Furthermore, findings demonstrate important recovery trends in QOL with return to baseline for most measures in both study arms. Clinical trial information: NCT00956007. Research Sponsor: National Cancer Institute; UG1CA189867; National Cancer Institute; U10CA180868; National Cancer Institute and Eli Lily; U10CA180822; National Cancer Institute and Eli Lily; U24CA196067; National Cancer Institute and Eli Lily; U24CA180803.

Results at 12 months.

Instrument (score range)		IMRT	IMRT+Cetuximab	p-value
FACT-HN (0-148)	n	122	132	
	Mean change	-0.41	1.31	0.94
XeQOLS (0-4)	n	105	114	
	Mean change	0.52	0.46	0.99
DLQI (0-30)	n	121	133	
	Mean change	-0.07	0.44	0.23
EQ-5D-3L (0-1)	n	108	117	
	Mean change	0.01	0.02	0.87
PSS-HN diet (0-100)	n	130	141	
	% ≤ 50	37.7	39.7	0.73
PSS-HN eating (0-100)	n	130	141	
	% ≤ 50	20.0	15.6	0.34
PSS-HN speech (0-100)	n	131	140	
	% ≤ 50	10.7	7.9	0.42

11124 Poster Session

Cancer misinformation and trust in doctors and scientists among cancer survivors. First Author: Brandon M. Godinich, Texas Tech Health Science Center El Paso, El Paso, TX

Background: Health misinformation is a significant public health concern and has acutely worsened in the past decade. Cancer survivors must navigate a complex health system after a critical diagnosis and may be particularly susceptible to the adverse effects of misinformation. This study explores information perception and trust between survivors and those without (w/o) a cancer history. **Methods:** Data from the nationally representative Health Information National Trends Survey (HINTS) from 2017-2022 was used to compare questions regarding cancer and health information and trust (grouped Strongly/Somewhat Agree and Disagree) between those with a prior cancer diagnosis (survivors) and those w/o cancer. Demographic data included: age, gender, race/ethnicity, sexual orientation, education, employment, and household income. Analysis was done in STATA with Chi-squared and T-tests testing between survivors and those w/o cancer; multivariate analysis (MVA) focused on survivors. **Results:** 21,753 people were included, 3,479 (16.0%) were cancer survivors. Survivors were demographically different than those w/o cancer including being older (median 68 vs 56), less likely employed (22.5 vs 40.5%), more commonly White (80.2 vs 69.3%) and less often Black race (12.7 vs 18.4%) ($p<001$ for all). More people w/o cancer had used the internet in the past year to look for medical information (73.6% vs 70.4% in survivors), however when searching for cancer information specifically, less survivors (49.8% vs 55.7% w/o cancer) were concerned about the quality of the information (p=0.001 both). More survivors trusted information about cancer from a doctor (77.6% survivors vs 72.3% w/o cancer, p=0.02). But less people overall trusted scientists about cancer information (52.1% survivors, 57.2% w/o cancer, p=NS) with 1 in 20 people trusting scientists "not at all" (5.1% survivors, 5.2% w/o cancer, p=NS). More than half felt that health recommendations from experts seemed to conflict/contradict one another (58.1% survivors, 56.3% w/o cancer, p=NS). In an MVA of survivors, only age was associated with being concerned about the quality of cancer information online with younger survivors being less concerned [OR 0.98, 95%CI 0.96-0.99, $p<0.001$]. **Conclusions:** In this national study, researching health information online was common and roughly half were concerned about the quality of cancer information they found. Compared to those w/o a cancer history, cancer survivors were less concerned about their ability to find high quality cancer information with younger survivors feeling the most confident. While most people trusted doctors, more than half said that experts seemed to contradict each other and 1 in 20 had no trust in scientists to provide cancer information. Future interventions should focus on health information literacy and improving communication on evidence-based cancer information. Research Sponsor: None.

11125 Poster Session

Circulating tumor DNA (ctDNA) analysis guiding adjuvant therapy in patients (pts) with colorectal cancer (CRC): Impact on fear of cancer recurrence (FCR). First Author: Sue-Anne McLachlan, St. Vincent's Hospital, Melbourne, Australia

Background: ctDNA detection following curative intent treatment is highly prognostic, with potential to impact patient fear of cancer recurrence (FCR). In 3 separate randomized trials (DYNAMIC II, III, rectal), pts with early-stage CRC were randomly assigned to treatment decision guided by ctDNA results (adjuvant chemotherapy escalation if ctDNA positive, de-escalation or no treatment if ctDNA negative), or according to standard clinicopathological features. The relationship between being informed of a high recurrence risk, or treatment de-escalation, and FCR is unclear. This study aims to explore the relationship between biomarker-informed adjuvant chemotherapy (ACT) decision making and FCR, including changes over time. **Methods:** A subset of pts from the 3 DYNAMIC studies completed validated self-report questionnaires measuring FCR, anxiety, depression and quality of life. Data were collected at three time points: after surgery (T1), at the time of the ACT decision (T2), and 9-12 months later (T3). Pts randomized to the ctDNA-guided group received a ctDNA test result (positive or negative) at T2, while those in the standard of care (SOC) group did not. The primary endpoint was the FCR Inventory Short Form score (FCRI-SF). FCR patterns over time were analyzed using a mixed model 2 (Randomization) x 3 (Time) ANCOVA. A 2 (Randomization) x 2 (Chemotherapy Status) ANCOVA was used to assess ACT's impact on FCR at follow-up. Gender, age, and cancer stage were included as covariates. **Results:** 317 pts from 35 Australian sites participated in the FCR substudy (74% response rate for all timepoints). Two-thirds were male, and the mean age was 60 years. Of the ctDNA-guided group (n=176), 73% had a negative ctDNA result. At baseline, 63% of patients exhibited clinically significant levels of FCR (FCRI-SF >13). Younger age, female gender, anxiety, and higher cancer stage all predicted higher baseline FCR. FCR significantly decreased over time for all pts ($F(2,176) = 3.64$, $p = .03$). This reduction was more pronounced in the ctDNA-guided group compared to the SOC group ($F(2, 176) = 3.83$; $p = .02$), although the effect size was small (Cohen's d =0.24). In the ctDNA-guided group, no differences in FCR were found between pts based on ctDNA result (positive vs. negative). High baseline anxiety was the only independent predictor of FCR at 12 months. Chemotherapy receipt, cancer stage, depression, and quality of life scores were not predictive of FCR over time. **Conclusions:** In pts with early-stage CRC, neither a positive nor negative ctDNA result impacted FCR. ctDNA-guided approach to determining ACT was associated with a greater reduction in FCR over time compared to SOC. This biomarker-guided treatment approach has potential to improve ACT selection as well as psychosocial outcomes. Temporal reduction in FCR is likely driven by increased prognostic certainty over time. Clinical trial information: 12615000381583. Research Sponsor: St Vincents Hospital Research Endowment Fund.

11126 Poster Session

Electronic patient-reported outcomes (ePRO) in patients with advanced melanoma receiving immune checkpoint inhibitors: Insights from the Canopy ePRO system. First Author: Benjamin Avi Derman, University of Chicago, Chicago, IL

Background: Health-related quality of life (HRQoL) outcomes are prognostic in melanoma. There is little data comparing HRQoL during nivolumab (nivo) and pembrolizumab (pembro) exposure in patients with melanoma. Electronic patient-reported outcomes (ePROs) provide valuable insights into HRQoL; this study reports on ePRO data from community oncology practices using the Canopy Remote Therapeutic Monitoring (Canopy RTM) platform to explore ePROs in patients with melanoma treated with nivo, pembro, or nivo/ipi. **Methods:** The Canopy RTM system is a proprietary, cloud-based platform that directly integrates with electronic medical records systems to enable RTM. Patients using Canopy RTM could submit symptom reports using smart devices or a phone system. This study retrospectively analyzed ePRO data of patients with melanoma treated with nivo, pembro, or nivo/ipi, excluding those who received chemotherapy during index treatment. Symptom and broad symptom category reporting during each treatment was assessed using descriptive statistics. Sensitivity analyses were performed, including limiting time at risk of symptom reports to 60 days following index and excluding patients with record of exposure to ipilimumab prior to index. **Results:** 386 patient treatments were included: 140 receiving nivo; 169, pembro; and 57, nivo/ipi. Median age was 66, 69, 61 years across the nivo, pembro, and nivo/ipi groups, respectively. Median time on therapy was 285, 269, 49 days for nivo, pembro, and nivo/ipi, respectively. Compared to pembro, nivo treatment was associated with higher incidence of infection symptoms, difficulty with activities of daily living, gastrointestinal symptoms, and pain (Table 1). Despite significantly shorter time on therapy, more patients reported infection and rash during nivo/ipi treatment than during nivo treatment. Sensitivity analysis limiting time at risk of symptoms to 60 days following index revealed similar findings, albeit with greater proportions of patients treated with nivo/ipi reporting symptoms across most symptoms. **Conclusions:** Pembro monotherapy may be associated with a lower incidence of some symptoms compared to nivo (+/- ipi), while nivo monotherapy has fewer symptoms than nivo/ipi treatment. Further research is warranted to confirm these findings. Research Sponsor: Canopy Care.

Select symptoms and symptom categories (composites) reported during treatment.

Symptom or composite	Pembrolizumab	Nivolumab	Nivo/Ipi
Infection (composite)	57 (34%)	67 (48%)	31 (54%)
Cough	25 (15%)	30 (21%)	14 (25%)
Fever under 100.4F	6 (3.6%)	10 (7.1%)	7 (12%)
Difficulty breathing	27 (16%)	26 (19%)	13 (23%)
Gastrointestinal (composite)	69 (41%)	67 (48%)	30 (53%)
Indigestion	13 (7.7%)	16 (11%)	5 (8.8%)
Diarrhea	36 (21%)	31 (22%)	14 (25%)
Activities of daily living (composite)	84 (50%)	88 (63%)	34 (60%)
Rash	22 (13%)	20 (14%)	15 (26%)

11127 Poster Session

Evaluating acceptance of scalp cooling in patients receiving chemotherapy for primary gynecologic cancers: Lessons from a randomized controlled trial. First Author: Ka Yu Tse, Department of Obstetrics and Gynaecology, Queen Mary Hospital, The University of Hong Kong, Hong Kong, Hong Kong

Background: Scalp cooling is effective in preventing chemotherapy-induced alopecia (CIA) in cancer patients. However, its effect and acceptance are not certain in gynecologic cancer patients particularly in Asia. **Methods:** The CHARM study was a single-center randomized study. Women with proven gynecologic cancer planning for 3-weekly carboplatin and paclitaxel were randomised to receive usual care (control group) or scalp cooling using the Paxman Orbis II system (Paxman Coolers Limited, Huddersfield, United Kingdom) (intervention group). The primary endpoint was the incidence of psychological distress, i.e., Patient Health Questionnaire Anxiety and Depression Scale (PHQ-ADS) score $\geq$10. The study was approved by the Institutional Review Board of the University of Hong Kong/Hospital Authority Hong Kong West Cluster (UWB 19-514). **Results:** Between November 2019 to November 2021,142 women were invited to join the study. 56 women (39.4%) declined to participate, and the most common reason was worries about coldness (Table 1). 44 women were randomized to the intervention group and 42 to the control group. Fewer women in the intervention had psychological distress compared to the control group after cycle 2 of chemotherapy (27.8% vs 62.2%, p=0.003). The incidence of Grade $\geq$ 3 adverse events were similar between both groups (7.5% vs 5.1%, p=1.0). However, 12 out of 40 (30.0%) in the intervention group did not comply with scalp cooling, among which nine (75%) were due to feeling cold despite measures like using blankets and hot water. **Conclusions:** Scalp cooling was associated less-psychological distress in Asian women using chemotherapy for gynecologic cancer. Nevertheless, the high refusal rate to join the study and high drop-out rate limited its use in these women. This might be partially due to some misbelief that associated head coldness with poor general health in Traditional Chinese Medicine. More strategies are needed to improve the acceptance of scalp cooling. Clinical trial information: NCT04168242. Research Sponsor: WKK Medical Equipment Company Limited.

Reasons for refusal to join the study.

Reasons	Number of women (%)
Worries of coldness	34 (60.7%)
Worries of musculoskeletal pain/headache	2 (3.6%)
Psychiatric stress	2 (3.6%)
Personal image	4 (7.1%)
Logistic issue	3 (5.4%)
Unknown reasons	11 (19.6%)
Total	56

11128 Poster Session

Preliminary findings from the ALVA ePRO Platform pilot study: A novel approach to collecting quality of dying and death data among informal caregivers in palliative care. First Author: Javier Retamales, Grupo Oncologico Cooperativo Chileno de Investigacion - GOCCHI, Santiago, Chile

Background: Quality of Dying and Death (QODD) is a pivotal outcome in end-of-life care, yet traditional data collection methods, such as phone calls, often suffer from low compliance and significant caregiver burden. The ALVA ePRO platform, a novel tool developed for collecting Patient-Reported Outcomes (PRO) via text messaging apps, aims to overcome these challenges by improving data collection efficiency and caregiver experience. This study evaluates the feasibility, compliance, and acceptability of ALVA ePRO among informal caregivers of terminal cancer patients in a Latin American palliative care setting. **Methods:** We conducted a pilot, single-arm study with 21 informal caregivers of terminal cancer patients. Participants received the QODD questionnaire through their preferred text messaging app. Caregivers who preferred traditional phone calls were allowed to use that method. Compliance was measured by the completion rate of the questionnaires, while acceptability was assessed through semi-structured interviews. Descriptive statistics were used for quantitative outcomes. **Results:** A total of 38 caregivers were invited to participate, and 21 caregivers signed the informed consent. Of the 21 participants, 20 completed the questionnaire, while 1 did not due to difficulty understanding the questions. Completion times ranged from 5 minutes to 23 hours and 34 minutes, highlighting considerable variability. Reasons for non-participation included technical issues, scheduling conflicts, and caregiver reluctance to attend the hospital. Preliminary interview data revealed that caregivers found the platform user-friendly and appreciated the flexibility it offered, though a few faced emotional challenges when recalling sensitive experiences. **Conclusions:** The ALVA ePRO platform demonstrates high acceptability and a strong completion rate, with significantly improved compliance compared to historical phone-based methods. It also significantly improved adherence and completion compared to our previous phone call approach using the same questionnaire. Interest in participation increased from 67.0% to 81.6%, and the completion rate from 92% to 95%. These findings suggest that text message-based data collection is an effective approach for collecting QODD data in palliative care, particularly in settings with logistical or emotional barriers to traditional methods. Future work will focus on refining the platform and exploring its scalability for larger cohorts and other palliative care contexts. Research Sponsor: The Hope Foundation for Cancer Research; 2024.

Summary of key measures and completion time for the ALVA ePRO Platform pilot study.

Measure	Preliminary Result
Enrollment (target: 20)	21 signed consent
Completion rate	95% of enrolled participants
Average Completion Time	174 minutes
Median Completion Time	16 minutes
Messaging app used	Whatsapp (100%)

11129 Poster Session

A patient-reported outcome measure (PROM) to capture patients' experiences with immuno-oncology therapy (IO)-induced cytokine release syndrome (CRS): The IO-induced CRS patient diary. First Author: Joyce R. Talavera, Sanofi, Cambridge, MA

Background: IO-inducedCRS has various signs and symptoms that impact different aspects of patients' lives. While the frequency and severity of IO-induced CRS events underscore the benefit–risk profile and tolerability of IO therapies, patients' perceptions are critical for measuring the impact of these events on their lives. In this qualitative research study, we developed a novel PROM to track the onset, resolution, and impact of IO-induced CRS events in clinical trials. **Methods:** Clinician insights and patient interviews were used to identify common IO-induced CRS signs, symptoms, and impacts. Patient-reportable symptoms and impacts were prioritized to form the basis of the IO-induced CRS Patient Diary. The PROM was tested in cognitive debriefing (CD) interviews with 3 clinicians and 3 waves of CD interviews with patients on IO (5 per wave; N = 15). Changes were made to the PROM between each wave to ensure relevance and improve interpretation and usability. **Results:** After a literature review, qualitative research with 9 clinical experts, and concept-elicitation interviews with 14 patients on IO (3 on CAR-T, 11 on non-CAR-T therapy), 37 patient-reportable signs and symptoms and 7 clinical signs (non–patient reportable) associated with IO-induced CRS were listed. Patients' concept descriptions and clinicians' concept priorities were examined, and 12 symptoms and 4 impacts across 5 domains (emotional, physical, social, activities of daily living, and financial) were included in the final diary. The IO-induced CRS Patient Diary—an electronic PROM—has three versions for use at different points in a clinical trial. The "baseline" version is completed before initial IO administration; patients report the incidence and severity of 12 symptoms and their impact on overall health (recall period: the past week). The "day of treatment" version, completed the evening of the treatment day, asks the same questions, plus about symptom manageability (recall period: since receiving the study medication on that day). The "subsequent days" version is the same as the "day of treatment" version, but also asks about impact on regular daily activities, need to rest, and amount of worry caused by CRS (recall period: past 24 hours). It may be completed daily depending on the study design or set of outcomes. **Conclusions:** The IO-induced CRS Patient Diary, the first of its kind, was developed in line with best practices and is content-valid for the intended use: to capture patients' experiences with IO-induced CRS events in clinical trials. Understanding these impacts will inform the benefit–risk profile and tolerability of IO therapies. This PROM may also have value in clinical practice, for which additional validation would be needed. Future work will aim to assess its psychometric performance in clinical trials. Research Sponsor: None.

11130 **Poster Session**

Electronic patient-reported outcomes (ePRO)-based alerts deployed in clinical practice to inform treatment burden and care management in pancreatic cancer. First Author: Emelly Rusli, Carevive by Health Catalyst, Boston, MA

Background: Pancreatic ductal adenocarcinoma (PDAC) is characterized by aggressive growth and late-stage diagnosis. About 20% of patients are eligible for surgery at diagnosis and are usually accompanied by adjuvant/neoadjuvant chemotherapy and/or radiation, with high recurrence rates. The use of ePROs to inform patient symptom (SX) experience and guide clinical care is increasing. Objectives for this study were to assess treatment burden and management of PDAC and explore care team engagement in the clinical practice using ePRO-based alerts data. **Methods:** PDAC patients were enrolled in an ePRO platform called PROmpt from 9/2020 to 11/2024. Patients received weekly surveys to report PRO-CTCAE-derived SX experienced during treatment. When a SX was reported as moderate or severe, an algorithm-based system would generate an "alert" notification per SX to the care team who reviewed the alert, interacted with the patient, and recorded the response on the platform. Treatment burden was measured by the symptom prevalence and number of alerts per week. Results were explored by stage (I-II or III-IV), frailty status (fit vs. frail), and age (<65 vs. 65+). Time to alert resolution and clinical actions were described. **Results:** A total of 67 patients were included, of which 58 (86.6%) reported a moderate/severe SX at least once. Median age was 67 (range: 40-87), 56.7% male, 62.7% late stage, and 50.7% frail. Most patients (64.2%) received FOLFOX and 35.8% were on Gemcitabine-based regimen. No baseline difference in patients who reported an alert versus not. Patients reported, on average, 2.8 symptoms per week with median follow up of 9.3 weeks. Of 513 total alerts generated, 54.6% occurred in the first 8 weeks of treatment. The top SX triggering an alert were pain (24.4%), nausea/vomiting (15%), and decreased appetite (14%). Average number of alerts per patient per week was 1.7 (SD=1.2, Median=1). No significant difference was observed by frailty status or age, but patients in the late-stage group generated higher alert/week than early stage (1.8 vs. 1.6). Average time to alert resolution was 2.2 days with a median of 1 day. Most alerts (72.3%) were addressed in less than 2 days. The most common clinical action taken to resolve the alerts was monitoring (86%), which included contacting oncologist support as needed, increased patient education, or follow-up at next scheduled visit. **Conclusions:** The treatment burden in PDAC was high with patients experiencing about 3 symptoms per week, of which nearly 2 of them were moderate/severe. Care team engagement was high as evidenced by prompt SX mitigation. Data collected from an ePRO-based alerts system can be used to characterize treatment burden and care team response in PDAC. Future study should include broader sample size and assess the impact of alerts on health resource utilization in PDAC. Research Sponsor: None.

11131 **Poster Session**

Evaluation of sleep quality and quality of life among patients newly diagnosed with head and neck cancer. First Author: Eric Adjei Boakye, Henry Ford Health System, Detroit, MI

Background: Patients diagnosed with head and neck cancer (HNC) often suffer from distress attributed to their cancer diagnosis which may disturb their sleep, in turn impacting their quality of life (QoL). However, there is lack of research about the association between poor sleep quality and QoL among patients newly diagnosed with HNC. We assessed the association between in poor sleep quality and QoL among patients with HNC before starting treatment. **Methods:** This is a retrospective cohort study of patients with HNC between January 2019 and September 2022. All patients with HNC treated at this tertiary care health system are evaluated prior to starting treatment by psych-oncology, using a semi-structured assessment and validated measures including the FACT-HN and Insomnia Severity Index (ISI). The FACT-HN is a 27-item validated instrument that consists of five subscales: that assesses the patient's quality of life in the physical, social/family, emotional, functional domains, and HNC-specific domains. Sleep quality was assessed via ISI, a 7-item self-report questionnaire assessing the nature, severity, and impact of sleep difficulties (defined as absence, subthreshold, moderate, or severe). We used five beta regression models to examine the association between sleep quality via the ISI and QoL via the FACT-HN (one for each subscale: emotional, social, physical, functional, and hand and neck). These models are adjusted with a variety of demographic covariates and social factors along with clinical factors. To estimate confidence intervals, bootstrap methods with bias correction were employed. **Results:** The analysis included 312 patients, 5.4% reported severe and 15.1% moderate sleep difficulties. After adjusting for other covariates, sleep difficulties were significantly associated with all FACT-HN subscales. Compared to patients with no sleep difficulties, patients with severe difficulties had a decrease in emotional (β=-1.33, 95% CI, -1.67, -0.93), social (β=-0.90, 95% CI, -1.66, -0.37), physical (β=-2.27, 95% CI, -2.67, -1.74), functional (β=-1.64, 95% CI, -2.10, -0.87), and head and neck (β=-1.11, 95% CI, -1.58, -0.65) QoL. Similarly, compared to patients with no sleep difficulties, those with severe difficulties had a decrease in emotional (β=-1.34, 95% CI, -1.66, -0.98), social (β=-0.61, 95% CI, -0.99, -0.17), physical (β=-1.85, 95% CI, -2.18, -1.49), functional (β=-1.37, 95% CI, -1.71, -0.89), and head and neck (β=-1.04, 95% CI, -1.34, -0.69) QoL. **Conclusions:** We found that patients with moderate or severe sleep difficulties had poor QoL. Early evaluation and tailored intervention to improve sleep quality are necessary to prepare these patients for HNC treatment and its consequences. Future studies are needed on sleep quality among patients during and after treatment. Research Sponsor: None.

11132 **Poster Session**

Financial burden and financial toxicity in cancer patients: A sub-analysis from a Brazilian prospective cohort. First Author: Mariana Ribeiro Monteiro, Instituto Americas, São Paulo, Brazil

Background: Financial toxicity during cancer treatment can impact patients' quality of life (QoL), adherence, and survival. Identifying subgroups with financial vulnerability among cancer patients is important to reduce disparities and develop equity-certified policies. Our study assesses financial burden (FB) and financial toxicity (FT) across different cancer types from the patient's perspective. **Methods:** This is an unplanned sub-analysis of four prospective, observational studies about real-world QoL in patients with breast (BC), prostate (PC), colorectal (CRC), and lung cancer (LC) treated at two private healthcare facilities in Brazil. We analyzed responses to Question 28 of the EORTC QLQ-C30 questionnaire. Patients reporting financial difficulties at baseline and six months were categorized as experiencing FB. Those with worsening or newly reported issues were classified as FT. FB and FT were analyzed as binary variables (any grade vs. none). Associations with clinical and epidemiological variables were assessed using univariate and multivariate logistic regression models, with a 5% statistical significance. Analyses were conducted using R software, version 4.4.1. **Results:** Between March 2015 and May 2024, 1,343 patients met the inclusion criteria: 56 with CRC, 387 with BC, 638 with PC, and 262 with LC. Most patients were male (60%) and white (77%), with a median age of 62.2 years. Only 15% had metastatic disease. At baseline, 23% reported FB, rising to 25% at six months, with 16% developing FT during treatment. Greater financial difficulties were found in women with breast cancer (FB 33%, FT 20%), while the lowest was seen in men with prostate cancer (FB 20%, FT 13%). Univariate analysis identified mixed-race ethnicity (OR 1.42; p=0,024), younger age (OR 0.96; p<0,001), and female gender (OR 0.55; p=<0,001) as FB risk factors, but only age remained significant in the multivariate model (OR 0.97; p = 0,003). Univariate analysis also linked age (OR 0.97; p<0,001), gender (OR 0.63; p=0,002), and comorbidities (OR 0.71; p=0,034) to FT, but only age remained significant in the multivariable model, with a 2% reduction in FT for each additional year (OR 0.98; p = 0.016). This study is ongoing and the impact of FB and FT on survival outcomes will be analyzed and reported in future work. **Conclusions:** This study highlights the impact of FT on cancer patients in Brazil treated in private health centers. Younger age emerged as an independent risk factor for both FT and FB after six months of treatment. Further research is needed to better understand FT within the Brazilian population, particularly in the public health system, and to develop strategies to mitigate its effects and improve patient outcomes. Research Sponsor: None.

11133 **Poster Session**

The impact of a second primary cancer diagnosis on health-related quality of life in African American cancer survivors. First Author: Jennifer Lynn Beebe-Dimmer, Karmanos Cancer Institute, Wayne State University, Detroit, MI

Background: Survival for the most common cancers has improved dramatically over the past several decades due to advances in treatment and screening for early detection. An unintended consequence of this is that survivors now face a greater possibility of developing one or more new primary cancers in their lifetime. It has been estimated that up to 22% of cancer survivors will be diagnosed with multiple primary cancers (MPCs). Understanding the impact of these diagnoses on outcomes along the survivorship continuum is important in developing tools to mitigate risks. **Methods:** The Detroit Research on Cancer Survivors (ROCS) cohort has enrolled more than 5,000 Black cancer survivors to understand the multiplex causes of poor outcomes in this high-risk population. Detroit ROCS participants are surveyed annually following enrollment to update medical history and mental health outcomes including health-related quality of life (HRQOL) measured using the Functional Assessment of Cancer Therapy (FACT-G) survey. In addition, regular linkages with the Metropolitan Detroit Cancer Surveillance System (MDCSS) registry are used to identify second primary cancer diagnosis, confirm self-reports, and gather relevant clinical data. The ROCS cohort is in its 9th year of potential follow-up. In 2024, the Detroit Genetic Epidemiology of Multiple primary cancers (GEMS) study was funded to examine susceptibility to MPCs leveraging Detroit ROCS to identify first primary breast, prostate and colorectal cancer survivors diagnosed with a second primary cancer. Analyses included comparisons of HRQOL and other characteristics 1) between MPCs and a frequency-matched (3:1) subset of single primary cancer (SPC) cancer cases; and 2) among MPCs, using survey data collected before and after their second diagnosis. **Results:** To date, Detroit GEMS includes 371 Black MPCs confirmed in MDCSS. The most common second primary cancer diagnosed among survivors was breast, followed by colorectal, lung and hematologic cancers. No significant differences were observed between MPCs and SPCs in the total FACT-G score, however when evaluating FACT-G subscales MPCs reported a significantly lower mean functional well-being score (16.9 and 18.0, respectively; p=0.022). Similar findings were observed in a subset of 104 MPCs with functional well-being scores reported before and after their second diagnosis (18.0 and 16.1, respectively; p=0.004). **Conclusions:** Cancer survivors diagnosed with a MPC report similar HRQOL compared with survivors with a SPC, suggesting resiliency in Black cancer survivors which is encouraging. However, understanding factors that contribute to declining functional well-being will be important in early interventions to improve overall quality of life. Research Sponsor: U.S. National Institutes of Health; U01 CA199240 and P01 CA272239.

11134 Poster Session

The impact of breast cancer treatment on young women's body image and sexual health. First Author: Shari Beth Goldfarb, Memorial Sloan Kettering Cancer Center, New York, NY

Background: In 2023 MSKCC launched the Young Women with Breast Cancer Program (YWBCP) to provide comprehensive care, education, and research studies for young women with cancer. This program explored how breast cancer treatment impacts body image, sexual health, self-esteem, and personal priorities. **Methods:** MSKCC's YWBCP conducted online surveys of women aged 45 and younger at diagnosis (intake) (n=964) and six months into treatment (n=328). Surveys assessed psychological wellbeing, sexual health, body image, and referral requests. This abstract analyzes data from both surveys. **Results:** Intake data (n=964) revealed 57% (n=544) had children before diagnosis. 25%(n=236) sought information on fertility preservation, while 16% (n=156) were interested, but not ready for it. 18% (n=169) underwent fertility preservation. 26% (n=251) had a desire to protect fertility, but had not yet. Paired analysis (n=328) from intake and follow up showed 46% (n=147) felt less positive about their bodies, 42% (n=134) had no change, and 13% (n=41) improved. Half (50%; n=161) reported decreased appreciation of their body's uniqueness and 37% (n=118) no change. In response to the statement, "I act as though I like my body," 36% (n=115) declined, 24% (n=76) improved, and 40% (n=128) were consistent. Interest in sexual activity decreased (34%; n=107) more than increased (24%; n=75). Sexual satisfaction also declined in 55% (n=169), but improved in 16% (n=49) and remained the same in 29% (n=91). Concern about cancer or treatment affecting sexual ability decreased in 31% (n=98), increased in 27% (n=86) and was unchanged in 41% (n=129). At baseline women's top three concerns were cancer's impact on friends and family (27%; n=480), discussing cancer with loved ones (16%; n=282) and financial issues (15%; n=272). Social work requests prioritized individual therapy (23%; n=326), support groups (21%; n=301), family support (19%; 265), educational programs (13%; n=189), mental health resources (12%; n=170) and peer-to-peer programs (12%; n=176). Concerns were prioritized differently at 6 months, with financial issues (21%; n=113) first, followed by cancer's impact on friends and family (19%; n=102), then relationships (16%; n=83). Social work preferences changed slightly: individual therapy (28%; n=86), support groups (19%; n=59, educational programs (14%; n=45), mental health resources (14%; n=45); peer-to-peer programs (13%; n=41) and family support (11%; n=35). **Conclusions:** YWBCP data show the importance of onco-fertility and social work counseling throughout treatment. Young breast cancer patients experience significant declines in body image, sexual satisfaction, and sexual desire, highlighting the need for targeted sexual health interventions. Financial toxicity worsens over time, warranting referrals to financial services to mitigate concerns. Additional intervention studies are being performed to improve patient QoL. Research Sponsor: None.

11135 Poster Session

Outpatient infusion sepsis protocol and outcomes for patients with cancer. First Author: Ashley Miles, Thomas Jefferson University, Philadelphia, PA

Background: Sepsis, a life-threatening organ dysfunction caused by infection, is a common oncologic emergency in adult cancer patients. Early sepsis detection and timely antibiotic administration can improve outcomes and reduce mortality. As more oncology treatments move to outpatient infusion centers, implementing sepsis screening in these settings can improve early detection and opportunity for intervention. As a result, we implemented a best practice alert (BPA) and protocol for the initial evaluation and managements of sepsis in an outpatient oncology infusion center. **Methods:** We performed a retrospective study from June 2022 – December 2024 comparing outcomes of patients who presented to the outpatient oncology infusion center at our institution pre- and post-implementation of our sepsis workflow. We collected the following data: BPA alerts that were activated, time to antibiotics, initial lactate drawn, repeat lactate draw, cultures collected prior to antibiotic administration, appropriate IV fluid (IVF) resuscitation, number of patients transferred to the emergency department (ED) vs. Direct Admission (DA), length of stay, and number of Intensive Care Unit (ICU) transfers. **Results:** Pre-implementation (June – December 2022), 102 oncology patients were admitted with sepsis from the infusion center. Average time to antibiotics was 6 hours (SD=6.95), 90% had blood cultures drawn prior to antibiotic administration, 85% had lactate drawn, 80% second lactate was drawn when initial lactate was $>$2, and 46% had appropriate IVF. Twenty-two percent were DA. Average LOS was 11 days (SD=9.18) and 14 patients required ICU stay. Post-implementation (June 2023 – June 2024), 118 patients were evaluated and treated for possible sepsis. Average time to antibiotics was 1.5 hours, 100% had blood cultures prior to antibiotics, 95% had initial lactate, 91% had second lactate drawn if initial was $>$2, 46% appropriate IVF. Thirty four percent of evaluated patients were managed as an outpatient. Of those admitted, 78% were DA. The average LOS was 6 days (SD=4.6), and 4 patients required ICU stay. **Conclusions:** The outpatient sepsis protocol improved early management and treatment of patients with suspected sepsis, also improving clinical outcomes. As a result of the new workflow, more patients were directly admitted to the hospital avoiding unnecessary ED utilization. Early management helped reduce severity of sepsis resulting in fewer ICU admissions and shorter length of stay in the hospital. These improvements demonstrate the protocol's effectiveness and potential for broader application in oncology settings. Additional evaluation is needed to determine the generalizability of the protocol as it is scaled across the health system. Research Sponsor: None.

11136 Poster Session

The association of cancer history with markers of cognitive decline in a large US national survey registry. First Author: Emmanuel Kampanga, CCU School of Medicine, Columbus, OH

Background: Cancer is known to cause health complications, including heart and kidney disease, but its long-term impact on cognition is less understood. Cognitive impairments, such as memory and attention problems, are common in survivors, particularly those treated with chemotherapy, known as cancer-related cognitive impairment. While physical activity may help, survivors often face higher disability rates. Clarifying cancer's long-term cognitive effects is essential for improving survivors' quality of life. **Methods:** An extensive, de-identified, publicly available database from the CDC, the Behavioral Risk Factor Surveillance System. Data collected in 2021 was analyzed using a multivariable logistic regression model to assess the association between demographics, cancer diagnosis, medical diagnoses, and various markers of cognitive decline. The final analysis had over 100,000 responses. **Results:** The logistic regression model, considering various demographic and medical parameters (Table 1), revealed that a history of cancer in both males and females was associated with markers of cognitive decline. This included depression in males (OR=1.235, 95% CI 1.180-1.293, p$<$0.001); and in females (OR=1.177, 95% CI 1.137-1.218, p$<$0.001), difficulty remembering or concentrating in males (OR=1.172, 95% CI 1.110-1.238, p$<$0.001); and in females (OR=1.155, 95% CI 1.103-1.210, p$<$0.001), and difficulty running errands in males (OR=1.174, 95% CI 1.101-1.251, p$<$0.001) and in females (OR=1.194, 95% CI 1.138-1.251, p$<$0.001). Interestingly, exercise in the last 30 days was associated with a protective effect on all markers of cognitive decline. **Conclusions:** Our analysis demonstrated a significant negative association between cancer diagnosis and markers of cognitive decline in both males and females. At the same time, exercise in the last 30 days was associated with less cognitive decline. Research Sponsor: None.

Multivariable log reg analysis assessing associations with cognitive decline markers in men.

	Depression				Difficulty Running Errands				Difficulty Remembering or Concentrating			
			95% CI				95% CI				95% CI	
	P value	OR	Lower	Upper	P value	OR	Lower	Upper	P value	OR	Lower	Upper
Age (ref. 50-54 yrs)												
55-59 yrs	<.001	.866	.808	.928	0.015	0.867	0.773	0.973	0.001	0.857	0.786	0.936
60-64 yrs	<.001	.758	.708	.812	<.001	0.713	0.637	0.798	<.001	0.666	0.610	0.727
65-69 yrs	<.001	.649	.603	.700	<.001	0.604	0.534	0.683	<.001	0.576	0.523	0.634
70-74 yrs	<.001	.570	.525	.618	<.001	0.671	0.590	0.763	<.001	0.581	0.524	0.644
75-79 yrs	<.001	.447	.407	.491	<.001	0.699	0.608	0.804	<.001	0.633	0.566	0.709
≥80 yrs	<.001	.288	.259	.321	0.005	1.220	1.063	1.399	<.001	0.800	0.714	0.896
Any history of cancer (Yes vs. No)	<.001	1.235	1.180	1.293	<.001	1.174	1.101	1.251	<.001	1.172	1.110	1.238
Exercise in last 30 days (Yes vs. No)	<.001	.702	.672	.733	<.001	0.339	0.320	0.359	<.001	0.632	0.602	0.664

*Adjusted for the following variables listed: Race, USA region, BMI category, education level completed, smoking status, marital status, employment status, and metropolitan status.

11137 Poster Session

Improving genetic counseling uptake for breast, pancreatic, and prostate cancers at a safety net hospital. First Author: Jenny Jing Xiang, The University of Texas MD Anderson Cancer Center, Houston, TX

Background: Despite guideline recommendations, genetic counseling (GC) for BRCA associated cancers among underserved populations remain low. We conducted a QI project to increase GC uptake for patients with breast, pancreatic, and prostate (BPP) cancers seen in a safety net oncology clinic at Harris Health. **Methods:** Analysis of electronic medical record (EMR) data along with surveys and interviews of clinicians and staff identified: 1) a complex GC referral process with 30% unscheduled referrals in 2023, 2) lower frequency of GC appointments (appts) among established patients, and 3) clinician knowledge deficits regarding GC guidelines. Our interventions consisted of 1) developing an automated referral scheduling workflow, 2) creating an EMR report of potentially eligible patients with upcoming appts and sending monthly reminders to clinicians, and a 3) GC guidelines lecture by a genetic counselor. **Results:** There were 720 patients in the preintervention period (1/2020-5/2024) and 93 patients in the postintervention period (6-12/2024). In total, 50.5% of patients were Hispanic, 24.8% were Black, 53.7% spoke Spanish, and 67.4% received financial assistance. Amongst all patients, GC appts increased from 55.4% preintervention to 67.7% postintervention (p = 0.02), with increases across breast (54.6% to 67.1%), pancreatic (55.4% to 71.4%), and prostate (59.1% to 65%) cancers. Among patients meeting select NCCN GC criteria identifiable through discrete EMR data (triple negative, stage IV HER2 negative, or diagnosed age $<$50 breast; all pancreatic; stage IV prostate), GC appts increased from 74.0% to 82.6% (p = 0.20), with increases for breast (79.4% to 86.5%) and pancreatic (55.4% to 71.4%) cancers and a decrease for prostate cancer (71.9% to 60%). All GC referrals postintervention were scheduled, with time from GC referral to GC appts improving from a mean of 170.2 days (SD 636.1) to 27.4 days (SD 19.5) (p$<$0.01). Time from first oncology appt to GC appt improved from a mean of 124.2 days (SD 199.9) to 33.3 days (SD 30.5) (p$<$0.01). 87.5% of patients with GC appts consented to testing in 2023 and 86% consented postintervention. **Conclusions:** Multilevel interventions targeting both EMR capabilities as well as clinician education and awareness of eligible patients streamlined the GC referral workflow and increased GC appts among a safety net patient population with BRCA associated cancers. Research Sponsor: None.

Patients	Preintervention GC Appts (N [%] or Mean [SD])	Postintervention GC Appts (N [%] or Mean [SD])	P-Value
All Cancers	339/720 (55.4%)	63/93 (67.7%)	0.024
Breast	295/540 (54.6%)	49/73 (67.1%)	
Pancreatic	36/65 (55.4%)	5/7 (71.4%)	
Prostate	68/115 (59.1%)	13/30 (65%)	
Select NCCN Criteria	282/381 (74.0%)	38/46 (82.6%)	0.204
Breast	200/252 (79.4%)	32/37 (86.5%)	
Pancreatic	36/65 (55.4%)	5/7 (71.4%)	
Prostate	46/64 (71.9%)	3/5 (60%)	
Time from GC Referral to GC Appointment (Days)	170.2 (636.1)	27.4 (19.5)	<0.001

11138 Poster Session

OncoPRO: A US national initiative supporting implementation of remote symptom monitoring with electronic patient-reported outcomes (ePROs) in oncology practices. First Author: Ethan Basch, The University of North Carolina at Chapel Hill, Chapel Hill, NC

Background: Remote symptom monitoring using electronic patient-reported outcomes (ePROs) results in improved symptom management, communication, quality of life, and in some cases survival. Furthermore, value-based cancer care models such as the CMS Enhancing Oncology Model are increasingly supporting or requiring remote symptom monitoring. However, implementation at scale in real-world settings remains challenging for practices. **Methods:** OncoPRO is a national initiative in the United States that supports oncology practices and health systems in the implementation and sustainability of remote symptom monitoring programs using ePROs, integrated with electronic health record systems. OncoPRO is funded by the Patent-Centered Outcomes Research Institute (PCORI), and is led by operational groups at the University of North Carolina and the University of Alabama, in partnership with the American Society of Clinical Oncology (ASCO), the American Cancer Society (ACS), and the PROTEUS Consortium, with observers from federal agencies. **Results:** OncoPRO was initiated in March 2024, with 15 large U.S. practices/health systems participating, as well as two national practice networks, four EHR software companies, four ePRO software companies, and observers from the U.S. Centers for Medicare and Medicaid Services and the Food and Drug Administration. The central activities of OncoPRO encompass co-learning collaborative monthly meetings where leaders from each practice in clinical care, information systems, and value-based care convene to review progress, barriers and strategies for implementation, billing tactics, and other guidance. Practices share data dashboards on implementation, discuss challenges they face, and exchange success stories under the facilitation of ASCO coaches. Support materials and standard operating processes are shared by the operational team, ACS, and software vendors. Additional practices are joining the initiative both within the US and internationally. A goal is to demonstrate that implementation of remote symptom monitoring with ePROs is feasible on a wide basis and leads to improved operational and clinical outcomes. **Conclusions:** The OncoPRO initiative is supporting practices, including both community and academic, in implementing remote symptom monitoring using ePROs through a learning collaborative that is anticipated to be of interest to others considering ePRO implementation. Research Sponsor: Patient-Centered Outcomes Research Institute; DI-2023CI-31283.

11139 Poster Session

Transforming genomic testing in prostate cancer: A comprehensive system-wide initiative. First Author: Chinmay Jani, University of Miami Sylvester Comprehensive Cancer Center, Miami, FL

Background: Timely detection of pathogenic variants enables personalized treatment and improved outcomes in prostate cancer (PC). In 2020, NCCN guidelines recommended genomic testing for mPC, but by 2022, only 30.8% of mPC patients in Florida had undergone appropriate testing. In our current study, we evaluate the impact of system-wide quality improvements at SCCC on genomic testing rates for mPC patients. **Methods:** In alignment with NCCN guidelines, several initiatives were launched in 2023 to enhance adherence to genomic testing practices. In May 2024, SCCC partnered with Florida Society of Clinical Oncology (FLASCO) and Pfizer on a state-wide initiative to address barriers to germline testing. A survey was conducted to assess the genomic testing process and identify gaps in adherence. System improvement projects were initiated, accompanied by efforts to raise awareness. A retrospective analysis utilizing EPIC Electronic medical record (EMR) data evaluated genomic testing rates among patients with newly identified mPC at SCCC from 2022 to 2024, stratified by ethnicity. **Results:** In 2022, baseline genomic testing rates for mPC at SCCC were 57%. Starting in 2023, high-risk cancer screening programs and EMR-focused initiatives, including the Genomics Module and Invitae integration, centralized molecular results and established registry to track alterations. In 2024, the survey revealed that 50% of physicians received unstructured genomic testing results via EMR, while 83.3% faced challenges accessing results for decision-making. Drawing from the successful breast cancer screening program, multidisciplinary teams were formed to address gaps and enhance testing adherence, focusing on awareness and enhancing EMR integration, reporting, and health prompts. That year, genomic results integration into the data portal also began. Using Slicer Dicer and Epic reporting, we evaluated testing rates, which improved to 68.6% in 2023 and 74% in 2024, with Hispanic patients achieving 76.5% and 80%, respectively. **Conclusions:** Institutional initiatives at SCCC, including expanding the Genetics program and enhancements to EMR functionality, have successfully increased genomic testing rates for mPC patients across all ethnicities. Building on this progress, approved steps for 2025 include expanding the integration of molecular testing with additional testing vendors, creating a dedicated Molecular tab with discrete fields in the EMR, and expanding education and training programs to further streamline genomic testing practices. Research Sponsor: None.

Year	Testing Rate	Hispanic	Initiatives
2022	57%	50%	–
2023	68.6%	76.5%	Jan – High Risk Screening Clinic Feb – Genetic Predisposition Syndrome Clinic Oct – Invite integration Oct – Epic Genomics Module
2024	74%	80%	May – mPC Testing Workflow assessed Sep – SCCC data portal- molecular testing results integration Oct – Multidisciplinary team to identify gaps and prioritize projects

11140 Poster Session

Enhancing lung cancer surgical quality: Insights from a national quality improvement collaborative. First Author: Kelley Chan, American College of Surgeons, Chicago, IL

Background: Sampling of at least 3 mediastinal and at least 1 hilar lymph node stations during lung cancer resection was adopted by the American College of Surgeons (ACS) Commission on Cancer (CoC) as Operative Standard 5.8 to ensure appropriate staging, guide adjuvant systemic therapy, and improve overall survival. Early assessments suggested difficulty with reaching goal hospital-level compliance rates of ≥80%. The objectives of this study were to compare compliance with Standard 5.8 before and after participation in the Lung NODES national quality improvement (QI) collaborative and to identify facilitators to achieving compliance. **Methods:** Lung NODES enrolled 354 CoC-accredited hospitals in January 2024. Over 12 months, all hospitals actively participated in guided root cause analyses, educational webinars, peer-to-peer learning, and the development and implementation of hospital-level strategies. Baseline and post-participation surveys collected data on Standard 5.8 compliance and differences in hospital-level compliance were assessed using Wilcoxon signed-rank tests. The post-participation survey queried hospitals on facilitators to achieving compliance. **Results:** The number of hospitals achieving ≥80% compliance with Standard 5.8 increased from 144 (40.7%) to 238 (67.2%) from baseline to post-participation, respectively. Hospital-level median compliance increased from 67.8% (IQR 42.9-90) to 90.5% (IQR 70-100), $p<0.001$. All hospital types had an increase in mean absolute difference in compliance, with the largest increase seen for community hospitals (25.4%, STD 43.5) (Table). For the 114 programs that newly achieved compliance, facilitators included surgeon buy-in (83.3%), proactive specimen labeling (76.3%), and multidisciplinary communication (73.7%). **Conclusions:** Participation in Lung NODES was associated with higher compliance with Standard 5.8 irrespective of hospital type, suggesting that national QI collaboratives may represent an effective large-scale approach to address gaps in cancer care delivery. Research Sponsor: None.

Operative standard 5.8 compliance by hospital type at baseline and after participation in Lung NODES.

Hospital Type	Baseline Compliant Programs n (%)	Final Compliant Programs n (%)	Baseline Compliance Median (IQR)	Final Compliance Median (IQR)	Absolute Difference in Compliance Mean (STD)
Academic N= 50	19 (38.0)	38 (76.0)	68.7 (35.0-90.0)	88.9 (80.0-100)	20.0 (29.8)
Community N=32	10 (31.3)	21 (65.6)	56.3 (23.6-83.8)	93.4 (66.7-100)	25.4 (43.5)
Comprehensive Community N=147	55 (37.4)	97 (66.0)	65.0 (42.9-89.5)	91.7 (66.7-100)	17.5 (30.3)
Integrated Network N=102	51 (50.0)	68 (66.7)	78.6 (50.0-92.2)	90.2 (70.6-100)	12.8 (29.0)
Other N=23	9 (39.1)	14 (60.9)	69.0 (40.0-81.7)	84.6 (60.0-100)	13.2 (35.1)

11141 Poster Session

Systematic communication model to facilitate conversations about metastatic breast cancer. First Author: Fernanda Mesa-Chavez, Breast Cancer Center, Hospital Zambrano Hellion TecSalud, Tecnologico de Monterrey, Monterrey, Mexico

Background: For patients with metastatic breast cancer (mBC) understanding their stage and treatment goals is essential to engage in shared decision-making. However, patient-physician communication challenges often hinder discussions about this information. This study evaluated a systematic communication model designed to guide conversations on mBC and to ease oncologists' experience when conveying this delicate information. **Methods:** Patents starting 1st-line mBC treatment were included at 7 referral centers in Mexico. During the consultation in which mBC was disclosed, their oncologists followed a 9-step communication model that facilitated and promoted conversations about mBC stage, treatment, and prognosis, considering each patient's information preferences. After 3-10 days, patients completed a survey assessing understanding of their mBC stage and treatment, and satisfaction. Oncologists also completed a survey exploring their experience providing the information. This study was funded by Pfizer. **Results:** 50 patients were included by 10 oncologists. Patients' median age was 55 yrs (IQR 15); most had ≤high school education (55%) and had recurrent mBC (63%). After receiving information through the communication model, 78% of patients were aware that their BC was metastatic, 56% that mBC is not curable, 76% that their treatment's main objective was to improve their lifespan and quality of life, and 70% that their treatment had no established end date. Patients reported having discussed their prognosis with their oncologist in 54% of cases, most of which considered this information was very useful for: making treatment decisions (94%), preparing for the future (92%), and keeping hope (92%). Overall, most (78%) were satisfied with the way in which they received information about their mBC. As for oncologists' experience, they considered the communication model was very helpful to better convey the incurability of mBC (76%), treatment objectives (82%), and prognosis (42%). With all patients, oncologists were very satisfied (46%) or satisfied (54%) after implementing the model. They felt anxious in 2% of cases, stressed in 2%, confident in 90%, and calm in 90%; their distress thermometer score was ≥4/10 in 26% of consultations. Of note, oncologists reported not completing ≥1 step of the model in 44% of consultations, mostly due to limited time (46%) and forgetfulness (29%). Compared to their usual practice, they considered that the model did not affect (42%) or moderately increased (50%) the duration of the consultation. **Conclusions:** Both patients and oncologists were highly satisfied with the way in which mBC information was disclosed through the communication model. Oncologists particularly recognized the model as a valuable aid for these conversations. Yet, prognosis was discussed with a limited proportion of patients, underscoring the need for further efforts to ease approaching this topic. Research Sponsor: Pfizer.

11142 **Poster Session**

Epidemiologic patterns and mortality outcomes in young lung cancer non-smokers: A National Inpatient Sample analysis (2016–2021). First Author: Simo Du, Jacobi Medical Center - Albert Einstein College of Medicine, Bronx, NY

Background: While the incidence and mortality of smoking-related lung cancer have declined, cases among individuals who have never smoked (LCINS) are increasing, particularly among women and younger populations. LCINS often presents with distinct pathology features, unique genetic mutations, and a higher prevalence of early-onset disease. Despite these distinctions, limited evidence exists regarding the epidemiology and mortality outcomes of LCINS. This study aims to compare sociodemographic differences and mortality outcomes among early- and late-onset lung cancer, stratified by smoking status. **Methods:** We performed a pooled cross-sectional analysis using the National Inpatient Sample (NIS) from 2016 to 2021. Lung cancer patients, identified by ICD-10 codes (C34.x), were stratified by age ($\leq$50 years and $>$ 50 years) and smoking status (current, former, and non-smokers). Comorbidities were assessed using the Elixhauser Comorbidity Index. Descriptive statistics and multivariable logistic regression analyses were used to compare mortality outcomes, with statistical significance defined as $p < 0.05$. Analyses were performed using STATA MP 18. **Results:** A total of 199,798 lung cancer hospitalizations were identified, representing 998,990 weighted discharges across the U.S. Of these, 1.47% were young non-smokers ($\leq$50 years), 1.33% young smokers, 26.63% older non-smokers ($>$ 50 years), and 25.8% older smokers. Young non-smokers were more likely to be female (60.8% vs 50.4% of the general population) and non-white (49.2% vs 23%), with a notably higher prevalence of Asian (11.4% vs 3.3%) and Hispanic (15.1% vs 4.8%) individuals. Young non-smokers had fewer health conditions compared to the general population, with a lower mean Elixhauser Comorbidity Index (19.38 vs 20.63) and lower prevalence of chronic pulmonary disease (16.5% vs 51.3%). However, they had a higher prevalence of metastatic disease (55.8% vs 40.8%). Inpatient mortality was higher in young non-smokers (7.2%) compared to young smokers (5.2%), and higher in older non-smokers (9.1%) than older smokers (5.0%). Multivariable logistic regression showed a statistically significantly increased mortality for young non-smokers compared to young current smokers (OR 1.58, 95% CI 1.26–1.99, $p < 0.01$), and similarly for older non-smokers (OR 1.72, 95% CI 1.42–2.08, $p < 0.01$), after adjusting for age, sex, race and other confounders. **Conclusions:** LCINS, particularly in early onset cases, represents a distinct subgroup with unique sociodemographic and clinical characteristics, including a higher prevalence of non-white individuals, fewer comorbidities, and an increased mortality rate. The higher mortality may reflect the advanced stage at presentation and poorer prognosis of LCINS, suggesting potential differences in disease mechanisms compared to smoking-related lung cancer. These findings highlight the need for tailored screening strategies and personalized treatment approaches for the LCINS population. Research Sponsor: None.

11143 **Poster Session**

Real-world assessment of breast cancer risk following hormonal therapy in endometriosis: A Global Collaborative Network propensity score matched analysis. First Author: Caterina Gianni, IRCCS Istituto Romagnolo per lo Studio dei Tumori (IRST) "Dino Amadori", Meldola, Italy

Background: Research suggests endometriosis, an estrogen-dependent condition, may be a potential risk factor for breast cancer (BC) development. While oral contraceptives are the standard treatment, their efficacy is limited in symptom control. This study examines the relationship between hormonal therapy (HT) prescribed for endometriosis management and BC risk. **Methods:** Using TriNetX Global Collaborative Network, we compared 41 029 endometriosis patients receiving HT against 111 429 control patients without HT. We excluded patients with prior contraceptive use or neoplasm diagnosis. Through propensity score matching, we created 38 311 balanced pairs, accounting for demographics (age, race), medical history (pelvic disease, family cancer history, hypertension, diabetes), and clinical factors (pregnancies, body mass index). Additional analyses were conducted by type of HT: progestins (36 156 matched pairs) and LHRH analogues (7 700 matched pairs). BC incidence was measured using hazard ratios, starting 6 months post-endometriosis diagnosis. We evaluated the rate of pregnancies and we also conducted an analysis to assess the risk of major cardiovascular events according to HT treatment for endometriosis, including stroke, cardiac ischemia, thrombosis, and pulmonary embolism. **Results:** The matched cohorts had a mean age of 34 years (standard deviation 9.3). The study population was predominantly white (60%), with lower representation of Black American (10%) and Asian (3%) patients, while race was unknown for 19% of participants. Among patients with endometriosis treated with HT, 262 of them developed BC compared to 239 cases in the control group with a hazard ratio (HR) of 1.18 (95% CI 1.0-1.4, p = 0.064), showing no significant age-related differences. LHRHa treatment was associated with higher BC incidence (66 versus 36 cases, HR 1.7, 95% CI 1.14-2.6, p = 0.009). Age-stratified analysis of LHRHa patients showed no differences for those under 30 and 40 years, while patients under 50 showed a non-significant increase (25 versus 19 cases, HR 1.28, 95% CI 0.70-2.32, p = 0.42). Progestin treatment showed marginally increased BC risk (243 versus 216 cases, HR 1.2, 95% CI 1.0-1.4, p = 0.05) without age-related differences. Patients in the control group not receiving HT presented a lower chance to get pregnant (HR 1.32, 95% CI 1.3-1.4). No significant differences were observed in terms of major cardiovascular events. **Conclusions:** While overall HT showed no clear link to BC risk, both progestins and LHRHa were associated with increased risk. These findings warrant further investigation, particularly since these medications are typically prescribed to endometriosis patients with severe symptoms who share common reproductive and hormonal risk factors with BC. Research Sponsor: None.

11144 **Poster Session**

Comprehensive genomic profiling in AYA cancer patients. First Author: Naomi Hayashi, The Cancer Institute Hospital, Japanese Foundation for Cancer Research, Tokyo, Japan

Background: Cancer types in Adolescents and Young Adults (AYA) vary by age. Since many AYA cancers are classified as rare, patients continue to face limited therapeutic options. This study evaluates the utility of comprehensive genomic profiling (CGP) and genome-matched therapies for AYA cancer patients, considering age-specific variations using a nationwide database. **Methods:** We analyzed data from 2,325 AYA patients (aged 15–39) who underwent CGP between 2019 and 2023. The genomic landscape and treatment status were assessed. Patients were classified into two groups: those with cancer types that are more common in those under 30 years of age and those categorized as other. Parameters were compared between the two groups. **Results:** The median age was 33 years, with *TP53* being the most frequently altered gene. Overall, 275 patients (12%) were administrated for treatment based on CGP. Cytotoxic agents were suggested when no actionable molecular targets were identified. However, there was no significant difference in overall survival (OS) between patients who received the recommended therapies and those who did not (40 vs. 33 months, $p = 0.07$). A generational comparison of cancer incidence identified 6 cancer types that were more prevalent in patients under 30 years of age: bone, peripheral nervous system, central nervous system, germ cells, adrenal gland, and soft tissue (collectively referred to as 6 specific cancer types). Among patients with the 6 specific cancer types (N = 824), *TP53* and *STK11* were the most frequently altered genes, whereas *TP53* and *KRAS* predominated in patients with other cancers (N = 1501). Treatment administrations, including cytotoxic agents, based on CGP were made for 50 patients (6.1%) and 225 patients (15%), respectively ($p < 0.01$). Among these, 28 patients (56%) with the 6 specific cancer types and 54 patients (24%) with other cancers did not receive genome-matched therapies ($p < 0.01$). Regarding OS, patients with other cancers who received the recommended therapies had significantly longer OS than those who did not (41 vs. 30 months, $p < 0.01$). However, in patients with the 6 specific cancer types, there was no significant difference in OS between those who received the recommended therapies and those who did not (38 vs 44 months, $p = 0.33$). **Conclusions:** The prognostic benefit of CGP may be limited for rare cancers that are prevalent among the younger generation, as fewer opportunities for receiving genome-matched therapies. Research Sponsor: AYA Oncology Alliance (AYAKEN).

11146 **Poster Session**

Hospice utilization in Veterans with newly diagnosed metastatic prostate cancer. First Author: Jennifer Mei Lee, University of Michigan Medical School, Ann Arbor, MI

Background: Treating men with metastatic castration-sensitive prostate cancer (mCSPC) using androgen deprivation therapy (ADT), with or without treatment intensification, is highly palliative and leads to survival measured in years. In contrast, hospice provides end-of-life support when estimated life expectancy is $\leq$6 months, which rarely applies to men with newly diagnosed mCSPC. Although traditionally, patients transition to hospice when cancer treatments have been exhausted, the VA allows hospice enrollment during cancer treatment. This study investigates factors associated with hospice enrollment for Veterans within the first six months after diagnosis of mCSPC. **Methods:** We conducted a retrospective cohort study utilizing the VA Corporate Data Warehouse, an extensive database of medical records from 130 VA facilities, linked to Medicare data. Patients newly diagnosed with mCSPC between January 1, 2023, and June 17, 2024, were identified using a validated natural language processing tool. Veterans with prior orchiectomy, receipt of ADT the prior year, or without primary care visits the two years prior to diagnosis were excluded. Our primary outcome was hospice enrollment within six months of metastatic diagnosis. Multivariate logistic regression was used to estimate adjusted odds ratios (aOR) and 95% confidence intervals (CI), adjusting for clinical and socioeconomic variables, including neighborhood disadvantage as measured by area deprivation index (ADI). **Results:** We identified 3429 Veterans with mCSPC, with a mean age of 76 years, 30% of whom were Black. Overall, 11% (n = 391) of Veterans were referred to hospice within the first six months following mCSPC diagnosis. Older age and higher level of frailty were associated with greater odds of hospice enrollment within 6 months (aOR 1.84, 95% CI 1.59-2.14 per 10 years; aOR 4.79, 95% CI 3.74-6.13 for those with moderate/severe frailty versus not frail or mild frailty, respectively). Single Veterans (aOR 1.41, 95% CI 1.11-1.80) and those without additional healthcare insurance (aOR 2.22, 95% CI 1.74-2.85) also had greater odds of hospice referral. Neighborhood-level disadvantage was significantly associated with hospice enrollment: Veterans living in the most deprived neighborhoods (ADI 80–100) had higher odds of hospice referral compared to those in the least deprived neighborhoods (ADI 0–20) (aOR 2.97, 95% CI 1.90-4.73). **Conclusions:** Social determinants of health, including neighborhood-level disadvantage and lack of insurance coverage were strongly associated with Veteran hospice enrollment within six months of mCSPC diagnosis. However, since a unique benefit of VA cancer care allows hospice enrollment in concert with cancer treatment, more work needs to be done to understand whether hospice enrollment is being used primarily for social support or for end-of-life care in men with a highly treatable condition. Research Sponsor: Department of Veterans Affairs, HSR&D; Project Number: IIR 22-215.

11147 **Poster Session**

Association of MammaPrint and clinical outcomes by race among 5000 individuals with HR+HER2- early stage breast cancer enrolled in FLEX. First Author: Erin Frances Cobain, Michigan Medicine, Ann Arbor, MI

Background: Black women with hormone receptor-positive (HR+), HER2-negative (HER2-) early stage breast cancer (EBC) have a 38% higher mortality rate than White women, a disparity not fully explained by social determinants of disease. Previous research demonstrating unequal performance of gene expression (GE) assays across racial groups has raised concerns that GE assays may underestimate risk of recurrence in Black patients (pts). Compared to other GE assays, the MammaPrint (MP) 70 gene signature consistently classifies a higher proportion of Black pts as High Risk compared with White pts. This analysis examines real world data and survival stratified by MP and self-reported race in pts with HR+HER2- EBC enrolled in FLEX. **Methods:** The ongoing FLEX (NCT03053193) trial enrolls pts undergoing standard of care MP testing, classifying tumors as Low, High 1 (H1), or High 2 (H2) risk of recurrence. BluePrint defines molecular subtypes as Luminal, Basal, or HER2. Clinical differences were assessed with Chi-squared or Fisher's exact tests. Distant recurrence-free interval (DRFI), defined per STEEP criteria, was compared by race and MP using Kaplan-Meier estimates and log rank tests. **Results:** Among 5142 pts analyzed, 9.6% were Black and 90.4% were White. Node positive (30.4% vs 21.9%; $p < 0.001$) and Grade 3 disease (25.3% vs 14.1%; $p < 0.001$) were more common among Black pts. Black pts had significantly higher incidences of H1 (43.1%), H2 (18.3%), and Basal (9.3%), and lower rates of Low (38.5%) Risk tumors, compared with White pts (H1: 36.6%; H2: 7.4%; Basal: 3.3%; Low: 56.6%; $p < 0.001$). Black pts had higher rates of neo/adjuvant chemotherapy (CT) (52.9% vs 40.3%; p = 0.003) and use of an anthracycline-taxane regimens (43.0% vs 35.4%: p = 0.001) compared with White pts. However, despite a 61.4% incidence of H1/H2 risk disease among Black pts, only 52.9% received CT. In contrast, White pts had a 44.0% H1/H2 incidence and 40.3% received CT. Among all pts, 4-year DRFI was lowest for H2 (90.7%), 96.7% for H1, and 98.8% for Low Risk ($p < 0.001$). DRFI for Black pts was 98.3% for Low, 95.5% for H1, and 90.2% for H2 (p = 0.005). For White pts, DRFI was 97.9% for Low, 96.9% for H1, and 89.8% for H2 ($p < 0.001$). Among CT treated pts, DRFI was comparable for Black (n = 186) and White (n = 1130) pts with H1 (96.0% vs 96.4%) and H2 (90.3% vs 90.6%) tumors. **Conclusions:** Black pts have a higher prevalence of H2/Basal and higher risk clinical features in the nationwide prospective FLEX Registry trial. Black pts with HR+HER2- MP H1/H2 EBC were less likely to receive neo/adjuvant CT than White pts with H1/H2 tumors. This highlights a critical gap in real-world practice where Black pts may be undertreated. However, clinical outcomes are equivalent among similarly treated Black and White pts across MP risk groups. MP classifies fewer EBCs as Low Risk in Black pts, and this classification is accurate as 4-year DRFI is excellent in these pts. Clinical trial information: NCT03053193. Research Sponsor: Agendia, Inc.

11148 **Poster Session**

Adherence to vaccination recommendations in the adult cancer population. First Author: Kimberly Feng, Beth Israel Deaconess Medical Center, Boston, MA

Background: In 2024, the American Society of Clinical Oncology (ASCO) published a strong recommendation that clinicians should ensure that all adults with cancer are up to date on seasonal and age- and risk-based vaccinations. The recommended vaccines are drawn from CDC guidelines and include annual influenza, COVID-19, Tdap, Hepatitis B, Zoster (shingles), and Pneumococcal vaccines for all adults, and RSV and HPV for specific groups. Recent studies have found that patients undergoing treatment for cancer had lower COVID-19 vaccination rates mediated by area-level social determinants of health; to our knowledge, rates of adherence to and mediators of other recommended vaccinations in the adult cancer population have not been adequately quantified. **Methods:** We used data from the nationally representative National Health Interview Survey (NHIS) from 2019-2023 to evaluate vaccination rates among individuals with a history of cancer. We identified all individuals aged ≥50 with a diagnosis of cancer within the past 5 years and extracted data on self-reported receipt of three vaccines: annual influenza, pneumonia, and shingles vaccinations. We adjusted for age, race, sex, insurance type, education, US census region, metropolitan statistical area, and used ordinal logistic regression to model determinants of greater degrees of vaccination. **Results:** Between 2019 and 2023, only 30.6% (95% CI [29.3, 31.9]) of all adults aged ≥50 with cancer reported receiving all three studied vaccines. Individually, 69.6% (95% CI [68.2, 71.0]) received the influenza vaccine, 58.4% (95% CI [56.9, 59.9]) received the pneumococcal vaccine, and 42.5% (95% CI [41.0, 44.0]) received the shingles vaccine. The likelihood of receiving more vaccines increased with age (for age 65-74: OR 4.16, CI [3.63, 4.76], $p < 0.001$; for age 75+: OR 5.33, CI 4.62-6.15, $p < 0.001$), whereas variables associated with receiving fewer recommended vaccines included being Hispanic (OR 0.70, CI [0.52, 0.93], p=0.01) or Black (OR 0.61, CI [0.49, 0.77], $p < 0.001$), having Medicaid (OR 0.77, CI [0.63, 0.95], p=0.01), and having high school education or less (OR 0.65, CI [0.59, 0.73], $p < 0.001$). We did not find a significant association between living in a non-metropolitan area and vaccination receipt. **Conclusions:** Between 2019 and 2023, less than one-third of respondents aged ≥50 years diagnosed with cancer within 5 years reported receiving all three appropriate age-related vaccinations. Race-ethnicity, lower socioeconomic status, and lower education were all associated with receiving fewer of the recommended vaccinations. In order to meet ASCO recommended guidelines, efforts to improve vaccination uptake among adults with cancer may need to include targeted interventions for these at-risk populations. Research Sponsor: None.

11149 **Poster Session**

Association between body mass index and overall survival in veterans receiving immune checkpoint inhibitors. First Author: Abhishek Bhattacharya, NYU Langone Department of Internal Medicine, New York, NY

Background: While obesity is a well-established risk factor for cancer development, patients with obesity paradoxically demonstrate better survival rates compared to those with normal body mass index (BMI) in certain malignancies. Studies suggest this phenomenon extends to patients receiving immune checkpoint inhibitors (ICI), with emerging evidence showing improved progression-free and overall survival across multiple cancer types. Despite recognition of this relationship, its magnitude and consistency in real-world populations remain uncertain. The Veterans Affairs (VA) healthcare system, with its comprehensive electronic health records and distinctive demographic composition, presents a unique opportunity to validate these findings in routine clinical practice. **Methods:** We conducted a retrospective analysis using the VA Corporate Data Warehouse, selecting de-identified patients who received ICI therapy between March 2011 and June 2024 (VA COIN grant #1I50HX004009, IRB #1575166). From an initial cohort of 37,863 veterans, we chose a random 20% subset (n = 7,302) for preliminary analysis. We extracted demographic data (age, sex, race), vital signs for BMI calculation, cancer diagnoses (ICD-9/10 codes), and ICI records. BMI categories were: underweight (< 18.5 kg/m²), normal (18.5-25 kg/m²), overweight (25-30 kg/m²), and obesity (> 30 kg/m²). We calculated overall survival from ICI initiation to death or last follow-up. Survival analyses included Kaplan-Meier methodology with Cox proportional hazards models. **Results:** The cohort of 7,302 veterans was predominantly male (97%) and White (74%), with most patients aged 65-75 years (51%). Pembrolizumab (45%) and nivolumab (29%) were the most frequently prescribed ICIs. Survival was significantly associated with BMI class (log-rank test $p < 0.01$). Using normal BMI (18.5-25, n = 2,422) as reference, Cox proportional hazards analysis showed progressively lower mortality risk with increasing BMI, ranging from 13% reduction in overweight patients (HR 0.87, 95% CI 0.82-0.93) to 27% reduction in patients with BMI 35-40 (n = 481, HR 0.73, 95% CI 0.65-0.83, $p < 0.01$). Underweight patients showed increased mortality risk (HR 1.31, 95% CI 1.15-1.51). **Conclusions:** The 27% mortality reduction among patients with higher BMI demonstrates a clinically meaningful survival advantage in immunotherapy outcomes and suggests BMI might be an important factor in risk stratification and treatment discussions. The increased mortality risk in underweight patients may reflect cancer-related cachexia. These findings, derived from a large cohort of veterans, corroborate the obesity paradox in cancer immunotherapy and suggest potential applications for personalized immunotherapy approaches. Research Sponsor: None.

11150 **Poster Session**

Impact of palliative chemotherapy in hospitalized patients with advanced solid tumors. First Author: Sydney Roussel, Inova Fairfax Medical Center, Falls Church, VA

Background: The role of palliative chemotherapy (PC) in patients with advanced solid tumors and poor performance status (PS) remains uncertain since this population is underrepresented in clinical trials. Retrospective studies of patients with an Eastern Cooperative Oncology Group-Performance Status (ECOG-PS) > 2 consistently demonstrate poorer survival and increased treatment-related toxicities. This study aimed to evaluate the clinical impact of PC in hospitalized patients and its association with PS and outcomes. **Methods:** This retrospective chart review was conducted between January 2018 and July 2024 across a five-hospital health system. The primary endpoint was overall survival (OS), defined as the time from the first dose of inpatient chemotherapy to death or last follow-up. Secondary outcomes included in-hospital mortality, length of stay, 30- and 60-day mortality, and toxicity. Continuous variables were compared using the Mann-Whitney *U* test or the two-sample t-test and categorical variables were compared using the Chi-squared or Fisher's exact test. Time to event data were assessed using the Kaplan-Meier method. A p-value < 0.05 was considered statistically significant. **Results:** A total of 383 patients were included in this study. Of these, 227 patients had an ECOG-PS ≤ 2, and 156 patients had an ECOG-PS > 2. The median age was 60 years, and 57% were female. Common primary tumor sites included gastrointestinal, gynecologic, and lung. At presentation, 288 patients were chemotherapy-naïve, and 88% were hypoalbuminemic. The median OS was 188 days. Patients with an ECOG-PS ≤ 2 had a significantly longer median OS compared to those with an ECOG-PS > 2 (293 vs 77 days, $p < 0.0001$). Mortality rates were higher in patients with ECOG-PS > 2 during the index hospitalization (17% vs 6%, p=0.0005), at 30 days (24% vs 14%, p=0.015), and at 60 days (36% vs 21%, p=0.001). Despite these differences, bleeding and infection rates were similar between groups. Median duration of hospitalization was 13 days, with significantly longer stays observed in patients with poor PS (16 vs 10 days, $p < 0.0001$). Although toxicity rates were comparable overall, patients with ECOG-PS > 2 experienced significantly higher rates of thrombocytopenia (39% vs 25%, p=0.018) and neutropenia (40% vs 27%, p=0.028). In univariate analysis, significant predictors of shorter survival included ECOG-PS > 2 ($p < 0.0001$), age > 60 (p=0.0097), Charlson Comorbidity Index ≥ 8 (p=0.02), hypercalcemia (p=0.0014), and hypoalbuminemia (p=0.0014). In multivariate analysis, all factors except age > 60 remained independent predictors of shorter survival. **Conclusions:** PC in hospitalized cancer patients with ECOG-PS > 2 was associated with shorter survival, longer hospital stays, and higher rates of early mortality. These findings emphasize the importance of careful patient selection and the need for further research to optimize care strategies in this population. Research Sponsor: None.

11151 **Poster Session**

Association of co-administration of a vaccine with immune checkpoint inhibitors with survival. First Author: Justin Dejia Wang, Mercy Scripps Hospital, San Diego, CA

Background: Patients undergoing chemotherapy are less likely to complete recommended routine vaccination. Vaccination during immune checkpoint inhibitor (ICI) therapy elicits a significant cytokine response, which could enhance antitumor effects. This study investigates whether co-administration of vaccination with ICI improves cancer patient survival. **Methods:** Using the California Immunization Registry and Scripps Health's electronic medical record, we validated vaccination status for patients at a large healthcare system in San Diego and conducted an observational cohort study of all ICI recipients from January 1, 2018, to June 1, 2024. Overall Kaplan-Meier survival curves were compared between patients who received vaccination within 100 days of ICI initiation and those who did not using log rank test. Subgroup analyses focused on patients with stage IV non-small cell lung cancer (NSCLC) and stage IV melanoma. The ICI cohort was propensity matched 1:1 by demographics to non-cancer patients to evaluate immunization rates. **Results:** 1,854 ICI-treated patients and 1,854 matched patients without cancer were identified for analysis. Vaccination within 100 days of ICI initiation was associated with improved overall survival (HR: 0.43, 95% CI: 0.37 – 0.49, $p<.0001$). Among NSCLC patients ($n=241$), overall survival improved when any vaccination was administered within 100 days of ICI initiation (HR 0.37, $p<.0001$), with benefits observed specifically for COVID-19 (HR: 0.43, $p<.0001$) and influenza (HR: 0.38, $p<.0001$) vaccinations. Similarly, melanoma patients ($n=216$) demonstrated improved overall survival with COVID-19 (HR: 0.53, $p=.0214$) and influenza (HR: 0.59, $p=.0468$) vaccinations. Findings remained robust upon censoring deceased unvaccinated patients within 100 days of ICI initiation to mitigate guarantee-time bias. No significant differences were observed in demographics, BMI, smoking status, medical comorbidities, PD-L1 expression (for NSCLC), or LDH levels (for melanoma) between patients who had received a vaccine within 100 days of ICI initiation and those that did not, that would otherwise explain this difference in mortality. There was no difference between the vaccinated and unvaccinated groups in terms of vaccination-related infection mortality. Active ICI patients were more likely to receive routine vaccinations than non-cancer patients (Influenza 2023 OR: 1.51, $p=.0016$), though vaccination rates have declined since their 2020 peak (Influenza vaccination rate: 2020, 71%; 2023, 59%). **Conclusions:** Co-administration of vaccination with ICI therapy improves survival, independent of infection-related outcomes. The associated cytokine response from vaccination during ICI therapy may enhance antitumor effects. Vaccination rates among ICI-treated patients have declined since 2020, highlighting the need for interventions to improve uptake and outcomes. Research Sponsor: NIH CTSA; K12TR004410.

11152 **Poster Session**

Trends in place of death among breast cancer patients in the United States (1999–2023): A 25-year analysis of racial and regional disparities. First Author: Fatima Ali, Ascension St Vincent, Evansville, IN

Background: Breast cancer is the second most prevalent cancer among women in the United States, associated with significant morbidity and mortality related to treatment. The place of death (PoD) significantly influences patient and caregiver preferences, access to home-based supportive care, and the overall cost of caregiving. This study evaluates trends in PoD for patients with breast cancer in the U.S. from 1999 to 2023 using data from the CDC WONDER (Wide-ranging Online Data for Epidemiologic Research) database. **Methods:** We conducted a comprehensive analysis of data from the CDC WONDER database covering the period from January 1, 1999, to December 31, 2023. Deaths attributed to breast cancer were identified using the International Classification of Diseases-10th Revision (ICD-10) code C50. We collected demographic data to calculate descriptive statistics based on race, PoD, census region, and home and hospice utilization over the past 25 years. **Results:** Our analysis revealed a total of 1,047,098 breast cancer-related deaths from 1999 to 2023. Among these, 513,231 deaths (49.01%) occurred in home or hospice facilities (H&H), while 471,297 deaths (45.01%) were reported in medical facilities and nursing homes (M&N). The proportion of H&H deaths increased from 37.1% in 1999, peaked at 62.6% in 2020, and then declined to 56.9% in 2023. Racial disparities were evident, with all racial groups experiencing an increase in percentage of H&H mortality from 1999 to 2023. Black or African American individuals exhibited the highest relative percentage increase at 66.04%. In 2023, the highest rates of H&H mortality were observed in white patients (58.99%), followed by Hispanic patients (56.36%), American Indian or Alaska Native patients (50.51%), and Black or African American patients (48.90%). Regional analysis indicated that all regions saw an increase in H&H mortality from 1999 to 2023, with the Midwest showing the highest relative percent increase at 60.58%. In 2023, the South had the highest percentage of H&H mortality (59.80%), followed by the West (58.45%), Midwest (55.53%), and Northeast (49.33%). **Conclusions:** The trends in place of death for breast cancer patients over the past 25 years highlight significant shifts in mortality patterns, with increasing reliance on home and hospice care, particularly among certain racial and regional groups. These findings highlight the need for targeted interventions to improve access to palliative care services and support for patients and caregivers, particularly in underserved populations and regions. Research Sponsor: None.

11153 **Poster Session**

Regional trends in disability adjusted life years (DALYs) and mortality of pancreatic cancer among older adults (70+): A global burden of disease study (1990–2021). First Author: Nana Sardarova, Henry Ford Health System, Warren, MI

Background: Pancreatic cancer is a major health challenge, particularly for older adults, with significant regional disparities in its burden over the decades. This study analyzes 30-year trends in pancreatic cancer DALYs and deaths among older adults across regions. **Methods:** We used Global Burden of Disease (GBD) data (1990–2021) to analyze age-standardized DALYs and deaths for individuals aged 70+. Trends were assessed using AAPCs and APCs, stratified by region and socio-demographic index (SDI). **Results:** Regions with lower SDI (e.g., Sub-Saharan Africa, South Asia) showed higher AAPCs, indicating greater increases in DALYs and deaths compared to high-income regions (e.g., North America, Western Europe). Low-middle SDI regions, Central Asia, and Southeast Asia saw significant increases in deaths, while Southern Latin America and the Caribbean experienced slight declines. In Eastern Europe, pancreatic cancer DALYs and deaths increased at an AAPC of 1.45% and 1.50%, respectively, showing a moderate but concerning rise in burden. Meanwhile, Central Sub-Saharan Africa experienced a sharp increase, with DALYs and deaths rising at an AAPC of 2.10% and 2.15%. In contrast, Oceania saw only a slight increase, with DALYs and deaths rising at an AAPC of 0.50% and 0.55% showing a relatively stable burden compared to other regions. The highest death rates are observed in High-income Asia Pacific (109.30 in 2021) and Southern Latin America (85.01 in 2021), while the lowest death rates are in South Asia (12.17 in 2021) and Low SDI regions (14.00 in 2021). For DALYs, the highest rate was 1462.27 per 100,000 population in High-income Asia Pacific in 2016, while the lowest rate was 131.06 per 100,000 population in South Asia in 1990. **Conclusions:** The burden of pancreatic cancer among older adults is increasing at a faster rate in regions with lower socio-demographic development, while more affluent areas are seeing relatively stable trends. These stark disparities highlight the urgent need for focused healthcare efforts, better distribution of resources, and stronger preventive measures in regions where the impact of pancreatic cancer is growing most rapidly. Tackling these inequalities will demand global collaboration and customized strategies to lessen the rising toll of pancreatic cancer on older populations around the world. Research Sponsor: None.

Region	DALYs AAPC (%)	Deaths AAPC (%)	Trend
Western Sub-Saharan Africa	2.25 (2.22–2.28)	2.31 (2.28–2.35)	Highest increase, growing burden
North Africa & Middle East	1.67 (1.62–1.72)	1.77 (1.73–1.82)	Steady rise
Low-middle SDI Regions	1.59 (1.56–1.63)	1.65 (1.62–1.70)	Substantial increases
High-income North America	0.22 (0.18–0.26)	0.29 (0.25–0.32)	Lowest increases
Southern Latin America	-0.18 (-0.27–-0.10)	-0.03 (-0.08–0.02)	Decrease in burden
Caribbean	-0.12 (-0.21–-0.02)	-0.03 (-0.14–0.06)	Decrease in burden

11154 **Poster Session**

Characterizing health related quality of life among individuals living with non-small cell lung in the United States: Findings from the Cancer Experience Registry. First Author: Erica Fortune, Cancer Support Community, Washington, DC

Background: Lung cancer is the second most common cancer and the leading cause of cancer-related deaths. Non-small cell lung cancer (NSCLC), which comprises ~85% of cases, is aggressive, often diagnosed late, and associated with significant symptom burden, and poor health-related quality of life (HRQoL) overall, as well as poor prognosis. However, the factors contributing to variation in HRQoL among NSCLC patients are poorly understood. This study aims to assess the role metastatic status and treatment history play in HRQoL. **Methods:** We conducted a retrospective analysis of Cancer Support Community's Cancer Experience Registry (CER) survey data collected between Feb 2015 – Nov 2023. The sample included 279 U.S. adults with NSCLC. HRQoL, specifically physical and psychological symptom burden and function, was assessed using the 7 domains of PROMIS29v2.0: anxiety, depression, pain, fatigue, sleep disturbance, physical function, and social function. Preliminary analyses (not shown here) found that non-metastatic patients were *more* likely to report higher pain, fatigue, and physical and social impairments compared to metastatic patients. We hypothesized that treatment history could partially explain this outcome: 62% of nonmetastatic patients reported history of surgery vs. 31% of metastatic patients. Thus, an interaction term (metastatic status x surgery) was created for further analysis in backward elimination linear regression models. **Results:** Participants were 68% women and 88% Non-Hispanic White, with a mean age of 64 (SD=10 years). The mean time since initial diagnosis was 5 years (SD=7). 16% were nonmetastatic with no history of surgery and 27% with a history of surgery; 39% were metastatic with no surgery and 18% with surgery. After adjusting for sociodemographic and clinical variables, treatment history showed associations with HRQoL, though findings were inconsistent in most groups. Those who were nonmetastatic without surgery reported more sleep disturbance (b = 3.58), those with clinical trial history reported less anxiety (b = -3.61), and those with immunotherapy reported less depression (b = -2.55). Metastatic individuals without surgery reported less pain (b = -3.75) and fatigue (b = -3.06) and better physical (b = 3.67) and social functioning (b = 4.19). Metastatic surgery group was not significant for any domains. **Conclusions:** Results underscore the complex factors that contribute to HRQoL in those with NSCLC. The findings emphasize the importance of a holistic, value-based care approach, considering not just survival but also patients' preferences and quality of life. A full understanding of treatment side effects and their implications for HRQoL is essential to aligning care with patient preferences. Future research should investigate how treatment history impacts HRQoL outcomes. Research Sponsor: Gilead Sciences.

11155 Poster Session

Use of targeted therapy in patients with advanced non-small cell lung cancer in response to broad genomic profiling. First Author: Xiao Wang, Yale Cancer Center, New Haven, CT

Background: Broad genomic profiling (BGP) is increasingly performed for patients with advanced non-small cell lung cancer (aNSCLC) to inform the use of targeted therapy (TT). The approach to specific BGP results has evolved, alongside changes in evidence, FDA approval status, and professional guidelines. Limited data exist characterizing impact of BGP on treatment selection in a real-world patient population. **Methods:** We identified patients diagnosed with aNSCLC 2017–2023 using the nationwide deidentified Flatiron Health-Foundation Medicine aNSCLC Clinico-Genomic Database, containing data from ~280 US cancer clinics (~800 sites of care). We classified each patient's BGP results by contemporaneous FDA approvals and NCCN guidelines, categorizing findings as actionable with on-label TT (first- [1L] vs. later-line [2+]), potentially actionable with off-label TT (NCCN recommended vs. not recommended), or not actionable. We then categorized actual 1L treatments received relative to these standards. **Results:** Of 5781 patients with aNSCLC who underwent BGP testing (Table), on-label 1L TT was used in 13.1% of patients, while 3.3% (1.3% guideline recommended + 2.0% not recommended) received off-label 1L TT. Overall, 17.6% had a 1L targetable alteration (74.5% of whom received on-label TT), while 6.0% had a 2L+ on-label targetable alteration (9.7% received TT in 1L, against label + recommendation). In addition, 4.7% had a potentially actionable alteration with recommended off-label TT (11.4% of whom received off-label 1L TT), while an additional 23.3% had potentially actionable alterations without recommended TT (4.3% received off-label TT in 1L, against NCCN recommendation). **Conclusions:** In this cohort of patients with aNSCLC, half had actionable or potentially actionable BGP results. One in four patients with 1L actionable findings did not receive corresponding on-label 1L TT (potential missed opportunity), while one in ten with 2L+ actionable findings received TT as off-label 1L treatment in contrast to guidelines (potential indication creep). 1L off-label TT use was uncommon and largely guideline discordant. Research Sponsor: U.S. National Institutes of Health; 5R01CA280359-02; National Cancer Institute/U.S. National Institutes of Health; T32CA233414.

First-line treatments by mutation actionability in patients with advanced non-small cell lung cancer, as recommended (Rec'ed) by contemporaneous clinical guidelines.

Mutation Category	On-Label TT	Rec'edOff-Label TT	NOT Rec'ed Off-Label TT	Non-Targeted Systemic Therapy
Actionable, TT 1st Line N = 1018 (17.6%)	758 (74.5%)	44 (4.3%)	≤5 (≤0.5%)	≥211 (≥20.7%)
Actionable, TT 2nd Line N = 349 (6.0%)	.	.	34 (9.7%)	315 (90.3%)
Potentially actionable – Off-Label TT Rec'ed N = 273 (4.7%)	.	31 (11.4%)	≤5 (≤1.8%)	≥237 (≥86.8%)
Potentially actionable – Off-Label TT NOT Rec'ed N = 1348 (23.3%)	.	.	58 (4.3%)	1290 (95.7%)
Not actionable N = 2793 (48.3%)	.	.	16 (0.6%)	2777 (99.4%)
TOTAL N = 5781	**758 (13.1%)**	**75 (1.3%)**	**115 (2.0%)**	**4833 (83.6%)**

Cells ≤5 patients censored; TT = targeted therapy.

11156 Poster Session

Real-world outcomes in patients living with HIV with lung cancer and treated with immune checkpoint inhibitors. First Author: Melinda Laine Hsu, University Hospitals Seidman Cancer Center, Case Western Reserve University, Cleveland, OH

Background: Lung cancer is one of the most common non-AIDS defining cancers in People Living with HIV (PLWH) and a leading cause of cancer death in PLWH. PLWH were initially excluded from clinical trials of immune checkpoint inhibitors (ICIs) due to concerns for safety and efficacy. Little is known about the real-world rates of immune-related adverse events (irAEs) and survival outcomes in PLWH with lung cancer treated with ICIs. **Methods:** Adults (age≥18) diagnosed with lung cancer and treated with ICIs between 2015-2021 were identified from the Merative MarketScan database, which contains de-identified healthcare claims of > 250 million patients in the US. We categorized patients into two cohorts based on HIV status: People Living with HIV (PLWH) and those without HIV (PLWoH). We evaluated rates of irAEs and Kaplan-Meier (KM) survival analysis estimated overall survival (OS) in both cohorts; survival function was calculated from first ICI treatment to death or last follow-up. We used the log-rank test to assess statistical differences in survival between the cohorts. **Results:** 21,259 people with lung cancer and treated with ICIs were identified, and 105 were identified as PLWH. More PLWH treated with ICIs were male (81.9%) and younger (median age 61 yrs) than PLWoH (53.4%, 64 yrs). There was no significant difference in median OS of PLWH (343 days) and PLWoH (364 days, p=0.62). PLWH experienced a similar rate of irAEs (53.3%) as PLWoH (54.6%). Most patients experienced one irAE (55.36% PLWH, 54.33% PLWoH). PLWH experienced irAEs in up to 3 organ systems, and PLWoH in up to 7 organ systems. The most common irAEs in PLWH were neurologic (41.07%), endocrine (39.29%), and renal (32.14%). In PLWoH, endocrine (52.26%), renal (34.93%), and cutaneous (27.82%) were the most common. Patients who experienced irAEs had statistically significantly improved OS in both cohorts compared to those without irAEs (both p<0.0001). **Conclusions:** We found similar rates of irAEs and OS in a large, real-world population of PLWH with lung cancer treated with ICIs, and people without HIV and lung cancer treated with ICIs. Further research is needed to improve early identification of lung cancer in PLWH and identify predictors of toxicities. Research Sponsor: National Cancer Institute; U54CS254566.

11157 Poster Session

ARIMA prediction model for mortality caused by metastatic cancers in the United States population up to the year 2050: A CDC WONDER Database analysis. First Author: Nisar Ahmed, Liaquat National Hospital and Medical College, Karachi, Pakistan

Background: Metastatic cancers are the leading cause of mortality in the United States (US). In this study of death certificates, obtained from data registry spanning from 1999 to 2024, we examined mortality trends among individuals suffering from any metastatic cancer in US. **Methods:** Our aim was to analyze the trends in mortality among US residents by demographic characteristics and predict future years based on the existing data by Autoregressive Integrated Moving Average (ARIMA) forecasting modeling. The national mortality data from the multiple causes of death files in the CDC WONDER Database were queried by applying the ICD-10 codes as C77-C79 for secondary cancers. Trends in age-adjusted mortality rate (AAMR) were assessed and results were expressed as average annual percentage changes (AAPC) from Join point regression. **Results:** There were a total of 2,098,842 deaths due to metastatic cancers in US from 1999-2024 with a crude mortality rate of 25.97 per 100,000 population, about 52% of them being males and 48% were females. Mortality rates (AAMR) continue to trend down from 1999-2008 in both gender, but showed an increase from 2009 onwards with females showed significant AAPC of +0.44. ARIMA predictive model exhibits a significant decline of mortality rates up to the year 2050 in Black population (AAMR: 24.45), Northeast region (AAMR: 10.84) and metropolitan areas (AAMR: 19.93). **Conclusions:** These findings provide valuable insights of mortality patterns among US population with metastatic malignant diseases. Certain subgroups with specific demographic and geographic characteristics such as White Population, non-metropolitan areas and those belonged to West region had higher future prediction of AAMR. Research Sponsor: None.

ARIMA forecasting model for predicting AAMR in metastatic cancer population in U.S.

Variables	AAMR in 1999	Lowest AAMR (year)	AAMR in 2024	AAPC	ARIMA forecast (2050)
Total	27.65	18.34 (2008)	29.13	+0.30 (0.20 – 0.40)*	29.90
Gender					
Female	23.89	15.73 (2008)	26.23	+0.44 (0.34 – 0.54)*	26.04
Male	33.48	22.03 (2008)	33.19	+0.06 (-0.32 – 0.44)	32.31
Race					
White	27.74	18.70 (2008)	30.89	+0.51 (0.40 – 0.63)*	32.95
Black	35.32	21.30 (2014)	30.67	-0.54 (-1.43 – 0.36)	24.45
Hispanic	19.07	12.93 (2008)	21.68	+0.42 (0.30 – 0.55)*	24.68
Asian or Pacific Islander	16.32	11.60 (2008)	19.37	+0.54 (0.25 – 0.89)*	23.15
American Natives	20.35	15.19 (2005)	21.68	+0.33 (-0.15 – 1.15)	24.28
Census Region					
Northeast	27.29	15.62 (2014)	20.53	-1.03 (-1.57 – -0.49)*	10.84
Midwest	29.51	18.55 (2010)	31.96	+0.35 (0.21 – 0.47)*	30.74
South	28.23	19.18 (2008)	30.77	+0.43 (0.31 – 0.56)*	33.30
West	24.81	17.18 (2008)	30.72	+0.97 (0.77 – 1.19)*	39.18
Urbanization†					
Metropolitan	27.17	17.76 (2008)	24.66	-0.46 (-0.60 – -0.33)*	19.93
Non-metropolitan	29.87	20.73 (2010)	30.39	+0.02 (-0.75 – 0.80)	26.56

AAMR per 100,000 population.
†For urbanization, AAMR 1999-2020.
*P-value <0.05.

11158 Poster Session

Determinants of overall survival in the South African Breast Cancer and HIV Outcomes cohort. First Author: Maureen Joffe, University of Witwatersrand Faculty of Health Sciences, Johannesburg, South Africa

Background: Sub-Saharan Africa (SSA) has very low breast cancer (BC) survival. South Africa, unlike most SSA countries, is an upper middle-income country where patients are less burdened with cancer diagnostic and treatment costs. We aimed to provide five-year overall survival (OS) estimates and determinants among South African women with BC diagnosed and treated within the public health system. **Methods:** The South African Breast Cancer and HIV Outcomes prospective cohort study enrolled adult women recently diagnosed with invasive BC from four South African academic hospitals. We collected detailed sociodemographic, clinical, treatment, and outcomes data. Women were followed for five years or until December 31, 2023, whichever was earlier, and our primary outcome was five-year OS. Impacts of potential determinants on OS were assessed using individual Cox proportional hazard models focused on nine variable domains (*i.e.,* treating hospital, social status, BC risk factors, smoking, cardiovascular disease (CVD), HIV status, BC type, BC treatments, and age) and a combined model that also included adjustments for background mortality. **Results:** Between July 2015 and Feb 2019, we enrolled 2,838 women newly diagnosed with histopathologically confirmed invasive BC, of whom 58% had III or IV disease. At the end of follow-up, 1555 (55%) of the women had died, 1191 (42%) survived for five years, 33 (1%) were censored at study's end, and 59 (2%) were lost to follow up. The five-year OS was 44.3% (95% CI 42.5-46.2). In the full model, the variables with the largest impact on five-year survival were late-stage at diagnosis (HR 2.4 [95% CI 2.0-2.7] for stage III and HR 5.0 [95% CI 4.1-6.1] for stage IV disease, both compared with stage I/II) and differing degree of treatments received (no treatment received: HR 8.2 [95% CI 5.9-11.3]; chemotherapy and endocrine therapy: HR 1.9 [95% CI 1.4-2.6]; endocrine therapy only: HR 2.2 [95% CI 1.6-3.2]; chemotherapy only: HR 4.8 [95% CI 3.4-6.6]; surgery only: HR 3.0 [95% CI 1.9-4.8]; surgery and chemotherapy: HR 1.8 [95% CI 1.3-2.5], all compared with surgery and endocrine treatments). Other variables significantly associated with survival were treating hospital, relationship status, employment, education, family history of cancer, CVD, and HIV infection. **Conclusions:** Interventions to improve BC survival in South Africa's public health system should prioritize earlier diagnosis of cancer and expansion of the infrastructure supporting diagnostic and treatment services. Concurrently, South African BC patients with low socioeconomic status, HIV infection, and/or comorbid CVD are uniquely vulnerable and their barriers to accessing care must be better understood. Research Sponsor: National Institute of Health and South African Medical Research Counsel.

11159 Poster Session

Implementation and evaluation of multi-cancer early detection testing at the Dana-Farber Cancer Institute: A retrospective analysis of clinical outcomes and diagnostic pathways. First Author: Elizabeth O'Donnell, Dana-Farber Cancer Institute, Boston, MA

Background: Early detection and interception of cancer is a growing field at the intersection of primary care and oncology. Technological innovation has facilitated the development of multi-cancer early detection (MCED) tests, which allow for the detection of a broad range of cancers in a single screening test. These tests are entering clinical practice as laboratory developed tests but little has been reported about their implementation. In 2023, Dana-Farber introduced an MCED Program to facilitate the evaluation of patients who have received MCED testing and to study novel MCED strategies. **Methods:** We conducted a retrospective chart review of patients seen at the Dana-Farber between 12/1/2023 and 12/1/2024 who had a cancer signal detected by a Grail Galleri MCED test. **Results:** Thirteen patients were evaluated for a positive cancer signal detected by the Grail Galleri MCED test. The median age was 62.7 (54.9-81.4), 61.5% (8/13) were male, and 84.6% (11/13) were white. Following diagnostic evaluation 76.9% (10/13) had a confirmed cancer diagnosis and 23.1% (3/13) were deemed false positives. The time from MCED test result to presentation at DFCI was a median of 25 days (6-368) and the median time to conduct the diagnostic evaluation was 23 days (5-104), which was shorter in true positive cases (15 days) compared to false positives (98 days). A total 6 of the 10 (60%) signal detected cases were solid tumors which included triple negative breast, testicular, liver, cholangiocarcinoma, tonsillar, and lung (non-smoker); and 4 (40%) cases were hematologic malignancies (3 lymphoma, 1 myeloma). Of the malignancies detected, 9 (90%) have no current screening guidelines. Screening mammography was up to date in the patient found to have triple negative breast cancer. Six cancers (60%) were diagnosed at stage I/II and 4 (40%) were stage III/IV. All 3 false positive cases received a repeat MCED test a median of 118 days (87-161) after the initial test and all had no signal detected at re-test. The median number of tests/procedures to reach diagnostic resolution was 4 for true positive cases (2-7) and 5 for false positive cases (4-6). All patients required advanced imaging. The first or second cancer signal origin was accurate in 90% (9/10). There were no issues encountered obtaining prior authorizations for diagnostic tests and no adverse events were reported. **Conclusions:** The majority of patients that presented with a positive MCED test were true positives with a cancer consistent with the cancer signal origin. Patients with signal detected tests were quickly adjudicated in our clinical program, although some patients initially experienced significant delays in finding a provider to work-up their test result. These findings support a role for dedicated cancer diagnostic clinical expertise in the evaluation of MCED tests. Research Sponsor: None.

11160 Poster Session

Evaluation of large language model (LLM)-based clinical abstraction of electronic health records (EHRs) for non-small cell lung cancer (NSCLC) patients. First Author: Kabir Manghnani, Tempus AI, Inc., Chicago, IL

Background: Abstraction is a critical step for converting clinical data from unstructured EHRs into a structured format suitable for real-world data analyses. Typically this is a manual, labor-intensive activity requiring substantial training. While prior work has shown that abstraction by humans is reliable, advances in LLMs may improve the efficiency of abstraction. We aim to measure the performance of LLMs in abstracting a diverse set of oncology data elements. **Methods:** Two clinical abstractors independently abstracted unstructured records of 222 advanced or metastatic NSCLC patients (mean: 248 pages per case). A two-stage LLM system balancing cost and comprehensiveness was used to abstract clinical elements for demographics, diagnosis, third-party lab biomarker testing, and first line (1L) treatment. The initial stage extracted 16 documents semantically similar to the abstraction query and input them, along with abstraction rules, into an LLM (GPT-4o). The LLM was instructed to provide both the abstracted field and a completeness assessment of provided context. If the first phase resulted in a low completeness score, the entire patient record was then input into a long-context LLM (Gemini-Pro-1.5) to re-attempt abstraction. Gwet's agreement coefficient (AC) was the primary measure of agreement between the LLM and each abstractor. Date agreement was calculated within $\pm$30 days. **Results:** The LLM system yielded abstracted values for 90% of elements where both abstractors provided non-missing values. In these cases, the LLM also demonstrated high agreement with each abstractor ($\geq$0.81 across all categories). Agreement was highest in demographic and diagnosis domains and lower for 1L treatment domain, which require deeper understanding of a patient's temporal journey. For elements where neither abstractor provided values, the LLM sometimes provided outputs (frequency: 4.9% for non-biomarker elements; 38.5% for biomarker elements). These discrepancies were primarily driven by nuances in abstraction rules; the LLM often included Tempus-tested biomarkers, while abstractors were more rigorous in abstracting only third-party biomarker results. **Conclusions:** LLMs show high completion rates and high agreement with human abstractors across a variety of critical abstraction fields. The use of LLMs may significantly reduce the burden of human abstraction and allow for large-scale curation of oncology records. Challenges in handling nuanced contexts underscore the need for careful refinement and evaluation prior to deployment. Research Sponsor: Tempus AI, Inc.

Domain	LLM agreement with abstractors (AC, min-max)
Demographic (birth date, sex, race, smoking status)	0.96-1
Diagnosis (stage, histology, year of diagnosis)	0.92-0.98
Third Party Biomarker (EGFR, ALK, ROS1, PDL1, BRAF, RET, NTRK)	0.87-1
1L Treatment (agents, initiation date)	0.81-0.86

11161 Poster Session

Real-world analysis of factors influencing turnaround time (TAT) for tissue comprehensive genomic profiling (CGP) in non-small cell lung cancer (NSCLC). First Author: Adam Fox, Medical University of South Carolina, Charleston, SC

Background: CGP is an integral part of the standard of care for many solid tumor malignancies, and especially for NSCLC, as testing informs first-line treatment selection at most stages. CGP TAT is understudied but has implications for appropriate treatment delivery and patient outcomes. **Methods:** In this retrospective cohort analysis, TAT was calculated for U.S. tissue CGP testing orders received between January 2021 and September 2023 at a centralized commercial molecular laboratory (Foundation Medicine, Inc., Cambridge, MA, USA). Ordering TAT (specimen collection to CGP ordering), Specimen TAT (CGP ordering to specimen receipt at testing lab), Molecular TAT (specimen receipt to results reporting), and Overall TAT (specimen collection to results reporting) were calculated. Cases were excluded if CGP was ordered $>$6 months after specimen collection or if missing TAT data. Descriptive statistics and linear regression modeling for association of TAT with available clinical and molecular factors were performed. **Results:** A total of 40,728 NSCLC biopsies from 547 institutions were included in the analysis. The median Overall TAT for all samples was 29.8 days (IQR: 21.7, 44.6). Median times for Ordering TAT, Specimen TAT, and Molecular TAT were 14.8 days (IQR: 8.4, 27.8), 3.2 days (IQR: 1.3, 6.2), and 9.0 days (IQR: 7.7, 11.0), respectively. Aggregating and calculating TAT at the institution level, the median Overall TAT was 40.6 days (IQR: 38.5, 43.8) versus 21.9 days (IQR: 20.7, 23.7) among the slowest and fastest Overall TAT quintiles, respectively; Ordering TAT [median 15.1, IQR: 11.6, 18.9] and Specimen TAT [median 3.9, IQR: 1.9, 5.1] contributed to this variability, while Molecular TAT [median 9.0, IQR: 8.6, 9.3] remained consistent. Higher institutional order volume was the strongest predictor of shorter Overall TAT (-6.59 days [95% CI: -7.46, -5.71] for institutions with [100-200) vs $<$20 orders, P $<$ .001), largely driven by variability in Ordering TAT (-4.13 days [95% CI: -4.95, -3.31] for institutions with [100-200) vs $<$20 orders, P $<$ .001) and Specimen TAT (-2.25 days [95% CI: -2.47, -2.04] for institutions with [100-200) vs $<$20 orders, P $<$ .001). **Conclusions:** This study demonstrates that NSCLC CGP TAT is highly variable and is influenced by institutional factors, particularly higher institutional ordering volume. For patients with an established diagnosis, the time between specimen collection/diagnosis and CGP ordering likely represents the longest and most modifiable component of Overall TAT. This study raises the hypothesis that adoption of coordinated interventions, such as reflex testing, could reduce Ordering TAT, and thus Overall TAT, for many patients. Research Sponsor: None.

11162 Poster Session

Assessing biosimilar entry in the market for biologic cancer drugs. First Author: Xiaoyu Liu, UCLA, School of Public Health, Los Angeles, CA

Background: Biosimilars are biological drugs highly similar to and without clinically meaningful differences from their biological reference products. As of 2023, out of 39 biosimilars available in the US, 22 (56%) are indicated for cancer treatment (n=12) or supportive care (n=10). This study described the trends in uptake, pricing, and out-of-pocket (OOP) costs between 2014 and 2023. **Methods:** Using MarketScan claims data and Average Sales Price (ASP) data from the Centers for Medicare & Medicaid Services, we calculated quarterly ASP and the market share of reference products for treatment and supportive care biologics in the commercial and Medicare Part B markets, 2014 to 2023. We also estimated the average monthly out-of-pocket costs (deductible + copayment + coinsurance) before and after biosimilar entry. We identified biologics using Healthcare Common Procedure Coding System codes and adjusted costs to 2024 USD using the prescription drugs Consumer Price Index. **Results:** Analyses included 1,040,456 claims of 28 biological products (6 reference products and 22 biosimilars). On average, the ASP of reference products for treatment and support care decreased by 1.3% and 2.8% per quarter, respectively, after biosimilar entry. Market share of reference products declined over time after biosimilar entry, though the decline was smaller in the Medicare market than in commercial insurance market as of 2023 Q4. The average quarterly reduction ranged between 2.2% and 14.6% across reference products, with larger reduction for treatment drugs. Compared to monthly OOP averaging over 12 months before first biosimilar launch, monthly OOP costs of biologics (including reference and biosimilars) in 2023 fell for 4 reference drugs in the commercial market, and 5 in the Medicare market. **Conclusions:** Biosimilar entry has lowered the price and led to a substantial reduction in market share of biologic reference products, especially for cancer treatment drugs. Nevertheless, trends in OOP costs for biologics indicated biosimilars did not always lower financial burden for patients. Research Sponsor: None.

			Commercial insurance			Medicare Part B		
Drug	1st biosimilar entry	Reference product ASP quarterly change	Market share of reference product, 2023 Q4 (quarterly change)	Mean monthly OOP before biosimilar entry	Mean monthly OOP, 2023	Market share of reference product, 2023 Q4 (quarterly change)	Mean monthly OOP before biosimilar entry	Mean monthly OOP, 2023
Bevacizumab	2019 Q2	-0.61%	9.29% (-14.65%)	$55.88	$47.07	17.67% (-10.91%)	$23.31	$27.52
Rituximab	2019 Q4	-1.38%	14.91% (-13.62%)	$96.28	$88.28	18.42% (-12.20%)	$48.31	$36.90
Trastuzumab	2019 Q2	-1.91%	12.67% (-12.87%)	$44.39	$44.71	15.39% (-11.73%)	$25.37	$24.80
Epoetin alfa	2018 Q4	-2.04%	54.46% (-3.32%)	$17.61	$25.76	62.22% (-2.60%)	$17.75	$10.38
Filgrastim	2015 Q3	-0.01%	4.17% (-10.05%)	$11.72	$10.76	2.27% (-11.86%)	$7.40	$2.36
Pegfilgrastim	2018 Q2	-6.50%	65.13% (-2.23%)	$65.92	$57.97	61.70% (-2.51%)	$54.41	$30.36

11163 **Poster Session**

A real-world data claims-based review of CAR-T procedures, time to adverse events, patient characteristics and social factors. First Author: Karina D'Angelo, Parexel International, Durham, NC

Background: With the increasing utilization of Chimeric antigen receptors T-cell therapies (CAR-T), administrative claims can provide insights into approved CAR-T therapies, procedures, associated adverse events (AEs) and population characteristics. **Methods:** We used administrative open claims with medical and pharmacy encounters of 330 million US patients (PurpleLab). We identified patients with a coded AE as the principial diagnosis following the first initial claim with any CAR-T. CAR-T claims were identified with drug and procedure coding. The AEs included were Cytokine release syndrome (CRS), Immune effector-cell associated neurotoxicity (ICANS), complication of immune effector cellular therapy, tumor lysis, and cardiovascular events such as arrhythmias. The time to the AE and death were noted. In cases where social determinants of health (SDOH) are noted, race, gender, marital status, occupation, and education were analyzed. **Results:** The number of patients with CAR-T related claims within the database was 20,003. Of those patients, approximately 10% (2166) had at least one claim with an AE code as the principal diagnosis reported following the very first CAR-T claim. For those with an initial AE claim, 38% had a cardiovascular event, 36% had a complication of immune effector cellular therapy, 13% had a CRS event, 7% had an ICANS, 2% had a tumor lysis event, and 1.3% had a secondary lymphoma. Most AEs occurred within the first 30 to 90 days from the first documented CAR-T claim procedure. Cardiac and complication AEs were higher in patients aged greater than 65, while tumor lysis was higher in patients under 65. Death was reported in a quarter of the patients (532 patients) with 65% of those recorded deaths occurring within a year post first CAR-T related claim. Of those patients with a documented social demographic factor, patients with AEs were white males (41%), Asian males (2.6%), African American males (2.7%), and unspecified males (17%) making up the other races and gender. In terms of occupation and education, 34% were white collar, 5% blue collar, and 4% retired, and 29% had some level of high school, 23% college-level education, and 13% were postgraduate. More patients were identified as married (34%) than single (14%) and approximately 57% had an income below $100,000, while 11% were above $100,000, with the remaining incomes were not recorded. **Conclusions:** Real-world data can provide insights into CAR-T and AEs, patient social factors, and temporal trends. Age greater than 65 seemed the more prevalent SDOH with higher AE seen in this subgroup. Additional investigation on AEs within the different patient population subgroups are needed to provide deeper insights into treatment effects. Research Sponsor: None.

11164 **Poster Session**

Risk of fracture following androgen receptor pathway inhibitors (ARPIs): A population-based study. First Author: Grace L. Lu-Yao, Division of Population Science, Department of Medical Oncology, Sidney Kimmel Medical College, Sidney Kimmel Cancer Center at Jefferson Health, Philadelphia, PA

Background: Androgen deprivation therapy is associated with an increased risk of fracture. ARPIs are widely used to manage advanced prostate cancer (PCa). However, there is limited long-term data on fracture risk following ARPIs and how the risk might vary with different health conditions. This study aims to fill these gaps. **Methods:** This study used the SEER-Medicare linked files to identify men diagnosed with PCa between 1/1/1999 and 12/31/2019 and who received abiraterone with prednisone (AAP) or enzalutamide (ENZA) between 1/1/2013 and 12/31/2020. The primary endpoint is the time to first fracture after the index date (first date of AAP or ENZA). The history of fracture was based on claims one year before the index date. Fine and Gray's subdistribution hazard model was used to estimate the effect of various risk factors. We used the cumulative incidence function to quantify fracture risk. **Results:** This study comprised 10,463 patients (6,037 with AAP and 4,426 with ENZA). Most patients were over 75 with a comorbidity score of 1 or higher. Among 1,445 patients who had a fracture the year before the index date, the risk of fracture after ARPI reached 50% (95% CI 47% - 53%) within 3 years, compared to 26% (95% CI 25%-27%) among those without a fracture. After adjusting for bone health agent use, comorbidities, and sociodemographic factors, a history of fracture was associated with 2.8 fold risk of fracture after AAP (RR=2.80, 95% CI 2.47 – 3.18) and 2.85 fold risk after ENZA (RR=2.85, 95% CI 2.45-3.30). Use of bone health agents within 3 months before the index date was associated with a 20-25% lower fracture risk. **Conclusions:** This large population-based study shows that the risk of fracture following ARPIs is substantial, especially among those who suffered a fracture before ARPIs. It is crucial to consider the history of fracture when making treatment choices and monitoring strategies. Better management of bone health is crucial for men treated with ARPIs. Research Sponsor: Pennsylvania Department of Health; 4100088563; NCI/NIH; 5P30CA056-036 NCI.

11166 **Poster Session**

Validation of real-world event-free survival (rwEFS) in early-stage triple-negative breast cancer. First Author: Carole Berini, Ontada, Boston, MA

Background: Real-world (RW) evidence has been used to demonstrate effectiveness of early-stage cancer treatments. Early-stage clinical endpoints such as event-free survival (EFS) have the potential to support clinical decision-making as an indicator of real-world effectiveness for novel therapies. However, less is known regarding real-world replicability of rwEFS in early triple negative breast cancer (eTNBC). We therefore applied selected target trial emulation methods to examine the concordance between rwEFS and KEYNOTE-522 (KN-522) trial 'chemotherapy only' arm EFS estimates. **Methods:** Electronic health records from the US Oncology Network were used to identify stage II-III triple negative breast cancer patients who initiated neoadjuvant chemotherapy only from 1/1/20 to 3/31/22. Patients were followed through 07/18/23. Patients who received immunotherapy at any time during this observation period were excluded. KN-522 trial eligibility criteria and endpoint definitions were applied to develop the rwEFS endpoint. Matching-Adjusted Indirect Comparison (MAIC) was used to adjust the real-world cohort based on available baseline demographic and clinical characteristics (age, stage, and ECOG performance status) to approximate the KN-522 population. Kaplan-Meier curves and unadjusted and adjusted hazard ratios with 95% CIs were used to compare EFS between the RW cohort and the control arm of KN-522. **Results:** Real-world patients (n=199) were older (median age 59 vs 48), in more advanced stages (61% vs 25% stage III), and more often ECOG$>$0 (40% vs 13%) than participants in the control arm of KN-522. Median EFS was not reached in either the RW cohort or control arm of KN-522. At 36 months, estimated EFS was 76% for patients in the RW cohort and 77% in the KN-522 control arm. There was no statistically significant difference in EFS between the RW and KN-522 cohorts in unadjusted analysis (HR: 0.99, 95% CI: 0.68 - 1.46), indicating concordance between the estimates. After MAIC weighting, baseline values of age, stage, and ECOG performance were balanced between the two cohorts. The difference between RW and trial estimates was also not statistically significant in the adjusted analysis (HR: 0.76, 95% CI: 0.50 - 1.14). **Conclusions:** EFS is a valuable endpoint for evaluating the effectiveness of neoadjuvant therapy in eTNBC patients. With the application of real-world definitions to align key study design elements with the trial and leveraging curated real-world data, it is possible to reproduce the trial EFS estimate in a real-world cohort. The development of a robust, replicable rwEFS endpoint may support clinical decision-making and guide the choice of effective treatments for eTNBC patients. Research Sponsor: Merck & Co., Inc.

11167 **Poster Session**

Impact of AI medical scribes on physician productivity and satisfaction in medical oncology. First Author: Nima Toussi, University of Saskatchewan, Saskatoon, SK, Canada

Background: AI Scribes are a leading example of AI implementation in clinical settings, with Oncology practices demonstrating exponential uptake since their introduction. Despite their ever-increasing usage, there are limited studies which directly interrogate the impact of AI Scribes on physician productivity metrics, and few which assess qualitative interpretations of the technology. **Methods:** This single-center, multi-site study enrolled 27 Medical Oncologists and 3 Primary Care Physicians randomly assigned in a 1:2 ratio to exposure to the Knowtex AI scribe in the initial phase (Phase 1) or control phase (Phase 2). Billing data was collected for 6 months prior to Phase 1 onboarding with Knowtex and for 16 weeks afterward—all within the 2024 fiscal year. During the same period, Phase 2 physicians billing data served as a non-exposed comparison group. Physicians completed opt-in surveys at Week 0 and Week 8 post-exposure assessing confidence and motivation to use the AI Scribe, documentation burden, documentation quality, and experience with the electronic medical record (EMR). **Results:** All providers adopted the Knowtex AI scribe during their study phase. 4 Phase 2 physicians were excluded from data analysis due to incomplete 2024 fiscal year data. Phase 1 physicians exhibited an increase in mean units ($t(10) = 4.44$, $p < 0.01$, $d = 1.34$, CI [0.90, 2.72]) and mean total billings per working day ($t(10) = 4.30$, $p < 0.01$, $d = 1.28$, CI [$377.55, $1206.75]), a pattern not observed in Phase 2 during the same period. There was no change in the number of diagnostic codes per unit amongst Phase 1 physicians. No learned effect emerged over time in Phase 1 billing metrics or diagnostic coding. Survey findings revealed a strong positive association between Week 0 self-assessed Knowtex understanding and increased units ($r(13) = .579$, $p = 0.024$). Physicians reported increased satisfaction with documentation workflow, a reduction in-clinic hours spent on documentation, and increased time spent with patients. Physicians' net impression of EMR challenges markedly decreased following the implementation of the AI scribe ($U = 274.5$, $z=4.054$, $p < 0.0001$). **Conclusions:** Adoption of an AI Scribe in oncology may enhance certain billing metrics and positively shift physician perceptions of EMR interactions, without affecting the quality of documentation. These findings highlight potential benefits of AI Scribes in improving physician productivity and satisfaction. As AI Scribes trend towards delivering multimodal clinical support tools, future research may focus on the adjunctive effects of AI scribes on procedural efficiencies, such as consistency in billing codes. Research Sponsor: None.

11168 Poster Session

Factors associated with decreased treatment intensity in patients with metastatic colon cancer: A real world analysis. First Author: Rebecca Forman, Yale New Haven Hospital, New Haven, CT

Background: The frontline treatments for metastatic colon cancer (mCC) include intensive therapies (e.g., doublet or triplet chemotherapy backbones with biologic agents) and non-intensive therapies (e.g., chemotherapy monotherapy, biologic agents alone, or a combination thereof). Randomized trials have shown that non-intensive therapies offer shorter overall survival compared to intensive therapies; thus, they are recommended only for those unable to tolerate intensive therapy, such as those with poor performance status (PS). There is a need to identify which patients are receiving non-intensive therapies in the real world to ameliorate disparities in undertreatment. **Methods:** We conducted a retrospective cohort study by leveraging the nationwide Flatiron Health electronic health record-derived deidentified database. This database is longitudinal, comprising deidentified patient-level structured and unstructured data, curated via technology-enabled abstraction. Patients included presented with mCC during 2013-2024 and received one of the first line treatments listed in the National Comprehensive Cancer Network (NCCN) guidelines. Therapies were categorized as intensive or non-intensive based on NCCN guidelines. Frailty was defined as baseline ECOG PS≥2, and older age was defined as ≥65 years (yrs) at diagnosis. Multivariable logistic regression was performed between treatment intensity and patient characteristics (age, frailty, sex at birth, year of diagnosis, race, socioeconomic status (SES)) to estimate odds ratios and 95% confidence intervals. Age and frailty were combined into multiple variables given significant interaction term. **Results:** Among 21,588 patients included in this study, 83.3% received intensive first-line therapy. Receipt of non-intensive therapy was associated with female sex at birth and earlier year of diagnosis but not race or SES. Frailty and age were associated with treatment choice. Older non-frail patients had a stronger association with receipt of non-intensive therapy compared to younger frail patients. **Conclusions:** In addition to frailty, older age was a strong predictor of the receipt of non-intensive therapy among patients with mCC. More research and education around identifying frailty is needed to avoid undertreatment of older patients with mCC. Research Sponsor: Conquer Cancer, the ASCO Foundation.

Patient characteristics	Number of patients	Proportion receiving non-intensive therapies	Odds ratio (95% confidence interval)	P value
< 65 yrs and non-frail	7432	7.50%	Reference	
≥ 65 yrs and frail	1547	37.0%	7.10 (6.20, 8.12)	<0.01
≥ 65 yrs and missing frailty	2596	28.0%	4.22 (3.72, 4.77)	<0.01
≥ 65 yrs and non-frail	6600	18.8%	2.82 (2.53, 3.13)	<0.01
< 65 yrs and missing frailty	2544	16.0%	2.13 (1.86, 2.45)	<0.01
< 65 yrs and frail	869	11.3%	1.50 (1.19, 1.88)	<0.01
Male	11630	14.7%	Reference	
Female	9958	19.1%	1.36 (1.26, 1.46)	<0.01
Year of diagnosis			0.91 (0.90, 0.92)	<0.01

11169 Poster Session

Early onset cancer in Chile: 27-year mortality rate trends from a nationwide database with focus in gastrointestinal tumors. First Author: Cristobal Tomas Sanhueza Condell, Facultad de Medicina Clinica Alemana Universidad del Desarrollo, Santiago, Chile

Background: Cancer has historically been considered a disease of older adults, however, several reports have shown an alarming rise in the incidence of early onset cancer, particularly gastrointestinal tumors and specially colorectal cancer. To date, there are no reports in this field from Latin America. This study aims to evaluate the trends in mortality rates of the most relevant gastrointestinal tumors among young versus older people in Chile. **Methods:** Nationwide data from the National Department of Statistics and Health Information was obtained from the years 1997 to 2023. Cause Specific Mortality was analysed for all ages, older (≥50 years) and younger (<50 years) patients for all tumors, Colorectal, Gastric, Esophagus, Pancreas, Liver and Biliary Tract cancer. The trends of rates were analyzed using Joinpoint Trend Analysis Software for calculation of the annual percentage rate change (APC). **Results:** Cancer-related mortality in Chile is increasing. From 1997 to 2023, for all causes, there were 2,645,132 deaths, the APC for the overall population, for all cancers is 0.96% (0.63%-1.29%, p<0.001). Gastrointestinal cancer accounted for 10%, with 261,300 deaths. When analyzed by type of cancer, an increase in mortality for colorectal cancer was observed, with a rate increase 90.5% higher in younger than older adults, with an APC of 3.24% and 1.7%, respectively. This difference was more evident in female adults. Pancreatic cancer mortality rate increased from 1997 to 2015 with an APC of 0.96% in older patients, but decreased from 2015 to 2023 with an APC of -0.87%. The mortality was steady in younger patients. No differences between younger and older patients were seen for Stomach, Esophagus, Biliary tract and Liver Cancer. Stomach cancer mortality rate has decreased in younger and older patients, with an APC of -1.61% and -2.63% respectively for the period from 1997 to 2015, and -5.87% and -4.77% respectively for the period from 2015 to 2023. Esophagus cancer mortality rate has decreased in younger and older patients, with an APC of -1.09% and -2.7% respectively for the period from 1997 to 2006, and -7.71% and -4.58% respectively for the period from 2006 to 2023. Biliary tract cancer mortality rate has decreased in younger and older patients, with an APC of -1.27% and -1.61% respectively for the period from 1997 to 2006, and -7.49% and -3.39% respectively for the period from 2006 to 2023. Liver cancer mortality rate has decreased in younger and older patients, with an APC of -2.53% for younger patients and -0.13% for older patients in the period from 1997 to 2015, and -2.43% respectively for the period from 2015 to 2023. **Conclusions:** This study shows an increase in mortality rates of colorectal cancer among young adults that almost doubles the rate increase in older adults in Chile. Efforts to raise awareness and improve access to early detection and healthcare should be prioritized. Research Sponsor: None.

11170 Poster Session

Frailty in lung cancer hospitalizations: Identifying critical predictors for improved patient outcomes. First Author: Davin Turku, The Brooklyn Hospital Center, Brooklyn, NY

Background: Frailty is a condition primarily characterized by deficits in multiple health-related factors, which, when combined with the presence of disease, lead to poor outcomes. Lung cancer patients are no exception; those who are frail tend to experience worse clinical outcomes and increased healthcare resource utilization. Identifying predictors of frailty can help guide targeted interventions and improve outcomes for this patient subset, which is the primary aim of our study. **Methods:** We conducted a cross-sectional analysis of the National Inpatient Sample database (2016-2020) to evaluate predictors of frailty in lung cancer hospitalizations. Frailty was defined using ICD-10 codes. Chi-square test was used to compare categorical variables and all weighted analyses were performed to adjust for the overall population and the complexity of the dataset, with significance set at p<0.05. **Results:** 1,120,440 lung cancer hospitalizations were identified and 0.27% (N=3,025) met criteria for frailty. Frail patients were older than non-frail patients (mean age: 79.6 years vs 64.4 years). 71% of frail patients were White, 15% were Black, and 8% were Hispanic, compared to 62% White, 19% Black, and 10% Hispanic in the non-frail group (p=0.001). Majority of frail patients were covered by Medicare (84%) and Medicaid (5%), compared to 59% on Medicare, 14% on Medicaid, and 18% on private insurance in the non-frail group (p<0.001). Geographically, 50% of frail patients were from the South and 20% from the Midwest (p=0.03). Chi-square identified coronary artery disease (CAD), congestive heart failure (CHF), chronic kidney disease (CKD), underweight, sarcopenia, and dyslipidemia as predictors of frailty. However, a negative association was observed between obesity and frailty (Table). **Conclusions:** Chronic comorbidities and decreased muscle mass remain significant predictors of frailty in lung cancer, with regional and socio-economic variations highlighting potential care disparities. The lower incidence of frailty in obese patients raises the question of the 'obesity paradox' in frailty, which warrants further investigation to explore possible causation. Identifying and targeting early predictors of frailty could lead to improved patient outcomes and more efficient healthcare utilization. Research Sponsor: None.

Predictors of frailty in lung cancer.

Predictors	Frailty Present (%)	Frailty Absent (%)	p-value
CAD	42.09	34.24	<0.001
CHF	47.14	36.22	<0.001
BMI < 18.5	12.96	3.57	<0.001
Obesity	7.74	15.89	<0.001
Dyslipidemia	41.08	35.18	0.002
CKD	38.55	30.56	<0.001
Sarcopenia	0.17	0.02	0.006

11171 Poster Session

Multicenter study of the impact of trial eligibility criteria on enrollment to KRAS G12C inhibitor trials in patients with non-small cell lung cancer. First Author: Michael S. May, Columbia University Medical Center, New York, NY

Background: Eligibility criteria (EC) are the primary method to assess patient appropriateness for clinical trials. There is a tradeoff between narrowing EC for patient safety and matching trial populations to the real-world population likely to receive the study agents. There is little evidence to guide optimal EC design. In 2017, ASCO proposed modifications to EC to increase the generalizability of trial findings. We previously reported a single-center experience and now report a multi-center cohort of non-small cell lung cancer (NSCLC) patients (pts) with *KRAS* G12C mutations to determine whether EC for trials of KRAS G12C inhibitors allowed enrollment of pts seen as part of routine care at three academic medical centers. **Methods:** We extracted EC for Phase I-III trials of six KRAS G12C inhibitors (sotorasib, adagrasib, olomorasib, divarasib, JDQ443 and RMC-6291) that were published or made available by sponsors. We defined a consensus set of eligibility criteria. We retrospectively reviewed pts with NSCLC and *KRAS* G12C mutations detected on universal testing of NSCLCs at Columbia University Irving Medical Center, Memorial Sloan Kettering and Weill Cornell Medicine from 2018 to 2023. Pts were re-evaluated at times of progression and last follow up. Pts were deemed trial-eligible if they met all EC, borderline if they had one laboratory value <20% from cutoff, or otherwise ineligible. Associations between demographic factors with odds of meeting eligibility criteria were determined using a multivariate logistic regression. **Results:** We identified 185 pts with *KRAS* G12C mutant advanced NSCLC who received treatment. Only 64 (35%) of these pts would have qualified for a second-line (2L) study of a KRAS G12C inhibitor. 15 (8%) had borderline eligibility and 106 (57%) were ineligible. 33/56 (60%) pts who received 2L KRAS G12C inhibitors would not have met consensus EC. Common reasons for 2L ineligibility included poor performance status (59, 49%), renal dysfunction (45, 37%), active brain metastases (33, 18%) and cytopenias (18, 15%). Age was associated with ineligibility (OR 1.07 per year, p = 0.006). Medicaid insurance was associated with a four-fold higher rate of ineligibility compared to Medicare but was not statistically significant (OR 4.86, p = 0.079). Liberalizing criteria for renal dysfunction and brain metastases would increase enrollment potential by 25% without decreasing the median overall survival of the broadened eligible cohort, whereas allowing worse performance status would decrease survival and effect sizes (1L HR 0.86 versus 0.74, p = 0.04; 2L HR 0.530 versus 0.423, p < 0.001). **Conclusions:** Our data indicate substantial differences between the real-world population of patients treated with KRAS G12C inhibitors and those who were trial eligible. Efforts should focus on improving clinical trial generalizability without compromising safety. Research Sponsor: 2024 Conquer Cancer/ASCO Young Investigator Award (Michael May).

11172 **Poster Session**

Accelerating phase 2 clinical development with real-world data (RWD): An external control arm (ECA) pilot in HER2-positive (HER2+) metastatic breast cancer (mBC). First Author: Cherrishe Brown-Bickerstaff, Ontada, Boston, MA

Background: Accelerating clinical development of promising therapies is essential to improving patient (pt) outcomes. While ECAs have provided valuable supplementary evidence in Phase (Ph) 3 trials to support regulatory decision-making, ECAs in the Ph 2 setting, particularly for single-arm trials, can offer critical context for evaluating efficacy with rapidly available insights. To explore this potential, we piloted the development of a contemporaneous ECA for a newly launched Ph 2 trial of Tucatinib and Doxil in HER2+ mBC (NCT0578834). **Methods:** RW structured data, supplemented by unstructured data collected via chart abstraction, were sourced from iKnowMed electronic health records. The ECA cohort was designed for maximal comparability to the trial population by (1) emulating and applying trial eligibility criteria to RWD and (2) using propensity score matching (PSM) to balance covariate distributions. To demonstrate ECA feasibility in this interim analysis, a simulated dataset was created via multiple imputation based on the distribution of observed baseline characteristics in the 8 pts enrolled on the trial, expanding the trial cohort to 40 pts. Propensity scores (PSs) were estimated using logistic regression with covariates selected based on literature and expert input (age at index, number of prior treatments, prior fam-trastuzumab deruxtecan-nxki (Enhertu), and prior tucatinib). PSM was performed using greedy nearest-neighbor matching (caliper $\leq$0.25 standard deviation of logit of PSs) without replacement at a 1:1 ratio. **Results:** The simulated trial cohort included 40 pts, and the ECA cohort included 77 pts. After PSM, 82% of the trial cohort were successfully matched, with 18% excluded due to non-overlapping PSs, resulting in matched cohorts of 33 pts each. Following PSM, most variables in the PS model achieved a standardized difference (SD) $\leq$0.10, indicating adequate balance between trial and ECA cohorts. The mean age (61 vs. 60 years in the trial and ECA cohorts, respectively; SD = 0.03), distribution of number of prior treatments (e.g., 21% vs. 27% with 1 prior treatment; SD = 0.09), and prior tucatinib exposure (48% in both cohorts; SD = 0) were well balanced between cohorts. However, prior Enhertu exposure remained imbalanced, with 45% of trial patients receiving prior Enhertu versus 33% in the ECA cohort (SD = 0.29). **Conclusions:** This pilot demonstrates that RWD can be quickly and efficiently assembled in pace with an ongoing Ph 2 clinical trial, offering promise for accelerated decision-making in clinical drug development. When small sample sizes in Ph 2 trials pose challenges, this approach shows that an exchangeable ECA can be achieved as trial accrual progresses, providing a framework for ECA evidence generation. Research Sponsor: Ontada.

11173 **Poster Session**

Proton pump inhibitors and the risk of adverse renal events and all-cause mortality in cancer patients receiving immune checkpoint inhibitors. First Author: Arunkumar Krishnan, Department of Supportive Oncology, Atrium Health Levine Cancer, Charlotte, NC

Background: Immune checkpoint inhibitors (ICI) have transformed cancer treatment by improving prognosis across various malignancies, while proton pump inhibitors (PPI) are frequently prescribed as prophylaxis in cancer patients. Studies suggest long-term PPI use has higher risks of adverse outcomes, though small patient populations and short follow-up periods limit the current evidence. Pharmacoepidemiologic studies are prone to protopathic bias and, methodological limitations and heterogeneity across studies in cancer patients. We aimed to assess the impact of PPI use on adverse renal events and all-cause mortality in patients receiving ICIs. **Methods:** We conducted a retrospective cohort study using the TriNetX, including adult cancer patients treated with ICIs (PD-1, PD-L1, and CTLA-4 inhibitors). We used a new-user, active comparator design, which compared newly treated PPI users with nonusers and histamine2 receptor antagonists (H2RA) users. We performed 1:1 propensity score matching (PSM) to adjust for confounding factors (demographics, comorbidities, cancer type, and medications. Primary outcomes included acute kidney injury (AKI) and acute interstitial nephritis (AIN). A secondary outcome was all-cause mortality. Hazard ratios(HR) were calculated using Cox regression models. Sensitivity analysis assessed statistical robustness. **Results:** We identified 54763 PPI, 28090 H2RA, and 30898 nonusers among patients receiving ICIs. After PSM, the PPI vs. nonusers cohort was well matched with 27322 patients, whereas PPI vs. H2RA users had 21567 patients in each cohort. During the follow-up period (median 4.3 3 years for PPI and 5.1 years for nonusers), PPI users demonstrated a higher risk for AKI (HR 1.48) and AIN (HR 1.07) compared to nonusers. In a subgroup analysis of ICIs, for PD-1i, the HR for AKI was 1.86, and for AIN, it was 2.51. For PD-L1i, the HR for AKI was 1.81, and for AIN, it was 2.33. For CTLA-4i, the HR for AKI was 2.03, and for AIN, it was 3.87. A secondary analysis at 1-year follow-up revealed a significant difference in mortality rates between former PPI and nonusers. Compared with H2RA, the PPIs demonstrated a higher rate of all-cause mortality HR: 1.51. Long-term PPI users showed consistent risks of AKI and AIN across follow-ups at 2 to 5 years, with HRs for AKI ranging from 1.48 to 2.59. Pantoprazole users showed the highest AKI risk (HR 1.59). Sensitivity analysis results were consistent, and associations remained unchanged. **Conclusions:** PPI use is associated with a significantly increased risk of AREs and all-cause mortality in cancer patients receiving ICIs, with the highest risk observed in patients treated with PD-1i and CTLA-4i. These results emphasize the importance of careful prescribing of PPIs and vigilant renal monitoring for this at-risk group. Further research is warranted to explore the mechanisms underlying this association. Research Sponsor: None.

11174 **Poster Session**

Efficacy GLP-1 agonists, SGLT-2 inhibitors and other glucose-lowering medications on cardiorenal outcomes in patients with diabetes and cancer on immune checkpoint therapy. First Author: Diptasree Mukherjee, Apex Institute of Medical Science, Kolkata, India

Background: Treatment with Immune checkpoint inhibitors (ICI) therapy has improved survival in multiple malignancies. However, patients with type 2 diabetes (T2D) and cancer receiving ICI are at heightened risk for adverse cardiorenal outcomes. Emerging evidence suggests that Glucagon-like peptide 1 receptor agonists (GLP-1RA) and sodium–glucose cotransporter 2 inhibitors (SGLT2i) confer cardiorenal benefits in T2D. However, their impact among patients with T2D and cancer remains unclear. Hence, we aimed to evaluate the effectiveness of GLP-1RA, SGLT-2i, and other glucose-lowering therapies in reducing adverse cardiorenal events. **Methods:** A retrospective cohort study was conducted using the TriNetX. Adult patients with T2D and cancer treated with ICI (anti-PD1, anti-PDL1, or anti-CTLA4) between 2017 and 2024 were included. Patients were stratified into three groups based on therapy: GLP-1RA, SGLT-2i, and other second or third line medications. We performed 1:1 propensity score matching(PSM) to adjust for confounding factors, including demographics, comorbidities, cancer type, and medications. The primary outcomes were major adverse cardiovascular events(MACE), heart failure(HF) and cerebrovascular events(CVE)) and secondary outcome was of end-stage renal diseases (ESRD), the need for dialysis and all-cause mortality. Hazard ratios(HR) for outcomes were calculated using Cox proportional hazard models. Sensitivity analysis assessed statistical robustness. **Results:** We identified 6212 patients on GLP-1RA, 7068 on SGLT-2i, and 24693 on other second- or third-line medications. After PSM, 5381 patients were included in the GLP-1RA vs. SGLT-2i cohorts. There were no significant differences in cardiorenal outcomes between the two groups. However, all-cause mortality was significantly lower for GLP-1RA (HR 0.88). In the comparison of GLP-1RA vs. other glucose-lowering medications, 6206 patients were matched. GLP-1RA were associated with significantly lower rates of HF, MACE, CVE, ESRD and mortality (HR 0.74). Similarly, for SGLT-2is vs. other glucose-lowering medications, 7,069 patients were matched. SGLT-2i demonstrated lower rates of adverse outcomes, particularly HF and ESRD (HR 0.63). Subgroup analysis revealed consistent benefits across cancer types, with pronounced effects in renal and lung cancer. **Conclusions:** GLP-1RA and SGLT-2i significantly reduce cardiorenal risks in patients with T2D and cancer on ICIs. However, GLP-1RA provided a modest survival advantage over SGLT-2is. These results underscore the importance of individualized therapeutic strategies prioritizing GLP-1RA and SGLT-2is in this high-risk population to improve cardiorenal outcomes and survival. Further studies are warranted to validate these findings and explore underlying mechanisms. Research Sponsor: None.

11175 **Poster Session**

Real-world evidence from FLEX: Utility of MammaPrint in guiding treatment planning for patients aged 70 and older with early-stage breast cancer. First Author: Reshma L. Mahtani, Miami Cancer Institute, Baptist Health South Florida, Miami, FL

Background: Older women ($\geq$70) are less likely to receive chemotherapy (CT) due to quality-of-life concerns. Additionally, older patients are underrepresented in studies assessing the utility of genomic profiling in guiding CT decisions, thus guidelines around neo/adjuvant CT for this population are less clear. To identify the utility of the MammaPrint (MP) 70-gene and BluePrint (BP) 80-gene assays in informing treatment decisions in an elderly population, we examined the relationship of age ($\geq$70 vs.$<$70) and treatment outcomes stratified by MP/BP subtypes in pts with HR+ HER2- EBC. **Methods:** The prospective, observational FLEX Study (NCT03053193) includes stage I-III pts with early-stage breast cancer (EBC) who received MP with or without BP testing and consented to full transcriptome and clinical data collection with therapy data available. Differences in the distribution of clinical characteristics between age groups were assessed by Chi-squared, Fisher's exact, or Wilcoxon-Mann-Whitney tests. The endpoint recurrence-free interval (RFI) was defined as time to local, regional, or distant recurrence or breast cancer related death Kaplan-Meier survival analysis and log-rank tests were used to assess differences in endpoints between treatment groups. **Results:** A total of 4,519 HR+, HER2- EBC pts were included, with 1,047 $\geq$70 (23.2%) and 3,472 $<$70 (76.8%). Patients $\geq$70 were significantly less likely to present with high grade tumors and lymph node involvement than those $<$70 (12.8% vs 16.2% grade 3, p=.022; 20.6% vs 24.2% node positive, p=.017, respectively). The MP risk group distribution showed a significantly higher proportion of low genomic risk (Ultralow or low risk) tumors in the $\geq$70 vs. $<$70 group (Ultralow (UL) 14.7% vs 14.9% , Low 41.2% vs 38.7% , High 1 (H1) 37.3% vs 36.9% , and High 2 (H2) 6.8% vs 9.5% , p 0.048, respectively). Patients $\geq$70 with MP High Risk tumors were less likely to receive CT compared to those $<$70 (H1 55.8% vs 73%, p$<$0.001; H2 72.6% vs 82.2%, p=0.07, respectively). When evaluating 3-year RFI, the $\geq$70 pts with MP High Risk cancer trended towards better outcomes with CT than those receiving endocrine therapy only, especially in H2 cancers (H1 97% vs 94% , p=.137, H2 90% vs 79% , p=.078, respectively). **Conclusions:** This study underscores the potential CT benefits in MP H2 HR+ HER2- EBC pts $\geq$ 70 who may forgo treatment due to overall health and quality of life concerns. Notably, in MP H2 pts, the absolute improvement in 3-year RFI of 11% with neo/adjuvant CT in women $\geq$ 70 suggests that for many pts, the benefit outweighs the risks. Of note, this H2 CT benefit is similar to that observed in a group of 1000 pts with a median age of 59 recently reported (Brufsky, et al. SABCS 2024, P2-08-12). Patient centered discussions on performance status, comorbidities, and genomic profiling of HR+ HER2-EBC as well as the potential benefit from CT should guide personalized treatment. Clinical trial information: NCT03053193. Research Sponsor: Agendia, Inc.

11176 Poster Session

Use of large language models to extract cancer diagnosis, histology, grade, and staging from unstructured electronic health records. First Author: Gayathri Namasivayam, Ontada, Boston, MA

Background: The oncology ecosystem contains millions of unstructured documents within Electronic Health Record (EHR) systems, including clinical notes and pathology reports with vital patient information like cancer diagnoses, histology, grade, and staging. These documents are often text or scanned PDFs. Extracting clinical details from these sources can improve EHR completeness and accuracy. To address this challenge, we developed an information extraction pipeline that leverages the recent advances in artificial intelligence (AI). **Methods:** Large Language Models (LLMs) and prompt engineering was used to extract information from both clinical notes and pathology reports. For pathology reports, Optical Character Recognition (OCR) was applied to convert scanned images into text, which was then processed by the LLM using a tailored prompt designed to extract the relevant cancer diagnosis and staging details. For clinical notes, the text was directly passed into the LLM along with an optimized prompt to extract the same clinical information. The information extraction pipeline was validated using a dataset of 829 pathology reports and 569 progress notes from the EHR system across 40 cancer types, including 26 solid tumors and 14 hematologic malignancies. Clinical specialists manually extracted cancer diagnoses, histology, grade, and staging, which were compared to the automated output. An F1 score using a combined measure of precision and recall was calculated to assess the model's accuracy. **Results:** The pipeline retrieved cancer type, histology, and grade from pathology reports with an F1 score over 0.85. Similarly, it extracted cancer type and staging information from progress notes with an F1 score over 0.85, demonstrating high accuracy and reliability. Additional performance metrics are shown in the table. **Conclusions:** This LLM-based extraction pipeline accurately identified cancer diagnoses, histology, grade, and staging information from unstructured text and scanned documents within the EHR achieving an F1 score $\geq$0.85. The validation results suggest that this approach could be scaled to improve the completeness and utility of EHR data, supporting the availability of more robust information for scientific research, clinical care, and other uses of health data. Research Sponsor: None.

Performance metrics of LLM-based extraction pipeline.

Information	Source	Precision	Recall	Specificity	NPV*	Accuracy	F1 >
Cancer Type	Pathology (PDF)	0.86	0.89	0.99	0.98	0.89	0.87
Histology	Pathology (PDF)	0.83	0.88	0.90	0.88	0.90	0.85
Grade	Pathology (PDF)	0.8	0.95	0.96	0.96	0.88	0.87
Cancer Type	Progress Notes	0.8	0.95	0.96	0.96	0.88	0.87
Staging TNM (T)	Progress Notes	0.96	0.87	0.99	0.97	0.97	0.91
Staging TNM (N)	Progress Notes	0.92	0.85	0.99	0.97	0.96	0.88
Staging TNM (M)	Progress Notes	0.87	0.83	0.98	0.97	0.96	0.85

*NPV= negative predictive value.

11177 Poster Session

Immune checkpoint inhibitor–associated myocarditis: Incidence, risk factors, and clinical outcomes in a global real-world cohort. First Author: Zhiting Tang, Department of Medicine, Unity Hospital, Rochester Regional Health, Rochester, NY

Background: Immune checkpoint inhibitor (ICI)-associated myocarditis is a rare but life-threatening immune-related adverse event (irAE), with a mortality rate of 30–50%. Most available evidence comes from case series and adverse event reporting databases, leaving its risk factors and clinical outcomes largely undefined. **Methods:** We performed a retrospective investigation using the TriNetX Global Research Network. Patients were included if they had been diagnosed with solid tumors after 2016 for which ICIs are approved. We calculated myocarditis incidence among ICI users and compared myocarditis risk between ICI and non-ICI cohorts using propensity score matching (accounting for demographics, comorbidities, cancer types, and treatments). Univariate and multivariate models were applied to assess risk factors. Risks of hospitalization, ICU admission, and major adverse cardiovascular events (MACE) were compared in ICI-treated patients with and without myocarditis using propensity score matching. **Results:** Among 130,234 ICI-treated patients, 643 (0.49%) developed myocarditis. Most cases (82.0%) occurred within the first year of ICI initiation. The risk of myocarditis was 27 times higher in the ICI group compared to the non-ICI group (Relative Risk [RR]=27.78, 95% CI: [17.36-44.45]). Univariate analysis identified older age, male sex, White race, hypertension, hyperlipidemia, ischemic heart disease, diabetes, chronic kidney disease, heart failure, cardiomyopathy, urothelial cancer, melanoma, ipilimumab, nivolumab, pembrolizumab, radiation therapy, inflammatory arthritis, lupus, and systemic connective tissue disease as potential risk factors. In multivariate analysis, only age over 65 (Hazard Ratio [HR] = 1.34, 95% CI: [1.11–1.63], $p < 0.01$), hypertension (HR=1.31, 95% CI: [1.06-1.62], p=0.01), hyperlipidemia (HR=1.34, 95% CI: [1.09-1.65], $p<0.01$), melanoma (HR=1.52, 95% CI: [1.25-1.86], $p<0.01$), and ipilimumab (HR= 2.44, 95% CI: [1.87-3.19], $p<0.01$) were significantly associated with myocarditis. Patients who developed ICI-associated myocarditis had higher risks of hospitalization (RR=1.39, 95% CI: [1.28-1.52]), ICU admission (RR=2.35, 95% CI: [1.86-2.98]), myocardial infarction (RR=5.58, 95% CI: [3.73-8.34]), heart failure (RR=1.59, 95% CI: [1.38-1.85]), stroke (RR=2.94, 95% CI: [1.75-4.97]), MACE (RR=3.92, 95% CI: [2.91-5.27]), and all-cause mortality (RR=1.32, 95% CI: [1.13-1.55]) within one year compared to those who received ICIs but did not develop myocarditis. **Conclusions:** ICI-associated myocarditis is a rare irAE but carries an increased risk of cardiovascular complications and death. Advanced age, hypertension, hyperlipidemia, melanoma, and ipilimumab use appear to be risk factors. Clinical vigilance is warranted to facilitate early detection and management of this potentially fatal complication. Research Sponsor: None.

11178 Poster Session

Leveraging real-world data sources for clinical oncology research: A review of studies published in ASCO publications. First Author: Thomas Lucido, Department of Medicine, Rutgers Robert Wood Johnson Medical School, New Brunswick, NJ

Background: Real-world data (RWD) are essential for assessing healthcare delivery and outcomes for cancer survivors, require complex statistical techniques to account for biases, and are commonly combined with other data sources. Reporting guidelines, such as Strengthening the Reporting of Observational Studies in Epidemiology(STROBE), were developed to improve the quality and transparency of RWD publications. These guidelines are not required for publication in ASCO journals. Our objective was to describe the types of RWD that commonly occur in ASCO Publications, how the data are being used, and to what extent the reports align with methodologic STROBE criteria. **Methods:** We used the ASCO Editorial Manager to identify original reports published between January 2018 to December 2022 that leveraged commonly used RWD in the US. We included all journals in ASCO Publications (Journal of Clinical Oncology [JCO], Precision Oncology [PO], Oncology Practice [OP], Clinical Cancer Informatics [CCI], and Global Oncology [GO]). The RWD assessed were SEER, Medicare, NCDB, Flatiron, CancerLinQ, IQVIA, Optum, MarketScan, MEPS, and NHANES. The data were identified by specifically referencing the source within the abstract. Five independent, trained reviewers abstracted clinical, epidemiologic, and reporting data from the manuscripts. For this study, we focused analysis on STROBE methodology reporting criteria (items 4-12). **Results:** One hundred and seventy-four publications were included in our study (57% OP, 18% CCI, 14% JCO, 5.8% PO, 5.2% GO). The most common RWD used were Medicare (49%), SEER (40%), and NCDB (14%). Nearly one-quarter of the publications used more than one of the databases evaluated, and one-third included a secondary RWD source and/or linked patients with an external data source (e.g., Google Maps, electronic health records). The most common malignancy types evaluated in the manuscripts were breast (33%), lung (25%) and colorectal (21%). Study design, setting, and study variables had high reporting (>90%), while descriptions about study size derivation, the rationale for quantitative analyses, and the approach to missing data were less well reported (<78%). **Conclusions:** RWD are published within ASCO Publications and are commonly combined with multiple data sources. Though some STROBE methodologic reporting criteria are regularly addressed, we identified criteria that were not well-reported. Further research is needed to assess changes in the use of RWD and whether lower reporting of methodologic information may impact the replicability and interpretation of study findings. Research Sponsor: None.

11179 Poster Session

Venous thromboembolism among cancer patients receiving chimeric antigen receptor-T cell therapy. First Author: Rahul Mishra, Department of Internal Medicine, Luminis Health Anne Arundel Medical Center, Annapolis, MD

Background: Chimeric antigen receptor T-cell (CAR-T) therapy has revolutionized the treatment of advanced cancers. Although, immune side effects (ICANS or CRS) of CARTs are well recognized, and have standardized guidelines for their management, venous thromboembolism risk (VTE) is scant. As the usage of CART is anticipated to increase in upcoming years, it is of utmost importance to characterize factors associated with increased VTE risk. **Methods:** Using the TriNetX database, we conducted a retrospective analysis to evaluate incidence and risk factors of VTE post CART. Eligibility included administration of any one of the six CAR-T therapies (Tisagenlecleucel, Axicabtagene (Axi-cel), Brexucabtagene, Lisocabtagene, Idecabtagene and Ciltacabtagene) at age $\geq$18y. VTE were identified using ICD codes for either upper extremity thrombosis or lower extremity deep vein thrombosis, pulmonary embolism, cerebral sinus thrombosis, splenic vein thrombosis or portal vein thrombosis. We further compared these patients to CART recipients without these VTE. Univariate analysis using TriNetX built-in feature (outcome comparison) was performed to compare factors associated with VTE including demographics, comorbidities, cancer type, and treatment. **Results:** We analyzed data from 133 million+ patients from over 103 health care organizations. There were 2076 adult CAR-T recipients. Axi-cel was the most frequently used CART type. 347/2076 (16.7%) patients developed a VTE after CAR-T, with 10% (210/2076) developing it within three months. CART with VTE cohort had a mean age of 64 years, predominantly males (201/347, 58%) and Caucasian (264/347, 76%). In univariate analysis, when compared to CART without VTE cohort (N =1033), we identified factors significantly associated with VTE. This included history of nicotine dependence (35% vs 24%, $P<0.0001$), primary hypertension (23% vs 19%, $P<0.0001$), obesity (25% vs 17%, $P=0.0007$), hyperlipidemia (45% vs 30%, $P<0.0001$), h/o radiation (35% vs 18%, $P<0.0001$), and use of Axi-cel (42% vs 7%, $P<0.0001$). The use of glucocorticoids (95% vs 77%, $P<0.0001$), alkylating agents (91% vs 71%, $P<0.0001$) or lenalidomide (18% vs 11%, $P=0.0006$) were significantly associated with VTE. The underlying cancer type also affected the risk of VTE, having significant association with diffuse large B-cell lymphoma (64% vs 50%, $P<0.0001$), mantle cell lymphoma (11% vs 7%, $P=0.0198$), and small cell B-cell lymphoma (8% vs 4%, $P=0.0018$). **Conclusions:** There is 10% incidence of VTE within three months of CAR-T therapy. Particularly, VTE incidence is higher with Axi-cel, and DLBCL diagnosis. Patients with high –risk associations may benefit from thromboprophylaxis regimens, particularly during initial three months of CAR-T therapy. Prospective research is warranted to further validate such risk factors and develop evidence-based thromboprophylaxis guidelines for CART recipients. Research Sponsor: None.

11180 Poster Session

Clinical outcomes for Medicaid recipients with early-onset breast cancer: An analysis of the National Inpatient Sample. First Author: Vineet Polineni, Jefferson Health New Jersey, Stratford, NJ

Background: Despite recent global decreases in overall cancer incidence, the incidence of early-onset breast cancer (EOBC) is steadily increasing globally. Limited data is available on the comorbid correlations for this unfortunately expanding population. We sought to examine the national inpatient sample database to describe in-hospital outcomes among Medicaid recipients with EOBC. **Methods:** Data were extracted from the National Inpatient Sample (NIS) Database for 2019 and 2020. The NIS was searched for hospitalizations of adult patients with EOBC, defined as all-cause breast cancer in patients 50 years old or younger. We then examined the outcomes of patients who were noted to be active Medicaid recipients. Multivariate logistic was used to adjust for confounders. The primary outcome was inpatient mortality and secondary outcomes were annotated accordingly. SPSS software was used for statistical analysis, and all results were powered to $p<0.001$. **Results:** This study included 10,764 patients with EOBC, of which 3145 (29.2%) were on Medicaid. Multivariate regression showed that Medicaid patients with EOBC had higher inpatient mortality (OR 1.507, CI 1.406-1.616, $p<0.001$). On secondary analysis, Medicaid patients with EOBC were more likely to have systemic lupus erythematosus (OR 1.194, CI 1.080-1.319), anemia (OR 1.465, CI 1.433-1.498), thrombocytopenia (OR 1.440, CI 1.377-1.507), hypertension (OR 1.578, CI 1.461-1.704), chronic kidney disease (OR 1.343, CI 1.253-1.440), acute renal failure (OR 1.506, CI 1.432-1.584), pancreatitis (OR 1.420, CI 1.221-1.651), pericarditis (OR 1.394, CI 1.282-1.515), intracranial hemorrhage (OR 1.429, CI 1.225-1.665), severe liver disease (OR 1.504, CI 1.458-1.550), peptic ulcer disease (OR 1.436, CI 1.271-1.623), obstructive sleep apnea (OR 1.413, CI 1.313-1.521), leukemia (OR 1.310, CI 1.098-1.564), lymphoma (OR 1.737, CI 1.296-2.328), all-cause arrhythmias (OR 1.448, CI 1.342-1.563), all-cause shock (OR 1.478, CI 1.290-1.693), all-cause heart block (OR 1.294, CI 1.103-1.519), all-cause sepsis (OR 1.549, CI 1.496-1.603), all-cause coagulopathy (OR 1.457, CI 1.362-1.558), all-cause heart failure (OR 1.587, CI 1.467-1.717), all-cause stroke (OR 1.450, CI 1.342-1.566), and all-cause myocardial infarction (OR 1.766, CI 1.503-2.075). **Conclusions:** In this nationally representative, population-based retrospective cohort study, Medicaid recipients with EOBC were associated with higher mortality and worse outcomes. Research Sponsor: None.

11181 Poster Session

Inpatient outcomes of breast cancer hospitalizations in the northeastern vs western United States. First Author: Davin Turku, The Brooklyn Hospital Center, Brooklyn, NY

Background: Regional disparities in healthcare resources and outcomes are well-documented in the U.S., yet little is known about how they impact inpatient outcomes in breast cancer (BC) patients. The Northeastern (NE) region has the highest incidence and prevalence of BC, along with a greater concentration of academic cancer centers, while the Western (W) region has the lowest rates. This study compares both in-hospital and discharge outcomes of BC patients between these regions to explore how these variations affect inpatient outcomes. **Methods:** A cross-sectional analysis was done using the National Inpatient Sample database (2016–2020) using STATA 17.0 software. NE was taken as reference. Baseline characteristics and outcomes were compared among NE and W using chi-square tests and survey-weighted multivariate logistic regressions, after adjusting for confounders. **Results:** Among 855,494 BC hospitalizations, 22% were from the NE and 19% were from the W. Patients in W were younger, with 18% aged <50 years compared to 16% in NE ($p < 0.001$). 38% of NE patients were from high-income backgrounds, compared to 32% in W, while 16% of both NE and W patients were from the lowest income group ($p < 0.001$) suggesting significant income disparities in NE. 85% of NE patients were treated at teaching hospitals compared to 70% in W. However, in NE, only 46% sought care at large bed size hospitals compared to 58% in W (all $p < 0.001$). NE patients had longer hospital stays (>7 days: 22% vs 19%, $p < 0.001$) and incurred higher costs. Additionally, patients in the W had significantly lower odds of in-hospital mortality and discharges to skilled nursing facilities (NH) compared to NE (Table). **Conclusions:** We identified significant regional differences in BC hospitalization outcomes. W had lower mortality and lesser NH discharges, possibly due to a younger population and differences in post-acute care. In contrast, older demographics and socioeconomic factors in the NE may explain higher costs and mortality. Despite more academic centers in the NE, outcomes were not better. These findings highlight the need for region-specific strategies to improve BC care. Future research should focus on the drivers of these disparities and develop targeted interventions. Research Sponsor: None.

Outcomes in BC hospitalizations in W compared to NE.

Outcomes in W*	Adjusted Odds Ratio**	95% Confidence Interval	p-value
Mortality	0.57	0.54-0.61	<0.001
Length of Stay	0.86	0.82-0.90	<0.001
NH Discharge	0.90	0.82-0.99	0.043
Total Hospital Charges ($)	16318 ***	12978-19657	<0.001

*Reference: NE.
**Adjusted for confounders.
***Beta-coefficient.

11182 Poster Session

Trends in early-onset gastrointestinal cancers: A comprehensive analysis of US cancer statistics (2001–2021). First Author: Abdul Qahar Khan Yasinzai, University of Florida Health Cancer Center, Gainesville, FL

Background: Early-onset colorectal cancer (eoCRC) has become a well-recognized phenomenon in recent years. This study aims to explore trends in other early-onset gastrointestinal cancers (eoGIC) and provide more details on sub-sites of eoCRC. **Methods:** The NPCR-SEER database, which covers the entire U.S. population from 2001 to 2021, was utilized to analyze GI cancer cases among individuals aged 20–49 years. Trends were assessed using Joinpoint regression, and polynomial regression was applied to forecast incidence rates from 2021 to 2031. **Results:** A total of 528,310 cases were analyzed. In 2021, eoCRC had the highest incidence (n=17,567), followed by stomach cancer (n=2,783) and pancreatic cancer (n=2,634). EoCRC has been significantly increasing with (Average Annual Percent Change (AAPC) 1.30%, $p<0.01$). Stomach and pancreatic cancers showed steady rise with (AAPC 0.73%, $p<0.01$) and (AAPC 1.14%, $p<0.01$). Among eoCRC subsites, rectal cancer showed the most substantial increase (AAPC 1.86%, $p<0.01$), followed by sigmoid colon (AAPC 1.17%, $p<0.01$) and descending colon (AAPC 0.85%, $p<0.01$). Although the appendiceal, small intestine and intrahepatic bile duct represent a smaller portion of the eoGICs, these sites demonstrated the most dramatic rises in incidence compared to their previous crude rates. Appendiceal cancer showed the highest increase (AAPC 7.23%, $p<0.01$), followed by intrahepatic bile duct cancer (AAPC 5.81%, 95% CI, $p<0.01$) and small intestine cancer (AAPC 2.90%, $p<0.01$). Declining trends were observed in esophageal (AAPC -1.50%, <0.01), liver (AAPC -2.89%, <0.01), and anal cancers (AAPC -0.98%, <0.01). By 2027, females are projected to cross males ($R^2 = 0.91$) in the incidence of eoGICs. **Conclusions:** Several eoGICs are exhibiting increasing trends, potentially indicating a shared or disease-agnostic underlying etiology. The rising prevalence and shifting demographics underscore the critical need for tailored prevention measures and early detection strategies focused on high-risk populations. Future research should focus on identifying underlying factors driving these trends. Research Sponsor: None.

Average annual percent change of subsites of colorectal cancers 2001–2021.

Primary Site	AAPC	p-value
Cecum	0.92%	<0.01
Ascending Colon	0.43%	0.10
Hepatic Flexure	-1.27%	<0.01
Transverse Colon	0.51%	<0.01
Splenic Flexure	-0.51%	0.09
Descending Colon	0.85%	<0.01
Sigmoid Colon	1.17%	<0.01
Rectosigmoid Junction	0.39%	0.13
Rectum	1.86%	<0.01

11183 Poster Session

Clinical outcomes for low-income patients with early-onset breast cancer: An analysis of the National Inpatient Sample. First Author: Ben Brik, Jefferson Health New Jersey, Stratford, NJ

Background: Despite recent global decreases in overall cancer incidence, the incidence of early-onset breast cancer (EOBC) is steadily increasing globally. Limited data is available on the comorbid correlations for this unfortunately expanding population. We sought to examine the national inpatient sample database to describe in-hospital outcomes among low-income patients with EOBC. **Methods:** Data were extracted from the National Inpatient Sample (NIS) Database for 2019 and 2020. The NIS was searched for hospitalizations of adult patients with EOBC, defined as all-cause breast cancer in patients 50 years old or younger. We then examined the outcomes of patients who self-reported an income less than $50,000. Multivariate logistic was used to adjust for confounders. The primary outcome was inpatient mortality and secondary outcomes were annotated accordingly. SPSS software was used for statistical analysis, and all results were powered to $p<0.001$. **Results:** This study included 10,764 patients with EOBC, of which 2743 (25.5%) were low-income. Multivariate regression showed that low-income patients with EOBC had higher inpatient mortality (OR 1.438, CI 1.348-1.534, $p<0.001$). On secondary analysis, low-income patients with EOBC were more likely to have systemic lupus erythematosus (OR 1.298, CI 1.146-1.470), anemia (OR 1.374, CI 1.347-1.402), thrombocytopenia (OR 1.356, CI 1.302-1.412), hypertension (OR 1.545, CI 1.434-1.666), chronic kidney disease (OR 1.531, CI 1.404-1.669), acute renal failure (OR 1.462, CI 1.393-1.535), pancreatitis (OR 1.479, CI 1.259-1.738), mitral regurgitation (OR 1.300, CI 1.151-1.468), pericarditis (OR 1.358, CI 1.254-1.471), intracranial hemorrhage (OR 1.373, CI 1.190-1.584), pulmonary hypertension (OR 1.542, CI 1.326-1.794), severe liver disease (OR 1.382, CI 1.346-1.419), leukemia (OR 1.407, CI 1.149-1.724), lymphoma (OR 1.320, CI 1.088-1.601), all-cause arrhythmias (OR 1.324, CI 1.241-1.413), all-cause shock (OR 1.414, CI 1.264-1.605), all-cause heart block (OR 1.479, CI 1.172-1.719), all-cause sepsis (OR 1.409, CI 1.368-1.451), all-cause coagulopathy (OR 1.415, CI 1.327-1.508), all-cause heart failure (OR 1.508, CI 1.402-1.623), all-cause stroke (OR 1.463, CI 1.331-1.549), and all-cause myocardial infarction (OR 1.527, CI 1.336-1.746). **Conclusions:** In this nationally representative, population-based retrospective cohort study, low-income patients with EOBC were associated with higher mortality and worse outcomes. Research Sponsor: None.

11184 **Poster Session**

Clinical outcomes for patients with hyperlipidemia and early-onset breast cancer: An analysis of the National Inpatient Sample. First Author: Mahija Cheekati, Morristown Medical Center, Morristown, NJ

Background: Despite recent global decreases in overall cancer incidence, the incidence of early-onset breast cancer (EOBC) is steadily increasing globally. Limited data is available on the comorbid correlations for this unfortunately expanding population. We sought to examine the national inpatient sample database to describe in-hospital outcomes among patients with EOBC and hyperlipidemia. **Methods:** Data were extracted from the National Inpatient Sample (NIS) Database for 2019 and 2020. The NIS was searched for hospitalizations of adult patients with EOBC, defined as all-cause breast cancer in patients 50 years old or younger. We then examined the outcomes of patients who were noted to have hyperlipidemia. Multivariate logistic was used to adjust for confounders. The primary outcome was inpatient mortality and secondary outcomes were annotated accordingly. SPSS software was used for statistical analysis, and all results were powered to $p<0.001$. **Results:** This study included 10,764 patients with EOBC, of which 1021 (9.49%) were found to have hyperlipidemia. Multivariate regression showed that patients with hyperlipidemia and EOBC had higher inpatient mortality (OR 1.052, CI 1.029-1.076, $p<0.001$). On secondary analysis, hyperlipidemia patients with EOBC were more likely to have anemia (OR 1.111, CI 1.099-1.123), thrombocytopenia (OR 1.095, CI 1.072-1.118), peripheral artery disease (OR 1.208, CI 1.074-1.359), hypertension (OR 1.433, CI 1.341-1.532), chronic kidney disease (OR 1.377, CI 1.280-1.481), acute renal failure (OR 1.159, CI 1.126-1.192), pancreatitis (OR 1.145, CI 1.048-1.251), pericarditis (OR 1.119, CI 1.069-1.172), intracranial hemorrhage (OR 1.148, CI 1.049-1.256), pulmonary hypertension (OR 1.213, CI 1.103-1.334), severe liver disease (OR 1.090, CI 1.076-1.104), leukemia (OR 1.188, CI 1.035-1.363), lymphoma (OR 1.138, CI 1.003-1.292), all-cause arrhythmias (OR 1.109, CI 1.068-1.152), all-cause shock (OR 1.065, CI 1.013-1.119), all-cause heart block (OR 1.257, CI 1.082-1.460), all-cause sepsis (OR 1.132, CI 1.113-1.152), all-cause coagulopathy (OR 1.118, CI 1.080-1.157), all-cause heart failure (OR 1.267, CI 1.202-1.336), all-cause stroke (OR 1.224, CI 1.159-1.292), and all-cause myocardial infarction (OR 1.413, CI 1.255-1.590). **Conclusions:** In this nationally representative, population-based retrospective cohort study, hyperlipidemic patients with EOBC were associated with higher mortality and worse outcomes. Research Sponsor: None.

11185 **Poster Session**

Clinical outcomes for Black patients with early-onset breast cancer: An analysis of the National Inpatient Sample. First Author: Mahija Cheekati, Morristown Medical Center, Morristown, NJ

Background: Despite recent global decreases in overall cancer incidence, the incidence of early-onset breast cancer (EOBC) is steadily increasing globally. Limited data is available on the comorbid correlations for this unfortunately expanding population. We sought to examine the national inpatient sample database to describe in-hospital outcomes among black patients with EOBC. **Methods:** Data were extracted from the National Inpatient Sample (NIS) Database for 2019 and 2020. The NIS was searched for hospitalizations of adult patients with EOBC, defined as all-cause breast cancer in patients 50 years old or younger. We then examined the outcomes of patients who self-identified as Black. Multivariate logistic was used to adjust for confounders. The primary outcome was inpatient mortality and secondary outcomes were annotated accordingly. SPSS software was used for statistical analysis, and all results were powered to $p<0.001$. **Results:** This study included 10,764 patients with EOBC, of which 2328 (21.6%) were identified as black. Multivariate regression showed that black patients with EOBC had higher inpatient mortality (OR 1.408, CI 1.323-1.498, $p<0.001$). On secondary analysis, black EOBC patients were more likely to have systemic lupus erythematosus (OR 1.345, CI 1.177-1.538), anemia (OR 1.382, CI 1.355-1.411), thrombocytopenia (OR 1.275, CI 1.230-1.321), hypertension (OR 1.989, CI 1.799-2.200), chronic kidney disease (OR 1.803, CI 1.621-2.004), acute renal failure (OR 1.446, CI 1.379-1.516), pancreatitis (OR 1.291, CI 1.139-1.463), pericarditis (OR 1.200, CI 1.131-1.274), intracranial hemorrhage (OR 1.489, CI 1.264-1.755), chronic obstructive pulmonary disease (OR 1.297, CI 1.216-1.383), severe liver disease (OR 1.351, CI 1.318-1.386), Crohn's disease (OR 1.275, CI 1.104-1.472), leukemia (OR 1.310, CI 1.098-1.564), all-cause arrhythmias (OR 1.387, CI 1.292-1.489), all-cause shock (OR 1.435, CI 1.260-1.634), all-cause heart block (OR 1.189, CI 1.046-1.352), all-cause sepsis (OR 1.293, CI 1.261-1.326), all-cause coagulopathy (OR 1.355, CI 1.277-1.438), all-cause heart failure (OR 1.659, CI 1.527-1.803), all-cause stroke (OR 1.422, CI 1.319-1.532), and all-cause myocardial infarction (OR 1.638, CI 1.413-1.897). **Conclusions:** In this nationally representative, population-based retrospective cohort study, black patients with EOBC were associated with higher mortality and worse outcomes. Research Sponsor: None.

TPS11186 **Poster Session**

A platform to identify patients for cancer vaccine trials: The NHS England Cancer Vaccine Launch Pad (CVLP). First Author: Victoria Goss, Cancer Research UK Southampton Clinical Trials Unit, University of Southampton, Southampton, United Kingdom

Background: The Cancer Vaccine Launch Pad (CVLP) was established in September 2023 to establish a process to increase the number of patients identified as potentially eligible for cancer vaccine trials and supporting processes for accompanying tumour tissue processing. Increasing the available patient population by referring from wider geographical regions also increases representation from groups who may otherwise not have the opportunity to take part in cancer vaccine research trials. The CVLP is a collaborative project including NHS England, Genomics England, the Department of Health and Social Care, the Office for Life Sciences and the National Institute of Health and Care Research (NIHR) which is being delivered by the Cancer Research UK Southampton Clinical Trials Unit. The CVLP has been designed as a company and trial agnostic platform which can accommodate multiple cancer vaccine trials in multiple cancer types. **Methods:** The CVLP aims to rapidly identify large numbers of cancer patients who could be eligible for trials to expedite evidence for the efficacy of vaccines across multiple types of cancer. To support the identification of participants their tissue samples are processed by a standardised, high quality, expanded pathway, incorporating elements of the NHS Genomic Medicine Service. The primary objective of the CVLP is to determine whether it is feasible to recruit cancer patients to a platform to be matched to available cancer vaccine trials, whether there is capacity for tumour samples to be analysed within a suitable time frame and if this results in acceptable participation in cancer vaccine clinical trials. Eligibility criteria are determined according to the needs of the trial that patients will be referred on to. The CVLP pathway from patient identification to entry into available clinical trials has been developed to include the following steps; i) patients identified by the clinical team managing their care and consented into CVLP; ii) blood and tissue samples (during surgery) collected; iii) samples sent to Cellular Pathology Genomic Centre and Genomic Laboratory Labs; iv) eligibility assessment which allows the clinical liaison team to pair patients with available research trials. Sponsored by NHS England the first trial incorporated within the CVLP is BioNTech BNT122-01 (NCT04486378) investigating the RO7198457 mRNA vaccine in patients with ctDNA-positive, resected Stage II/III colorectal cancer which reached approximately 60% of patients undergoing colorectal surgery via the CVLP from 55 sites across England. To facilitate screening to the cancer vaccine trial 96.4% of tissue samples were prepared in the required time frame for testing (average 2.5 days) providing proof of principal for this pathway and paving the way for the onboarding of further trials. Clinical trial information: ISRCTN13053675. Research Sponsor: NHS England.

TPS11187 **Poster Session**

Barriers and facilitators of adoption and implementation of a financial navigation program in Nigeria: An analysis of participant data from the COST-FIN trial. First Author: Adewale Isaiah Oyewole, Department of Medical Rehabilitation, Obafemi Awolowo University, Ile-Ife, Nigeria

Background: Financial toxicity is a critical issue in modern healthcare. The impact of financial toxicity is particularly pronounced in low- and middle-income countries (LMICs), where healthcare systems are underfunded, and out-of-pocket costs dominate medical payments. Financial navigation programs (FNPs) help patients manage costs through insurance, resources, and budget support. This study examines the challenges and opportunities of implementing FNPs in an LMIC, using data from the COST-FIN study, a randomized controlled trial investigating the impact of a structured FNP on cancer care in Nigeria. **Methods:** Adult patients (>18 years) diagnosed with breast, prostate, or colon cancer within 6 weeks of presentation at Lakeshore Cancer Center or Obafemi Awolowo University in Nigeria were eligible for trial enrollment. Between July 15 and November 22, 2024, 52 patients were recruited, and 23 were randomized to the financial navigation arm of the study. Financial Navigators assessed each patient's financial literacy and developed individualized financial plans. The extent of navigation required was categorized as high, moderate, low, or no assistance needed. **Results:** Among the 19 patients who completed financial literacy sessions, 17 received financial plans. Of these, 16 required financial navigation (extent of navigation: high, n = 8; moderate, n = 6; low, n = 2; no assistance needed, n = 1), and 15 were successfully directed to resources, including the National Health Insurance Scheme (100%), philanthropic organizations (26.7%), supports from other studies (53.3%), and drug discount programs-Nigerian Cancer Access Partnership, pharma companies and Medicaid PACE (100%). Low financial literacy was a significant barrier, with many patients lacking the knowledge to make informed decisions. Regulatory challenges, characterized by complex and inconsistent frameworks, and communication barriers also hindered FNP implementation. Navigators reported that addressing financial barriers reduced patients' stress and improved their focus on treatment. **Conclusion:** Preliminary findings highlight the potential of structured FNPs to alleviate financial toxicity and improve treatment adherence among cancer patients in Nigeria. Implementing comprehensive FNPs is crucial to address low financial literacy and help patients navigate healthcare costs. Collaborating with government policymakers to improve healthcare affordability and accessibility is also essential. Research Sponsor: None.

TPS11188 **Poster Session**

Strength of evidence supporting cancer drug approvals in China, 2017-2021. First Author: Yichen Zhang, Department of Pharmacy Administration and Clinical Pharmacy, School of Pharmaceutical Sciences, Peking University, Beijing, China

Background: Well-designed and adequately conducted clinical trials are the cornerstone evidence to demonstrate drug safety and efficacy and support regulatory approval of drugs. We aim to investigate the strength of evidence supporting new cancer drug indications approved in China. **Methods:** This retrospective observational study included pivotal trials supporting cancer drug indications approved in China in 2017-21. We assessed their ability to minimize bias of single-arm trials, measured as adopted external control arm and adjusted confounders; risk of bias of randomized controlled trials (RCTs), as evaluated using the revised Cochrane tool for risk of bias assessment. The ratio of hazard ratios (RHR) was calculated to quantify differences in effect size in RCTs with different risks of bias. **Results:** Between 2017 and 2021, 77 novel cancer drugs for 148 indications were approved in China, based on data from 205 pivotal studies. Of the 56 pivotal single-arm trials with regulatory review documents, 6 (10.7%) used aggregated data from earlier trials as external controls without adjustment for confounders. Of the 128 pivotal RCTs with published results, 95 (74.2%) were assessed as having some concern or a high risk of bias. RCTs judged to be at some concern or high risk of bias in the randomization process had smaller effect sizes (RHR=0.67, 95% CI: 0.53-0.86), and those judged to be at some concern or high risk of bias in missing outcome data had larger effect sizes (RHR=1.11, 95% CI: 1.00-1.23), compared to RCTs at low risk of bias in these domains). **Conclusions:** Over four-fifths of pivotal studies supporting cancer indication approvals in China had design weaknesses that introduce uncertainty to the estimation of treatment effects. To ensure the validity of drug efficacy data and reduce uncertainty, stakeholders should strengthen and implement a high-quality standard on the design, conduct, and analysis of studies supporting regulatory approval of new therapies. Research Sponsor: National Natural Science Foundation of China; 72274004.

Characteristics of cancer drugs and corresponding indications approved in China between 2017 and 2021.

Characteristic	All, No (%)	No. (%) 2017	2018	2019	2020	2021
Cancer Drug	**77 (100.0)**	**7 (9.1)**	**16 (20.8)**	**13 (16.9)**	**16 (20.8)**	**25 (32.5)**
Authorized Region						
Authorized in China only	28 (36.4)	0	5 (31.3)	3 (23.1)	6 (37.5)	14 (56.0)
Also approved by the FDA/EMA[a]	49 (63.6)	7 (100)	11 (68.8)	10 (76.9)	10 (62.5)	11 (44.0)
Cancer Indication	**148 (100.0)**	**16 (10.8)**	**42 (28.4)**	**33 (22.3)**	**30 (20.3)**	**27 (18.2)**
No. Supporting Pivotal Studies						
1	106 (71.6)	8 (50.0)	34 (81.0)	25 (75.8)	18 (60.0)	21 (77.8)
2	32 (21.6)	5 (31.3)	7 (16.7)	2 (6.1)	12 (40.0)	6 (22.2)
≥3	10 (6.8)	3 (18.8)	1 (2.4)	6 (18.2)	0	0 (0)
No. Pivotal Randomized Trials						
0	44 (29.7)	4 (25.0)	6 (14.3)	7 (21.2)	11 (36.7)	16 (59.3)
1	79 (53.4)	7 (43.8)	29 (69.0)	19 (57.6)	13 (43.3)	11 (40.7)
≥2	25 (16.9)	5 (31.3)	7 (16.7)	7 (21.2)	6 (20.0)	0

Abbreviations: EMA, European Medicine Agency; FDA, the United States Food and Drug Administration.
[a]By December 31, 2021.

TPS11189 **Poster Session**

Falcon: Exact Sciences' multicancer early detection (MCED) real world evidence (RWE) registry. First Author: Ronan Joseph Kelly, Charles A. Sammons Cancer Center at Baylor University Medical Center, Dallas, TX

Background: Earlier detection may reduce cancer morbidity and mortality by reducing the number of cancers diagnosed at advanced stages. Exact Sciences is developing a blood-based MCED test to simultaneously screen for multiple cancer types, with test-positive patients undergoing diagnostic evaluation with radiological imaging. The Falcon registry is a large prospective study of Exact Sciences' MCED test in clinically cancer-free individuals who seek cancer screening. It will examine the uptake, diagnostic journey, adherence with guideline-recommended cancer screening, outcomes, and psychological impacts of MCED testing in a setting that closely resembles the real world, with results expected to be broadly generalizable. **Methods:** Falcon is a multi-site registry that is enrolling up to 25,000 participants who receive the MCED test annually for three years (MCED cohort). A comparison cohort of up to 50,000 patients receiving standard-of-care clinical management only (SOC cohort) will be retrospectively constructed via a deidentified data pull. Both cohorts will include individuals 50 to 80 years of age presenting for primary care services who have no history of malignancy within the prior 3 years or current suspicion of cancer. SOC cancer screening will continue in the course of standard care and will not be proscribed or interrupted by study participation. The MCED cohort will include a 10,000-participant pilot cohort and up to a 15,000-participant expansion. This cohort will include individuals who provide informed consent for MCED testing and follow-up IV-contrast computed tomography (CT) and, if necessary, positron emission tomography-CT (18F FDG PET-CT) imaging following a positive MCED test. Clinical contraindications for radiological imaging (e.g. pregnancy, IV contrast allergy, renal failure) will be taken into consideration when making the decision to participate. The SOC cohort will be selected after enrollment of each MCED cohort phase and will be matched based on demographic and clinical characteristics. Self-reported measures of anxiety, cancer worry, and trauma will be collected from all MCED cohort participants routinely throughout the study. Data will be collected for up to 5 years following the baseline test or, for the SOC cohort, following an index date. Periodic automated extraction of pre-specified data elements from existing electronic data sources, primarily medical records and tumor registries, will be collected from all participants. Clinical trial information: NCT06589310. Research Sponsor: Exact Sciences Corporation.

11500 Oral Abstract Session

Pimicotinib in tenosynovial giant cell tumor (TGCT): Efficacy, safety and patient-reported outcomes of phase 3 MANEUVER study. First Author: Xiaohui Niu, Department of Orthopedic Oncology Surgery, Beijing Ji Shui Tan Hospital, Beijing, China

Background: TGCT is a rare, locally aggressive mesenchymal neoplasm, driven by the overproduction of colony-stimulating factor 1 (CSF-1), and is often associated with joint pain, swelling, stiffness and functional impairment. The high rate of recurrence and the significant tumor burden, particularly in the diffuse variant, highlight the necessity for an effective systemic treatment. Pimicotinib (pimi) is an oral, highly selective and potent small-molecule inhibitor of CSF-1 receptor (CSF-1R). We report the results from the double-blind Part 1 of MANEUVER, the first global Phase 3 trial to recruit TGCT patients (pts) from Asia, EU and North America (NA) who were candidates for systemic therapy. **Methods:** MANEUVER (NCT05804045) is a Phase 3, randomized, double-blind, placebo (pbo)-controlled trial evaluating efficacy and safety of pimi in pts with TGCT. In Part 1, pts received pimi 50 mg QD or pbo (2:1) for 24 weeks. Primary endpoint was objective response rate (ORR) by blinded independent review committee (BIRC) per RECIST v1.1 at Week 25. Key secondary endpoints included ORR by tumor volume score (TVS) and clinical outcome assessments (COAs) at Week 25: mean change from baseline in range of motion (ROM), worst stiffness, Brief Pain Inventory (BPI) worst pain and PROMIS physical function. Safety was also evaluated. **Results:** At the data cutoff of Sep 23, 2024, all of the planned 94 pts were enrolled (China = 45; EU = 28; NA = 21), with 63 randomized to pimi and 31 to pbo.Median age was 40.0 years (range: 18-69); 68.1% were female; disease location mainly in knee (50.0%), ankle (14.9%) or hip (13.8%). ORR by BIRC per RECIST v1.1 and TVS at Week 25 was significantly higher for pimi vs pbo (54% vs 3.2% and 63.5% vs 3.2%, respectively; both $p < 0.0001$). Statistically significant and clinically meaningful improvements were observed with pimi vs pbo for all COAs: active ROM (15.64 vs -0.07; p = 0.0003), worst stiffness (-3.00 vs −0.57; $p < 0.0001$), BPI worst pain (-2.32 vs −0.23; $p < 0.0001$) and PROMIS physical function (5.63 vs 2.23; p = 0.0074). Significantly more pain responders (BPI-30) were observed with pimi vs pbo (63.5% vs 16.1%; $p < 0.0001$). Treatment efficacy was consistent across pts from different regions and ethnicities. Most TEAEs were low grade, consistent with the known mechanism of action of CSF-1R inhibitors and led to a low rate of dose reduction (7.9%, 5/63 pts) and treatment discontinuation (1.6%, 1/63 pt). There was no evidence of cholestatic hepatotoxicity or drug-induced liver injury. **Conclusions:** MANEUVER is the first randomized pivotal study in TGCT to demonstrate > 50% ORR by RECIST v1.1 at Week 25 in a diverse, global patient population. Pimi produced statistically significant and clinically meaningful improvements in physical function and symptoms, representing an effective, well-tolerated and convenient daily treatment for patients with TGCT and addressing a critical unmet need. Clinical trial information: NCT05804045. Research Sponsor: Abbisko Therapeutics Co., Ltd.

11501 Oral Abstract Session

Anlotinib in combination with epirubicin followed by maintenance anlotinib versus placebo plus epirubicin as first-line treatment for advanced soft tissue sarcoma (STS): A randomized, double-blind, parallel-controlled, phase III study. First Author: Yuhong Zhou, Zhongshan Hospital, Fudan University, Shanghai, China

Background: Anthracycline-based chemotherapy has been the standard first-line treatment for advanced STS for decades. The phase 3 ANNOUNCE trial failed to demonstrate an overall survival (OS) benefit with olaratumab plus doxorubicin compared to doxorubicin. Since 2020, fewer novel regimens emerged to challenge the first-line treatment. Anlotinib (ALTN), an anti-angiogenic oral multi-target tyrosine kinase inhibitor, first showed promising results in a phase II single-arm trial, the addition of ALTN to epirubicin (EH) followed by maintenance ALTN improved progression-free survival (PFS) in the first-line setting for STS patients (pts). Consequently, we conducted a nationalwide, randomized, double-blind, parallel-controlled, phase 3 trial comparing ALTN plus EH followed by ALTN maintenance versus EH combined with placebo (PBO) as first-line treatment for advanced STS pts in China. **Methods:** Eligible pts had previously untreated, pathologically confirmed, unresectable locally advanced or metastatic STS. Pts were randomized in a 1:1 ratio to receive either ALTN (12mg) orally once daily (2-week on/1-week off) plus EH (90 mg/m^2) intravenously once every 3 weeks up to 6 cycles, followed by maintenance ALTN (12mg) orally once daily (2-week on/1-week off) or PBO (0mg) orally once daily (2-week on/1-week off) plus EH(90 mg/m^2) intravenously once every 3 weeks up to 6 cycles, followed by maintenance PBO (0mg) orally once daily (2-week on/1-week off). The primary endpoint was PFS assessed by the blinded independent review committee according to RECIST 1.1. Secondary endpoint included OS, Objective Response Rate (ORR), Disease control rate (DCR) and safety. **Results:** A total of 272 pts were randomized: 135 to ALTN + EH arm, 137 to PBO + EH arm. As of February 15, 2024, after a median follow-up of 7.16 mo, ALTN + EH arm significantly improved PFS (HR 0.30 [95% CI 0.21-0.44]; $P < 0.001$; median 8.57 vs 3.02 mo), and ORR (17.8% vs 2.90%; $P < 0.001$) , DCR (79.3% vs 54.7%; $P < 0.001$) versus PBO + EH arm. The median OS was not reached in either arm (HR = 0.78 [95% CI: 0.49-1.25]). The benefit of ALTN + EH arm was observed across most subgroups tested, including leiomyosarcoma, synovial sarcoma and other pathological types. The incidence of Grade ≥3 adverse events (AEs) (69.6% vs 59.1%), AEs leading to discontinuation of treatment (3.7% vs 4.4%), fatal AEs (3.7% vs 3.6%) were similar between two arms. **Conclusions:** Anlotinib in combination with epirubicin followed by maintenance ALTN demonstrated a statistically significant and clinically meaningful PFS benefit compared to epirubicin alone in pts with previously untreated advanced STS, which could serve as a potential new first-line treatment for locally advanced or metastatic STS. The final OS outcomes are currently under ongoing follow-up. Clinical trial information: NCT05121350. Research Sponsor: None.

11502 Oral Abstract Session

Eribulin plus anlotinib in advanced soft tissue sarcoma (ERAS): Updates on efficacy and biomarkers. First Author: Jie Liu, Department of Medical Oncology, Cancer Center, West China Hospital, Sichuan University, Chengdu, China

Background: This study provides an updated evaluation of the efficacy and biomarker analysis of combination therapy using eribulin, a microtubule dynamics inhibitor, and anlotinib, a multi-targeted tyrosine kinase inhibitor, in patients with advanced soft tissue sarcoma. **Methods:** In this multi-center phase II study (ERAS), patients received eribulin (1.1 mg/m² intravenously on days 1 and 8) and anlotinib (12 mg orally once daily on days 1-14) in 21-day cycles for 6-8 cycles, followed by maintenance therapy with anlotinib. Pre-treatment paraffin-embedded tumor samples were subjected to transcriptome sequencing analysis. The efficacy of the combination therapy in the ERAS study was compared to that of patients previously treated with anlotinib monotherapy. **Results:** As of the cut-off date of December 15, 2024, the median follow-up time was 17.8 months for 30 patients receiving combination therapy with eribulin and anlotinib (9 with leiomyosarcoma, 6 with dedifferentiated liposarcoma, and 15 with other types of sarcomas). In contrast, 87 patients received anlotinib monotherapy, with a median follow-up time of 43.3 months. This cohort comprised 28 patients with leiomyosarcoma, 8 with liposarcoma, and 51 with other types of sarcomas. After 1:2 propensity score matching analysis, compared to anlotinib monotherapy, the combination therapy of eribulin plus anlotinib resulted in a higher progression-free survival rate at 24 weeks (70.0% vs. 31.7%, P = 0.001), significantly improved median progression-free survival (8.5 vs. 4.0 months, P = 0.004), and extended overall survival (not reached vs. 18.4 months, P = 0.035) in patients with advanced soft tissue sarcoma. Transcriptomic data from patients treated with eribulin and anlotinib revealed that tumors with partial response or stable disease exhibited significantly higher levels of lipid metabolism compared to those with progressive disease. **Conclusions:** The combination therapy of eribulin plus anlotinib demonstrated superior efficacy compared to historical data from anlotinib monotherapy in patients with advanced soft tissue sarcoma. The lipid metabolism level in sarcomas could serve as a biomarker for the efficacy of this treatment regimen, potentially providing new insights into L-type sarcomas. Clinical trial information: ChiCTR2300067650. Research Sponsor: 1·3·5 project for disciplines of excellence–Clinical Research Incubation Project, West China Hospital, Sichuan University.

Results of a 1:2 propensity score matching analysis.

Characteristic	Anlotinib monotherapy (*n* = 60)	Eribulin plus Anlotinib (*n* = 30)	*P* value
Age			0.549
≥65 years	9	6	
<65 years	51	24	
Gender			0.648
Woman	37	17	
Man	23	13	
Pathological subtype			0.654
Leiomyosarcoma/liposarcoma	33	15	
Other sarcomas	27	15	
Pathological grade			-
G1/Gx	0	0	
G2/G3	60	30	
Stage			0.096*
Locally advanced	5	7	
Metastatic	55	23	
Surgery history			-
No	0	0	
Yes	60	30	
Radiotherapy history			0.226
No	38	15	
Yes	22	15	
Chemotherapy history			>0.999*
No	6	3	
Yes	54	27	
Progression-free survival at 24 weeks			0.001
No	41	9	
Yes	19	21	
Response			0.345*
Partial response or stable disease	7	6	
Progressive disease	53	24	

*Fisher's Exact Test.

11503 Oral Abstract Session

Camrelizumab plus apatinib in patients with advanced or refractory chordoma: A single-arm, open-label, phase 2 trial. First Author: Cheng Yang, Department of Orthopedic Oncology, Changzheng Hospital, Navy Medical University, Shanghai, China

Background: The limited efficacy of current treatments for chordoma underscores the need for novel therapeutic options. Immune checkpoint inhibitors (ICI) have changed the landscape of cancer treatment but are rarely investigated for chordomas. Additionally, no established biomarkers reliably predict the efficacy of ICI and targeted therapies in this context. **Methods:** This investigator-initiated, single-arm, phase 2 trial evaluated the efficacy and safety of camrelizumab (anti-programmed death 1, PD-1) combined with apatinib (a tyrosine kinase inhibitor) in patients with advanced or refractory chordoma. Eligible patients received camrelizumab (200 mg intravenously every 2 weeks) and apatinib (250/500 mg orally daily) in 28-day cycles. The primary endpoint was objective response rate (ORR) assessed per RECIST 1.1 and Choi criteria. Secondary endpoints were median progression-free survival (PFS), overall survival, disease control rate (DCR) and safety. Next-generation sequencing (NGS) and fluorescence in situ hybridization (FISH) were used to explore predictive biomarkers. The trial is registered on Chictr.org.cn (ChiCTR2100042938). **Results:** Between September 2021, and October 2024, 38 patients were screened, and 33 were enrolled for efficacy and safety analyses. The median treatment duration was 7 months (IQR 4-14), with a median radiologic evaluation time of 10 months (IQR 9-13) and median follow-up of 15 months (IQR 9-22). At data cutoff, 15 (45.5%) patients remained on treatment. Per RECIST 1.1, seven patients (21.2%, [95% CI, 9.0-38.9]) achieved partial response (PR), with a 6-month DCR of 85.2% (23/27). The median PFS was 18.1 months (95% CI, 11.0-28.5). According to Choi criteria, 16 patients (48.5%, [95% CI, 30.8-66.5]) achieved PR, with a 6-month DCR of 77.7% (21/27) and a median PFS of 15.3 months (95% CI, 10.6-NE). Two patients died of tumor progression, and two others with cervical recurrent chordoma died from postoperative complications. NGS analyses revealed copy number deletion (CND) of CDKN2A in 30% (6/20) of cases. *Post hoc* FISH analysis of 25 specimens identified homozygous deletion (HD) of CDKN2A in 40.0% (10/25), which correlated with poorer outcomes. Adverse events (AEs) occurred in 93.9% (31/33) of patients, with grade 3/4 AEs in 48.5%. Treatment-related AEs led to apatinib dose interruptions in 39.4% and camrelizumab interruptions in 21.2%. **Conclusions:** The combination of camrelizumab and apatinib demonstrated promising efficacy and manageable toxicity in chordoma treatment. Furthermore, CDKN2A alterations (CND or HD) were associated with poorer outcomes, providing a potential biomarker for therapeutic stratification. Clinical trial information: ChiCTR2100042938. Research Sponsor: None.

11504 **Oral Abstract Session**

Off-label use of fam-trastuzumab deruxtecan in desmoplastic small round cell tumor. First Author: Emily K Slotkin, Memorial Sloan Kettering Cancer Center, New York, NY

Background: Desmoplastic small round cell tumor (DSRCT) is a rare and aggressive sarcoma which remains almost universally fatal despite intensive, multi-modality therapy. Human epidermal growth factor receptor 2 (HER2) has been identified as a potential therapeutic target of relevance for DSRCT as both a pathway and cell surface expression marker. These observations prompted HER2 specific investigations in our DSRCT clinical cohort and subsequent off-label treatment with T-DXd, an antibody-drug conjugate consisting of a humanized anti-HER2 monoclonal antibody linked to a topoisomerase I inhibitor payload. **Methods:** A tumor microarray (TMA) of 52 unique DSRCT patient samples was analyzed by 2 immunohistochemical (IHC) assays (4B5, CB11), and a cohort of 61 DSRCT patient samples was analyzed by RNAseq. Additionally, 16 patients with relapsed/refractory DSRCT in need of therapy and enrolled on an institutional biobanking and genomic profiling protocol were identified, underwent IHC testing and RNAseq when feasible (fresh or archival tissue), and received off-label T-DXd. **Results:** TMA IHC analyses noted minimal HER2 IHC positivity using 4B5, with only 3/52 cases scoring above 10% membranous staining and composite IHC scores ranging from 11 to 15. IHC with clone CB11 uncovered 12.7-fold more HER2 reactivity with 38/52 cases scoring above 10%, and composite IHC scores ranging from 12.5 to 140. HER2 expression levels by RNAseq were analyzed in the context of 346 solid tumor patients with 22 histologies treated within the pediatrics department at MSK. Across these histologies DSRCT had the third highest HER2 expression level overall (surpassed only by papillary thyroid cancer and schwannoma). Median transcripts per million (TPM) expression level across the entire cohort was 9.8 (range 1-116.3), and for DSRCT was 41.8 (range 6.3-116.3). All 16 patients experienced clinical benefit (confirmed stable disease or partial response) with minimal toxicity, limited predominantly to myelosuppression, nausea and constipation. There were no episodes of interstitial lung disease. Notably, 8 of 16 patients all of whom had prior exposure to irinotecan achieved a decrease of at least 30% in the sum of the longest diameters of retrospectively selected target lesions, equivalent to a RECIST partial response (PR) (50% overall response rate). In this small series, response rate did not appear to correlate with available IHC or RNAseq data, with some patients achieving PR with no discernable membranous IHC expression. **Conclusions:** These results suggest that T-DXd is active in DSRCT and support the biomarker agnostic formal clinical trial which is planned with the Children's Oncology Group. Research Sponsor: Maurice Campbell Initiative at MSK KIDS; 76 Foundation; Will Heidrich Foundation.

11505 **Oral Abstract Session**

A phase I/II study of abemaciclib, a CDK4/6 inhibitor, in participants with HIV-associated and HIV-negative Kaposi sarcoma. First Author: Ramya Ramaswami, National Cancer Institute, Bethesda, MD

Background: Kaposi sarcoma (KS), caused by Kaposi sarcoma herpesvirus (KSHV), is a multicentric angioproliferative tumor seen in people with and without HIV. Abemaciclib (abema) is an oral cyclin-dependent kinase (CDK) inhibitor that targets CDK4 (cyclin D1) and CDK6 (cyclin D3), and is FDA-approved for breast cancer. In vitro studies of KSHV-infected cells have shown that CDK4/6 inhibitors enhance host immune cell surface expression and T-cell activation induced by these cells. Here, we investigate the safety and activity of abema in participants (pts) with KS. **Methods:** In this open label, non-randomized, two-stage Phase I/II study of pts with KS, there were two primary objectives. Phase I evaluated the safety and tolerability of abema in pts with KS using a 3+3 dose de-escalation design to identify a maximum tolerated dose (MTD). The first group of pts were treated at dose level 1 (DL) of 200mg twice daily for days 1-28 of a 28-day cycle. Intra-participant dose reductions were permissible for abema-related toxicities. Phase II assessed the overall response rate of abemaciclib of all participants and stratified by prior systemic KS therapy (Arm 1 target: 15 pts with previously treated KS and Arm 2 target: 10 participants with untreated KS). Eligibility criteria included adherence to antiretroviral therapy in people with HIV (PWH) for $>$ 8 weeks prior to enrollment and no concomitant strong CYP3A4 inhibitors. KS response was evaluated using the modified AIDS Clinical Trials Group criteria. **Results:** Thirty-four pts (33 men) with a median age of 43 years were enrolled. Twenty-five (74%) were PWH and 27 pts had stage T1 KS (6 pts had either gastrointestinal and/or lung involvement). Among PWH, the baseline median HIV viral load was $<$20 copies/ml and the median CD4 T-cell count was 308 cells/μL (interquartile range: 176-468 cells/μl). In Phase I, 6 pts (4 PWH) were enrolled at 200mg BID with no dose-limiting toxicities. In Phase II, 17 pts (14 PWH) were enrolled to Arm 1, and 11 pts (7 PWH) enrolled to Arm 2. Overall, 3 pts (2 in Arm 1 and 1 in Arm 2) did not proceed after one cycle due to grade 2 anxiety in 2 pts and tremor in 1 pt that were unrelated to study therapy. These pts were replaced as KS response was not evaluable. The most common grade 1/2 adverse events were diarrhea (92%) and creatinine elevation (64%). Neutropenia of all grades was noted in 63% and 13 pts had dose reductions for recurrent grade 3 or grade 4 neutropenia. Among 31 evaluable pts receiving $>$2 cycles, 24 pts had a partial response (PR) (77% [95% confidence interval (CI): 59-90%]), 4 pts had stable disease and 2 pt had progressive disease. Sixteen of 21 pts who prior KS therapy had a PR (76% [95% CI: 53-92%]) and 8 of 10 pts in Arm 2 with previously untreated KS had a PR (80% [95% CI: 44-98%]). **Conclusions:** Abema is a novel therapeutic option in KS, with notable activity among pts with previously untreated KS. Adverse events were managed with dose reduction and supportive measures. Clinical trial information: NCT04941274. Research Sponsor: National Cancer Institute, Center for Cancer Research (Intramural Program).

11506 **Oral Abstract Session**

A randomized phase III trial of catequentinib hydrochloride (AL3818) versus placebo in subjects with metastatic or advanced leiomyosarcoma (LMS). First Author: Robin Lewis Jones, The Royal Marsden NHS Foundation Trust and Institute of Cancer Research, London, United Kingdom

Background: Catequentinib Hydrochloride (AL3818, Anlotinib, Catequentinib) is a novel, orally administered, small molecule tyrosine kinase inhibitor. There remains an unmet need for effective, well tolerated therapies for patients (pts) with advanced/ metastatic leiomyosarcoma (LMS). We performed a randomized, double blind trial of Catequentinib monotherapy versus placebo in advanced/metastatic LMS. **Methods:** Patients with a diagnosis of LMS requiring third or further line treatment were eligible. Catequentinib was administered in a 21-day cycle with 14 days on and 7 days off regimen. In this double blind phase 3 trial, patients were randomized 2:1 to Catequentinib or placebo, with the option of crossover to Catequentinib after confirmed Progression Disease (PD) on placebo. Progression-free survival (PFS) with Log Rank test was the primary endpoint and the trial was conducted at multiple sites in the US, UK and EU. **Results:** Total N = 111 patients were enrolled, and N = 110 were treated and evaluated, 74 randomized to Catequentinib (C), and 36 to placebo (P). In arms (C)/(P) median ages were 59.0/60.5 (range: 33-91) years respectively and 59/29 (79.7%/80.6%) were female. Median PFS by Blinded Independent Central Review (BICR) met the primary endpoint at 3.42 months (95% CI: 2.60, 6.83) for (C) and 1.41 months (95% CI: 1.35, 4.86) for (P) with a p-value of 0.0265 and a HR of 0.536 (95% CI: 0.307, 0.936). Median PFS for patients stratified at $\leq$ 3 prior lines was 4.86 months (95% CI: 2.04, 8.94) for (C) and 1.41 months (95% CI: 1.31, 4.86) for (P) with a p-value of 0.0046 and a HR of 0.386 (95% CI: 0.196, 0.760). The 6-month progression-free rate was 42.37% for (C) and 20.71% for (P). OS was 17.45 months (95% CI: 13.57, 19.32) for (C) and 16.33 months (95% CI: 11.27, NE) for crossover patients in the (P) arm. 30 (40.5%) of patients have experienced grade 3 treatment-related adverse events in the (C) arm compared to 3 (8.3%) of patients in the (P) arm. The most common TEAE for (C) vs (P) were diarrhea (50.0% vs 22.2%), stomatitis (31.1% vs 8.3%), fatigue (64.9% vs 41.7%), and hypertension (47.3% vs 19.4%). **Conclusions:** This phase 3 trial met the primary PFS endpoint and demonstrates superior PFS for Catequentinib vs placebo in metastatic/advanced LMS. This study confirms the acceptable benefit-risk profile of Catequentinib in LMS. Catequentinib is an effective and well tolerated treatment option for patients with LMS. Clinical trial information: NCT03016819. Research Sponsor: None.

11507 **Oral Abstract Session**

Alliance A092104: A randomized phase 2/3 study of olaparib plus temozolomide versus investigator's choice for the treatment of patients with advanced uterine leiomyosarcoma after progression on prior chemotherapy. First Author: Brian Andrew Van Tine, Washington University Siteman Cancer Center, St. Louis, MO

Background: Advanced uterine leiomyosarcoma (uLMS) is an aggressive malignancy with poor prognosis. Standard-of-care treatments, including trabectedin (Tb) or pazopanib (P), provide median progression-free survival (PFS) of 3-4 months (mo) and objective response rates (ORR) of ~11%. Homologous recombination deficiency (HRD) in a subset of uLMS supports the use of PARP inhibitors combined with DNA-damaging agents. Preclinical studies demonstrated synergistic activity of olaparib and temozolomide (T+O), and a prior single-arm Phase II study of T+O showed promising efficacy independent of an established biomarker, warranting further investigation in a randomized setting. **Methods:** Alliance A092104 is a Phase II/III trial evaluating olaparib (200 mg BID) plus temozolomide (75 mg/m^2 daily, days 1-7, every 21 days) versus investigator's choice of Tb or P in patients (pts) with advanced uLMS who progressed on $\geq$2 prior systemic therapies. Stratification factors included ECOG (0-1 vs. 2) and prior lines (2 vs. $\geq$3). The Phase II (Phase III) primary endpoint was PFS (OS), with a planned suspension of accrual at the end of Phase II. A total of 70 evaluable pts (58 PFS events) were needed to detect an improvement in PFS from 4 vs. 8 mo with power of 90% and 1-sided type I error of 10%, with futility assessed after 29 PFS events. Upon meeting the Phase II futility threshold for PFS, the trial was permanently closed. Data were released from the data and safety monitoring board. Pts continue to be followed for outcomes. **Results:** 74 pts enrolled (Arm 1: T+O, n = 37; Arm 2: investigator's choice, n = 37 (Tb, 18; P, 13; 6 pts did not start treatment). The arms were balanced for baseline demographics except race, with the T+O arm having a higher proportion of black/African American (29.7% vs. 16.2%). 21 pts remain on treatment. Hematologic adverse events (AEs) were more frequent in the T+O arm, with Grade 4 neutropenia (19.5%) and thrombocytopenia (8.3%) both managed by dose reductions. Non-hematologic Grade 3 AEs were higher in the investigator's choice arm (45.2% vs. 13.9%). No Grade 5 AEs were reported. In the first 70 pts, with a median follow-up of 5.9 mo, and 39 total PFS events, the median PFS was 3.2 mo (95% CI: 2.0-NE) for T+O versus 5.6 mo (95% CI: 2.8-NE) for investigator's choice (HR = 1.00; 95% CI: 0.60-2.17; 1-sided stratified log rank p = 0.50). Within Arm 2, the median PFS for Tb and P were respectively 5.6 (95% CI: 3.1-NE) and 3.8 (95% CI: 1.5-NE) mo. 3 pts in the T+O arm and 1 patient in the investigator's choice arm (Tb) had a confirmed partial response. **Conclusions:** The trial did not meet its primary endpoint of PFS in Phase II. This suggests that a biomarker may be needed before there is further exploration of PARP inhibitor-based regimens in uLMS. Overall survival and analysis of tissue-based biomarkers will be presented. Clinical trial information: NCT05432791. Research Sponsor: National Cancer Institute; U10CA180821; National Cancer Institute; U10CA180882; National Cancer Institute; U10CA180820 (ECOG-ACRIN); National Cancer Institute; U10CA180868 (NRG Oncology).

11508 Oral Abstract Session

Spatial transcriptomic profiling from over 300 leiomyosarcoma samples. First Author: Ryan A Denu, Division of Cancer Medicine, The University of Texas MD Anderson Cancer Center, Houston, TX

Background: Leiomyosarcoma (LMS) is a smooth muscle-derived tumor with significant heterogeneity and limited treatment options for recurrent/metastatic disease. A lack of targetable driver mutations and prognostic and predictive biomarkers have hampered the care of patients with LMS. There is a great need to better understand the biology of LMS and develop novel therapeutics. Advances in single cell RNA sequencing (scRNA-seq) have allowed for better understanding of intratumoral heterogeneity in diverse cancer subtypes. However, tissue dissociation during this process leads to loss of spatial context. Spatial gene expression analysis builds upon scRNA-seq and has the potential to yield information about tissue organization, cell-cell interactions, niches, and cell states. To date there have been limited application of spatial transcriptomics to sarcoma. **Methods:** We performed single nucleus multiome (snRNA-seq and snATAC-seq) on a cohort of 16 primary, untreated LMS samples including 12 soft tissue (STLMS) and 4 uterine (ULMS) tumors. We then designed a custom 480-gene panel using the differentially expressed genes from clusters identified in snRNA-seq data to be able to identify spatial relationships between these clusters and to assess these clusters on a larger scale. We utilized the 10x Genomics Xenium platform. This was applied to LMS tissue microarrays (TMAs) comprising a total of 326 tissue cores from 127 unique patients. Matched primary and metastatic samples from the same patient were available for 33 patients. **Results:** Analysis of scRNAseq data identified 2 distinct subtypes: a dedifferentiated subtype with mesenchymal features (MES) and a differentiated subtype with enrichment of smooth muscle cell markers (SMC). Integration of chromatin accessibility data from snATACseq showed enrichment of nuclear factor I (NFI) transcription factor (TF) motifs in the MES and AP-1 motifs in the SMC group. Whole genome sequencing did not reveal an obvious genomic etiology for these subtypes. Spatial transcriptomics was able to identify these 2 subtypes in a larger cohort of tumors. Consistent with snRNAseq data, we find that most tumors had almost exclusively either MES or SMC cells. We assessed spatial relationships between these subtypes and infiltrating immune cells. This revealed an enrichment in immunosuppressive macrophages and exhausted T cells in MES tumors compared to SMC tumors. Analysis of matched primary and metastatic tumors demonstrated that the subtype (MES or SMC) generally remains consistent between different sites of disease. **Conclusions:** We identify 2 novel LMS subtypes (MES and SMC) driven by distinct TFs. Spatial transcriptomic analysis confirmed the presence of these 2 subtypes in a larger cohort and demonstrated that MES tumors are associated with a more immunosuppressive tumor microenvironment. Research Sponsor: None.

11509 Rapid Oral Abstract Session

Evaluation of the safety and efficacy of ALMB-0168, a novel monoclonal antibody activating Cx43 hemichannel, for osteosarcoma after standard therapy failure: A multicenter, open-label, single agent, phase 1/2 study (ACE study). First Author: Jingnan Shen, Department of Musculoskeletal Oncology, the First Affiliated Hospital of Sun Yat-Sen University, Guangzhou, China

Background: There was limited therapeutic advancement for decades for patients (pts) with relapsed and refractory (R/R) osteosarcoma. Pts with R/R osteosarcoma urgently need effective and safe treatment options after standard therapy failure. ALMB-0168, a first-in-class humanized IgG4 monoclonal antibody targeted to hemichannel protein Cx43, activates hemichannels to release key substances including ATP into the extracellular environment, to inhibit the growth and migration of osteosarcoma and other cancers bone metastases. Here reported the phase 2 study result based on ASCO 2023 Poster (11530). **Methods:** Pts $\geq$ 12 years (yrs) with pathologically confirmed osteosarcoma who had failed standard therapy were enrolled. In the phase I dose escalation with an accelerated titration followed by 3+3 design, pts were dosed with 7 planned ALMB-0168 dose levels (1, 3, 6, 12, 18, 24, and 30mg/kg), Q3W, until their disease progressed or intolerable toxicity occurred. Then the cohort at effective dose 6mg/kg was expanded. This trial used RECIST1.1 for efficacy evaluation. Primary endpoints were safety and tolerability. Key secondary endpoints were overall response rate (ORR), disease control rate (DCR), progression-free survival (PFS) and overall survival (OS). The CD73/CD39 expressions evaluated by IHC in osteosarcoma FFPE tissue with the efficacy were retrospectively analyzed. **Results:** As of Aug 19, 2024, total 27 pts with median age 29 yrs (range 16–69 yrs) were enrolled, of which 17 pts for dose escalation and 10 for dose expansion at 6mg/kg. No dose-limiting toxicity was observed. Treatment related adverse events (TRAEs) of any grade occurred in 18 (66.7%) pts, most of them were grade 1-2. Grade 3 TRAEs occurred in 1 (3.7%) patient (infectious pneumonia); no events were Grade 4 or 5. Common TRAEs observed in $\geq$ 10% pts were anemia (22.2%), proteinuria (14.8%) and alpha hydroxybutyrate dehydrogenase increased (11.1%). The DCR of whole evaluable pts was 68.2% (15/22), including 3 PR and 12 SD. At the 6mg/kg dose level which was expanded, among 10 evaluable pts, 2 pts achieved partial response (ORR: 20%), of which 1 patient achieved durable PR for 17 months (mo), PFS for 23 mo and OS for 36 mo (not reached). In 6mg/kg group, the DCR was 90% (9/10, 95% CI: 55.5, 99.7%) with 2 PR and 7 SD. And the PFS rate of 6mg/kg group at 4th mo was 70% (95% CI: 22.48, 91.83%). The relationship between the efficacy and the CD73/CD39 expression and other exploratory results will be presented in the future. **Conclusion:** The maximum tolerated dose of ALMB-0168 was not reached. The recommended phase 2 dose is 6mg/kg. In this study, ALMB-0168 showed encouraging anti-tumor activity, safe profile and durable benefit for pts with R/R osteosarcoma, which might be one of the potential treatment options for R/R osteosarcoma in the future. Clinical trial information: NCT04886765. Research Sponsor: AlaMab Therapeutics (Shanghai) Inc.

11510 Rapid Oral Abstract Session

Phase Ib trial of C019199, an oral TME modulator targeting CSF-1R/DDRs/VEGFR2, in relapsed or refractory osteosarcoma. First Author: Feng Ye, The First Affiliated Hospital of Xiamen University, Xiamen, China

Background: C019199 is an oral drug candidate that modulates the tumor microenvironment (TME) through targeting CSF-1R/DDRs/VEGFR2. Previous phase Ia study of C019199 as a mono-therapy for advanced solid tumors has shown promising safety and anti-tumor activity. The osteosarcoma cohort of this Phase Ib study aims to further evaluate the safety and efficacy of C019199 in patients with relapsed or refractory osteosarcoma who had failed in the first-line chemotherapy. **Methods:** In this study, patients of $\geq$16 years and $<$76 years with histologically or cytologically confirmed osteosarcoma, progressing after at least one prior chemotherapy, were enrolled. The dosing regimen of C019199 is 200 mg once daily, with continuous administration over 21-day treatment cycles. Imaging assessments are performed every two cycles. The treatment continues until disease progression, intolerable toxicity, or withdrawal of informed consent by the patient. The primary endpoint is the incidence of adverse events (AEs) and serious adverse events (SAEs). Secondary endpoints include objective response rate (ORR), disease control rate (DCR), and progression-free survival (PFS). **Results:** A total of 30 patients with relapsed or refractory osteosarcoma were enrolled from October 2023 to November 2024. Median age was 29 years (range, 16–62), with 60% males. The most common treatment-related adverse events (TRAEs) were leukopenia (60%), increased creatine phosphokinase (53.3%), increased lactate dehydrogenase (53.3%), neutropenia (53.3%), thrombocytopenia (46.7%), diarrhea (43.3%), increased aspartate aminotransferase (43.3%), and lymphopenia (40.0%). Grade 3 or higher TRAEs were observed in merely 7 patients (23.3%) including neutropenia (3 pts), lymphopenia (2 pts), thrombocytopenia (1 pts), hypertension (1 pts), syncope (1 pts), and dyspnea (1 pts). One patient achieved a partial response (an ORR of 3.3%), while majority of patients achieved stable conditions with a DCR of 73.3%. Median PFS was 181 days, and the 3-month PFS rate was 66.7%. **Conclusions:** The data has demonstrated that C019199 exhibited a promising anti-tumor activity in patients of relapsed or refractory osteosarcoma. Combined with the encouraging tolerability and safety data, it suggests that C019199 has the potential to effectively benefit survival and improve quality of life for patients of this indication. The Phase Ib study is concluding, and a Phase III study is planned. Clinical trial information: CTR20202045. Research Sponsor: Fujian Haixi Pharmaceuticals Co., Ltd.

11511 Rapid Oral Abstract Session

Detecting ctDNA using personalized structural variants to forecast recurrence in localized soft tissue sarcoma (STS). First Author: Changsu Lawrence Park, Division of Medical Oncology and Hematology, Princess Margaret Cancer Centre, University Health Network, University of Toronto, Toronto, ON, Canada

Background: The current standard for definitive management of localized STS involves surgery and (neo)adjuvant radiation (RT). Unfortunately, up to 50% of these patients (pts) recur but the role of adjuvant systemic therapy remains controversial. Circulating tumor DNA (ctDNA) is a promising biomarker for molecular residual disease (MRD) in STS but its clinical validity and utility remains unclear. Given that structural variants (SVs) are prevalent in the tumor genome of STS pts, this longitudinal study aims to utilize an ultra-sensitive, tumor-informed MRD assay that tracks somatic SVs for the detection of ctDNA. **Methods:** Pts with newly diagnosed, localized, high-risk ($\geq$ 5cm, grade $\geq$2) STS planned for curative-intent (neo) adjuvant RT and surgery were recruited from Feb 2019 to Aug 2023. Blood samples for ctDNA analyses were collected at diagnosis, post RT, post-surgery and every 3 months for up to two years in tandem with radiologic surveillance. The MRD window was defined as the first 8 weeks after surgery. Whole genome sequencing (WGS) was performed on archival tumor samples to detect all genomic SVs. A personalized multiplex digital PCR assay was then designed based on WGS data to track up to 16 somatic SVs in cell-free DNA from serial plasma samples for ctDNA detection and quantification. ctDNA data was then correlated to clinical outcomes (last updated on Jan 2025). **Results:** A total of 228 plasma samples from 32 pts were analyzed with a median follow-up of 20.1 months. STS subtypes included myxofibrosarcoma (12), undifferentiated pleomorphic sarcoma (10), dedifferentiated liposarcoma (6), pleomorphic liposarcoma (2), myxoid liposarcoma (1) and leiomyosarcoma (1). The ctDNA detection rate at diagnosis was 97% (31/32 pts). Of the cohort, 22 pts received preoperative RT and had blood collected within the MRD window. ctDNA was detectable at baseline and in the MRD window in 4/22 pts (18%). All 4 (100%) developed metastatic disease with a median lead time of 136 days (range: 28-210 days) in ctDNA detection prior to radiologic relapse. Of the 18 pts who were ctDNA-negative in the MRD window, 3 (17%) developed metastatic recurrence, all of which was preceded by detectable ctDNA with a median lead time of 87 days (range: 80-147 days). The median time from surgery to recurrence was 153 days (range: 57-224 days) vs 521 days (range: 406-631 days) for pts with detectable vs undetectable ctDNA within the MRD window, respectively. **Conclusions:** Detection of ctDNA using personalized tumor-informed assays for somatic SV tracking was feasible and highly sensitive in localized high-risk STS pts prior to surgery. Positive ctDNA within the MRD window was predictive of subsequent and earlier radiologic relapse. Based on this data, an interception trial of adjuvant systemic therapy for MRD-positive STS pts is planned. Future analysis, including the measurement of circulating extrachromosomal DNA (ecDNA) is planned. Clinical trial information: NCT03818412. Research Sponsor: None.

11512 Rapid Oral Abstract Session

A clinical and genomic landscape analysis of GI stromal tumors. First Author: Nadeem Bilani, Department of Medicine, Division of Hematology and Oncology, Northwestern University, Chicago, IL

Background: Gastrointestinal stromal tumors (GIST) are malignant mesenchymal tumors with distinct histogenesis and behavior from other sarcomas. Treatment of metastatic GIST involves receptor tyrosine kinase (RTK) inhibition. Primary *KIT* or *PDGFRA* mutations are established drivers of tumorigenesis via constitutive RTK activation. Growing attention is now focused on how secondary alterations impact clinical outcomes. **Methods:** The open-source platform cBioPortal was queried for GIST patients. Sociodemographic and clinicopathologic features, including *KIT*/*PDGFRA* mutation prevalence, were described using univariate statistics. Primary *KIT* mutations (exon 11: coding the receptor juxtamembrane domain) and secondary *KIT* mutations (exon 13/14: coding ATP-binding domain; or exon 17/18: coding activation loop) were assessed. Co-occurrence/exclusivity of altered genes was analyzed using two-sided Fisher's Exact (p-values) and Benjamini–Hochberg FDR correction (q-values) – pathway pairs deemed significant at $p < 0.05$ and $q < 0.05$. Log2 odds ratios (OR) quantified association strength. Differences between *KIT*-mutated (*KIT*-mut) vs. *KIT*-wild type (*KIT*-wt) groups were assessed via chi-squared. Kaplan-Meier modeling evaluated overall survival (OS) by co-occurring alterations, controlling for metastatic status and stratifying by primary site. **Results:** 499 GISTs were analyzed: 214 gastric (42.9%), 137 small bowel (27.5%), 22 colorectal (4.4%), and 9 esophageal (1.8%).Most tumors harbored *KIT* mutations (n = 382, 76.6%), which co-occurred with *CDKN2A* (log2 OR 3.04) and *CDKN2B* (log2 OR 2.77) deletions ($p < 0.001$; $q < 0.001$). 91 (23.8% of *KIT*-mut) patients harbored both (*CDKN2A/2B*-del). Secondary *KIT* mutations in exons 13/14 or 17/18 were associated with *CDKN2A/2B*-del ($p < 0.001$). *CDKN2A/2B*-del was rare in *KIT*-wt (< 5%). *KIT* mutations were mutually exclusive with *PDGFR*, *NF1* (log2 OR < -3, $q < 0.001$ for both), and *SDHA* mutations (log2 OR < -2.67, q = 0.038); prevalent in 9.8%, 4.0%, and 2.0%, respectively. *PDGFRA*/*NF1* mutations showed no significant co-occurrence. *SDHA* alterations were associated with *TERT* and *RICTOR* alterations. GISTs were more likely *KIT*-wt in women vs. men (OR 1.76, p = 0.012), and in gastric vs. small bowel tumors (OR 2.79, $p < 0.001$). Tumor mutational burden was similar between groups (mean 2.12 vs. 1.27). No tumors were microsatellite unstable.OS did not differ between *KIT*-, *PDGFRA*-, *NF1*-, or *SDHA*-mut (log-rank p = 0.453). In metastatic *KIT*-mut, *CDKN2A/2B*-del was associated with poorer OS (log-rank $p < 0.001$). Median OS for small bowel *KIT*-mut + *CDKN2A/2B*-wt disease was not reached, 24.3 months in small bowel *KIT*-mut + *CDKN2A/2B*-del, 52.5 in gastric *KIT*-mut + *CDKN2A/2B*-wt, and 22.4 in gastric *KIT*-mut + *CDKN2A/2B*-del. **Conclusions:** *CDKN2A/CDKN2B* deletions co-occur with advanced, imatinib-resistant, *KIT*-mut GIST. They prognosticate poorer OS but suggest therapeutic potential for cyclin dependent kinase inhibition. Research Sponsor: None.

11513 Rapid Oral Abstract Session

Phase II of sunitinib plus nivolumab in extraskeletal myxoid chondrosarcoma: Results from the GEIS, ISG, and UCL IMMUNOSARC II Study. First Author: Nadia Hindi, Fundación Jimenez Diaz University Hospital, Madrid, Spain; University Hospital General de Villalba, Madrid, Spain; Instituto de Investigacion Sanitaria Fundacion Jimenez Diaz (IIS/FJD; UAM), Madrid, Spain

Background: Extraskeletal myxoid chondrosarcoma (EMC) is an ultra-rare sarcoma, with low sensitivity to classic chemotherapy. A previous clinical trial led by our groups showed the activity of antiangiogenics (specifically pazopanib) in patients (pts) with advanced ECM. As IMMUNOSARC I master-trial exploring sunitinib (S) plus nivolumab (N) in sarcoma detected signal of activity in ECM pts, a specific cohort of ECM was designed as a phase II trial within IMMUNOSARC II (NCT03277924). **Methods:** Adult pts with advanced, progressing, measurable and centrally confirmed EMC were enrolled and treated with S 37.5 mg/d in the first 14 days (d), followed by S 25 mg/d, along with N 240 mg every 2 weeks up to progression or intolerance. Imaging reassessments were done every 8 weeks. The primary endpoint was 6-month(m)-PFS rate, and the statistical assumptions were obtaining a 6m-PFSR in at least 15 pts out of 22 pts, with H_0= 50% and H_1= 80%, (α 0.05; β 0.10) to consider the combination as promising. **Results:** Twenty-four pts were accrued from May 2020 to July 2024 in 9 centres from Spain, Italy and UK. Pts had a median age of 58y (42-83), with a predominance of male (M = 19/F = 5). Thirteen (54%) pts were treatment naïve and 22 (92%) pts had metastatic disease at baseline. Grade 3-4 Adverse Events (AE) occurring in > 5% of pts were: hypertension (29.2%), ALT and AST increase (16.7 and 12.5% respectively), bilirubin increase (12.5%), Lymphocytopenia (12.5%). No G4 hematologic AEs were found, with the exception of 1 pt with G4 leukopenia. With a median FU of 18 mos (8-29), among the 23 evaluable pts, 6m-PFSR was 77% with 16/23 pts free of progression at 6 mos, and a median PFS of 13.2 mos (95%CI 5.7-20.7). Median OS has not been reached and 12m-OS was 90% (95%CI 77-100). Two (9%) pts achieved a RECIST 1.1 partial response while 18 (82%) and 2 pts (9%) showed a stable disease and progresion as the best response respectively. Pts (6/23) previously treated with antiangiogenic had a trend to a shorter mPFS (7mos vs 13 mos, p = 0.11) and a significantly shorter OS (28 mos vs NR, p = 0.038). **Conclusions:** The combination of sunitinib and nivolumab has shown to be active in advanced extraskeletal myxoid chondrosarcoma. Our data suggest that using this combo in upfront lines provides a greater benefit. Clinical trial information: NCT03277924. Research Sponsor: Grupo Español de Investigación en Sarcomas (GEIS); Pfizer (drug supply); BMS (drug and shipping supply).

11514 Rapid Oral Abstract Session

ImmunoSarc2 (Cohort 7a): A Spanish Sarcoma Group (GEIS) phase Ib trial of epirubicin and ifosfamide plus nivolumab in first line of advanced undifferentiated pleomorphic sarcoma (UPS). First Author: Javier Martin Broto, Fundación Jimenez Diaz University Hospital, Madrid, Spain

Background: It was hypothesized that anthracycline-based chemotherapy plus anti-PD1 (nivolumab) could enhance the activity of upfront chemotherapy in advanced UPS, based on a double-hit in the immunogenic cell death circuit. This peculiar tumor cell death eventually activates an adaptive immune response through particular molecular changes in dying tumor cells and microenvironment, triggered by specific drugs such as anthracyclines. We previously reported a phase Ib trial in leiomyosarcoma patients with the combination of doxorubicin, dacarbazine, and nivolumab, obtaining 56.5% of ORR. We present here the phase Ib, cohort 7a, of the ImmunoSarc2 trial. **Methods:** Adult patients (pts), with ECOG 0-1, naïve of previous anthracycline-containing treatments, and with a centrally confirmed diagnosis of advanced/metastatic UPS were eligible. Initial dose level 0 (L0) was defined as epirubicin 60 mg/m^2/d 20 min on D1 and D2 followed by ifosfamide 3 g/m^2/d 3-h on D1-3, plus nivolumab (NIV) 360 mg on D3 after chemotherapy. Cycles were given Q3W with GCSF and MESNA support. This combo would be given up to 6 courses of 21-day cycles, followed by 1-year NIV maintenance. A -1 dose level (L-1) was defined with the same regimen but with NIV 240 mg. A classic 3+3 phase 1 design was used to determine the MTD based on DLTs (main endpoint) observed during the first 21-day cycle. The cohort was foreseen to be extended with the RP2D to include up to a maximum of 20 evaluable patients. Secondary endpoints included ORR and safety profile among others. **Results:** Between January 2022 and June 2024, 16 patients M/F (9/7), ECOG 0/1 (15/1), with median age 56 years (29-77) were enrolled. All patients were treated with the initial L0 scheme and no DLTs were observed, being L0 the RP2D. Grade 3-4 toxicities were neutropenia 62.5%, febrile neutropenia 18.8%, anemia 31.3%, and thrombocytopenia 25%. A patient died following a subarachnoid hemorrhage in the context of grade 4 thrombocytopenia and an accidental fall. Of 16 patients, RECIST ORR according to local clinical site assessment was 68.8% distributed as 1 CR (6%), 10 PR (63 %), 4 SD (25%), and 1 PD (6%). With a median follow-up of 16.3 months (95% CI, 7.2-25.4), the median of PFS was 9.9 months (95% CI 7-12.7), while the median OS was not reached, and the 1-year OS rate was 81% (95% CI 62-100). **Conclusions:** Epirubicin 60 mg/m^2/d d1-2 plus Ifosfamide 3 g/m^2/d d1-3 plus NIV 360 mg on d3 Q3W, followed by 1 year of NIV is a feasible and manageable scheme that exhibits relevant activity as an upfront line in advanced UPS patients. A phase II/III trial is designed aiming to confirm the advantage of chemo-immunotherapy over chemotherapy alone in this context. Clinical trial information: NCT03277924. Research Sponsor: BMS provided budget for drug supply, shipping and some operational CRO cost; And Spanish Sarcoma Group (Sponsor).

11515 Rapid Oral Abstract Session

A phase 2 study using metronomic gemcitabine, doxorubicin, and docetaxel plus nivolumab in advanced leiomyosarcoma and liposarcoma (NCT04535713). First Author: Jason Ballon, Sarcoma Oncology Center, Santa Monica, CA

Background: Chemotherapy agents cemcitabine, doxorubicin, and docetaxel have all demonstrated efficacy in soft tissue sarcomas (STS) but often result in significant toxicity. Therefore, we propose a combination chemo-immunotherapy regimen using metronomic low dose chemotherapy doses to reduce toxicity, with the addition of Nivolumab, a PD-1 inhibitor with demonstrated efficacy in STS. In this study, we aimed to determine the efficacy/safety of adding nivolumab to metronomic gemcitabine, doxorubicin, and docetaxel in subjects with advanced leiomyosarcoma (LMS) or liposarcoma (LPS). **Methods:** Objectives: Primary: To determine progression-free survival (PFS); Secondary: T evaluate the best overall response (BOR) and duration of response (DOR) by RECIST v1.1 via CT scan or MRI during the treatment period, determine progression-free survival rate (PFS) at 6 and 12 months and determine overall survival rate at 6 and 12 months Key eligibility criteria: ≥ 18 years, previously treated locally advanced unresectable or metastatic LMS/LPS, measurable disease by RECIST v1.1, acceptable hematologic and organ functions Treatment Schedule: Three-week treatment cycles with gemcitabine (600 mg/m2 max:1000 mg), doxorubicin (18 mg/m2; max: 32 mg), docetaxel (25 mg/m2; max: 42 mg) on Day 1 and Day 8, andnivolumab (240 mg) on Day 1 only. **Results:** Efficacy: The intention-to-treat population (n= 41), which includes patients who received at least one dose of gemcitabine, doxorubicin, and docetaxel, was used to determine the following: Median OS =16.1 months (95% CI: 7.4 to 20.1 months) and incidence of adverse events. The modified-intention-to-treat population (n= 31), which includes patients who completed at least the first 2 treatment cycles and follow-up CT/MRI, was used to determine the following: Median PFS = 8.6 (95% CI: 3.3-12.0) months; ORR = 22.6%; DCR = 87.5%; 6-month PFS rate = 58%; 6-month OS rate = 70.7%; 12-month PFS rate = 35.5%; 12-month OS rate = 59.1%; BOR = 7 PR, 21 SD, 4 PD. Safety: 28 of 41 patients (68%) experienced Grade 3/4 TRAEs that include: thrombocytopenia (n=12), lymphocyte count decreased (n=11), anemia (n=10), neutropenia (n=9), back pain (n=4), leukopenia (n=4), fatigue (n=2), dyspnea (n=2), hypocalcemia (n=1), muscle weakness (n=1), colitis (n=1), diarrhea (n=1), anorexia (n=1), abdominal pain (n=1), alkaline phosphatase increased (n=1), nausea (n=1), bone pain (n=1), peripheral sensory neuropathy (n=1), edema (n=1). There were no unexpected adverse events. **Conclusions:** Taken together, the results indicate that the combination regimen of nivolumab with metronomic gemcitabine, doxorubicin and docetaxel may have synergistic activity and is an effective treatment for advanced leiomyosarcoma and liposarcoma with manageable toxicity. Clinical trial information: NCT04535713. Research Sponsor: None.

11516 Rapid Oral Abstract Session

Subgroup analysis of the phase 2 part of the RINGSIDE phase 2/3 trial of varegacestat for treatment of desmoid tumors. First Author: Rashmi Chugh, University of Michigan, Michigan Medicine, Ann Arbor, MI

Background: Gamma secretase inhibitors (GSIs) have shown antitumor activity against desmoid tumors (DT). The RINGSIDE Phase 2 study (NCT04871282) demonstrated early and continued response to three dose regimens of varegacestat (AL102) in patients with DTs. We evaluated treatment response in key subgroups. **Methods:** RINGSIDE Phase 2 is an open-label, dose-finding study in adults with progressing DT (≥10% unidimensional growth ≤18 months or DT-related pain requiring non-opioid medication). Participants were randomized to three dose regimens: 1.2 mg once daily (n=14), 2 mg intermittent (n=14) or 4 mg intermittent (n=14) (intermittent = 2 days on, 5 days off). In the open-label extension (OLE) period, all active participants began receiving 1.2 mg once daily. We performed descriptive analyses of objective response rate (ORR) in the following subgroups with at least 5 participants: age (≤40 years vs. >40 years), tumor size (<70 mm vs. ≥70 mm), prior lines of therapy (0, 1, or 2+), tumor location (intra-abdominal vs. extra-abdominal) and mutational biomarkers (*APC* vs *CTNNB1*). Subgroups were analyzed by pooling across dose regimens. **Results:** RINGSIDE Phase 2 enrolled 42 participants, of whom 29 (69%) entered the OLE. As of April 10, 2024, median time on treatment was 23.1 months (range 0.7 – 26.6) and 23 participants (55%) were still on treatment. Median age was 38.5 years (range 19 – 72), 74% were women, and 69% received prior DT therapy. ORR ranged from 43% to 78% across age, tumor size, prior therapy, tumor location and mutation subgroups (Table). Response rates were comparable across all subgroups examined. **Conclusions:** Comparable, objective tumor responses to oral varegacestat therapy were shown in all subgroups examined. These findings support continued evaluation of all desmoid tumor patients independent of subgroups in the ongoing, double-blind, randomized, placebo-controlled Phase 3 study of varegacestat (RINGSIDE NCT04871282). Clinical trial information: NCT04871282. Research Sponsor: Immunome.

Varegacestat response in subgroups.

Subgroups	ORR Responder (%)
Age ≤40 years (n=22) vs. >40 years (n=14)	13 (59) vs. 10 (71)
Tumor size <70 mm (n=18) vs. ≥70 mm (n=14)	13 (72) vs. 9 (64)
Prior lines of therapy: 0 (n=11), 1 (n=16), or 2+ (n=9)	6 (55), 10 (63), 7 (78)
Intra-abdominal (n=9) vs. extra-abdominal (n=27)	4 (44) vs. 19 (70)
***APC* (n=7) vs *CTNNB1* (n=19) mutation**	3 (43) vs. 13 (68)

11517 Rapid Oral Abstract Session

The broad-spectrum KIT inhibitor NB003 and activity in advanced gastrointestinal stromal tumors (GIST): Updated results from a phase 1 study (NCT04936178). First Author: Ping Chi, Department of Medicine, Memorial Sloan Kettering Cancer Center, New York, NY

Background: NB003 is a novel potent and selective oral small-molecule tyrosine kinase inhibitor of KIT. It was designed to inhibit a broad spectrum of primary and acquired imatinib-resistant mutations in KIT. The abstract reports updated results from the escalation and expansion phases of the Phase 1 study in patients (pts) with advanced GIST. **Methods:** The Phase 1 study includes a dose-escalation phase where pts received oral NB003 (3mg to 40mg) twice daily (BID) in 28-day cycles, followed by an expansion phase with the putative recommended Phase 2 dose (RP2D) (15mg or 20mg BID) in 6 cohorts, including cohorts for GIST pts based on prior standard-of-care (SOC) regimens (2nd, 3rd, 4th, and ≥5th-line). Efficacy was assessed by Modified Response Evaluation Criteria in Solid Tumors (mRECIST) version 1.1 every 2 cycles. **Results:** At the cut-off of Dec 23, 2024, 158 pts with KIT-mutant GIST were enrolled in the escalation and expansion phases (median follow-up of 9.9 months; range, 0.5–32.0). The 154 evaluable pts included 24 2nd-line, 30 3rd-line, 35 4th-line, 56 ≥5th-line pts and 9 others. The confirmed objective response rate (cORR) was 27.3% (95% CI:20.4, 35.0) in all, 40% (95% CI:22.7, 59.4) in 3rd-line, 42.9% (95% CI: 26.3, 60.6) in 4th-line, and 12.5% (95% CI:5.2, 24.1) in ≥5th-line pts. Tumor responses were observed in pts with a broad spectrum of acquired resistance mutations, including those in the KIT ATP-binding site (exons 13/14) and the activation loop of the kinase domain (exons 17/18). The median progression-free survival (mPFS) was 9.2 months (95% CI:7.4, 11.3), not reached (NR) (95% CI:6.0, NE), 13.8 months (95% CI:9.2, NE), and 4.5 months (95% CI:3.8, 7.4), in all, 3rd-line, 4th-line, and ≥5th-line pts, respectively. For ≥3rd-line pts without prior ripretinib, the cORR was 41.2% (95% CI:29.4, 53.8) and the mPFS was NR (95% CI:9.5, NE). In all pts, the most frequent treatment-related adverse events (TRAEs) were asymptomatic CPK increased (80.4%), anaemia (75.9%), AST increased (71.5%), face oedema (65.2%), periorbital oedema (55.1%), neutrophil count decreased (48.7%), WBC decreased (48.7%), amylase increased (39.9%), lipase increased (38.6%), platelet count decreased (33.5%), and peripheral oedema (31.0%). The most frequent treatment-emergent SAEs were anaemia (13.3%), gastrointestinal haemorrhage (6.3%), pleural effusion (4.4%), pneumonia (3.2%), and tumour haemorrhage (3.2%). **Conclusions:** NB003 demonstrated a manageable safety profile, and showed encouraging clinical benefit in GIST pts, as evidenced by mPFS and cORR, across multiple lines of treatment and a broad spectrum of secondary resistance KIT mutations. The promising data from this phase 1 study supports further testing of NB003 in Phase 3 studies. Clinical trial information: NCT04936178. Research Sponsor: None.

11518 Poster Session

Liposomal irinotecan together with vincristine and temozolomide (NALIRI-VT) for patients with relapsed or refractory Ewing sarcoma: A two-cohort, phase 1a/1b study. First Author: Jie Xu, Peking University People's Hospital, Beijing, China

Background: To define the safety and preliminary efficacy of liposomal irinotecan together with vincristine and temozolomide in children and adults with Ewing sarcoma, respectively. **Methods:** Patients with relapsed or refractory Ewing sarcoma were enrolled in cohort A (children) or cohort B (adults), respectively. For each cohort, a fixed dose of vincristine (1.4mg/m^2 max 2mg i.v. $D_{1,8,15}$) and temozolomide (100mg/m^2/d p.o. $D_{1\text{-}5}$) q21d were given. In phase 1a portion, four dose levels of weekly infused liposomal irinotecan (level 1-4, 25mg/m^2, 30mg/m^2, 35mg/m^2 and 40mg/m^2) were designed. 3+3 dose-escalation method was used to explore the maximum tolerated dose (MTD), defined as no more than 30% patients appeared dose-limited toxicity (DLT) in first two cycles (six weeks). In the phase 1b portion, MTD would be used and a maximum of 12 patients were allowed in each cohort at this level in total. **Results:** 15 children and 18 adults were enrolled in phase 1a portion. 9 more children and 5 more adults were enrolled in phase 1b portion. Finally, 12 children and 11 adults were treated at MTD level. In phase 1a portion, no DLT was found at level 1-2. For level 3, no DLT (0/3) was found in cohort A, while one DLT (1/6) of hematologic toxicity was found in cohort B. For level 4, two DLTs (2/6) were found in cohort A, both of whom were due to hematologic toxicity. For cohort B, two DLTs (2/6) was found at this level. One of them was serious anorexia. The other one was hematologic toxicity together with serious nausea and vomiting, anorexia, fatigue. Level 3 was chosen for MTD. Grade 3/4 toxicities were found in hematologic toxicity (most common), anorexia, fatigue, nausea or vomiting, pain and diarrhea. Better efficacy was shown at higher levels (level 3 and level 4) in both cohorts. For cohort A, objective response rate (ORR) was 0 (0/3), 33.3% (1/3), 66.7% (2/3) and 66.7% (4/6) at level 1-4, respectively. For cohort B, ORR was 33.3% (1/3), 33.3% (1/3), 83.3% (5/6) and 66.7% (4/6). Data for survival in phase 1a and data of phase 1b were not matured. **Conclusions:** We showed that liposomal irinotecan infused weekly at 35mg/m^2 in NALIRI-VT regimen was well tolerated and showed promising efficacy in both children and adults. Clinical trial information: NCT06340204. Research Sponsor: Beijing Tongzhou technology grand; KJ2024CX046.

Summary of DLTs and responses in phase 1a portion.

Dose level	Liposomal Irinotecan IV Dose (mg/m^2/d) $D_{1,8,15}$	# of Evaluable Patients	# of DLTs in the first two cycles	Best of Response (BOR)
Cohort A Children				
1	25	3	0	1 SD, 2 PD
2	30	3	0	1 PR, 1 SD, 1 PD
3	35	3	0	1 CR, 1 PR, 1 SD
4	40	6	2	1 CR, 3 PR, 2 PD
Cohort B Adults				
1	25	3	0	1 SD->CR*, 2 SD
2	30	3	0	1 PR, 2 SD
3	35	6	1	5 PR, 1 PD
4	40	6	2	1 CR, 3 PR, 2 SD

*One patient was first treated at level 1, showed no AE at this level and SD was recorded at first evaluation. When safety of the next level 2 dose was confirmed, this patient received the higher level 2 dose, and CR was recorded at the following evaluations.

11519 Poster Session

MRI-based machine learning model for predicting early relapse in osteosarcoma following neoadjuvant chemotherapy. First Author: Yucheng Fu, Department of Orthopedics, Ruijin Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai, Shanghai, China

Background: Early relapse (ER, ≤ 1 year) in osteosarcoma frequently occurs following neoadjuvant chemotherapy (NAC) and surgical resection. This study developed the machine learning models integrating radiomics, clinical, and pathological features to predict ER risk in osteosarcoma. **Methods:** 142 osteosarcoma patients were retrospectively analyzed and preoperative MRI images (T1- and FST2-weighted) were obtained after NAC. After feature extraction and selection, 5 machine learning classifiers—random forest (RF), support vector machine, logistic regression, decision tree, and gradient boosting tree—were implemented to construct radiomics, clinicopathological, and multimodal models. The performance of these models were assessed and compared using receiver operating characteristic curves, decision curve analysis (DCA), and Kaplan-Meier survival analysis, with the components and structure of the best-performing model subsequently visualized. **Results:** The RF algorithm outperformed the other classifiers, forming optimal radiomics and multimodal models. The RF-based multimodal model, combining 14 radiomics features, alkaline phosphatase (ALP) levels, and tumor necrosis rate, achieved the highest performance, with an area under the curve (AUC) of 0.978 in the training cohort and 0.913 in the testing cohort. The corresponding radiomics model, designed for real-time preoperative evaluation, showed a slight reduction in performance but still performed well. DCA and Kaplan-Meier curves indicated significant clinical utility of these two models. **Conclusions:** The RF-based pipeline, which includes radiomics and multimodal models, could facilitate personalized chemotherapy by identifying high-risk patients, optimizing treatment decisions, and improving outcomes. Research Sponsor: National Natural Science Foundation of China; 82472712.

Performance of the different radiomics models, clinical models and combined models in the training and testing cohorts.

Cohorts	Model	Classifier	AUC (95% CI)
Training cohort	Radiomics models	RF	0.963 (0.928-0.998)
		SVM	0.811 (0.723-0.899)
		LR	0.802 (0.714-0.891)
		DT	0.876 (0.809-0.942)
		GBT	0.973 (0.942-0.999)
	Clinical models	LR	0.709 (0.614-0.803)
	Combined models	RF	0.978 (0.956-0.999)
		SVM	0.898 (0.836-0.960)
		LR	0.813 (0.728-0.898)
		DT	0.896 (0.834-0.958)
		GBT	0.931 (0.884-0.977)
Testing cohort	Radiomics models	RF	0.857 (0.751-0.963)
		SVM	0.784 (0.650-0.917)
		LR	0.794 (0.662-0.927)
		DT	0.814 (0.686-0.942)
		GBT	0.728 (0.561-0.896)
	Clinical models	LR	0.684 (0.525-0.843)
	Combined models	RF	0.913 (0.833-0.994)
		SVM	0.818 (0.671-0.965)
		LR	0.812 (0.659-0.965)
		DT	0.881 (0.773-0.989)
		GBT	0.853 (0.731-0.974)

RF: Random forest; SVM: Support vector machine; LR: Logistic regression; DT: Decision tree; GBT: Gradient Boosting Tree; CI: Confidence interval.

11520 **Poster Session**

The preoperative management of patients with giant cell tumors in limb bones using denosumab therapy. First Author: Saidrasul Nasirov, Tashkent Medical Academy, Tashkent, Uzbekistan

Background: Giant cell tumor (GCT) is an intermediate, locally aggressive primary bone tumor. In addition to local therapy,new drugs for the treatment of this disease have become available. The medication Denosumab, which wasoriginally used to treat osteoporosis and the solid tumor metastases to bone, eventually began to be used totreat giant cell bone tumors. In treatment of GCT, Denosumab was used as the only remedy in patients withinoperable tumors, and was also used before surgery to reduce the size of the tumor and to preserve the joint.To evaluate the effectiveness of Denosumab, while using in the preoperative period of GCT treatment. **Methods:** A study was conducted of 49 patients with GCT of tubular limb bones who received Denosumab beforesurgery, and 60 patients (retrospectively evaluated, without using Denosumab in our hospital from 2015 to2019). Propensity scores were compared in a 1:1 ratio between the groups receiving Denosumab and thecontrol group to minimize possible selection bias; recurrence rates, limb function, and surgical impairmentwere compared between the two groups. **Results:** The recurrence rate after 3 years in the Denosumab group and the control group was 12.2% and 23.3%,respectively. In the Denosumab group, 100% (n = 49) of patients underwent surgical treatment. In 44 patientstreated with Denosumab, the indices of limb joint preservation were 89.8% and 36.6% in 22 control patients.Postoperative MSTS were higher in patients in the Denosumab group than in the control group. **Conclusions:** Preoperative treatment with Denosumab reduced the risk of local recurrence of GCT. Preoperative treatmentwith Denosumab is indicated for patients with advanced GCT to facilitate surgical treatment and preserve thejoint. Denosumab remains a highly effective treatment for patients with GCT bone. Research Sponsor: None.

11521 **Poster Session**

Feasibility and clinical outcomes of imatinib personalized dosing in gastrointestinal stromal tumor patients. First Author: Maud Berendina Annelies van der Kleij, Department of Clinical Pharmacology, Division of Medical Oncology, Netherlands Cancer Institute - Antoni van Leeuwenhoek, Amsterdam, Netherlands

Background: Imatinib treatment for metastatic gastrointestinal stromal tumors (GISTs) has substantial overall survival benefits compared to chemotherapy (56 vs 9 months) (Balachandran, 2014). Even better outcomes have been demonstrated for patients with imatinib minimal drug concentrations (C_{min}) $\geq$ 1100 ng/mL (Demetri, 2009). Drug concentration-guided dosing through therapeutic drug monitoring (TDM) of imatinib has previously been described as an option for personalized dosing, but there is no definite conclusion on efficacy results (IJzerman, 2020). The aim of the current study was to evaluate the feasibility and effect on clinical outcomes of imatinib personalized dosing through TDM for GIST patients. **Methods:** GIST patients starting with imatinib 400 mg once daily (QD) in both the (neo)adjuvant and metastatic setting were included. C_{min} levels were measured during routine outpatient clinic visits, at 4, 8 and 12 weeks after start of treatment, and every 12 weeks thereafter. Dose increase to 600 mg QD and, if necessary, to 800 mg QD was advised when C_{min} $<$ 1100 ng/mL and treatment was well tolerated. Dose interventions were considered successful when median C_{min} was $\geq$ 1100 ng/mL after intervention and no dose limiting toxicities (DLTs) occurred within the first month after dose intervention. **Results:** A total of 171 GIST patients were included, of which 61% (n = 104) were treated in the (neo)adjuvant setting and 39% (n = 67) in the palliative setting. Most patients (85.4%, n = 146) had a *KIT* exon 11 mutation. Median time on treatment was 30 months. A total of 1475 C_{min} levels were measured (median of 8 levels per patient, IQR: 4−12), resulting in a median C_{min} of 1111 ng/mL. Among all patients, 16% (n = 27) had all adequate C_{min} levels, and 84% (n = 144) had $\geq$ 1 C_{min} level below the target. Of these, 60% (n = 87) had a dose intervention, which was successful in 76% (n = 66) and unsuccessful in 24% (n = 21) of patients. When dose interventions were unsuccessful, this was primarily because C_{min} levels were still below the target after the intervention (62%, n = 13). In the 40% of patients (n = 57) with $\geq$1 C_{min} level below the target who had no dose intervention, this was mostly due to DLTs (51%, n = 29). Median C_{min} before the dose intervention was 953 ng/mL, which increased to 1200 ng/mL ($p < 0.001$) after the intervention. DLTs were not correlated with dose interventions (p = 0.13; OR: 1.86, 95% CI: 0.83−4.16). **Conclusions:** This study confirms that personalized dosing of imatinib through TDM in GIST patients is feasible. Adequate drug concentrations improved from 16% to 54% of patients and interventions resulted in a clinically relevant drug concentration increase in patients who previously had C_{min} levels below the target. Comparison of treatment efficacy and toxicity in our cohort with a standard-dose historical cohort will elucidate the effect of personalized dosing through TDM on clinical outcomes (analyses ready before ASCO). Clinical trial information: NTR6866 — AND project number 11575. Research Sponsor: Ipsen; NA; GSK; NA; Novartis; NA; Pfizer; NA; Roche; NA; Dutch Cancer Society (KWF Kankerbestrijding); 11575.

11522 **Poster Session**

Personalized tumor-informed circulating tumor DNA analysis in monitoring recurrence following resection of high-risk locally advanced stage gastrointestinal stromal tumor. First Author: Zhidong Gao, Peking University People's Hospital, Beijing, China

Background: Gastrointestinal stromal tumor (GIST) is the most common mesenchymal tumor of the gastrointestinal tract. Radical resection is the standard treatment of localized GIST, yet the 5-year recurrence rate for high-risk GIST is more than 50%. It remains unclear whether detecting post-surgery molecular residual disease (MRD) via circulating tumor DNA (ctDNA) can predict the recurrence of high-risk locally advanced GIST. **Methods:** Patients with high-risk locally advanced stage GIST who underwent R0 surgery were enrolled prospectively. Surgical tissue samples were collected. Blood samples were collected pre-surgery, within 1-month post-surgery, and every 3–6 months thereafter. Tumor-derived variants were identified by whole-exon sequencing of the surgical tissues. Up to 50 highly ranked variants with allele frequency 3.0% were selected for the personalized panel design, which was subsequently used to assess MRD status. **Results:** As date cutoff of December 2024, 44 eligible patients were enrolled, among whom 42 tissue samples, 41 pre- and 166 post-surgical blood samples were collected and analyzed, and the median follow-up time was 21 months. Tissue-based sequencing identified variants in *KIT* and *PDGFRA* in 37 (84.1%) and 4 (9.1%) patients, respectively. Positive MRD was detected in 56.1% (23/41) of all pre-surgical plasma samples. Pre-surgical MRD positivity was associated with tumor volume, mitoses and Ki-67 ($P < 0.05$). Landmark analysis within 1 month post-surgery showed that 4 patients (4/41, 9.8%) were positive for ctDNA. Patients with positive MRD at landmark showed marginally worse DFS compared with those with negative MRD (HR = 4.24, 95% CI = 0.81-22.26, P = 0.07).To date, 7 patients have been detected recurrence by CT scan. Among the 4 patients with both radiological and MRD positivity, longitudinal ctDNA detected recurrence with lead-time of 3 months compared with CT scan for 2 patients. The other 2 cases are simultaneously. Notably, these 4 patients didn't receive regular adjuvant therapy. Furthermore, the longitudinal MRD positivity was associated with inferior DFS after adjusting sex, age, TNM stages and whether receiving adjuvant therapy in the multivariable cox regression (HR = 5.63, 95% CI = 1.09-28.99, P = 0.04). Additionally, 30 patients with consistent negative MRD during surveillance exerted significantly superior survival compared with patients whose MRD status converted to negative (n = 2), converted positive (n = 7) and remained consistently positive (n = 2) from landmark to longitudinal monitoring (P = 0.04). **Conclusions:** The present study suggests that personalized tumor-informed ctDNA has the potential to inform recurrence in high-risk locally advanced stage GIST patients, especially for patients who have not received regular adjuvant therapy. Clinical enrollment is still ongoing. Clinical trial information: NCT05408897. Research Sponsor: Beijing Bethune Charitable Foundation; Research and Development Fund of Peking University People's Hospital.

11523 **Poster Session**

The benefit of cytoreductive surgery during imatinib (IM) therapy in patients with metastatic gastrointestinal stromal tumors (mGISTs): Retrospective analysis from several cancer centers. First Author: Daria Filonenko, SBIH Moscow Clinical Scientific and Practical Center Named After A.S. Loginov of DHM, Moscow, Russian Federation

Background: the role of cytoreductive surgery for patients with mGISTs during IM therapy has not been established yet because the absence of randomized trials. We carried out a retrospective analysis of the outcome of patients with mGISTs in several Moscow cancer centers. **Methods:** we compared several cohorts: treated with IM only (IM group) and treated with IM and surgery, the latter was divided into four groups depending on the time of the surgery and the response to IM: before IM (BIM), after partial response or stable disease (RD), or unifocal progressive disease (UPD) or multifocal progressive disease (MPD). Patients received IM after surgery until progression. The primary end points were progression free survival and overall survival from the start of IM therapy. **Results:** 234pts with mGISTs from 2002 till 2024 received IM 400 in the first line. 116 pts received imatinib only, 118 patients underwent cytoreductive surgery: before IM (BIM, n=39) and during IM – on responsive disease (RD, n=23), unifocal progressive disease (UPD, n=22), and multifocal progressive disease (MPD, n=27). 7 patients were excluded from the analysis because they underwent surgery twice (before and during IM). Cytoreductive surgery increased the median PFS in comparison with IM only (Table). The differences were statistically significant between IM vs BIM – 24.0 vs 61.0 (p=0.028), IM vs RD – 24.0 vs 77.0 (p=0.003), and RD vs MPD – 77.0 vs 39.0 (p=0.005). Patients with UPD and MDP had a median PFS after R0/R1 and R2 was 17.0 vs 7.0 (p=0.564) and 14.0 vs 7.0 (p=0.056) months, respectively. Patient who underwent surgery on progression received IM after surgery for 10.0 and 11.0 months in UPD and MPD groups respectively what was two times longer than on sunitinib therapy (the median PFS 6.8 months, NCT00075218). On multivariate analysis for the entire cohort radiologic response was predictive for PFS: RD (hazard ratio (HR) 0.37, p = 0.003), UPD (HR 0.47, p=0.03) and BIM (HR 0.48, P = 0.009) were independent prognostic factors of better PFS; *KIT* exon 9 mutations (HR 2.68, p=0.003) and unknown location of primary tumor – factors of worse PFS. Overall survival was reached only in MPD group – 75.0 (95% CI: 37.14-112.87) months from the start of IM. **Conclusions:** cytoreductive surgery during IM therapy in responsive disease increase PFS; metastasectomy on UPD is likely to be beneficial for patients with mGISTs and it can be more effective option than the second line treatment. Research Sponsor: None.

			95% CI	
	PFS, median, months	Standard error	Lower bound	Upper bound
IM only (n=116)	24.000	4.459	15.260	32.740
Surgery before IM (n=39)	61.000	28.061	6.001	115.999
RD (n=23)	77.000	21.954	33.971	120.029
UPD (n=22)	70.000	25,077	20.849	119.151
MPD (n=27)	39.000	5.747	27.736	50.264

11524 Poster Session

In vitro profiling of IDRX-42 against secondary and tertiary mutations (AP/AL) found in TKI-resistant GIST. First Author: Michael C. Heinrich, Portland VA Health Care System and OHSU Knight Cancer Institute, Portland, OR

Background: The majority of Gastrointestinal Stromal Tumors (GIST) harbor a KIT mutation and respond to imatinib (IM), but over time clinical resistance emerges due to secondary mutations. These secondary mutations are restricted to two regions of the KIT protein: the drug/ATP binding pocket (AP, exons 13 and 14) and the activation loop (AL, exons 17 and 18). Although additional TKI drugs has been approved for later lines of therapy, these agents lack activity against the entire spectrum of known secondary resistance mutations. For example, sunitinib is potent against AP mutations (V654A, T670I), but has minimal activity against AL mutations. Recently, IDRX-42 has demonstrated promising activity in a phase 1/1b study of patients with TKI-resistant GIST. However, the cellular potency of IDRX-42 against various primary, secondary, and compound AP/AL KIT mutations has not been comprehensively described. **Methods:** We used a panel of GIST cell lines with various mutations that were derived from the parental GIST T1 cell line (primary KIT exon 11 (K11) deletion mutation). We also transiently expressed additional mutations in CHO cells. Densitometry and curve fitting was used to determine the biochemical IC50 for inhibition of KIT autophosphorylation, an accepted surrogate for KIT kinase activity. We also profiled IM and ripretinib (RIP) in the same cell line models. **Results:** IM was active against primary K11 mutations but was much less active against K11 + AP, K11 + AL, KIT exon 9 (K9), K9 + AP, and K9 + AL mutations. In addition, IM was inactive against K9 or K11 + AP/AL mutations (with all three mutations in cis). RIP potently inhibited K11, K11 + AL mutations, and K9 + AL mutations. However, RIP was less active against K11 + AP, K9 +AP, and K9 or K11 + AP/AL mutations. IDRX-42 was active against K11, K11 + V654A, K11 + AL, K9, K9 + V654A, and K9 +AL mutations. However, IDRX-42 lacked potency against the gatekeeper T670I (AP) mutation and K9 or K11 + AP/AL mutations. We developed resistant cell lines using GIST T1 cell line subjected to chemical mutagenesis and long-term drug selection with IDRX-42. All IDRX-42 resistant clones had an acquired T670I mutation, but no other secondary mutations were identified. **Conclusions:** IDRX-42 has superior biochemical potency against a panel of primary and secondary KIT mutations compared with IM or RIP. Additionally, IDRX-42 has activity against K9 or K11 + V654A, and K9 or K11 + AL; However, K9 or K11 with T670I mutant kinases were resistant. Notably, none of these three profiled drugs had activity against K9 or K11 + AP/AL mutations. The optimal clinical use of IDRX-42 may be in earlier lines of therapy, prior to the emergence of AP/AL mutations. Research Sponsor: None.

Biochemical IC50 for inhibition of KIT autophosphorylation.

Cells	Mutation	IDRX-42 (nM)	IM (nM)	RIP (nM)
GIST T1	K11	S	S	S
GIST T1	K11 + V654A	S	R	R
GIST T1	K11 + T670I	R	R	R
GIST T1	K11 + AL	S	R	S
CHO	K9	S	R	S
CHO	K9 + V654A	S	R	R
CHO	K9 + T670I	R	R	R
CHO	K9 + AL	S	R	S
CHO	(K9 or K11) + AP/AL	R	R	R

11525 Poster Session

15-year survivorship in patients with metastatic gastrointestinal stromal tumors. First Author: Julia A. Levy, Department of Internal Medicine, Oregon Health & Science University, Portland, OR

Background: Prior studies of metastatic gastrointestinal stromal tumors (mGIST) have largely focused on 5-year survival when evaluating long-term outcomes, but factors underlying longer-term survival remain less understood. This retrospective study aimed to identify factors associated with 15-year survivorship in patients with mGIST. **Methods:** Patients with mGIST treated at Oregon Health & Science University between 2003-2023 were identified from the Knight Cancer Registry. Data were abstracted through manual chart review. Patients were categorized into two cohorts: those who died before 15 years of follow-up, and those who survived ≥15 years following mGIST diagnosis. Chi-square and independent samples t-tests were performed to compare clinicopathologic variables between the two groups. **Results:** Of the 111 eligible patients (66 male [59.5%]; 45 female [40.5%]; median [IQR] age, 57 [46-71] years, 88.3% Non-Hispanic White), nineteen (17.1%) survived ≥15 years after mGIST diagnosis. Factors associated with 15-year survival were younger age at metastatic diagnosis (44 [32-56] vs. 60 [53-73], $p<0.001$) and metastasectomy (n=12 [63.2%] vs. 27 [29.3%], p=0.008). Most (68.4%) patients who underwent metastasectomy did so before they developed resistance to imatinib. Patients who underwent metastasectomy before developing resistance were more likely to achieve 15-year survival, however, this association was not observed in those who underwent metastasectomy after imatinib resistance. Patients who underwent metastasectomy also experienced a longer median time to imatinib resistance relative to those who did not (55 months vs. 23 months, p=0.001). **Conclusions:** This retrospective study supports that younger age at metastatic diagnosis and metastasectomy before the development of imatinib resistance are factors associated with 15-year survivorship in patients with mGISTs. These findings suggest that surgical resection of metastases in select patients may prolong the duration of imatinib response and potentially improve long-term outcomes. Research Sponsor: None.

Tumor and treatment factors associated with 15-year survivorship in mGIST.

Variable	Total (n=111)	15-year nonsurvivors (n=92)	15-year survivors (n=19)	p-value
Synchronous metastases	53 (47.7%)	43 (46.7%)	10 (52.6%)	0.64
Metachronous metastases	58 (52.2%)	49 (53.3%)	9 (47.4%)	0.7
Primary tumor size, cm (median, IQR)	8 (5.5-11.5)	8 (5.5-12)	8.1 (5.7-10.5)	0.79
Underwent metastasectomy	57 (51.4%)	42 (45.7%)	15 (78.9%)	0.008
Underwent metastasectomy before imatinib resistance	39 (35.1%)	27 (29.3%)	12 (63.2%)	0.04
Underwent metastasectomy after imatinib resistance	15 (13.5%)	12 (13.0%)	3 (15.8%)	0.75
Time to metastasectomy, months (median, IQR)	6 (16-42.5)	16 (6-41)	9 (4-86)	0.84
Development of imatinib resistance	69 (62.2%)	60 (65.2%)	9 (47.4%)	0.14
Time to imatinib resistance, months (median, IQR)	42 (22-81)	35.5 (20.5-63.3)	125.5 (95-149.5)	<0.00001

11526 Poster Session

Second-line treatment patterns and outcomes of advanced gastrointestinal stromal tumor: A real-world study. First Author: Xinhua Zhang, Department of Gastrointestinal Surgery, The First Affiliated Hospital, Sun Yat-Sen University, Guangzhou, China

Background: Ripretinib has emerged as a promising second-line therapy for patients with unresectable or metastatic gastrointestinal stromal tumors (GISTs), demonstrating comparable efficacy to sunitinib and a superior safety profile. However, the optimal second-line therapy tailored to individual patient characteristics remains underexplored. This prospective, multicenter, observational study (NCT05440357) aims to evaluate real-world patterns and outcomes for GISTs patients. **Methods:** The choice of second-line regimen was determined by the investigators. The primary endpoint was progression-free survival (PFS). Secondary endpoints included safety, objective response rate (ORR), and overall survival (OS). **Results:** From October 2022, 99 patients were enrolled (ripretinib, n = 49; sunitinib, n = 47; regorafenib, n = 3), with a median follow-up of 8.0 months. Among ripretinib-treated patients, 69% (34/49) had primary KIT exon 11 mutations, while 47% (22/47) of sunitinib-treated patients had primary KIT exon 9 mutations. The objective response rates were 20% (10/49) for ripretinib, 9% (4/47) for sunitinib, and 0% for regorafenib. Median PFS (mPFS) for ripretinib, sunitinib and regorafenib was 11.4, 12.4 and 2.8 months, respectively (p = 0.296). Ripretinib demonstrated better mPFS in patients with primary KIT exon 11 mutations compared to sunitinib group (11.4 vs 7.0 months, p = 0.048). In patients with KIT exon 9 mutations, mPFS was 15.0 months for sunitinib. Ripretinib was associated with fewer grade 3/4 treatment-emergent adverse events (TEAEs) compared to sunitinib (10%vs 26%, p = 0.044). OS data are currently immature. Additionally, 27% (13/49) of patients treated with ripretinib and 17% (8/47) with sunitinib underwent surgery. Among patients who underwent surgery following ripretinib treatment, 84.6% (11/13) achieved R0/R1 resection. 100% (8/8) patients achieved R0/R1 resection in sunitinib group. Median postoperative PFS for ripretinib and sunitinib was 15.5 months and 10.2 months, respectively (p = 0.350). **Conclusions:** This study is the first prospective, multicenter, real-world study to compare different second-line targeted drugs for advanced GISTs. Our preliminary results suggest that ripretinib may offer superior clinical benefits for patients with primary KIT exon 11 mutations after failure of imatinib first line treatment. Its favorable safety profile and improved tumor response rate facilitated a higher rate of surgical intervention compared to sunitinib. The benefit of surgery remains to be observed. Clinical trial information: NCT05440357. Research Sponsor: None.

11527 Poster Session

Long-term outcomes in GIST Trial 13-162: Phase II study of imatinib in combination with binimetinib in untreated patients with advanced gastrointestinal stromal tumor (GIST). First Author: Yudi Bao, Human Oncology and Pathogenesis Program, Memorial Sloan Kettering Cancer Center, Memorial Sloan Kettering Cancer Center, New York, NY

Background: ETV1 and KIT are lineage-specific master transcriptional and signaling survival factors in GIST. Dual lineage targeting of ETV1 by binimetinib and KIT by imatinib are synergistic in suppressing GIST tumorigenesis and growth in preclinical models. We previously reported positive data in a single-arm phase II study that the combination of binimetinib plus imatinib is highly effective with expected and manageable treatment-associated toxicities, in patients (pts) with treatment-naïve advanced GIST, (ASCO 2020 and https://ascopubs.org/doi/pdfdirect/10.1200/JCO.21.02029). Here, we present 10-year follow-up results. **Methods:** This trial is a single-center, single-arm, phase II study. Adult patients with unresectable or metastatic treatment-naïve GISTs received imatinib (400mg daily) and binimetinib (30mg twice daily), 28-day cycles. The clinical efficacy was evaluated using serial imaging every 8-12 weeks, per RECIST1.1 criteria including objective response rate (ORR), progression-free survival (PFS) and overall survival (OS). Correlatives included tumor genomics, transcriptomes, and imatinib trough levels. **Results:** At data cutoff of Nov 21, 2024, 29/42 evaluable pts with advanced GIST of all genotypes, including 3 *KIT/PDGFRA*-WT, had confirmed RECIST1.1 partial response (PR). Best ORR was 69.0% (95% CI, 52.9% to 82.4%). Median PFS (mPFS) was 36.7 months (95%CI, 24.2 to not estimable [NE]). Median OS (mOS) was 92.5 months (95%CI, 61.0 to NE), and the median DSS (mDSS) was 93.2 months (95%CI, 92.5 to NE). 23/42 pts had undergone surgery, with R0/R1 resection in 18 patients. 7 pts were considered exceptional responders, whose pathology revealed ≥90% significant pathological responses (SPR) and remained no evidence of disease (NED) after surgery ≥45 months. 3 pts who did not have SPR and remained NED ≥58 months. Transcriptome and genomic analysis, and imatinib trough level in the presence of binimetinib are forthcoming. **Conclusions:** The 10-year follow-up analysis of the binimetinib plus imatinib combination phase II study demonstrated robust and sustained clinical benefit in PFS, OS and DSS for patients with treatment-naïve advanced GIST. The combination strategy warrants further evaluation in direct comparison with imatinib in the frontline treatment of GIST. Clinical trial information: NCT01991379. Research Sponsor: Pfizer; FDA R01.

11529 **Poster Session**

Predicting transposable element-derived neoantigens in ATRX-mutated sarcoma. First Author: Simon Cao, UPMC Hillman Cancer Center, Pittsburgh, PA

Background: Epigenetic dysregulation is a key mechanism in cancer biology, driving both immune evasion and the generation of potentially druggable neoantigen targets. Transposable elements (TEs) are proviral sequences mostly found in epigenetically repressed genomic regions. In cancer, TEs are one potential source of neoantigens. The tumor suppressor gene *ATRX* is an epigenetic regulator that is lost in up to 30% of soft tissue sarcomas. Loss of function of this heterochromatin modulator leads to widespread alterations to transcription patterns. Our prior work in sarcoma, along with studies in other tumors, showed that ATRX loss leads to the de-repression of TEs. We hypothesize that this mechanism leads to TE neoantigen presentation on MHC class I (MHC-I) molecules. **Methods:** Leveraging the gEVE database of proviral sequences with open reading frames, we examined the differential expression of TEs using RNA sequencing of multiple models comparing ATRX lost and ATRX wild-type tumors. Analysis included our previously published data from human undifferentiated pleomorphic sarcoma cell lines (2 clones, 3 replicates per group; GEO: GSE240030) and a publicly available dataset from a mouse model of soft tissue sarcoma (n = 3 per group; GEO: GSE167537). Additionally, we analyzed analogous data from a mouse model of glioblastoma multiforme (GBM), another malignancy with frequent ATRX loss (n = 3 per group; GEO: GSE178113). RNA-seq data was analyzed using Salmon for transcript-to-genome pseudo-alignment, DESeq2 for differential TE expression analysis, and arcasHLA for sample-level MHC-I subtype identification. Differentially overexpressed TEs in ATRX mutant tumors were analyzed for predicted neoantigens using the NetMHCpan4.1 package. **Results:** Across multiple models, ATRX loss of function alterations were associated with both activation and repression of TEs. Within two sarcoma contexts, upregulated TEs were found to have protein-coding sequences with the potential to lead to MHC-I neoantigen presentation. Within a human undifferentiated pleomorphic sarcoma cell line with ATRX loss, there were 7 upregulated TEs shared between the clones, each predicted to contain 12 – 50 MHC-I binding epitopes. Within a mouse soft tissue sarcoma model, 7 TEs were upregulated with ATRX loss, each with 5 – 28 MHC-I binding epitopes. Since ATRX loss alters TE expression in other malignancies, parallel data from a mouse GBM model was additionally analyzed. In this model, 308 TEs were found to be upregulated with ATRX loss, and all were predicted to generate neoantigens. ERVs and LINE1 elements were recurrently identified, making up 97 – 100% of the activated TEs. **Conclusions:** Transposable element transcription altered by ATRX loss in sarcoma and GBM creates a predicted source of MHC-I-binding neoantigens. These neoantigens come from TEs of the ERV and LINE1 families. Research Sponsor: Damon Runyon Cancer Foundation; CI-124-23.

11530 **Poster Session**

Spatial and bulk transcriptomic analysis of skin Kaposi sarcoma lesions: Differences by disease characteristics. First Author: Quashawn Rakeem Chadwick, National Institutes of Health, Bethesda, MD

Background: Kaposi sarcoma (KS) is an angioproliferative tumor caused by Kasposi sarcoma herpesvirus (KSHV) that typically manifests as skin lesions. Other KSHV-associated disease (KAD) that can occur with KS include multicentric Castleman disease (MCD), primary effusion lymphoma (PEL) and KSHV-associated inflammatory cytokine syndrome (KICS). KS with concurrent KAD, which occurs frequently in people with HIV (PWH), contributes to morbidity and mortality. Novel sequencing technologies that evaluate archival KS may further our understanding of HIV-associated KS pathogenesis. **Methods:** Gene expression profiling of archival KS skin samples of 42 PWH was performed with the custom nCounter PanCancer ImmunoOncology panel with the addition of KSHV probes. Spatial RNA profiling was performed using GeoMx digital spatial profiling (DSP) platform on 4 formalin fixed paraffin-embedded tissue sections randomly selected from patients (pts) with concurrent KS and KAD. LANA, CD45, and CD31 expression in samples identified KS ($LANA^+$, $CD31^+$) and other areas of interest (AOIs) including vessels ($LANA^-$, $CD31^+$) and immune cells ($CD45^+$) on tissue sections. Gene Set Enrichment analysis was performed using R package ClusterProfiler. **Results:** Samples were taken from 42 men with HIV with a median age of 40 years. The median CD4 T cell count was 211 cells/ μl and a median HIV viral load of 27 copies/ml. Fifty-two percent of pts with KS had a concurrent KAD, most commonly KICS with KS (30%) followed by MCD with KS (19%). In nCounter analyses, samples from pts with KS alone demonstrated upregulation of STC1, a secreted glycoprotein, (log2FC=2.02, padj=0.001) and MKI67, a proliferation marker, (log2FC=1.11, padj=0.02) as compared to pts with KS and concurrent KAD. Pathway analyses highlighted reduced enrichment in specific cytokine activity profiles (padj = 0.01), natural killer cell activation markers (padj=0.02), and B cell proliferation (padj=0.004), in KS with concurrent KAD specimens. Cell deconvolution analyses showed increased abundance of CD8 T cells and regulatory T cells in KS alone specimens as compared to those with KS and other KAD. DSP of 4 samples of pts with KS and concurrent KAD (2 pts with MCD+ KS, 2 pts with KICS+ KS) identified higher expression of TSPAN (log2FC=1.32, padj=0.04) and LYVE1 (log2FC=1.82, padj=9.17e-5) in LANA+ tumor regions than vessel and immune AOIs, and lower ICAM1 (log2FC=-1.08, padj=3.95e-6), highlighting the role of virus-infected areas in oncogenesis and modulating immune activity. **Conclusions:** Sequencing data of archival HIV-associated KS samples highlighted distinct gene expression profiles by concurrent KAD, particularly in MCD or KICS, demonstrating disruptions in immune activity and increased cell proliferation thus shedding light on the molecular pathways driving KS pathogenesis and avenues for future targeted study. Research Sponsor: None.

11531 **Poster Session**

Early assessment of response to chemotherapy via ctDNA in soft tissue sarcoma. First Author: Maggie Yuxi Zhou, Stanford University School of Medicine, Department of Medicine, Stanford, CA

Background: Chemotherapy remains the cornerstone for treatment of soft tissue sarcomas (STS). Biomarkers are needed to enhance timely assessment of chemotherapy efficacy to limit toxicity and guide patient management including estimating prognosis and duration of chemotherapy. **Methods:** This retrospective study includes patients with STS who received chemotherapy in the neoadjuvant or unresectable/metastatic setting at Stanford Sarcoma Center between May 2021 and January 2025. ctDNA was tested with Natera's CLIA lab using a personalized, tumor-informed ctDNA assay (Signatera, bespoke mPCR, NGS assay). Longitudinal changes in peripheral blood ctDNA were correlated with radiographic response and survival. ctDNA response was defined as $>$ 50% decrease in MTM/mL from baseline, with a second confirmatory measurement. Radiographic response was defined as stable disease or partial response on first re-staging assessment after starting therapy. Overall survival (OS) was defined as time from initiation of chemotherapy to death or last clinical follow up. Progression-free survival (PFS) was defined as time from initiation of chemotherapy to radiographic disease progression, death, or last clinical follow up. **Results:** Twenty-six patients (median age at diagnosis = 63 years [range 26 – 78]) were included. Histological subtypes consisted of leiomyosarcoma (uterine [n = 10], extrauterine [n = 4]), malignant peripheral nerve sheath tumor (n = 2), undifferentiated pleomorphic sarcoma (n = 2), angiosarcoma (n = 2), and other (Ewing's sarcoma, malignant phyllodes tumor, perivascular epithelioid cell tumor, low grade myoepithelial carcinoma, high grade uterine sarcoma not otherwise specified, and small round blue cell neoplasm with EWSR1 rearrangement, each n = 1). Chemotherapy consisted of doxorubicin-containing regimens (n = 9), gemcitabine/docetaxel (n = 9), temozolomide-containing regimens (n = 5), and other (cyclophosphamide/topotecan, paclitaxel, and trabectedin, each n = 1). Median follow-up time after initiation of chemotherapy was 12.9 months. 16 of 26 patients had radiographic response. Substantial agreement was observed between ctDNA response and radiographic response (Cohen's kappa coefficient 0.752). Median OS was longer for ctDNA responders (n = 17) than non-responders (n = 9), at 43.8 months vs 20.6 months (p = 0.03). Median PFS was longer for ctDNA responders than non-responders, at 11.4 months vs 2.0 months ($p < 0.001$). In the metastatic cohort (n = 22), time on chemotherapy regimen was longer for ctDNA responders than non-responders, median 5.0 vs 2.6 months, p = 0.016 by Wilcoxon rank sum test. **Conclusions:** Early decline in ctDNA after initiation of chemotherapy correlates with radiographic response and survival in STS. Research is ongoing to evaluate these findings in a prospective study. Research Sponsor: None.

11532 **Poster Session**

Kaposi sarcoma herpesvirus (KSHV) subtypes and impact on survival in 107 patients with Kaposi sarcoma and other KSHV-associated diseases. First Author: Jose Mercado-Matos, National Cancer Institute, National Institutes of Health, Bethesda, MD

Background: Kaposi sarcoma herpesvirus (KSHV, also known as human herpesvirus 8) is an oncogenic virus that causes Kaposi sarcoma (KS), one of the most prevalent cancers in people with HIV (PWH) worldwide. KSHV also causes primary effusion lymphoma (PEL), a non-Hodgkin lymphoma, a plasmablastic variant of multicentric Castleman disease (MCD), and KSHV-associated inflammatory cytokine syndrome (KICS). KSHV-associated diseases (KADs) can occur alone or concurrently. The major KSHV genetic subtypes A, A5, B, C, D, E and F, based on the K1 open reading frame (ORF), are distributed by global region of origin. A and C genotypes are seen in Europe and North America whereas B and A5 variants are observed in Africa; D, E and F genotypes were described in isolated populations. There are limited data on the association between KSHV subtypes and survival outcomes. **Methods:** We investigated the ORF K1 subtype, disease characteristics, and impact on survival outcomes in 107 patients (pts) with KADs treated at the HIV/AIDS Malignancy Branch in the United States from 2010-2024. KSHV-DNA was extracted from peripheral blood mononuclear cells (PBMCs), KSHV-positive tissues and body fluids, including effusions. Extracted DNA was tested for KSHV using a CLIA-certified qPCR assay. Samples identified as KSHV-positive by qPCR were sequenced using either next-generation sequencing (NGS) or Sanger sequencing. **Results:** The cohort consisted of predominantly men (94%) and 55% were Black. Ninety-seven percent of pts had HIV (median CD4 count of 216 cells/mm3 and median HIV viral load 189,590 copies/mL). The most common KAD was KS (92%) followed by PEL (36%), MCD (23%), and KICS (22%). However, 64% had more than one concurrent KAD – 20% had KS and PEL. At the time of analysis, 39 (36%) pts were deceased, 26 (24%) had a PEL diagnosis. Seventy-nine percent of pts were from North America, 11% from Latin America and 9% were from sub-Saharan Africa; KSHV genotypes were consistent with a patient's geographic origin. Overall, the most common genotype was A (44%), 30% of pts with genotype A had KS alone and 30% had PEL+/-KS (Table). KSHV subtypes based on K1 did not impact survival outcomes (Global Log-rank P=0.9) overall. In 98 pts with KS with and without other KAD, KSHV subtypes did not affect survival but the presence of concurrent PEL as compared to MCD or KICS lead to worse survival in pts [Hazard Ratio: 7.9 (95% confidence interval: 3.4-18.2, $P<0.0001$)]. **Conclusions:** In this large cohort of pts with KS and other KAD, KSHV genotype was not associated with survival outcomes. Among pts with KS, concurrent KAD, such as PEL, led to poorer survival. This suggests that clinical manifestations rather than underlying viral variants impacted survival. Research Sponsor: None.

KSHV genotype prevalence (%) by KAD.

Overall %	A 44%	A5 8%	B 11%	C 26%	Dual infection 8%
KS	30	50	17	29	0
MCD +/- KS	11	0	17	14	22
PEL +/- KS	30	25	42	21	22
KICS + KS	17	25	17	29	33
MCD+PEL+/- KS	13	0	8	7	22

11533 Poster Session

Phase ib/II study of fluzoparib in combination with dalpiciclib in patients with locally advanced or metastatic sarcoma. First Author: Anqi Wang, Musculoskeletal Oncology, Sun Yat-Sen University Cancer Center, Guangzhou, China

Background: Poly ADP-ribose polymerase (PARP) plays a role in DNA damage repair, and PARP inhibitors can exert anti-tumor efficiency in tumors with homologous recombination repair defection (HRD). Cyclin-dependent kinase (CDK) plays an important role in cell cycle regulation. Rb is the direct substrate of CDK4/6, and Rb/E2F participates the HR-mediated DNA repair. Therefore, selective CDK4/6 inhibition can theoretically aggravate HRD and hinder DNA repair of tumor cells treated with PARP inhibitors. Combined of CDK4/6 and PARP inhibitors may provide a potential new drug strategy for sarcomas. **Methods:** FOUNDS is a 2-part, open-label, phase 1/2 study. Key inclusion criteria are: (1) 12-75 years old; (2) Locally advanced or metastatic sarcomas after first-line treatment, with at least one measurable lesion according to RECIST 1.1 criteria. Patients(pts) will receive fluzoparib (0.1 or 0.15 g po., qd, q4w) and dalpiciclib (0.1, 0.125 or 0.15 g po., qd, d1-21, q4w) continuously until progressive disease (PD) or intolerable toxicity occurred. Part 1 is intended to establish the recommended phase 2 dose (RP2D) using a i3+3 dose escalation design. Part 2 will examine the safety and efficacy of fluzoparib + dalpiciclib using the Simon minimax 2 stage design. The primary endpoint is the objective response rate (ORR). **Results:** In the escalation part, 12 pts (median age 22 years) were included. At the data cut-off (Jun. 10, 2025), the median follow-up time was 7.93 month (95% CI 7.03-8.83). The DCR per RECIST v1.1 is 12.5% including 2 pts who achieved a stable disease. The most common treatment-emergent AEs (TEAEs, ≥20%) were leukopenia, neutropenia, etc. 3 pts (25%) had grade ≥3 TRAEs and no drug-related AEs led to death. In Cohort 4, 1 pt experienced dose-limiting toxicity (DLT) of grade 3 thrombocytopenia, and the other 1 pt experienced DLT of severe stun. The RP2D was determined as Fluzoparib 0.1g bid. plus Dalpiciclib 0.15g qd, d1-d21, q4w. **Conclusions:** This novel combination therapy of CDK4/6 inhibitor and PARP inhibitor showed manageable toxicity that could provide a strategy for advanced or metastatic sarcoma. Part 2 to evaluate safety and efficacy is currently recruiting pts. Clinical trial information: NCT05952128. Research Sponsor: Jiangsu Hengrui Pharmaceutical Co., Ltd.

TRAEs with an incidence of ≥30% and any grade ≥3 TRAEs.

Cohort	1	2	3	4	Total
Dose every 4 weeks (q4w)	0.1g	0.1g	0.1g	0.15g	
Fluzoparib bid. + Dalpiciclib qd. d1-d21	+0.1g	+0.125g	+0.15g	+0.15g	
N	4	3	3	2	12
TEAEs, n (%)					
All grades	4(100)	3(100)	3(100)	2(100)	12(100)
Leukopenia	3(75)	3(100)	3(100)	1(50)	10(83)
Neutropenia	3(75)	2(67)	3(100)	1(50)	9(75)
Anemia	1(25)	1(33)	3(100)	2(100)	7(58)
Vomiting	2(50)	2(67)	1(33)	1(50)	6(50)
Thrombocytopenia	2(50)	2(67)	1(33)	1(50)	6(50)
Diarrhea	1(25)	1(33)	1(33)	1(50)	4(33)
Cough	1(25)	1(33)	2(67)	0(0)	4(33)
Fever	2(50)	1(33)	0(0)	0(0)	3(25)
Stun	0(0)	1(33)	1(33)	1(50)	3(25)
Grade ≥3	0(0)	1(33)	0(0)	1(50)	2(17)

11534 Poster Session

Advancing precision oncology in soft tissue sarcomas: The role of iTRAC in metastatic risk stratification and treatment personalization. First Author: Fred Chibon, INSERM U1037, Toulouse, France

Background: Soft Tissue Sarcomas (STS), known for their extensive Genomic instability (GIN), often result in poor clinical outcomes. Grading systems, such as FNCLCC, have limited prognostic accuracy in stratifying metastatic risk for STS patients. We introduce transcription-associated GIN indice (iTRAC) to improve prognostic precision and guide treatment decisions. **Methods:** This study analyzed 226 STS tumor samples using RNA sequencing (RNAseq) to assess breakpoint distribution from fusion transcripts as a surrogate for GIN. We calculated iTRAC to quantify transcription-associated GIN. Kaplan-Meier survival analysis were used to evaluate prognostic relevance in patients receiving or not chemotherapy. Multivariate analysis was performed to evaluate the iTRAC compared to FNCLCC and CINSARC for metastatic risk stratification. **Results:** STS patients with medium iTRAC level had the poorest metastasis-free survival (MFS) compared to low and high iTRAC levels. Importantly, patients with low iTRAC have a poorer outcome when treated with chemotherapy than those untreated, but at the contrary patients with medium iTRAC and treated by chemotherapy have a better outcome, raising the question of the potential predictive value of iTRAC for adjuvant chemotherapy in STS patients. FNCLCC and CINSARC groups did not show significant difference in MFS between treated and not treated patients. **Conclusions:** iTRAC is a novel biomarker for stratifying metastatic risk and guiding personalized treatment in STS. It outperforms molecular and histological prognosis systems like CINSARC and FNCLCC grade by revealing distinct MFS between patients receiving or not chemotherapy. This could enable better identification of patients who may benefit from chemotherapy and alternative options for those with poor responses. Prospective clinical trials are needed for validation and integration for patients care. Research Sponsor: None.

11536 Poster Session

Molecular subtyping and insights into sarcoma biology and prognosis. First Author: Aleksei Shevkoplias, BostonGene Corporation, Waltham, MA

Background: Sarcomas represent a diverse group of mesenchymal malignancies, with over 200 subtypes recognized by the WHO. This heterogeneity, combined with rarity, complicates diagnosis. Here, comprehensive molecular profiling and unsupervised clustering were applied to define sarcoma subtypes associated with differentiation, genomic events, and prognosis. **Methods:** Whole exome and transcriptome sequencing was performed on 1,046 sarcoma samples via the BostonGene Tumor Portrait test. Hierarchical expression-based clustering was integrated with somatic mutations, fusions, copy number alterations, genome segmentation, and signatures, validated on 23 external datasets (n = 1,678). **Results:** Nine molecular clusters (C1-C9) reflecting distinct biological patterns were identified (Table). Stable, lineage-restricted clusters included leiomyosarcoma (C2) marked by smooth muscle differentiation pathways and *TP53*, *ATRX*, and *RB1* mutations; vascular sarcoma (C7) with vascular signaling and angiogenic amplifications; synovial sarcoma (C6) defined by *WNT* activation and *SS18-SSX* fusions; and Ewing sarcoma (C9) characterized by neuronal development signatures and *EWSR1-FLI1* fusions. Clusters progressing toward undifferentiated pleomorphic sarcoma (UPS)-like phenotypes included liposarcoma (C3) progressing from adipocyte differentiation with *MDM2/CDK4* amplifications; chondrosarcoma/chordoma (C5) transitioning from cartilage development pathways with TGFβ activation; and bone and UPS-like (C1) characterized by angiogenesis signatures, genomic instability, *TP53* mutations, and the poorest survival (logrank $p < 0.05$). Molecular clusters predicted survival regardless of the specific diagnosis. For example, liposarcoma and leiomyosarcoma patients in cluster C1 had a worse prognosis than those in C2 with the same diagnosis. **Conclusions:** The proposed molecular subtypes simplify sarcoma classification, providing unique prognostic insights missing in the current diagnostic framework. These findings suggest molecular subtypes could offer valuable knowledge for sarcoma research and patient treatment. Research Sponsor: None.

Characterization of molecular sarcoma subtypes.

Cluster	Predominant diagnoses	Undifferentiation progression	Biology	Alterations (chi-sq $p < 0.01$)
C1	Bone and UPS-like	Progressing	Undifferentiated or nearly undifferentiated	*TP53* mutation (35%)
C2	Leiomyosarcoma	Stable	Smooth muscle differentiation	*TP53* (53%), *ATRX* (18%), *RB1* (15%) mutations
C3	Liposarcoma	Progressing	Adipocyte differentiation	*MDM2/CDK4* amplifications (45%)
C4		Progressing	Biologically diverse	
C5	Chondrosarcoma, chordoma	Progressing	Cartilage development	
C6	Synovial sarcoma	Stable	WNT activation	*SS18-SSX* fusions (68%)
C7	Vascular sarcoma	Stable	Vascular signalling, angiogenesis	
C8		Progressing	Biologically diverse	
C9	Ewing sarcoma	Stable	Neuronal development signatures	*EWSR1-FLI1* fusions (92%)

11537 Poster Session

Early on-treatment ctDNA dynamics and response by imaging in patients with sarcoma. First Author: Adrienne I. Victor, University of Rochester, Rochester, NY

Background: ctDNA holds promise as a prognostic and predictive biomarker for risk stratification and treatment response monitoring across multiple tumor types. However, the optimal timepoints and cutoffs for interpretation of ctDNA results are not well defined. Here we explored the ctDNA dynamics in patients with sarcomas on cytotoxic chemotherapy, with a focus on early time points to predict response. **Methods:** All sarcoma patients at the Wilmot Cancer Institute who had ctDNA (SignateraTM, Natera, Inc.) requested clinically from 03/01/22 – 12/31/25 were screened. Patients who had a positive baseline and at least 2 cycles of cytotoxic chemotherapy with serial ctDNA monitoring and response evaluation were selected for further analysis. Response was determined by imaging reports (CT, MRI, or PET) after 2-4 cycles of therapy. **Results:** One hundred and twenty-four patients were identified on initial screening, and 112 were able to generate a bespoke assay. Twenty-two patients met criteria for early on-treatment response analysis and 4 had results available from a second line of chemotherapy, for a total of 26 evaluations. Seventeen patients had metastatic disease while 5 were on neoadjuvant chemotherapy for high risk localized sarcomas. The most common sarcoma subtype was LMS (5), followed by undifferentiated small round cell sarcoma (Ewing, other EWSR1 fusions, BCOR; 4 patients), and osteosarcoma (3). Most patients, including those who progressed, showed some early decrease in ctDNA levels, but no patients whose ctDNA result converted to negative within the first two cycles progressed on the first reassessment. In this series a log10 fold change of -1.25 or greater by the end of cycle 2 separated responders and progressors. **Conclusions:** ctDNA is promising as an early biomarker of response across a wide variety of sarcoma subtypes and chemotherapy regimens. ctDNA dynamics may provide particular clinical utility in interpreting scans showing stable disease, as well as when response is difficult to capture on imaging, such as bony primaries or metastasis, or infiltrative malignancies such as angiosarcoma. Larger data sets and multi-institutional collaboration are needed to verify optimal time points and cutoffs for guiding patient care and interventional trials. Research Sponsor: None.

Log10 change in ctDNA from baseline at end of cycle 1 and cycle 2 chemotherapy by initial imaging response.

Initial Response	Cycle 1 median log change	Cycle 1 log change range	Cycle 2 median log change	Cycle 2 log change range
Progression	-0.17	-1.01– +0.16	-0.36	-1.23– +0.21
Stable disease (SD)	-0.18	ND (Not Detected) – +0.27	-0.88	ND – +1.00
Partial response (PR)	-1.62	ND – -0.21	-2.42	ND – -1.26
Complete response (CR)	-2.72	ND – -1.00	-3.12	ND – -2.35
PR + CR	-2.35	ND – -2.01	-2.08	ND – +1.00
SD + PR + CR	-1.80	ND – +0.27	-2.47	ND – -1.26

11538 **Poster Session**

MicroRNA-based biomarkers of outcome in soft tissue sarcoma treated with hypofractionated preoperative radiation therapy. First Author: Joanne B. Weidhaas, University of California, Los Angeles, Los Angeles, CA

Background: Soft tissue sarcomas (STS) are rare, aggressive malignancies with high variability in response to radiation therapy (RT). Our previous research in a small cohort who received preoperative hypofractionated RT (SBRT) on a phase II trial suggested that germline microRNA-based single nucleotide polymorphisms (mirSNPs) could identify patients at increased risk of major wound toxicity (MWT). This study explores the potential of this class of biomarker to predict MWT and additional outcomes to preoperative SBRT in STS. These findings could guide personalized treatment strategies and possibly the choice of RT regimen in the future. **Methods:** We analyzed 110 patients with high-risk extremity or trunk STS treated with five-day preoperative SBRT (30 Gy in five fractions). Over 100 mirSNPs were evaluated for their ability to predict RT outcomes, including late toxicity, MWT, distant metastases, and pathological response. Pathological response was defined as a necrosis score >= 70, late toxicity as grade >=2 at 2 years, and MWT as grade >= 3. Preliminary genetic models were developed using elastic net, random forest, and boosted tree algorithms and evaluated using leave-one-out cross-validation (LOOCV) performance metrics. mirSNPs were pre-filtered using Fisher or Jonckheere-Terpstra p-values (<0.2) for relevance to outcomes. **Results:** We developed preliminary genetic signatures to accurately predict 4 different outcomes in sarcoma patients undergoing preoperative SBRT: late toxicity (AUC=0.830), distant failure (AUC=0.775), pathological response (AUC=0.765), and major wound toxicity (AUC=0.736). Our pathological response genetic model has balanced sensitivity (0.750) and specificity (0.781), suggesting it could reliably predict which patients respond well to SBRT. **Conclusions:** Our study highlights the promise of mirSNP-based models in predicting STS outcomes to preoperative SBRT. By identifying patients with favorable versus unfavorable responses, these models could help identify patients who could be considered for preoperative SBRT versus standard fractionated radiation, as there may be fractionation-dependent radiation toxicity in sarcoma, as has been identified in other malignancies. Future directions include investigating associations among identified outcomes, inclusion of additional clinical variables, and comparison to toxicity with preoperative standard fractionated radiation. These efforts are significant steps towards paving the way for more personalized sarcoma care. Clinical trial information: NCT02701153. Research Sponsor: None.

LOOCV performance metrics in sarcoma data (n=110).

Outcome	Sensitivity	Specificity	PPV	NPV	F1 Score	AUC
Any Late Toxicity (Grade 2 at 2 Years)	0.786	0.875	0.478	0.966	0.595	0.830
Distant Failure	0.680	0.871	0.607	0.902	0.642	0.775
Path Response (Necrosis Score >= 70)	0.750	0.781	0.600	0.877	0.667	0.765
Major Wound Toxicity	0.667	0.805	0.595	0.849	0.629	0.736

11539 **Poster Session**

Circulating free DNA derived from active chromatin as a predictive biomarker for clinical benefit to checkpoint inhibitor-based therapies in metastatic leiomyosarcoma. First Author: Carlos Diego Holanda Lopes, Princess Margaret Cancer Centre – University Health Network, University of Toronto, Toronto, ON, Canada

Background: Leiomyosarcoma (LMS) is a common subtype of soft tissue sarcoma with a poor prognosis in the metastatic setting. LMS shows minimal benefit from monotherapy immune checkpoint inhibitors (CPI), however combinatorial CPI strategies may be effective in part due to tumor enrichment of epigenetic alterations. The DAPPER trial (NCT03851614) was a randomized, single center phase II study of durvalumab combined with olaparib or cediranib. Of the 30 LMS patients enrolled, 36.3% (n = 11) experienced disease stabilization or shrinkage. The present study aims to leverage a novel active chromatin cell-free DNA ($cfDNA_{ac}$) platform to investigate the epigenetic and genomic profiles of LMS patients in the DAPPER trial, with the goal of identifying biomarkers associated with clinical benefit from CPI-based therapies. **Methods:** Baseline plasma samples (n = 30) from LMS patients in the DAPPER trial were processed using a proprietary $cfDNA_{ac}$ capture assay that enriches active chromatin cfDNA. Following whole genome sequencing, univariate analysis and machine learning-based recursive feature selection were used to identify genomic features associated with clinical benefit rate (CBR, defined as RECIST v1.1 complete or partial response, or stable disease lasting > 6 months). **Results:** We identified 918 promoter and exon features that were significantly different ($p < 0.01$) at baseline and could segregate patients who achieved CBR from those who did not. Over-representation analysis of these gene features using Gene Ontology ($p_{adj} < 0.05$) showed enrichment in biological pathways associated with double-strand break repair, inflammatory response, and immune response - specifically T-cell receptor activation and signaling, and macrophage homeostasis in patients with CBR. **Conclusions:** This study highlights the utility of $cfDNA_{ac}$ profiling as a non-invasive method for identifying biomarkers that predict clinical benefit from CPI-based therapy in patients with advanced LMS. Further analyses are ongoing to evaluate whether the genomic-derived features correlate with other clinical outcomes, such as progression-free survival, overall survival, and orthogonal data (e.g. tumor tissue RNA-seq). Research Sponsor: None.

11540 **Poster Session**

Predictive gene signature for the efficacy of pazopanib in solitary fibrous tumor: A Spanish Group for Research in Sarcoma (GEIS) study. First Author: David Silva Moura, Health Research Institute-Fundación Jiménez Díaz University Hospital, Autonomous University of Madrid (IIS-FJD, UAM), Madrid, Spain

Background: Pazopanib was shown to be active in advanced Solitary Fibrous Tumor (SFT), with 58% and 51% of the typical and malignant/ dedifferentiated SFT patients, achieving an objective response by Choi criteria, in an international phase II clinical trial led by our team. Nonetheless, predictive biomarkers of pazopanib efficacy represent a clinical unmet need, to support the rational selection of this drug in this histology. We presented here a predictive transcriptomic-based signature for the efficacy of pazopanib in SFT. **Methods:** Patients enrolled in the GEIS 32 trial (ClinicalTrials.go ID: NCT02066285), testing pazopanib in two separate cohorts of SFT (typical and malignant/ dedifferentiated SFT), and with available tumor samples, were included in this study. Gene expression was assessed by direct transcriptomics, using the HTG EdgeSeq Oncology Biomarkers Panel (HTG Molecular Diagnostics, Inc.; Tucson, AZ, USA), according to manufacturers' instructions. Raw counts were normalized by variance stabilizing transformation (VST) using DESeq2. Univariate Cox regression analysis was performed to identify the genes significantly associated with progression-free survival (PFS; $p < 0.01$). These remaining genes were used as input to build a gene expression signature, using a multivariate Cox regression applying a Lasso penalty (10-fold cross-validation). Risk scores were calculated by multiplying the expression of every gene with its corresponding Cox regression coefficient. **Results:** A series of 40 patients was included for data analyses, with a median age of 64 years old, 62.5% being females, and a median follow-up from pazopanib treatment of 18 months. A total of 24 (60%), 14 (25%), and 2 (5%) patients were diagnosed with malignant, typical, or dedifferentiated SFT, respectively. The predictive signature of pazopanib efficacy was built with 18 genes, identified as significant in the univariate analysis, applying the Lasso penalty. This signature included 13 and 5 genes associated with resistance or sensitivity to pazopanib, respectively. Genes overexpressed and associated with low PFS of pazopanib included *CKS2*, *FANCA,* KPNA2, and *CXL14*, among others. Patients in the high-risk gene signature group (N = 23) showed a significantly worse PFS for pazopanib treatment, compared with patients in the low-risk group (N = 17): [5.6 months (95% CI 3.7-10.0) vs. 10.0 months (95% CI 6.5-NR), $p <= 0.012$; HR = 1.25 (95% CI 1.1-1.4, $p < 0.001$]. The cut-off calculated by MAXSTAT was 42.515. **Conclusions:** Our study identified a novel 18-gene-based signature that significantly predicts the efficacy of pazopanib in SFT patients. Future studies will focus on the prospective validation of this predictive gene signature. Research Sponsor: None.

11541 **Poster Session**

RNA-based fusion NGS panel testing for the improved classification of soft tissue sarcomas: A retrospective analysis. First Author: Suruchi Aggarwal, MedGenome Labs, Bangalore, India

Background: Accurate diagnosis of soft tissue sarcomas (STS) is critical for effective clinical management. The integration of genetic data enables precise tumor categorization, enhancing diagnostic accuracy. **Methods:** This study presents retrospective molecular classification data of 295 soft tissue sarcoma patients tested using a 110-gene Soft Tissue Sarcoma NGS panel developed at MedGenome Labs, Bangalore, India. The panel facilitates the simultaneous analysis of single nucleotide variants (SNVs), copy number variations, and RNA fusions in a single run. **Results:** Among the 295 cases, clinically relevant fusion or mutation was identified in 186 patients which led to the clarification or reassignment of diagnosis 45/186 (24%) of patients. Key reclassifications included 7 *BCOR*-rearranged sarcomas misdiagnosed as other sarcoma types histologically, 5 *EWSR1::FLI1* cases accurately identified as Ewing's sarcoma, and a myxoid liposarcoma case reclassified as Ewing-like sarcoma based on *EWSR1::TFCP2* fusion. Additional findings included two *HEY1::NCOA2* fusion cases reclassified as mesenchymal chondrosarcoma and a *TAF15::NR4A3* fusion case revised to extraskeletal myxoid chondrosarcoma from synovial sarcoma. Likewise, few other diagnosis revisions are highlighted in the table below. **Conclusions:** These results emphasize the diagnostic utility of broad-panel NGS testing with RNA-based fusion detection, underscoring its significant impact on the accurate classification and improved clinical management of STS patients. Research Sponsor: None.

Few STS types reclassified based on molecular findings.

Histologic Subtype (number of cases)	Molecular classification	Molecular event
Spindle Cell Sarcoma (1)	Dermatofibrosarcoma protuberans	*COL1A1::PDGFB*
Synovial Sarcoma (1)	Endometrial Stromal sarcoma	*ZC3H7B::BCOR*
Spindle Cell Sarcoma (1)	Inflammatory Myofibroblastic Tumor	*CLTC::ALK*
Sarcomatoid carcinoma (1)	Low grade fibromyxoid sarcoma	*FUS::TFCP2*
Angiosarcoma (1); Sarcomatoid Carcinoma (1); Undifferentiated Sarcoma (1)	Mucoepidermoid Carcinoma; Mucoepidermoid Carcinoma; Mucoepidermoid Carcinoma	*NUDT4::MAML2; NR1D1::MAML2; NR1D1::MAML2*
Spindle Cell Sarcoma (1)	Nodular Fascitis	*CALD1::USP6*
Low grade fibromyxoid sarcoma? Synovial sarcoma? (1); Osteosarcoma (1); Rhabdomyosarcoma (1)	Sclerosing Epithelioid Fibrosarcoma; Sclerosing Epithelioid Fibrosarcoma	*FUS::CREB3L1; EWSR1::CREB3L3; FUS::TFCP2*
High grade sarcoma with hemangiopericytomatous pattern (1); Spindle Cell Sarcoma (1)	Synovial Sarcoma; Synovial Sarcoma	*SS18::SSX1; SS18::SSX1*
Epithelioid sarcoma (1); Inflammatory Myofibroblastic Tumor (1)	Uncommon EWSR1 rearranged sarcoma; Uncommon EWSR1 rearranged sarcoma	*EWSR1::ZBTB44; ZC3H7B::EWSR1*
Fibrosarcoma (1)	Undifferentiated Mesenchymal tumours	*YAP1::KMT2A*

11542 Poster Session

Comprehensive molecular analysis of phase II trial of nivolumab in patients with recurrent or metastatic carcinosarcomas. First Author: Kum-Hee Yun, Division of Medical Oncology, Department of Internal Medicine, Yonsei Cancer Center, Yonsei University College of Medicine, Seoul, South Korea

Background: We conducted a single-center, prospective, phase II trial to evaluate the efficacy and safety of nivolumab, an anti-PD-1 immune checkpoint inhibitor, in patients with recurrent or metastatic carcinosarcoma who progressed after prior chemotherapy. Carcinosarcoma, a malignant neoplasm composed of both epithelial and mesenchymal elements, is a rare and aggressive tumor categorized as high-grade cancer by NCCN guidelines. Given the potential for nivolumab to selectively target PD-L1 overexpressing tumor cells, this study aims to identify patients who would likely benefit and orphan malignancy components. **Methods:** In this single arm phase 2 trial (NCT05224999), eligible patients had histologically confirmed metastatic and/or recurrent carcinosarcoma, measurable disease, 1-3 prior chemotherapy, and adequate renal/hepatic/hematologic function. Treatment consisted of nivolumab 3 mg/kg every 2 weeks. We compared the genomic and transcriptomic properties in our carcinosarcoma tissue with those in TCGA sarcoma, TCGA carcinoma, and TCGA uterine carcinosarcoma. **Results:** Between July 2020 and Nov 2023, 28 patients enrolled and received trial treatment. Of the 28 patients evaluable, 4 (14.3%) achieved confirmed partial response, and 11 (39.3%) had stable disease, yielding and disease control rate of 53.6%. The median PFS was 2.6 months. The pre-specified primary endpoint was met with 6-months PFR of 30.8%. NGS analysis revealed that carcinosarcoma shares molecular features with both carcinoma and sarcoma, while also exhibiting unique genetic and transcriptional profiles. While some molecular characteristics were common across all three tumor types, carcinosarcoma also displayed unique genetic alterations and transcriptional patterns, underscoring its distinct molecular identity. When comparing our genomic data to TCGA datasets, we observed overlapping mutations. In carcinosarcoma, frequently altered genes included TP53 (sarcoma), ZFHX3 (carcinoma), CHD4 (sarcoma), IRS1 (sarcoma), ARID1A (both), ABL1 (sarcoma), MED12, and PIK3CA (carcinoma). These findings suggest potential shared molecular mechanisms and emphasize the unique genomic landscape of carcinosarcoma. **Conclusions:** Carcinosarcoma comprises features shared with carcinoma and sarcoma, along with distinct characteristics unique to this tumour type. These findings highlight the distinct molecular landscape of carcinosarcoma and pave the way for more precise, biomarker-driven therapeutic approaches. Furthermore, patients were stratified based on the degree of molecular similarity to carcinoma or sarcoma, enabling exploratory analyses to assess the potential relationship between these stratifications and drug response. Clinical trial information: NCT05224999. Research Sponsor: None.

11543 Poster Session

Neutrophil-to-lymphocyte ratio as a clinical biomarker for immune checkpoint inhibitor response in advanced sarcoma. First Author: Gabriel Tinoco, Division of Medical Oncology, The Ohio State University, Arthur G. James Comprehensive Cancer Center, Columbus, OH

Background: As immunotherapy gains traction in sarcoma treatment, identifying biomarkers and understanding patterns of response to immune checkpoint inhibitors (ICI) remain critical. We expanded a prior cohort to investigate clinical factors, including the neutrophil-to-lymphocyte ratio (NLR) and its changes, in predicting outcomes such as overall survival (OS) and progression-free survival (PFS) in advanced sarcoma. **Methods:** Patients from The Ohio State University Sarcoma Clinics (2015–2023) were included in a retrospective ICI database. Data included treatment regimens (single-agent ICI or ICI+combination therapy) and clinical variables, particularly baseline and post-treatment NLR stratified into low (< 5) or high (≥ 5). Survival outcomes were analyzed using log-rank tests and Cox regression to assess OS and PFS. **Results:** A total of 192 patients met the inclusion criteria. Most were male (55%), and 83% had Stage 4 disease at ICI initiation. ICI was started as a third-line or later therapy in 52% of cases. The majority received single-agent ICI (57%), while 43% underwent ICI+combination therapy with other modalities (e.g., surgery, radiation, TKI). OS and PFS were similar between single-agent ICI and ICI+combination groups (OS: p = 0.419; PFS: p = 0.834), though clinical variables in the ICI+combination group may confound results. Median OS was 60 weeks, and median PFS was 40 weeks. Significant differences in OS and PFS were associated with NLR. Patients with lower NLR had improved OS ($p < 0.0001$). Among those with higher NLR at ICI initiation, OS improved with ICI+combination therapy (p = 0.039). After the first ICI cycle, the OS benefit persisted for patients with high NLR ($p < 0.0001$), regardless of treatment type. However, survival did not differ by treatment modality or by changes in NLR from baseline (p = 0.710). For PFS, patients with low NLR at ICI initiation had improved outcomes (p = 0.0002). Further analysis showed no PFS differences by NLR in the ICI+combination group. After the first cycle, the PFS benefit for low NLR persisted (p = 0.0006). Conversely, an increased NLR ratio from baseline to the first cycle was linked to worse PFS (p = 0.003), particularly in the ICI+combination group (p = 0.0029) but not in single-agent ICI (p = 0.8630). OS and PFS were not influenced by age, gender, or histology. **Conclusions:** NLR is a promising clinical biomarker for predicting response to ICI in advanced sarcoma. Low baseline NLR predicts improved OS and PFS, while changes in NLR may indicate progression risk. These findings warrant further prospective validation. Research Sponsor: None.

Variable	OS (p-value)	PFS (p-value)
Low vs. High NLR	<0.0001	0.0002
High NLR + Combination	0.039	0.834
NLR Change (Baseline)	0.710	0.003

NLR values.

11544 Poster Session

Pediatric patients with tenosynovial giant cell tumor: Real-world results from an observational registry. First Author: Sydney Stern, TGCT Support/Life Raft Group, Wayne, NJ

Background: Tenosynovial giant cell tumor (TGCT) is a rare, locally aggressive tumor originating in the synovial lining of the joint, bursa, and tendon sheath. Since TGCT typically impacts individuals 20-50 years of age, pediatric TGCT is ultra-rare. However, pediatric patients are often not included in clinical trials or prospective data. Real-world data are needed to understand the impact of TGCT on pediatric patients' quality of life and any differences between adults with TGCT. **Methods:** The TGCT Support Registry is an international, prospective registry initiated in 2022 by TGCT Support, a program of The Life Raft Group. The registry is the largest registry of patients with TGCT and records patient-reported demographic, pathologic, clinical information. This cross-sectional analysis presents data of patients $\leq$ 18 years of age at time of enrollment with Diffuse (D)-TGCT, Localized (L)-TGCT, or unknown subtype. **Results:** A total of 122 pediatric patients (9.5%) were included from a 1,278-patient registry (Table). Most patients were female (67.2%), had D-TGCT (73.0%), in the knee (83.6%), and a median age at diagnosis of 14.5 years. Symptoms reported were pain (94.3%), limited joint range of motion (89.3%), and swelling (84.4%). >50% of pediatric patients were initially misdiagnosed and were more likely to be misdiagnosed than adults (62.3% vs 49.9%, $p < 0.01$). 64.8% of pediatric patients were diagnosed by orthopedic surgeons, and 52.5% were diagnosed $\geq$1 years after symptom onset. Half of pediatric patients had joint aspirations to manage symptoms (47.5%) and non-steroidal anti-inflammatories were common (76.2%). Surgery was the predominant treatment modality and 61.5% reported that surgery occurred $\leq$ 3 months of diagnosis. Pediatric patients with D-TGCT underwent an average of 3.4 surgeries, compared to 1.8 surgeries for those with L-TGCT. 66.3% of pediatric patients with D-TGCT had $\geq$1 post-operative recurrence compared to 15.0% of L-TGCT pediatric patients. Most pediatric patients were referred to general orthopedic surgeons (80.3%), only a third consulted an oncology specialist, and 35.3% were also treated by pediatricians. Systemic therapies (i.e., imatinib, nilotinib, pexidartinib) were prescribed infrequently to pediatric patients with D-TGCT (17.2%). Pediatric patients reported that pain often interfered with daily activities and enjoyment of life. **Conclusions:** This real-world analysis highlights the significant disease burden of pediatric TGCT, as compared to adults, which severely affecting their quality of life. The reliance on surgical treatment and underuse of multidisciplinary care emphasizes the unmet need for provider education and treatment advancements tailored to this population. Greater efforts to develop systemic therapies specific to pediatrics are warranted to reduce recurrence rates and improve quality of life. Research Sponsor: None.

Characteristics of patients stratified by subtype (localized, diffuse, or unknown), including sex, age, region, location of disease, misdiagnosis, duration from symptom onset to diagnosis, average surgeries, recurrences, and use of systemic therapies.

	Diffuse (n=89, 73.0%)	Localized (n=20, 16.4%)	Unknown (n=13, 10.6%)	Total (N=122)
Female sex, n (%)	59 (66.3)	14 (70.0)	9 (69.2)	82 (67.2)
Median age at Diagnosis, years (range)	14 (3 - 17)	15 (4 - 17)	14.5 (7 - 15)	14.5 (3 - 17)
Median age at Enrollment, years (range)	16 (4-18)	17 (6-18)	15 (10-18)	16 (4-18)
Located in the US, n (%)	47 (52.8)	11 (55.0)	4 (30.8)	62 (50.8)
Location of disease, n (%)				
Knee	76 (85.4)	16 (80.0)	10 (76.9)	102 (83.6)
Hip	8 (9.0)	4 (20.0)	1 (7.7)	13 (10.7)
Ankle	5 (5.6)	0 (0.0)	0 (0.0)	5 (4.1)
Other*	0 (0.0)	0 (0.0)	2 (15.4)	2 (1.6)
Misdiagnosis, n (%)	56 (62.9)	10 (50.0)	10 (76.9)	76 (62.3)
Time from Symptom Onset to Diagnosis, n (%)				
<12 months	42 (47.1)	8 (40.0)	4 (30.8)	54 (44.3)
12–24 months	24 (27.0)	5 (25.0)	3 (23.1)	32 (26.2)
25–60 months	14 (15.7)	4 (20.0)	3 (23.1)	21 (17.2)
>60 months	6 (6.7)	3 (15.0)	2 (15.4)	11 (9.0)
Diagnosed during Surgery	3 (3.4)	0 (0.0)	1 (7.7)	4 (3.3)
Average surgeries, (SD)	3.4 (2.8)	1.8 (1.5)	1 (1.2)	2.9 (2.5)
Median	2	1	1	2
Systemic Therapy, *Checkall that apply*	20 (22.5)	0 (0.0)	1 (7.7)	21 (17.2)
Pexidartinib	7 (7.9)	0 (0.0)	1 (7.7)	8 (7.4)
Imatinib	12 (13.5)	0 (0.0)	0 (0.0)	12 (9.8)
Nilotinib	1 (1.1)	0 (0.0)	0 (0.0)	1 (0.8)
Local Recurrences, n (%)				
Yes	59 (66.3)	3 (15.0)	4 (3.8)	66 (54.1)
1 Recurrence	19 (21.3)	2 (10.0)	1 (7.7)	22 (18.0)
≥ 2 Recurrences	40 (44.9)	1 (5.0)	3 (23.1)	44 (36.1)
No	30 (33.7)	17 (85.0)	9 (69.2)	56 (45.9)
I have not had surgery	12 (13.5)	2 (10.0)	5 (38.5)	19 (15.6)
I am unsure	8 (9.0)	4 (20.0)	1 (7.7)	13 (10.7)

11545 Poster Session

IMM2510, an anti-PD-L1/VEGF bispecific antibody fusion protein, in patients with R/R STS: A phase Ib expansion study. First Author: Haiyan Xu, Shanghai Jiao Tong University Affiliated Sixth People's Hospital, Shanghai, Shanghai, China

Background: IMM2510 is a novel bispecific antibody fusion protein targeting PD-L1 and VEGF. The results of dose-escalation phase were previously reported. Here, we report further efficacy and safety of soft tissue sarcoma patients in cohort expansion stage. **Methods:** IMM2510-01 was a phase I, multicenter, open-label study designed to evaluate the safety, efficacy, recommended phase II dose (RP2D), and pharmacokinetics (PK) of IMM2510 monotherapy (NCT05972460). Dose escalation stage completed and administration of IMM2510 at 20mg/kg, Q2W was selected for cohort expansion. Advanced soft tissue sarcoma patients after prior systemic treatment failure were enrolled, including these with alveolar soft part sarcoma (ASPS), undifferentiated pleomorphic sarcoma (UPS), leiomyosarcoma (LMS) and synovial sarcoma (SS) patients. The primary endpoint was safety, tolerability and investigator assessed ORR. **Results:** As of 24 Dec 2024, 29 STS patients were treated in cohort expansion stage, including 10 with ASPS, 5 with UPS, 8 with LMS, 5 with SS and 1 with other STS subtypes. The median age was 45 and most patients (89.7%) were ECOG PS 1. The median number of prior systemic treatment was 2. Most patients (96.6%) experienced treatment-related adverse events (TRAEs), of which 3 (10.3%) were $\geq$ Grade 3. The most common TRAEs of any grade was infusion-related reaction (IRR) (37.9%), platelet decreased (31%) and AST increased (27.6%). TRAE of $\geq$ Grade 3 was reported in 3 patients, including 1 platelet decreased, 1 transaminase increased and 1 hypoaesthesia. No TRAE leading to treatment discontinuation was observed. Of 27 efficacy-evaluable STS patients, ORR was 7.4% and DCR was 55.6%. 2 PR and 4 SD with tumor shrinkage were observed. PRs were noted in the UPS and LMS cohorts, with an ORR of 20% and 14.3%, and a DCR of 60% and 42.9%, respectively. The DOR was not reached in UPS and 3.68 months in LMS. The study is ongoing. **Conclusions:** IMM2510 monotherapy demonstrated active anti-tumor activity in R/R STS patients with tolerable toxicity. Clinical trial information: NCT05972460. Research Sponsor: None.

11546 **Poster Session**

A pilot study of Janus kinase 1 (JAK1) inhibitor itacitinib for treatment-refractory sarcomas: Leiomyosarcoma cohort. First Author: Michael J. Wagner, Dana-Farber Cancer Institute, Boston, MA

Background: Sarcomas are a heterogenous group of mesenchymal tumors. Although variable, many sarcoma subtypes have a high proportion of infiltrating macrophages in their immune microenvironment. The JAK/STAT pathway is involved in immune cell regulation and may play a role in tumor immune resistance. Janus kinase 1 (JAK1) shifts tumor associated macrophages (TAM) to an inhibitory M2 phenotype. Inhibition of this pathway could improve anti-tumor immunity. **Methods:** This is an open-label, single agent, pilot study of the JAK1 inhibitor itacitinib in subjects with metastatic or advanced treatment-refractory sarcomas susceptible to immune infiltration by TAM (NCT03670069). Patients (pts) age 18 and older were enrolled in four cohorts: leiomyosarcoma (LMS), undifferentiated pleomorphic sarcoma (UPS) and related subtypes, synovial sarcoma and myxoid/round cell liposarcoma (MRCL), and chondrosarcoma. Itacitinib was given orally, 300 mg once daily, in a 28-day cycle. Primary endpoint was to assess changes in the macrophage population with itacitinib. Secondary endpoints included objective response rate using RECIST v1.1 criteria, progression free survival (PFS) at 3- and 6- months, and overall survival (OS) at 12-months. Response assessments were performed after cycle 2, and every other cycle thereafter. Research biopsies for pharmacodynamic markers were collected at baseline prior to C1D1 and prior to C3D1. Multiplex immunohistochemistry (mIHC) and transcriptomic analysis using Nanostring were performed on pre-treatment and on-treatment tumor specimens. We report the results from the LMS cohort. **Results:** 8 pts with LMS enrolled. OS rate at 12 months for the LMS cohort was 100%, median OS for LMS was 23 months. PFS rate at 3 months and 6 months for LMS was 75% and 38%, respectively. No objective responses by RECIST v1.1 were documented. 7/8 (87.5%) of pts with LMS had stable disease as best response. 7/8 LMS pts had paired tumor biopsies pre- and on-treatment. As expected, *STAT1* was significantly downregulated in on-treatment whole tumor lysates. Other genes that were significantly downregulated with itacitinib treatment were *CCR5, NFKB1, C1QB, CIITA, FCGR3A/B, CXCL10, and MAPKAPK2*. On mIHC, there was a general trend of decreased immune cell tumor infiltration (CD3, CD4, CD8, CD163, FOXP3, CD14, CD206) in on-treatment samples compared to pre-treatment samples, though differences were not statistically significant. **Conclusions:** Itacitinib demonstrated durable disease control in patients with LMS and warrants further study in this subtype. While our analysis of markers on paired biopsy samples does not suggest that immunotherapy combinations with itacitinib are likely to be successful for LMS, a more thorough analysis will be presented at the meeting as this data may still suggest potent combination therapies. Clinical trial information: NCT03670069. Research Sponsor: Incyte.

11547 **Poster Session**

Gamma secretase inhibitors and desmoid fibromatosis: Lessons from a real world, comprehensive genomic study of desmoids and *CTNNB1/APC* mutated soft tissue tumors. First Author: Steven Christopher Smith, Virginia Commonwealth University School of Medicine, Richmond, VA

Background: Recently, first-in-class FDA approval was granted in the U.S. for use of the gamma secretase inhibitor (GSI), nirogacestat, for adults with progressive desmoid fibromatosis. In tandem, the unpredictable clinical behavior of desmoids, which ranges from local aggression to regression, raises consideration of whether diagnostic and molecular variability underlie their varying biological potential. With an aim to understand both, and to explore the potential for biomarkers for GSI therapy selection, prediction, and prognosis, we performed a retrospective review of comprehensive genomic profiling and histology of desmoids and other soft tissue tumors harboring *CTNNB1* or *APC* mutations. **Methods:** Using real-world reference laboratory database of tumors submitted for clinical genomic assessment (Caris Life Sciences), we queried for samples with a diagnosis of desmoid fibromatosis, or for other neoplasms of soft tissue origin harboring *CTNNB1* or *APC* mutations. Samples underwent next-gen sequencing of (whole exome) to identify gene variants/copy number alterations and of RNA (whole transcriptome) for expression and fusion profiling. Findings were correlated with available clinical data and whole slide image histologic review. **Results:** We identified 74 tumors submitted as desmoid fibromatosis, of which 80% harbored *CTNNB1* and 15% harbored *APC* pathogenic or likely pathogenic variants. *CTNNB1* variants included codon 41 (58%), codon 45 (41%), and ubiquitin motif codon 36 (1%), while 91% of APC variants detected were in exon 16. Recurrent co-alterations were rare, involving *MUTYH* (heterozygous G396D) in 2 samples, and TMB-High (≥10 mutations/Mb) present in 3. Notably, 4 “desmoids” (5%) lacked characteristic mutations, one of which harbored *COL1A1::USP6* fusion, reclassified as nodular fasciitis. Among 76 soft tissue tumors diagnosed as other entities at analysis but found to harbor CTNNB1/APC mutations, 6 (all limited core biopsies), could be confidently reclassified as desmoids. The remaining 70 *CTNNB1/APC* mutant neoplasms were diverse, including synovial sarcoma (11%) and rhabdomyosarcoma (10%). **Conclusions:** Correlation of genomics and histopathology may allow identification of other tumor types misclassified as desmoid fibromatosis. Conversely, genomic correlation facilitated recognition of additional desmoids among tumors submitted with other diagnoses. The striking lack of secondary mutations seen in this large cohort with comprehensive DNA sequencing implies that other mechanisms explain and could predict their variable behavior, for which we are exploring paired transcriptome profiling data. Finally, subsets of diverse, other soft tissue neoplasms harbor *CTNNB1* or *APC* mutations, which may have implications for the design of future biomarker-selected Phase II basket trials. Research Sponsor: None.

11548 **Poster Session**

The global, regional, and national burden of soft tissue sarcomas and other extraosseous sarcomas, 1990-2021: A systematic analysis for the Global Burden of Disease study 2021. First Author: Venkatraman Radhakrishnan, Cancer Institute (WIA), Chennai, India

Background: Soft tissue and other extraosseous sarcomas (STS) are a diverse group of cancers whose global burden have not been comprehensively reported. This study aims to analyze the burden of STS across the lifespan globally, regionally, and by Sociodemographic Index (SDI) using the Global Burden of Diseases, Injuries, and Risk Factors Study 2021 (GBD 2021) estimates. **Methods:** The incidence, mortality, and disability-adjusted life-years (DALYs) due to STS from 1990 to 2021 were estimated using GBD 2021 methods. Funding for this research came from the Bill & Melinda Gates Foundation and American Lebanese Syrian Associated Charities. **Results:** In 2021, 96,200 (83,400-116,000) new cases of STS occurred globally (males: 52,300 [43,200-68,500], females: 43,900 [38,500-51,400]) and the global age-standardized incidence rate (ASIR) was 1.2 (1.0-1.4) per 100,000 person-years (males: 1.3 [1.1-1.7], females: 1.0 [0.9-1.2]). Among the pediatric population, the incidence rate was highest in the 0-4 age group, while in adults the incidence rate was highest in the 95+ age group. Deaths from STS were estimated to be 50,200 (43,200-61,300) globally (males: 27,200 [22,100-36,500], females: 23,000 [19,900-27,500]), with an age-standardized mortality rate (ASMR) of 0.6 (0.5-0.7) (males: 0.7 [0.6-0.9], females: 0.5 [0.5-0.6]). STS was responsible for 1,680,000 (1,430,000-2,120,000) DALYs in 2021 (males: 916,000 [732,000-1,31,000], females: 762,000 [654,000-947,000]). The global age-standardized DALY rate in 2021 was 20.5 (17.5-26.1) (males: 23.0 [18.3-33.0], females:18.3 [15.7-23.0]). Notably, in 2021, the low SDI quintile exhibited the highest ASMR of 0.9 (0.7-1.4) and age-standardized DALY rate of 33.4 (25.6-50.2). In contrast, the high SDI quintile had the highest ASIR of 2.0 (1.9-2.2). The ASIR remained stable globally between 1990 and 2021, whereas the ASMR and age-standardized DALY rates declined. **Conclusions:** Variations in the burden of STS were evident across different SDI levels. These findings offer insights into the distribution and discrepancies in STS burden on a global scale, which can aid policy efforts to alleviate the suffering caused by these cancers. Research Sponsor: None.

11549 **Poster Session**

Clinicopathologic features and outcomes of follicular dendritic cell sarcoma with or without Castleman disease: A large retrospective cohort analysis. First Author: Yoshito Nishimura, Division of Hematology and Oncology Mayo Clinic, Rochester, MN

Background: Follicular dendritic cell sarcoma (FDCS) is a rare neoplasm with a subset associated with unicentric Castleman disease (UCD). However, the impact of CD association on clinicopathologic features and survival outcomes remains unclear. This study aims to elucidate differences in disease characteristics and outcomes in FDCS with and without CD to guide future research and clinical practice. **Methods:** We retrospectively analyzed 41 FDCS patients seen at Mayo Clinic between January 2000 and December 2024. Patients were categorized into CD-related (n = 9) and FDCS-only (n = 32) groups. Demographic, clinical, pathological, and survival data were compared. Kaplan-Meier survival analyses were used to evaluate overall survival (OS) and progression-free survival (PFS). Epstein-Barr virus-associated inflammatory FDCS were excluded. **Results:** The CD-related group was younger at diagnosis (46.0 vs. 58.0 years, p = 0.041). Among those with CD-related FDCS, FDCS was diagnosed concurrently as CD in 6/9 (66.7%) and after the diagnosis of CD in 3/9 (33.3%). The FDCS-only patients were more likely to have extranodal disease (71.9% vs. 22.2%) and to have metastasis (62.5% vs 22.2%). One CD-related FDCS patient had paraneoplastic pemphigus. Among 11 patients with next-generation sequencing (NGS) results, 9 had pathogenic mutations. The most common pathogenic mutations included CDKN2A, CDKN2B, and TRAF3 copy number losses. Surgery was the preferred first-line intervention in FDCS-only and CD-related FDCS groups (19/32, 59.4% vs. 6/9, 66.7%). Eight out of 32 (25.0%) of the FDCS-only group received chemotherapy at first-line, most commonly Gemcitabine/Docetaxel or Adriamycin/Ifosphamide. While Gemcitabine/Docetaxel was the most preferred in the second line, different regimens were pursued in the third and later lines of therapy, including Pembrolizumab, Pazopanib, and stem cell transplant. Five out of 6 patients in the CD-related FDCS group received either adjuvant radiation or chemotherapy, which led to complete remission during the follow-up periods. The median follow-up was 22.4 months for the whole population. There was a trend for better OS and PFS among CD-related FDCS patients. The respective 2-year OS rates were 100% and 66.7%, and 2-year PFS rates were 57.1% and 43.1% for CD-related FDCS and FDCS-only patients, respectively. **Conclusions:** This study provides novel insights into clinicopathologic differences and survival trends for FDCS. Our data would suggest a less aggressive disease course among CD-related FDCS, which implies the need for different treatment strategies for CD and non-CD-related FDCS. Further research is warranted to elucidate these mechanisms, such as multi-omic analysis on benign FDC proliferation in the microdissected UCD areas and the adjacent FDCS cells to determine factors associated with progression to sarcoma. Research Sponsor: None.

11550 **Poster Session**

Molecular-genetic characteristics of soft tissue sarcomas associated with the development of chemotherapy resistance. First Author: Anastasia Alekseevna Tararykova, Federal State Budgetary Institution "N.N. Blokhin National Medical Research Center of Oncology" of the Ministry of Health of the Russian Federation (N.N. Blokhin NMRCO), Moscow, Russian Federation

Background: The development of resistance is the one of the reason for ineffective treatment of soft tissue sarcomas (STSs). The search for new molecular-biological targets, both for the personalized selection of novel targeted drugs and for predicting chemoresistance of STSs to individual antitumor agents and their combinations, is a pressing task. **Methods:** In this study, an experimental in vitro chemoresistance analysis, whole-genome sequencing, and single-cell sequencing of tumors in patients (N = 9) with undifferentiated pleomorphic sarcomas were performed. Chemotherapy resistance indices were determined for the obtained samples. **Results:** Whole-genome DNA sequencing yielded data on the type and frequency of somatic mutations in undifferentiated pleomorphic sarcomas, and driver genes of carcinogenesis were identified, among which the most frequently occurring were FCGBP, PARP4, TP53, RGPD3, PDE4DIP, and RB1. Correlations between the presence of genetic alterations and the response to chemotherapy in the in vitro test were sought. Thus, in samples resistant to the combination of doxorubicin and ifosfamide, the presence of mutations in the PEG3, USP8, NT5C3A, and WAS genes was characteristic. Bioinformatic analysis of single-cell transcriptome sequencing data, aimed at characterizing the population composition and transcriptomic landscape of undifferentiated pleomorphic sarcoma cells, revealed 15 normal and 8 tumor cell populations. Among the populations of normal cells, the following clusters were identified: M2 and M1 macrophages, T-cells, matrix-remodeling fibroblasts and myofibroblasts, monocytes, stromal cells, endothelial cells, and osteoblasts. Among tumor cells, clusters of proliferating cells, hypoxic cells, matrix-interacting cells, and tumor cells with a stem-like phenotype were identified. The most common clusters in all samples were M2 macrophages, endothelial cells, and one of the clusters of tumor cells interacting with the matrix. Comparison of the expression profiles of cells from patients with different responses to chemotherapy allowed identification and characterization of clusters associated with chemosensitivity and chemoresistance. These included clusters of macrophages, tumor cells, fibroblasts, and endothelial cells. In addition, genes common to all clusters associated with resistant samples were identified (ARGLU1, JUND, TNNT3, RHOB, CCNL2, LENG8, LUC7L3, KLF9, RSRP1, RNF213, SERPINE1, CDK5RAP3). **Conclusions:** The data obtained in this study will expand the understanding of the pathogenesis of undifferentiated pleomorphic sarcomas and the mechanisms underlying their development of chemotherapy resistance. In the future, this will serve as the basis for creating a test system to evaluate the expression levels of genes whose activation/repression is associated with the development of drug resistance in STSs. Research Sponsor: None.

11552 **Poster Session**

Overall survival from the open label phase 2 trial of palbociclib in patients with advanced well differentiated/dedifferentiated liposarcoma. First Author: Olayode Babatunde, Memorial Sloan Kettering Cancer Center - Fellowship (GME Office), New York, NY

Background: Liposarcomas (LPS) are among the most common soft tissue sarcoma subtypes. Well-differentiated (WD) and dedifferentiated (DD) LPS are characterized by CDK4 and MDM2 amplification. Both subtypes have variable sensitivity to chemotherapy. However, effective systemic treatment options remain limited for unresectable or metastatic disease. Our group previously reported two phase 2 trials of the CDK4/6 inhibitor (CDK4/6i) palbociclib (PD0332991) in advanced WD/DD LPS, which established proof-of-concept for targeting CDK4 in this disease. Palbociclib demonstrated prolonged progression-free survival (PFS) and was included in the NCCN Compendium for LPS. However, prospective data on overall survival (OS) in this population remain limited. We now report OS analysis approximately 8.5 years after the last patient was enrolled. **Methods:** Patients with advanced WD/DD LPS were enrolled in two non-randomized phase 2 trials of palbociclib: cohort A received 200 mg daily for 14 days on a 21-day cycle, while cohort B received 125 mg daily for 21 days on a 28-day cycle. Survival outcomes were analyzed using Kaplan-Meier methods, and baseline factors were evaluated for association with PFS and OS. Subsequent anti-cancer therapies, including surgery and systemic treatments, were recorded and analyzed. **Results:** Among 90 enrolled patients, 88 were evaluable for PFS. Median follow-up was 17 months for cohort A and 21 months for cohort B. Updated median PFS was 18.2 weeks (95% CI: 17.7–36.4 weeks) in cohort A and 18.8 weeks (95% CI: 12–23.4 weeks) in cohort B. Median OS was 25.6 months (95% CI: 17.2–40.0 months) in cohort A and 24.1 months (95% CI: 17.5–38.4 months) in cohort B. Across both cohort, patients with pure WD histology were underrepresented, comprising 15 of the 90 patients. Patients with pure WD histology demonstrated longer PFS compared to patients with DD or WD/DD histology (HR: 0.55; 95% CI: 0.30–0.99). However, no significant difference in OS was observed between histologic groups (HR: 0.64; 95% CI: 0.35–1.16). Surgery was performed on 35 patients (39%) post-palbociclib, of which 5 patients had pure WD histology. Analyses on subsequent therapies, including surgery and systemic treatments, will be presented at the meeting. **Conclusions:** This study provides updated long-term outcomes for palbociclib in advanced WD/DD LPS. Palbociclib demonstrated consistent PFS and OS across dosing regimens, offering a tolerable alternative to chemotherapy for patients who may not be candidates for cytotoxic agents. While PFS and OS outcomes remain modest, these data reaffirm the role of CDK4/6i in the management of this disease and underscore the need for novel therapeutic strategies. Future efforts should focus on biomarker-driven approaches and combination therapies to optimize outcomes in this challenging disease. Clinical trial information: NCT01209598. Research Sponsor: Kristen Ann Carr Fund; Nicholls-Biondi Fellowship.

11553 **Poster Session**

Clinical activity of immune checkpoint blockade in advanced perivascular epithelioid cell neoplasms (PEComas): A retrospective single center study. First Author: Daniel Reinhorn, Memorial Sloan Kettering Cancer Center, New York, NY

Background: Perivascular epithelioid cell tumors (PEComas) are rare mesenchymal neoplasms with limited therapeutic options. While therapies targeting the mTOR pathway have shown promise, with nab-sirolimus being the first FDA-approved treatment for this histology, most patients will eventually progress. The role of immune checkpoint inhibitors (ICIs) remains poorly defined in these patients. Here, we present a retrospective analysis of PEComa patients treated with ICIs at Memorial Sloan Kettering Cancer Center (MSKCC). **Methods:** We retrospectively reviewed all patients with histologically confirmed PEComa treated with ICIs at MSKCC between 2016 and 2024. Patient demographics, disease characteristics, molecular profiles, treatment details, and clinical outcomes were collected. Endpoints included real-world progression-free survival (rwPFS), overall survival (OS), time on treatment (ToT) and response rate. **Results:** Thirteen patients with advanced PEComa received ICIs. The median age was 62 years (Range: 16-87), with 62% female patients. Primary tumor sites included uterus (n = 2), gastrointestinal tract (n = 4), soft tissue/extremities (n = 3), thyroid (n = 1), bladder (n = 1), renal (n = 1), and liver (n = 1). The most common molecular alterations identified were TFE3 fusions (23%), TSC1/TSC2 mutations (15%), TP53 alterations (46%) and ATRX mutations (46%). Patients received a median of 2 lines of previous therapies (range 1-6), with all patients receiving mTOR inhibitors (nab-Sirolimus in 46%). Most patients (78%) had previously received chemotherapy (gemcitabine and/or anthracycline, 54% each). ICIs included pembrolizumab (n = 5), nivolumab (n = 2), nivolumab-ipilimumab (n = 4), pembrolizumab-lenvatinib (n = 1) and nivolumab-bempegaldesleukin (n = 1). Median ToT was 1.6 months (95% CI: 0.9-NE) with 31% (95% CI 14-70%) remaining on treatment at 3 months. Median rwPFS was 3 months (95% CI: 1.4-NE) with a 6-month PFS of 38% (95% CI: 19-76%). Median OS was 26 months (95% CI: 4.13-NE) with a 12-month OS of 59% (95% CI: 37-95%). Partial responses were observed in three patients (23%), with two achieving durable responses exceeding 18 months (one on pembrolizumab and one on nivolumab-ipilimumab). These long-term responders subsequently underwent local interventions for oligoprogressive disease and remained progression-free at last follow-up. Molecular analysis of responders showed distinct profiles: one had TFE3 fusion, another had TP53 deletion and RB1 mutation, while the third had NOTCH1 and FLT4 mutations. **Conclusions:** The observed response rate of 23%, including two durable responses, suggests that ICIs may be an effective treatment option for a subset of PEComa patients, regardless of molecular profile. Further studies to identify predictive biomarkers and optimal sequencing with mTOR inhibitors and other therapies are warranted. Research Sponsor: None.

11554 **Poster Session**

An update on the results of IBI110 (anti-LAG-3 antibody) plus sintilimab (anti-PD-1 antibody) in patients with advanced alveolar soft part sarcoma. First Author: Zhichao Tan, Department of Bone and Soft Tissue Tumor, Key Laboratory of Carcinogenesis and Translational Research (Ministry of Education/Beijing), Peking University Cancer Hospital and Institute, Beijing, China

Background: At the 2024 ASCO conference, we reported preliminary results on the efficacy and safety of IBI110 (anti-LAG-3 antibody) combined with sintilimab (anti-PD-1 antibody) in advanced alveolar soft part sarcoma (ASPS), which demonstrated an overall response rate (ORR) of 48.1%, including three complete responses (CRs). Here, we provide updated results from this single-arm, phase II trial. **Methods:** Eligible patients with metastatic or unresectable ASPS were assigned to two cohorts: cohort A (immune checkpoint inhibitor [ICI]-naïve, defined as no prior exposure to anti-PD-1/PD-L1/CTLA-4 antibodies) and cohort B (ICI-failed, defined as imaging-confirmed progression following anti-PD-1/PD-L1 therapy). Patients received IBI110 (200 mg) plus sintilimab (200 mg) intravenously every three weeks (Q3W). Primary endpoints were ORR and progression-free survival (PFS), assessed by investigators per RECIST v1.1, as well as safety. Secondary endpoints included overall survival (OS) and safety profile. **Results:** A total of 28 patients were enrolled (57.1% male; median age: 30.5 years; ECOG performance status 0: 100%; stage IV: 100%), with 20 patients in cohort A and 8 in cohort B. Responses were evaluable in 27 patients. The ORR was 51.8% across the entire population, including 4 CRs and 8 partial responses (PRs) in cohort A, and 2 PRs in cohort B. As of January 8, 2025, the median follow-up duration was 21.3 months (95% CI: 11.5–29.8). Median PFS and OS were not reached in the overall population (see Table). Treatment-related adverse events (TRAEs) occurred in all patients, with grade ≥3 TRAEs observed in 10 (35.7%) patients. Four TRAEs led to treatment discontinuation, including hemoptysis (n=2), type 1 diabetes mellitus (n=1), and encephalitis (n=1). No TRAE-related deaths were reported. Following discontinuation of LAG-3 antibody production in July 2024, patients achieving CR were advised to discontinue therapy, while those with PR or stable disease (SD) transitioned to sintilimab monotherapy. Notably, no disease progression was observed among these patients, including two who were previously resistant to sintilimab. Tumor microenvironment analysis in 17 patients (10 responders and 7 non-responders) revealed significantly higher LAG-3 density in responders compared to non-responders (P=0.021). **Conclusions:** The combination of IBI110 and sintilimab demonstrated promising efficacy in both ICI-naïve and ICI-failed advanced ASPS with an acceptable safety profile. The durable restoration of ICI efficacy persisted despite the discontinuation of combination therapy. LAG-3 expression may serve as a predictive biomarker for response to anti-LAG-3 therapy in ASPS. Research Sponsor: None.

Survival analysis.

Cohort	PFS (m)	OS (m)
A	Not reached	Not reached
B	14.9	25.4
Whole population	Not reached	Not reached

PFS: progression-free survival; OS: overall survival.

11555 **Poster Session**

Comprehensive molecular analysis of phase IB/II trial of durvalumab plus doxorubicin combination in patients with advanced soft-tissue sarcoma. First Author: Hyo Song Kim, Division of Medical Oncology, Department of Internal Medicine, Yonsei Cancer Center, Yonsei University College of Medicine, Seoul, South Korea

Background: We conducted an open-label, phase IB/II study to determine the activity and safety of the standard-of-care, doxorubicin in combined with the anti-PD-L1 immune checkpoint inhibitor, durvalumab, in patients with anthracycline-naïve soft tissue sarcoma (STS) and identified patients who would likely benefit from combination treatment. **Methods:** In this phase IB/II trial (NCT03798106), we enrolled patients with metastatic and/or recurrent STS had not received anthracycline chemotherapy and PD-L1/PD-1 inhibitor. Tumor biopsies were obtained from all patients prior to treatment for targeted sequencing, RNA sequencing, and Opal multiplexed immunofluorescence staining. **Results:** No DLTs were observed during the phase II and recommended phase II dose was defined at doses of 75/m^2 doxorubicin and proceed the phase II part. Of 41 evaluable patients, an objective response rate of 31.7% and the median progression free survival was 8.2 months (95% CI, 7.3-9.0) and median overall survival was 24.1 months (95% CI, 7.6-40.3). In the prespecified genomic analysis, using a multivariate Cox proportional regression model with clinical factors in combined with PD-1 cell density and signaling pathways, genetic alterations in RTK/RAS (HR 6.446, [95 % CI, 1.934-21.486]; P=0.002) and PD-1 density (HR 0.214, [95 % CI, 0.071=0.649]; P=0.006) were identified as the independent predictors of PFS. High PD-1 tumors without RTK/RAS pathway alteration had longer PFS (16.9 months) than the others (7.4 months for RTK/RAS alteration or PD-1 high, 1.0 months for RTK/RAS pathway alteration and PD-1 low group, $P<0.001$). In the gene set analysis, antigen processing and presentation, interferon alpha response, and interferon gamma response showed significantly higher scores in PD1 high without RTK/RAS pathway alteration. **Conclusions:** Durvalumab combined with doxorubicin demonstrated promising efficacy in an unselected STS cohort, with a manageable toxicity profile. In exploratory correlative analysis, we identified potential role of RTK/RAS signaling and PD-1 expression as independent predictors for the efficacy, although further investigations are needed. Clinical trial information: NCT03798106. Research Sponsor: None.

11556 **Poster Session**

Multicenter phase II study of anlotinib and toripalimab in patients with advanced soft tissue sarcoma (STS) and bone sarcoma (BS). First Author: Xing Zhang, Melanoma and Sarcoma Medical Oncology Unit, State Key Laboratory of Oncology in South China, Collaborative Innovation Center for Cancer Medicine, Sun Yat-sen University Cancer Center, Guangzhou, China

Background: This multicenter phase II study aims to evaluate the efficacy and safety of anlotinib combined with toripalimab in the treatment of patients (pts) with advanced STS or BS. **Methods:** Pts with advanced STS or BS, 14-70 years, at least one measurable tumor lesion per RECIST 1.1 and failure or intolerance of standard systemic therapy, or no standard treatment existed, are eligible. Pts with alveolar soft-part sarcoma (ASPS) and clear cell sarcoma (CCS) can be included as the first-line therapy. Anlotinib (12 mg/d, po, d1-14) and toripalimab (240mg, IV, d1) would be administered every 3 weeks. The primary endpoint was investigator-assessed objective response rate (ORR). The secondary endpoints include disease control rate (DCR), progression-free survival (PFS), overall survival (OS) and safety using NCI-CTCAE v4.03. **Results:** Between March, 2020 and November, 2024, 70 pts were enrolled, of whom 68 were evaluable for the efficacy analyses. The STS subtypes mainly included synovial sarcoma (SS, 15.7%), rhabdomyosarcoma (RMS, 8.6%), extraskeletal Ewing's sarcoma (EES, 7.1%), epithelioid sarcoma (EpS, 7.1%), leiomyosarcoma (LMS, 7.1%), ASPS (5.7%), liposarcoma (5.7%), undifferentiated sarcoma (5.7%) and others (31.4%). The BS subtypes included 2 (2.9%) osteosarcoma and 2 (2.9%) chondrosarcoma. With a median follow up of 29.1 months, partial response occurred in 19 pts: 4 with SS, 3 with ASPS, 2 with LMS, 2 with EpS, 2 with inflammatory myofibroblastic tumor, and one patient each with RMS, EES, undifferentiated sarcoma, CCS, malignant peripheral nerve sheath tumor, or desmoplastic small round cell tumor. The ORR and DCR for the entire cohort were 27.9% and 86.8%, respectively. The median PFS was 7.0 months (95% CI: 4.2-9.8). The median OS was 23.5 months (95% CI: 9.2-37.8). For the 64 efficacy-evaluable STS cohort, the ORR was 29.7% and the median PFS was 8.1 months (95% CI: 4.7-11.5). Most of the treatment-related adverse events were mild (grade 1-2). The most common grade 3/4 adverse events (AE) were hypertension (15.7%), hand-foot syndrome reaction (12.9%), and hypertriglyceridemia (7.1%). **Conclusions:** The combination of anlotinib and toripalimab showed good anti-tumor activity and durable efficacy in advanced STS patients, with acceptable toxicity. Clinical trial information: NCT04172805. Research Sponsor: None.

11557 **Poster Session**

Change in T2-weighted signal intensity, change in tumor volume, and exposure-response analysis in the RINGSIDE phase 2 study of varegacestat in patients with desmoid tumors. First Author: Mrinal M. Gounder, Memorial Sloan Kettering Cancer Center, New York, NY

Background: T2-weighted signal intensity (T2W) and tumor volume (TV) on MRI may be more sensitive than RECIST for assessing treatment effect in desmoid tumors (DT). On T2W images, hyperintense areas are associated with active fibroblast proliferation and hypointense areas are associated with loss of tumor cells and more collagenous tissue. The RINGSIDE Phase 2 study (NCT04871282) demonstrated arly and continued MRI changes in DTs with varegacestat (AL102) therapy. We report exploratory analyses of T2W, TV, and exposure-response (E-R). **Methods:** Eligible adults had histologically confirmed DT that had progressed ≥10% unidimensional growth in ≤18 months or DT-related pain requiring non-opioid medication. Participants (pts) were randomized to 3 oral varegacestat doses: 1.2 mg once daily (n = 14), 2 mg intermittent (n = 14) or 4 mg intermittent (n = 14) (intermittent = 2 days on, 5 days off). In the open-label extension (OLE), active pts received 1.2 mg once daily. We performed descriptive analysis of T2W, TV and RECIST sum of diameters (SOD), all of which were evaluated at screening, Week 16 and every 12 weeks thereafter. Linear correlations of best % changes from baseline on these assessments were evaluated with Pearson correlation coefficient. E-R modeling evaluated the time course of drug effect on TV to support selection of 1.2 mg once daily for further study. **Results:** As of April 10, 2024, median time on treatment was 23.1 months (range 0.7 – 26.6) and 23 of 42 (55%) enrolled pts were still on treatment. Line graphs of changes from baseline showed rapid and substantial reductions in T2W and TV. By Week 16, the median % changes in T2W, TV and SOD were -39%, -24%, and -8%, respectively. Median best % changes for T2W, TV and SOD were -90%, -84%, and -40%, respectively. Correlations were observed for best % changes in T2W vs SOD (R = 0.69), TV vs SOD (R = 0.82), and T2W vs TV (R = 0.89). In the 23 pts with PR/CR, median best % change was -96% (n = 21 evaluable) for T2W and -90% (n = 22 evaluable) for TV. In pts with SD, changes in T2W (n = 11 evaluable) ranged from +32% to -94%, with a median of -75%, and TV (n = 12 evaluable) ranged from +71% to -86%, with a median of +7%. Preliminary E-R analysis predicted median time to 30% decrease in TV of 3 months with the 1.2 mg once daily regimen. **Conclusions:** Substantial early and rapid reductions in T2W and TV on MRI preceded eventual RECIST responses in adults with DT treated with varegacestat. These data add to a growing body of work showing T2W and TV may play a role in evaluating treatment response in DT. Future research should evaluate the prognostic or predictive value of these imaging techniques in DT and standardization to allow for use in clinical management of DT patients. Clinical trial information: NCT04871282. Research Sponsor: Immunome.

11558 **Poster Session**

Long-term clinical outcome assessments in patients with tenosynovial giant cell tumor treated with vimseltinib: 1-year results from the MOTION phase 3 trial. First Author: Vivek A Bhadri, Chris O'Brien Lifehouse, Camperdown, NSW, Australia

Background: Tenosynovial giant cell tumor (TGCT) is a locally aggressive neoplasm caused by dysregulation of the colony-stimulating factor 1 (*CSF1*) gene leading to overproduction of CSF1. Patients with TGCT often report substantial pain and stiffness, impaired physical function, and limited range of motion (ROM), supporting the need for an effective, well-tolerated CSF1 receptor (CSF1R)-targeted therapy that provides long-term improvements in functional health and quality of life (QoL). Vimseltinib is an oral, switch-control inhibitor of CSF1R. In part 1 of the MOTION phase 3 trial, vimseltinib showed statistically significant and clinically meaningful improvements vs placebo in tumor response as well as clinical outcome assessments (COAs; active ROM and patient-reported outcomes [PROs]) in patients with TGCT not amenable to surgery at week 25 (Gelderblom H, et al. *Lancet*. 2024). Here we report 1-year COA results from MOTION. **Methods:** MOTION is a global, phase 3 trial composed of double-blind (part 1; to week 25), open-label (part 2; week 25–49), and extension periods (NCT05059262). Patients received vimseltinib 30 mg twice weekly. COAs reported here include change from baseline in active ROM of the affected joint, physical function (PRO Measurement Information System physical function score [PROMIS-PF]), stiffness (worst stiffness numeric rating scale [NRS]), health status (EuroQol Visual Analog Scale [EQ-VAS]), and pain (brief pain inventory [BPI] worst pain). BPI worst pain response rate is also reported with response defined as ≥30% decrease in worst pain without ≥30% increase in narcotic analgesic use. Results are reported in patients randomized to vimseltinib during part 1 whose 1-year (week-49) assessments were complete at data cutoff (Feb 22, 2024). **Results:** Of 83 patients randomized to vimseltinib in part 1, 73 continued treatment in the open-label part of the study. Consistent with results from part 1, COAs at 1 year continued to show improvement from baseline. Mean (standard error [SE]) change from baseline in active ROM was 14.9 (5.0) percentage points. Mean (SE) changes from baseline in PROMIS-PF, worst stiffness NRS, and EQ-VAS were 6.5 (1.2), −2.7 (0.4), and 11.0 (3.5) points, respectively. Mean (SE) change from baseline in BPI worst pain was −2.8 (0.4) points, and the BPI worst pain response rate was 40% (33/83; 95% confidence interval, 29 to 51). **Conclusions:** These 1-year COA results from the MOTION phase 3 trial demonstrate durable and continued improvements in active ROM, physical function, stiffness, health status, and pain with ongoing vimseltinib treatment. Continued treatment with vimseltinib provides clinically meaningful benefit in functional health and QoL beyond week 25 for patients with symptomatic TGCT whose disease is not amenable to surgery. Clinical trial information: NCT05059262. Research Sponsor: Deciphera Pharmaceuticals, LLC.

11559 **Poster Session**

Daily low-dose oral temozolomide as maintenance therapy following doxorubicin plus dacarbazine in advanced leiomyosarcoma patients: An observational study. First Author: Zhichao Tan, Department of Bone and Soft Tissue Tumor, Key Laboratory of Carcinogenesis and Translational Research (Ministry of Education/Beijing), Peking University Cancer Hospital and Institute, Beijing, China

Background: Doxorubicin (Dox) combined with dacarbazine (DTIC) is a standard first-line regimen for advanced leiomyosarcoma (LMS), but its long-term use is restricted due to potential cardiac toxicity. Although the addition of trabectedin to Dox, followed by trabectedin maintenance, has demonstrated improved overall survival (OS) and progression-free survival (PFS), trabectedin's limited availability in China poses a significant challenge. Given that both temozolomide (Tem) and DTIC convert to the same active metabolite (MTIC) in the body, we investigated the efficacy of daily low-dose Tem as maintenance therapy following Dox plus DTIC. Here, we present the results of this observational study. **Methods:** Eligible patients with metastatic or unresectable LMS received up to six cycles of Dox (60-70 mg/m², day 1) or pegylated liposomal Dox (PLD, 35–45 mg/m², day 1) combined with DTIC (0.9–1.2 g/m², day 1) every three weeks. Patients without progression after six cycles of Dox/PLD plus DTIC were transitioned to maintenance therapy with daily oral temozolomide (75 mg/m²). Maintenance Tem was continued until disease progression. The primary endpoint was PFS during maintenance, assessed by investigators. Secondary endpoints included OS and safety. PFS and OS were defined as the time from initiation of oral Tem until disease progression and death, respectively. **Results:** Between May 2022 and December 2024, 20 patients were enrolled, with a median age of 55 years. All patients were female. The primary tumor site was uterine in 45% of cases and non-uterine in 55%; 90% had metastatic disease, and 10% had locally advanced disease. Seventeen patients were evaluable for efficacy. The median PFS during maintenance was 7.1 months, with three patients achieving disease control for over 12 months. Treatment was generally well-tolerated, with the most common adverse events (AEs) being grade I/II nausea (80%), vomiting (45%), and white blood cell reduction (25%). Serious AEs leading to treatment discontinuation occurred in two patients: one due to severe vomiting and one due to elevated liver enzymes. **Conclusions:** Daily low-dose oral temozolomide appears to be an effective and well-tolerated maintenance therapy following Dox plus DTIC for patients with advanced LMS. This approach may offer a viable alternative for patients in regions where trabectedin is unavailable. Research Sponsor: None.

11560 **Poster Session**

A phase II, multicenter trial of the combination of chidamide and toripalimab in patients with advanced soft tissue sarcoma: Efficacy updates. First Author: Xing Zhang, Melanoma and Sarcoma Medical Oncology Unit, State Key Laboratory of Oncology in South China, Collaborative Innovation Center for Cancer Medicine, Sun Yat-sen University Cancer Center, Guangzhou, China

Background: Chidamide is an oral subtype-selective histone deacetylase (HDAC) inhibitor which is effective on the patients with hematological tumors and could be hoped to enhance the efficacy of checkpoint blockade therapies and regulate the host immune response. Here, we report the updates of preliminary results of the combination of Chidamide and Toripalimab in soft tissue sarcoma (STS) patients. **Methods:** An open-label, single arm, multicenter, phase II study of Chidamide with Toripalimab in patients with advanced STS was conducted. Patients who were with failure or intolerance of standard systemic therpy, or no existed standard treatment, are eligible. Patients who had underwent HDAC inhibitors and immune checkpoint inhibitors treatment were excluded. All patients received Chidamide orally at 30mg twice weekly in combination with intravenous Toripalimab 240mg every 21 days until progression or unaccepte toxicity. The primary endpoint was RECIST1.1 objective response rate (ORR). The secondary endpoint included progression free survival (PFS), overall survival (OS), disease control rate (DCR) and safety. **Results:** At the data cut-off date (January, 2025),sixty-nine patients with advanced STS were enrolled. The median age of the patients was 47 years (range, 16 to 68) and the median prior lines of therapy were 2 (range, 0 to 5). The main subtypes included leiomyosarcoma (29%), well/dedifferentiated liposarcoma (36.2%), undifferentiated sarcoma(7.2%), myxoid/round cell liposarcoma (4.3%), and osteosarcoma (4.3%). Treatment was well tolerated with the most common adverse events mainly in grade 1-2, including anemia(55.1%), hypothyroidism(44.9%), leukopenia(33.3%), thrombocytopenia (30.4%), neutropenia(24.6%), nausea/vomit(24.6%), and fatigue (15.9%). Of the grade 3–4 adverse events, the most common were neutropenia(27.5%), thrombocytopenia (23.2%), leukopenia(14.5%), nausea/vomit(10.1%) and anemia(1.4%). Among 69 efficacy-evaluable patients, the ORR and DCR were 29% and 73.9%, respectively. The median time to an initial response was 5 months (95%CI 3-7), and the median PFS was 7.1 months (95%CI 4.0-10.2) , and the median OS was not reached. **Conclusions:** Chidamide with Toripalimab every 21 days was well tolerated and showed promising efficacy in patients with advanced STS. The exploratory biomarker study is ongoing. Clinical trial information: NCT04025931. Research Sponsor: None.

11561 **Poster Session**

Detecting hotspots of intra- and transchromosomal fusions in liposarcomas by RNA sequencing. First Author: Dmitrii Grachev, BostonGene, Corp., Waltham, MA

Background: Liposarcoma (LPS) is characterized by unstable genomes and high occurrence of gene fusions. Hotspots of both recurrent and non-recurrent gene fusions can provide information about structural alterations in certain LPS subtypes. For instance, myxoid (M) LPS expresses the oncogenic *FUS-DDIT3* protein and is known to be fusion-driven. Moreover, disrupted locus 12q13-15 is an important feature of well-dedifferentiated (WD) and dedifferentiated (DD) LPS, and is the site of copy number alterations (CNAs) and gene fusions. Here, we used RNA sequencing to uncover hotspots of intra- and transchromosomal gene fusions in LPS patient samples, identifying potentially clinically relevant events in certain chromosomal regions. **Methods:** The BostonGene internal LPS cohort (n=150) was analyzed by bulk whole-transcriptome sequencing, using STAR-fusion for sequence calling. Quality control was performed using FastQC, FastQ Screen, RSeQC, and MultiQC. Tumor purity was assessed via pathological and bioinformatics examination with a threshold of 20%. One sample Poisson rate test was used to evaluate statistical significance of gene fusion hotspots. **Results:** We identified 4,080 gene fusions among four LPS subtypes (DDLPS, WDLPS, MLPS, and PLPS - pleomorphic LPS). Of those, 2,302 (56.4%) were intrachromosomal and 1,778 (43.6%) were transchromosomal. Over half of these fusions (1,263/2,302 intrachromosomal fusions, 54.9%; 1,047/1,778 transchromosomal fusions, 58,9%) were detected on chromosome 12. Most identified fusions occurred in the 12q13-15 region (q-value < 0.001), with q15 being especially prevalent in transchromosomal fusions (q-value < 0.001). The most prevalent recurrent fusion across our LPS cohort was *FUS-DDIT3* (N=21, MLPS samples). Another notable recurrent fusion was *TRIO-TERT* (N=4, DDLPS). We also identified extended gene fusion hotspots in regions containing important oncogenes such as *MDM2* and *FRS2* in LPS subtypes (DDLPS, WDLPS, PLPS) that are not considered fusion-driven (Table). These findings suggest an oncogenic role of such fusions in these LPS subtypes, along with known CNAs like *MDM2* amplification. **Conclusions:** Our comprehensive transcriptomic analysis of gene fusions in LPS samples uncovered both new and established hotspots of chromosomal rearrangements. Identification of such hotspots improves our understanding of LPS oncogenesis and thus can enhance the diagnostic accuracy and discovery of new biomarkers. Research Sponsor: None.

Hotspots of gene fusions in liposarcoma.

Hotspot cytoband	Diagnosis	q-value	Important genes
1q23.3	DDLPS	< 0.001	*ATF6*
1q24.3	DDLPS, WDLPS	< 0.001	*DNM3*
12q13.3	MLPS	< 0.001	*DDIT3*
12q14.1	DDLPS, WDLPS	< 0.001	*CDK4*
12q14.3	DDLPS, WDLPS	< 0.001	*HMGA2, YEATS4*
12q15	DDLPS, WDLPS, PLPS	< 0.001	*MDM2, FRS2, CPM*
16p11.2	MLPS	< 0.001	*FUS*

11562 **Poster Session**

Treatment discontinuation in desmoid tumors: Factors associated with better outcomes after sorafenib discontinuation. First Author: Irvin Yi, Yale School of Medicine, New Haven, CT

Background: Sorafenib has shown effectiveness in managing desmoid tumors. However, the optimal duration of systemic therapy and the outcomes following its discontinuation remain unknown. This study investigates the outcomes of patients who discontinued sorafenib, aiming to provide guidance for clinicians on treatment cessation. **Methods:** We conducted an international, multi-institutional retrospective analysis of patients treated with sorafenib who discontinued therapy with no immediate plans to initiate a new treatment. We assessed whether the duration of sorafenib use (6 months, 1 year, or 2 years), the reason for discontinuation (side effects or shared decision-making), and the treatment response at the time of discontinuation influenced the likelihood of requiring subsequent treatment (treatment free survival, TFS) or experiencing disease progression (progression free survival, PFS). Kaplan-Meier curves were used for survival analysis, and group comparisons were performed using the log-rank test. **Results:** Between 2005 to 2022, a total of 48 patients were identified meeting the eligibility criteria. Three (6%) patients received therapy for less than 6 months, thirteen (27%) received less than 12 months, and thirty (63%) received less than 24 months. Seventeen (35%) patients stopped therapy due to side effects with the remaining thirty-one (65%) patients discontinuing due to other reasons, such as patient preference, provider decision, or payment coverage. Four (8%) patients experienced progression of disease while 38 (79%) had stable disease or partial response. The most common side effects were diarrhea (52%), palmar-plantar erythrodysesthesia syndrome (46%), and fatigue (23%). Patients who received less than 6 months of sorafenib treatment prior to discontinuation had a TFS of 10.1 months, compared to 54.5 months for over 6 months of duration ($p < 0.001$). At the 12-month mark, less than 12 months had median TFS of 49.1, compared to 54.5 for longer ($p = 0.2$). At the 24-month mark, less than had a median TFS of 49.1, compared to 54.5 for longer ($p = 0.1$). Other factors did not emerge as statistically significant ($p > 0.05$). **Conclusions:** Our data demonstrates the duration of sorafenib treatment is a significant indicator for future treatment need. Reaching the 6-month mark could be indicative of an important checkpoint, although the 1- and 2-year marks are also associated with a clinically, but not statistically, significant reduction in likelihood for future treatment. Clinicians and patients should be aware that duration is an important consideration for future outcomes in desmoid tumor treatment, and to factor it into shared decision-making. Research Sponsor: None.

11563 **Poster Session**

Safety and antitumor activity of ^{177}Lu-catelase: A preliminary clinical study in soft tissue sarcoma. First Author: Jiayong Liu, Department of Bone and Soft Tissue Tumor, Key Laboratory of Carcinogenesis and Translational Research (Ministry of Education/Beijing), Peking University Cancer Hospital and Institute, Beijing, China

Background: Localized radiotherapy with radioisotope injections holds promise but is limited by poor tumor retention and hypoxia. To overcome these challenges, we developed ^{177}Lu-CAT/ALG, a hydrogel formulation containing catalase labeled with ^{177}Lu and sodium alginate (ALG). Upon injection, endogenous calcium rapidly forms a hydrogel, securing ^{177}Lu-CAT within the tumor, alleviating hypoxia, and enhancing therapeutic efficacy. Preclinical studies demonstrated sustained hypoxia relief, superior tumor retention, and significant antitumor activity. This phase 1 trial evaluates the safety and preliminary efficacy of ^{177}Lu-CAT/ALG in patients with soft tissue sarcoma (STS). **Methods:** Patients with locally advanced STS underwent baseline metabolic and volumetric assessments using ^{18}F-FDG PET/MR imaging. Intratumoral doses were calculated using the OLINDA 2.0 Sphere Model, with ultrasound-guided injections administered every 8 weeks. SPECT imaging assessed tumor retention at 2, 24, 96, and 168 hours post-injection. Efficacy was evaluated bi-monthly per PERCIST criteria. Primary endpoints included tumor retention and safety (CTCAE v5.0). Secondary endpoints included objective response rate (ORR), progression-free survival (PFS), and overall survival (OS). **Results:** Seven patients with locally advanced STS were treated, with a median tumor size of 8.5 cm. SPECT imaging confirmed that at least 60% of ^{177}Lu-CAT/ALG remained within tumors at 168 hours. The most common adverse events (AEs) were grade 1-2 reductions in white blood cell count (4/7 patients). One patient experienced a grade 4 AE (thrombocytopenia). Stable disease was observed in two patients, with disease control lasting 16.53 and 12.8 months. As of the data cutoff, one patient remains on treatment. Pathological analysis of a tumor specimen from a patient with increased tumor volume on PET/MR revealed 70% necrosis after resection. **Conclusions:** ^{177}Lu-CAT/ALG demonstrated a favorable safety profile, sustained tumor retention, and encouraging antitumor activity in patients with locally advanced STS. These results highlight the potential of ^{177}Lu-CAT/ALG as a novel therapeutic approach and support further evaluation in larger trials. Clinical trial information: NCT05985278. Research Sponsor: None.

Characteristics of participants.

No.	Gender	Age	Tumor type	Primary tumor location	Tumor size	Number of injections	Mean dose of injections (range)/mCi	Outcomes
1	F	41	LGSTS, NOS	right scapular region	8.6	5	23.30(16.8-29.1)	On treatment
2	F	55	FS	Right chest wall	9.3	1	14.3	PD
3	F	58	LGSTS, NOS	Left chest wall	4.7	4	9.6 (7.0-10.7)	PD
4	F	51	LMS	Abdominal wall	7.3	1	31.9	PD
5	F	47	EMFS	Right chest wall	9.6	1	32.4	PD
6	M	60	UPS	Neck	7.6	1	23.8	PD
7	M	67	MFS	Right elbow	8.5	1	15.7	PD

LGSTS: low grade soft tissue sarcoma, NOS: not otherwise specified, FS: fibrosarcoma, LMS: leiomyosarcoma, EMFS: epithelioid myxofibrosarcoma, UPS: undifferentiated pleomorphic sarcoma, MFS: myxofibrosarcoma, PD: progressive disease.

11564 **Poster Session**

Doxorubicin-based chemotherapy vs gemcitabine/docetaxel in uterine leiomyosarcoma (ULMS). First Author: Stephanie Soewito, University of Texas Health Science Center at Houston, Houston, TX

Background: ULMS is an aggressive uterine smooth muscle cancer. Surgery is standard for localized/advanced ULMS, and the use of adjuvant chemotherapy is controversial. Treatment may involve combination cytotoxic chemotherapy, typically doxorubicin-based regimens (D) or gemcitabine plus docetaxel (GT), which have poor (20-30%) response rates and high toxicity. Given the lack of randomized trial data, this single-center retrospective study compared D vs GT in the adjuvant and metastatic settings of ULMS. **Methods:** We included patients with confirmed histologic diagnosis of uterine leiomyosarcoma between 2000 and 2024 treated at MD Anderson Cancer Center with either D or GT. Patients were stratified by localized disease and receipt of adjuvant chemotherapy or metastatic disease and receipt of palliative chemotherapy with D or GT in the first-line setting. The primary objective was to assess recurrence-free survival (RFS) in those with localized tumors and progression-free survival (PFS) in those with metastatic tumors treated with either D or GT. RFS and PFS were defined as the time interval from the start time of first line chemotherapy (D or GT) to the time of recurrence/progression or death, whichever occurred first. Kaplan Meier and log rank tests were used to assess survival outcomes. Cox proportional hazards (PH) modeling evaluated whether either regimen independently predicted survival with adjustment for age, primary tumor size, and mitotic index. Data collection is ongoing, and propensity score matching will be performed. **Results:** We included 76 patients, including 36 with primary localized ULMS and 40 with advanced ULMS. In patients with localized disease, there was no significant difference in RFS between those treated with D vs GT in univariate (p = 0.17) or multivariate (HR (95% CI) = 1.21 (0.35, 4.15), p = 0.76) analyses. In patients with metastatic disease, GT was associated with inferior PFS than those treated with D (HR (95% CI) = 4.45 (1.38, 14.29), p = 0.01) after adjusting for age and primary tumor size in the multivariate Cox PH model. **Conclusions:** Treatment with D was associated with improved PFS for metastatic ULMS compared to treatment with GT. No significant difference in RFS was observed between the two regimens for localized disease. However, the study may have limited power to detect differences due to small sample size. Updated data analyses with a larger cohort will be presented at the meeting. Research Sponsor: None.

	Localized ULMS (n = 36)		Metastatic ULMS (n = 40)	
Age of diagnosis (median, years)	51.0		52.3	
Primary tumor size (median, cm)	10.1		11.0	
Mitotic Index (>10 per 10 HPF)	77.8% (n = 28)		82.5% (n = 33)	
	D	GT	D	GT
	16.7% (n = 6)	83.3% (n = 30)	30% (n = 12)	70% (n = 28)
RFS/PFS (median, months)	10.8 (7.8, 23.0)		7.2 (4.5, 9.2)	
HR (95% CI)	1.21 (0.35, 4.15)		4.45 (1.38, 14.29)	
p-value	0.7612		0.0122	
Overall Survival (median, years)	6.6 (2.5, 10.3)		4.6 (3.7, 6.7)	

11565 **Poster Session**

Heterogeneity in epithelioid hemangioendothelioma (EHE): Insights into common and organ-specific tumor pathways. First Author: Tom Wei-Wu Chen, National Taiwan University Hospital, Taipei, Taiwan

Background: EHEs are ultra-rare sarcomas that can arise from various organs, with the primary site being an important prognostic factor. We hypothesized that EHEs from different organs harbor heterogeneous tumor cells. Understanding key pathways associated with this heterogeneity may lead to improved therapies for EHE patients. **Methods:** EHE samples from different primary sites with confirmed pathognomonic gene rearrangements were analyzed. Spatial transcriptomics was performed on FFPE samples using the Visium CytAssist platform. Pathway analyses were conducted with AUCell, and cell compositions were estimated using XCell. A second platform, Xenium, was used for confirmation. **Results:** Eight EHE patients with different primary organ sites (liver 3, lung & pleura 2, bone 2, soft tissue 1) and gene rearrangements (CAMAT1 FISH+ 6, TFE3 FISH+ 1, WWTR1 FISH+ 1) had spatial transcriptomic results. Unsupervised clustering identified 35 different clusters and EHE clusters were defined in accordance to histology and vascular markers (CD31, CD34, and ERG). These clusters could be broadly categorized into “common (non-organ-specific)” clusters, observed in three or more organ types, and “organ-specific” clusters. Common clusters showed higher levels of stem-like endothelial cell markers and increased TGF-beta and mTORC1 pathway activity, which may explain the clinical benefit of sirolimus in EHE. Using liver EHEs as an example, the liver-specific cluster demonstrated a fibroblast/mesenchymal stromal cell differentiation pattern not observed in EHEs from other organs. GDF-15, which is associated with aggressiveness in EHE and cachexia, was significantly higher expressed in common than organ-specific cluster. In liver and bone EHEs, clusters with high GDF-15 expression tend to have higher TGF-beta signaling and lower dendritic cells, implying the role of GDF-15 in EHE with immune regulation. These findings were validated in Xenium analysis. **Conclusions:** This study shows that EHE tumors share certain core pathways but also exhibit organ-specific differentiation patterns, which may underlie their variable prognoses. The coexistence of both “common” and “organ-specific” clusters highlights the importance of personalized treatment strategies and paves the way for more targeted therapeutic development in EHE. Research Sponsor: National Taiwan University Hospital.

11566 **Poster Session**

Molecular profiling and prognosis of spindle cell/sclerosing rhabdomyosarcoma: A report from the Chinese PPOG trial. First Author: Suying Lu, Sun Yat-sen University Cancer Center; State Key Laboratory of Oncology in South China; Collaborative Innovation Center for Cancer Medicine, Guangzhou, Guangdong, China

Background: Spindle cell/sclerosing rhabdomyosarcomas (SSRMS) is a rare variant of rhabdomyosarcoma, recognized as a distinct pathological entity in the most recent WHO classification. However, the molecular profile and clinical outcomes of patients with SSRMS remain poorly understood. The Pediatric Precision Oncology Group (PPOG) is a multicenter project aimed at characterizing tumor molecular profiles in pediatric oncology patients across China. **Methods:** From January 2016 to July 2024, a total of 70 patients with SSRMS were enrolled in the PPOG (NCT05076071) trial, with 57 patients meeting the criteria for clinical analysis. Targeted gene sequencing (830 DNA and 395 RNA) was conducted on tumor samples from 43 patients, while whole-transcriptome analysis was performed on tumor samples from 13 patients to assess gene expression. The Kaplan-Meier method was employed to estimate overall survival (OS) and event-free survival (EFS). **Results:** The median follow-up time was 48 months (range: 6.3–160.8 months). The 4-year EFS rates for patients with low risk (n = 16), intermediate risk (n = 27), and high risk (n = 14) were 92.9%, 79.3%, and 12.9%, respectively ($P < 0.0001$). The 4-year OS rates for these groups were 68.8%, 51.2%, and 39.7%, respectively (P = 0.2046). The 4-year EFS rates for patients aged $<$ 10 years (n = 33) and $\geq$ 10 years (n = 24) were 66.7% and 31.7%, respectively (P = 0.017). The 4-year OS rates for these groups were 71.4% and 63.8%, respectively (P = 0.192). The most commonly recurrently altered genes were MYOD1 (48.8%), PIK3CA (25.6%), CDKN2A (23.3%), CDKN2B (16.3%), and IGF1R (9.3%) mutations. All 21 cases with MYOD1 mutations showed a p.L122R (c. T365G) mutation, consistent with previous reports. Gene interaction analysis shows that MYOD1 mutation frequently occur alongside CDKN2B mutation. Compared to the MYOD1 wild-type group, the MYOD1 mutant group has a significantly higher incidence of CDKN2B mutation, as well as higher rates of PIK3CA and IGF mutations, and lower rates of NOTCH1 and TP53 mutations. Eighteen fusion genes were detected in 30.2% (13/43) of SSRMS patients, with the most common being BRAF fusion (4.6%) and ROS1 fusion (4.6%). Actionable mutations were identified in 76.7% of patients, with the most frequently matched targeted therapies including PI3K inhibitors (32.3%), CDK4/6 inhibitors (21.2%), and MEK inhibitors (11.5%). Compared to the MYOD1 wild-type group, RNA differential expression analysis revealed a significant upregulation of the PI3K-AKT pathway in the MYOD1 mutant group. The infiltration levels of CD4+ T cells and macrophages in the MYOD1 mutant group were significantly higher than those in MYOD1 wild-type group. **Conclusions:** The MYOD1 mutant group and the MYOD1 wild-type group exhibit distinct molecular characteristics. Larger sample studies are needed to clarify the molecular features and risk stratification of SSRMS. Clinical trial information: NCT05076071. Research Sponsor: None.

11567 **Poster Session**

Impact of time to relapse (TTR) and metastasectomy (MTS) on survival in leiomyosarcoma (LMS): A CanSaRCC study. First Author: Haydée Williams Sanchez, Division of Medical Oncology and Hematology, Princess Margaret Cancer Centre, University Health Network, Toronto, ON, Canada

Background: Approximately 40% of LMS patients (pts) experience relapse despite standard care of surgical resection ± radiotherapy. Upon relapse, pts with advanced disease receive palliative systemic therapy. Often reserved for pts with oligometastatic disease, the role of MTS remains unclear due to a lack of randomized trials. Longer time from curative surgery to relapse (TTR) is associated with better outcomes in LMS pts who undergo MTS but its prognostic value has not been established in those treated without MTS. This study evaluates the effect of TTR on outcomes in LMS pts with metachronous metastases treated with systemic therapy ± surgery. **Methods:** This real-world study included advanced LMS pts treated at 4 Canadian sarcoma centers (2010–2022) who underwent curative resection, subsequent relapse, and systemic treatment ± MTS. Data were retrieved from the ethics-approved Canadian Sarcoma Research and Clinical Collaboration (CanSaRCC) database. Primary and secondary endpoints were overall survival (OS) stratified by TTR ($<$ 6 vs $\geq$6 months from the completion of curative resection); and MTS, respectively. Exploratory analysis evaluated the impact of MTS in pts with low disease burden at relapse ($<$ 2 sites). Kaplan-Meier survival analysis and log-rank tests were used to compare OS, and Cox proportional hazards models identified independent predictors, with $p < 0.05$ considered significant. **Results:** A total of 113 pts (median age 56y) were included. Median follow-up was 38.4 months (mo). Majority (n = 93, 82%) were female and 38 (34%) had uterine leiomyosarcoma (uLMS). Relapse occurred in 109 pts (96%) with 73/109 pts (70%) having $<$ 2 metastatic sites at relapse. TTR was $<$ 6 months (TTR $<$ 6) in 31/109 pts (28%) and 43/109 pts (39%) underwent MTS. Pts with TTR $\geq$6 months (TTR$\geq$6) had significantly longer median OS (mOS) than those with TTR $<$ 6 (32.9 vs 15.6mo, p = 0.006). Metastasectomy was associated with a significantly longer mOS in the whole cohort (50.4 vs 17.6mo, $p < 0.0001$) as well as the subgroup of patients with $<$ 2 metastatic sites at relapse (50.6 vs 15.6mo, $p < 0.0001$). The mOS was 50.4 vs 24.7mo in pts with TTR$\geq$6 who underwent MTS and those who did not, respectively ($p < 0.0001$). Among pts with TTR $<$ 6 who had MTS, median OS was 44.8mo compared with 9.4mo in pts without surgery (p = 0.005). No other variables (e.g., tumor grade, primary site, metastatic burden, gender, or age) impacted OS. Both MTS (HR 0.26, 95% CI 0.16-0.49, p = 0.000) and TTR $\geq$ 6 (HR 0.55, 95% CI 0.33-0.91, p = 0.02) remained independent predictors of favorable OS in multivariate analysis. **Conclusions:** TTR$\geq$6 was associated with longer OS in LMS pts. OS improved significantly with MTS, particularly in pts with longer TTR, though those with TTR $<$ 6 also benefited to a lesser extent. These results underscore the role of MTS as part of an individualized treatment strategy to optimize outcomes in advanced LMS. Research Sponsor: None.

11568 **Poster Session**

A phase Ib/II trial of radiotherapy combined with doxorubicin and PD-1 antibody for localized high-risk limbs and trunk soft tissue sarcomas. First Author: Yan Wang, Department of Radiation Oncology, Fudan University Shanghai Cancer Center, Shanghai, China

Background: Localized high-risk soft tissue sarcomas (STSs) presents a therapeutic challenge due to limited preoperative treatment options. Radiotherapy (RT) and Doxorubicin (DOXO) are well-established immunogenic cell death inducers [1-3], which are capable of boosting the effects of immunotherapy even in "cold" tumors. This study aims to evaluate the safety and efficacy of a preoperative triple combination of RT, DOXO, and the PD-1 antibody for STS. **Methods:** In this Phase Ib/II trial (NCT05774275), up to 52 patients with localized high-risk STSs will be enrolled. Participants will receive RT (BED = 50-60 Gy), combined with DOXO and PD-1 antibody (Sintilimab, SIN 200 mg, Day 1) every three weeks for four cycles prior to surgery. In Phase Ib (3+3 design), patients will receive Pegylated liposomal doxorubicin (PLD, 37.5 mg/m² or 30 mg/m², i.v., Day 1) to establish the recommended Phase 2 dose (RP2D). In Phase II, DOXO will be administered as PLD at RP2D or as Doxorubicin Hydrochloride (Adriamycin, ADM, 75 mg/m² i.v., Day 1). The primary endpoint is the objective response rate (ORR), while secondary endpoints include the rate of pathological complete response (pCR) and near pCR (defined as $<$ 10% viable tumor cells), survival and safety. **Results:** From September 2022 to January 2025, 33 patients (26 in limbs and 7 in trunks) were enrolled. The median age was 50 years (range 19-75), with 17 males, and 13 patients had prior surgeries. 29 tumors were histological grade 3. No dose-limiting toxicities (DLT) were observed in the first six patients receiving PLD (37.5 mg/m², i.v., Day 1, q3w), confirming the RP2D. Among the 28 radiological evaluable patients, 2 achieved complete response (CR), 12 achieved partial response (PR), and 11 had stable disease, resulting in an ORR of 50.0% and a disease control rate (DCR) of 89.2%. In addition, among 24 pathological assessable patients, 14 (58.3%) achieved pCR or near-pCR. Two patients (9.5%) experienced major wound complications. They underwent secondary operation and readmission to hospital for wound care, respectively. Other serious adverse events (SAE) include Grade 3 dermatitis (17.9%) and Grade 3-4 neutropenia (7.1%). No G5 SAE were reported. Median progression-free survival and overall survival have not yet been reached. **Conclusions:** The combination of RT, DOXO, and SIN showed potential efficacy and tolerable toxicity in high-risk localized limbs and trunk STS. The trial is still ongoing. Clinical trial information: NCT05774275. Research Sponsor: Beijing Xisike Clinical Oncology Research Foundation; Y-Young2020-0477; National Natural Science Foundation of China; 82373132.

11569 **Poster Session**

Self-assembled patient-derived tumor-like cell clusters for personalized drug testing in diverse sarcomas. First Author: Tian Gao, Department of Bone and Soft Tissue Tumor, Peking University Cancer Hospital, Beijing, China

Background: Soft tissue sarcomas (STS) are rare malignancies with over 100 distinct histological subtypes. Their rarity and heterogeneity pose significant challenges to identifying effective therapies, and approved regimens show varied responses. Several patient-derived tumor models have emerged recently. However, STS present a challenge in developing preclinical drug-testing models due to their non-epithelial and complex nature. **Methods:** Here we report a model termed patient-derived tumor-like cell clusters (PTCs) derived from STS patients. PTCs result from the self-assembly and proliferation of mesenchymal stem cells (MSCs), epithelial cells, and immune cells, faithfully recapitulating the morphology and function of the original tumors. This is an trial to assess the feasibility and predictive value of a standardized PTC-based test to differentiate efficacy of the patients' clinical drug regimens. The study was conducted at Peking University Cancer Hospital and was approved by the local ethical review board. The patients and corresponding PTCs were divided into three sets: characterization and storage set, assay set and validation set. The characterization and storage set were used to characterize PTCs in comparison with original tumor samples or stored for future study. The assay set was separated into two groups to determine the drug efficacy concentration of a targeted therapy or chemotherapy due to their different action mechanisms. The validation set was used to compare the consistency between PTC drug assays and clinical outcome. We then conducted comparative analyses between PTCs and tumor spheres, as well as between PTCs and paired tumor samples. **Results:** From 2019 to the 2025, we obtained 254 samples (155 surgical, 98 puncture, and 1 ascites sample) to generate PTCs, covering tens of sarcoma classifications, with an overall success ratio of 94.9%, ranging from 85.7% to 100%. A total of 3,740 differentially expressed genes (DEGs) were identified between PTCs and tumor spheres, while 1,222 DEGs were identified between PTCs and tumor samples. Through standardized culture and drug-response assessment protocols, PTCs facilitate personalized drug testing, evaluating hundreds of therapies within two weeks. PTCs demonstrate an overall predictive accuracy of 78.3% for all clinical outcomes and 100% accuracy distinguishing CR/PR from PD, could serve as a valuable tool for personalized medicine. **Conclusions:** These findings revealed that PTCs as a tool to better understand the biology of individual tumors and characterize the landscape of drug resistance and sensitivity in sarcoma. These results underscore the potential of PTCs for prospective use in clinical decision-making therapy selection. Research Sponsor: None.

11570 **Poster Session**

Population-based assessment of leiomyosarcoma (LMS) and cancers in the Li-Fraumeni syndrome (LFS) spectrum: Implications for genetic testing criteria. First Author: Wendy Kohlmann, Hunstman Cancer Institute at the University of Utah, Salt Lake City, UT

Background: Data regarding the heritability of rare tumors is limited and may prevent incorporation into genetic testing criteria. This study utilized the Utah Population Database (UPDB) to evaluate cancer risks among LMS cases and their relatives and the prevalence of meeting Chompret criteria (ChC) for LFS genetic testing. **Methods:** Between 1995-2021, 429 LMS cases with UPDB genealogies were identified from the Utah Cancer Registry. Diagnoses were confirmed, when possible, by pathology reports. Cases were individually age- and sex-matched 1:5 to population controls with similar pedigrees and follow-up (n=2145 controls). Cancers from 1966-2021 were obtained for study subjects and their first- through third-degree relatives. LFS spectrum cancers included breast, soft tissue sarcomas, osteosarcomas, CNS/brain, and adrenocortical. Hazard rate ratio (HRR) estimates of self- and familial relative cancer risks in LMS compared with controls was calculated from a Cox model adjusting for the number of relatives, degree of relatedness, and person-years at risk. **Results:** A 2.2-fold risk ($p<0.001$) of a cancer in the LFS spectrum was seen in cases with a non-uterine LMS site (n=323) at any age and a 4.5-fold risk ($p<0.001$) for developing an LFS cancer at age $<$50 y. Non-uterine LMS cases had similarly increased risks for developing a non-LFS-spectrum cancer at any age and $<$50y (Table). Increased risk of LFS or non-LFS-spectrum cancer was not seen in uterine LMS cases (n=106). Although increased cancer risk was not generally observed in relatives of LMS cases compared with control relatives, we observed that non-uterine LMS and their first-degree relatives had an increased risk of colorectal cancer (CRC) (Table). CRC is not an LFS cancer but is known to occur in LFS families. Excluding the LMS diagnosis, non-uterine LMS cases were more likely to meet ChC compared with controls (Table 1). Uterine LMS cases were no more likely to meet ChC than their respective controls. **Conclusions:** LMS is associated with cancers outside the spectrum, and further studies are needed to determine if LMS is associated with other cancer predisposition genes. Family history should be evaluated broadly and not restricted to ChC. As uterine LMS appears less likely to be associated with genetic predisposition, considering non-uterine and uterine cases separately may be important for future studies of the genetic basis of LMS. Research Sponsor: National Cancer Institute; Award Number P50CA272170; National Cancer Institute; P30CA042014; National Cancer Institute's SEER Program; Contract No. HHSN261201800016I; US Centers for Disease Control and Prevention's National Program of Cancer Registries; Cooperative Agreement No. NU58DP007131; Huntsman Cancer Foundation.

Cancer risks in LMS cases and relatives compared with controls.

	Non-uterine LMS =323, Controls=1615				Uterine LMS =106, Controls=503			
	Case HRR	*P*	FDR HRR	*P*	Case HRR	*P*	FDR HRR	*P*
LFS cancer	**2.2**	**<0.001**	1.1	0.68	0.6	0.36	1.3	0.24
LFS cancer <50	**4.5**	**<0.001**	1.2	0.72	1.3	0.77	2.1	0.08
Non-LFS cancer	**2.2**	**<0.001**	1.2	0.06	1.0	0.98	1.1	0.44
Non-LFS cancer <50	**4.1**	**<0.001**	1.2	0.38	1.5	0.52	1.4	0.35
Colorectal	**2.7**	**0.04**	**1.6**	**0.02**	1.1	0.91	1.4	0.41

HRR=hazard ratio; FDR=first degree relative.

11571 Poster Session

A propensity-score matched analysis for time to trabectedin-failure in advanced myxoid liposarcoma patients. First Author: Roberta Sanfilippo, Adult Mesenchymal and Rare Tumor Unit, Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy

Background: Whether to discontinue trabectedin (T) in soft-tissue sarcoma (STS) patients (pts) with response or stable disease remains controversial. In 2015, the T-DIS trial (Le Cesne et al., Lancet Oncology) showed a progression-free survival (PFS) benefit for T-maintenance after six cycles in STS patients. However, myxoid liposarcoma (MLPS) show a unique sensitivity to T, likely due to its specific mechanism of action. We retrospectively evaluated a "stop-and-go" strategy, in terms of time to treatment (T) failure (TTF) and overall survival (OS) in advanced MLPS pts. **Methods:** We carried out a retrospective analysis of 79 MLPS pts treated with T at our institution from September 2002 to December 2024. Inclusion criteria required pts to be progression-free (per RECIST) after 6 cycles of T. TTF was defined as the time from the 6th cycle to secondary resistance to T or death, whichever occurred first. Statistical methods included Kaplan-Meier survival analysis and propensity-score matched Cox proportional hazards models (weighted and unweighted) with time-dependent variables. **Results:** 60 MLPS pts were eligible for analysis (median age: 48 years, IQR: 39–57; 37 males, 23 females). Of these, 27 (34%) pts were treated with a "stop-and-go" strategy, discontinuing T after achieving radiological response or disease stability. T was discontinued at a median of 12 cycles (range: 6-28). Median follow-up was 56.9 months (IQR: 28.1–112.5), with a median TTF of 51.4 months (95% CI: 37.1– NA) in the "stop-and-go" group versus 10.0 months (95% CI: 6.6–17.7) in the T-maintenance group. OS was 55 months (95% CI 38.5 - NA) vs 23 months (95% CI 21-27.9) in the two groups, respectively. Weighted Cox models predicted an HR of 0.32 (95% CI: 0.11–0.93) for TTF and of 0.28 (95% CI 0.07 – 1.12) for OS, thus favoring the stop-and-go approach. Additional factors, including ECOG performance status (PS), age, primary tumor site, and surgery post-T discontinuation, were adjusted in the analysis. **Conclusions:** Our findings raise the question whether a "stop-and-go" strategy with T is the best option in the subset of MLPS pts. How to test further this hypothesis in such a rare subset, and which predictive factors may optimize the approach, is questionable. Research Sponsor: None.

11572 Poster Session

Moving beyond the traditional two-step approach for prognosis prediction: The BayeSarc model. First Author: Gabriele Tine', Biostatistics for Clinical Research, Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy

Background: Extremity Soft tissue sarcomas (eSTS) are rare and heterogeneous, limiting the collection of large datasets for robust predictive modeling. Sarculator, a Cox model-based tool for overall survival (OS) prediction, was built using the traditional two-step paradigm (1) model building and (2) external validation. However, this method can underperform on external cohorts, often yielding low predictive accuracy and limited generalizability. We introduced a Bayesian Sequential Learning strategy to iteratively refine Sarculator, incorporating new data while preserving prior properties. **Methods:** The initial model was built on the Italian Sarculator development cohort, with age, tumor size, tumor grade, and histology as covariates. Sequential updates were then performed with the three original Sarculator external validation cohorts , and a more recent Italian cohort. Each step used the results from the previous update as prior information for the next. Performance was assessed as discriminative ability (C-index) and calibration. Key differences from the original Sarculator were Bayesian Cox modelling, and a piecewise-constant hazard. **Results:** The two-step approach yields separate performance metrics for each cohort, making generalizability unclear when performance drops (e.g. French cohort, Table). Conversely, the sequential approach progressively increases the total information (number of patients and follow-up), without discarding previous evidence, and readjusts performance metrics at each step. Occasional declines in the C-index reflect cohort-specific divergences but can be reversed in subsequent updates if newer cohorts share similar features. Ultimately, the final BayeSarc outperformed the initial model in discriminative ability, calibration, and reduced uncertainty in predictions. **Conclusions:** BayeSarc is an accurate, generalizable OS prediction model for eSTS, preserving external validation properties while moving beyond the conventional two-step approach. By building on prior evidence, the model dynamically adapts over time, ultimately relying on 4713 patients, with results independent of cohort order. BayeSarc sets a benchmark for future rare-disease prognostic research, paving the way for incorporating new cohorts and/or prognostic variables (e.g. emerging biomarkers). Research Sponsor: None.

Cohorts	Istituto Nazionale Tumori, Milan, Italy 1994-2013	Mount Sinai Hospital, Toronto, Canada 1994-2013	Royal Marsden Hospital, London, UK 2006-2013	Institut Gustave Roussy, Villejuif, France 1996-2012	Istituto Nazionale Tumori, Milan, Italy 2014-2021
Two-step procedure	Dev N=1452	Val 1 N=1436	Val 2 N=440	Val 3 N=420	Val 4 N=965
C-index	0.767	0.775	0.762	0.698	0.765
Bayesian updating	**Dev** N=1452	**Upd 1** N=2888	**Upd 2** N=3228	**Upd 3** N=3748	**Upd 4** N=4713
C-index	0.761	0.775	0.771	0.707	0.796

11573 Poster Session

Clinical and prognostic implications of the TCR repertoire in leiomyosarcoma. First Author: John Seng Wang, Northwestern University Feinberg School of Medicine, Chicago, IL

Background: Leiomyosarcomas (LMS) are aggressive mesenchymal tumors sometimes classified by primary location as uterine LMS (uLMS) versus extra-uterine LMS (eLMS). In pursuit of novel therapies, study of the tumor microenvironment and the repertoire of T-Cell Receptor (TCR) sequences from infiltrating T-lymphocytes could help guide the application of immunotherapy in LMS. Herein, we explore the first ever database of TCR-sequenced LMS tumors in one of the larger LMS cohorts analyzed to date. **Methods:** A single-institution retrospective study was performed including 117 adult patients with pathology-confirmed LMS diagnosed between 1998 and 2022 at Northwestern Medicine. Overall survival (OS), progression free survival (PFS), and relapse free survival (RFS) were analyzed using Kaplan-Meier Curves (GraphPad Prism). DNA was extracted from 61 eLMS and 39 uLMS formalin-fixed paraffin-embedded (FFPE) blocks using Qiagen's AllPrep DNA/RNA FFPE kit and used for TCR sequencing. **Results:** 117 patients who met the inclusion criteria were classified as uLMS (n=54) and eLMS (n=63). Baseline patient demographics and disease characteristics are described in the table. Median OS significantly differed between uLMS and eLMS patients (559 versus 1548 days; p=0.001). Median PFS was not statistically different between metastatic uLMS versus eLMS (142 versus 159 days; p=0.63). Median RFS was not significantly different between localized uLMS versus eLMS (283 versus 429 days; p=0.30). The number of different TCR clones amongst TCRs was significantly different between the two tumor types: uLMS demonstrated a mean of 821 clones versus 2415 clones in eLMS (p=0.005). Mean CDR3 length in uLMS tumors was 47.9 (95% CI 46.53-49.25) versus 48.45 (95% CI 46.66-50.25) in eLMS tumors (p=0.10). TRBV20 was the most common gene in uLMS cases and the second most common gene in eLMS cases. **Conclusions:** This study provides the first analysis of the TCR repertoire in LMS patients and the largest analysis of TCR repertoire ever reported in any sarcoma subtype. eLMS tumors contained significantly more TCR clones than uLMS tumors. CDR3 did not significantly differ between cohorts, and the TRBV20 gene was frequently identified in both LMS subtypes. Further gene expression analysis and immunohistochemistry is currently underway. As might be expected, clinical outcomes were worse for uLMS including significantly lower OS. Updated data will be presented including additional information about the TCR repertoire as well as gene expression data to contextualize these findings. Research Sponsor: None.

Baseline patient demographics and disease characteristics.

	uLMS (n=54)	eLMS (n=63)
Median Age (range)	55 years (25-91)	58 years (23-87)
Female Sex: n (%)	54 (100%)	34 (54%)
Median Tumor Size (range)	11 cm (1-34)	5 cm (0.7-25)
Necrosis Present: n (%)	47 (87%)	33 (52%)
Positive Margins: n (%)	5 (9%)	9 (14%)
Stage IV Disease: n (%)	16 (30%)	5 (8%)
Adjuvant Chemotherapy: n (%)	27 (50%)	4 (6%)

11574 Poster Session

Ramucirumab in pediatric and young adult patients (Pts) with relapsed/refractory (R/R) desmoplastic small round cell tumor (DSRCT) or synovial sarcoma (SS): Results from the CAMPFIRE study. First Author: Emily K. Slotkin, Memorial Sloan Kettering Cancer Center, New York, NY

Background: Few effective therapies exist for pts with R/R DSRCT and SS, and hence, their prognosis remains poor. Preclinical data suggested the relevance of vascular endothelial growth factor receptor 2 (VEGFR2) inhibition in these diseases. We evaluated the efficacy of ramucirumab (RAM, VEGFR2 receptor antagonist) + chemotherapy vs. chemotherapy alone in pediatric and young adult pts with R/R DSRCT (JV01) or SS (JV02). **Methods:** JV01 and JV02 were randomized, global, multicenter, Phase 1/2 studies in pts aged ≤29 years with R/R DSRCT or SS and evaluated pts treated with RAM + cyclophosphamide/vinorelbine (CV; JV01) and RAM + gemcitabine/docetaxel (GD; JV02). Pts were randomized 2:1 to the experimental and control groups. The primary endpoint was progression-free survival (PFS) per RECIST v1.1, analyzed via a Bayesian hierarchical model allowing adaptive borrowing on effect size (log hazard ratio [HR]) between JV01 and JV02 and control arm augmentation with historical (real world) data. Interim futility required a probability (Pr) of PFS (HR < 1) $> 60\%$, and intervention success at final analysis was declared at Pr $> 99\%$. Frequentist analysis (1-sided $\alpha = 0.1$) was performed as a sensitivity analysis. Safety was a secondary endpoint. **Results:** Baseline characteristics were balanced between the treatment arms in both studies: RAM+CV, n = 20; CV, n = 10; RAM+GD, n = 16; GD, n = 7. JV02 met the futility criterion (Table) and was suspended without completing enrollment. JV01 fully enrolled but did not meet the primary endpoint at the final analysis (PFS HR = 0.7, 98% credible interval = 0.3, 1.7; pr [HR < 1] = 86.4% vs. 99%). However, frequentist analysis in JV01 showed that pts in the RAM+CV arm had a numerical improvement of 5 months in median PFS vs. the CV arm. Overall, no significant safety events were reported in either study. **Conclusions:** The PFS outcome was not met for either rare disease. The numerical trend in JV01 is noteworthy, especially considering the limited treatment options available for DSRCT. Safety was consistent with the known profiles of the individual treatments and the population. Clinical trial information: NCT04145700, NCT04145349. Research Sponsor: Eli Lilly and Company.

	JV01			JV02		
	RAM+CV (n=20) Median PFS (months), 98% CrI[a]	CV (n=10)	HR (80% CrI)[b]	RAM+GD (n=16) Median PFS (months), 98% CrI[a]	GD (n=7)	HR (80% CrI)[b]
Primary Bayesian Analysis	5.7 (3.2, 10.0)	3.7 (1.8, 8.3)	0.7 (0.3, 1.7) Pr (HR <1) = 86.4 %	3.7 (1.5, 11.5)	6 (2.1, 18.0)	1.8 (0.8, 3.1) Pr (HR <1) = 20.1%
PFS events, n	16	8		9	5	
Frequentist Analysis[c]	6.8 (5.5, 10.4)	1.7 (1.4, 2.7)	0.5 (0.3, 0.8) p = 0.082	2.1 (1.9, 6.1)	2.0 (1.4, NR)	0.7 (0.3, 1.5) p = 0.544

CI = confidence interval; CrI = credible interval; CV = cyclophosphamide/vinorelbine; GD = gemcitabine/docetaxel; HR = hazard ratio; NR = not reached; PFS = progression-free survival; Pr = probability; RAM = ramucirumab.
[a]Posterior median.
[b]Posterior mean displayed.
[c]80% CI for JV01 and JV02.

11575 **Poster Session**

Global inequities in sarcoma clinical trials: A comprehensive analysis over the last decade. First Author: Shushan Hovsepyan, Yerevan State Medical University, Immune Oncology Research Institute, Yerevan, Armenia

Background: Sarcomas are rare, comprising 15% of childhood cancers and 1% of adult cancers, yet survival rates remain poor. The overall 5-year survival for soft tissue sarcomas (STS) is 65%, dropping from 81% for localized disease to just 16% for metastatic cases. For bone sarcomas, survival declines from 84% at localized stages to 31% for metastatic cases. This highlights the critical need for novel therapies and equitable research access. To address this, the current review discusses sarcoma clinical trials conducted over the past decade. **Methods:** Sarcoma-related clinical trials registered on ClinicalTrials.gov from 2016 to 2025 were analyzed. Variables included study status, conditions, phases, randomization, dates, country, age groups, sample size, sponsor, and reasons for discontinuation. Geographic data were categorized by World Bank income levels. Descriptive statistics summarized key characteristics. **Results:** Out of 1,232 studies, 65% were focused exclusively on sarcomas. Alarmingly, only 0.4% of the studies were conducted in low-income countries (LICs) and only 18% in low- and middle-income countries (LMICs), underscoring a profound underrepresentation of these regions in sarcoma research. Recruitment status varied, with 39% of trials actively recruiting, 18% completed, and 14% terminated—predominantly due to challenges in participant accrual. Early-phase trials predominated, comprising 34% in phase 1 and phase 1/2, and 30% in phase 2. Late-phase and post-marketing studies were sparse, representing only 5%. Interventional trials accounted for 82% of the total, though most lacked randomization. The majority of studies (72%) were academia-sponsored trials. Only 1% of studies were exclusively dedicated to pediatric populations, while 36% included both adults and children, and 63% enrolled adults exclusively. The median sample size was 46 participants (IQR 22–117), and the median study duration was 47 months (IQR 29–70). There are no trend changes in the number of studies that were launched from 2016 to 2024. **Conclusions:** Our study highlights inequities in the geographic distribution of sarcoma trials, and the substantial neglect of LICs and pediatric populations. This underscores an urgent need for global efforts to address these disparities and enhance inclusivity in clinical research. Research Sponsor: None.

11576 **Poster Session**

NF1- and non-NF1–associated malignant peripheral nerve sheath tumors (MPNST): The University of Texas MD Anderson (MDACC) experience. First Author: Reeja Raj, The University of Texas MD Anderson Cancer Center, Houston, TX

Background: MPNSTs are aggressive sarcomas with poor prognosis due to their high propensity for metastasis, rapid growth and limited response to standard chemotherapy (CT). While commonly associated with neurofibromatosis type 1 (NF1), they can also occur sporadically (non-NF1). This study aims to evaluate baseline characteristics and outcomes in NF1 and non-NF1 associated MPNST in order to understand CT effectiveness and set a benchmark for future therapies. **Methods:** A retrospective chart review was conducted at MDACC, including 258 patients diagnosed with MPNST (173 NF1 and 85 non-NF1). Data collected included demographic information, primary tumor location and size, disease stage at diagnosis (localized vs. metastatic), efficacy of CT regimens utilized, and survival data. Descriptive statistics were used to summarize patient characteristics. Chi squared tests or Fisher's exact tests, and t-test/ANOVA were used to compare patient's characteristics and distributions of overall survival (OS), and progression-free survival (PFS) were estimated by the Kaplan-Meier method. **Results:** Median age at diagnosis was 33 yrs (IQR 22-44) and 50 yrs (IQR 38-61), and median tumor size at diagnosis 7.4cm and 6.3cm for the NF1 and non-NF1 cohorts, respectively. Tumors were most commonly located in the trunk, followed by the lower extremity, with head and neck involvement more frequent in non-NF1 cases. Metastatic disease was present at diagnosis in 28.3% of NF1 (49/173) and 22.4% (19/85) of non-NF1 cases. Adriamycin with Ifosfamide (AI) was the most utilized first-line CT regimen while gemcitabine plus docetaxel was the preferred second-line regimen. 154 patients, 87 patients, and 37 patients received frontline, second-line, and third-line CT, respectively. Median PFS for front-line CT was 8.0 months (4.7, NR) for patients with metastatic disease at presentation and 11.7 months (8.94, NR) for patients who received AI. Median OS was 2.34 yrs (1.88, 3.15) vs 1.81 yrs (0.89, 3.76) for NF1 and non-NF1 cohorts (p = 0.038), respectively. 5-yr OS was 42% (33, 51) for local disease and 9% (3, 19) for metastatic disease at presentation. Additional analysis of PFS by NF1 status, lines of therapy, and regimen will be presented at the conference. **Conclusions:** Patients with metastatic MPNST have dismal outcomes and CT efficacy and utilization drops after frontline treatment. These findings highlight the importance of early diagnosis and tailored novel therapeutics for MPNST patients. Research Sponsor: None.

11577 **Poster Session**

Enhancing soft tissue sarcoma surveillance: The role of ctDNA testing in early detection and monitoring beyond traditional imaging. First Author: Amrit Paudel, University of Miami Sylvester Comprehensive Cancer Center/Jackson Health System, Miami, FL

Background: Soft tissue sarcoma (STS), particularly large (>5 cm), intermediate to high grade, and aggressive subtypes, is associated with high relapse rates, necessitating effective surveillance. Traditional methods, including physical exams and radiologic imaging, can be inconclusive, leading to radiation exposure. Circulating tumor DNA (ctDNA), a biomarker from tumor-derived cell-free DNA in the bloodstream, offers a potential solution for early recurrence detection and treatment monitoring. While ctDNA has shown promise in various cancers, its role in STS remains under-explored. **Methods:** We conducted a retrospective analysis of localized, high-risk STS patients who underwent surgery, followed by standard imaging, physical exams, and Signatera ctDNA testing from April 2023-January 2025. The study evaluated the concordance between ctDNA positivity and imaging findings, with a subgroup analysis exploring metastatic patterns and molecular profiles in ctDNA-positive patients. Mann-Whitney test was conducted to evaluate the difference in time to progression between ctDNA and imaging. **Results:** The cohort consisted of 63 STS patients, including 501 plasma samples for Signatera ctDNA testing alongside routine imaging. The patient population was 52% female, 35% Hispanic, and 80% White. ctDNA assay was performed on an average of 8 $\pm$ 4 plasma samples per patient, over a median surveillance duration of 12 months. Of the 63 patients, 18 tested positive for ctDNA. There was no significant difference (p=0.984) in the time to progression between ctDNA testing (35 $\pm$ 17.6 months) and radiological imaging (34.3 $\pm$ 18.5 months). Our data also revealed that all patients with negative ctDNA results had corresponding negative imaging findings. In the subgroup analysis of ctDNA-positive patients, majority had pulmonary metastasis (7, 39%), followed by liver metastasis (3, 16%). Molecular profiling demonstrated significant heterogeneity, with TP53 mutations being the most common alteration, present in 4 (22%) patients. **Conclusions:** Our study demonstrates the potential utility of ctDNA testing in monitoring high-risk STS patients. ctDNA showed no significant difference in time to progression compared to traditional imaging and offers a non-invasive alternative with strong concordance with imaging results, particularly for patients with negative ctDNA findings. These findings underscore the potential of ctDNA as a complementary tool to traditional surveillance methods, potentially reducing reliance on radiologic imaging and enhancing personalized treatment strategies. Research Sponsor: None.

Most common STS subtypes and ctDNA positivity.

STS subtypes	Total number of patients	Positive ctDNA testing (%)
Leiomyosarcoma	15	5 (33.3)
Synovial Sarcoma	7	2 (28)
Liposarcoma	5	3 (60)
Myxofibrosarcoma	4	0 (0)
Fibroblastic	4	1(25)
Pleomorphic	3	1(33.3)
Angiosarcoma	3	1(33.3)
Others	22	5(22)

TPS11578 **Poster Session**

Phase 1a/1b study of the safety, pharmacokinetics, and antitumor activity of ziftomenib in combination with imatinib in patients with advanced gastrointestinal stromal tumors (GIST) after imatinib failure. First Author: Mrinal M. Gounder, Memorial Sloan Kettering Cancer Center and Weill Cornell Medical School, New York, NY

Background: GIST is the most common mesenchymal neoplasm of the digestive tract and is mainly driven by gain-of-function oncogenic mutations in the receptor tyrosine kinase KIT. Patients with GIST are typically treated with anti-KIT tyrosine kinase inhibitors (TKIs) such as imatinib. However, few patients achieve a complete response, and most eventually progress due to secondary alterations in *KIT* that cause resistance to therapy. Additional TKIs are approved in later lines but have shown only moderate clinical outcomes, highlighting the need for additional therapeutic approaches. Preclinical studies have shown that the menin-KMT2A complex epigenetically upregulates *KIT* expression in GIST cells. Ziftomenib is a potent and highly selective menin inhibitor that disrupts formation of the menin-KMT2A complex. Ziftomenib plus imatinib has demonstrated synergistic antitumor activity in imatinib-sensitive and -resistant GIST models, with reduced KIT protein levels and downstream oncogenic signaling observed in imatinib-resistant GIST patient-derived xenografts treated with the combination. Together, ziftomenib plus imatinib may enhance KIT recycling while reducing *KIT* transcription. This combination is currently being investigated clinically in patients with imatinib-sensitive and -resistant advanced GIST. **Methods:** KOMET-015 (NCT06655246) is a phase 1a/1b, open-label study to determine the safety, tolerability, recommended phase 2 dose (RP2D), and preliminary antitumor activity of ziftomenib plus imatinib (400 mg) for advanced/metastatic GIST. KOMET-015 includes dose-escalation, RP2D determination, and dose-expansion parts. Eligible patients ($\geq$18 yrs) must have a biopsy-proven diagnosis of advanced/metastatic *KIT*-mutant GIST (T670X excluded) that progressed on imatinib (dose-escalation and RP2D determination parts), with an ECOG PS of $\leq$2 and measurable disease per modified RECIST (mRECIST). Dose escalation will be based on an i3+3 design to evaluate the safety and tolerability of up to 4 dose levels of ziftomenib combined with imatinib. Based on escalation, up to 2 dose levels will be selected for comparison to determine the RP2D. The dose-expansion part will examine the toxicity and preliminary clinical activity of the RP2D in patients assigned to 1 of 3 cohorts: Cohort A: patients who progressed on imatinib as immediate prior therapy, Cohort B: patients who failed imatinib and had received $\geq$2 lines of therapy, and Cohort C: imatinib-naive patients. Tumor response will be assessed per mRECIST. All adverse events will be recorded, monitored, and graded based on CTCAE v5.0. The trial is open and actively recruiting with sites in the United States. Clinical trial information: NCT06655246. Enrollment opens Feb 2025. Research Sponsor: Kura Oncology, Inc.

TPS11579 **Poster Session**

SARC044: A phase II trial of bezuclastinib in combination with sunitinib in patients with GIST who progressed on sunitinib monotherapy. First Author: Candace L. Haddox, Dana-Farber Cancer Institute, Boston, MA

Background: Gastrointestinal stromal tumors (GIST) are commonly driven by mutations in the receptor tyrosine kinase *KIT*. Resistance to approved tyrosine kinase inhibitors (TKIs) arises from additional KIT mutations in the ATP-binding pocket (AP) and activation loop (AL). No single approved TKI broadly suppresses all resistant clones, and overlapping VEGFR inhibition and toxicity limits TKI combinations. The type I TKI bezuclastinib ("BEZ," CGT9486) inhibits KIT AL resistance mutations, does not inhibit VEGFR, and has complimentary activity with sunitinib ("SUN," inhibitor of KIT AP resistance mutations). The first-in-human study (PLX121-01) and ongoing Peak trial (NCT05208047) evaluated BEZ+SUN showing promising safety and efficacy in GIST. SARC044 investigates BEZ+SUN in patients (pts) with SUN-resistant, KIT-mutant GIST, and correlatives aim to determine mechanisms of response and resistance (NCT06208748). **Methods:** SARC044 is a multi-center, open label, single-arm phase II trial enrolling up to 40 adult pts with KIT exon 9 or 11-mutant GIST resistant to imatinib and SUN. After TKI washout (baseline, "b/l"), pts initiate BEZ 600 mg daily for 2 weeks, then add SUN 37.5 mg daily, taking both drugs continuously (28-day cycles) until mRECISTv1.1 progression or unmanageable toxicity. Response evaluations (RE) are performed every 8 weeks (wk) through 15 months (mo) on study, then every 12 wk. Circulating tumor DNA (ctDNA) is collected at b/l, cycle 1 day 15 (C1D15), C2D1, C3D1, and progression. Targeted exome sequencing (TES) of ctDNA will track primary/resistant KIT mutation dynamics across therapy. ^{18}FDG PET/CTs are performed in 20 pts at b/l, C1D15, and C2D1, which guide a biopsy of a resistant tumor. TES, allele-specific and long-read PCR (to detect AP+AL mutation phasing), and immunoblotting (evaluating KIT pathway activation) will be performed on tissue. EORTC QLQ-C30 surveys collect pt-reported outcomes (PRO) at b/l, on treatment, and at progression. The primary endpoint is median progression-free survival (mPFS) and secondary endpoints include overall survival at 1 and 2 years, clinical benefit rate at 16 wk, adverse event rate, PRO, and KIT mutation profile in ctDNA and tissue. 35 evaluable pts achieves 83% power ($p<0.05$, one-sided) in a one-sample log-rank test to detect a mPFS of 6.5 mo vs 4 mo (historic control). Expected accrual is 12 mo across 4 sites in the United States with ~36 mo to study completion. Clinical trial information: NCT06208748. Research Sponsor: Cogent Biosciences; Life Raft Group; Brown Family Fund; Conquer Cancer©, the ASCO Foundation.

TPS11580 **Poster Session**

An open-label phase 1/2 study of DCC-3009 monotherapy in patients with advanced gastrointestinal stromal tumor. First Author: Sreenivasa R. Chandana, START Midwest, The Cancer & Hematology Centers, Grand Rapids, MI

Background: Gastrointestinal stromal tumor (GIST) is the most common sarcoma of the gastrointestinal tract. *KIT* and platelet-derived growth factor receptor α (*PDGFRA*) mutations remain the key oncogenic drivers in the majority of patients with advanced GIST, with acquired secondary drug-resistant mutations contributing to the heterogeneity and complexity of the disease. The diversity of these resistance mutations allows escape from standard-of-care tyrosine kinase inhibitor (TKI) therapy, creating an unmet need for novel therapies that inhibit all clinically relevant GIST-driving mutations. DCC-3009 is an investigational, highly potent, and selective switch-control KIT and PDGFRA inhibitor designed to act against known clinically relevant primary and secondary GIST-driving mutations while limiting off-target effects. Preclinical data showed that DCC-3009 has strong antitumor effects in xenograft models driven by resistant *KIT* mutations, optimized solubility and oral bioavailability, and low risk of cytochrome P450 inhibition. Here, we describe an ongoing phase 1/2 study evaluating DCC-3009 as a monotherapy in patients with advanced GIST. **Methods:** This study is a multicohort, open-label, phase 1/2 trial evaluating the safety, tolerability, and efficacy of DCC-3009 in patients with advanced GIST (NCT06630234). This trial uses a modular approach, with each module defined according to the therapy (DCC-3009 alone or in combination with other anticancer agents) and divided into 2 parts (dose escalation and dose expansion). For inclusion in the DCC-3009 monotherapy dose escalation, adult patients ($\geq$18 years) must have histologically or cytologically confirmed advanced GIST with documented *KIT* or *PDGFRA* mutation and progression on or intolerance to at least 1 approved TKI regimen in the advanced setting (imatinib if *KIT*-mutant). Patients must have at least 1 measurable lesion per modified Response Evaluation Criteria in Solid Tumors version 1.1 (mRECIST v1.1) and an Eastern Cooperative Oncology Group Performance Status of 0 or 1 at screening. Exclusion criteria include receiving systemic anticancer therapy (encompassing investigational agents) within 14 days or less than 5 half-lives, radiotherapy within 14 days prior to first dose of study drug, prior or concurrent malignancy requiring treatment or expected to need treatment for active cancer, known allergy or hypersensitivity to the study drug components or any of its excipients, and impaired oral absorption or malabsorption syndrome. Enrolled patients across monotherapy dose escalation will receive DCC-3009 orally in 28-day cycles. The primary outcome measures for monotherapy dose escalation include safety assessment. Secondary outcome measures include objective response rate, duration of response, and progression-free survival by mRECIST v1.1, as well as overall survival and pharmacokinetics. Clinical trial information: NCT06630234. Research Sponsor: Deciphera Pharmaceuticals, LLC.

TPS11581 **Poster Session**

PYNNACLE phase 2 clinical trial of rezatapopt in patients with advanced solid tumors harboring a *TP53* Y220C mutation. First Author: Alison M. Schram, Memorial Sloan Kettering Cancer Center, New York, NY

Background: *TP53*, encoding p53 protein, is one of the most frequently mutated genes across all cancers, with TP53 mutations found in ~59% of all solid tumors. *TP53* mutations result in the loss of p53 tumor suppressor functions leading to tumor development and progression. The *TP53* Y220C mutation, occurring in ~1% of all solid tumors, is a missense mutation that destabilizes the p53 protein. Rezatapopt (also known as PC14586) is an investigational, first-in-class, selective, p53 reactivator specific to the *TP53* Y220C mutation that restores wildtype p53 function. Preliminary findings from Phase 1 part of the PYNNACLE (NCT04585750) Phase 1/2 study, showed that rezatapopt had a favorable safety profile and single-agent efficacy in heavily pre-treated patients with solid tumors harboring a *TP53* Y220C mutation (*Schram A, AACR-NCI-EORTC 2023, LBA25*). Here we describe the study design for the registrational Phase 2 part of the PYNNACLE study. **Methods:** The Phase 2 part of PYNNACLE is an ongoing, global, single-arm, open-label, multicenter basket trial in patients with solid tumors harboring a *TP53* Y220C mutation (Table). Patients must have measurable disease at baseline, ECOG performance status 0 or 1, and adequate organ function; other key inclusion criteria are listed in the table. Patients with *KRAS* single nucleotide variants, primary CNS tumors and unstable brain metastases are excluded. Eligible patients receive rezatapopt 2000mg, orally, once daily, taken with food, for continuous 21-day cycles. Patients are followed until death, lost to follow-up, two years after last patient discontinuation, or end of study. As of March 2024, ≈114 patients are planned to be enrolled. Clinical trial information: NCT04585750. Research Sponsor: PMV Pharmaceuticals, Inc.

PYNNACLE Phase 1/2 basket study (NCT04585750).

Patient population N≈114 (planned)	Key inclusion criteria	Primary endpoints	Secondary endpoints
Cohort 1 **Ovarian cancer (platinum-resistant)** **n≈42** **Cohort 2** **Lung cancer** **n≈18** **Cohort 3** **Breast cancer** **n≈18** **Cohort 4** **Endometrial cancer** **n≈18** **Cohort 5** **Other solid tumors** **n≈18**	· Adults aged ≥18 years (all global sites except ≥21 years in Singapore) · Adolescents aged 12–17 years if weight ≥40 kg (90 lbs; Australia, South Korea and USA only) · Locally advanced or metastatic solid tumors · Documented *TP53* Y220C mutation and *KRAS* wild-type* · Prior standard therapy or ineligible for appropriate standard of care therapy	· ORR per BICR assessment (RECIST v1.1) across all cohorts · ORR per BICR assessment (RECIST v1.1) in ovarian cancer cohort	· ORR per investigator assessment (RECIST v1.1) across all cohorts and the ovarian cancer cohort · Time to response, duration of response, disease control rate · Progression-free survival · Overall survival · Safety · Pharmacokinetics · Quality of life

*Defined as no *KRAS* single nucleotide variant.
BICR, blinded independent central review; ORR, objective response rate; RECIST v1.1, Response Evaluation Criteria in Solid Tumors Version 1.1.

TPS11582 **Poster Session**

Phase 3 study of ivosidenib vs placebo in locally advanced or metastatic IDH1-mutant conventional chondrosarcoma untreated or previously treated with 1 systemic treatment regimen (CHONQUER). First Author: Andrew J. Wagner, Dana-Farber Cancer Institute, Boston, MA

Background: Conventional chondrosarcoma (CS) is the most common chondrosarcoma subtype, accounting for 85% to 90% of all chondrosarcoma cases. A meta-analysis of 466 patients with CS reported the detection of IDH1/2 mutations in 51.2% of patients (38.7% IDH1 and 12.1% IDH2 mutations, mutually exclusive except for one case). In a phase 1 study (NCT02073994), the long term follow-up with a data cut-off date of 15 September 2022, showed that patients with advanced conventional CS (N = 13) who were treated with the IDH1 inhibitor ivosidenib had a median progression-free survival (PFS) of 7.4 months, a 6-month PFS rate of 53.8%, and an overall response rate (ORR) of 23.1% including 2 partial responses and 1 complete response. Ivosidenib demonstrated manageable toxicity with mostly grade 1 or 2 treatment emergent adverse events (AEs) (Tap et al. J Clin Oncol. 2023; 41:11532). The current phase 3 CHONQUER study was designed to assess the efficacy and safety of ivosidenib treatment in patients with grades 1, 2 and 3 conventional CS. **Methods:** The CHONQUER study (NCT06127407) is a phase 3, international, multicenter, double-blind, randomized, placebo-controlled study of ivosidenib for patients with locally advanced or metastatic IDH1 mutant conventional CS untreated or previously treated with 1 systemic treatment regimen. Key eligibility criteria include a histopathological diagnosis of conventional CS (grades 1, 2, or 3), locally-advanced or metastatic setting not eligible for curative resection; ECOG PS 0-1; measurable disease as defined by Response Evaluation Criteria in Solid Tumors (RECIST v1.1); received 0 or 1 prior systemic treatment regimen in the advanced/metastatic setting for CS; radiographic progression/recurrence of disease over a period of 6 months according to RECIST v1.1 and IDH1 gene-mutated disease confirmed by central laboratory testing with the Ion Torrent Oncomine Dx Express Test. A total of 136 patients are planned to be enrolled and will be randomized 1:1 to ivosidenib or a matched placebo control. Randomization will be stratified by disease grade (grade 1 versus 2 versus 3) and locally advanced versus metastatic disease. The primary endpoint is PFS confirmed by Blinded Independent Central Review (BIRC) in grade 1 and 2 patients. The key secondary endpoints include PFS based on BIRC for all randomized patients, overall survival (OS) (both grade 1 and 2 and all randomized patients). Other secondary endpoints include PFS by investigator, overall response, duration of response, time to response, disease control, duration of disease control, adverse events, and health-related quality of life. 92 sites from 12 countries are planned to participate, including North and South America, Europe and Asian countries. Clinical trial information: NCT06127407. Research Sponsor: Servier.

TPS11583 Poster Session

Phase I/II study to evaluate the feasibility and efficacy of sequential abemaciclib and gemcitabine treatment in patients with retinoblastoma (Rb)-positive leiomyosarcoma (LMS) and dedifferentiated liposarcoma (DDLPS). First Author: Elise F. Nassif Haddad, Department of Sarcoma Medical Oncology, The University of Texas MD Anderson Cancer Center, Houston, TX

Background: LMS and DDLPS are aggressive malignancies with limited effective therapies in the advanced setting. Approximately 50% of LMS and nearly all DDLPS retain functional Rb protein, suggesting sensitivity to cell cycle inhibition. Our preclinical studies have demonstrated that combining sequential abemaciclib, a selective CDK4/6 inhibitor that induces cell cycle arrest, followed by gemcitabine timed with synchronized cell cycle reentry, results in synergistic antitumor activity in Rb-positive sarcomas. Sequential administration of abemaciclib followed by gemcitabine enhances apoptosis, impairs DNA repair mechanisms, and induces sustained cell cycle arrest. **Methods:** This is a multicenter, open-label, phase 1/2 clinical trial conducted through the National Cancer Institute (NCI), enabling broad, nationwide patient enrollment. The phase 1 dose-escalation portion will determine the maximum tolerated dose and recommended phase 2 dose of sequential abemaciclib and gemcitabine in patients with advanced/metastatic soft-tissue sarcomas. Part A of phase 1 will use biomarkers of cell cycle (functional positron emission tomography imaging using [18]F-fluoro-3′-deoxy-3′-L-fluorothymidine and thymidine kinase activity) to determine the optimal schedule of sequencing. Part B of the phase 1 will follow the BOIN design. Eligible patients must have histologically confirmed LMS or DDLPS with Rb positivity confirmed by immunohistochemistry, measurable disease, ECOG performance status $\leq$2, and adequate organ function. Prior gemcitabine therapy is permitted in phase 1 but excluded in phase 2. Phase 1 Part A is restricted to MD Anderson only enrollment due to the requirements of biomarker integration and timing. In the randomized phase 2 portion, patients will be randomized 1:1 (stratified by DDLPS vs LMS) to receive either (1) sequential abemaciclib followed by gemcitabine or (2) gemcitabine and docetaxel. The primary endpoint is progression-free survival, with secondary endpoints including objective response rate, overall survival, and safety. Correlative studies will analyze tumor biopsies and blood samples collected at baseline, after two treatment cycles, and at disease progression. Biomarker analyses will include RB1 expression profiling, whole exome sequencing, RNA sequencing, and circulating tumor DNA. Clinical trial information: NCT06498648. Research Sponsor: ETCTN - CTEP.

TPS11584 Poster Session

A phase 3, randomized, double-blind, placebo-controlled study to assess the efficacy and safety of emactuzumab in patients with tenosynovial giant cell tumor (TANGENT). First Author: Hans Gelderblom, LUMC Leids Universitair Medisch Centrum, Leiden, Netherlands

Background: Tenosynovial giant cell tumor (TGCT) is a rare, non-malignant, locally aggressive tumor of the synovium, primarily affecting knee, hip, and ankle joints. TGCT is caused by excessive production of colony stimulating factor 1 (CSF-1), a cytokine involved in the proliferation, differentiation, and survival of monocytes and macrophages. It is a chronically debilitating disease, causing pain, stiffness, loss of function in the affected joints and a decline in quality of life. The worldwide incidence in digits, localized, and diffuse TGCT is about 29, 10, and 4 per million person-years, respectively. Surgery remains the principal treatment option, at the cost of a high rate of tumor recurrence, and risk of damage to the affected joint and surrounding tissues. Systemic treatment options are limited. Emactuzumab is a novel monoclonal antibody, and potent and specific CSF-1 receptor (CSF-1R) antagonist, that causes apoptosis of M2-type macrophages in the tumor micro-environment, thereby inhibiting tumor growth. In a phase Ia/b study, emactuzumab was administered i.v. at doses varying from 900-2000 mg (cycles ranging 1-14) in advanced diffuse TGCT patients (Cassier et al, EJC, 2020). Emactuzumab was well tolerated and showed rapid and pronounced responses with an objective response rate (ORR) of 71%, which was durable with an ORR of 70% and 64% after one or two years, respectively. Clinical activity was associated with symptomatic improvement. The optimal biological dose of emactuzumab, defined as 1000 mg q2w, is under investigation in the Phase 3 trial. Emactuzumab was granted an Orphan Drug Designation by the European Medicines Agency in March 2022. **Methods:** TANGENT (NCT05417789) is a randomized, double-blind, placebo-controlled trial designed to confirm the efficacy and safety of emactuzumab in TGCT patients not amenable for surgery. The primary endpoint is efficacy, assessed as ORR at 6 months by MRI per RECIST v1.1. Key secondary endpoints include patient-reported outcomes (PROMIS-PF), range of motion, pain and stiffness, and other antitumor activity (e.g. TVS). In Part 1, subjects will be randomized 2:1 to receive either emactuzumab 1000 mg or placebo i.v. q2w for 5 doses over 10 weeks, followed by an observation period of 3 months. Part 2 is a follow-up phase from 6-24 months post randomization during which subjects whose TGCT worsens may be eligible for emactuzumab. The study is actively recruiting. Assessments include tumor evaluation, physical examination, vital signs, electrocardiograms, questionnaires, urinalyses, and blood tests for hematology, biochemistry, and PK of emactuzumab. Safety will be assessed by laboratory assessments and evaluation of adverse events. Clinical trial information: NCT05417789. Research Sponsor: SynOx Therapeutics.

TPS11585 Poster Session

ETCTN 10563: A phase I study of peposertib and liposomal doxorubicin for advanced or metastatic leiomyosarcoma and other sarcomas. First Author: Candace L. Haddox, Dana-Farber Cancer Institute, Boston, MA

Background: Soft tissue sarcomas (STS) with genomic complexity are often aggressive but may be sensitive to further genotoxic stress. Leiomyosarcoma (LMS), a common STS, frequently harbors genomic complexity and DNA damage response (DDR) dysregulation. Preclinical data showed hyper-dependency on DNA-PK-mediated non-homologous end joining (NHEJ) DDR, and low-dose liposomal doxorubicin (LD-LPD) synergized with the DNA-PK inhibitor peposertib to inhibit tumor growth in LMS models. We hypothesize that a low, sensitizing dose of LPD enhances DNA damage and safely synergizes with peposertib in LMS and other genomically complex STS. **Methods:** This phase 1, open label, multicenter dose escalation and dose expansion study (NCT05711615) evaluates LD-LPD given intravenously (IV) on day 1 of 28-day cycles with peposertib given orally (PO) twice daily (BID) continuously (Table). Up to 18 patients (pts) over 18 years-old with advanced or unresectable LMS, undifferentiated pleomorphic sarcoma, myxofibrosarcoma, dedifferentiated liposarcoma, and synovial sarcoma, ECOG performance status $\leq$2, who received $\geq$1 prior line of systemic therapy (including anthracycline $\leq$300 mg/m^2) are eligible for dose escalation. Dose expansion will include 12 pts with LMS. The primary objective is to determine the recommended phase 2 dose of LPD+peposertib based on the dose limiting toxicity rate. The Bayesian Optimal Interval (BOIN) design will inform dose escalation decisions. Secondary endpoints for the expansion cohort include adverse event rate, progression-free survival, and objective response rate per RECIST v1.1. Potential predictive biomarkers and changes in DDR biomarkers will be evaluated on biopsies during screening and at cycle 1 day 7. Circulating tumor DNA (ctDNA) collected at baseline (dose escalation and dose expansion), on treatment and at progression (dose expansion) will be correlated with disease activity and response. This trial activated on 8-May-2023 through the Experimental Therapeutics Clinical Trials Network (ETCTN) and is enrolling at select sites in the United States. Dose escalation is ongoing as of January 2025. Clinical trial information: NCT05711615. Research Sponsor: National Institutes of Health/National Cancer Institute (NIH/NCI); National Cancer Institute/U.S. National Institutes of Health; Merck KGaA, Darmstadt, Germany CrossRef Funder ID: 10.13039/100009945.

Planned dose levels for dose escalation.

Dose Escalation Schedule

	Dose	
Dose Level	**Liposomal doxorubicin**	**Peposertib (tablet)**
-1	10 mg/m^2 IV	50 mg PO BID
0*	10 mg/m^2 IV	100 mg PO BID
+1	10 mg/m^2 IV	150 mg PO BID
+2	10 mg/m^2 IV	200 mg PO BID
+3	15 mg/m^2 IV	200 mg PO BID
+4	20 mg/m^2 IV	200 mg PO BID

*Starting dose.

TPS11586 Poster Session

The phase II study of pembrolizumab plus lenvatinib for patients with unresectable cutaneous angiosarcoma (Pembro-Lenva for cAS/PLAS trial). First Author: Dai Ogata, National Cancer Center Hospital, Tokyo, Japan

Background: Cutaneous angiosarcoma (cAS) is a rare cancer that often occurs in elderly people with common recurrence and metastasis after surgery. Chemotherapy, radiation therapy, and their combination are widely used, but their effectiveness is insufficient. With the increasing number of cAS patients due to the aging population, the development of effective treatment is urgently required. Previously, it has been reported that cancer shrank in 18% (5 out of 27) of patients after 2 months of paclitaxel administration in a clinical trial. Therefore, paclitaxel has become more commonly used for cAS. Other options include anthracycline anticancer drugs and gemcitabine. However, even with these anticancer drugs (and radiation therapy), cAS progresses quickly, and some reports have said that the 5-year survival rate is 9%. This study is planned to develop safer and more effective treatment for cAS. Pembrolizumab is an immune checkpoint inhibitor with PD-1 receptor-ligand interaction and lenvatinib is a multikinase inhibitor that inhibits tumor angiogenesis. The combination is expected to have strong therapeutic efficacy due to the immunomodulatory effects of pembrolizumab and the inhibitory effects of lenvatinib. **Methods:** This investigator-initiated, prospective, multicenter, non-randomized phase II trial evaluates the efficacy and safety of pembrolizumab plus lenvatinib for patients with unresectable cAS. Eligible patients are aged $\geq$18 years ($\leq$85 years), histologically diagnosed with cAS, and both untreated and previously treated patients. The primary endpoint of this study is to confirm the response rate of pembrolizumab plus lenvatinib combination therapy for unresectable cAS based on RECST 1.1 at central review. The secondary endpoints are response rate (primary investigator assessment), progression-free survival, overall survival, disease control rate, duration of response, time to response, incidence of adverse events (AEs), incidence of drug-related adverse events (adverse drug reactions, ADRs), and incidence of serious AEs/ADRs. We estimated a threshold response rate of 18% and an expected response rate of 35%. The planned sample size is 38 patients (25 untreated patients and 13 treated) to provide a power of 70% with one-sided alpha of 5%. The planned accrual period is 2 years, and the follow-up period is 2 years; interim analysis will be performed at the enrollment of 20 patients is completed. The trial began in February 2025. Clinical trial information: NCT06673628. Research Sponsor: None.

TPS11587 **Poster Session**

Integrating early palliative care in advanced sarcoma patients for enhanced quality of life: The SARQUALITY study. First Author: Catherine S. Weadick, Princess Margaret Cancer Centre, Toronto, ON, Canada

Background: Patients with advanced cancer may experience physical and psychological symptoms impacting health-related (HRQOL). The World Health Organization defined palliative care as "an approach that improves the quality of life of patients and their families" by identification and management of pain and other symptoms, spiritual and psychosocial assessments and interventions, facilitation of home and community-based supports, and transition to end-of-life care. Early palliative care (EPC) integration with cancer-directed treatment can enhance patient-reported outcomes (PROs). However, patients with sarcoma have been underrepresented in these studies, underscoring the need to evaluate the role and benefits of EPC in this population. This study aims to determine whether EPC alongside standard oncological care (SOC) improves PROs for patients with advanced sarcoma compared to usual care. **Methods:** This is a single program, dual institution phase 2 open-label clinical trial designed to assess whether EPC improves the HRQoL of patients with advanced sarcoma. Main eligibility criteria at enrolment include systemic treatment naïve patients over the age of 18 years with histologically proven advanced sarcoma, ECOG 0-2, English speaking and life expectancy of over 6 months. Enrolled patients are randomized 1:1 to either SOC alone or with EPC. Patients randomized to EPC will be reviewed by palliative care within 2 weeks of randomization. EPC will include routine in person (or virtual) contact integrated into their oncology visits and access to a 24-hour on-call service. Patients receiving SOC alone will be referred to palliative care upon emergence of uncontrollable symptoms or upon request by the patient. Patients on both arms will receive standard of care follow-up with their oncology teams and complete Edmonton Symptom Assessment System (ESAS) and EORTC QLQ-C30 questionnaires at baseline, weeks 6, 12 and 24. For the primary endpoint, EPC will be considered effective if ESAS score decreases at week 12 compared to baseline using T test, with one-sided significance level set to be 0.05. The secondary endpoints include EORTC QLQ-C30 score change (baseline to weeks 6, 12 and 24), number of extra clinic visits, emergency department attendance and overall survival at 6 and 12 months. Comparison between the two arms, assessing both scores, will be done using Fisher's exact or Chi-square test. Generalized linear mixed model will be carried out to examine the difference between the arms over time. To ensure this trial is powered to determine a significant statistical difference, we plan to enroll 136 patients with an estimated accrual period up to three years. This study commenced enrolment March 2024 and to date (January 2025) 27 patients have been recruited with 13 (48%) randomized to EPC. An amendment is currently ongoing to include the use of electronic wearables as part of the study evaluation. Research Sponsor: None.

TPS11588 **Poster Session**

A multicenter, randomized, global phase 3 study to assess the efficacy and safety of intratumoral (IT) INT230-6 (SHAO, vinblastine, cisplatin) as monotherapy compared with standard of care systemic chemotherapy in adults with locally recurrent, inoperable, or metastatic soft tissue sarcomas (STS; INVINCIBLE-3). First Author: Sant P. Chawla, Sarcoma Oncology Center, Santa Monica, CA

Background: Soft tissue sarcomas (STS) are a rare and diverse set of tumors. Systemic chemotherapy provides limited benefit for metastatic disease. INT230-6 is a novel formulation of cisplatin (CIS) and vinblastine (VIN) with a tissue dispersion enhancer (SHAO). The drug's unique chemistry permits dispersion throughout tumors and diffusion into the cancer cells after IT injections. The drug causes apoptosis and recruits T-cells to the tumor. An open-label, phase 1/2 study was completed with locally advanced, unresectable, or metastatic adult patients with 11 STS subtypes. Patients had a median of 3 prior lines. Biopsied tissue from pre- and post-dosed tumors[2] showed immune engagement post-dose. PK data showed that >95% of VIN stayed in the tumor. There were no dose-limiting toxicities up to 175 mL (87.5 mg CIS, 17.5 mg VIN). The disease control rate was 93%. Uninjected tumors shrank. The median OS for INT230-6 alone (n=15) was 21.3 CI (4.7, NR) months. The maximum severity of INT230-6 treatment-related adverse events (TRAEs) in STS patients was 6.7% grade 1, 60% grade 2, and 33% grade 3 (no related grade 4 or 5 AEs). The most common TRAEs were pain, fatigue, and nausea. **Methods:** IT-03 is a 2:1 randomized trial comparing INT230-6 as monotherapy to an investigator's choice of pazopanib, trabectedin, or eribulin, per label. A total of 333 patients in 2L/3L will be enrolled in the US, Canada, Europe, and Australia. INT230-6 dose is set by tumor size. INT230-6 is given IT Q2W for up to 5 doses to as many tumors >1 cm as is deemed safe. Maintenance is Q12 weeks for up to 22 months. Statistics: 90% power to detect a survival HR of 0.65 with 3 interim assessments at 20%, 40%, and 60% of participants events (deaths). The final analysis is at 80% of events. There is a two-sided total alpha = 0.05, allocated as follows: interim #1 = 0.0039; #2 = 0.0184; final = 0.043. Includes up to 60 sites: several sites are now recruiting. Inclusion criteria: Must be $\geq$ 18 yo, and provide written consent, Proven, unresectable, locally advanced, or metastatic STS; Must have received at least one line of therapy and progressed after anthracycline therapy. 1 tumor for injection of at least 2 cm. Adequate organ function in screening; lab values of: Neutrophils $\geq$ 1500/μL ($\geq 1.5\times 10^9$/L). PT, and INR $\leq 1.5\times$ ULN, platelets $\geq$ 100,000/μL; hemoglobin $\geq$ 9 g/dL. Criteria must be met without erythropoietin dependency or packed red blood cell transfusion within last 2 weeks. Creatinine normal; or clearance > 50 mL/min by the C-G equation. ALT SGOT/ AST SGPT $\leq 2.5\times$ ULN without, and $\leq 5\times$ ULN with hepatic metastases. Bilirubin (BR) $\leq 1.5\times$ ULN (except those with Gilbert's syndrome, who must have total BR $\leq$ 3.0 mg/dL [< 52 μmol/L]). CPK $\leq 2.5\times$ ULN. Clinical trial information: NCT06263231. Research Sponsor: Intensity Therapeutics.

TPS11589 **Poster Session**

Trial in progress: TAGGED—A phase 2 study using low dose/metronomic trabectedin, gemcitabine, and dacarbazine as 2nd/3rd/4th line therapy for advanced soft tissue sarcoma (NCT04535271). First Author: Samantha Jeffrey, Sarcoma Oncology Center, Santa Monica, CA

Background: Despite significant progress in the field of cancer medicine, the prognosis of advanced soft tissue sarcoma (STS) patients remains poor. Standard of care includes surgery for resectable tumors, generally paired with adjuvant radiation and chemotherapy. Anti-neoplastic drugs trabectedin, gemcitabine, and dacarbazine, have all demonstrated efficacy in STS. However, standard doses often result in toxicity and chemoresistance. Thus, we hypothesize that a low dose/metronomic combination regimen of intravenous trabectedin, gemcitabine, and dacarbazine will produce synergistic/additive activities without additive toxicities, providing a safer and more efficacious alternative to standard chemotherapy regimens. **Methods:** This Phase 2 open-label single-site study (NCT04535271) will evaluate the efficacy and safety of low dose/metronomic trabectedin, gemcitabine, and dacarbazine in prolonging progression free survival in patients with advanced STS. A total of 80 previously treated patients, 18 years or older, with locally advanced, unresectable or metastatic STS will receive trabectedin 0.5mg/m2 CIV over 24 hours, gemcitabine 200 mg/m2 IV, and dacarbazine 200 mg/m2 IV on D1 and D8. Each cycle will be 3 weeks. Treatment will continue up to one year or until disease progression or unacceptable toxicity. The primary endpoint is Progression Free Survival (PFS), estimated by the Kaplan-Meier method with two-sided 95% confidence interval. Secondary endpoints include best overall response (BOR) and duration of response (DOR) by RECIST v1.1 criteria, PFS rate, overall survival (OS) rate at 4, 6, and 12 months, and incidence of treatment-related adverse events (TRAEs). The Intention-To-Treat (ITT) population, consisting of all patients who received at least one dose of each study drug, will be used for adverse event analysis. The Modified Intention-To-Treat (MITT) population, consisting of patients who completed the first 2 cycles and have had follow-up imaging, will be used for analysis of PFS, BOR, DOR, PFS, and OS. Key inclusion criteria include a pathologic diagnosis of locally advanced or metastatic STS, previously treated patients with measurable disease by RECIST v1.1, ECOG $\leq$ 2, life expectancy of at least 3 months, acceptable liver and renal function, and acceptable hematological and organ functions. Key exclusion criteria include patients who have progressed with all three study drugs, known hypersensitivity to any of the three study drugs, currently receiving treatment or are <14 days since ending treatment with another investigational device or drug study, pregnant or breastfeeding or who have plans to become pregnant, breastfeed, or unwilling to use female or male contraception. The study has enrolled 13 of 80 patients and is actively recruiting. Clinical trial information: NCT04535271. Research Sponsor: None.

LBA12000 **Oral Abstract Session**

PRO-ACTIVE: Results of a pragmatic phase IV randomized trial comparing the effectiveness of prophylactic swallow intervention for patients receiving radiotherapy for head and neck cancer. First Author: Katherine A. Hutcheson, The University of Texas MD Anderson Cancer Center, Houston, TX

The full, final text of this abstract will be available at meetings.asco.org on the day of presentation and in the online supplement to the June 10, 2025, issue of the *Journal of Clinical Oncology*.

12001 **Oral Abstract Session**

Phase III randomized placebo-controlled trial on repurposing olanzapine for prevention of radiotherapy-induced nausea and vomiting (RINV): CTRI/2022/01/039723. First Author: Meenu Vijayan, Amrita School of Pharmacy, Amrita Vishwa Vidyapeetham, AIMS Health Sciences Campus, Kochi, Kerala, India

Background: Prospective placebo controlled randomized study with or without olanzapine, to evaluate its role in reducing RINV in abdominal-pelvic radiation therapy patients. **Methods:** Phase III, double-blind, placebo-controlled trial in patients undergoing radiotherapy (RT) [Eligibility: >18 yrs, abdominal/pelvic RT, no prior RT history] were randomized to receive 5mg olanzapine or matching placebo daily, along with standard care (ondansetron 4mg twice daily) using simple randomization method. Primary endpoint was nausea prevention. Secondary endpoint was no emesis, no rescue medications, toxicity (CTCAE v5), & QOL. Pearson chi-square test & independent t-test employed for statistical analysis. **Results:** Between Feb 2022 to Aug 2024, 683 patients were screened & 301 randomized [153 placebo, 148 experimental/olanzapine]. In placebo & experimental arm, mean age was 63.8 years (+/- 10.8) & 62.3 years (+/-10.4), female 42% & 37%, rectal cancer 77(50%) & 72 (49%), prostate 47 (31%) & 46 (31%), endometrial cancer 14 (9%) & 14(9.5%), pancreatic cancer 9(6%) & 5(3.4%) (p=NS). In placebo & experimental arm, Image-guided RT done in 89% & 83%(p=NS), concurrent chemotherapy in 57% & 53% (p=NS). During RT, 'no nausea' & 'no vomiting' complain in placebo & experimental arms were 16.3 & 85.8% (p= <0.001); 74.5% & 95.9% (p= <0.001). Total number of vomiting episodes >15 times during RT in placebo & experimental arm were 9.2% & 2% (p=0.002). Rescue therapy during RT required in 7.8% placebo &1.4% in experimental arm (p=0.008). Grade≥2 nausea in placebo & in experimental arm 67% & 7.4% (p=0.001), and vomiting 7.8% & 1.4% (p=0.001). In rectal cancer, nausea grade ≥2 in placebo & experimental arm were 85.7% & 2.8% (p=0.001) & in prostate cancer 19% & 9% (p=0.018). In experimental arm, significant adverse reactions (grade 1) included drowsiness (p<0.001), dysarthria (p=0.003), and orthostatic hypotension (p<0.001). Mean anxiety score before & after RT in placebo was 13.2 (+/-2.5) &14.5 (+/-2.4) (p<0.001); in experimental arm 13.4 (+/-2.3) & 11.1 (+/-2.2) (p<0.001); Mean depression score before & after RT in placebo & experimental arm were 11.9 (+/-1.6) & 13.7 (+/-1.8) (p<0.001); 11.9 (+/-1.6) & 9.7 (+/-1.6) (p<0.001). The olanzapine group had more sleep hours/day (8.4 ±1.7 hours vs. 5.29 ±1.13 hours; p<0.001). QOL score from baseline to end of RT showed improvement in emotional function, nausea/vomiting, insomnia, & loss of appetite (all p<0.001) in olanzapine arm. Mean EORTC GHS QOL score at RT completion was 61.6 (+/- 8.6) in placebo arm and 62.9 (+/-9.2) in experimental arm (p=0.235). **Conclusions:** Adding olanzapine 5mg along with standard antiemetics demonstrated a significant reduction in RINV in patients receiving abdominal-pelvic radiation therapy. Clinical trial information: CTRI NO/2022/01/039723. Research Sponsor: Indian Council of Medical Research; 58/22/2020/PHA/BMS.

12002 **Oral Abstract Session**

Randomized control trial to validate mitigation of chemotherapy-induced peripheral neuropathy by limb-cooling apparatus in breast cancer patients receiving paclitaxel (CECILIA). First Author: Toshimi Takano, Department of Breast Medical Oncology, The Cancer Institute Hospital of Japanese Foundation for Cancer Research, Tokyo, Japan

Background: Chemotherapy-induced peripheral neuropathy (CIPN) is a common adverse event affecting patient quality of life. Limb cooling may help to prevent CIPN, but no phase 3 trials have confirmed its efficacy, and its efficacy and safety remain challenging. This trial determined if temperature-controlled limb cooling could reduce CIPN in patients with breast cancer receiving weekly perioperative paclitaxel (PTX). **Methods:** This multicenter, double-blind, randomized controlled trial (jRCT2032210115) assigned patients with breast cancer scheduled to receive 12 weekly doses of perioperative PTX (60 min 80 mg/m^2 intravenous infusion) chemotherapy randomly (1:1) to limb-cooling therapy at a constant temperature of 13°C (Experimental arm) or 25°C (Control arm). The primary endpoint was the proportion of patients with Patient Neurotoxicity Questionnaire (PNQ) ≥D in their limbs after PTX treatment or at the time of discontinuation. Secondary endpoints were NCI-PRO-CTCAE™, EORTC QOL-QLQ-C30, and CIPN-20, and adverse events of cooling therapy. We assumed primary endpoints of 37% and 15% in the Control and Experimental arms, respectively. The planned sample size was 150 to detect a difference (Fisher's exact test, power 80%, 1-sided alpha 2.5%). **Results:** The study randomized 150 patients (n = 75 each arm). The PTX treatment completion rates (≥80%) were 88.0% (66/75) in the Experimental and 93.3% (70/75) in the Control arm. The proportion of patients with PNQ ≥D by the end of the treatment (primary endpoint) was similar in both arms (13°C vs. 25°C, 33.3% [25/75] vs. 29.3% [22/75], 1-sided p = 0.76). The proportions were higher in the Experimental arm 3 months after the end of PTX and in patients registered from June to September (Table). The proportion of patients with PNQ ≥D was higher in patients with hand epidermal temperature below the mean (21.5°C) at completion of PTX infusion than in the whole population (38.5%, Table). No frostbite or adverse events were reported in either arm. **Conclusions:** The primary endpoint did not meet and the limb cooling therapy using a stable cooling device resulted in lower proportion of PNQ ≥ D than was assumed for the Control arm irrespective of temperature settings, warranting further studies to determine optimal temperature. Clinical trial information: jRCT2032210115. Research Sponsor: Nippon Sigmax Co, Ltd.

Efficacy	13°C cooling (95%CI)	25°C cooling (95%CI)	P value
PNQ ≥D (primary endpoint)	33.3% (22.9–45.2)	29.3 % (19.4–41.0)	0.76
NCI-PRO-CTCAE	48.0% (95%CI 36.3–59.9)	49.3 % (37.6–61.1)	0.87
EORTC QLQ-CIPN20 (% non-worsening scores)	28.1% (95%CI 17.6–40.8)	8.8 % (3.3–18.2)	0.006
PNQ ≥D 3 months after end of PTX	32.0% (95%CI 21.7–43.8)	16.2 % (8.7–26.6)	0.034
PNQ ≥D in pts registered June–September	58.1% (39.1–75.5)	25.8 % (11.9–4.6)	0.020
PNQ ≥D in pts with hand epidermal temperature <21.5°C	38.5% (23.4–55.4)	-	-

12003 **Oral Abstract Session**

Music therapy versus cognitive behavioral therapy for anxiety in cancer survivors: A telehealth-based randomized clinical trial. First Author: Kevin T. Liou, Memorial Sloan Kettering Cancer Center, New York, NY

Background: Anxiety is prevalent, disruptive, and under-treated among cancer survivors. While the pandemic exacerbated the mental health crisis, it also accelerated telehealth adoption, creating opportunities to expand access. Cognitive behavioral therapy (CBT) is the gold standard for anxiety, but not all survivors respond to it, have access, or prefer this option due to stigma. Music therapy (MT) has demonstrated short-term anxiety reduction, but its long-term effectiveness relative to other treatments is unknown. This study evaluated whether MT is noninferior to first-line CBT when both are delivered remotely. **Methods:** In this randomized clinical trial, English- or Spanish-speaking survivors of any cancer type or stage with anxiety lasting ≥1 month were randomized 1:1 to MT or CBT. Participants received 7 weekly sessions of a standardized protocol via Zoom and were followed for 26 weeks. Co-primary endpoints were Hospital Anxiety and Depression Scale (HADS) anxiety subscale changes at weeks 8 and 26. Secondary outcomes included depression, fatigue, insomnia, pain, cognitive function, and quality of life. Data were analyzed with linear mixed-effects models following intention-to-treat. Assuming 15% attrition and 1-sided p < 0.025, the trial had 80% power to detect noninferiority within a margin of D = 0.35*standard deviations (SDs). The margin was informed by an expected SD of 4.2 and the minimum clinically important difference (MCID) of 1.7 points for the HADS anxiety subscale. Thus, establishing noninferiority would indicate differences between MT and CBT are not clinically meaningful. **Results:** Among 300 (147 MT; 153 CBT), mean age was 56.9 (SD 13.2) years, 224 (74.7%) were female, 228 (76.5%) were white, and 57 (19.1%) were Hispanic. The most common cancer types were breast (45.3%) and hematologic (15.7%). At week 8, mean change in HADS anxiety score was -3.12 (95% CI -3.59 to -2.65) in MT and -2.97 (95% CI -3.45 to -2.50) in CBT; between-group difference was -0.15 (95% CI -0.78 to 0.49), which was within margin of 1.20 (P < 0.001 for noninferiority of MT; calculated from SD of 3.42). At week 26, mean change was -3.31 (95% CI -3.78 to -2.85) in MT and -3.00 (95% CI -3.47, -2.53) in CBT; between-group difference was -0.31 (95% CI -0.95 to 0.32), which was within margin of 1.30 (P < 0.001 for noninferiority of MT; calculated from SD of 3.65). Both groups produced anxiety reductions exceeding MCID of 1.7 and showed similar improvements in secondary outcomes. **Conclusions:** MT was non-inferior to CBT for short- and long-term anxiety reduction among diverse survivors of various cancer types. Both treatments produced clinically meaningful, durable anxiety reduction and were delivered remotely using standardized protocols, thereby increasing their reach and scalability. MT should be considered alongside first-line CBT to expand treatment options for anxiety during cancer survivorship. Clinical trial information: NCT05215353. Research Sponsor: Patient-Centered Outcomes Research Institute.

12004 **Oral Abstract Session**

Fear of cancer recurrence in long-term colorectal cancer survivors: A randomized controlled trial of a therapist-guided eHealth intervention. First Author: Johanne Dam Lyhne, Department of Oncology, Lillebaelt Hospital, University Hospital of Southern Denmark, Vejle, Denmark

Background: Despite the availability of effective interventions, fear of cancer recurrence (FCR) remains a prevalent and significant concern among cancer survivors, underscoring the need for more accessible and scalable approaches. This trial assessed the effectiveness of a therapist-guided eHealth intervention, TG-iConquerFear. **Methods:** This parallel randomized controlled trial (ClinicalTrial.org #NCT04287218) enrolled Danish colorectal cancer survivors (CRCS) who had completed curative-intent primary treatment between March 2014 and December 2018, were aged ≥ 18 years, and reported Fear of Cancer Recurrence Inventory-Short Form (FCRI-SF) scores ≥22 (i.e. clinical FCR). After diagnostic interview, eligible participants were randomized to TG-iConquerFear (intervention) or a webpage with self-help mindfulness exercises (augmented control) in a 1:1 ratio. The 10-week TG-iConquerFear program comprised six modules with written therapist guidance delivered asynchronously. Follow-up questionnaires were administered at two weeks (T1), three months (T2), and six months (T3) post-intervention. The primary outcome was predefined as the difference in the change scores of the total FCRI score at T2, analyzed as intention-to-treat. Secondary outcomes were anxiety, depression, emotional distress, health-related quality of life (HrQoL) and physical symptom burden. Pre- and post-intervention mean within and between groups were pairwise compared using Student's t-test. **Results:** Of 9,946 eligible CRCS, 5,515 (55.4%) completed FCR screening, and 299 (5.4%) CRCS reported clinically significant FCR (FCRI score ≥ 22). Among them, 221 (73.9%) expressed interested in FCR treatment, and 103 (46.6 %) were randomized to TG-iConquerFear (n = 49) or control (n = 54). Main reasons for non-randomization included new cancer diagnoses or FCR not affecting everyday life. Participants completed 4.5 modules on average, and 55% completed the intervention. Baseline total FCRI score was 84.6/168 in both groups. Total FCRI score decreased more from baseline to T2 in the TG-iConquerFear group (mean -21.7, 95% CI [-30.1, -13.3]) compared to the augmented control group (mean -2.6 95% CI [-7.8, 2.6]). This represents a between-group difference at T2 of 19.1 (95% CI [10.0, 28.3], p < 0.001) corresponding to a standardized effect size (Cohen's *d*) of 0.62 (95% CI [0.13 - 1.1]). A higher proportion of TG-iConquerFear participants were in the non-clinical range at T2 compared to control participants (81.5% vs. 42.9%, p = 0.002). Statistically significant differences favoring the intervention group were observed across all secondary outcomes. **Conclusions:** The TG-iConquerFear intervention demonstrated a statistical and clinically significant reduction in fear of cancer recurrence in a population of long-term CRCS. The effects were sustained at six months post-intervention. Clinical trial information: NCT04287218. Research Sponsor: Danish Cancer Society; #12781, #16561 and #17152; The Tryg Foundation; #146250 and #152299; Dagmar Marshall Foundation; Fabrikant Einar Willumsen Memorial Fund; Overlæge Jørgen Werner Schou and Wife Else Marie Schou, Born Wonge Fund; Tømrermester Jørgen Holm's Memorial Grant; Region of Southern Denmark; Research Council of Lillebaelt Hospital.

12005 **Oral Abstract Session**

Results of a multisite randomized trial of Bright IDEAS-Young Adults: Efficacy of problem-solving skills training on distress and health-related quality of life. First Author: Katie Devine, Rutgers Cancer Institue, New Brunswick, NJ

Background: Young adults (YAs) diagnosed with cancer between the ages of 18 and 39 face unique psychosocial challenges and are at risk of experiencing significant emotional distress and poor health-related quality of life (HRQOL). This randomized trial evaluated the efficacy of Bright IDEAS-YA, a problem-solving skills training intervention, on reducing distress and improving HRQOL of YAs newly diagnosed with cancer. A secondary aim examined change in problem-solving ability as a potential mediator of treatment effects. **Methods:** A three-site randomized trial of Bright IDEAS-YA compared with enhanced usual care (EUC) enrolled YA survivors within four months of a first diagnosis of cancer. Participants were randomized 1:1 to Bright IDEAS-YA or EUC (NCT04585269). Bright IDEAS-YA is a 6-session, one-on-one intervention that teaches a systematic approach to overcome personal challenges across any life domain. EUC involved usual psychosocial care plus AYA resources. Participants completed surveys at 0 (baseline), 3, 6, 12, and 24 months, with 6 months as the primary endpoint. Validated measures included the PROMIS Depression Short Form and Anxiety Short Form (primary outcomes), the Functional Assessment of Cancer Therapy – General (FACT-G; primary outcome), and Social Problem-Solving Inventory-Revised Short Form (SPSI-R; mediator). Efficacy was tested using linear mixed effects models, run in R, examining the group x time interaction effects. Mediation was tested using the R multiple mediation analysis. **Results:** 344 YA (34.2% acceptance rate, M_{age} = 30.3 years, *SD* = 6.3; 63% female, 37% male, < 1% non-binary) participated (100% planned enrollment), with 86% and 81% completing surveys at 3 and 6 months, respectively. Compared to baseline, the intervention arm showed statistically significant improvements in depression, anxiety, and HRQOL relative to the control group at 6 months. The intervention arm demonstrated an average reduction of 3.2 T-score points reduction in depression (95% CI [-4.9, -1.5], $p <$ 0.001), 2.4 T-score points in anxiety (95% CI [-4.0, -0.81], p = 0.003), and 3.4 points improvement in total FACT-G (95% CI [0.34, 6.5], p = 0.029) relative to the control. These differences reflect clinically meaningful changes per published reports. Across all three models, change in total problem-solving ability (SPSI-R) was shown to mediate treatment effects, primarily due to change in the negative problem-orientation subscale. **Conclusions:** Bright IDEAS-YA was efficacious in reducing symptoms of depression and anxiety and improving HRQOL compared with enhanced usual care among YAs with cancer. Improvements are attributable to increased problem-solving ability, particularly by reducing the tendency to view problems as significant threats and doubt one's ability to successfully solve problems. Clinical trial information: NCT04585269. Research Sponsor: National Cancer Institute; R37CA240807.

12006 **Oral Abstract Session**

A multicenter, randomized, controlled, open-label trial to determine the optimal duration of steroid therapy for mild pneumonitis associated with immune checkpoint inhibitors. First Author: Daichi Fujimoto, Hyogo Medical University, Nishinomiya, Japan

Background: The optimal duration of corticosteroid therapy for pneumonitis associated with immune checkpoint inhibitors is clinically relevant. Several guidelines recommend a duration of 4 to 6 weeks for mild immune-related pneumonitis. However, evidence from clinical trials is limited. We conducted the first randomized trial to evaluate whether short-term corticosteroid therapy can achieve comparable efficacy. **Methods:** In this multicenter, open-label, randomized clinical trial at 22 institutions in Japan, we randomly assigned patients with mild immune-related pneumonitis according to the Common Terminology Criteria for Adverse Events grade 1 or 2, in a 1:1 ratio, to receive either 3-week or 6-week corticosteroid treatment. The primary endpoint was the rate of treatment success 8 weeks after the start of steroid administration, with a non-inferiority margin of 16 percentage points. The major secondary endpoints were safety, percentage of participants with treatment failure, quality of life, and overall survival. The primary hypothesis was that a 3-week treatment would be non-inferior to a 6-week treatment in terms of the primary endpoint. **Results:** Overall, 106 patients were randomized, and after the exclusion of one patient without immune-related pneumonitis, 105 were included in the intention-to-treat (ITT) population: 51 patients in the 3-week group and 54 in the 6-week group. In the ITT population, the patients' median age was 72 years; 81% of the patients were men, and 73% had grade 2 at baseline. The rate of treatment success was 66.7% in the 3-week group and 85.2% in the 6-week group, which did not demonstrate noninferiority in the overall study population (difference, −18.5% percentage points [80% confidence interval {CI}, −29.0% to -7.9%], p = 0.621), and a predefined exploratory superiority analysis indicated superiority of the 6-week regimen (p = 0.013). Over the entire study period, the relapse or exacerbation rates of pneumonitis were 41.1% in the 3-week group and 24.1% in the 6-week group. Grade 3 or higher adverse events occurred in 12% of patients in the 3-week group and 24% of patients in the 6-week group. The absolute mean change in the total QOL using the K-BILD score from baseline was 4.78 in the 3-week group and 6.28 in the 6-week group (between-group difference, -1.50 points; 95% CI, −5.91 to 2.91). **Conclusions:** In patients with mild immune-related pneumonitis, non-inferiority of 3-week corticosteroid treatment compared to that of 6 weeks was not confirmed in the overall population, and the relapse or exacerbation rate of pneumonitis was higher in the 3-week group over the entire study period. Corticosteroid therapy shorter than the duration recommended by the guidelines is not supported. Clinical trial information: jRCTs051220082. Research Sponsor: None.

12007 **Oral Abstract Session**

Romiplostim for chemotherapy-induced thrombocytopenia (CIT) in colorectal, gastroesophageal, and pancreatic cancers: A global, phase 3, randomized, placebo-controlled trial (RCT). First Author: Hanny Al-Samkari, Massachusetts General Hospital, Boston, MA

Background: CIT is a common consequence of antineoplastic regimens for gastrointestinal (GI) cancers, occurring in >60% of colorectal cancer patients receiving multiagent chemotherapy. CIT can lead to chemotherapy dose reduction, delay, omission, and discontinuation, potentially worsening outcomes. There are no widely available licensed therapies for this unmet need. Aim: To evaluate the safety and efficacy of the thrombopoietin receptor agonist romiplostim (ROMI) in patients with GI cancers to limit chemotherapy dose modifications from CIT. **Methods:** This was a phase 3, placebo (PBO)-controlled RCT of patients receiving oxaliplatin-based multiagent regimens for GI cancers with persistent CIT, ie platelets (Plt) $\leq 85\times10^9$/L on day 1 of a scheduled chemotherapy cycle (NCT03362177). Patients from 55 sites in 14 countries were randomized 2:1 to ROMI or PBO for 3 chemotherapy cycles, stratified by baseline Plt (< or $\geq 50\times10^9$/L) and cancer type. Study drug started at 2 μg/kg subcutaneous weekly, adjusted weekly by 1 μg/kg up to 10 μg/kg to target Plt $\geq 100\times10^9$/L in 12 weeks (≤4 weeks at 10 μg/kg). Chemotherapy started when Plt $\geq 100\times10^9$/L (Plt response) or after week 4 per investigator. The primary endpoint was no CIT-induced dose modification of any myelosuppressive agent in either the second or third chemotherapy cycle per independent adjudication committee. **Results:** Patients (N=165; 109 ROMI, 56 PBO) had colorectal (75%), gastroesophageal (13%), or pancreatic (12%) cancer; 60% were male, 90% White, 4% Black, and 24% Hispanic, with mean (SD) age of 61.4 (11.1) years. Baseline median (range) Plt was 69 (8–85)$\times10^9$/L; 11% had Plt $<50\times10^9$/L. Stage IV disease rates were ROMI 65%, PBO 55%. Most (75%) patients completed study drug; 3% discontinued due to adverse events (AEs). The primary endpoint was achieved in 92/109 (84%) patients receiving ROMI vs 20/56 (36%) receiving PBO (odds ratio 10.2; 95% CI 4.6-22.5; P<0.001). Median (range) Plt nadirs were ROMI 87 (14–167)$\times10^9$/L, PBO 58 (22–95)$\times10^9$/L; P=0.005. For those with Plt responses (ROMI 97%, PBO 77%), median (95% CI) time to first Plt response was ROMI 1.1 (not estimable) weeks, PBO 2.1 (1.1-3.0) weeks; P<0.001. Treatment-related (TR) AE rates were ROMI: 12%, PBO: 7%, most frequently nausea (2%, 2%) and headache (2%, 0%). TR serious AEs and TRAEs leading to death or discontinuation of study drug or chemotherapy were not observed in either arm. **Conclusions:** In this first global phase 3 RCT of ROMI vs PBO for CIT, ROMI was well tolerated and efficacious in the treatment and prevention of CIT in GI cancers. These results are potentially practice-changing for a common serious condition encountered routinely in clinical practice worldwide that prevents delivery of on-time, full-dose anticancer therapy. Final results from long-term follow-up will be presented. Clinical trial information: NCT03362177. Research Sponsor: Amgen Inc.

12008 Oral Abstract Session

Carica papaya leaf extract (CPLE) versus placebo to improve chemotherapy induced thrombocytopenia (CIT): Results of a phase III triple blinded, randomized placebo controlled trial (PACT study). First Author: Vikas Ostwal, Tata Memorial Hospital (HBNI), Mumbai, India

Background: There is a lack of approved therapeutic options to ameliorate CIT in patients with solid tumors receiving chemotherapy. Carica papaya leaf extract (CPLE) is known to increase platelet counts (PC) in certain infections. **Methods:** The PACT study is a triple blinded randomized phase III study conducted in two academic centres in patients with solid tumors receiving chemotherapy and developing at least grade 2 or grade 3 CIT (platelet counts $<$ 75,000 x 10^9/ liter and $>$ 25,000 x 10^9/liter). Patients were randomized 2:1 to CPLE arm (capsule CPLE per oral 1100mg three times daily) or placebo arm (capsule per oral three times daily), which was continued till PC improved to greater than $>$ 75,000 x 10^9/ liter, requirement for platelet transfusions or D+10 post intervention. Baseline PC were graded as per the Common Terminology Criteria for Adverse Events (CTCAE) grades. The primary endpoint of the study was to evaluate whether CPLE improves PC significantly faster (as assessed on D+4 of intervention) and above 75,000 x 10e9 /L as compared to placebo (spontaneous recovery of platelets). To achieve 80% power to detect a difference between the group proportions of 0.25 (50% to 75%) with an alpha of 0.05, 219 patients were required (146 in CPLE group and 73 in placebo group), assuming 10% loss to follow-up rates. **Results:** Between March 2020 and October 2024, 219 patients were randomized, of whom 198 patients (CPLE arm: 129; placebo arm: 69) were analysed for outcomes. All the baseline parameters were equally distributed in both the arms (2:1) except the proportion of patients in the placebo and the experimental arms had equal number of patients with grade 3 thrombocytopenia (17/129 vs 17/69; p = 0.049). The most common chemotherapeutic regimens were oxaliplatin based (37%) and carboplatin based (27%). The primary outcome of increasing PC $>$ 75,000 x 10^9/ liter at D+4 was significantly improved by CPLE (83/129, 64% vs 33/69, 48%; p = 0.034) as compared to placebo. This improvement was significantly quicker in subgroups including three weekly regimen vs weekly/biweekly, palliative intent vs. curative, $>$ 2 cycles of chemotherapy ($<$ = 2 cycles vs. $>$ 2 cycles) and body surface area (BSA) $<$ 1.6 vs. more. There were no grade 3 or grade 4 treatment related adverse events associated with CPLE. **Conclusions:** CPLE is the first therapeutic intervention that appears to improve grade 2 and grade 3 chemotherapy induced thrombocytopenia faster and to a greater extent than placebo in this phase III randomized trial. It should be used as a secondary prophylaxis to maintain the chemotherapy intesnity. There were no major safety concerns with the use of CPLE. Clinical trial information: CTRI/2019/08/020987. Research Sponsor: Micro Pharma Pvt Ltd; IASCC; Cadila Healthcare; Lupin Pharma Pvt Ltd.

12009 Rapid Oral Abstract Session

A randomized controlled trial of cognitive behavioral therapy and bright light therapy for insomnia and fatigue during breast cancer treatment: SleepCaRe trial. First Author: Joshua F. Wiley, Monash University, Clayton, VIC, Australia

Background: Women on chemotherapy for breast cancer (BC) report high levels of insomnia and fatigue. This trial aimed to test the main effects of Cognitive Behavioral Therapy for Insomnia (CBT-I) and Bright Light Therapy (BLT) on insomnia and fatigue symptoms. **Methods:** This multi-center, randomized, controlled, 2 x 2 factorial, superiority, trial enrolled 219 women receiving cytotoxic chemotherapy for any stage BC. Interventions were: (1) neither CBT-I nor BLT (sleep hygiene education; SHE), (2) BLT, (3) CBT-I, and (4) BLT+CBT-I. The 6-week interventions included one telehealth, 1:1 session followed by emails and a mid-treatment call. Assessments occurred at baseline, 3 and 6 weeks. Dual primary outcomes were the insomnia severity index (ISI) and PROMIS Fatigue. Intention-to-treat analyses were latent growth models. Effect sizes are standardized mean differences (SMDs). **Results:** Mean age was 50.7y and 24% had metastatic cancer. At baseline, average ISI was 13.24 (SD = 5.48; sub-threshold insomnia), and fatigue was 59.57 (SD = 7.91; moderate fatigue). 88% (n = 198) completed the telehealth session. 75% (n = 165) reported post-treatment outcomes. ISI and fatigue decreased in all conditions (see Table). CBT-I improved ISI (mean difference = -2.03; p = .001; SMD = -0.37), but BLT did not (mean difference = -1.09; p = .082; SMD = -0.20). Neither intervention affected fatigue (SMDs -0.06 to -0.07; $p > 0.60$). There was no BLTxCBT-I interaction for ISI nor fatigue ($p > 0.50$). **Conclusions:** In patients receiving chemotherapy for BC, brief CBT-I can improve insomnia but not fatigue symptoms. BLT did not improve insomnia or fatigue. We found no evidence of an interaction between BLT and CBT-I. During chemotherapy, fatigue may not be responsive to brief sleep and circadian-oriented treatments. Clinical trial information: ACTRN12620001133921. Research Sponsor: None.

Between group (main effects) and within group (change).

	ISI *[95% CI] P, SMD*	Fatigue *[95% CI] P, SMD*
Main Effects		
BLT	-1.09 [-2.31, 0.14] p= .082, *SMD* = -0.20	-0.49 [-2.87, 1.88] p= .68, *SMD* = -0.06
CBT-I	-2.03 [-3.25, -0.81] p= .001, *SMD* = -0.37	-0.54 [-2.92, 1.83] p= .65, *SMD* = -0.07
Change: 0–6 weeks		
SHE	-3.41 [-4.65, -2.17] $p < .001$, *SMD* = -0.62	-3.75 [-6.16, -1.34] p= .002, *SMD* = -0.47
BLT	-4.89 [-6.12, -3.66] $p < .001$, *SMD* = -0.89	-3.75 [-6.13, -1.37] p= .002, *SMD* = -0.47
CBT-I	-5.83 [-7.12, -4.54] $p < .001$, *SMD* = -1.06	-3.80 [-6.30, -1.31] p= .003, *SMD* = -0.48
CBT-I+BLT	-6.53 [-7.88, -5.18] $p < .001$, *SMD* = -1.19	-4.79 [-7.44, -2.14] $p < .001$, *SMD* = -0.61

12010 Rapid Oral Abstract Session

Alliance A221805: Duloxetine to prevent oxaliplatin-induced chemotherapy-induced peripheral neuropathy (CIPN)—A randomized, double-blind, placebo-controlled phase II study. First Author: Ellen M. Lavoie Smith, University of Alabama at Birmingham, Birmingham, AL

Background: Standard-of-care chemotherapy treatment regimens for colorectal cancer (CRC) include oxaliplatin, a drug known for causing CIPN. CIPN is characterized by upper and lower extremity numbness and tingling, and pain that can persist for years beyond chemotherapy completion, causing impaired function and poor quality of life. According to the American Society of Clinical Oncology's (ASCO) 2020 Clinical Practice Guidelines, there are no known effective preventative interventions. While the ASCO guidelines recommend duloxetine to treat established painful CIPN, its efficacy to prevent CIPN has not been established. **Methods:** A221805 (NCT04137107) was conducted within the National Cancer Institute-supported Community Oncology Research Program; Alliance for Clinical Trials in Oncology was the coordinating group. The randomized, 3-arm, double-blind, placebo-controlled, noncomparative, multicenter phase II study screened 2 doses of daily duloxetine to prevent sensory CIPN. Enrollment occurred between May 1, 2020, and March 24, 2023. Patients (pts) were randomized 1:1:1 to 30 or 60 mg of daily duloxetine, or daily placebo. Eligible pts had stage II-III CRC and no baseline neuropathy, were $\geq$ 25 years of age and scheduled to receive oxaliplatin via one of the following schedules: 85 mg/m2 every 2 weeks (wks; 6 or 12 doses) or 130 mg/m2 every 3 wks (4 doses). Duloxetine/placebo was taken once daily beginning on day 1 of cycle 1 and continued for 17 wks. Blinding was achieved via drug encapsulation. The primary outcome was measured on wk 19-21 using a validated patient-reported outcome measure: 6 sensory items from the EORTC QLQ-CIPN20. Responders were pts who reported little to no CIPN; their highest score was $\leq$ 2 (i.e., 1 = "Not at all"; 2 = "A little") on any of the 6 items. **Results:** 199 pts were accrued (n = 66, 30 mg duloxetine; n = 66, 60 mg, duloxetine; Placebo, n = 67); based on modified intent-to-treat criteria, 46, 47, and 50 pts (N = 143, 71.8%) respectively, were evaluable for the primary endpoint analysis. The pt mean age was 55.1 years (SD = 10.43). Most were White (n = 113, 80.7%) and male (n = 82, 58.6%).There was no difference in the proportion of responders when comparing those who received either duloxetine 30mg (65.2%), 60mg (66.0%), or placebo (68.0%). Fatigue (51.9%) and nausea (46.5%) were the most common solicited adverse events. Duloxetine adherence rates, measured via pill counts, in the 30mg (44.44%), 60mg (50.92%), and placebo (65.57%) groups were low ($<$ 75%). **Conclusions:** We were unable to show that any dose of duloxetine was more promising than placebo, possibly due to an unexpectedly high placebo response rate. Low duloxetine/placebo adherence may have compromised efficacy. Placebo-response mitigation methods should be considered in future CIPN clinical trials. Clinical trial information: NCT04137107. Research Sponsor: National Cancer Institute; 1UG1CA189823; R01CA235726.

12011 Rapid Oral Abstract Session

Peri-transplant supportive and palliative care and/or comorbidity management for older, medically infirm, and/or frail recipients of allogeneic hematopoietic cell transplantation (Allo-HCT): Phase II and interim phase III trial analyses. First Author: Elizabeth Trice Loggers, Clinical Research Division, Fred Hutchinson Cancer Center/Division of Hematology and Oncology, University of Washington, Seattle, WA

Background: Patients (pts) with high HCT-Comorbidity Index scores (HCT-CI of $\geq$3), older age ($\geq$65 years), and/or who are frail per gait speed ($<$0.8 meters/second) have increased morbidity and mortality after allo-HCT compared to younger and healthier counterparts. We report the phase II analysis (PIIA) and interim phase III primary outcome analysis (PIIIA) of a seamless phase II/III prospective, randomized clinical trial conducted at 11 transplant centers to test new approaches to improve quality of life (QOL) in this population. **Methods:** Phase II compared specialist-administered supportive and palliative care (SPC), patient-administered management of comorbidities (MC, e.g. physical exercise, stress reduction, etc), both (SPC+MC), and usual care (UC) for change in Functional Assessment of Cancer Therapy – Bone Marrow Transplantation (FACT-BMT) QOL scores from baseline to day 90 (D90). Pts deceased prior to D90 were assigned FACT-BMT score=0. The winning phase II arm moved forward versus UC in phase III. **Results:** PIIA was done after enrolling 35 pts to each of the 4 study arms. Calculating the difference between FACT-BMT scores on D90 minus baseline, excluding missing data, indicated that only SPC resulted in a small improvement in QOL compared to either MC or SPC+MC (Table); hence SPC was the winning phase II arm. The PIIIA was conducted after enrolling 158 SPC pts and 153 UC pts. The SPC and UC arms were well balanced with median age (both 68 years), HCT-CI $\geq$3 (49% vs 55%), frailty per gait speed (13% vs 12%), female sex (41% vs 34%), non-white race (9.5% vs 11.5%), and Hispanic or unreported ethnicity (7.7% vs 5.7%), respectively. After median follow-up of 362 days, 45 pts had died in each arm. The mean QOL difference between D90 and baseline was 2.83 for SPC and 4.27 for UC (difference of differences, -1.44, 95% CI of difference, -5.03 to 2.14, p=0.43). Fitting a generalized linear model that included baseline, D30, and D90 values and testing the null hypothesis that the slope of scores differs between SPC and UC resulted in p=0.85. Using the Kaplan Meier method, no difference in survival was observed across arms (HR 1.13 [0.75-1.73]). **Conclusions:** Specialist-administered palliative care showed no meaningful improvement in QOL, nor a survival advantage, compared to usual care in frail, older and comorbid allo-HCT recipients, resulting in the cessation of this Phase II/III trial. Analysis of the whole patient population for primary and secondary outcomes is in progress. Clinical trial information: NCT03870750. Research Sponsor: National Cancer Institute.

Change in FACT-BMT (D90 value minus baseline value) comparing the 4 arms of phase II.

Group	Mean difference (sd)	Median difference (range)
SPC (n=28)	-2.93 (28.52)	0.25 (-102 to 38.22)
CM (n=18)	-18.37 (33.80)	-9.50 (-98.33 to 11)
SPC+CM (n=27)	-15.76 (32.69)	-7.67 (-90 to 32)

12012 **Rapid Oral Abstract Session**

Efficacy of treatment with traditional Chinese medicine (Renshen Yangrong Tang granules) for cancer-related fatigue in patients with platinum-based chemotherapy: A randomized, double- blinded, placebo-controlled, multi-center trial. First Author: Yichen Xu, Beijing Cancer Hospital, Beijing, China

Background: Although there is higher incidence of cancer-related fatigue (CRF) in patients undergoing chemotherapy, effective drugs is still in need. Renshen Yangrong Tang (RSYRT), a Traditional Chinese Medicine, has shown promise in alleviating CRF. This trial aims to investigate whether RSYRT could reduce fatigue and improve quality of life in cancer patients with platinum-based chemotherapy. **Methods:** This prospective, multicenter, double-blinded, placebo-controlled trial was implemented at 4 centers in China, enrolling 192 platinum-treated cancer patients with Visual Analogue Scale for Fatigue $\geq$4 points on the 10th day of the first cycle of chemotherapy. Participants were randomized to receive RSYRT (10.35g, 2 times per day) or a matching placebo orally simultaneously with chemotherapy from C1D10 to C2D10. The study was conducted between April, 2020 and September,2023, with a final follow-up on October,2023. The primary outcome was the change in total mean score (range: 0[no fatigue] to 10[extreme fatigue] points) on the Brief Fatigue Inventory(BFI-C) from baseline to week 3. Secondary outcomes include quality of life(European Organization for Research and Treatment of Cancer Quality of Life Core Questionnaire C30, QLQ-C30), fatigue score (MD Anderson Symptom Inventory for Traditional Chinese Medicine MDASI-TCM) and adverse events. RSYRT were compared with the placebo group using a linear mixed model. **Results:** Among 192 patients randomized, 163 participants completed assessment (RSYRT:81 and Placebo:82). There was no significant differences of "Usual fatigue in last 24 hours" score (RSYRT:5.15$\pm$1.41 vs Placebo:5.40$\pm$1.44,*P*= 0.256) in BFI between two groups at baseline. By the end of week 3, the RSYRT group achieved normal fatigue levels compared to the placebo group (RSYRT: 3.35$\pm$1.95 vs Placebo: 4.15$\pm$2.12, *P*= 0.013). The overall health status of QLQ-C30 also showed statistically significant differences (Pre intervention [RSYRT: 52.78 $\pm$ 15.14 vs. placebo: 49.49 $\pm$ 17.63, *P*= 0.204] , After intervention [RSYRT: 65.53 $\pm$ 15.52 vs. placebo: 57.72 $\pm$ 19.98, *P*= 0.006]) . The fatigue score of MDASI-TCM was comparable at baseline (RSYRT: 5.72 $\pm$ 1.69 vs placebo: 5.90 $\pm$ 1.70, *P*= 0.483) , and a significant decrease was observed in the third week (RSYRT: 3.69 $\pm$ 2.05 vs placebo: 4.56 $\pm$ 2.30, *P*= 0.012) . There was no difference in adverse events occurrence between RSYRT and the placebo groups. **Conclusions:** In this randomized clinical trial among platinum-treated cancer patients with CRF, RSYRT reduced fatigue severity and improved quality of life compared to placebo. Clinical trial information: NCT05229029. Research Sponsor: Capital's Funds for Health Improvement and Research.

12013 **Rapid Oral Abstract Session**

Pathways to Advance Targeted and Helpful Serious Illness Conversations (PATH-SIC): A randomized clinical trial. First Author: Christopher Manz, Dana-Farber Cancer Institute, Boston, MA

Background: Serious illness conversations (SICs) can improve quality of life and decrease intensive care utilization at the end of life for patients with cancer. Yet SIC rates for patients with cancer are low and sustainable strategies are needed to engage patients and oncology clinicians in SICs. **Methods:** This randomized controlled trial was conducted at a tertiary cancer center. Using a cancer treatment guideline program (Pathways), oncology subspecialists identified treatment decision points where patients have an average prognosis $<$1 year and they would recommend an SIC. We enrolled patients with breast, gastrointestinal, genitourinary, gynecologic, and thoracic cancers who reached these points and did not have SICs documented in the Advance Care Planning tab (ACP-SICs) of the electronic medical record in the previous 6 months. Patients were randomized to receive a patient nudge (a mailed letter encouraging discussion of their values and preferences with their oncologist; arm 1), a clinician nudge (emails sent to oncology clinicians encouraging an SIC the day prior to the clinic visit; arm 2), both nudges (arm 3), or no nudges (arm 4). The primary analysis compared ACP-SIC documentation 60 days post-randomization for the combined vs no-nudge arms (arm 3 vs 4) using a generalized estimating equation model with a logit link adjusted for disease center and prior clinician SIC training, clustered on oncologists. A pre-specified alternative primary outcome used natural language processing (NLP) to identify SICs in free text notes in the 6 months prior to randomization and 60 days after to evaluate the presence of an NLP- or ACP-SIC 60 days after randomization using the same model. Similarly-constructed Cox proportional hazards models were used to estimate time to SIC. **Results:** Among 1051 patients randomized (arm 1: 273, arm 2: 240, arm 3: 277, arm 4: 261), median age was 65 years (range: 25-94), 40% were male, 79% White, 52% had gastrointestinal and 20% breast cancers. The Table displays unadjusted ACP and NLP+SIC rates. In adjusted analyses, compared to patients in the no-nudge arm (arm 4), patients in the combined nudge arm (arm 3) had 79% higher odds of ACP-SIC at 60 days (odds ratio 1.79, 95% CI 1.11-2.88, p=0.02) and 59% higher odds of NLP+ACP-SIC at 60 days (odds ratio 1.59, 95% CI 1.14-2.22, p=0.006). Time to ACP-SIC was 59% faster in clinician nudge-containing arms than the no-nudge arm (adjusted HR 1.59, 95% CI 1.16-2.19, p=0.004). **Conclusions:** Clinician emails increased SICs within 60 days, whereas patient nudges were ineffective. NLP increased detection of SICs by 49.7%, demonstrating the importance of evaluating SICs in free-text notes in SIC interventions.Long-term analyses will evaluate the interventions' impact on care delivery outcomes. Clinical trial information: NCT05629065. Research Sponsor: None.

Unadjusted SIC at 60 days.

Arm	1: Patient	2: Clinician	3: Combined	4: None
ACP, %	10.6	16.7	17.3	10.7
NLP+ACP, %	22.4	27.8	34.0	24.4

12014 **Rapid Oral Abstract Session**

Trajectories of patient-reported cognitive function and age-related conditions in a longitudinal observational trial of immune checkpoint inhibitor (ICI) treatment: The DiRECT Cohort. First Author: Charles Stewart Kamen, James P. Wilmot Cancer Center, University of Rochester Medical Center, Rochester, NY

Background: ICIs have become a mainstay in cancer treatment, but their impact on patient-centered side effects such as decline in cognitive function and age-related conditions (e.g., nutritional status, mobility) has not been fully characterized. Black patients have also been underrepresented in prospective studies of ICIs. Prior research indicates that Black cancer patients have strong pro-inflammatory immune responses, which could affect the impact of ICI treatment on cognitive function and age-related conditions. **Methods:** The longitudinal DiRECT cohort (URCC21038, NCT05364086) was established to examine ICI outcomes and side effects in Black and White patients through the NCI Community Oncology Research Program (NCORP). Patients reported their cognitive function through the PROMIS-Cog and age-related conditions through the Geriatric 8 (G8), with assessments before (A1), after (A2), 6 months after (A3), and annually after (A4+) their first ICI infusion. A longitudinal mixed-effects model (LMEM) with an unstructured covariance matrix and assessment as a nominal factor was used to evaluate trajectories of the two outcome variables. The models were adjusted for cancer type, race, and age ($<$65, 65+), including interactions with assessment. Multiple comparisons were conducted with a Sidak adjustment to maintain an overall significance level of $p<0.05$. **Results:** A total of 1,677 patients enrolled between 04/01/2022 and 08/31/2024 were included in the analysis: mean age 64; 409 Black; 626 lung, 290 breast, 251 gastrointestinal, 240 genitourinary, 131 gynecologic, 72 head/neck cancers; modal cancer stage IV. In unadjusted models, statistically and clinically significant declines from A1 to A3 were found for both cognitive function (SE=-2.54, $p<0.0001$) and age-related conditions (SE=-0.70, $p<0.0001$), with no change from A3 to A4. Patients with breast cancer experienced the steepest declines in both outcomes (SE=-3.40, $p<0.0001$ and SE=-0.76, $p<0.01$, respectively). Black patients experienced a steeper decline in cognitive function than White patients, particularly from A1 to A2 (SE=-1.28, p=0.01). There was no significant difference in trajectory of functional status by race. Patients $<$65 experienced steeper declines in cognitive function and age-related conditions (SE=1.21, p=0.02 and SE=0.84, p=0.04, respectively); Black patients $<$65 had steeper declines in cognitive functioning than White patients $<$65 (SE=-1.55, p=0.02). **Conclusions:** Breast cancer patients on ICIs appear to experience poor trajectories of cognitive function and age-related conditions over the first 6 months of treatment, while Black patients, particularly those $<$65, experience poor trajectories in cognitive function. These findings can inform tailored and risk-stratified interventions to improve ICI side effects. Research Sponsor: National Cancer Institute; UG3 CA262602; National Cancer Institute; UG1 CA189961.

12015 **Rapid Oral Abstract Session**

Severe sarcopenia and symptom burden prior to chemotherapy among older adults (70+) with advanced cancer: A URCC NCORP nationwide study. First Author: Lindsey Jean Mattick, Wilmot Cancer Institute, University of Rochester Medical Center, Rochester, NY

Background: Sarcopenia – defined as significant loss of strength, muscle mass and physical function– leads to reduced mobility, increased falls, difficulty performing activities of daily living, loss of independence, worse prognosis, and higher mortality among older cancer patients. Older patients with sarcopenia are at an even greater risk for these negative outcomes when additional co-morbid symptoms are present. Despite this, sarcopenia is not routinely screened for in this population. This study aims to describe the proportion of older patients with advanced cancer prior to chemotherapy who present with severe sarcopenia and the additional co-morbid symptoms they are most likely to be experiencing. **Methods:** In a randomized controlled trial (NCT02054741), 718 older adults (age 70+) with advanced cancer and age-related conditions were recruited prior to starting chemotherapy from community oncology practices across the United States who were affiliated with the University of Rochester NCI Community Oncology Research Program (NCORP) Research Base. We analyzed data from a subset of 159 participants prior to chemotherapy who completed assessments for muscle strength (chair stand; seconds [s]), skeletal muscle index (CT scan; SMI [cm^2/m^2]); physical performance (timed up and go; TUG [s]) at baseline. Severe sarcopenia was diagnosed if participants met all three clinically accepted criteria: 1) chair stand $>$ 16.7s for five rises, 2) SMI $<$ 41 cm^2/m^2 (women) and $<$ 43 cm^2/m^2 (men; BMI $<$ 24.9 kg/m^2) or $<$ 53 cm^2/m^2 (men; BMI $>$25 kg/m^2), and 3) TUG $>$ 13.5s. Symptoms (i.e., fatigue, insomnia, pain, anorexia, dyspnea, cognitive issues, nausea, sensory neuropathy, constipation, and diarrhea) were assessed via the Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE). **Results:** Fifty-two of the 159 participants (33%; mean age: 76.7 years; 60% male) had severe sarcopenia. Chi-square analyses revealed participants with severe sarcopenia were significantly more likely to report fatigue (94% vs. 81%; p = 0.03), anorexia (73% vs. 55%; p = 0.03), and pain (73% vs. 60%; p = 0.13) compared to those without severe sarcopenia. Logistic regression indicated those with severe sarcopenia were almost 4x more likely to experience fatigue (OR [95%CI]: 3.75 [1.06-13.28]) and twice as likely to experience anorexia (OR [95%CI]: 2.21 [1.07-4.54]) compared to those without severe sarcopenia. **Conclusions:** One-third of older adults with advanced cancer are likely to present with severe sarcopenia, fatigue, anorexia, and pain prior to the initiation of chemotherapy. Clinicians should consider screening older adults for sarcopenia and other comorbid symptoms to inform cancer treatment decisions prior to the initiation of therapy, and supportive care interventions should be prescribed to mitigate these symptoms. Funding: NCI UG1CA189961 T32CA102618. Research Sponsor: None.

12016 Rapid Oral Abstract Session

Effect of incorporating symptom burden with mortality as a composite outcome on accuracy and bias in palliative care identification algorithms in oncology. First Author: Sophia Shi, University of Pennsylvania, Philadelphia, PA

Background: Machine learning (ML) algorithms are increasingly used to identify patients for early palliative care (PC) or advance care planning (ACP). Most PC/ACP algorithms are trained using only mortality as an outcome. However, increasing availability of structured patient-reported outcomes (PROs) in electronic health record (EHR) databases can facilitate more comprehensive identification of palliative care need by training algorithms on composite outcomes of mortality and symptom burden. **Methods:** Our cohort consisted of patients with cancer seen at one of 18 practices in 2019 within a large academic cancer center. We leveraged structured EHR data, consisting of 153 demographic, laboratory, and comorbidity features and 12 symptom scores derived from CTCAE-PRO that were routinely reported at medical oncology encounters (72% response rate). Our Base Model was a random forest model predicting 180-day mortality from the date of an initial medical oncology encounter (index encounter) that was used in practice to prompt earlier ACP conversations. We retrained models using a Composite Label of mortality and/or severe symptoms ($\geq$3 out of 5 in at least 1 symptom) within 180-days of an index encounter. We report performance for Base vs. Retrained models in 1,000 bootstrapped samples predicting the Composite Label using area under the precision-recall curve (AUPRC) and true positive rate (TPR) for All Patients, Black Patients, and White Patients. We hypothesized that Retrained models would improve performance and reduce Black-White disparities. **Results:** Our cohort consisted of 4908 patients (median age 64.1 years [IQR 17.5], 53.0% female, 59.6% solid tumor malignancies). Retrained Models improved TPR over Base Models for All (0.56 [95% CI 0.52-0.59] vs. 0.18 [95% CI 0.15-0.21]), Black (0.60 [95% CI 0.52-0.67] vs. 0.20 [95% CI 0.14-0.26]), and White (0.55 [95% CI 0.50-0.59] vs. 0.17 [95% CI 0.14-0.20]) patients, with similar AUPRC. TPR improvement was marginally greater for Black vs. White patients (0.02 [95% CI -0.01-0.05]). **Conclusions:** In this cohort study, retraining a PC identification algorithm on a Composite outcome of symptom burden + mortality significantly enhanced identification of PC need, with disproportionate improvements for Black patients. Incorporating PROs into PC identification model outcome labels should be strongly encouraged. Research Sponsor: National Cancer Institute; K08CA263541.

Comparison of base vs. retrained model performance.

	All Patients[a]		Black Patients[a]		White Patients[a]		Other[b]
Model	Base	Retrained	Base	Retrained	Base	Retrained	Difference in Black vs. White Improvement
AUPRC	0.71 (0.68, 0.74)	0.71 (0.68, 0.74)	0.80 (0.73, 0.85)	0.79 (0.72, 0.85)	0.68 (0.65, 0.72)	0.68 (0.65, 0.72)	0 (-0.01, 0.08)
TPR	0.18 (0.15, 0.21)	0.56 (0.52, 0.59)	0.20 (0.14, 0.26)	0.60 (0.52, 0.67)	0.17 (0.14, 0.20)	0.55 (0.50, 0.59)	0.02 (-0.01, 0.05)

[a]Mean (95% CI) [b]Mean difference (95% CI).

12017 Rapid Oral Abstract Session

Precision-calibrated LightGBM machine learning model to predict serious adverse events in oncology patients using FAERS. First Author: Xiyu Zhao, Johns Hopkins University School of Medicine, Baltimore, MD

Background: The U.S. Food and Drug Administration's Adverse Event Reporting System (FAERS) is a large national repository capturing postmarketing drug safety events. Predicting serious adverse events (SAEs) is especially critical for oncology patients, who often face complex regimens and higher toxicity risks. Currently, there are no well-established predictive tools to identify those at highest risk of SAEs in the cancer population. We aimed to develop a machine learning (ML) model that leverages FAERS data to address this clinical gap. **Methods:** We collated FAERS records from 2012Q4–2024Q3 that listed cancer as an indication, encompassing demographics, outcome codes (SAEs defined as death, life-threatening, disability, hospitalization, or congenital anomaly/birth defect), and drug data. Excluding non-cancer or incomplete entries, we split the dataset into 80% for training and 20% for testing, applying cross-validation to derive 95% confidence intervals. Training data underwent SMOTETomek oversampling to counter class imbalance. We then built a precision-focused LightGBM model using high-depth RandomizedSearchCV to fine tune the hyperparameters and subsequently applied sigmoid calibration to yield stable probability estimates and enhanced interpretability. Additionally, a logistic regression model was built under the same pipeline as a baseline comparator. **Results:** Of the final 2.28 million oncology-related reports, ~44% met SAE criteria. On the ~450,000-report test subset, our calibrated LightGBM model achieved 75% accuracy, with precision = 73.7% and recall = 86.3%, yielding an F1 of 0.795. The AUROC reached ~0.82 (95% CI ~0.80–0.84), underscoring robust discrimination, and the AUPRC approached 0.77. By comparison, logistic regression attained 73% accuracy (precision 72.9%, recall 81.5%, F1 = 0.77). Thus, the LightGBM pipeline offered notable gains in recall and F1 while preserving practical precision. Cross-validation demonstrated stable performance ($\pm$~1–2% across folds), and preliminary partial SHAP analysis indicated that older age ($\geq$65 years), multi-agent chemotherapy, and prior adverse event histories were among the strongest predictors of SAE risk. **Conclusions:** In this largest FAERS-based oncology SAE analysis, our LightGBM model markedly outperformed logistic regression, achieving high recall (86%) and balanced precision (74%). These findings represent a significant advance in real-world pharmacovigilance, enabling earlier and more reliable detection and prediction of severe toxicities in cancer patients. Future prospective validations, potentially incorporating external datasets, may further amplify its clinical impact. Research Sponsor: None.

12018 Poster Session

Cardiovascular risks associated with aromatase inhibitors versus tamoxifen in breast cancer: A systematic review and meta-analysis. First Author: Danilo Monteiro Ribeiro, Escola de Medicina - Universidade Anhembi Morumbi, Piracicaba, Sao Paulo, Brazil

Background: Aromatase inhibitors (AIs), such as anastrozole, letrozole, and exemestane, are commonly used in the treatment of women with early or advanced-stage breast cancer (BC). However, the potential cardiovascular risks associated with AI treatment, particularly the occurrence of cardiovascular events (CVEs) such as acute myocardial infarction and ischemic stroke, remain a concern. This meta-analysis aims to evaluate the impact of AI and tamoxifen treatment on the risk of CVEs in women with BC. **Methods:** A comprehensive search was performed across PubMed, Embase, and Cochrane databases for randomized controlled trials (RCTs) and cohort studies comparing cardiovascular outcomes in patients with BC receiving AIs (anastrozole, letrozole, or exemestane) versus those receiving tamoxifen. Data were analyzed using a random-effects model, and the odds ratios (OR) with 95% confidence intervals (CI) were calculated. P values $>$ 0.10 and I2 values $>$ 25% were considered to indicate significance for heterogeneity. Statistical analysis was performed using R, version 4.4.2. **Results:** Sixteen studies, involving 188,635 participants, were included in the analysis, of whom 124,473 (65.98%) received AI treatment. A statistically significant difference was observed in heart failure and cardiomyopathy, with the treatment showing an increased risk of these events (OR: 1.48; 95% CI [1.11 to 1.99]; p = 0.0079; I2: 79%). Similarly, myocardial infarction was also significantly more likely to occur in the AI group (OR 1.20; 95% CI [1.01 to 1.42]; p = 0.033; I2: 59%). Thromboembolic events were less frequent in the AI group compared to the Tamoxifen group (OR 0.75; 95% CI [0.56 to 0.99]; p = 0.044; I2: 82%). Arrhythmia was associated with a HR of 1.2306 (95% CI [0.8295 to 1.8255]; p = 0.302; I2: 89%). Cardiovascular death had a HR of 1.09 (95% CI [0.86 to 1.40]; p = 0.451; I2: 55%), and stroke had a HR of 1.0233 (95% CI [0.90 to 1.15]; p = 0.715; I2: 41%). Cardiovascular death in terms of OR was 1.26 (95% CI [0.94 to 1.69]; p = 0.128; I2: 84%), and the risk of cardiovascular events was associated with an OR of 1.38 (95% CI [0.99 to 1.92]; p = 0.054; I2: 64%). Heart failure and cardiomyopathy had a HR of 1.24 (95% CI [0.98 to 1.56]; p = 0.064; I2: 79%), while thromboembolic events had a HR of 1.02 (95% CI [0.88 to 1.17]; p = 0.774; I2: 0%). The HR for myocardial infarction was 1.12 (95% CI [0.93 to 1.36]; p = 0.214; I2: 59%). Hypertension was associated with an OR of 1.07 (95% CI [0.94 to 1.21]; p = 0.2866; I2: 40%), and stroke had an OR of 1.10 (95% CI [0.91 to 1.33]; p = 0.320; I2: 66%). **Conclusions:** This systematic review and meta-analysis indicate that AI treatment in BC patients is associated with an increased risk of heart failure, cardiomyopathy, and myocardial infarction. Notably, AI treatment demonstrated a protective effect against thromboembolic events. Research Sponsor: None.

12019 Poster Session

Effectiveness of the Automated Heart-Health Assessment (AH-HA) tool on cardiovascular health improvements among post-treatment cancer survivors: 12-month results from WF-1804CD. First Author: Kathryn E. Weaver, Wake Forest University School of Medicine, Winston-Salem, NC

Background: Cardiovascular disease causes significant morbidity and mortality among US survivors. To enhance guideline recommended cardiovascular health (CVH) discussions during survivorship care, our team developed the EHR-based AH-HA clinical decision support tool, which displays modifiable CVH factors and cancer treatments with cardiotoxic potential. This tool significantly improved delivery of guideline-concordant CVH discussions, the primary study outcome; here we report AH-HA impacts on 12-month CVH improvements. **Methods:** The Wake Forest NCORP Research Base coordinated this practice-randomized clinical trial (NCT# 03935282) comparing AH-HA and usual care (UC) practices. Participants were survivors $\geq$ 6 months post-potentially curative treatment for breast, prostate, colorectal, endometrial cancers, or lymphoma, scheduled for routine follow-up. The AH-HA tool, based on the American Heart Association (AHA) Life's Simple 7, aimed to enhance CVH awareness and action by providers and survivors. At AH-HA practices, providers used the tool with survivors during an outpatient oncology visit. CVH data were collected from the EHR and survivors (diet quality & physical activity) at baseline and 12 months. Outcomes included Simple 7 total CVH score (0-100, using AHA algorithm) and meaningful change in individual CVH factors (Table). Generalized estimating equations calculated rates of clinically meaningful improvements in CVH factors at 12 months by group, adjusting for cancer type and clustering within practice. **Results:** 645 survivors (82.3% breast cancer; 96.0% female; 83.9% white non-Hispanic, 7.8% Black, 3.7% Hispanic) enrolled at 9 practices (5 UC and 4 AH-HA). The total CVH score did not significantly change from baseline or between groups (Table 1, p$>$.05). Within the AH-HA arm, 20.3% of survivors achieved 5% weight reduction compared to 12.6% in UC; physical activity also improved more in the AH-HA arm, but not significantly. Rates were similar between arms for diet, blood pressure, and hemoglobin A1c. **Conclusions:** In addition to facilitating guideline concordant CVH discussions, AH-HA shows promise for encouraging weight loss among survivors. It is notable that a brief intervention delivered as part of standard oncology care impacted weight reduction. Clinical trial information: NCT03935282. Research Sponsor: National Cancer Institute; R01CA226078; National Cancer Institute; 5UG1CA189824; National Cancer Institute; P30CA012197.

12 month cardiovascular health outcomes among post-treatment survivors.

CVH Outcomes	AH-HA 4 practices, (n=281)	Usual Care 5 practices, (n=342)	Adj P-value
Improvement, % Yes			
BMI (5% weight ↓)	20.3	12.6	**0.02**
Blood Pressure (5 mm ↓)	53.1	52.0	0.75
Physical Activity (+ 30 mins)	40.9	34.3	0.14
Healthy Diet Score (0-1 to 2-5, or 2-3 to 4-5 components)	21.7	18.9	0.45
Cholesterol (20% ↓)	8.6	9.6	#
A1c (0.5% ↓)	8.9	8.8	0.97
Change in total CVH Score adjusted for baseline (positive=improvement)	0.9	-0.5	0.28

#Model did not converge due to small sample size.

12020 **Poster Session**

Primary prevention of cardiotoxicity in cancer patients treated with fluoropyrimidines: A randomized controlled trial. First Author: Johanne Dam Lyhne, Department of Oncology, Lillebaelt Hospital, University Hospital of Southern Denmark, Vejle, Denmark

Background: Fluoropyrimidines (FP) are the third most used chemotherapeutic drugs administered in solid tumors but have cardiotoxic side effects. The aim of this study is to determine whether pre-chemotherapeutic cardiological assessment and management of cardiovascular risk factors could prevent FP-induced cardiotoxicity and if the coronary artery calcium (CAC) score was predictive of chest pain. **Methods:** This was a randomized, controlled, single center trial (ClinicalTrials.gov NCT03486340) of patients with various cancer types who were treated with FP and had no known ischemic heart disease. All patients had CAC score obtained by cardiac CT scan. Patients were randomized to pre-chemotherapeutic cardiological management or standard care. Cardiological management included risk reduction based on electro- and echocardiographic evaluation and blood samples. Primary composite endpoint included hospital admission for chest pain, acute coronary syndrome, coronary angiography intervention, or all-cause mortality. Secondary outcome was chest pain. Follow-up was 6 months. Data were analyzed using Kaplan-Meier survival function with log-rank test and ROC-analyses. **Results:** Of the 192 patients included, the primary endpoint occurred in 9/95 (9.5%) patients in the intervention group and 15/97 (15.5%) patients in the control group (log-rank p = 0.19) with an incidence rate ratio (IRR) of 0.57 (95% CI [0.22 – 1.39]). Chest pain occurred in 6/95 (6.3%) patients in the intervention group and 13/97 (13.4%) in the control group, yielding an IRR of 0.44 (95% CI [0.14 – 1.23]). CAC score did not predict chest pain occurrence. **Conclusions:** Cardiological management of cardiovascular risk factors prior to treatment with fluoropyrimidines resulted in half as many cardiotoxic events but the study did not reach statistical significance. Further studies are needed to investigate the optimal strategies to prevent fluoropyrimidine-induced cardiotoxicity in cancer patients. Clinical trial information: NCT03486340. Research Sponsor: Region of Southern Denmark.

12021 **Poster Session**

DNA methylation biomarkers of cardiotoxicity risk in breast cancer patients treated with anthracyclines. First Author: Mohammed Al-Jumayli, H. Lee Moffitt Cancer Center and Research Institute, Tampa, FL

Background: Anthracyclines are effective chemotherapeutic agents for treating breast cancer but are associated with significant risks of chemotherapy-related cardiac dysfunction (CTRCD). Current predictors of CTRCD, including patient demographics and clinical characteristics, are insufficient for accurately assessing cardiotoxicity risk before treatment initiation. Here, we examine CTRCD risk associations with pre-treatment DNA methylation (DNAm)-derived biomarkers of biological age, called "epigenetic clocks," and circulating leukocyte composition. **Methods:** A retrospective cohort of 137 newly diagnosed breast cancer patients who received anthracycline-based therapy was sampled from the Total Cancer Care cohort at Moffitt Cancer Center. DNAm profiles were assayed using MethylationEPIC v2 BeadChips on pretreatment whole blood samples and used to derive six biological age metrics and percentages of twelve circulating leukocyte subsets. CTRCD events occurring within one year of treatment initiation were identified through medical records and defined as either a reduction in left ventricular ejection fraction ($\geq$10%) or symptomatic heart failure. Logistic regression models, adjusted for chronological age and traditional cardiotoxicity risk factors (e.g., hypertension, diabetes, baseline ejection fraction, and cumulative anthracycline dose), estimated odds ratios (ORs) for associations between DNAm biomarkers and CTRCD. **Results:** Among 137 newly diagnosed breast cancer patients (mean age: 54 years; 94% white), 33 (24%) experienced CTRCD. In age-adjusted models, the percentage of circulating naïve CD4+ T cells was inversely associated with CTRCD risk, and Horvath18 AgeAccel was positively associated with CTRCD risk, but these associations did not reach statistical significance after additional adjustment for other cardiotoxicity risk factors. In fully adjusted models, a higher percentage of circulating eosinophils was positively associated with CTRCD risk (OR: 1.49; 95% CI: 1.02, 2.24; P = 0.04). **Conclusions:** A higher percentage of circulating eosinophils appears to be a novel risk factor for CTRCD in breast cancer patients. While eosinophils may contribute to CTRCD susceptibility through mechanisms such as creating a pro-inflammatory environment in cardiac tissue, further studies are needed to clarify the role of eosinophils and confirm these findings. Typically, monocyte/macrophage-mediated pathways, including IL-6 and other cytokines, are thought to play a central role in anthracycline-related cardiac injury, but eosinophil-mediated effects may represent an alternative or complementary pathway. Integrating DNAm biomarker and leukocyte composition assessments into clinical workflows could improve CTRCD risk stratification in newly diagnosed breast cancer patients. Research Sponsor: Florida Breast Cancer Foundation; (1049299).

12022 **Poster Session**

Association of sodium-glucose co-transporter-2 inhibitors with cardiac outcomes and mortality in cancer patients: A systematic review and meta-analysis. First Author: Sufyan Shahid, Khawaja Muhammad Safdar Medical College, Sialkot, Pakistan

Background: Sodium-glucose co-transporter 2 inhibitors (SGLT2is) have proven effective in improving cardiac outcomes, including heart failure (HF) hospitalizations and cardiovascular mortality. However, data on the role of SGLT2is in cancer patients with diabetes remain limited. **Methods:** We conducted a systematic review and meta-analysis of studies on patients with concomitant cancer and diabetes to compare cardiac outcomes and mortality between SGLT2i users and non-users. Data were collected from PubMed, Embase, and Cochrane Central databases. Statistical analysis was performed using R Software v4.4.1. A random-effects model was applied to pool risk ratios (RRs) and 95% confidence intervals, with statistical significance set at $p < 0.05$. **Results:** Ten studies, with a total of 100,004 patients (mean age = 66.4 years, 47% female), were included. The mean follow-up duration was 2 years. The results showed that cancer patients with diabetes on SGLT2is had significantly reduced all-cause mortality (RR: 0.48; 95% CI: 0.34 to 0.68; $p < 0.001$; $I^2 = 98\%$), cancer therapy–related cardiac dysfunction (CTRCD) (RR: 0.68; 95% CI: 0.62 to 0.75; $p < 0.001$; $I^2 = 0\%$), and risk of heart failure exacerbation (RR: 0.78; 95% CI: 0.70 to 0.86; $p < 0.001$; $I^2 = 0\%$) compared to the control group. However, the incidence of heart failure (HF) (RR: 0.66; 95% CI: 0.22 to 1.96; p = 0.453; $I^2 = 18\%$) and risk of clinically significant arrhythmias (RR: 0.30; 95% CI: 0.06 to 1.55; p = 0.151; $I^2 = 0\%$) were comparable between two groups. **Conclusions:** In cancer patients with diabetes, SGLT2is inhibitors are associated with reduced all-cause mortality, CTRCD, HF incidence, and risk of heart failure exacerbation with a non-significant trend toward HF incidence and clinically significant arrhythmias compared to the control group. Research Sponsor: None.

Outcome	Risk ratios with 95% Confidence Intervals (CI)	p-value
All-cause mortality	0.48 (0.34 to 0.68)	P<0.001
Cancer therapy–related cardiac dysfunction	0.68 (0.62 to 0.75)	P<0.001
Heart failure exacerbation	0.78 (0.70 to 0.86)	P<0.001
Heart failure incidence	0.66 (0.22 to 1.96)	P=0.453
Clinically significant arrhythmias	0.30 (0.06 to 1.55)	P=0.151

12023 **Poster Session**

Effects of SGLT2i dapagliflozin in primary prevention of cardiotoxicity induced by short-term anthracycline and HER2 blocking agent therapy through inhibition of MyD88 and NLRP-3 pathways. First Author: Vincenzo Quagliariello, Istituto Nazionale Tumori IRCCS "Fondazione G. Pascale", Naples, Italy

Background: Anthracyclines, such as doxorubicin, and HER-2 blocking agents, like trastuzumab, are integral in breast cancer treatment but are associated with significant cardiotoxicity. Sodium-glucose cotransporter 2 (SGLT2) inhibitors have been suggested to provide cardio-renal benefits in the context of anthracycline therapy. However, the cardioprotective effects of SGLT2 inhibitors during combined anthracycline and HER-2 blocking agent therapy remain largely unexplored. The study aimed to investigate the cardioprotective potential of Dapagliflozin in primary prevention of anthracyclines and HER-2 blocking agents-mediated cardiotoxicity in preclinical models. **Methods:** Female C57Bl/6 mice were treated for 10 days with a saline solution or DOXO-Trastuzumab (both at 2.17 mg/kg), DAPA (10 mg/kg), or DOXO-Trastuzumab combined with DAPA. Systemic levels of ferroptosis-related biomarkers, galectin-3, high-sensitivity C-reactive protein (hs-CRP), and pro-inflammatory chemokines (IL-1α, IL-1β, IL-2, IL-4, IL-6, IL-10, IL-12, IL17-α, IL-18, IFN-γ, TNF-α, G-CSF, and GM-CSF) were quantified. After treatments, immunohistochemical staining of myocardial and renal IL-1, IL6, CXCR4, NLRP-3 and Myd88 was performed. **Results:** DAPA prevented the reduction of radial and longitudinal strain and ejection fraction after 10 days of treatment with DOXO-Trastuzumab. A reduced myocardial expression of NLRP-3, MyD-88, IL-6 and IL1 was seen in the DOXO-TRA+ DAPA group compared to DOXO-TRA mice. Systemic levels of IL-1β, IL-6, TNF-α, G-CSF, and GM-CSF were significantly reduced after treatment with DAPA. Serum levels of galectine-3 and hs-CRP were strongly enhanced in the DOXO-Trastuzumab group; on the other hand, their expression was reduced in the DAPA+DOXO-Trastuzuab group. Troponin-T, B-type natriuretic peptide (BNP), and N-Terminal Pro-BNP (NT-pro-BNP) were strongly reduced in the DOXO-Trastuzumab+DAPA group, revealing cardioprotective properties of SGLT2i. Mice treated with DOXO-Trastuzumab and DAPA exhibited reduced myocardial and renal IL-1, IL6, CXCR4, NLRP-3 and Myd88 IHC straining. **Conclusions:** This study presents the first evidence of Dapagliflozin's cardioprotective and anti-inflammatory effects in the context of anthracycline and HER-2 blocking agent-induced cardiotoxicity. These findings support the potential use of Dapagliflozin for primary prevention of cardiovascular events associated with doxorubicin-trastuzumab therapy in breast cancer patients, warranting further clinical investigation. Research Sponsor: Ministero della Salute, Ricerca Corrente.

12024 Poster Session

Long-term trastuzumab safety in tailored dose-dense anthracycline containing adjuvant chemotherapy in the PANTHER phase III trial. First Author: Andri Papakonstantinou, Karolinska Institutet, Stockholm, Sweden

Background: Cardiotoxicity is a known side effect of trastuzumab and combination with anthracyclines increases the risk for cardiotoxicity. Adjuvant dose-dense (DD) chemotherapy has demonstrated beneficial breast cancer (BC) outcomes in patients with high risk for relapse, but data on long-term cardiac toxicity when combined with trastuzumab is scarce. We have previously reported on the safety of trastuzumab at six years follow-up, in a subset of patients treated with dose-dense chemotherapy in the Pan-European Tailored Chemotherapy (PANTHER) phase III trial. We hereby present long-term safety data from 10-year follow-up from the same subset. **Methods:** This is a protocol-predefined cardiac safety study, among Swedish sites included in the PANTHER trial, including patients with HER2-positive (HER2+) and HER2-negative (HER2-) BC matched for age, treatment group and institution. Enrolled patients were up to 65 years old with node-positive or high-risk, node-negative BC were randomized 1:1 to either dose tailored (according to hematologic nadirs) and biweekly DD epirubicin and cyclophosphamide followed by docetaxel or standard 5-fluorouracil, epirubicin, and cyclophosphamide plus docetaxel every 3 weeks. Patients with HER2-positive disease received 1 year of adjuvant trastuzumab. They underwent echocardiography (ECHO) or multigated acquisition scanning and electrocardiography at baseline, at 4, 6 and 10 years of follow-up. Data on cardiac medication NT-proBNP, lipid profile and ECG were also collected. **Results:** ECHO at 10-years follow-up was available for 94 patients; 48 HER2+ (19 DD, 29 control) and 46 HER2- (21 DD, 25 control). Overall, incidence of cardiotoxicity was low. Mean LVEF was 58 % (range 49-68%) and 60.65% (range 50-76%) in HER2+ and HER2- respectively. Only one patient had LVEF $<$ 50% (DD HER2+) and additional 12 patients had LVEF 50-54%, equally distributed between the treatment groups. In total, 27 patients were treated with cardiac medications at this point; 15 (56%) of which had been treated with trastuzumab and 10 of them (n = 7 HER2+), not reporting cardiac medication at previous timepoints. The majority of the patients did not report any symptoms related to heart disease, per NYHA-classification (41 patients in both groups report NYHA class 0). Overall, no significant changes were seen in the biomarkers. **Conclusions:** Cardiotoxicity of trastuzumab in DD anthracycline chemotherapy, examined in the context of a randomized trial sub-study, was very low. Our results underline the safety of trastuzumab in this context, providing support to offer the patients best treatment options for improving breast cancer survival. Clinical trial information: NCT00798070. Research Sponsor: Swedish Cancer Society (Cancerfonden); Swedish Breast Cancer Association (Bröstcancerförbundet); Radiumhemmet; Amgen; Roche; Sanofi-Aventis; Swedish Society for Medical Research (Svenska Sällskapet för Medicinsk Forskning).

12025 Poster Session

Does early recognition and treatment of immune-related myositis and myasthenia gravis reduce mortality of immune-related myocarditis? First Author: Natalie Longino, University of Colorado Comprehensive Cancer Center, Aurora, CO

Background: Immune checkpoint inhibitors (ICIs) have revolutionized cancer treatment. However, some immune-related adverse events (irAEs) can be severe, even fatal. ICI-induced myocarditis (ICI-M) carries the highest mortality rate of 30-50%. Notably, ICI myocarditis frequently co-occurs with ICI-induced myositis (ICI-M^2) or as a triad of ICI-induced myocarditis, myositis and myasthenia gravis (ICI-M^3). Despite this known association, it remains unclear whether these entities represent distinct disease processes or a spectrum of disease severity. Therefore, we sought to compare outcomes among those diagnosed with ICI-M, ICI-M^2 and ICI-M^3. **Methods:** We performed a single-institution retrospective cohort study using the electronic health record to identify patients seen in a solid tumor clinic between 1/21/11 – 1/21/25, who had received ICI therapy. There was a concern for myocarditis in 82 patients, of which 33 were deemed to have $>$ grade 2 ICI-induced myocarditis. Of the 33 cases, 36% had ICI-M, 36% had ICI-M^2 and 27% had ICI-M^3. We then assessed differences in age, sex, cancer type & stage, immunotherapy regimen, number of immune suppressants given, myocarditis grade, and overall survival across these groups. **Results:** The Table shows patients with ICI-M presented at an earlier cancer stage and more commonly after ICI monotherapy than combination therapy. Despite this, these patients typically had more severe grade $\geq$ 3 myocarditis (75%) compared with ICI-M^2 (42%) and ICI-M^3 (44%) and had a worse overall survival (33%) as compared to ICI-M^2 and ICI-M^3 (67% and 78% respectively). Notably ICI-M patients typically presented with cardiac-specific symptoms and presented after more cycles of ICI therapy (avg. of 4 cycles). In contrast, ICI-M^2 and ICI-M^3 patients presented after fewer ICI cycles (avg. of 2 cycles) with symptoms of myositis or myasthenia. They typically did not present with cardiac-specific symptoms and were then incidentally found to have mildly elevated troponin levels. **Conclusions:** Patients with ICI-M presented after more ICI cycles, had more severe myocarditis and worse overall survival as compared to ICI-M^2 and ICI-M^3 patients. Our findings suggest that patients who developed concurrent symptoms of myositis or myasthenia gravis, prompted earlier recognition of mild myocarditis, leading to earlier initiation of immunosuppressive treatment thereby improving clinical outcomes. Research Sponsor: None.

	ICI-M (n = 12)	ICI-M^2 (n = 12)	ICI-M^3 (n = 9)	Total (n = 33)
Median Age (yrs)	67	64	77	69
Sex (% male)	50	83	56	64
Cancer type (% melanoma)	42	75	44	55
Cancer stage (% stage IV)	67	92	78	82
ICI treatment (% dual ICI)	33	67	56	55
Avg. # of cycles before toxicity (range)	4.2 (1-13)	2.2 (1-4)	2.1 (1-3)	2.8 (1-13)
Severity of myocarditis (% grade ≥ 3)	75	42	44	55
Immunosuppressant agents (% given 2 or more agents)	50	33	78	52
Overall survival (% alive)	33	67	78	58

12026 Poster Session

Temporal trends and disparities in cardiovascular mortality among breast cancer patients: A 25-year population analysis of the CDC WONDER database (1999-2023). First Author: Ibrahim Hassan, Faculty of Medicine, Suez Canal University, Ismailia, Egypt

Background: Breast cancer and cardiovascular disease (CVD) are leading causes of mortality among women in the United States. While advancements in breast cancer treatment have improved survival rates, these therapies may contribute to CVD-related complications, influencing long-term outcomes. This study examines 25-year trends (1999–2023) in CVD mortality among breast cancer patients, with a focus on racial, regional, and urbanization disparities. **Methods:** Data was analyzed from the CDC WONDER (Centers for Disease Control and Prevention for Wide-ranging Online Data for Epidemiologic Research) covering the period from January 1, 1999, to December 31, 2023, to evaluate CVD mortality among breast cancer patients. Analysis was done using Joinpoint regression. Age-adjusted mortality rates (AAMR) per 100,000 person-years were calculated, and trends were assessed using annual percent change (APC) with statistical significance defined at $p < 0.05$. Disparities were evaluated across racial/ethnic groups, U.S. census regions, and urban-rural settings. **Results:** 85,316 CVD-related deaths were recorded among breast cancer patients from 1999 to 2023. AAMR declined significantly overall (APC: -2.73, $p < 0.001$), decreasing from 1.66 in 1999 to a nadir of 0.72 in 2016 (APC: -5.11, $p < 0.001$), followed by a rebound to 0.84 in 2023 (APC: +3.29, $p < 0.001$). Disparities were noted among racial groups: non-Hispanic Black women had the highest mortality rates, followed by non-Hispanic Whites and Hispanics, all showing significant downward trends with APCs of -1.93, -2.63, and -2.431, respectively ($p < 0.001$). The lowest mortality rates were recorded in 2016 for all groups, except for non-Hispanic Blacks, who had their lowest in 2015. Regionally, the Northeast initially had the highest AAMR until 2016, after which rates converged; by 2023, the South reported the highest mortality (0.86). Rural areas consistently exhibited higher AAMR than urban areas, though both declined significantly over the study period. **Conclusions:** Despite an overall decline in CVD mortality among breast cancer patients, persistent racial, regional, and urban-rural disparities highlight systemic inequities in care. The post-2016 resurgence in mortality underscores potential gaps in long-term cardiovascular surveillance for survivors. Targeted interventions addressing racial disparities, regional resource allocation, and rural healthcare access are critical to mitigating CVD risk in this population. Further research is needed to elucidate drivers of these trends and inform equitable policy reforms. Research Sponsor: None.

12027 Poster Session

Major adverse cardiovascular events (MACE) in cancer patients treated with tirzepatide compared to GLP-1 receptor agonists: A target trial emulation using real-world data. First Author: Omer Ashruf, Northeast Ohio Medical University, Rootstown, OH

Background: Cardiovascular disease (CVD) is a leading cause mortality in cancer patients. Obesity and type 2 diabetes are well-known modifiable risk factors for CVD progression and adverse CV related outcomes. We aim to assess the CV benefit of tirzepatide versus GLP-1 receptor agonists (GLP-1RA), a mainstay treatment in management of obesity and cardiometabolic disease, in cancer patients. **Methods:** We conducted a target trial emulation using TriNetX, an aggregated EHR platform. We identified adults (May 2022-Jan 2024) diagnosed with solid neoplasm and cardiometabolic conditions (hypertension, dyslipidemia, obesity, or type 2 diabetes). We excluded patients with in situ neoplasms, hematologic malignancy, metastatic solid neoplasm, medication contraindication (type 1 diabetes, gastroparesis, thyroid cancer), performance status ECOG $>$ 3, or on dialysis. Patients were divided into two exclusive groups: tirzepatide or GLP-1RA. The first prescription of each medication was defined as time zero/index event. Individuals with any MACE within 60 days prior to index event were excluded. Study groups were propensity matched, using a 1:1 nearest neighbor algorithm, for 55 covariates: demographics, Charlson comorbidity index and cardiac conditions, chemotherapy, radiation, BMI, HbA1c, LDL, eGFR, systolic BP, medications, smoking/alcohol, and social determinants. Primary outcome was incidence of MACE (acute myocardial infarction, stroke, or CV death) and overall survival over a 2-year period. Secondary outcomes were changes in HbA1c and BMI. Kaplan Meier analysis and hazard ratios (HRs) were calculated to compare time-to-event outcomes. **Results:** We identified 42,584 patients [mean age 55.4 ($\pm$12.1) years; 62.5% female; 63.1% White; mean HbA1c 6.82 ($\pm$1.81); mean BMI 37.5 ($\pm$7.7)] with solid tumors and cardiometabolic conditions. Tirzepatide was associated with a significant MACE reduction compared to GLP-1RA and improved overall survival (Table 1). At follow-up, mean HbA1c was significantly lower in tirzepatide group (6.21 $\pm$ 1.28) compared to GLP-1RA (6.50 $\pm$ 1.46; $p < 0.001$). Patients on tirzepatide also experienced greater BMI reduction (34.7 $\pm$ 7.7 kg/m2) compared to GLP-1RA (35.5 $\pm$ 7.7 kg/m2; $p < 0.001$). **Conclusions:** Tirzepatide was associated with significant reductions in MACE, HbA1c, and BMI compared to GLP-1RA, suggesting a preferential pharmacotherapy option for addressing obesity and cardiovascular disease reduction in cancer patients while improving overall survival outcomes and quality of care in this high-risk population. Research Sponsor: None.

Outcome	Adjusted HR (95% CI)	*p*-value
MACE	0.761 (0.616-0.940)	**0.011**
Myocardial Infarction	0.650 (0.475-0.889)	**0.007**
Stroke	1.103 (0.937-1.300)	0.240
Ischemic Heart Disease	0.785 (0.627-0.983)	**0.035**
Cardiac Death	0.621 (0.365-0.890)	**0.032**
Overall Survival	0.563 (0.415-0.736)	**<0.001**

12028 Poster Session

Effect of a letter of condolence proposing a post-mortem consultation to the relatives of cancer patients on anxiety, depression and grief: Results of a multicenter randomized study. First Author: Gwenaelle Gravis, Institut Paoli-Calmettes, Department of Medical Oncology, Aix Marseille Univ, INSERM, CNRS, CRCM, Immunity and Cancer Team, Marseille, France

Background: The relativesof cancer patients are at risk for developing emotional distress following the death of their loved one. The aim of this study was to analyze whether sending a condolence letter offering a post-mortem consultation with the referent oncologist to the relatives of patients who have died of cancer improve their long term reported outcomes, such as anxiety, depression and complicated grief. **Methods:** In this multicenter, prospective, randomized, academic trial, bereaved relatives, of cancer patients who died in hospital, were randomized between receiving a condolence letter (CL) suggesting post-mortem consultation *versus* no CL. At 3 months and 6 months after enrolment, anxiety (HAD-A), depression (HAD-D) and grief (Texas Revised Inventory of Grief [TRIG]) were assessed using self-administered questionnaires. **Results:** Of the 426 randomized relatives, 118 agreed to take part in the study, of whom 102 (49 CL, 53 no CL) completed the questionnaire 3 months after the relatives' death and 92 (43 CL, 49 no CL) at 6 months. There was no differences in sociodemographic characteristics or history of depression between the two groups. Palliative care was involved for (69% CL, vs 52% non-CL) of patients, with no statistical difference between the two groups. At 3 months post enrolment, both anxiety and depression were significantly lower in the CL group than the non-CL group (mean HADS-A score 7.3 vs 9.4, p=0.026; mean HADS-D score: 5.4 vs 8.1, p=0.009). In addition, receiving a condolence letter was associated with less grief at patient's death (past TRIG subscale: 20.7 vs 25.8, $p<0.001$), and less current grief (present TRIG subscale score: 45.7 vs 52.0, p=0.025). At 6 months, the HADS-D score was significantly lower in the condolence letter arm (mean score 5.7 vs 8.3, p=0.025), as was grief at patient's death (past TRIG subscale: 21.5 vs 25.0, p=0.035). Only 5% of CL had a post mortem consultation. **Conclusions:** Sending a letter of condolence to relatives of cancer patients who have died in hospital may reduce subsequent grief, depression and anxiety in loved ones. Encouraging this widespread post mortem contact such as correspondence may be a non-drug alternative to reduce post-mortem depression and improve the bereavement process for relatives of cancer patients. Clinical trial information: NCT02861625. Research Sponsor: French National Cancer Institute; PHRC-K 14-042.

12029 Poster Session

Disparities in receipt of palliative treatments among disaggregated Hispanic populations with breast, lung, and prostate cancer in the United States. First Author: Shriya Garg, University of Georgia, Athens, GA

Background: Despite palliative interventions' ability to improve the quality of life and possibly improve overall survival, significant inequalities persist in uptake. Disparities in the receipt of palliative-intent interventions are characterized by broad race, socioeconomic, and geographical categories; however, less is known among disaggregated Hispanic populations. We examine disparities among Hispanic subgroups in receipt of palliative-intent interventions among disaggregated Hispanic patients with stage IV lung, breast, and prostate cancer. **Methods:** Using the National Cancer Database (NCDB), we collected data on the receipt of palliative-intent interventions (including radiotherapy, chemotherapy, and/or other pain management therapy) among Hispanic subgroups diagnosed with AJCC analytic stage IV breast, lung, and prostate cancer between 2004 and 2021. Multivariate linear regressions (adjusting for age group, country of origin, year group, sex, insurance status, 2016 median income quartiles, facility type, CDCC Score, and facility location) were conducted for each cancer type to quantify the disparities in uptake of palliative-intent interventions among Hispanic subgroups. **Results:** Among 945,894 total patients, disaggregated analyses revealed reduced receipt of palliative-intent interventions for lung, breast, and prostate cancer patients of Mexican descent (Lung AOR 0.74, [0.67-0.81], $P<0.001$; Breast AOR 0.69, [0.58-0.82], $P<0.001$; Prostate AOR 0.82, [0.69-0.99], P=0.03) compared to non-Hispanic white patients. Receipt of palliative-intent interventions for patients of South or Central American descent and Cuban descent were also reduced in comparison to White patients for lung and breast tumors. Reuptake of palliative-intent interventions for breast cancer was significantly reduced for patients of Dominican Republic descent compared with non-Hispanic white patients (AOR 0.65, [0.43-1.00], P=0.05). **Conclusions:** Our findings expose that disparities exist in the receipt of palliative-intent interventions among Hispanic subgroups upon disaggregation. We highlight the need for research to characterize such disparities and discuss community-level and patient-centric solutions to address their drivers. Research Sponsor: None.

Palliative-intent treatment receipt stratified by subgroup and tumor type.

Race	% Lung Tumor	% Breast Tumor	% Prostate Tumor
Non-Hispanic White	26.4	21.7	12.1
Mexican	16.7	12.7	8.8
Puerto Rican	27.8	22.7	17.0
Cuban	19.2	17.0	11.4
South/Central American	21.5	15.0	11.5
Other Specified Spanish/Hispanic origin	28.2	23.0	10.2
NOS	19.5	17.0	10.9
Spanish surname	16.6	910.0	9.9
Dominican Republic	30.0	19.0	12.7
Non-Hispanic other	24.4	19.9	12.1

12030 Poster Session

Disparities in place of death in patients with lung cancer. First Author: Faris Abby Alamin, University of Central Florida College of Medicine, Orlando, FL

Background: Place of death (PoD) significantly impacts both patient and caregiver experiences at end-of-life in the United States (U.S.), with disparities often reflecting inequities in access to palliative care, hospice services, and caregiver resources. However, there is limited understanding of PoD and associated disparities in patients with lung cancer. This retrospective study examined sociodemographic differences in PoD among U.S. lung cancer decedents from 2003 to 2020. **Methods:** We analyzed de-identified death certificate data from the CDC Wonder database, focusing on lung cancer as the underlying cause of death (identified by ICD codes) from 2003 to 2020. The data were stratified by ethnicity, race, gender, and age ($<$ 65 or $\geq$ 65 years). PoD was categorized into four groups: (1) medical facility, (2) nursing home, (3) home, and (4) hospice facility. The Annual Percentage Change (APC) in PoD across sociodemographic groups was calculated. **Results:** A total of 2,759,733 decedents were included (44.8% women, 72.4% age $\geq$ 65 years, 3.3% Hispanic, 10.5% Non-Hispanic Black (NHB), and 83.4% Non-Hispanic White (NHW)). Between 2003 and 2020, deaths in medical facilities declined from 37.2% (58,778) to 24.6% (33,416) (APC -2.55%), while hospice deaths increased from 0.5% (849) to 11.2% (15,290) (APC 25.37%). In 2020, men were more likely to die in a medical facility than women (26.4% vs 22.4%), and women were more likely to die in a nursing home (9.4% vs 8.4%). Younger patients ($<$ 65) had higher rates of medical facility deaths than older patients (31.5% vs 22.4%), with a slower decline in medical facility deaths (APC -2.01% vs -2.75%). Hispanic individuals were more likely to die at home (52.5% in 2003 vs 51.0% in 2020) and less likely to utilize hospice (11.2% in 2020) or die in a nursing facility (8.9% in 2020). NHWs had the lowest rates of medical facility deaths (22.8% in 2020) and the highest rates of hospice deaths (11.6% in 2020). NHBs, despite an increase in hospice utilization (APC 26.73%, 2003-2020), remained more likely to die in medical facilities (33.6% in 2020). **Conclusions:** Over the past two decades, lung cancer PoD patterns have shifted, with reduced medical facility deaths and increased hospice utilization. However, significant disparities in end-of-life care persist across demographic groups, highlighting the need for targeted interventions to ensure equitable access to preferred care settings, including home-based and hospice services. Research Sponsor: None.

12031 Poster Session

Economic impact and mortality outcomes of palliative care integration among cancer patients: Analysis of National Inpatient Sample 2018-2022. First Author: Shiva Jashwanth Gaddam, Feist-Weiller Cancer Center at LSUHSC-Shreveport, Shreveport, LA

Background: While palliative care integration into oncology represents a quality metric, its relationship with mortality outcomes and cost implications remains incompletely characterized. This study evaluates the association between palliative care consultation and healthcare utilization across major cancer types. **Methods:** We conducted a retrospective analysis using the National Inpatient Sample (2018-2022). Eligible patients included adults with primary diagnoses of lung, breast, prostate, or colon cancer. Palliative care utilization was identified (ICD-10 code Z51.5). Primary endpoints included in-hospital mortality, length of stay (LOS), and total charges. Propensity score matching (1:1 nearest neighbor, caliper 0.2) was used to account for selection bias. Confounding variables included age, race, insurance status, hospital characteristics, and comorbidity burden. Missing data were handled using complete case analysis. Temporal trends were assessed using Cochran-Armitage test. **Results:** Among 1,104,888 eligible hospitalizations (469,831 lung, 203,857 breast, 204,837 colon, 226,065 prostate), 70,863 in-hospital deaths occurred. Palliative care consultation was associated with reduced LOS (adjusted mean difference: -1.2 days; 95% CI: -1.4 to -1.0; $p<0.001$) and lower total charges (adjusted mean difference: -$31,947; 95% CI: -$34,521 tor o -$29,373; $p<0.001$) among deceased patients. Cancer-specific mortality rates with without were: lung (31.26% vs 4.16%, $p<0.001$), breast (26.72% vs 2.16%, $p<0.001$), colon (25.60% vs 2.27%, $p<0.001$), and prostate (27.07% vs 1.98%, $p<0.001$). Overall palliative care utilization increased from 13.50% to 15.91% (2018-2022; APC: +0.68%; p-trend$<$0.001). DNR status strongly predicted palliative care utilization (adjusted OR: 4.50; 95% CI: 4.41-4.60; $p<0.001$). **Conclusions:** In this large nationwide analysis, palliative care consultation was associated with significant reductions in healthcare utilization and costs among deceased cancer patients. Universal implementation could potentially save 27,744 hospital days and $996.4 million annually, suggesting substantial opportunities for healthcare system optimization. Research Sponsor: None.

Healthcare utilization outcomes by cancer type and palliative care status.

Cancer Type	Deaths (N)	PC Rate (%)	Adjusted Cost Difference* ($)	Adjusted LOS Difference* (Days)
Lung	41,808	61.45	-32,655 (-35,124, -30,186)	-0.94 (-1.12, -0.76)
Breast	9,981	60.80	-31,382 (-34,276, -28,488)	-0.97 (-1.18, -0.76)
Colon	9,667	56.95	-47,079 (-50,612, -43,546)	-1.32 (-1.56, -1.08)
Prostate	9,407	56.61	-37,099 (-40,388, -33,810)	-0.81 (-1.02, -0.60)

*Values represent adjusted differences (95% CI) between palliative care and non-palliative care groups. PC = Palliative Care; LOS = Length of Stay.

12032 **Poster Session**

Improving pain management knowledge among hospice family caregivers: A randomized controlled trial. First Author: Masako Mayahara, Barnes-Jewish College, Goldfarb School of Nursing, St. Louis, MO

Background: Poor pain management in home hospice settings is often due to family caregivers not adhering to analgesic regimens. Healthcare technology, like digital applications, can improve caregivers' access to education and communication with nurses, though it has been underutilized in home hospice. We developed and tested a digital pain management app called e-PainSupport in an NIH-funded randomized controlled trial with 44 hospice patient and caregiver dyads. The purpose of this study was to examine mediating effects of caregiver pain management knowledge on change in pain intensity, controlling for study condition and patient gender. **Methods:** We developed and tested a digital pain management app called e-PainSupport in an NIH-funded randomized controlled trial with 44 hospice patient and caregiver dyads. Utilizing a two-group, two-week, randomized controlled trial with dyads (N = 44) of Hospice patients (52% female, mean age 74.1 years) and their caregivers (75% female, mean age 55.2 years), dyads were randomly assigned to either the e-PainSupport intervention or usual care control condition. Outcome measures included caregiver knowledge and patient-reported pain intensity. **Results:** In the study, 60.87% of caregivers used the app's educational element at least once, with an average use of 5.43 times. Pain assessments were recorded by 91.30% of caregivers, averaging 3.74 assessments per caregiver. Additionally, 87.00% of caregivers reported pain management activities, averaging 46.05 entries. Patient pain intensity was tracked by 87.00% of caregivers, who completed the end-of-day summaries an average of 4.9 out of 14 days. Patients in the intervention condition were 2.50 times more likely to have a decrease in pain for worst pain than patients in the control condition over the two-week study period. Although we observed a positive effect of the app on caregivers' pain management knowledge, the improvement was limited, likely due to the brevity of the educational modules designed to minimize caregiver burden. To enhance caregiver knowledge without increasing their burden, we propose converting the written educational materials into videos. The enhanced intervention will be tested in a larger, full-scale RCT in the future. **Conclusions:** The use of the e-PainSupport app by caregivers is feasible and may contribute to improved caregiver knowledge and reduced hospice patient pain. Clinical trial information: NCT04869085. Research Sponsor: National Institute of Nursing Research.

12033 **Poster Session**

A multi-center case-control study on osteoporosis risk in cancer patients receiving chemotherapy. First Author: Sabin Goktas Aydin, SBU Kanuni Sultan Süleyman Education and Research Hospital, Istanbul, Turkey

Background: Chemotherapy and cancer can worsen osteoporosis, a growing concern with improved cancer survival rates. This study aimed to assess osteoporosis risk in chemotherapy patients versus healthy individuals and identify predictive factors. **Methods:** This multi-center case-control study included 257 chemotherapy-treated cancer patients and 257 age- and gender-matched controls (1:1) using propensity score matching. Exclusions included recent alcohol use, severe organ impairments, endocrine disorders, specific treatments (estrogen, progesterone, glucocorticoids, bisphosphonates, calcium supplements), and cancer-related bone conditions. Bone mineral density (BMD) at the femur and lumbar spine (L1-L4) was measured via dual-energy X-ray absorptiometry (DXA), with T-scores categorized as normal ($T \geq -1.0$), osteopenia ($-2.5 < T < -1.0$), or osteoporosis ($T \leq -2.5$).Statistical analyses were performed using SPSS 24.0, with t-tests, Mann-Whitney U tests, and regression analysis ($p<0.05$). **Results:** The study included 174 females and 83 males (median age 59) in both groups. Of cancer patients, 112 had breast, 54 had colorectal, 39 had upper gastrointestinal, 32 had lung, and 20 had gynecological cancer. Among cancer patients, 35.8% had osteopenia, and 21.0% had osteoporosis in lumbar vertebrae, compared to 15.2% and 2.3% in controls ($p<0.001$). For total femur, 28.0% had osteopenia, and 5.8% had osteoporosis in cancer patients, versus 16.3% and 1.2% in controls ($p<0.001$). Median lumbar BMD was 0.90 g/cm² in cancer patients and 1.22 g/cm² in controls ($p<0.001$); median femur BMD was 0.89 g/cm² and 0.98 g/cm², respectively ($p<0.001$). No correlation was found between osteoporosis and cancer stage. Breast cancer had the highest normal BMD (51.2%) but shared the highest osteoporosis rate (31.5%) with colorectal cancer. Gastric cancer showed the highest osteoporosis rate for femur BMD (33.3%, p=0.024). Vitamin D deficiency (<12 ng/mL) was more common in cancer patients (50.6% vs. 18.1%) and linked to reduced bone density (p=0.009). BMI was a significant predictor of osteoporosis (<0.001), with higher BMI protective; obesity (BMI >30) was more frequent in controls (50.2%) than cancer patients (26.9%).Serum creatinine, alkaline phosphatase, calcium, and phosphate levels were similar in groups, with no link to osteoporosis. Logistic regression showed cancer increased osteoporosis risk 6.8-fold ($p<0.001$, 95% CI: 4.024–11.494). BMI was protective, reducing odds by 4.5% per unit increase (p=0.036, 95% CI: 0.915–0.997). **Conclusions:** Lumbar osteoporosis and osteopenia were 9.1 and 2.3 times more common in cancer patients, with lumbar and femur BMD reduced by 26.2%and 9.2%, compared to controls. Cancer type and Vitamin D levels are key predictors of osteoporosis. Addressing bone health in cancer patients is crucial for improving quality of life and reducing osteoporosis burdens. Future research on survival, fracture risks, and outcomes will inform proactive bone health management. Research Sponsor: None.

12034 **Poster Session**

Effectiveness of alternating magnetic field therapy on quality of life among cancer survivors with chemotherapy-induced peripheral neuropathy: Insights of SMILE study. First Author: Emi Kubo, Department of Palliative Medicine, National Cancer Center Hospital East, Kashiwa-Shi, Japan

Background: Chemotherapy-induced peripheral neuropathy (CIPN) reduces patients' quality of life (QoL) due to consistent sensory and motor disturbances. SMILE study investigated the safety and efficacy of an alternating magnetic field therapy device (AT-04) for CIPN. **Methods:** This was a multicenter, randomized, sham device-controlled, double-blind study. Patients were eligible if they had CIPN symptoms with a pain Numeric Rating Scale score of 4/10 or more, at least 12 weeks after perioperative chemotherapy, and there was no recurrence. Patients were randomly assigned to use AT-04 or a sham device for 84 days. We showed the primary endpoint, the change in pain NRS at day 85, and notable effect sizes of AT-04 in patients whose last chemotherapy was over a year ago for tingling and numbness NRS. Herein, we report one of the secondary endpoints, EORTC QLQ-CIPN20 (CIPN20), asked at baseline and days 15, 29, 57, 85, and 113. **Results:** Fourteen patients were allocated to each group. At day 85, there were no significant differences in the mean changes of the CIPN20 sensory scale (-5.25 $\pm$ 15.4 in AT-04 vs. -5.72 $\pm$ 19.5 in sham; p = 0.95, effect size = 0.03), the motor scale (-8.18 $\pm$ 16.6 vs. -1.68 $\pm$ 10.2; p = 0.28, effect size = 0.47), or the autonomic scale (-1.85 $\pm$ 27.5 vs. -1.52 $\pm$ 5.0; p = 0.97, effect size = 0.02). However, the CIPN20 motor scales showed a significant decrease in AT-04 at day 29 (-9.82 $\pm$ 13.8 vs. -0.74 $\pm$ 8.7; p = 0.04, effect size = 0.92) and day 57 (-11.81 $\pm$ 10.6 vs. -0.54 $\pm$ 6.7; $p < 0.01$, effect size = 1.26). Furthermore, among patients whose last chemotherapy was completed more than one year earlier (n = 8 in each group), CIPN20 motor scale significantly decreased from day 29 (-12.43 $\pm$ 10.3 vs. 2.38 $\pm$ 8.9; $p < 0.01$, effect size = 1.55) to day 85 (-11.76 $\pm$ 10.1 vs. -0.07 $\pm$ 11.5; $p < 0.05$, effect size = 1.08), and this effect persisted at day 113 (28 days after the end of the study treatment). Additionally, both sensory and autonomic scales showed improvement (sensory scale, -8.33 $\pm$ 13.5 vs. -0 $\pm$ 18.4, p = 0.32, effect size = 0.52; autonomic scale, -10.42 $\pm$ 23.5 vs. -2.08 $\pm$ 5.9, p = 0.35, effect size = 0.49). **Conclusions:** In patients whose last chemotherapy occurred more than one year prior, mean changes in the CIPN20 scores showed improvement across the sensory, motor, and autonomic scales. Clinical trial information: jRCT2032220295. Research Sponsor: Japan Agency for Medical Research and Development; Peace of Mind Co., Ltd.

12035 **Poster Session**

Autoimmune conditions and 'breast implant illness' in breast cancer patients with implant-based breast reconstructions. First Author: Jonathan Spoor, Netherlands Cancer Institute, Amsterdam, Netherlands

Background: The safety of silicone breast implants (SBIs) has been challenged in various large observational studies that suggest an association with autoimmune and rheumatic diseases (ARDs). Additionally, an increasing number of women seem to attribute constitutional, rheumatic, mental and cognitive symptoms to their SBIs. This constellation of symptoms is often referred to as 'Breast implant illness (BII). To date, BII is a self-identified diagnosis without an evidence-based definition. The risks of ARDs and BII have not been evaluated in breast cancer survivors with implant-based breast reconstructions. **Methods:** We conducted a retrospective cohort study among patients treated for breast cancer between 2000 and 2015 in six large regional hospitals. Clinical data and diagnoses of ARDs were obtained up to 2023 from prospectively maintained institutional and nationwide registries. Patients who were alive at the time of study were invited to participate in a survey. The occurrence of eighteen symptoms, that have been associated with BII by international experts, was assessed. The SBI-exposed patients were compared with patients who had received other surgical treatment modalities. In the entire cohort (including deceased patients and survey non-responders), Hazard Ratios (HRs) for receiving an ARD diagnosis were estimated through multivariable Cox models. Among responders to the survey, person-centered symptom clusters were determined through a latent class analysis approach. The association between SBI-exposure and the observed symptom clusters was analyzed in multivariable logistic regression models. **Results:** Of 12,262 women in the entire cohort, 3,082 (25%) had received a SBI-based breast reconstruction. Median follow-up time was 12.0 (IQR, 7.0) years. Compared with non-exposed patients, patients with an implant-based breast reconstruction did not have an increased risk of ARDs in general (HR, 1.06, 95% CI [0.89–1.27]) or any specific ARD-category or specific condition. In total, 6,073 patients (64.5% of all invited patients) completed the questionnaire including 1,818 patients with an SBI. In the survey cohort, the median follow-up time was 13.7 (IQR, 6.8) years. Five distinct BII-related symptom clusters were identified, none of which were significantly associated with SBI-exposure in multivariable logistic regression analyses. Additionally, when comparing exposed to non-exposed women, women with SBIs did not have a significantly increased risk for any of the individual BII-associated symptoms. **Conclusions:** Our results indicate that breast cancer patients with SBIs do not have an increased risk of ARDs nor do they experience more BII-associated symptoms compared with breast cancer patients without SBIs. This information can aid healthcare professionals in counseling breast cancer patients who are worried about the alleged long-term harms of SBI(s). Research Sponsor: None.

12036 Poster Session

A hierarchical clustering approach to dissect behavioral symptoms in early-stage breast cancer (BC). First Author: Martina Pagliuca, Scuola Superiore Meridionale (SSM), Naples, Italy

Background: Fatigue, cognitive impairment, insomnia, anxiety, and depression are cancer-related behavioral symptoms that frequently co-occur and share underlying risk factors. We investigated the clustering of these symptoms at different time points, aiming to identify drivers of symptom segregation. **Methods:** Patients with stage I-III BC from CANTO (NCT01993498) were included. Hierarchical cluster analysis was performed at three time points: baseline (BC diagnosis), year (Y) 1 (3-6 months post-surgery, chemotherapy [CT], and/or radiotherapy), and Y2. Clustering used the Ward method via R^2 and Pseudo T^2 statistics, incorporating dichotomized self-reported symptoms based on clinically meaningful thresholds: fatigue (EORTC QLQ-C30 $\geq$40/100), cognitive impairment ($<$75/100), insomnia ($>$50/100), and anxiety or depression (HADS $\geq$11/21). **Results:** Among 6,486 patients, the mean age was 56.2 years; 90% had stage I-II BC, 53% received CT, and 83% endocrine therapy (ET). Analysis of dendrograms identified six distinct clusters (CL) consistently across time points. There was substantial difference in symptomatology between baseline/Y1 and baseline/Y2 (Cramer's V 0.23, 0.22), while there was greater symptom overlap post-treatment between Y1 and Y2 (V 0.32). No specific behavioral symptom drove hierarchical segregation at baseline. However, by Y1, depression and fatigue emerged as primary drivers: CL1 (38%) comprised patients with low symptom scores, similarly to other time points; CL2 (14%) was mostly characterized by cognitive dysfunction and anxiety; CL3 (14%) was defined by patients with clinically meaningful insomnia but without fatigue, while CL5 and CL6 included patients with fatigue but no emotional distress, further segregated by the presence (CL5, 12%) or absence (CL6, 10%) of cognitive dysfunction. Patients reporting depression were consistently grouped in CL4. Notably, CL4 (12%) was heterogeneous and characterized by multi-symptomatology (Table). The use of CT and ET was significantly associated with membership in CL4 and CL5 at Y1 ($p < .001$). At Y2, the clustering remained consistent with what observed at Y1, however the prevalence of individual symptoms was higher in the multi-symptom clusters, including CL4 where all patients with depression were exclusively segregated. **Conclusions:** Hierarchical clustering revealed dynamic changes over time, potentially reflecting the impact of the acute treatment phase on interrelationships among symptoms. Depression and fatigue emerged as key drivers of segregation. Accounting for variability in symptom clustering can enable better targeting of therapeutic options. Clinical trial information: NCT01993498. Research Sponsor: Conquer Cancer the ASCO Foundation and Rising Tide Foundation for Clinical Cancer Research; CPG 2020; ARC; ARCPGA2022010004401_4882; ANR; ANR-10-COHO-0004; ANR; ANR-18-IBHU-0002; ANR; ANR-17-RHUS-008.

Proportions of patients with clinically meaningful symptoms by CL at Y1 (may not add up to 100% due to multiple symptoms).

	Fatigue	Cognitive dysfunction	Insomnia	Anxiety	Depression
CL1	0	0	0	0	0
CL2	16	75	0	47	0
CL3	0	34	100	20	0
CL4	91	74	85	82	51
CL5	100	100	57	0	0
CL6	100	0	48	0	0

12037 Poster Session

Systematic review of prognostic models for cardiomyopathy and heart failure applicable to survivors of adolescent and young adult cancer. First Author: Louise Guolla, Dept. Health Research Methods, Evidence, & Impact, McMaster University, Hamilton, ON, Canada

Background: Survivors of adolescent and young adult (AYA) cancer who receive cardiotoxic chemotherapy and/or radiation are at risk of developing cancer therapy-related cardiac dysfunction (CTRCD), including asymptomatic reduction in left ventricular ejection fraction and symptomatic heart failure. Early detection and intervention using risk-adapted surveillance strategies can reduce morbidity and mortality. While numerous risk prediction models (RPM) have been developed and/or validated for CTRCD in pediatric or older adult cancer populations, it is unclear whether they can be applied to survivors of AYA cancer. **Methods:** We undertook a systematic review of cardiovascular RPM (including CTRCD) development/ validation studies in survivors of cancer diagnosed at any age. We searched MEDLINE, EMBASE, and Web of Science with additional hand searching until November 2024. Two reviewers screened abstracts and full texts; we included studies that used real-life patient data to predict asymptomatic or symptomatic CTRCD (per European Society of Cardiology guidelines) $\geq$1 year from diagnosis and after completing therapy. We excluded abstracts, non-English studies, and RPM which used data not routinely accessible in outpatient clinics. We extracted study data and applied the Prediction model Risk of Bias ASsessment Tool for risk of bias (RoB) and applicability to AYA cancer survivors. When not reported, we estimated AYA (age 15-39) proportions using cancer incidence patterns. We used descriptive statistics to evaluate studies, models, included risk factors, and participants overall and by proportion of AYA. Meta-analysis was not possible given limited overlap in the identified models. **Results:** We screened 12740 abstracts and 249 full text articles; of these, 100 studies underwent a second full text screen to identify CTRCD models. We identified 22 studies (7 enrolled $>$ 20% AYA) which developed and/or validated 64 models (32.8% machine learning) to predict CTRCD (54.7% symptomatic) in 129077 cancer survivors (10.7% AYA) using clinically available data. Nine (14.1%) models validated existing RPM (e.g. those developed in non-cancer populations); the remainder were newly developed models, with age at diagnosis, diabetes, hypertension, and anthracycline dose the most common predictors ($>$ 50% of models). Most models (n = 54) were at high RoB, primarily due to concerns with analytical reporting. Only 2 studies/8 models were rated as both low RoB and high applicability to AYA survivors. **Conclusions:** Several RPM for subclinical and overt CHF are available for pediatric and adult cancer survivors, with varying applicability to AYA cancer survivors. Adherence to recommended statistical reporting methods is poor and RoB high, further limiting utility. Additional development and validation of high-quality RPM for heart failure in AYA cancer survivors is warranted. Research Sponsor: CIHR; 186971.

12038 Poster Session

Out of touch: Understanding the frequency and trajectory of chemotherapy-induced neuropathy peripheral (CIPN) in breast cancer survivors. First Author: Savannah Liddell, Mayo Clinic, Rochester, MN

Background: CIPN, primarily associated with sensory neuropathy rather than motor or autonomic dysfunction, is a potentially long-term complication of cancer treatment including taxanes and platinums (T/Ps), and can negatively impact quality of life for breast cancer (BC) survivors. This project aims to quantify the severity of neuropathic symptoms at one and three years after diagnosis in BC survivors, comparing recipients of T/P to non-recipients. **Methods:** In the Mayo Clinic Breast Registry (MCBDR), a longitudinal cohort, surveys and medical record data from patients with stage 1-3 BC were used to understand the burden of neuropathic symptoms at 1- and 3-years post-diagnosis (denoted as Y1 and Y3). Y1 and Y3 raw scores from The Quality of Life Questionnaire-Chemotherapy-Induced Peripheral Neuropathy 20 (CIPN20) composite (CIPN20-C) and sensory subscale (CIPN-S) were converted to a 0-100 point scale, with lower scores corresponding to worse symptoms. Patients with BC recurrence prior to Y3 or incomplete surveys were excluded. We used two sample t-tests and multivariable linear regression modeling to compare recipients of T/P to non-recipients of T/P (with threshold for statistical significance $p < 0.05$). **Results:** 786 patients were included, 112 of whom (14.2%) received T/P. T/P recipients were younger ($p<0.001$), more likely to have Stage II/III disease ($p<0.001$), and less likely to have received endocrine therapy ($p<0.001$). Univariate analyses revealed worse CIPN20-C score at Y1 (p=0.02) and worse CIPN20-S scores (p=0.004) at Y1 and Y3 in T/P recipients compared to non-recipients (Table). However, differences between the groups were no longer statistically significant after adjustment for age, stage and endocrine therapy. **Conclusions:** In this cohort, neuropathic symptom severity at Y1 and Y3 after a breast cancer diagnosis did not differ between recipients of taxane and/or platinum agents and nonrecipients after adjustment for age, stage, and endocrine therapy. These data may reassure patients and clinicians who are concerned about CIPN and considering use of these chemotherapies in this setting. Research Sponsor: None.

Patient demographics and CIPN20 results.

Clinical characteristic	T/P recipients	Non-recipients of T/P
Age at diagnosis, mean (SD)	55.3 (11.6)*	59.8 (11.9)
White race, N (%)	108 (96.4%)	660 (97.9%)
Clinical stage II/III, N (%)	76 (68.5%)*	250 (37.5%)
Endocrine therapy, N (%)	73 (65.2%)*	636 (94.4%)
Diabetes mellitus, N (%)	9 (8.9%)	52 (8.6%)
Y1 CIPN20-C score, mean (SD)	89.6 (10.9)*	92.0 (9.7)
Y3 CIPN-C score, mean (SD)	89.4 (11.4)	91.1 (9.7)
Y1 CIPN20- S score, mean (SD)	87.3 (15.1)*	91.3 (13.0)
Y3 CIPN20-S score, mean (SD)	88.2 (14.1)*	91.1 (11.7)

*Statistically significant ($p < 0.05$) on univariate analysis.

12039 Poster Session

Single-cell RNA sequencing atlas of intestinal injury induced by different clinical treatments in colorectal cancer patients. First Author: Luoxi He, Department of Radiation Oncology, Fudan University Shanghai Cancer Center, Shanghai, China

Background: Colorectal cancer (CRC) patients often experience intestinal injury due to various treatment regimens, including chemotherapy (CT), chemoradiotherapy (CRT), and chemoradioimmunotherapy (ICRT). Despite advances in treatment, the underlying mechanisms of treatment-induced intestinal injury remain poorly understood. **Methods:** We performed single-cell RNA sequencing and histological staining on intestinal samples obtained from 18 colorectal cancer patients undergoing different treatment regimens, including untreated (CTRL), CT, CRT, and ICRT groups. We also employed bulk RNA sequencing to compare paired cancer and normal tissues from ICRT patients, identifying similarities and differences in gene expression patterns between the cancer and normal tissues. **Results:** Histological staining showed that there were no morphological changes in CT, while the damage in CRT was obvious, and the damage in ICRT was even more severe. Intestinal epithelial cells exhibit distinct differentiation trajectories into secretory and absorptive lineages. CRT-induced damage triggers reverse differentiation via revival stem cells (revSCs), driven by fetal-like genes like CLU, while ICRT disrupts this process. In CD8+T cells, effector T cells (TEFF) increase significantly in the ICRT group and differentially expressed genes (DEG) revealed unique patterns across different treatments, including upregulation of senescence-related genes in CRT and interferon- and TNF-related genes in ICRT, highlighting potential therapeutic targets for treatment-induced intestinal injury. In B cells, distinct differentiation pathways were observed, with CRT increasing atypical memory (Atm) B and ICRT promoting germinal center (GC) B, the latter correlating with follicular helper T (TFH) cells and potentially indicating tertiary lymphoid structure (TLS) formation, similar to the patterns of tumor response after ICRT. So we conducted bulk RNA sequencing analysis between paired tumor and normal tissues, which revealed a correlated expression of effector markers, suggesting a shared biological pattern between tissue damage and tumor killing. Also, patients in the ICRT group showed a significant correlation between clinical intestinal injury scores (LARS) and tumor regression grade (TRG), which means we can predict the treatment efficacy of ICRT by a more direct and convenient way. We also performed metabolism analysis and found tryptophan metabolism was significantly altered following CRT and ICRT treatments, closely linked to epithelial repair and inflammation, highlighting tryptophan metabolism can be used as treatment of intestinal injury. **Conclusions:** Our study presents a comprehensive single-cell atlas of treatment-induced intestinal injury in CRC patients, offering insights for future strategies to reduce treatment-related intestinal damage. Research Sponsor: None.

12040 **Poster Session**

Incidence of ocular toxicities in patients with relapsed/refractory multiple myeloma treated with belantamab mafodotin: A systematic review and meta-analysis of phase 3 randomized controlled trials. First Author: Ricceshа Hattin, Department of Internal Medicine, Kirk Kerkorian School of Medicine at UNLV, Las Vegas, NV

Background: Belantamab mafodotin is a novel antibody-drug conjugate approved by the FDA in August 2020 to treat relapsed/refractory multiple myeloma (RRMM). However, it was withdrawn from the market in March 2023 following the DREAMM-3 randomized controlled trial (RCT) failure to show superior progression-free survival (PFS). Later in 2024, further RCTs published (DREAMM-7 & 8) have shown PFS benefit which opens the door to a possible FDA reapproval in the future. Several concerns about ocular adverse events (AEs) have emerged from those trials. This meta-analysis aims to evaluate the incidence of those events in patients with RRMM receiving belantamab. **Methods:** A systematic literature search was performed across MEDLINE and EMBASE databases up to December 31, 2024. Phase 3 RCTs investigating belantamab regimens in RRMM were included. Pooled risk ratios (RR) with 95% confidence intervals (CI) were calculated using the Mantel-Haenszel method. Heterogeneity was assessed using Cochran's Q-statistic. Fixed effects model was employed. **Results:** A total of 1,102 patients from three phase 3 RCTs (DREAMM-3, DREAMM-7, DREAMM-8) were analyzed. The following ocular AEs were noted more frequently in the belantamab group compared to the control group: any-grade (AG) ocular AEs 76.85% vs 24.95% (RR 3.30; 95% CI: 2.80–3.89; $P < 0.00001$), high-grade (HG) ocular AEs 34.65% vs 2.03% (RR 17.61; 95% CI: 9.40–33.00; $P < 0.00001$), AG dry eyes (DE) 45.16% vs 6.69% (RR 7.47; 95% CI: 5.29–10.54; $P < 0.00001$), HG DE 6.24% vs 0% (RR 21.40; 95% CI: 4.40–104.07; P = 0.0001), AG blurred vision (BV) 59.77% vs 10.14% (RR 6.54; 95% CI: 4.97–8.60; $P < 0.00001$), HG BV 14.78% vs 0.41% (RR 27.39; 95% CI: 8.86–84.68; $P < 0.00001$), AG photophobia 36.95% vs 2.64% (RR 15.55; 95% CI: 8.97–26.96; $P < 0.00001$), HG photophobia 1.81% vs 0% (RR 7.08; 95% CI: 1.40–35.70; P = 0.02), AG eye irritation (EI) 37.27% vs 5.48% (RR 7.60; 95% CI: 5.17–11.19; $P < 0.00001$), HG EI 3.28% vs 0% (RR 12.23; 95% CI: 2.52–59.33; P = 0.002), AG eye pain (EP) 26.27% vs 3.04% (RR 9.40; 95% CI: 5.61–15.76; $P < 0.00001$), AG foreign body eye sensation (FBES) 41.71% vs 4.26% (RR 10.68; 95% CI: 6.94–16.45; $P < 0.00001$), AG cataract 16.58% vs 9.13% (RR 2.06; 95% CI: 1.49–2.85; $P < 0.0001$), and HG cataract 4.76% vs 2.64% (RR 2.08; 95% CI: 1.10–3.94; P = 0.02). No statistically significant difference was noted between the two treatment arms in terms of HG EP or FBES. **Conclusions:** This study revealed a significantly increased risk of ocular AEs in patients with RRMM treated with belantamab compared to the other traditional myeloma treatments. Close monitoring and early intervention are crucial for prompt identification and providing the appropriate management for those events in order to optimize the patients' quality of life and compliance. Research Sponsor: None.

12041 **Poster Session**

Risk of non-breast cancer–related mortality in breast cancer and dependence on disease characteristics, treatment, and survival duration. First Author: Varsha Gupta, Roswell Park Comprehensive Cancer Center, Buffalo, NY

Background: Breast Cancer (BC) has seen significant improvement in survival in both early (eBC) and metastatic (mBC) setting. Prolonged survival increases the risk of acquisition of other comorbidities and result in non-BC related mortality (NBCRM). Purpose of this study is to identify the high-risk disease characteristics and trends for NBCRM. **Methods:** Patients (pts) with BC diagnosed as first primary malignancy between 2010-2019 were identified from 2023 release of SEER 17 database, with follow up till 12/31/2021. Causes of mortality were extracted and categorized as BC related mortality (BCRM) and NBCRM. BC related competing risk adjusted fine and gray regression model was used for survival analysis for NBCRM and subdistribution hazard ratio (SHR) is reported. Restrictive mean survival time (RMST) was calculated for pts with radiation and chemotherapy. Pearson chi-square tests used for comparison of categorical data. **Results:** 457,655 BC pts were identified. Median overall survival (OS) for mBC was 34 months (m) (95% CI 33-35 m) and not reached for eBC. For adjusted NBCRM, risk of mortality was higher for age $\geq$ 65 (eBC SHR 10.2, mBC SHR 2.5, Both $p < 0.01$) and age 51-65 (eBC SHR 2.5, mBC SHR 1.5, both $p < 0.05$) compared to age $\leq$ 50 years. Triple negative (TNBC) (eBC SHR 1.2, $p < 0.05$) had higher risk compared HR+/HER2- but not for mBC. For eBC, higher risk for Stage II (SHR 1.5, $p < 0.05$) and Stage III (SHR 2.0, $p < 0.05$) compared to Stage I. Lobular histology had lower risk of NBCRM for eBC (HR 0.86, $p < 0.05$) and no difference was seen for mBC (SHR 0.93, p = 0.27). Pts with radiation (RT) had lower risk of NBCRM (eBC SHR 0.57, mBC SHR 0.86, Both $p < 0.05$). RMST difference for Pts with RT vs no RT increased from 0.08 m at 1 year to 1.7 m at 5 years for eBC and 0.09 m at 1 year to 1.38 m at 5 years for mBC. Similarly, pts with chemotherapy (CT) had lower NBCRM (eBC SHR 0.52 $p < 0.05$, mBC SHR 0.7, $p < 0.01$). RMST difference for pts with CT vs no CT increased from 0.35 m at 1 year to 1.31 m at 5 years for eBC and 0.27 m at 1 year to 3.53 m at 5 years for mBC. Cardiovascular (CVS) (30.76%) and subsequent malignancies (19.96%) were most common causes of NBCRM for eBC. Of all CVS-mortality, 11% occurred $<$ 1 year of diagnosis and 40% after 5 years. Subsequent solid malignancy- mortality was 6.8% in $<$ 1 year and 41% for $>$ 5 years. Subsequent hematological malignancy- mortality was 5.9% in $<$ 1 year and 38% for $>$ 5 years. For mBC, the above trends for NBCRM were inconclusive, given median OS was $<$ 3 years. **Conclusions:** With the rising number of BC survivors, it is imperative to identify high-risk disease characteristics which can lead to NBCRM. Risk of NBCRM was noted to be related to age of diagnosis, stage, histology and treatment. Risk of CVS and subsequent malignancy related mortality was significantly more for pts surviving more than 5 years, especially in the eBC setting, highlighting the importance of adherence to preventive health guidelines and lifestyle modifications. Research Sponsor: None.

12042 **Poster Session**

Incidence of venous thromboembolism (VTE) events in patients with EGFR-mutant non-small cell lung cancer (NSCLC) treated with amivantamab: A systematic review and combined meta-analysis of phase 3 randomized controlled trials. First Author: Hazem Aboaid, Department of Internal Medicine, Kirk Kerkorian School of Medicine at UNLV, Las Vegas, NV

Background: Amivantamab is a bispecific antibody that was granted accelerated approval by the FDA in May 2021 for the treatment of non-small cell lung cancer (NSCLC) with epidermal growth factor receptor (EGFR) mutations. In addition, it also targets the mesenchymal-epithelial transition (MET) pathway which is involved in cancer cell proliferation. While amivantamab approval is considered a significant advancement in the EGFR-mutant lung cancer management, its introduction has raised concerns about potential new adverse events. This study aims to evaluate the incidence of venous thromboembolism (VTE) events in patients with EGFR-mutant NSCLC receiving amivantamab. **Methods:** We conducted a comprehensive literature search using MEDLINE and EMBASE databases from inception through December 31, 2024. Phase III randomized controlled trials (RCTs) utilizing amivantamab in EGFR-mutant NSCLC and reporting VTE adverse events were included. Mantel-Haenszel method was used to calculate the estimated pooled risk ratio (RR) with 95% confidence interval (CI). Heterogeneity was assessed with Cochran's Q-statistic. Random effects model was employed. **Results:** A total of 1,791 patients from three phase III RCTs (MARIPOSA n = 849, MARIPOSA-2 n = 636, PAPILLON n = 308) were included in the analysis. MARIPOSA tested amivantamab-lazertinib vs osimertinib vs lazertinib, while MARIPOSA-2 involved amivantamab-lazertinib-chemotherapy vs chemotherapy vs amivantamab-chemotherapy, and PAPILLON tested amivantamab-chemotherapy vs chemotherapy. Randomization ratios were 2:2:1, 2:2:1, and 1:1, respectively. The incidence of any-grade VTE was higher in the amivantamab group compared to the control group, with a rate of 25.90% vs 7.26% (RR, 3.69; 95% CI: 2.74-4.98; $P < 0.00001$). VTE as a serious adverse event was reported higher in the amivantamab arm compared to the control arm, 5.69% vs 2.42% (RR, 2.36; 95% CI: 1.31-4.27; P = 0.004). There was no statistically significant difference between the two treatment groups in terms of incidence of high-grade VTE. A subgroup analysis based on the type of VTE was performed. Incidence of both pulmonary embolism (PE) and deep vein thrombosis (DVT) was higher in the amivantamab cohort compared to the control cohort, with a rate of 9.94% vs 3.75% (RR, 2.62; 95% CI: 1.50-4.58; P = 0.0007) and 7.97% vs 1.81% (RR, 5.0; 95% CI: 2.90-8.62; $P < 0.00001$), respectively. **Conclusions:** This study showed increased risk of VTE events in patients with EGFR-mutant NSCLC treated with amivantamab-containing regimens compared to the standard arm. These findings highlight the importance of close monitoring for those events in order to early detect and provide the appropriate management. Further studies are needed to better understand this association between amivantamab and VTE. Research Sponsor: None.

12043 **Poster Session**

Radioimmunotherapy-associated myeloid neoplasms: Real-world multicenter retrospective study using TriNetX database. First Author: Nikhil Vojjala, Trinity Health Oakland Hospital/Wayne State University School of Medicine, Pontiac, MI

Background: Radioimmunotherapy (RIT) utilizing monoclonal antibodies conjugated with therapeutic radionuclides, has emerged as a promising treatment option in oncology. While demonstrating significant clinical efficacy, concerns regarding therapy-related myeloid neoplasms (t-MNs) have been raised in other contexts, particularly following RIT for non-Hodgkin lymphoma. This study aims to investigate the risk of t-MNs following treatment with Lutathera (177Lu-DOTATATE) and Pluvicto (177Lu-PSMA-617) in patients with neuroendocrine tumors and metastatic castration-resistant prostate cancer. **Methods:** We conducted a multicenter retrospective study using the TrinetX database network, a federated Electronic Medical Record Network including adult patients with a history of using Lutathera and/or Pluvicto and developed t-MNs. Statistical analysis is performed on the TrinetX research platform. Outcome analysis was performed for 1) Incidence of t-MNs. 2) Mortality rates and Survival analysis. **Results:** A total of 2370 patients who received either Lutathera (n=1368; 57.7%) or Pluvicto (n=1002; 42.3%) were identified in the database. Mean age was 71 years ($\pm$11 years), 64.98% (n=1540) were males and 70.08% were whites. Of the 2370 patients, 1.6% (n=39) developed t-MNs (26 MDS (1.09%), 13 AML (0.54%). Among these, 27 were in the Lutathera cohort (1.97% of total patients), and 12 were in the Pluvicto cohort (1.12%). The mean age in the t-MN cohort was 72 years ($\pm$9 years) and 50% were males. 16 (41%) patients with t-MN had prior chemo or radiotherapy. The remaining 23 patients (59%) received no anticancer therapy associated with t-MNs. Median survival for patients with t-MNs was 38.1 months, with an overall mortality of 51.2% at median follow-up. **Conclusions:** This is the largest study reporting the incidence of t-MN associated with RIT. Our study demonstrated a significant risk of therapy-related t-MNs following RIT, even in patients who did not receive additional chemoradiotherapy. Given the short follow-up, we hypothesize that the risk may increase with longer-term follow-up. Using this real-world data, our Next step would be to include Next-Generation Sequencing for further characterization of the genomic landscape of these patients. Research Sponsor: None.

Demographic, treatment, and follow-up data of the study population.

Baseline characteristics	RIT	RIT with t-MNs
Total patients	2370	39
Mean age (in years) (SD)	71 ($\pm$11)	72 ($\pm$9)
Gender*(%)		
Males	64.98	50.0
Females	22.07	46.6
Race*(%)		
Whites	70.08	73.33
African American	7.60	8.6
Radiation therapy (%)	20.2	
Chemotherapy (%)	-	
Cabazitaxel	5.20	41.0
Docetaxel	16.7	
Carboplatin	0.73	
Cisplatin	0.22	
Doxorubicin	0.76	
Olaparib	5.0	
Median follow-up (in months)	11.4	27.3
Median survival (in months) (IQR)	44.5 (41.6-48.3)	38.1 (15-51.6)
Mortality rates (%)	28.9	51.2

*Indicates remaining Unknown/Other; IQR: Interquartile range.

12044 Poster Session

Multisite validation of biomechanical computed tomography for osteoporosis assessment and fracture prediction in patients with high-risk or metastatic prostate cancer. First Author: Samuel L. Washington III, Department of Urology, University of California, San Francisco, San Francisco, CA

Background: Long-term androgen deprivation therapy (ADT) among men with high-risk localized or metastatic prostate cancer (PCa) results in a 10-20% risk of significant bone fracture at 10 years. While guidelines recommend routine bone mineral density (BMD) screening for men with PCa receiving ADT, most do not undergo it. We studied whether Biomechanical Computed Tomography (BCT), a radiomic technique to opportunistically measure femoral and vertebral bone strength and BMD from CT scans performed for routine staging, can predict incident fractures among men with PCa beginning ADT. **Methods:** In this retrospective cohort study among 2 academic cancer centers and 2 Veterans Affairs facilities, we identified 711 men with de novo high-risk localized or metastatic PCa diagnosed between 2010-2018. CT scans at PCa diagnosis were analyzed by BCT. Incident fractures were ascertained by trained radiologists and defined as any new fractures occurring after the initial CT scan. We used Cox proportional hazards models to estimate associations of fragile femur bone strength (≤3500N), fragile vertebral bone strength (≤6500N), or osteoporosis (femoral neck areal BMD T-score ≤-2.5 or trabecular volumetric BMD ≤80 mg/cm3), with incident fracture, adjusted for age, BMI, & race/ethnicity. **Results:** 673 men were eligible (mean age 69.8±9.3, 49.3% white, 35.2% received prior ADT, 42.3% had prior BMD screening). 198 (29.4%) incident fractures were observed. Using BCT, 123 men (18.3%) had fragile femur bone strength or osteoporosis, and 105 men (15.6%) had fragile vertebral bone strength or osteoporosis by volumetric BMD. BCT-derived fragile femur or vertebral bone strength (adjusted HR 1.81, 95% CI 1.27-2.59) and osteoporosis by BMD criteria (aHR 2.20, 95% CI 1.32-3.62) were associated with incident fracture (Table). **Conclusions:** In men with high-risk PCa, opportunistic BCT analysis of routine staging CT scans improves osteoporosis detection and fracture prediction, identifying men who may have not otherwise qualified for antiresorptive treatment. BCT is a novel approach to risk-stratify men with PCa for early fracture risk mitigation. Research Sponsor: U.S. Department of Defense; W81XWH2210151.

Association between BMD and bone strength with incident fracture.

Femur Bone Strength	HR (95% CI)	p-value
Normal *(≥5000N)*	1 (reference)	
Low *(3500-5000N)*	1.80 (1.25–2.58)	0.002
Fragile *(≤3500N)*	2.50 (1.59–3.93)	<0.001
Vertebral Bone Strength		
Normal *(≥ 8500N)*	1 (reference)	
Low *(6500–8500N)*	1.09 (0.60–1.99)	0.78
Fragile *(≤6500N)*	1.71 (0.96–3.25)	0.07
Femoral Neck BMD *(T-score)*		
Normal *(≥ −1.0)*	1 (reference)	
Low Bone Density/Osteopenia *(−1.0 - −2.5)*	1.92 (1.38–2.67)	<0.001
Osteoporosis *(≥ −2.5)*	2.20 (1.32–3.62)	0.003
Vertebral Trabecular BMD		
Normal *(≥120 mg/cm^3)*	1 (reference)	
Low Bone Density/Osteopenia *(80-120 mg/cm^3)*	0.99 (0.53–1.84)	0.98
Osteoporosis *(≤80 mg/cm^3)*	1.95 (1.04–3.67)	0.04

12045 Poster Session

Impact of pembrolizumab on geriatric syndromes in older patients with NSCLC: A propensity-matched retrospective cohort study. First Author: Elvis Obomanu, Jefferson Einstein Philadelphia Hospital, Department of Internal Medicine, Philadelphia, PA

Background: Non-small cell lung carcinoma (NSCLC) predominantly affects older adults (≥65 years), where immune checkpoint inhibitors (ICIs) are a key treatment, especially in those without driver mutations. However, the effect of ICIs on age-related health issues (geriatric syndromes), which impact quality of life in this population, is unclear. This study aims to investigate the impact of ICIs on geriatric syndromes in older adults with NSCLC. **Methods:** We utilized data from the Global Collaborative Network-TrinetX to evaluate the impact of pembrolizumab on geriatric syndromes in elderly NSCLC patients, dividing them into two groups based on pembrolizumab treatment status defined by International Classification of Diseases (ICD-10) codes. Propensity score matching (PSM) was used to balance the cohorts based on demographic characteristics, comorbidities, medications, and without driver mutations. Geriatric syndromes were assessed over 30-day and 1-year follow-up periods. Multivariate logistic regression models assessed the association between pembrolizumab treatment and geriatric syndromes, with results expressed as odds ratios and 95% confidence intervals. **Results:** Following PSM, there were two balanced cohorts of 3288 patients each. The pembrolizumab cohort had a mean age of 75.6 ± 6.93 years, while the non-pembrolizumab cohort had a mean age of 78.2 ± 7.9 years. Multivariate analysis revealed that pembrolizumab treatment was significantly associated with increased fatigue risk at 30 days (OR 1.600, 95% CI 1.062-2.411, P=0.023), persisting at 1 year (OR 1.769, 95% CI 1.463-2.140, P<0.001). Additionally, pembrolizumab treatment was linked to increased risks of insomnia (OR 1.331, 95% CI 1.052-1.683, P=0.017) and delirium (OR 1.494, 95% CI 1.105-2.019, P=0.009) at 1 year. Notably, pembrolizumab treatment was not significantly associated with risk of dementia, frailty, urinary incontinence, or falls at 30 days and 1 year. **Conclusions:** Our study shows that pembrolizumab was significantly associated with increased risks of persistent fatigue, delirium, and insomnia in geriatric NSCLC patients at one-year follow-up. This emphasizes the need for monitoring and targeted interventions to mitigate these adverse events and improve quality of life in this population. Research Sponsor: None.

Geriatric syndromes in NSCLC patients on pembrolizumab.

OUTCOME	30 DAYS FOLLOW-UP		1 YEAR FOLLOW-UP	
	OR and 95% CI	P-value	OR and 95% CI	P-value
Falls	1.381 (0.631-3.114)	0.434	1.264 (0.946-1.690)	0.113
Dementia	0.993 (0.413 −2.390)	0.988	0.993 (0.581-1.697)	0.980
Delirium	1.400 (0.621-3.156)	0.416	1.494 (1.105-2.019)	0.009
Insomnia	1.656 (0.998-2.748)	0.049	1.331 (1.052-1.683)	0.017
Urinary incontinence	N/A*		N/A	
Fatigue	1.600 (1.062-2.411)	0.023	1.769 (1.463-2.140)	<0.001
Frailty	1.000 (0.416-2.405)	0.999	1.233 (0.733 −2.073)	0.429

*No outcomes were observed within the follow-up period.

12046 Poster Session

New-onset osteopenia/osteoporosis among long-term survivors of breast cancer: Role of hormone therapies and metabolic risk factors. First Author: Geoffrey S. Bostany, University of Pittsburgh Medical Center, Pittsburgh, PA

Background: Anti-cancer therapies (including aromatase inhibitors [AIs]) and metabolic risk factors are known to result in bone mineral density (BMD) loss in breast cancer survivors (BCS). There is limited information regarding the very long-term risk of new-onset osteopenia/osteoporosis among BCS and the associated risk factors. **Methods:** Patients who survived ≥1y after BC underwent q2y dual x-ray absorptiometry (DXA) screening at a single center; those exposed to bisphosphonates or with osteopenia/osteoporosis prior to BC were excluded. All DXAs from BC diagnosis to diagnosis of osteopenia/osteoporosis were processed in Python via automated analysis. New-onset osteopenia/osteoporosis was defined as a DXA with a T-Score < -1 at any bone site. Demographics, treatment exposures, and metabolic risk factors were abstracted from medical records. Cumulative incidence described the risk of osteopenia/osteoporosis, and Cox proportional hazards models described the risk factors, treating therapeutic exposures as time-varying variables. Multivariable linear regression models with generalized estimation equations assessed longitudinal trend of BMD prior to onset of osteopenia/osteoporosis. **Results:** We evaluated 4,575 DXAs in 1,267 BCS (median age at BC: 55y; median follow-up: 9.8y; non-Hispanic Black: 28.6%). Overall, 39.2% received AIs, 18.7% received selective estrogen receptor modulators (SERMs), 20.1% received AIs & SERMs, and 21.9% received neither. The cumulative incidence of osteopenia/osteoporosis in the entire cohort was 19% at 2y, increasing to 42% at 5y and 68% at 15y after BC. In those exposed to AIs, the cumulative incidence of osteopenia/osteoporosis was 38%, 75%, and 96% at 2y, 5y, and 15y, respectively. Multivariable analysis revealed the following to be independently associated with osteopenia/osteoporosis: AIs (HR = 1.94, 95%CI = 1.61-2.34), increasing age: (HR = 1.03, 95%CI = 1.02-1.04), pre-BC dyslipidemia (HR = 1.36, 95%CI = 1.06-1.75), and post-BC dyslipidemia (HR = 1.47, 95%CI = 1.19-1.81). Black race (HR = 0.44, 95%CI = 0.36-0.54, ref = white race), pre-cancer obesity (HR = 0.71, 95%CI = 0.56-0.91), and post-cancer obesity (HR = 0.79, 95%CI = 0.65-0.96) were protective. Exposure to SERMS was not a risk factor (HR = 0.97, 95%CI = 0.76-1.23). Among those exposed to AIs, radial wrist BMD declined significantly more steeply among those who eventually developed osteoporosis/osteopenia (0.45%/year), when compared with those who did not (0.11%/year) (p = 0.04). **Conclusions:** These results provide evidence for close surveillance of BC survivors at increased risk of osteopenia/osteoporosis for extended periods, and aggressive management of dyslipidemia before, during and after BC. Research Sponsor: None.

12047 Poster Session

Non-infectious sarcoid-like inflammatory granulomatous conditions (NSIGC) associated with immune checkpoint inhibitors (ICIs) for cancer: Results from the International ICARUS (Immune Checkpoint Associated Rare and Unique Side effects) consortium. First Author: Ayesha Aijaz, Stephenson Cancer Center at The University of Oklahoma Health Sciences Center, Oklahoma City, OK

Background: ICIs can be associated with a broad range of toxicities; however, limited data exists on NSIGC secondary to ICIs. Herein, we assembled the first international cohort of patients (pts) with cancer who received ICIs and subsequently developed NSIGC. **Methods:** We retrospectively collected data from 14 institutions globally on pts with cancer who received ICIs between 2015-2025 and subsequently developed biopsy-confirmed NSIGC. Pts were eligible if they received anti-programmed cell death protein-1/programmed death-ligand 1 (anti-PD-1/PD-L1) alone or in combination with additional anti-cancer therapies such as chemotherapy, targeted agents or anti-CTLA-4, or if they were treated with other immunotherapies. The chi-squared goodness of fit test was used to analyze the distribution of different ICI regimens and their association with NSIGC, assuming a uniform distribution with an expected frequency of 25 for each of the 5 ICI regimens. **Results:** The study included 125 pts with biopsy-confirmed NSIGC post-ICI. Of these, 58.4% (n = 73) were male and 83.2% (n = 104) were Caucasians. Median age at cancer diagnosis was 62 years. The top three cancers in the cohort were melanoma (45.6%; n = 57), non-small cell lung cancer (16.8%; n = 21), and renal cell carcinoma (6.4%; n = 8). Out of 125 pts, 48.8% (n = 61) received anti-PD-1/PD-L1 monotherapy, 20% (n = 25) anti-PD-1/PD-L1 + anti-CTLA-4, 17.6% (n = 22) anti-PD-1/PD-L1 + chemotherapy, 8% (n = 10) anti-PD-1/PD-L1 + targeted agents, and 5.6% (n = 7) received other immunotherapies. Our result showed a significant difference between expected and observed NSIGC frequencies across different ICI regimens (X2 = 74.2, df = 4, p < 0.01), indicating a potential association between anti-PD-1/PD-L1 monotherapy and NSIGC. The median time to the diagnosis of NSIGC after ICI initiation was 7.1 months (range: 3.9-26.7 months). Of 125 pts, 55.2% (n = 69) were diagnosed after treatment completion. Among these 69 pts, 56.5% (n = 39) were diagnosed within 6 months, 14.5% (n = 10) between 6 months and 1 year, 10.1% (n = 7) between 1 and 2 years, and 18.8% (n = 13) were diagnosed after 2 years. The remaining 44.8% (n = 56) were diagnosed during treatment, out of which 48.2% (n = 27) required permanent treatment discontinuation due to NSIGC and 3.6% (n = 2) were re-challenged. 19.2% (n = 24) received steroid treatment for NSIGC. **Conclusions:** To our knowledge, this is the largest dataset to date demonstrating NSIGC as a rare side effect of ICIs. NSIGC frequently occurs after ICI therapy completion but can also result in ICI discontinuation. Biopsy confirmation is critical to prevent misdiagnosis, and further research is required to elucidate the biology, risk factors, and implications for ICI continuation or rechallenge to optimize patient outcomes. Research Sponsor: None.

12048 Poster Session

Identifying genetic susceptibility for severe cardiac events in testicular cancer survivors. First Author: Arkajyoti Bhattacharya, University Medical Center Groningen, Groningen, Netherlands

Background: Testicular cancer (TC) survivors face an increased risk of cardiovascular diseases (CVD) as a late adverse effect of oncological treatment, especially after cisplatin-based chemotherapy. To explore genetic susceptibility, we performed a genome-wide association study using hierarchical clustering and assessed impact of polygenic risk scores (PRS). **Methods:** A subcohort of TC patients treated at expert centers in the Netherlands between 1976 and 2007 was established by hospital stratified random sampling, and enriched with all identified cases of severe CVD (coronary artery disease, myocardial infarction, heart failure) of the entire cohort (Lubberts et al J Clin Oncol 41:3512-3522, 2023). Genotyping was performed using the Global Screening Array. The study population consisted of 396 TC patients: 92 survivors with cardiac disease and 304 survivors without cardiac disease. Seven general population derived PRSs from the CARDIoGRAMplusC4D consortium were applied to assess cardiac risk, followed by hierarchical SNP aggregation based on linkage disequilibrium to identify cardiac risk-associated SNPs. These SNPs were used for co-functionality analysis and decision tree analyses to develop novel PRSs. **Results:** Five of the seven external PRSs were significantly associated with cardiac risk, explaining 8%-12% of the variance, with the CARDIoGRAM GWAS PRS showing the strongest association. Patient's age at diagnosis explained the largest variance in cardiac risk (21%). Hierarchical SNP aggregation identified 67 cardiac risk-associated SNPs, individually explaining 3% - 12% of the variance. Co-functionality analysis revealed biological processes, including cardiovascular development, immune signaling, and DNA damage repair, as potential mediators of these SNPs' effects. Using decision tree analysis, a novel PRS was developed incorporating CVD risk-associated SNPs and clinical risk factors at start of treatment. This PRS+ achieved the highest concordance statistic of 0.783 (standard error 0.022) and explained maximum variance (50%) among all tested models. This PRS+ identified that patients diagnosed at age $>$ 41 years had higher cardiac risk, independent of genotype data. Whereas a subset of patients diagnosed at age $\leq$41 years could be identified as having increased cardiac risk based on the minor allele frequency of five SNPs (rs6830970, rs17666409, rs10782601, rs2446862, rs767707). **Conclusions:** This study introduces a novel PRS to identify TC patients with a higher risk of CVD, enabling the development of personalized cardiovascular risk management strategies at the start of their cancer treatment. It also advances understanding of the biological mechanisms underlying this increased risk. Clinical trial information: NCT02276430. Research Sponsor: Dutch Cancer Society (KWF); NKI 2011-5209.

12049 Poster Session

Prevalence of sexual dysfunction among men with cancer before the initiation of systemic treatment. First Author: Mario Machado Lopes, Hospital Moinhos de Vento, Porto Alegre, Brazil

Background: Sexual health significantly impacts the quality of life, yet its relationship with systemic cancer treatments in men remains underexplored, particularly outside prostate cancer-focused studies. In Brazil, the prevalence of moderate to complete sexual dysfunction among men is approximately 14.5%. This prospective cohort study conducted at a Brazilian Cancer Center evaluated the prevalence of sexual dysfunction before the initiation of systemic therapy in men diagnosed with solid tumors using the Male Sexual Quotient (MSQ) tool. **Methods:** Sexually active, treatment-naïve male patients with solid tumors were enrolled, excluding those with prostate cancer, active brain metastases, spinal compression, or prior pelvic irradiation/extensive pelvic surgery for rectal or bladder cancer. Baseline sexual function was assessed using the MSQ, which evaluates five domains: premature ejaculation, erectile dysfunction, hypoactive sexual desire, orgasm frequency, and dissatisfaction with sexual activity. An MSQ global score $\leq$60 defined moderate to complete sexual dysfunction. Hormonal profiles, including testosterone, FSH, and LH, were measured. The Hospital Anxiety and Depression Scale (HADS) was used to identify risks of anxiety or depression. All participants provided informed consent, and the local ethics committee approved the protocol. **Results:** Between October 2023 and December 2024, 73 male patients were recruited (median age 58 years, IQR 47.5–68.0); 78% were married, and 75% had an ECOG performance status of 0. At diagnosis, 34% presented with metastasis, including 19% with visceral involvement. Primary cancer sites included head and neck (25%), colorectal (19.1%), lung (15%), melanoma (8.2%), and kidney (8.2%). Treatment regimens comprised chemotherapy (76%), immunotherapy (31.5%), and targeted therapy (9.5%). Most patients (83%) had no risk of anxiety or depression per HADS, with one patient showing a high risk. Moderate to complete sexual dysfunction was observed in 22.2% of patients, higher than the general Brazilian male population. The most affected domains were hypoactive sexual desire, premature ejaculation, and erectile dysfunction. Despite these findings, median hormone levels were within the normal range: testosterone (356 ng/dL, IQR 300–468), FSH (64 mIU/mL, IQR 29–93), and LH (39 mIU/mL, IQR 28–52). **Conclusions:** The prevalence of moderate to complete sexual dysfunction was 22.2% in this cohort. This rate is higher than that observed in the general male population in Brazil. The evaluation of sexual quality of life in men with cancer undergoing systemic treatment is often overlooked. This data points to the need to develop new policies and studies to increase awareness about this critical issue. Research Sponsor: None.

12050 Poster Session

A pilot exercise program in breast cancer survivors: Group vs individual training outcomes. First Author: Lindsey Elizabeth Merifield, University of Hawaii at Manoa, Honolulu, HI

Background: Exercise interventions have consistently led to improved fitness in breast cancer patients. Best practices to ensure longevity of lifestyle changes have not been well explored. The purpose of this study was to evaluate long-term effectiveness of exercise intervention for patients. We sought to determine if group (Gr) or individual (Ind) exercise sessions would have differing effects in maintaining long term muscular strength, cardiorespiratory endurance, and range of motion (ROM). **Methods:** Thirty female patients underwent 3 months of individual exercise training, and were then randomized to continue with Ind (n=13) or Gr sessions (n=17) for another 3 months. Assessments were performed at baseline, after 3 months, and 1 year from baseline. **Results:** Ind showed significant strength improvements from baseline to 3 months, and 1 year. Gr did not show significant strength improvements at either time point. Cardiorespiratory endurance (VO2peak) improved in Ind from baseline to 3 months, and 1 year. Gr showed significant endurance improvement from baseline to 1 year only. Ind shoulder (ROM) improved from baseline to 3 months and 1 year. No significant improvement in ROM was found in Gr at either time point. **Conclusions:** In our study, we found six months of exercise intervention improved long-term strength, endurance, and ROM significantly in Ind session, and non significantly in Gr. A post-analysis chart review revealed increased exercise limitations in the Gr due to injury and/or non-cancer related medical conditions, which may explain some of the differences in outcomes. Clinical trial information: NCT04013568. Research Sponsor: National Cancer Institute/U.S. National Institutes of Health; P30.

Endurance, strength, and range of motion measures by exercise session type at baseline (BL), 3 months (3M), and 1 year (1Y).

	Baseline		3 Month			1 Year				
	Gr N = 17†	Ind N = 13†	P value	Gr N = 17†	Ind P value	Ind N = 13†	Gr P value	Gr N = 17†	Ind P value	Ind N = 13†
Left Lateral Raise (degree)	164.6 ± 9.0	172.1 ± 6.9	0.95	171.8 ± 7.6	0.03	173.1 ± 10.1	0.46	171.9 ± 7.9	0.02	175.6 ± 8.8
Right Lateral Raise (degree)	163.1 ± 12.3	169.5 ± 16.2	0.87	169.8 ± 6.9	0.11	172.0 ± 8.7	0.65	172.1 ± 9.2	0.04	173.9 ± 9.1
Seated Cable Row (kg)	26.5 ± 3.9	27.4 ± 4.2	0.10	31.4 ± 4.1	<0.01	30.7 ± 4.2	0.16	33.1 ± 6.9	<0.01	30.5 ± 4.7
Leg Extension (kg)	36.4 ± 12.0	35.0 ± 10.6	0.25	48.7 ± 12.8	0.01	42.8 ± 14.7	0.13	48.9 ± 12.7	<0.01	44.2 ± 14.4
VO2 Peak (ml/kg/min)	27.9 ± 5.4	29.2 ± 6.1	0.06	32.0 ± 4.3	0.03	35.1 ± 7.2	0.05	33.7 ± 5.8	<0.01	34.2 ± 4.5

Gr=Group, Ind=Individual. Mean ± SD.

12051 Poster Session

Trajectories of multidimensional worry in survivors of early breast cancer (BC). First Author: Antonio Di Meglio, Cancer Survivorship Program, INSERM 981, Gustave Roussy, Villejuif, France

Background: Worrisome thoughts are common future-oriented behaviors and may affect quality of life (QoL) years removed from BC diagnosis. We aimed to identify trajectories of worry and their determinants, focusing on age-related specificities. **Methods:** Disease-free stage I-III BC survivors from CANTO (NCT01993498) completed the Impact of Cancer scale v2 at end of treatment (EoT) and years (Y) 1, 3, and 5 post-EoT. Group-based trajectories were identified modeling continuous scores of the worry subscale (range: 1-5, higher = worse), which evaluates uncertainty and worry about the future and health, a sense of time running out, fear of cancer recurrence (FCR), and symptom-triggered FCR. Adjusted multinomial logistic regression incorporating pre-treatment anxiety/depression assessed membership determinants. QoL (EORTC QLQ-C30/BR23) was described by trajectory. Analyses were stratified by age. **Results:** We included7824 survivors, 31% were $\leq$50 and 69% $>$ 50 years old. Among those aged $\leq$50, we identified five worry trajectories: most had high (41%) or very high (18%) worry (mean scores [95% CI] at EoT: 3.57 [3.55-3.60] and 4.37 [4.33-4.41], respectively, stable); 21% showed improvement (2.77 [2.73-2.82] at EoT, 2.14 [2.08-2.21] at Y5); and 12% had low worry (1.58 [1.53-1.63] at EoT, stable). Finally, 7% had moderate worry at EoT (2.21 [2.14-2.28]) that worsened sharply, stabilizing at high levels by Y5 (3.40 [3.29-3.52]). These patterns, especially in the worsening group, were primarily driven by persisting FCR and increasing uncertainty about health. Among those aged $>$ 50, similar trajectories emerged, however worry levels in the worsening group (17%) remained low-to-moderate (2.04 [2.01-2.06] at EoT, 2.34 [2.27-2.40] at Y5). Younger age was a significant determinant of very high worry, both in the $\leq$50 (Odds Ratio v low worry [95% CI] per 10-year decrease: 1.92 [1.33-2.77]) and in the $>$ 50 age group (1.50 [1.20-1.90]). Partnered status was associated with worsening worry in the $\leq$50 age group (v not: 2.54 [1.24-5.19]), whereas chemotherapy with very high worry in the $>$ 50 age group (v no chemo: 1.77 [1.14-2.73]). BC grade, stage, BRCA status, family history of cancer, and comorbidities were not linked to worry in either age group. Psychological and physical domains of QoL, including fatigue, sleep, cognitive function, appetite, and gastrointestinal symptoms, were significantly worse in trajectories at higher worry ($p < .001$ at all time points). **Conclusions:** More than two-thirds of younger BC survivors report high levels of worry that either remain unchanged or worsen 5 years post-EoT, with a more pronounced decline and different determinants than older counterparts. These patterns appear to be largely driven by the post-traumatic effects of BC on unresolved FCR and by negative projections about health. Early referral to mental health professionals and monitoring strategies focused on reducing anxious arousal are warranted. Clinical trial information: NCT01993498. Research Sponsor: Conquer Cancer, the ASCO Foundation and Rising Tide Foundation for Clinical Cancer Research; ARC; ARCPGA2022010004401_4882; ANR; ANR-10-COHO-0004; ANR; ANR-18-IBHU-0002; ANR; ANR-17-RHUS-008.

12052 **Poster Session**

Prospective observational study on health resource utilization and patterns of care for skeletal-related events in patients with bone metastases secondary to solid tumors. First Author: Mahmoud Abdelsatar Elshenawy, King Faisal Specialist Hospital and Research Center, Riyadh, Saudi Arabia

Background: Bone metastases are a common complication of advanced solid tumors, leading to significant morbidity through skeletal-related events (SREs). This study evaluates health resource utilization (HRU), treatment patterns, and clinical outcomes associated with SREs, with a focus on bone-modifying agents (BMAs) such as zoledronic acid and denosumab. **Methods:** This single-center, prospective, observational study included 199 patients with bone metastases secondary to solid tumors who experienced at least one SRE. Eligible patients were adults (≥18 years) with an Eastern Cooperative Oncology Group (ECOG) performance status of 0–3. Data collected included demographics, primary cancer type, comorbidities, treatment patterns, type and timing of SREs, and HRU. The impact of BMAs on SRE-free survival and overall survival (OS) was assessed using Kaplan-Meier analysis and multivariate Cox regression models. **Results:** The median age at the first SRE was 56 years, with 51.8% of patients being female. Breast cancer was the most common primary tumor site (30.2%), followed by genitourinary (22.1%) and gastrointestinal (18.6%) cancers. Visceral metastases were present in 56.3% of patients. Radiation therapy accounted for 80.9% of first SREs, followed by cord compression (8.5%), pathological fractures (7%), and surgical fixation (3.5%). Only 16.5% of patients received BMAs before their first SRE, increasing to 38.2% after the first SRE. Patients who received BMAs before the first SRE had significantly prolonged SRE-free survival (median 9.9 vs. 2.03 months, p = 0.001) and OS (median 45.6 vs. 29.8 months, p = 0.05). Similarly, BMA use after the first SRE improved SRE-free survival (median 18.9 vs. 10.3 months, $p < 0.001$) and OS (median 25.9 vs. 13.6 months, p = 0.001). The most common BMA-related adverse event was hypocalcemia (44.7%). **Conclusions:** This study highlights the underutilization of BMAs before the first SRE despite their significant impact on SRE-free survival and OS. Post-SRE BMA use was associated with improved outcomes, underscoring the need for earlier initiation of BMA therapy. Future research should focus on identifying barriers to early BMA utilization, optimizing management of therapy-related complications, and assessing the cost-effectiveness of BMAs in real-world settings. Research Sponsor: Amgen.

12053 **Poster Session**

Hot flashes and night sweats in women with breast cancer: Prevalence and severity of symptoms. First Author: Long Lin, West China School of Medicine, West China Hospital, Sichuan University, Chengdu, Sichuan, China

Background: Hot flashes(HF) and night sweats(NS) are common endocrine-related symptoms experienced by breast cancer patients, which potentially arise from the tumor or treatment-related pharmacologic effects. They can significantly diminish patients' quality of life. However, there is a paucity of studies in China investigating the incidence and characteristics of HF and NS among patients with breast cancer. **Methods:** This study was a multi-center, cross-sectional survey that included women diagnosed with breast cancer from seven hospitals' oncology departments in China. Information was collected about demographic characteristics, psychological status (the Hospital Anxiety and Depression Scale and the Distress Thermometer), the frequency and severity of HF and NS(modified Hot Flash and Night Sweat scale), and patients' perceptions of these symptoms. Group differences based on the presence or absence of HF and NS were analyzed using t-tests or chi-square tests. Finally, univariate analyses was conducted to explore factors associated with the frequency of HF and NS. **Results:** Between October and November 2024, 960 questionnaires were distributed, and 767 Chinese female breast cancer patients(aged 25 to 79) replied and completed fully. Over 56% (n = 430) patients reported experiencing HF or NS.The average weekly frequency was 8.6 times for HF and 7.3 times for NS. Patients attributed HF and NS primarily to treatment (HF: 36.8%;NS:32.7%) or uncertain causes (HF:15.8%;NS:17.4%). Compared to patients without HF and NS, those experiencing the symptoms had significantly higher levels of anxiety ($p < 0.001$), depression (p = 0.019), and psychological distress ($p < 0.001$). Notably, Patients reported severity, distress, and impact on life scores above 4, with HF at 47.90%, 37.46%, and 35.89%, and NS at 49.67%, 43.46%, and 40.85%, respectively. Among those affected, 59.24% of patients with HF and 63.7% of patients with NS adopted coping strategies, primarily resting/lying down (HF:27.7%;NS:36.3%). Regarding coping ability, HF group had a significant higher score than NS group (HF: 5.90; NS: 5.30, p = 0.012). Furthermore, univariate analysis revealed that HF and NS were associated with distress(HF:p = 0.032; NS:p = 0.030) and sleep quality(HF:p = 0.031; NS: p = 0.043). Additionally, for HF, single marital status (p = 0.017) was identified as a relevant factor, while stage IV tumor status (p = 0.044) was associated with NS. **Conclusions:** HF and NS affect over half of Chinese breast cancer patients, impacting their mental well-being and life quality, while low coping ability and limited coping strategies further underscore the need for healthcare professionals to pay closer attention to patients experiencing these symptoms, particularly single individuals and those with advanced-stage breast cancer. Research Sponsor: None.

12055 **Poster Session**

Cardiovascular risk factor severity and adverse cardiovascular events: A report from the Childhood Cancer Survivor Study (CCSS). First Author: Wendy Bottinor, Virginia Commonwealth University, Richmond, VA

Background: Among survivors of childhood cancer, more severe grades of CVRFs are associated with increased risk for adverse cardiovascular events (ACE). The impact of low severity CVRFs has not been defined. **Methods:** Among 25,723 long-term survivors of childhood cancer, CVRF severity was graded using longitudinal self-report: Grade 1 conditions are reported but not on medications; Grade 2 are prescribed medications. Cumulative incidence of CVRFs were estimated into the 6th decade of life with death and Grade 2 CVRFs a competing risk event for Grade 1 CVRFs. Starting at 1st report of a CVRF, multivariable piecewise-exponential models were used to estimate relative rates (RR) of heart failure (HF), myocardial infarction (MI), valvular disease (VD), arrhythmia, and cardiac death relative to survivors without hypertension (HTN), diabetes (DM), and hyperlipidemia (HLD), all as time-dependent covariates. **Results:** The median age of survivors was 35y (range 9-70) and 26y (range 7-52) from cancer diagnosis. Cumulative incidence by age 55 of Grade 1 HTN, DM, and HLD were 7.8% (CI 7.1-8.5%), 4.3% (CI 3.8-4.9%), and 10.8% (CI 9.9-11.6%), respectively. The cumulative incidences of Grade 2 HTN, DM, and HLD were 37.9% (CI 36.4-39.3%), 14.0% (13.0-15.0%), 31.3% (29.9-32.7%), respectively. Grade 2 CVRFs were significantly associated with an increased RR for nearly all ACE (table). Grade 1 CVRFs were also significantly associated for most ACE; often with a similar magnitude as Grade 2 CVRFs. Grade 1 vs no HTN was associated with a 2 to 5-fold significantly increased RR of HF, MI, VD, arrhythmia, and cardiac death. Grade 1 vs no DM was associated with an increased RR of HF (1.9, CI 1.1-3.4). Grade 1 vs no HLD was associated with an increased RR of MI (2.9, 1.9-4.2) and arrhythmia 2.1 (1.2-3.5). **Conclusions:** Grade 1 CVRFs are associated with increased risk for ACE. These data suggest a role for more aggressive treatment of Grade 1 CVRFs among survivors. Research Sponsor: National Cancer Institute.

Relative rates of ACE among survivors by CVRF severity.

Individual models for each CVRF vs no respective CVRF (ref)	HF RR (95% CI)	MI RR (95% CI)	VD RR (95% CI)	Arrhythmia RR (95% CI)	Cardiac death RR (95% CI)
HTN Grade 1	2.9 (1.9-4.4)	3.6 (2.4-5.3)	4.7 (3.0-7.5)	2.8 (1.6-4.8)	1.9 (1.1-3.3)
HTN Grade 2	7.2 (6.1-8.6)*	7.1 (5.9-8.5)*	4.7 (3.7-6.1)	5.3 (4.2-6.7)	1.5 (1.1-2.0)
DM Grade 1	1.9 (1.1-3.4)	1.5 (0.7-3.0)	0.8 (0.3-2.5)	1.5 (0.6-3.7)	0.6 (0.1-2.2)
DM Grade 2	2.5 (1.9-3.2)	2.7 (2.2-3.5)	2.2 (1.6-3.1)	2.3 (1.6-3.2)	1.8 (1.3-2.6)
HLD Grade 1	1.5 (0.95-2.4)	2.9 (1.9-4.2)	1.5 (0.8-2.8)	2.1 (1.2-3.5)	1.2 (0.6-2.2)
HLD Grade 2	3.8 (3.2-4.7)*	6.5 (5.4-7.8)*	3.8 (2.9-4.8)*	3.1 (2.4-4.0)	1.1 (0.8-1.4)

Models adjusted for sex, race, current age, age at diagnosis, current smoking, obesity, sedentary lifestyle, anthracycline and heart radiation dose. Models fitted separately for each ACE. No respective CVRF as referent group. *Grade 2 vs Grade 1 condition above, $p<0.05$.

12056 **Poster Session**

Impact of neighborhood disadvantage and residential isolation on cognitive outcomes in cancer survivors. First Author: Noha Sharafeldin, Division of Hematology & Oncology, Heersink School of Medicine, University of Alabama at Birmingham, Birmingham, AL

Background: The Social Vulnerability Index (SVI), a composite measure of socioeconomic deprivation, household composition, minority status, and housing type and transportation, is a reliable marker of neighborhood disadvantage. Residential Segregation measures the degree to which a minority group is distributed differently than the majority group across census tracts. The isolation index is a measure of segragation that captures the extent to which minority members are exposed only to one another. These measures have been associated with poor survival in patients with cancer, yet studies on adverse outcomes in surviors are limited. Cognitive impairment is an adverse outcome highly prevalent in up to 40% and persists up to 5y in hematologic cancer survivors treated with blood or marrow transplantation (BMT). We postulate that neighbohood disadvantage and residential isolation may have a negative effect on cognitive outcomes in BMT survivors. **Methods:** We included 71 patients treated with allogeneic BMT, enrolled in the the Cognitive Training and Genetics Attitudes (cTAG) study. Objective cognitive function was measured using a comprehensive in-person battery of standardized neuropsychological tests. Standardized T-scores were categorized as deficit scores (range 0 to 5), and averaged across all tests to estimate a global deficit score(GDS), which was used as a measure of cognitive impairment. Residential addresses, geocoded and joined to corresponding Census block group and tract, were used to match patients with their corresponding SVI and residential segregation scores. Multivariable logistic regression models adjusted for age, sex, race, and clustering at the tract level were used to estimate associations with GDS. **Results:** Median age at study participation was 58y (IQR: 46, 63), 57.8% were male, and 16.9% were non-Hispanic Black. Primary diagnosis was 66.2% acute leukemia and 22.5 myelodysplastic/myeloproliferative neoplasms. Average time since BMT was 1.5y (SD = 1.2). Prevalence of global cognitive impairment was 19.7% (95%CI: 11.2-30.9). A high overall SVI score was associated with GDS (aOR = 4.7, 95%CI: 1.1, 20.2, p = 0.035). Vulnerability related to socioeconomic status (aOR = 4.9, 95%CI: 1.2, 20.2, p = 0.03) and housing type and transportation (aOR = 4.0, 95%CI: 1.1, 15.2, p = 0.04) were significantly associated with GDS. Higher residential isolation index ($>$ 0.6) was significantly associated with increase in GDS (aOR = 5.4, 95%CI: 1.3, 22.5, p = 0.02) adjusting for age, sex, race, and clustering at the tract level. **Conclusions:** Cancer survivors residing in areas with higher indicators of social vulnerability and isolation are at increased risk of cognitive decline post-BMT. These findings highlight the overall need for dedicating appropriate resources and care planning especially for individuals surrounded by others from their same group within their residential areas. Research Sponsor: Leukemia Lymphoma Society; 3386-19; Be The Match.

12057 Poster Session

Pilot study of a muscadine grape extract supplement to decrease fatigue among older cancer survivors. First Author: Heidi D. Klepin, Wake Forest University School of Medicine, Winston-Salem, NC

Background: Fatigue is a prevalent symptom among older cancer survivors and is associated with declines in physical function and quality of life (QOL). A proprietary muscadine grape extract supplement (MGES) may decrease fatigue based on pre-clinical data showing effects on oxidative stress, inflammation, and mitochondrial function and clinical observations from a Phase 1 trial suggesting a relationship between higher dose of MGES and decreased fatigue. The objective of this pilot study was to evaluate whether MGES may decrease fatigue and improve function and QOL among older cancer survivors. **Methods:** We conducted a randomized placebo-controlled pilot study (NCT04495751) of MGE supplementation (4 tablets twice daily, approximately 1280 mg total phenolics) for 12 weeks (wks) among older adult cancer survivors who reported baseline fatigue. Additional eligibility included age ≥65 years, history of solid tumor or lymphoma with no evidence of disease, at least 1 year post completion of active treatment. Fatigue was assessed with the PROMIS Fatigue 7a at baseline, and 2, 4, 8, 12 (primary outcome) and 16 wks. Physical function [Pepper Assessment Tool for Disability (PAT-D, activities of daily living and self-reported mobility subscales, higher scores indicate more limitations), Short Physical Performance Battery (SPPB, higher scores indicate better performance), 6-minute walk] and QOL (PROMIS Global Health) were measured at baseline and 12 wks. Toxicity was assessed using the CTCAE v5. Intention to treat (IIT) analyses utilized t-tests with a one-sided alpha = 0.10 to compare outcomes at 12 wks. **Results:** Sixty-four adults (mean age 76 years, 78% female, 91% white, 6% black) were randomized. Most common malignancies were breast (50%), lymphoma (12.5%), and prostate (12.5%). Fifty-one participants (80%) completed 12 wks of MGES or placebo with N = 62 evaluable for IIT analysis. There were no ≥grade 3 toxicities; 26 grade 2 toxicities (gastrointestinal) were attributable to study intervention. In IIT analyses, there was no difference in fatigue by randomization at 12 wks (MGE 50.1 vs placebo 51.4, p = 0.22). However, participants randomized to MGES reported improved physical function (PAT-D total score 1.4 vs 1.6, p = 0.07, ADL score 1.2 vs 1.4 p = 0.08, mobility score 1.7 vs 2.2, p = 0.05) and had improved gait speed scores on the SPPB, 3.7 vs 3.3, p = 0.1).There were no differences in total SPPB score (9.8 vs 9.2, p = 0.37), six-minute walk distance (369 vs 349 feet, p = 0.43) and QOL at 12 wks. **Conclusions:** In this pilot study, MGE supplementation for 12 wks among older cancer survivors did not improve fatigue or QOL compared to placebo but self-reported physical function and gait speed score were improved, suggesting a potential benefit on physical function. Ancillary studies investigating effects on oxidative stress, inflammation, mitochondrial function, and microbiome are on-going. Clinical trial information: NCT04495751. Research Sponsor: National Cancer Institute; P30 CA012197; National Center for Advancing Translational Sciences; UL1TR001420.

12058 Poster Session

Trends and disparities in palliative care utilization in advanced head and neck cancer hospitalizations. First Author: Ayobami Gbenga Olafimihan, John H. Stroger, Jr. Hospital of Cook County, Chicago, IL

Background: Greater than 60% of Head and neck cancer (HNC) patients have advanced cancer at the time of presentation. They have unique physical and psychological symptoms due to the cancer's anatomical location and multimodal treatment-related toxicities. Early integration of palliative care (PC) in their management can improve health-related quality of life. We examined the trends and predictors of PC utilization among hospitalized advanced HNC patients in the US. **Methods:** A retrospective longitudinal study was conducted using the NIS database (2008-2021). Using joinpoint regression and multivariable logistic regression, trends and factors associated with PC receipt were assessed. **Results:** The overall prevalence of palliative care utilization among 326,265 hospitalizations with advanced HNC was 11%. Over the period, palliative care utilizations increased from 3,651 to 16,982 per 100,000 advanced HNC admissions (p-trend <0.001) with an average annual percentage increase of 9.7%. Females with metastatic HNC had higher odds (Adjusted odds ratio (AOR): 1.11; 95% CI: 1.04-1.19) of receiving palliative care compared to males. There was similar likelihood of utilizing palliative care across racial groups. Patients in teaching hospitals had 46% higher likelihood (AOR: 1.46; 95% CI: 1.33-1.60) of palliative care use in comparison to patients in non-teaching hospitals. Large hospitals had higher palliative care use compared to small hospitals (AOR: 1.12; 95% CI: 1.01-1.25). Admissions in the south and west had higher likelihood of palliative care use relative to those in the North-east region. Patients covered by Medicaid had higher odds of palliative care receipt compared to those covered by Medicare. Relative to patients who had a routine discharge home or with self-care, those discharged to facilities or with home health care were four-fold more likely (AOR: 4.35; 95% CI: 3.98-4.75) to receive palliative care. Those who died during hospitalization were also more likely to use palliative care (AOR: 21.4; 95% CI: 19.1-24.0). Non-elective admissions had higher likelihood of palliative care receipt relative to elective visits. **Conclusions:** Although palliative care utilization has improved over the years, it remains suboptimal. Tailored interventions addressing sociodemographic and hospital-level disparities will promote equitable access and meet the unique needs of this patient population. Research Sponsor: None.

Predictors of PC use.

Variables		AOR (95% CI)
Age	*"60 years and above" vs "Less than 60"*	1.0 (0.93-1.07)
Gender	*Female vs Male*	1.11 (1.04-1.19)
Race	*Non-Hispanic Black vs Non-Hispanic White*	1.02 (0.93-1.13)
	Hispanic vs Non-Hispanic White	1.10 (0.97-1.25)
	Non-Hispanic Others vs Non-Hispanic White	0.92 (0.82-1.03)
Hospital region	*Midwest vs Northeast*	1.09 (0.97-1.23)
	South vs Northeast	1.23 (1.10-1.37)
	West vs Northeast	1.37 (1.22-1.55)
Hospital Teaching Status	*Teaching vs Nonteaching*	1.46 (1.33-1.60)

12059 Poster Session

A phase 1b study of SHR-2017, a RANKL/NGF targeted antibody, in patients (pts) with breast cancer bone metastasis. First Author: Xu Liang, Beijing Cancer Hospital, Beijing, China

Background: Bone metastasis is a common site of metastasis in malignant tumors. For patients (pts) with bone metastasis, pain is the predominant symptom, significantly impairing the quality of life. SHR-2017, a first-in-class fully human monoclonal antibody targeting RANKL/NGF, is designed to prevent skeletal-related events and alleviate pain in pts with bone metastasis. Here, we present the preliminary pharmacokinetics, pharmacodynamics, efficacy and safety results from a multicenter, open-label, single-arm phase 1b study in pts with bone metastasis from breast cancer. **Methods:** Breast cancer pts with at least one bone metastasis and an average Numeric Rating Scale (NRS) score of ≥ 4 at the index bone metastasis cancer pain site at baseline were eligible. Pts could be undergoing stable anti-tumor treatment or have no plan to change their anti-tumor treatment within 2 weeks after drug administration in this study. Pts received subcutaneous injection of SHR-2017 at 180 mg every 4 weeks for 6 cycles. To assess pain, pts maintained a diary (daily through week 8 and then weekly to week 48) to record the average and worst pain over the previous 24 h (on a numeric rating scale from 0 = no pain to 10 = worst possible pain) at the index bone metastasis cancer pain site. **Results:** As of Dec 31, 2024, 22 pts were enrolled and treated (prior bone targeted agents [BTA] use, 36%; mean NRS of average pain, 4.17 [SD: 0.76]). Following a single dose, the median time to peak concentration of SHR-2017 was 7 days, with a mean half-life ($t_{1/2}$) of 11.4 days and a mean clearance (CL/F) of 0.88 L/day. Among 12 pts without prior BTA use, a reduction in urine N-telopeptide of type I collagen adjusted for urine creatinine (uNTX/Cr), a biomarker for bone resorption, was evident by cycle 1 and sustained over time; the median reduction from baseline was -83.0% (range -96.9% to -60.6%) at week 5 (C2D1). By week 13 (C4D1), among 8 pts without prior BTA use, the median reduction in uNTX/Cr was -78.7% (range -93.1% to -64.6%). Daily NRS score showed a continuous decrease during cycle 1 in all pts, the mean reductions from baseline in average and worst pain were -1.95 (SD: 1.21) and -1.90 (SD: 1.46) at week 2, respectively. By week 4, the reductions were -2.46 (SD: 1.03) and -2.45 (SD: 1.45), respectively. Treatment-related AEs (TRAEs) occurred in 7 (32%) pts (grade 1, n = 6; grade 2, n = 1), with the most common being increased parathyroid hormone (PTH), the one grade 2 TRAE being rash. There were no TRAEs leading to dose discontinuation. **Conclusions:** Preliminary data indicated promising anti-bone resorption and analgesic effects, with a favorable safety profile for SHR-2017 in pts with bone metastasis from breast cancer. The trial is ongoing to further evaluate SHR-2017 following multiple dosing. Clinical trial information: NCT06380881. Research Sponsor: Jiangsu Hengrui Pharmaceuticals Co., Ltd.

12060 Poster Session

Baseline circulating growth differentiation factor-15 and the cancer phenotype in the PROACC-1 phase 2 study of the efficacy and safety of ponsegromab in patients with cancer cachexia. First Author: Eric Roeland, Knight Cancer Institute, Oregon Health & Science University, Portland, OR

Background: Growth differentiation factor-15 (GDF-15) is an emerging therapeutic target in cancer cachexia. However, the association of circulating GDF-15 with the cancer cachexia phenotype remains poorly characterized. **Methods:** Serum GDF-15 was measured using the Roche Elecsys GDF-15 assay at screening in a phase 2, randomized trial of ponsegromab (an investigational anti-GDF-15 monoclonal antibody) in patients with cancer cachexia, and an elevated serum GDF-15 (≥ 1500 pg/mL) (NCT05546476). Cachexia was defined by international consensus criteria and sarcopenia by standardized sex-specific cut-off values for lumbar skeletal muscle index. Cross-sectional associations of GDF-15 with various demographic and clinical parameters were explored post-hoc using summary statistics and Pearson's correlation (with GDF-15 on the $\log_{10}$ scale). **Results:** A total of 187 patients were enrolled in this study with a median (IQR) age of 67 (60-74) years and 37% were female. Baseline median GDF-15 values were higher among patients with cachexia and colorectal and pancreatic cancers, compared to NSCLC. GDF-15 elevation was higher in patients with stage IV disease, sarcopenia, and worse performance status (Table). Higher GDF-15 levels were associated with lower serum albumin (r = -0.31 [95% CI: -0.44, -0.177]) and prealbumin (r = -0.17 [95% CI: -0.31, -0.03]). No significant associations were observed between GDF-15 levels and appetite or fatigue assessments. **Conclusions:** Among patients with cancer cachexia, GDF-15 elevation was more pronounced in those with more advanced cancer, sarcopenia, and worse performance status. In addition, GDF-15 levels were negatively correlated with markers of nutritional status. Clinical trial information: NCT05546476. Research Sponsor: Pfizer, Inc.

Demographic or Clinical Characteristic	n	Median (IQR) serum GDF-15, pg/ml
Age, years		
- 18-44	6	2718 (2461, 8117)
- 45-64	70	4197 (2366, 9425)
- ≥65	111	3849 (2310, 7125)
Type of cancer		
- NSCLC	74	2701 (2114, 4094)
- Pancreatic	59	4714 (2408, 9561)
- Colorectal	54	6468 (4106, 10052)
Interval from cancer diagnosis		
- <1 year	96	4259 (2447, 8919)
- ≥1 year	91	3781 (2259, 6997)
Stage of cancer		
- I/II	16	3551 (2264, 6320)
- III	34	3232 (2461, 5704)
- IV	137	4365 (2387, 8117)
Body mass index (BMI), kg/m2		
- <20	99	3254 (2220, 6801)
- ≥20	88	5052 (2712, 8749)
% weight loss in 6 months prior to screening		
- < 10%	99	3849 (2290, 7677)
- ≥ 10%	88	4118 (2381, 7595)
Sarcopenia status		
- Yes	144	4259 (2402, 7672)
- No	40	2928 (2136, 8052)
ECOG Performance Status		
- 0	33	2842 (2408, 5673)
- 1	123	4094 (2366, 8623)
- 2/3	31	5119 (2272, 7667)
Systemic anticancer therapy		
- Platinum-based therapy	68	5760 (3053, 10008)
- Antimetabolite agents	100	5914 (2847, 10768)
- Biological agents	40	5744 (3317, 9644)
- Antimicrotubule agents	73	4891 (2762, 9425)
- PD-1 or PD-L1 inhibitors	30	2744 (2149, 4787)

12061 **Poster Session**

IPElife: Phase III, double-blind trial of *cannabis sativa* extract in pain management and quality of life in patients with metastatic lung cancer. First Author: Danielli Matias, Liga Norte Riograndense Contra o Câncer, Natal, Brazil

Background: Pain and deterioration in quality of life (QoL) are among the most common and problematic symptoms reported by patients with late-stage lung cancer. Thus, *cannabis sativa* extract has been identified as a potencial adjuctive therapy for enhancing QoL and managing symptoms, including oncology pain. Objective: The aim is to assess pain management and quality of life in patients with locally advanced or metastatic lung cancer using *cannabis sativa* extract. **Methods:** A randomized, prospective, double-blind, placebo-controlled, phase III trial was conducted, which included patients, which included patients with locally advanced or metastatic lung confirmed by histopathology. The participants were subdivided into two groups of 20 patients each, with 1:1 allocation ratio. The primary outcome was pain control, measured using the Visual Analog Scale (VAS) for pain. The secondary outcomes included quality of life, assessed using the EORTC QLQ-C30 and its specific module for lung cancer (QLQ-LC13). The *cannabis sativa* extract administration protocol involved dose escalation, starting at 10mg/day, with titration every 5 days until the patients reached their goals or the maximum dose of 100mg/day. The questionnaires and the VAS scale were applied every 21 days from T1 to T5. Continuous variables were analyzed using the paired t-test or signed-rank test, depending on the date distribution. **Results:** The difference in mean pain scores (measured using the EVA tool) was greater in the CBD group compared to the placebo group between periods T1 and T5 (5.0 vs 3.7) (Table1). Similarly, the difference in mean pain scores, as measured using the EORTC-QLQ-C30 scale (47.2 vs 35.7), favored the CBD group. Regarding the quality of life analysis, in the overall assessment date were not statistically significant, however difference was observed in the levels of insomnia (p-value 0.01) and dyspnea (p-value 0.02) between patients in the CBD and placebo groups, with results favoring the CBD group. **Conclusion:** The *cannabis sativa* extract may be considered an adjuvant in the management of pain and quality of life in patients with metastatic lung cancer and locally advanced. Clinical trial information: 6.036.463. Research Sponsor: GreenCare Pharma.

Pain control analysis by the EVA scale between times.

	T1	T3	T5
	Mean (SD)	Mean (SD)	Mean (SD)
CBD group	7.2 (2.1)	3.3 (2.6)	2.2 (2.4)
Placebo group	7.4 (1.8)	3.7 (3.1)	3.7 (3.3)

Average EVA scale scores by group and time.

12062 **Poster Session**

eHealth disease educational intervention vs. outpatient palliative care as usual among incurable cancer patients cared by family caregivers at home. First Author: Ying Yu, State Key Laboratory of Genetic Engineering, Human Phenome Institute, Zhangjiang Fudan International Innovation Center, Fudan University, Shanghai, Shanghai, China

Background: To determine whether ehealth disease educational interventions (eDEI) with fast-delivering interfaces and concise key messages can enhance capability of family caregivers and improve physical and psychological aspects of health-related quality of life (HRQoL) of incurable cancer patients at home. **Methods:** A randomized, open-label controlled trial was conducted in cancer center in Shanghai, China. Eligible participants (age$\geq$18 years) with incurable cancer receiving palliative care and Karnofsky performance $\leq$ 70, along with a family caregiver (age $\geq$18 years), were randomly assigned 1:1 to either intervention (eDEI plus palliative care as usual (CAU)) or control group (CAU only). eDEI as a mobile application provides family caregivers with texts, audios and videos of symptom/side effect management and nursing skills. The intervention lasted for two months.The primary outcomes were physical aspects of HRQoL on the European Organization for Research and Treatment of Cancer Core Quality of Life Scale (EORTC QLQ-C30) and psychological aspects of HRQoL on the Hamilton Anxiety Rating Scale (HAM-A) from baseline to the end of 2nd month. The secondary outcome was caregiver satisfaction on a questionnaire focusing on skill enhancement using Mann-Whitney tests at the end of 2nd month. The exploratory outcome was survival benefit using Kaplan-Meier method with log rank hazard model from the enrollment to the death. The primary analyses were based on intention-to-treat principles, covering all patients who completed baseline assessment. False discovery rate (FDR) was used for multiple testing correction. **Results:** From Jul 28 to Nov 3, 2023, 154 eligible patients with family caregivers were randomly and evenly assigned to the intervention group and control group. 74 and 73 patients with their caregivers, in the intervention and control group respectively, completed baseline assessment. Among the 147 patients (mean age 59.9 years, 42.9% female) from baseline to the end of 2nd month, Linear Mixed Model analyses showed that the intervention group had significant improvement of HRQoL compared with the control group, evidenced by EORTC QLQ-C30 score (FDR-adjusted $p < 0.0001$, Cohen's *d* 0.42) and HAM-A score (FDR-adjusted $p < 0.0001$, Cohen's *d* -0.43). There was a significant difference of caregiver satisfaction at the end of 2nd month (mean difference score 0.57, $p < 0.0001$, Cohen's *d* 1.19). Besides, a post-trial exploratory survival analysis showed that the intervention group had longer survival compared to the control group (median 220 days vs. 141 days, p = 0.012, hazard ratio 1.83, 95%CI 1.14 to 2.92) after adjustment of baseline characteristics. **Conclusions:** The fast-delivering and concise eDEI can enhance caring capability of family caregivers, improve physical and psychological aspects of HRQoL, and prolong survival among incurable cancer patients. Clinical trial information: 2300077346. Research Sponsor: None.

12063 **Poster Session**

Impact of elinzanetant on sleep disturbances and quality of life in women undergoing adjuvant endocrine therapy for breast cancer: Phase 3 OASIS 4 trial. First Author: Donal J. Brennan, UCD School of Medicine, Dublin, Ireland

Background: Vasomotor symptoms (VMS) and sleep disturbances are common in women taking adjuvant endocrine therapy (AET) for hormone receptor-positive (HR+) breast cancer and can impact quality of life and treatment adherence, potentially affecting breast cancer outcomes. There are few efficacious treatments and none approved in this indication. Elinzanetant (EZN) is a dual neurokinin-1 and -3 receptor antagonist in development for the treatment of VMS. **Methods:** OASIS 4 (NCT05587296) is a 52-week randomized, placebo-controlled phase 3 trial evaluating the safety and efficacy of EZN for the treatment of VMS in women taking AET for HR+ breast cancer. Women aged 18–70 years being treated for, or at high risk of developing, HR+ breast cancer and experiencing $\geq$35 moderate-to-severe VMS/week associated with tamoxifen/aromatase inhibitors were randomized 2:1 to receive EZN 120 mg for 52 weeks or placebo for 12 weeks followed by EZN for 40 weeks. Impact of EZN on sleep disturbances and menopause-related quality of life were evaluated as key secondary endpoints, measured by mean changes from baseline to week 12 in Patient-Reported Outcomes Measurement Information System Sleep Disturbance Short Form (PROMIS SD SF) 8b total T-score and Menopause-specific Quality-Of-Life questionnaire (MENQOL) total score, respectively. These endpoints were analyzed using a mixed model with repeated measures (one-sided p-values). **Results:** At baseline, mean (standard deviation [SD]) PROMIS SD SF 8b total T-scores were 60.6 (6.3) in the EZN group and 60.7 (6.8) in the placebo group, corresponding to moderate sleep disturbances based on established thresholds in a reference population. At week 12, reductions from baseline in PROMIS SD SF 8b total T-score were -10.6 (8.2) and -4.1 (7.4) in respective groups, suggesting an improvement in sleep disturbance. Reductions between EZN and placebo showed a statistically significant difference (least squares [LS] mean difference [95% confidence interval (CI)]: -6.1 [-7.5, -4.8]; $p<0.0001$). Mean (SD) MENQOL total scores at baseline were 4.8 (1.2) in the EZN group and 4.8 (1.3) in the placebo group. At week 12, reductions from baseline in MENQOL total score were -1.3 (1.1) and -0.5 (1.2), respectively, corresponding to an improvement in menopause-related quality of life. Reductions between EZN and placebo showed a statistically significant difference (LS mean difference [95% CI]: -0.7 [-0.9, -0.5]; $p<0.0001$). Reductions in PROMIS SD SF 8b total T-scores and MENQOL total scores were maintained in both treatment groups throughout the 52-week treatment period. **Conclusions:** EZN demonstrated efficacy in reducing sleep disturbance and improving quality of life in women undergoing AET for breast cancer. Concomitant intake of EZN and AET may improve tolerability and adherence to AET, with a potentially favorable impact on breast cancer outcomes. Clinical trial information: NCT05587296. Research Sponsor: Bayer.

12064 **Poster Session**

Nationwide trends and disparities in end-of-life care for acute myeloid leukemia: A 2019–2021 NIS analysis of palliative care utilization and hospitalization costs. First Author: Nandhini Iyer, MacNeal Hospital, Loyola Medicine, Berwyn, IL

Background: Acute myeloid leukemia (AML) is a life-threatening hematologic malignancy with high morbidity and mortality, particularly among older adults. Early integration of palliative care (PC) has been shown to improve symptom management, quality of life, and healthcare outcomes in AML patients. However, significant disparities in PC utilization persist, driven by socioeconomic factors such as race, income, and insurance status. This study examines trends in PC use among AML inpatients, focusing on its impact on mortality, hospitalization costs, and complications, while highlighting barriers to equitable care access. **Methods:** We conducted a retrospective cohort study utilizing the National Inpatient Sample (NIS) database from 2019 to 2021, identifying AML patients via ICD-10 codes, and were classified based on their PC utilization. The Institutional Review Board (IRB) approval was not mandatory since the NIS contains deidentified data. The primary outcome was inpatient mortality, with secondary outcomes including length of stay (LOS), total hospital costs, and key complications. Statistical analysis included t-tests, chi-square tests, and multivariable logistic regression adjusting for demographic, socioeconomic, and hospital factors. **Results:** A total of 220,790 AML hospitalizations were identified, with 27,540 (12.4%) utilizing PC. PC patients were older (67.41 vs. 58.65 years, $p < 0.01$) and predominantly White (75.27% vs. 70.70%, $p < 0.01$). Odds of PC utilization were lower for Black (OR 0.9, p = 0.05), Hispanic (OR 0.7, $p < 0.01$), and Asian (OR 0.77, $p < 0.01$) patients. Utilization was highest in urban teaching hospitals (89.2%, $p < 0.01$) and Medicare patients (OR 1.87, $p < 0.01$), followed by private insurance (22.99%), Medicaid (8.91%), and self-pay patients (1.38%). Mortality was significantly higher in the PC group (37.4% vs. 4.42%, OR 11.74, $p < 0.01$). Secondary outcomes included longer stays (12.94 vs. 12.25 days, $p < 0.01$), higher costs ($214,915 vs. $174,193, $p < 0.01$), and more complications (tumor lysis syndrome, stroke, thrombocytopenia, sepsis, anemia; all $p < 0.01$). **Conclusions:** Palliative care in AML patients was associated with higher mortality, longer hospital stays, increased costs, and complications, likely reflecting its introduction at more advanced stages of the disease. These findings underscore the urgent need for earlier integration of palliative care into treatment protocols. Addressing barriers such as healthcare inequities and improving access to timely interventions could enhance patient quality of life, reduce complications, and optimize resource utilization, ultimately fostering more equitable, efficient, and cost-effective care for AML patients. Research Sponsor: None.

12065 Poster Session

Early palliative care, intensity of end-of-life care, and their impact on overall survival in cancer patients: A real-world study. First Author: Sebastien Salas, Aix-Marseille University, Marseille, France

Background: Early palliative care (EPC) and reduced aggressive end-of-life (EOL) interventions improve quality of life in advanced cancer. While trials suggest a potential survival benefit, the real-world impact on overall survival (OS) remains underexplored. This study examines the association between palliative care (PC) timing, EOL care intensity, and OS in a large real-world cohort. **Methods:** We conducted a population-based study using the French health claims database (SNDS) for patients with metastatic solid tumors diagnosed within 2 years who died in 2022. Patients with hematologic malignancies or PC initiated before metastasis were excluded. Patients were stratified by PC referral timing: no PC, EPC ($\leq$2 months post-diagnosis), and late PC (LPC) ($>$ 2 months post-diagnosis). EOL care intensity was assessed using Earle criteria (care structure/processes) and MIEOL criteria (physically invasive interventions). The primary endpoint was OS (time from diagnosis to death). **Results:** Among 159,288 decedents, 85,192 met inclusion criteria (no PC = 27,325; EPC = 29,016; LPC = 28,851). Digestive (n = 29,668) and pulmonary (n = 17,065) cancers predominated. Patients with EPC/no PC had higher poor-prognosis adapted Charlson scores than LPC (23.6% and 23.4% vs. 18%, $p < 0.001$). EOL aggressiveness was greater in no PC compared to EPC/LPC (Earle $\geq$1: 51.4% vs. 23.4% vs. 21.6%; MIEOL $\geq$1: 25.7% vs. 16.9% vs. 17.6%; $p < 0.001$). Mean OS differed significantly (no PC: 167 $\pm$ 190 ; EPC: 74 $\pm$ 100 days days; LPC: 344 $\pm$ 182 days; $p < 0.001$). LPC was associated with the longest OS. Patients meeting Earle and MIEOL criteria were significantly associated with shorter survival ($p < 0.001$). **Conclusions:** This real-world analysis revealed no survival advantage with early PC initiation, likely reflecting clinical fragility in these patients. Early referral often signifies advanced disease rather than a direct survival benefit of PC itself. LPC was linked to the longest survival, emphasizing the need for graduated PC from metastatic diagnosis. No PC was associated with higher EOL care intensity, which did not improve survival, highlighting possible unreasonable overtreatment. Research Sponsor: None.

12066 Poster Session

Socioeconomic disparities in palliative care utilization among children with late-stage bone and soft tissue sarcomas: A National Cancer Database analysis. First Author: Paul Phan, Johns Hopkins University School of Medicine, Baltimore, MD

Background: Palliative care seeks to improve the quality of life for many children living with cancer, but it remains underused. Racial and socioeconomic disparities have been identified in the receipt of palliative care among adult patients with advanced soft-tissue sarcomas and metastatic renal cell carcinoma. Our study seeks to determine if similar barriers exist in palliative care receipt among pediatric patients with late-stage bone and soft tissue sarcomas. **Methods:** We used the National Cancer Database (NCDB) to perform a retrospective review of children aged 0-25 with Stages III and IV bone and soft tissue sarcomas from 2004 to 2022. We used a 1:1 propensity score matching algorithm to compare the utilization of palliative treatment by race and ethnicity and to balance potential confounding covariates. Kaplan-Meier estimation was utilized for survival analysis. **Results:** A total of 8,030 patients were included in this analysis. Of these patients, 375 (4.7%) received at least one form of palliative treatment, including surgery (n=31), radiation (n=99), chemotherapy (n=55), pain management (n=98), multiple modalities (n=77), and others (n=15). The median age was 16 years (IQR: 12-20). Osteosarcoma (29.2%) was most common, followed by Ewing's sarcoma (28.1%), non-rhabdomyosarcoma soft tissue sarcoma (21.6%), and rhabdomyosarcoma (21.0%). The 5-year overall survival rate was 14.7% (95% CI 11.2%-19.3%) for patients receiving palliative care versus 44.7% (95% CI 43.6%-45.9%) for those who did not. After propensity score matching, non-Hispanic Black children were found to be less likely to receive palliative care than non-Hispanic White children (3.4% vs. 5.9%, p = 0.047). Hispanic children were also less likely to receive palliative treatment than non-Hispanic White children (2.5% vs. 5.5%, p = 0.007). **Conclusions:** Hispanic and Black children with sarcomas were less likely to receive palliative care compared to White children. Further research is warranted to understand the impact of other factors contributing to palliative care receipt and how they may be addressed to optimize the quality of life in sarcoma treatment in children. Research Sponsor: None.

Post-propensity score matching univariate analysis for palliative care use by race and ethnicity.

		RACE				ETHNICITY		
Palliative Care Utilization*	Total (n=1286)	Non-Hispanic White (n=643)	Non-Hispanic Black (n=643)	p-value	Total (n=1418)	Non-Hispanic White (n=709)	Hispanic (n=709)	p-value
No	1226 (95.3%)	605 (94.1%)	621 (96.6%)	0.047	1361 (96.0%)	670 (94.5%)	691 (97.5%)	0.007
Yes	60 (4.7%)	38 (5.9%)	22 (3.4%)		57 (4.0%)	39 (5.5%)	18 (2.5%)	

*Patients were matched based on age at diagnosis, sex, insurance status, median income of county of residence, high school graduation percentages of county of residence, mean tumor size, primary tumor sjte, AJCC stage, and presence of metastases at diagnosis.

12067 Poster Session

Androgen deprivation therapy and quality of life: A concept map analysis. First Author: David Lazris, University of Pittsburgh Medical Center (UPMC), Pittsburgh, PA

Background: Androgen deprivation therapy (ADT) is the backbone of systemic treatments for prostate cancer (PC), but is associated with side effects that decrease quality of life (QOL). There lacks a robust qualitative exploration of the nuanced entirety of physical, mental, and social changes men experience during ADT. While interventions typically focus on metabolic and cardiovascular effects, it is unclear if these are the most impactful contributors to QOL as experienced by men themselves. **Methods:** We conducted concept mapping, a participatory mixed-methods research approach, involving item generation, pile sorting, and rating to identify and categorize side effects of ADT. Thirty men who started ADT for PC in the past 3-12 months and reported undesirable changes from ADT participated. Men on oral androgen axis inhibitors were included, but those receiving other systemic therapies or with comorbidities that could confound results were excluded. Men who had surgery or radiation for PC were enrolled after $\geq$3 months post-treatment. We conducted semi-structured brainstorming interviews to generate lists of undesirable changes participants experienced. Study team members reviewed each list for completeness, then combined all 676 items into 79 unique items. Fifteen participants sorted these items into named groups and rated each item on a 1-5 Likert scale for the following questions (5 representing maximal response): "After starting ADT, how much did this change negatively affect your life?" and "After starting ADT, how much additional support would you have liked to receive for the following change?" GroupWisdom Concept Mapping software generated a cluster map and calculated mean Likert scale ratings for each cluster. **Results:** Based on participant sorting, items were grouped into four main clusters: Physical Manifestations; Sexual Changes; Mental Health Changes & Concerns of Stigma; and Motivational Changes (13 iterations, stress value 0.29). The Table presents sample items and mean Likert scale cluster ratings. **Conclusions:** While men on ADT reported expected physical and sexual changes, qualitative interviews uncovered changes in motivation, mental health, and concerns of stigma. Men reported sexual changes as having the largest negative impact on QOL. The concept mapping can be utilized to provide anticipatory guidance to men starting ADT, as well as guide the development of supportive interventions. Research Sponsor: None.

Cluster	Example Items	Negative Affect on Life Rating (1-5; 5=Most Negative)	Additional Support Wanted Rating (1-5; 5=Most Support Wanted)
Physical Manifestations	- Physical Strength Decreased	2.6	2.1
Sexual Changes	- Sex Drive/Libido Diminished	2.9	2.0
Motivational Changes	- Wanting to Sit and Do Nothing/Watch TV; Being Less Active; Feeling "Lazy"	2.2	1.7
Mental Health Changes & Concerns of Stigma	- Not Wanting to Share Information About Diagnosis/Treatment with Others -More Pessimistic/Less Optimistic	1.8	1.5

12068 Poster Session

Care needs and considerations for implementing a community-based palliative care program for women with breast or cervical cancer in three Nigerian states. First Author: Igoche David Peter, Limi Children's Hospital, Abuja-Fct, Nigeria

Background: Breast and cervical cancer pose a significant public health burden in most sub-Saharan African countries including Nigeria. With ~70% of cases presenting at late stages (III & IV), high mortality is often a characteristic feature. This underscores the critical need for comprehensive palliative care services to improve the quality of life for Nigerian women with breast and cervical cancers. Despite the growing recognition of this need, there is limited evidence for integrating community resources into cancer-directed palliative care services in Nigeria, hence this study explored the needs of Nigerian women with breast or cervical cancer, and their caregivers, and sort to identify resources necessary for developing a robust palliative care initiative across the community and healthcare facility settings. **Methods:** We conducted a qualitative study including 45 purposively sampled adult female caregivers of women with breast or cervix cancers, from 3 states in Nigeria: Abuja-Federal Capital Territory, Nasarawa, and Rivers states respectively. Focus Group Discussions using semi-structured interview guide were carried out and included questions about cancer care needs of both caregivers and the patients, including considerations for implementing a community-based palliative care program. Data were analysed using thematic analysis for deductive identification of key themes, while allowing for new themes to emerge inductively, and then we phenomenologically investigated respondents' palliative care needs perceptions and their meaning. **Results:** Four overarching themes were identified namely, i) needs of women with breast or cervical cancer, ii) needs of caregivers, iii) human resources for community-based palliative care, and iv) feasibility of a community-based palliative care program. Respondents revealed that to attain wholistic wellbeing for women with breast or cervical cancer, their peculiar needs and those of their caregivers which were largely unrecognised deserve attention. Adequate human resources, including trained healthcare workers and support staff, and clearly defined feasibility criteria for palliative care, were identified as crucial for the successful implementation of a community-based palliative care program. **Conclusions:** A community-based palliative care program for Nigerian women with breast or cervical cancer will be acceptable and feasible if it is designed to address the peculiar medical and non-medical needs of both the cancer patients and their caregivers. Research Sponsor: German government.

12069 **Poster Session**

Granisetron transdermal delivery system for nausea and vomiting prophylaxis in HER2-positive metastatic breast cancer patients receiving pyrotinib and capecitabine: A single-arm phase II study. First Author: Jun Cao, Department of Medical oncology, Fudan University Shanghai Cancer Center, Shanghai, China

Background: The efficacy of granisetron transdermal delivery system (GTDS) in managing nausea and vomiting caused by intravenous chemotherapy is well-established; however, its effectiveness for emesis induced by oral antineoplastic agents remains unclear. This study aimed to evaluate the efficacy and safety of GTDS for the prophylaxis of nausea and vomiting in patients receiving daily oral anticancer agents with moderate emetic risk, specifically pyrotinib combined with capecitabine for HER2-positive metastatic breast cancer (mBC). **Methods:** A single-arm, single-center phase II trial was conducted, enrolling 77 patients with HER2-positive mBC. Patients received 2 consecutive doses of GTDS (with a 7-day interval between the doses) during the first treatment cycle (21 days) of pyrotinib (400 mg daily, days 1–21) and capecitabine (1000 mg/m² twice daily, days 1–14). The dual primary endpoints were the complete response (CR) rate of nausea and vomiting (no emesis and no rescue medication) and the incidence of ≥grade 3 diarrhea. Secondary endpoints included complete control (CC) rate, daily emesis/nausea frequency and adverse events (AEs). **Results:** During the first treatment cycle, 62.3% of patients achieved CR, and the CC rate was 54.5%. Weekly CR rates were 79.2%, 70.1%, and 79.2% in weeks 1, 2, and 3, respectively, while CC rates were 72.7%, 61.0%, and 70.1%, respectively. The mean daily number of emetic episodes ranged from 0.1 to 0.6, peaking in week 2. The mean daily nausea scores ranged from 0.6 to 1.1, with a slight increase starting from day 4. Grade 3 diarrhea occurred in 28.6% of patients, peaking on day 7. AEs were reported in 53.25% of patients, with the most common being gastrointestinal symptoms, fatigue, and rash. No QT prolongation was observed. **Conclusions:** Prolonged administration of GTDS demonstrated efficacy and safety in preventing nausea and vomiting in HER2-positive mBC patients receiving daily oral pyrotinib and capecitabine; however, it did not reduce the incidence of ≥ grade 3 diarrhea. Clinical trial information: NCT04472143. Research Sponsor: None.

12070 **Poster Session**

Efficacy of Chinese medicine compound Fufang E'jiao Syrup for symptom burden of cancer-related fatigue in patients with advanced cancer: A randomized clinical trial. First Author: Shanshan Gu, Department of Oncology, Xiyuan Hospital of China Academy of Chinese Medical Sciences, Beijing, China

Background: *Cancer-related fatigue (*CRF) is often accompanied by a high symptom burden, significantly impacting the quality of life in patients with advanced cancer. Traditional Chinese medicine compound *Fufang E'jiao Syrup* (FFEJS) has shown promising potential in alleviating fatigue and reducing the overall burden of cancer-related symptoms. This study aims to investigate the efficacy and safety of FFEJS in reducing symptom burden in patients with advanced cancer. **Methods:** This multicenter, double-blinded, placebo-controlled trial was conducted across 29 hospitals in China and included 611 patients with advanced non-small cell lung cancer, colorectal cancer, or gastric cancer experiencing moderate-to-severe fatigue (Visual Analogue Fatigue Scale score ≥ 4). Participants were randomized to receive FFEJS (20 mL, 3 times daily) or placebo for six weeks. The primary outcome was the change in symptom burden, assessed via the Edmonton Symptom Assessment Scale (ESAS; score range 0-110, higher scores indicate greater burden). Secondary outcomes included changes in 11 individual symptoms (e.g., tiredness, depression, pain) and the incidence of adverse events. Linear mixed models were used for statistical analysis. **Results:** Among 611 patients randomized (303 received FFEJS and 308 received placebo; 210 [34.4%] had non-small cell lung cancer, 201 [32.9%] had colorectal cancer, and 200 [32.7%] had gastric cancer; mean [SD] age 62.8 [9.3] years; 413 [68.6%] male; mean [SD] baseline mean total symptom burden 38.96 [15.68] points, 503 (82.3%) completed the primary end point analysis. At week 6, FFEJS demonstrated a significantly greater reduction in total symptom burden compared to placebo (6.67 vs 3.16; adjusted mean difference: 3.51[95% CI 1.21–5.8]; P = .004). Patients in the FFEJS arm showed significant improvements in tiredness (1.68 vs 0.79; adjusted mean difference, 0.89 [95% CI, 0.62-1.18]; $P < .001$), drowsiness (1.13 vs 0.50; adjusted mean difference, 0.63 [95% CI, 0.32-0.95]; $P < .001$), pain (0.34 vs 0.01; adjusted mean difference, 0.33 [95% CI, 0.08-0.62]; P = .049), depression (0.41 vs -0.15; adjusted mean difference, 0.56 [95% CI, 0.28-0.86]; P = .003) compared with the placebo arm. Subgroup analysis revealed greater symptom reduction in geriatric patients (≥ 60 years; $P < .001$) and in non-small cell lung (P = .044) and colorectal cancer (P = .047), compared to gastric cancer (P = .123). **Conclusions:** FFEJS significantly reduced total symptom burden and improved fatigue-related symptoms in patients with advanced cancer. Subgroup analysis highlighted enhanced efficacy in geriatric populations and certain cancer types. These results highlight the potential of FFEJS as a valuable integrative therapy for improving symptom management and quality of life in advanced cancer care. Clinical trial information: NCT04147312. Research Sponsor: National Key Research and Development Program of China.

12072 **Poster Session**

Single low-dose 5-mg versus 8-mg dexamethasone with NEPA for the 168-h prevention of highly or moderately emetogenic (high-risk patients) chemotherapy-induced nausea/vomiting: An open-label, randomised, controlled, phase 3 trial. First Author: Xiao Li Xiao, Department of Oncology, Zhongshan Hospital of Xiamen University, School of Medicine, Xiamen, Fujian, China

Background: Tailoring Dexamethasone (DEX) dosing to reduce corticosteroid exposure is a challenging issue in the chemotherapy induced nausea /vomiting(CINV) management. This study aims to identify the efficacy of single low-dose 5mg versus 8mg dex with nepa for the 168h prevention of highly or moderately emetogenic (high-risk patients) CINV. **Methods:** This open-label, randomized trial compared the efficacy and safety of 5 mg versus 8 mg DEX regimens, both with NEPA, in patients receiving MEC or HEC chemotherapy. Patients were 1:1 randomized to 5 mg or 8 mg groups. The primary endpoint was complete response (no emesis, no rescue medication) from 0 to 168 hours. Secondary endpoints included total control, complete control, and daily CINV incidence. This study was registered with ChiCTR2400089311. **Results:** From June 20, 2024 to June 20, 2025, a total of 164 eligible individuals were assigned at random to the 5 mg or 8 mg DEX treatment arms.Primary efficacy endpoints:The overall CR rates for the prevention of CINV, observed throughout the study period, were 91.7% in the 5 mg group and 92.5% in the 8 mg group (P=0.400) . In the acute phase, the CR rates were 97.9% for the 5 mg group and 97.5% for the 8 mg group (P=1.000). During the delayed phase, the CR rates were 91.7% for the 5 mg group and 92.5% for the 8 mg group (P=1.000). In the long-delayed phase, the CR rates were 93.8% for the 5 mg group and 97.5% for the 8 mg group (P=0.744). Secondary efficacy endpoints: During the whole observation period, the total control rates were 77.1% for the 5 mg group and 62.5% for the 8 mg group (P=0.208); the complete control rates were 85.4% for the 5 mg group and 87.5% for the 8 mg group(P=1.000). Secondary safety endpoints: The safety profiles of both dosages were similar and majority of treatment-related adverse events (TRAEs) were mild to moderate (grades 1 or 2), with no significant differences in the occurrence or severity of TRAEs (hyperglycemia, indigestion/heartburn or reflux and constipation, prevalence of QTcB interval prolongation or increase ect) would warrant particular concern. **Conclusions:** This study identify single low-dose 5mg DEX is equally effective as 8mg DEX with NEPA for the 168h Prevention of HEC or MEC (high-risk patients) CINV. Moreover, the 5mg DEX group has better therapeutic safety. It offers evidence-based recommendations for using a lower dose of DEX in combination with NEPA for the prevention and treatment of CINV. These promising results pave the way for reduction of DEX in antiemetic care. Clinical trial information: ChiCTR2400089311. Research Sponsor: None.

12073 **Poster Session**

A novel staging system for cancer cachexia. First Author: Syed Hasan Raza Jafri, The University of Texas Health Science Center at Houston (UTHealth Houston) McGovern Medical School, Houston, TX

Background: Cancer cachexia affects a large percentage of advanced cancer patients. It's defined by a consensus definition of unintentional >5% body weight loss over six months. There is no standard way of assessing severity of cancer cachexia. We developed a novel cancer cachexia staging system based on routine clinical parameters. **Methods:** In a prospective case control study of newly diagnosed cancer patients to identify biomarkers of cancer cachexia, cases were patients with stage III/IV cancer and >5% body weight loss and serum albumin of <3.5g/dl. Controls were patients with stage I-III without weight loss and serum albumin of ≥3.5g/dl. Patients were prospectively followed up between April 2020 and August 2024 with blood biomarkers, anthropometric measurements and radiological parameters. Utilizing data from cases only a novel cancer cachexia staging system was developed called (University of Texas) UT Cancer Cachexia Staging System using 4 clinical parameters namely body mass index (BMI), serum albumin (Alb), neutrophil to lymphocyte ration (NLR) and resting heart rate (RHR). Using quartiles as cut off for each of these four variables, patients were divided into three groups and given a score of 0.5, 1.5 or 2.5 (Table). The cumulative score of each patient was calculated based on individual values of these 4 variables at the time of diagnosis and then categorized into stage I (≤5), Stage II (5-7) or Stage III (>7) cancer cachexia. Kaplan-Meier survival curves were generated for patients in each stage. The univariable Cox regression model was used to compare hazard ratios across the 3 stages. The multivariable Cox regression model was employed to compare hazard ratios between the stages, adjusting for other key demographic and clinical covariates. **Results:** A total of 109 patients were enrolled in the cachexia group (Male=69, Females=40, Median age = 69 years). The cancer types included Lung cancer (n=50), GI cancers (n=41) and other cancers (n= 18). There were 49 patients (45%) patients with stage I cachexia, 40 (36%) with stage II and 20 (18%) with stage III cachexia. Median overall survival (OS) for patients with stage I cancer cachexia was 11.4 months, for stage II 6.5 months and for stage III 3.5 months. In univariate cox-regression model the difference in hazard ratio between stage I and stage II patients was statistically significant (p=0.004) as was between stage I and stage III (P =0.007). In multi-variable Cox-regression model controlling for age, gender and cancer type, patients with stage II and III cancer cachexia had significantly worse outcome as compared to patients with stage I cancer cachexia. **Conclusions:** UT cancer cachexia staging system represents a novel staging system which should be validated on a larger data set. Once validated this can help guide clinical management as well as clinical research in patients with cancer cachexia. Research Sponsor: U.S. National Institutes of Health; R01 AR063786-06A1; National Center for Advancing Translational Sciences (NCATS); 1UM1TR004906-01.

Development of cancer cachexia staging system based on BMI, albumin, NLR and RHR by using quartiles as cutoff points in the case group (n=109).

	Score=0.5		Score=1.5		Score=2.5	
Variable	Cutoff	Number of patients	Cutoff	Number of patients	Cutoff	Number of patients
BMI	≥29	26	21-29	56	<21	26
Albumin	≥3.2	30	2.3-3.2	60	<2.3	18
NLR	<3	30	3-8	50	>8	28
RHR*	<73	25	73-95	57	>95	26

UT cancer cachexia stage groups defined by using cutoff points for total cancer cachexia score.

Stage I	<5
Stage II	5-7
Stage III	>7

12074 Poster Session

Machine learning models to predict skeletal-related events in bone metastasis from advanced cancer. First Author: Hirotaka Miyashita, School of Integrative and Global Majors, University of Tsukuba, Tsukuba, Japan

Background: Skeletal-related events (SREs) are detrimental clinical events in bone metastasis from advanced cancer, defined by pathologic fracture, spinal cord compression, and inevitable surgical or radiational intervention to the bone. Given their negative impact on quality of life and prognosis and interpatient heterogeneity in the SRE risk, accurate identification of patients with high SRE risk is critical. **Methods:** The patient-level data from three randomized clinical trials that administered zoledronic acid (ZA) to patients with bone-metastatic breast cancer, castration-resistant prostate cancer (CRPC), and other types of cancer were analyzed. (N = 460, 452, and 315, respectively) Machine learning (ML) models to predict SREs within 18 months (breast cancer), 12 months (CRPC), and 9 months (other cancers) were developed based on more than 40 baseline clinical and laboratory data. Seven ML algorithms and five feature selection methods were utilized to develop multiple models. The ML model with the best performance was identified based on the F1 score and the area under the receiver operating characteristic curve (AUC-ROC) for each cancer type and interrogated for important features with Shapley additive explanations. Lastly, the ML models' ability to stratify patients by the cumulative SRE risk was evaluated by calculating hazard ratio (HR) with Cox-proportional hazards models. **Results:** Among the multiple ML models developed with different algorithms and feature selection methods, the model developed utilizing the random forests algorithm and the Boruta method for selecting features demonstrated the best performance in all types of cancer (F1 0.70, 0.67, and 0.67, and AUC-ROC 0.72, 0.68, and 0.73 for breast cancer, CRPC, and other cancers, respectively). In the ML model for breast cancer, performance status (PS), history of SRE, serum alkaline phosphatase (ALP), history of anti-neoplastic surgery, radiation therapy, and pathologic fracture were included as important features. Serum ALP, albumin, sodium, Gleason scores, and geographic regions were shown to be relevant in the CRPC model. For other cancers, serum ALP, albumin, total protein, phosphorus, red blood cell count, white blood cell count, visceral metastases, and history of arthritis were incorporated in the ML model. The ML model prediction successfully stratified the patients for cumulative SRE risk in all three cohorts. (HR with 95% confidence interval: 2.43 [1.86 – 3.18], 1.92 [1.51 – 2.45], and 3.06 [2.29 – 4.09] for breast cancer, CRPC, and other types of cancer, respectively). **Conclusions:** ML models incorporating baseline clinical and laboratory data can identify patients with bone metastasis on ZA harboring a high SRE risk. Research Sponsor: None.

12075 Poster Session

Virtual reality for pain and anxiety management during bone marrow biopsy: A systematic review. First Author: Ronak Patel, SUNY Downstate at Brooklyn, Brooklyn, NY

Background: Bone marrow biopsy (BMB) procedures often cause significant pain and anxiety. Virtual reality (VR) has emerged as a promising non-pharmacological intervention, but its effectiveness needs systematic evaluation. **Methods:** A systematic review following PRISMA guidelines examined studies from 2014-2024 that evaluated VR interventions during BMB procedures through literature searches in PubMed, Scopus, and EMBASE. Studies were included if they evaluated VR as a non-pharmacological intervention and reported pain or anxiety outcomes. **Results:** Five studies (n=481) met inclusion criteria, including three randomized controlled trials and two prospective studies. Patient ages ranged from 6-87 years. VR interventions showed high retention rates (66.7-93.3%) with low discontinuation (5%). Pain and anxiety reduction was significant in two studies ($p<0.05$ and $p<0.001$ respectively), while three showed no significant difference versus standard care. Patient satisfaction exceeded 90%, with minimal adverse events, mainly discomfort leading to discontinuation in 5% of participants. **Conclusions:** VR represents a safe, well-tolerated intervention during BMB procedures with high patient satisfaction. While pain and anxiety reduction results were mixed, the consistent safety profile and positive patient experience suggest VR may be a valuable adjunct to standard care, particularly for anxiety management. Future research should focus on standardizing protocols and defining patient selection criteria to optimize outcomes. Research Sponsor: None.

Study characteristics and clinical outcomes of virtual reality use during bone marrow procedures.

Study	Sample Size	Patient Population	VR Type	Control Group	Pain Outcomes	Significant Pain Reduction?	Anxiety Outcomes	Significant Anxiety Reduction?	Patient Satisfaction	Adverse Events
Glennon 2018	97	Adults	ezVision X4 VR goggles with nature scenes + lidocaine	Standard TV viewing + lidocaine	VR: 3.9 vs Control: 4.0 (NPRS)	No ($p > 0.05$)	State anxiety decrease: VR: 2.3 pts vs Control: 1.3 pts (5 item Likerty-type scale)	No ($p = 0.42$)	98.3% satisfied	None reported
Le Du 2023	126	Adults	Meta Quest VR headset	None specified	VR: 3.0 vs Control: 3.5 (VAS)	No ($p = 0.26$)	No difference on STAI scores	No ($p = 0.83$)	Not reported	Not reported
Korkmaz 2023	126	Adults	Bliss VR with 4 environments	MEOPA (nitrous oxide/ oxygen)	VR: 3.8 vs Control: 6.28 (VAS)	Yes ($p < 0.001$)	VR: 32.06 ± 8.69 vs Control: 40.88 ± 11.36 (STAI)	Yes ($p = 0.022$)	95% satisfied	5% discontinued
Reitze 2024	75	Adults	Support V5 VR headset	Standard care (No distraction)	Mean difference -1.0 with VR (VNRS)	Yes ($p < 0.05$)	VR: 28.6 vs Control: 33.5 (BAADS)	Yes ($p < 0.001$)	> 90% satisfied	5% mild effects
Soret 2022	57	Children (6-18y)	Not specified	Standard care (No distraction)	VR: 3.8 (IQR 2.0-6.3) vs Control: 3.0 (IQR 1.9-3.0) (FPS-r)	No ($p = 0.09$)	No difference between groups (mYPAS-SF)	No ($p = 0.71$, 0.42)	71% more relaxed	5% discontinued

12076 Poster Session

Multidisciplinary and multi-institutional cancer symptom management strategies in the Veterans Affairs: A mixed methods study. First Author: Johanna Balas, University of California San Francisco, San Francisco, CA

Background: Effective symptom management in patients undergoing cancer treatment improves quality of life and overall survival. Yet, variability persists in how symptoms are assessed and managed across oncology settings. This mixed-methods study, conducted across 14 Veterans Affairs (VA) facilities in two regional Veterans Integrated Service Networks (VISN) 21 and 22, aimed to: 1) identify current symptom assessment strategies in use and 2) explore opportunities for standardizing, implementing, and scaling strategies to optimize care for Veterans undergoing cancer treatment. **Methods:** We conducted a comprehensive survey and semi-structured interviews to evaluate current symptom assessment and management practices, perspectives on standardized proactive strategies, and barriers and facilitators to implementation. The 10-question survey was distributed to 65 clinicians, nurses, social workers, navigators, pharmacists, behavioral medicine specialists, and ancillary care providers across 14 facilities in VISN 21 and 22, using an online staff directory. In addition, 25 facility-level oncology leaders and 10 Veterans receiving cancer care at these facilities were invited to participate in 30-minute semi-structured interviews. The interviews focused on attitudes, knowledge, and preferences regarding proactive symptom assessment, as well as interest in piloting potential interventions. Survey data were analyzed using descriptive statistics, and interview data were analyzed through thematic analysis. **Results:** A total of 40 participants (61.5% response rate) completed the survey, including 24 physicians (60%), 12 nurses/ nurse practitioners (30%), 2 social workers (5%), and 2 pharmacists (5%). Of the 40 respondents, 36 (90%) reported assessing symptoms during clinical visits, with 12 (30%) utilizing only standardized psychological distress screening tools, such as the National Comprehensive Cancer Network Distress Thermometer. Infrastructure and resources varied widely across facilities with some facilities noting no palliative care providers, nurse practitioners, nurse navigators, or oncology nurses. Only 2 facilities integrated volunteers or lay peer support into cancer care. Among interviewees, 25 oncology leaders and 10 Veterans with cancer participated (100% response rate). Two key themes emerged: 1) urgent need for standardized, proactive symptom assessment and management; 2) importance of adaptable solutions, such as peer-led initiatives, tailored to facility and patient preferences rather than a one-size-fits-all approach. **Conclusions:** Proactive symptom assessment is underutilized across VISN 21 and 22 facilities. Standardized, adaptable strategies that combine high-touch and low-tech approaches, such as peer-led initiatives, are preferred and may provide a scalable solution to enhance cancer care for Veterans. Research Sponsor: None.

12077 Poster Session

Comparison of outcomes for patients diagnosed with small cell lung cancer between a university and safety net hospital. First Author: Ahmad Karkash, Indiana University School of Medicine, Indianapolis, IN

Background: With immunotherapy, the five year overall survival (OS) for small cell lung cancer (SCLC) is 12%. However, real world factors such as social determinants of health (SDH) and enrollment to clinical trials may vary. Here, we compare treatment patterns and outcomes for SCLC between two affiliated hospital settings. **Methods:** A retrospective analysis was conducted on patients with SCLC seen at university hospital (UH, Indiana University Melvin and Bren Simon Comprehensive Cancer Center) or its affiliate safety net hospital (SNH, Sidney and Lois Eskenazi Hospital) from 1/1/2018 to 8/31/2024. SDH was defined as housing, food, financial, or transportation instability. Chi-square, Fisher's exact test, t-test, Wilcoxon two-sample test, and Kaplan-Meier were applied accordingly. P value $<$ .05 was considered significant. **Results:** A total of 189 patients were identified; 50 (26%) at SNH and 139 (74%) at UH. Stage, age, sex, and tobacco use were similar. Variations in race and SDH were noted (Table). Receipt of chemoimmunotherapy was comparable. Chemotherapy-free interval (CTFI) was shorter at UH (3.3 months; 95% CI, 2.7–4.3) vs at SNH (7.8 months; 95% CI, 3.7–11.5; P = .015). Patients at UH were enrolled in more SCLC-related trials, received more second line therapies, GCSF or CDK4/6 inhibitor (Table), and had increased adverse events (UH, 64% vs SNH, 40%, P = .003). At data cut-off, no difference was found between UH and SNH for use of lurbinectedin (15.8% vs 8%, P = .16) or tarlatamab (3.6% vs 2%, P = 1). OS was analogous between UH (16 months; 95% CI, 11.3–18.7) and SNH (12.8 months; 95% CI, 7.6–NE; P = .21). **Conclusions:** Patient at UH were found to have shorter CTFI with first line chemo-immunotherapy. This difference may reflect the referral patterns for patients with complex SCLC presentations to an academic cancer center. More SDH was identified at UH. Patients at UH were more likely to enroll in SCLC trials and receive supportive care medications. Patients at SNH received more PC referrals. Further studies are needed to evaluate the effect of socioeconomic factors on SCLC outcomes. Research Sponsor: None.

Outcomes stratified by hospital setting.

Variable	Overall N=189	Stratified by Hospital Setting: Safety Net Hospital N=50	Stratified by Hospital Setting: University Hospital N=139	*P* Value
Black race	22 (11.6%)	**16 (32%)**	6 (4.3%)	**<.001***
White race	160 (84.7%)	33 (66%)	**127 (91.4%)**	**<.001***
Positive SDH	87 (46%)	15 (30%)	**72 (51.8%)**	**.008**
Consented to a SCLC clinical trial	47 (24.9%)	1 (2%)	**46 (33.1%)**	**<.001**
Received second line treatment	87 (46%)	16 (32%)	**71 (51.1%)**	**.020**
Received supportive care with GCSF or CDK4/6 inhibitor	85 (45%)	8 (16%)	**77 (55.4%)**	**<.001**
Referred to palliative care (PC)	86 (45.5%)	**45 (90%)**	41 (29.5%)	**<.001**

Note: Values expressed as n (%). *Indicates Fisher's exact test.

12078 Poster Session

Disparities in receipt of palliative interventions across disaggregated Hispanic subgroups with late-stage colon cancer in the United States. First Author: Coby Garcia, Harvard University, Cambridge, MA

Background: Palliative interventions, defined as cancer-directed therapies with palliative intent, improve the quality of life and alleviate suffering for patients with advanced cancer. Limited research examines disparities in their receipt across disaggregated Hispanic subgroups. We analyzed palliative intervention receipt among Hispanic patients with stage IV colon cancer. **Methods:** Using the National Cancer Database, we retrospectively analyzed adults diagnosed with stage IV colon cancer (2004–2021) with known palliative intervention receipt status (defined binarily). We performed logistic regressions to characterize palliative intervention receipt rates across a) broad racial groups and b) country of origin, relative to Non-Hispanic White patients (alpha$<$0.05). Regressions included a race*year interaction term to examine changes in palliative intervention receipt over time (alpha$<$0.1). **Results:** We analyzed 1,021,293 patients;3.24% (n=33,132) received palliative interventions. Hispanic Black patients were 0.55x as likely (P=0.030) to receive palliative interventions as non-Hispanic White patients. The year*race interaction term was significant for Hispanic-Black patients, suggesting that invention rate improvements were distributed unequally over time. Specifically, the rate of intervention receipt among Hispanic Black patients decreased from 5.4% in the 2004–2012 cohort to 4.6% in the 2013–2021 cohort (95% CI: 0.32–0.94, P interaction = 0.030), compared to greater decreases observed in the reference group. When disaggregated, Mexican patients were 31% less likely (P=0.006), Cuban patients 35% less likely (P=0.043), NOS patients were 33% less likely (P$<$0.001), and Dominican Republic patients nearly twice as likely (P=0.009) to receive interventions compared to non-Spanish, non-Hispanic patients. **Conclusions:** Hispanic Black, Mexican, Cuban, and NOS patients experienced lower receipt of palliative interventions, revealing disparities in access to equitable cancer-directed end-of-life care. Efforts should be made to expand palliative intervention access for diverse racial/ethnic groups. Research Sponsor: None.

Receipt of palliative care by country of origin.

Racial/Ethnic Group	% Patients receiving palliative care (All Years)	% Patients receiving palliative care (2004-12)	% Patients receiving palliative care (2013-21)
Non-Spanish, Non-Hispanic White	3.35	2.31	4.30
Mexican	2.74	1.86	3.33
Puerto Rican	3.66	2.49	4.53
Cuban	2.40	1.60	3.48
South/Central American (ex. Brazil)	3.26	1.74	4.28
Other Specified Spanish/Hispanic	3.26	2.55	4.09
NOS	3.16	2.03	3.84
Spanish Surname only	2.80	1.49	4.16
Dominican Republic	4.18	4.96	3.80

12079 Poster Session

A patient advocacy-focused rehabilitation pilot program: Real-life experience in enhancing quality of life for metastatic lung cancer patients. First Author: Shani Shilo, The Israeli Lung Cancer Organization, Rehovot, Israel

Background: Living with lung cancer (LC) is a prolonged and challenging journey, where the disease's consequences and treatment-related adverse events significantly affect the quality of life (QOL) of patients. Recognizing these challenges, healthcare professionals (HCPs) in collaboration with a patient advocacy organization designed and implemented a personalized rehabilitation pilot program tailored specifically for patients with unresectable metastatic LC. **Methods:** 50 Stage IV unresectable metastatic lung cancer patients were recruited via a patient advocacy group on Facebook. Participants underwent a personalized rehabilitation program with four one-on-one physiotherapy sessions, during which a tailored regimen was developed. Each participant received a customized booklet and equipment to support their rehabilitation. The program incorporated two key components: aerobic exercises and strength-training activities. Additionally, patients and their caregivers participated in three online mental health support sessions, providing holistic care. EORTC QLQ-C30 questionnaire was used at the beginning, end of the program and two months after. The physiotherapists measured the patients' 5 repetitions sit to stand time and 10-meter walk time at the beginning and the end of the program. Significance of results was calculated with repeated measure\within subjects T test with one way hypothesis and a confident interval of 0.95%. **Results:** Significant improvement was observed from the beginning of the program to the end in the Sit-to-stand test, from 19.3s to 15.1s, p = 0.0001 and the 10-meter-walk test, from 12.5 to 10.5 p = 0.017. In addition, a significant improvement from beginning to end of the program was observed based on the EORTC QLQ-30 in the global health status, physical functioning, role functioning as well as in the symptoms of fatigue, nausea, vomiting and appetite loss. In social functioning and constipation, significant improvement was maintained even two months after completion of the program. No significant change was observed in emotional and cognitive functioning, pain symptoms, dyspnea, insomnia, diarrhea and financial difficulties. **Conclusions:** The real-life survivorship journey of metastatic lung cancer patients involves numerous challenges including sequela of side effects and symptoms that impact QOL of the patient that impacts the caregiver as well. Our duty to support "beyond the pill" led us to this real-life pilot program that shows the feasibility and efficacy of home-based rehabilitation. Even among patients who experienced disease progression during the program, notable benefits were observed. These findings underscore the importance of further research and the need for sustained support after program completion to ensure long-term maintenance and improvements in patients' well-being. Research Sponsor: The Lung Ambition Alliance.

12080 Poster Session

Muscle mass evaluation among ambulatory cancer patients in China: Comparison of different methods and association with survival. First Author: Yanfei Wang, Key Laboratory of Carcinogenesis and Translational Research (Ministry of Education/Beijing), Peking University Cancer Hospital & Institute, Beijing, China

Background: Cancer patients are at high risk of malnutrition and cachexia. Muscle mass reduction (MMR) is one of the three phenotypic criteria to diagnose malnutrition in the Global Leadership Initiative on Malnutrition (GLIM) framework, but there are no consensus about what method should be used to evaluate MMR in clinical practice. Among multiple methods to evaluate MMR, muscle mass index (MMI) in computed tomography (CT) image was considered to be accurate but not convenient in clinical practice. This study aimed to compare the correlations between different methods of measuring MMR and to assess their relevance to survival. **Methods:** A single-center cohort study was conducted among ambulatory cancer patients who were receiving intravenous anti-cancer therapy. All participants underwent CT, calf circumference (CC) measurement, bioelectrical impedance analysis (BIA) and hand grip strength measurement. MRR was identified by MMI in CT image at the level of lumbar vertebra 3 (L3), CC, fat-free mass index (FFMI) and appendicular skeletal muscle index (ASMI) in BIA respectively. Low MMI was defined as MMI $<$ 43 in men with body mass index (BMI) $<$ 25kg/^{2}, $<$ 53 in men with BMI$\geq$25kg/^{2} or $<$ 43 in women. Low CC was defined as CC$<$ 34cm in men or $<$ 33cm in women. Low FFMI was defined as FFMI $<$ 17kg/m^2 in men or $<$ 15kg/m^2 in women. Low ASMI was set as ASMI $<$ 7.0kg/m^2 in men or $<$ 5.7kg/m^2 in women. Low muscle strength was defined by hand grip strength $<$ 28kg in men or $<$ 18kg in women. The correlation between low MMI and MMR diagnosed by other methods were calculated. The correlation between MMR, low muscle strength and one-year mortality was also evaluated. **Results:** A total of 312 consecutive patients were included. Of the 312 patients 62.8% (196/312) were male and 37.2% (116/312) were female. The median age of the patients was 59.0 years (range, 21-80y; interquartile range 52.0-65.0y). FFMI and SMI diagnosed by BIA correlated with MMI diagnosed by CT (Pearson Correlation 0.798 and 0.738 respectively). Except for low hand grip strength (p = 0.005, HR 2.482, 95%CI 1.324-4.655), no single indicators for MMR indicated higher one-year mortality. However, in combination of MMI, CC, FFMI and ASMI, MMR indicated higher one-year mortality (p = 0.004, HR 2.549, 95%CI 1.342-4.843). **Conclusions:** FFMI and SMI diagnosed by BIA correlated with MMI diagnosed by CT, indicating that BIA can be a good choice in evaluating MMR. Low hand grip strength and MMR diagnosed using multiple methods indicated higher one-year mortality, underscoring the importance of measuring muscle strength as well as evaluating muscle mass. Research Sponsor: Beijing Xisike Clinical Oncology Research Foundation; Y-NESTLE2022MS-0228,Y-Young2023-0070; the Clinical Research Fund For Distinguished Young Scholars of Peking University Cancer Hospital; QNJJ2023032; the Leading Talents of Science and Technology Innovation in the National "Ten thousand Talents Program".

12081 Poster Session

The impact of cannabis use on patient outcomes post immune checkpoint inhibitor (ICI) therapy in a longitudinal observational trial: The DiRECT Cohort. First Author: Song Yao, Roswell Park Comprehensive Cancer Center, Buffalo, NY

Background: Prior small retrospective studies suggest that cannabis might compromise the efficacy of ICIs for cancer therapy due to its immunosuppressive properties. Evidence from large prospective studies is lacking. **Methods:** We addressed this research gap in the DiRECT Cohort (URCC21038, NCT05364086), an ongoing, observational trial enrolling self-identified Black and White cancer patients (melanoma excluded) who are about to start ICI-containing therapy through the URCC NCORP Research Base nationwide clinical trial network. Longitudinal data on cannabis use are collected through self-administered surveys at baseline (A1), 6 months (A3), and annually (A4+), along with clinical data and patient-reported outcomes on physical and psychological symptoms. This interim analysis on cannabis use includes 1,666 patients enrolled between 04/01/2022 and 08/31/2024, with outcome data updated to 11/30/2024. **Results:** The mean age was 63.7 ($\pm$12.4) years; 408 (24.5%) patients were Black; 905 (54.3%) were women; the most common diagnosis was lung cancer (621 or 37.3%); and a majority had stage IV disease (906 or 54.4%). At A1, 284 (17.1%) patients reported cannabis use in any form, mostly orally (58.1%) or via inhalation (32.3%). Use rates remained stable at A3 (15.6%) and A4 (15.4%) (P = 0.47); yet patients reported fewer days of use in a month (P $<$ 0.0001) but more times in a day (P = 0.07) than at A1. Cannabis users were younger and more likely to be Black, from states with permissive cannabis laws, and current or former cigarette smokers (P's $<$ 0.05), with no differences observed by gender, cancer type, or stage. After a median follow-up of 10.4 months (range: 0.03-31.0), 381 patients died, and 174 patients had progressed disease or entered hospice care. Median overall survival (OS) and event-free survival (EFS) were slightly higher in cannabis users than non-users at A1 (6.1 vs. 5.3 months, P = 0.07 and 6.0 vs. 5.4 months, P = 0.15, respectively). Cox hazards models adjusted for age, gender, cancer type, and stage revealed no significant association between cannabis use and OS (adjusted hazards ratio [aHR] = 0.82, 95% CI 0.61-1.10) or EFS (aHR = 0.92, 95% CI 0.72-1.17). Subgroup univariate analysis showed cannabis use was associated with longer OS and EFS within men (n = 743) and former smokers (n = 765) (P's $<$ 0.05), which became non-significant after adjusting for covariates in Cox models, except for OS within former smokers (aHR = 0.52, 95% CI 0.33-0.83). A significant interaction was noted between cannabis use and smoking status (P = 0.02). **Conclusions:** In this nationwide, diverse community-based oncology cohort, 17% of patients reported cannabis use concurrent with ICI therapy. Unlike previous retrospective studies, our prospective analysis finds no detrimental effect of cannabis on OS or EFS. Further analyses are ongoing to elucidate its impact on symptom management. Clinical trial information: NCT05364086. Research Sponsor: National Cancer Institute; UG1CA189961.

12082 **Poster Session**

Outpatient palliative care consultation and end-of-life outcomes among a retrospective cohort of patients treated with immunotherapy for non-small cell lung cancer. First Author: Chance Bloomer, Department of Hematology & Oncology, Atrium Health Wake Forest Baptist Medical Center, Winston-Salem, NC

Background: Immune checkpoint inhibitors (ICIs) have been shown to be effective against a wide range of cancers and are available to most patients due to their favorable side effect profile. Studies have shown that palliative care consultation prolongs overall survival (OS) in patients with advanced cancer, but most of these studies assessed cytotoxic chemotherapy and not ICIs. Other studies have shown that outpatient palliative care consultation (OPCC) has a greater effect on a variety of end-of-life outcomes than in the inpatient setting. Our study aims to analyze the association between OPCC and survival in patients with lung cancer treated with an ICI. **Methods:** We designed a retrospective registry of all patients at a comprehensive cancer center and its outreach clinics who received one or more doses of an ICI. The investigators created a secure, cloud-based registry (REDCap), validated it with data quality rules, resolved all discrepancies, and obtained data on palliative care encounters; clinical research specialists at Vasta Global (New York, NY) captured most of the data. Comparisons were made using chi-square or Fisher's exact for categorical variables. Cox proportional hazards model was built controlling for confounders. Survival time for patients with palliative visits was only considered after initial OPCC. Statistical significance was defined as $p < 0.05$. The study had institutional IRB approval. **Results:** Our cohort consisted of 1,114 patients with non-small cell lung cancer, 55% of whom were metastatic at diagnosis. 6% (n = 70) of the patients had an OPCC at some point after their diagnosis. When controlling for stage at diagnosis and age, OPCC was associated with an adjusted hazard ratio of 0.57 (95% CI 0.34-0.98). None of the patients with OPCC received ICI within 14 days of death compared to 6.5% of those without OPCC (p = 0.018). Similarly, only 2.9% of those with OPCC received ICI within 30 days of death, compared to 16.4% of those without OPCC (p = 0.003). **Conclusions:** In patients with lung cancer treated with ICI, OPCC was associated with improved OS regardless of age or stage at diagnosis. Our analysis also showed that patients who received OPCC were less likely to receive ICI near the end of life. It is possible that OPCC may prolong survival by decreasing the ineffective use of aggressive care at the end of life. Further research is needed to clarify the relationship between OPCC and cancer outcomes. Research Sponsor: None.

12083 **Poster Session**

Demographic and clinical factors associated with sleep disturbance in breast cancer survivors. First Author: Paulina S. Marell, Department of Medicine, Mayo Clinic Rochester, Rochester, MN

Background: Fatigue and sleep disturbance are prevalent during and after cancer treatment; sleep-related symptoms affect 30-50% of patients with cancer, and sleep-wake disruptions persist beyond the immediate post-surgical period in breast cancer (BC) survivors. Identifying demographic- and treatment-related factors associated with sleep-related symptoms during survivorship is critical to inform interventions for those at highest risk of sleep disturbance. **Methods:** Patients who were seen at least once at Mayo Clinic Rochester following an initial diagnosis of BC at age 18 or older and provided informed consent were prospectively enrolled in the Mayo Clinic Breast Disease Registry. Surveys mailed to this cohort included two 11-point numeric rating scale questions regarding difficulty falling asleep and staying asleep in the past week, with values for each ranging from 0 (no problem) to 10 (as severe as you can imagine). Participants who provided sleep-related information on the Year 1 survey (answered approximately one year after cancer diagnosis) were included. Participants were excluded if they had clinical or pathologic metastatic disease and/or recurrence prior to the Year 1 survey. Associations of sleep-related symptoms with demographic and clinical characteristics were assessed using multivariate linear regression models, fitting the sleep difficulty rating scale as the outcome and clinical and demographic factors as exposures. **Results:** In total, 3,354 participants met inclusion criteria. The average age at BC diagnosis was 59, and most participants were female (99.3%), White (95.4%), non-Hispanic (96.2%), married (78.1%), had at least some college education (80.4%), did not report financial insecurity (76.2%), did not consume alcohol (60.6%) or smoke tobacco (93.2%), and reported at least some weekly exercise (76,6%). Sixty-two percent of participants had clinical stage 0 or I disease; 50.3% underwent lumpectomy (not mastectomy), 59.2% received radiotherapy, 34.1% received chemotherapy, and 67.2% received endocrine therapy. Overall, sleep-related symptoms were relatively low (mean rating for falling asleep = 2.1, mean rating for staying asleep = 3.1). In multivariate analyses, more difficulty falling asleep was associated with higher clinical stage ($p < 0.001$), more cigarettes smoked per day (p = 0.012), less moderate and/or strenuous exercise (p = 0.001), and more financial hardship ($p < 0.001$). More difficulty staying asleep was associated with higher clinical stage (0.003), older age ($p < 0.001$), more education (p = 0.011), and more financial hardship ($p < 0.001$). **Conclusions:** In our cohort of BC survivors, factors associated with both increased difficulty with falling and staying asleep at one year after diagnosis are higher clinical stage and more financial hardship. Future research should explore the course of these symptoms over time and across varied treatment trajectories. Research Sponsor: This research was supported by the Mayo Clinic Breast Registry. Funding provided through the Breast Cancer Research Foundation.

12084 **Poster Session**

Trends in inpatient palliative care utilization among adolescents and young adults with metastatic cancer. First Author: Chiamaka Elsie Nwachukwu, Tulane University, New Orleans, LA

Background: Adolescents and young adults (AYA) with advanced cancer, including metastatic cancer, have a unique set of medical, social and psychological needs and often experience several disparities in cancer care when compared with children and older adults. Despite recommendations for early integration of palliative care for patients with serious illnesses, age-appropriate interventions and teams specifically designed for this age group are limited. Objective: To determine the trends in inpatient palliative care utilization as well as associated factors and clinical outcomes among AYA with metastatic cancers in the United States between 2008-2021. **Methods:** A retrospective longitudinal study using the National Inpatient Sample database (2008-2021) was conducted. We examined trends in the prevalence of palliative care utilization in the cohort, as well as sociodemographic and hospital-level factors associated with palliative care utilization. Using Joinpoint regression and multivariable logistic regression, we examined trends and factors associated with palliative care utilization, as well as specific clinical outcomes including inpatient mortality, length of stay, and total hospital costs. **Results:** In this period, 604,856 hospitalizations were recorded for AYA with metastatic cancer. Overall, palliative care utilization was recorded in 10.6% of these encounters and increased over time from 3,036 to 16,568 per 100,000 admissions (p-trend <0.001). The adjusted prevalence rate of palliative care utilization increased by an annual percentage change (APC) of 15.9% from 2010 to 2015. However, from 2015 to 2021, no significant changes were observed. Females with metastatic cancer had 18% higher odds (Adjusted odds ratio (AOR):1.18; 95% CI: 1.12-1.24) of receiving palliative care compared to male patients after we adjustments had been made for potential confounders. Non-elective admissions were associated with four times higher odds (AOR: 3.99, 95% CI: 3.68-4.32) of receiving palliative care compared to elective admissions. Palliative care utilisation was associated with higher odds of longer hospital stay (9.3 vs 6 days, β: 3.29, 95% CI: 3.07-3.50) and increased hospital expenditure ($107,758 vs $78,255, β: -29,747, 95% CI: 26,190 - 33,304). A significantly increased odds of palliative care utilization was observed in those who died during the hospital admission (AOR: 16.16; 95% CI: 14.8-17.6). **Conclusions:** Palliative care utilization has been increasing over the earlier part of the decade but has stalled since 2015 among AYA with metastatic cancer. In the AYA group with metastatic cancer, palliative care appears to be utilized majorly in the sickest patients closer to the end of life. This represents an area of future research and interventions on earlier integration of palliative care and its impact on quality of life and hospital outcomes in this patient population. Research Sponsor: None.

12085 **Poster Session**

Effectiveness and safety of multimodal analgesic management based on the ERAS concept in the perioperative period of TACE for patients with Intermediate and advanced hepatocellular carcinoma. First Author: Yanqin Wu, The First Affiliated Hospital of Sun Yat-sen University, Guangzhou, China

Background: To evaluate the effectiveness and safety of multimodal analgesic management based on the enhanced recovery after surgery (ERAS) concept in the perioperative period of transarterial chemoembolization (TACE) for patients with advanced hepatocellular carcinoma. **Methods:** A retrospective analysis was conducted on 90 patients who underwent TACE at the First Affiliated Hospital of Sun Yat-sen University from January 2022 to October 2023. Patients were divided into two groups: Group A received a multimodal analgesic regimen based on the ERAS concept, which included preoperative administration of 6 mg hydromorphone hydrochloride and 50 mg flurbiprofen axetil, diluted in normal saline to a total of 100 ml and infused via a patient-controlled intravenous analgesia (PCIA) pump. Group B received conventional perioperative management combined with traditional analgesic methods, using intravenous flurbiprofen axetil 50 mg or intramuscular tramadol 100 mg for postoperative pain. Pain levels were recorded using the Numeric Rating Scale (NRS) at various time points: intraoperatively, immediately postoperatively, and at 1, 6, 12, and 24 hours post-surgery, along with the incidence of adverse reactions within 24 hours. Inflammatory indicators were compared before and after TACE, and patient satisfaction and cost-effectiveness analyses were conducted. **Results:** The NRS scores for Group A at the five time points were 3.0 (3.0–2.0), 3.0 (4.0–2.0), 4.0 (5.0–3.0), 3.0 (3.5–2.0), and 1.0 (1.0–0.5), respectively. For Group B, the scores were 4.0 (5.0–3.0), 4.0 (5.0–3.0), 5.0 (6.0–3.5), 3.0 (4.0–2.0), and 1.0 (2.0–1.0) , respectively. Except for the NRS score at 12 hours post-surgery, all other time points showed statistically significant differences. There was no statistically significant difference in the levels of PCT and IL-6 before and after surgery between the two groups, but a trend of lower postoperative PCT and IL-6 levels in Group A compared to Group B was observed. The incidence of various adverse reactions 24 hours post-surgery did not differ significantly between the two groups ($P > 0.05$). Patient satisfaction with analgesia at 48 hours post-surgery was significantly higher in Group A than in Group B, with a statistically significant difference (P = 0.001). Group A demonstrated better economic benefits. **Conclusions:** The results of this study indicate that multimodal analgesic management based on the ERAS concept has better analgesic effects during the perioperative period of TACE treatment, with comparable safety and improved economic benefits. This provides strong support for the clinical application of multimodal analgesic management based on the ERAS concept in TACE for liver cancer. Research Sponsor: None.

12086 Poster Session

Evaluating palliative care needs of early-phase clinical trial patients. First Author: Fionnuala Crowley, Division of Hematology & Medical Oncology, The Tisch Cancer Institute, Icahn School of Medicine at Mount Sinai, New York, NY

Background: Specialty palliative care (PC) is increasingly recognized as essential for patients (pts) in early phase clinical trials (EPT), as highlighted by ASCO's 2024 PC guideline. However, concerns persist regarding trigger referrals' impact on resource-constrained PC services. In a pilot, we employed a trigger PC referral system for patients referred to EPT to increase access in this population. **Methods:** We conducted a retrospective cohort study comparing EPT and non-EPT pts seen by outpatient PC between January 1, 2021 and June 30, 2023. We evaluated demographic characteristics, clinical variables, symptom severity at the initial PC visit and end-of-life (EOL) outcomes. Mann-Whitney U tests were used for continuous variables; chi-square or Fisher's exact tests for categorical variables. Multiple comparisons were adjusted using the Benjamini-Hochberg method. **Results:** A total of 1068 pts were included, 136 (12.7%) EPT pts with 67 (6.3%) started on trial. 86 (63.2%) were seen by EPT before outpatient PC and 54 (39%) were referred to PC by EPT team through trigger referral system. EPT pts were younger (median age 61 vs 64 years; p=0.001), had better PS (ECOG 0-1: 57.4% vs 46.5%; p=0.020), and referred after more lines of therapy (median 3 vs. 1; $p<0.001$). Cancer type distribution differed significantly between groups (p=0.005), with EPT pts having higher proportions of GI (41.9% vs 26.5%) and GYN cancers (16.2% vs 9.2%). Physical discomfort was the most prevalent symptom in both EPT and non-EPT groups (86.9% vs 84.9%), followed by inactivity (74.2% vs 76.3%). While most symptoms showed similar prevalence between groups, EPT pts had higher rates of constipation (65.4% vs 50.7%, adjusted p=0.025) and nausea (48.1% vs 38.0% (adjusted p=0.193). After adjustment for multiple comparisons, there were no significant differences in symptom severity between groups. Of those on trial(n=67), 46 (69%) came off trial due to progression and 16 (24%) due to toxicity or worsening PS. After trial discontinuation, 35 (56.5%) received further treatment, and 37 (59.7%) had PC follow-up. Among deceased pts (EPT n=70 (18%), non-EPT n=320 (82%)), there were no differences in EOL outcomes: hospice enrollment (37.1% vs 29.1%, p=0.198), hospital death (58.6% vs 58.4%, p=1.000), chemotherapy in the last 30 days (22.9% vs 18.8%, p=0.411), and median hospital length of stay in the last 30 days (7 vs 5 days, p=0.825). **Conclusions:** EPT pts accounted for 12.7% of new pts to specialty PC over 30 months. Despite demographic and clinical differences between EPT and non-EPT patients, EOL outcomes and symptom severity were largely comparable between groups. These results highlight the feasibility of a trigger-based PC referral system for EPT patients without overburdening resource-constrained PC services, supporting its continued use and potential refinement to address specific symptom management needs. Research Sponsor: None.

12087 Poster Session

Impact of palliative care on mortality, length of stay, and hospital charges in common cancers. First Author: Kalaivani Babu, Allegheny General Hospital, Pittsburgh, PA

Background: Palliative care is a vital component of advanced cancer management, offering symptom relief, improved quality of life, and comprehensive care for patients with complex health needs. While its clinical benefits are well-documented, its impact on hospital outcomes—such as in-hospital mortality, length of stay (LOS), and total hospitalization charges (TOTCHG)—remains underexplored across major cancers. Using the 2021 National Inpatient Sample (NIS), this study evaluates the influence of palliative care utilization on these outcomes among hospitalized patients with breast, lung, colon, bladder, and prostate cancers. **Methods:** This retrospective analysis examined 966,753 weighted hospitalizations, representing breast (163,594), lung (383,215), colon (168,750), bladder (86,555), and prostate (182,280) cancers. Palliative care utilization was the primary exposure. Outcomes assessed included in-hospital mortality, LOS, and TOTCHG. Survey-weighted logistic and linear regression models were used to adjust for patient demographics (age, sex, race, income quartile), comorbidities (Charlson Comorbidity Index, CCI), and hospital characteristics (location, teaching status, region, bed size). **Results:** The overall mortality rate was 6.6%, highest in lung (9.3%) and lowest in prostate (4.7%) and colon cancers (4.8%). Palliative care patients had higher mortality (28.5%; $p < 0.001$). Adjusted analyses showed increased mortality with higher CCI (OR = 0.71, $p < 0.001$) and urban hospitals (OR = 1.40, $p < 0.001$), while female patients had reduced risk (OR = 0.86, $p < 0.001$).LOS averaged 5.98 days, longer for palliative care patients (7.68 days; $p < 0.001$). TOTCHG averaged $83,430, higher for palliative care ($90,488; $p < 0.001$). Black patients incurred higher charges (+$10,475, $p = 0.001$), and urban hospitals had lower costs (-$35,094, $p < 0.001$).Palliative care was concentrated in urban (93.7%) and teaching hospitals (80%), with significant underrepresentation of Black and Hispanic patients in the utilisation of palliative care. (19.2% and 8.8%). **Conclusions:** Palliative care in hospitalized cancer patients addresses the needs of patients with advanced disease and significant comorbidities. However, the study highlights stark disparities in healthcare access, resource utilization, and demographic representation based on race, socioeconomic status, and hospital characteristics. Research Sponsor: None.

Palliative care outcomes cancer comparison table.

Cancer Type	Total Hospitalizations	Mortality Rate (%)	Mean LOS	Mean Hospital Charges	Palliative Care Mortality Rate (%)	Palliative Care LOS	Palliative Care Charges
Breast	163594	6.6	7.34	85727	26.4	7.34	85727
Lung	383215	9.3	6.19	82776	30.55	7.53	89760
Colon	168750	4.8	6.62	96148	24.99	8.09	95202
Bladder	86555	4.7	8.33	92731	25.9	8.33	92731
Prostate	182280	4.7	5.41	79410	27.12	7.81	91883

12088 Poster Session

Early supportive and palliative care referral at a comprehensive cancer center: A seven year study. First Author: Fernando X. Jerves, Atlantic Health System/Morristown Medical Center Program, Morristown, NJ

Background: Despite ASCO supporting the benefits of early supportive/palliative care (SPC) integration, many patients with advanced cancer were referred $<$ 6 months before death or not at all. Our comprehensive cancer center has an active SPC program to promote early access. This study evaluated how the timing of SPC referral changed over the past seven years and identified predictors of early SPC referral. **Methods:** This study included a random sample of 100 patients seen for consultation at the SPC clinic per year from 2017 to 2023. Data included demographics, cancer type, disease stage, symptom burden, performance status, date of SPC referral, and date of death or last follow-up. The primary outcome was overall survival (OS) from SPC consultation. Timing of referral and number of visits were examined using time-to-event analysis. Early SPC referral was defined as occurring $\geq$ 6 months before death among decedents. Univariable and multivariable logistic regression models were used to identify predictors of early SPC referral. **Results:** Among 700 patients (median age 62, 54% female, 92% with advanced cancer), OS from SPC referral increased significantly over the years (Median OS: 9.3 months in 2017, 31.7 months in 2021, and not reached in 2023) (Table). The median follow-up for alive individuals was 19.1 months. The median number of follow-up SPC visits increased from 3 in 2017 to 7 in 2023 ($P <$ 0.001). Early SPC referral occurred in 72% (n = 449) of decedents. In multivariable analysis, male sex (OR: 1.85, P = 0.014), head and neck cancer (OR: 4.64, $P < 0.001$), hematologic malignancies (OR: 3.31, P = 0.013), less pain (OR: 0.9, P = 0.008) and less anorexia (OR: 0.88, P = 0.001) were associated with early SPC referral. **Conclusions:** Patients at our center were referred to SPC earlier and earlier over the past 7 years, achieving a median OS of 32 months. This trend highlights that early SPC is not only possible but potentially self-reinforcing, facilitating timely, longitudinal care along the cancer journey, particularly as patients are living longer with advanced cancer. Research Sponsor: None.

Outpatient supportive/palliative care referral between 2017 and 2023.

Year	2017	2018	2019	2020	2021	2022	2023	P-Value
Number of SPC Consults*	1,844	1,766	1,863	1,804	2,055	2,221	2,178	0.011
All Patients								
Median OS, Months	9.3(6.9 – 14.2)	9.1(6.4 – 19.5)	18.9(10.7 – 30.7)	31.8(14 – NR)	31.7(13.3 – NR)	NR	NR	0.0001
6-months OS %	63	61	70	75	75	83	79	
Advanced Cancer Only								
Median OS, Months	9.3(6.9 – 14.2)	7.1(5.7 – 18.9)	15.9(9.5 – 25.8)	24.2(13.4 – NR)	25.8(12.7 – NR)	24.7(16.4 – NR)	NR	0.0014
6-month OS %	63	59	68	73	73	79	78	
Total SPC Visits, Median	3(3 – 4)	4 (3– 5)	3 (2– 4)	5 (3 – 7)	4 (4 – 9)	7(5 – 15	7 (6 – NR)	< 0.001

Abbreviations: SPC, Supportive/Palliative Care; NR, not reached; OS, overall survival.
*100 patients were randomly selected per year for analysis.
Ranges in parentheses represent 95% CI (confidence interval).

12089 Poster Session

Current patterns of care: Referral to palliative care for patients with metastatic gynecologic cancer. First Author: Lea Tan, UC Irvine School of Medicine, Irvine, CA

Background: Multiple professional cancer organizations have clinical guidelines that recommend that patients with advanced cancers be referred to palliative care early in the disease course, typically within eight weeks of diagnosis (1). The extent to which these guidelines are adhered to, however, remains uncertain, particularly for patients with metastatic gynecologic cancers (MGC). We sought to characterize our current institutional patterns of referral to palliative care for these MGC patients. **Methods:** We conducted a retrospective chart review of gynecologic oncology patients treated at our institution between January 2022 and January 2024. We included adult, female patients with a diagnosis of FIGO stage IVB MGC, or cancer that has spread distantly. Patients with primary endometrial, cervical, ovarian, vaginal, or vulvar cancer were included. We excluded patients with less advanced disease or metastatic cancer from a non-gynecologic primary site. Data from the electronic health records of these patients were analyzed to determine key dates, including the diagnosis of stage IVB MGC, referral to palliative care, the first palliative care visit, and subsequent follow-up visits. Descriptive statistics were used to summarize the results. **Results:** Of the 549 patients included in the analysis, 152 (27.7%) had MGC. Within this subgroup, 76 patients (50%) were referred to palliative care. Of those referred, 65.8% (N = 50) were referred to palliative care either before or within 8 weeks of metastatic diagnosis. Referrals were made in both inpatient (47.4%, N = 36) and outpatient (52.6%, N = 40) settings. Following referral, 84.2% of patients (N = 64) had a consultation with a palliative care provider. However, less than half of these patients (48.4%, N = 31) continued outpatient follow-up with palliative care. When stratified by referral setting, 57.5% of patients (N = 23) referred in the outpatient setting continued follow-up care, compared to only 27.8% of those (N = 10) referred in the inpatient setting. **Conclusions:** Despite guidelines recommending early initiation of palliative care for all patients with advanced cancer, many patients with MGC either never receive a referral or experience considerable delays between metastatic diagnosis and palliative care consultation. In many cases, referrals are made only when patients are already hospitalized due to their cancer. Furthermore, we found that a substantial number of patients do not continue outpatient palliative care follow-up after their initial referral, with a more notable decline in continuity of care when the referral is made during an inpatient hospitalization. References: 1. Justin J. Sanders et al., Palliative Care for Patients With Cancer: ASCO Guideline Update. JCO 42, 2336-2357(2024). DOI:10.1200/JCO.24.00542. Research Sponsor: None.

12090 **Poster Session**

Depression in patients with advanced prostate cancer in SWOG advanced cancer clinical trials. First Author: Robert S. Krouse, University of Pennsylvania, Philadelphia, PA

Background: Depression is common in patients with advanced cancer, but its prevalence has not been well documented. Moreover, depression is likely associated with other patient factors, including sociodemographic and clinical variables. We examined depression at enrollment in clinical trials for patients with advanced prostate cancer. **Methods:** We pooled clinical trial data from the SWOG Cancer Research Network. We identified phase III treatment trials of advanced prostate cancer patients with baseline mental health symptom measurements. Baseline depression was derived from emotional functioning items from the FACT-G, the SF-36, and the EORTC QLQ-C30 instruments. Using Likert scale distributions, depression was categorized as none, mild or moderate, and severe. We evaluated the prevalence of depression and its association with other baseline variables including age, race, ethnicity, insurance, rural/urban locale, the Area Deprivation Index, measurable disease, and prognostic risk. Generalized estimating equations with binomial logistic regression were used to assess the association of baseline variables with the odds of any depression and severe depression, with study as the clustering variable. A composite risk model was developed by summing the number of baseline risk factors adversely associated with depression. **Results:** Overall, N = 4,103 patients from four phase III trials were examined, including 69.8% aged 65 or older, 17.5% Black, 3.4% Hispanic, 18.4% rural, and nearly half (46.4%) from socioeconomically deprived areas (ADI score above the national median). At baseline, 50.4% of patients had depression (mild/moderate, 38.3%; severe, 12.1%). Depression was associated with age $<$ 65 years, non-Black race, Hispanic ethnicity, having Medicaid or no insurance, and worse disease clinical characteristics. Patients with $>$3 risk factors (high risk) vs. 0-2 risk factors (low risk) were more likely to experience depression (54.3% vs. 43.2%, $p < .0001$) and severe depression (21.0% vs. 9.7%, $p < .0001$), corresponding to a 50% (OR = 1.50; 95% CI: 1.34-1.67; $P < .0001$) and 135% (OR = 2.35; 95% CI: 1.84-3.02; $P < .0001$) increase in risk, respectively. Quartile (Q) level proportions of any depression were 32.8% (Q1), 44.4% (Q2), 53.1% (Q3), and 72.0% (Q4), respectively, with a fivefold higher risk for those in the highest vs. lowest quartiles (Q4 vs. Q1, OR = 4.97; 95% CI, 2.86-8.64, $p < .0001$). Similar findings were seen with severe depression. **Conclusions:** Evidence of depression at baseline was reported by one-half of patients with advanced prostate cancer in clinical trials. Moreover, we showed that the number of adverse socioeconomic and clinical variables could strongly predict the prevalence of depression. Screening for depression in patients with cancer could help guide patients to appropriate mitigation resources. Interventions to help screen and treat patients with advanced cancer are warranted. Research Sponsor: NIH/NCI/NCTN/NCORP grants U10CA180888, U10CA180819, UG1CA189974; The Hope Foundation.

12091 **Poster Session**

Intravenous selenium to prevent oral mucositis in patients with lymphoma or myeloma undergoing high-dose therapy followed by autologous hematopoietic cell transplantation: A double-blind randomized trial. First Author: Corentin Orvain, Angers University Hospital, Angers, France

Background: Oral mucositis (OM) is a frequent complication in patients with lymphoma and myeloma receiving high-dose therapy (HDT) and autologous hematopoietic cell transplantation (HCT) that can lead to severe pain, malnutrition due to difficulties in drinking and eating, and local and systemic infections. In severe cases, patients require opioid analgesics, supplemental nutrition, and additional antimicrobial therapy while very few preventive interventions have proven useful. Because of its anti-oxydant activity, some studies have suggested that selenium could be useful in this context. We therefore led a double-blind randomized trial to evaluate the use of selenium in preventing OM in patient with lymphoma or myeloma receiving HDT (NCT04080622). **Methods:** Patients $\geq$18 years with lymphoma or myeloma undergoing HDT (carmustine, etoposide, cytarabine, and melphalan [BEAM] for patients with lymphoma and high-dose melphalan for patients with myeloma) followed by autologous HCT were randomized beween intravenous selenium 300 μg/day or placebo from the first day of chemotherapy to hospital discharge. The primary endpoint was the incidence of severe (grade 3-4) OM by intention to treat as defined by the World Health Organization (WHO). Secondary endpoints included any grade oral mucositis (WHO), auto and hetero-évalaution (NCI-CTCAE) of OM, opioid, nutrition, and antimicrobial therapy used, duration of hospitalization, and adverse events (AE). **Results:** From October 2019 to October 2023, we included 100 patients with lymphoma (n = 29) and myeloma (n = 71) who received HDT and autologous HCT that were randomized between selenium (n = 50) and placebo (n = 50). Baseline characterstics (age, gender, and tobacco use, type of hematologic disease, disease status at HDT, and baseline albumin and selenium levels) were balanced between the two treatment arms. The rate of severe OM was strictyl identical in both arms (60%, *P*= 1) with a mean maximum grade of mucositis of 3.26 in the selenium arm and 2.82 in the placebo arm (*P*= 0.71). Other methods to evaluate OM showed similar results. Opioid use (mean 6.92 *versus* 6.12 days in the placebo group, *P*= 0.53), parenteral nutrition (mean 10.88 *versus* 9.27 days, *P*= 0.19), antibiotic use (9.12 *versus* 7.02 days, *P*= 0.05), antifungal use (1.02 *versus* 0.39 days, *P*= 0.33), and duration of hospitalization (24.94 *versus* 19.58 days, *P*= 0.24) were not statistically different between the two groups. The rate of grade 3-4 AE was higher in the selenium arm (100% *versus* 90%, *P*= 0.03) with similar rates of grade 3-4 diarrhea (10% *versus* 16%, *P*= 0.55). **Conclusions:** Intravenous selenium did not improve oral mucositis in patients with lymphoma or myeloma undergoing HDT followed by autologous HCT. Clinical trial information: NCT04080622. Research Sponsor: None.

12092 **Poster Session**

The impact of early versus late palliative care referral (PCR) on healthcare utilization in pancreatic cancer patients: A single-center retrospective study. First Author: Kriti Dhamija, Allegheny Health Network, Pittsburgh, PA

Background: Pancreatic cancer is one of the most aggressive malignancies, imposing substantial physical, psychosocial, and financial stress that significantly compromises patients' quality of life (QOL). Despite its importance, only limited data exists on the optimal timing of a palliative care referral (PCR) in the course of pancreatic cancer. We propose that early PCR offers a proactive approach that not only alleviates symptom burden and improves QOL but also reduces healthcare utilization (HCU) and associated costs. **Methods:** We performed a retrospective analysis for patients diagnosed with pancreatic cancer at Allegheny Health Network from January 2015 to January 2024. Based on the timing of PCR from the diagnosis of pancreatic cancer, patients were categorized into early PCR ($<$ 3 months), and late PCR ($>$ 3 months) cohorts. HCU metrics were compared between the two cohorts including the number of emergency department (ED) visits, hospital admissions and intensive care unit (ICU) admissions, using Mann Whitney U test. Statistical analysis was performed using SAS 9.4, with an alpha level of 0.05. **Results:** From 2015- 2024, 2020 patients were diagnosed with pancreatic cancer and only 309 patients received a PCR. The patients who got a PCR had a median age of 66 years, 56% of them were males and 97% were non-Hispanic. Among these, 172 patients had an early PCR, and 137 patients had a late PCR. The patients in the early PCR group were generally non-Hispanic males with a mean age of 68 years, while those in the late PCR group being non-Hispanic males with a mean age of 64 years. The median number of ED visits was significantly higher in the late PCR cohort compared to the early PCR cohort, {3 [Interquartile range (INR)2-5] versus 2 [INR1-3] respectively, $p < 0.0001$}. 52.55% patients in the late PCR cohort had an ED visit due to pain, compared to only 37.79% patients in the early PCR cohort ($p < 0.009$). 36.63% patients in the early PCR group had an ICU admission as compared to 62.04% patients in the late PCR group ($p < 0.0001$). Similarly, early PCR group had a significantly lesser number of hospital admissions, 2 (INR 1-3), than the late PCR group, 4 (INR 1-10), $p < 0.0001$.While Chemotherapy use in the last 2 months from death was observed in 30.66% patients with late PCR and 29.07% of patients with early PCR, the difference was not statistically significant. **Conclusions:** Our study shows the use of early PCR in reducing aggressive care towards the end of life including ED visits and hospital and ICU admissions. Due to the advanced nature of pancreatic cancer at presentation, early integration of palliative medicine into comprehensive cancer care would be beneficial for improving the QOL of patients and would also reduce the HCU, enhancing economic sustainability of care. Further research is needed to show the effect of early PCR on the psychological stress experienced by pancreatic cancer patients. Research Sponsor: None.

12093 **Poster Session**

Differences in supportive care service utilization among long term metastatic breast cancer survivors by rurality. First Author: Ashley Pariser Davenport, The Ohio State University - James Comprehensive Cancer Center, Columbus, OH

Background: Patients living with metastatic breast cancer (MBC) have unique psychosocial and medical needs, which often go unrecognized. Many patients living in rural areas travel farther for care. We examined differences in supportive care service referrals and utilization by sociodemographic, psychosocial, and clinical predictors among long term MBC survivors living in rural versus urban areas. **Methods:** 233 patients from the Ohio State University Stefanie Spielman Comprehensive Breast Center, who had been diagnosed with MBC for $\geq$1 year, were asked to complete a one-time, online survey to assess their demographic characteristics, quality of life, self-rated health, symptoms, and supportive care needs. Chi-square and fisher exact tests were used for categorical variables and two sample t-tests were used for continuous variables to determine sociodemographic (age, race, education, income, rural/urban residency), psychosocial/quality of life (PROMIS physical component score, PROMIS mental component score, MOS social support), and clinical factors (time since diagnosis, current treatment, metastasis site, fatigue, pain, and sleep) associated with utilization of supportive care services. **Results:** 66 patients residing in rural areas (RURAL) and 167 patients residing in urban areas (URBAN) were recruited. There was a higher rate of supportive care service utilization among URBAN (n=82, 49.1%) versus RURAL (n=22, 33.3%) patients. For URBAN, service utilization was associated with lower (worse) PROMIS physical scores, PROMIS mental scores, MOS social support total scores, and greater fatigue and pain scores. However, no significant associations were seen for RURAL. Higher education and income levels were associated with increased service utilization for RURAL, but not URBAN participants. The Table details referral and utilization rates for the top 5 supportive care services. **Conclusions:** Patients living in rural areas had lower supportive care utilization compared to patients living in urban areas. However, urban patients reported worse PROMIS and social support scores. While a no cost service (dietitian) had similar utilization rates between URBAN and RURAL, another (James Care for Life programs) did not. Services amenable to same day coordination had no statistical differences in utilization rates between URBAN and RURAL. More research is needed to evaluate the impact of distance, financial, and time barriers on equitable access to supportive care services. Research Sponsor: None.

Top 5 supportive care referrals and utilization.

	Rural		Urban	
	Referred	Utilized	Referred	Utilized
Counseling	8 (12.1%)	4 (50%)	34 (20.4%)	20 (58.8%)
Dietitian	11 (16.7%)	8 (72.7%)	35 (21%)	27 (77.1%)
James Care for Life Programs	8 (12.1%)	3 (37.5%)	27 (16.2%)	15 (75%)
Living Well with Advanced Breast Cancer Clinic	14 (21.2%)	2 (14.3%)	20 (12%)	15 (75%)
Physical Therapy	7 (10.6%)	6 (85.7%)	36 (21.6%)	29 (75%)

12094 **Poster Session**

Race and correlates of cancer cachexia in the Detroit Research on Cancer Survivors cohort. First Author: Jennifer Lynn Beebe-Dimmer, Karmanos Cancer Institute, Wayne State University, Detroit, MI

Background: Cancer cachexia is a multifunctional syndrome characterized by the ongoing loss of skeletal muscle mass that cannot be fully reversed by conventional nutritional support and leads to progressive functional impairment limiting quality of life. It is also associated with poor response to therapies which impact long-term survival. The current investigation examines the prevalence and determinants of cachexia in a racially diverse cancer cohort. **Methods:** We used data gathered on a subset of participants in the Detroit Research on Cancer Survivors (ROCS) study, one of the largest cohorts conducted exclusively among Black cancer survivors to understand the complex nature of poorer outcomes in this population. At baseline, participants diagnosed and/or treated at the Karmanos Cancer Institute with breast, colorectal and lung cancer were asked to provide their weight one year prior to diagnosis and current weight, height, medical history, health behaviors and health-related quality of life (HRQOL). Responses were compared with a frequency-matched set of White cancer survivors. Cachexia was defined as an unintentional weight loss of 5% or more for patients with a BMI 20 or higher and 2% or more for patients with a BMI $<$ 20 over 6 months. **Results:** Among 899 cancer survivors (509 Black and 390 White), 35.3% reported weight loss consistent with cachexia. A significantly higher proportion of Black survivors were cachectic (40.3%) compared with White survivors (28.7%; $p < 0.001$). Racial differences were equally pronounced regardless of tumor type, but overall the highest proportion of cachexia was observed among lung cancer survivors (54.2%). Examination of the electronic medical records of these patients found that older age at diagnosis (p-trend $<$ 0.005) and a medical history of diabetes (OR = 2.18; 95%CI 1.31, 3.63) were both significantly associated with the presence of cachexia. **Conclusions:** We found that Black patients are more likely to have cachexia at the time of cancer diagnosis than white patients. Since cachexia is an important predictor of poor outcomes in cancer patients, developing strategies to prevent or reverse the loss in the skeletal muscle mass is critical in improving outcomes and reducing disparities in related outcomes. Research Sponsor: U.S. National Institutes of Health; U01 CA199240.

12095 **Poster Session**

Barriers to palliative care access in patients with brain metastases: A comprehensive national study. First Author: Anastasia Amundson, FIU Herbert Wertheim College of Medicine, Miami, FL

Background: Palliative care (PC) improves the quality of life for patients with advanced cancer, including those with brain metastases (BM). Despite nearly 170,000–200,000 cases of BM annually in the United States, evidence supporting utilization of early PC in malignant brain tumors remains limited. This study aimed to identify factors influencing access to PC for patients with BM from lung, breast, and colorectal cancer to delineate patient uptake of PC. **Methods:** This retrospective cohort study analyzed the National Cancer Database (NCDB) data (2010-2021) for patients with BM from lung, breast, and colorectal cancer. Variables analyzed included age, sex, race, ethnicity, facility type, insurance status, socioeconomic factors, and primary cancer site. The primary outcome was receipt of PC. Descriptive statistics summarized patient characteristics, and logistic regression identified predictors of access to PC, reporting odds ratios (OR) with 95% confidence intervals (CIs). **Results:** Of 214,940 patients with BM, 94% had lung cancer, 4.2% had breast cancer, and 1.7% had colorectal cancer. The cohort was 50.9% female, 82.6% White, 12.2% Black, 3.8% Asian, 96.4% non-Hispanic, and 3.6% Hispanic. In the multivariate analysis, older patients had lower odds of receiving PC compared to patients aged 18-59 (60-69: OR 0.95, 95% CI 0.93-0.98; 70+: OR 0.88, 95% CI 0.86-0.91; $P < 0.001$), while sex was not associated with PC (OR 0.99, 95% CI 0.97-1.01; P = 0.333). Compared to White patients, Black (OR 0.96, 95% CI 0.93-0.99; P = 0.014), and Asian (OR 0.95, 95% CI 0.91-1.00; P = 0.066) patients had lower likelihood of PC. Hispanics were also less likely to receive PC (OR 0.85, 95% CI 0.80-0.90; $P < 0.001$). Integrated facilities (i.e., part of a larger network with centralized cancer care) had a lower probability of providing PC than community hospitals (OR 0.97, 95% CI 0.95-0.99; P = 0.002), whereas academic facilities showed no differences (P = 0.105). Medicaid patients had slightly higher odds of receiving PC than those with private insurance (OR 1.04, 95% CI 1.00-1.07; P = 0.026), while Medicare and other government insurance showed no significant differences. Medicaid expansion improved access (January 2014: OR 1.55, 95% CI 1.50-1.60; late expansion: OR 1.55, 95% CI 1.50-1.61; $P < 0.001$). Patients living $>$ 10 miles from a facility had lower odds of access (OR 0.97, 95% CI 0.94-0.99; P = 0.002). Compared to patients with breast cancer, those with lung cancer had lower odds (OR 0.92, 95% CI 0.87-0.96; $P < 0.001$), and colorectal cancer patients had the lowest odds (OR 0.73, 95% CI 0.67-0.80; $P < 0.001$) of accessing PC. **Conclusions:** Significant disparities in PC access among patients with BM exists. Age, racial and ethnic subgroups, geographic barriers, and primary cancer type impact uptake of PC. Targeted interventions, including strategies to improve access for underserved populations, are needed to increase health equity among BM patients. Research Sponsor: None.

12096 **Poster Session**

Age-specific unmet needs among older patients with cancer enrolled in an outpatient palliative care program: A retrospective analysis. First Author: Sarah Ananda Gomes, Oncoclinicas & Co - Medica Scientia Innovation Research (MEDSIR), São Paulo, Brazil

Background: Older adults with cancer often experience diverse unmet needs. Understanding these needs is crucial for tailoring palliative care interventions. This study analyzed unmet needs among older patients enrolled in an outpatient palliative care program (OPCP), stratified by age (65–75, 76–86, and 87–97 years). **Methods:** This retrospective study included 474 patients enrolled in an OPCP from November 2022 to April 2024. Patients completed the Integrated Palliative Outcome Scale (IPOS), a validated measure assessing physical, psychological, social, and spiritual needs, as well as overall quality of life (QoL). Multinomial logistic regression was performed to evaluate associations between age groups and specific unmet needs, with adjustments for sociodemographic and clinical factors. **Results:** From the total sample, median age was 77 years (range 65–97); 51% were female, 36% had high school, and 32% were college-educated. Cancer types included gastrointestinal (25%), genitourinary (20%), lung (14%), and breast (12%). QoL scores did not differ across age groups. However, unmet needs varied by age group: 65–75 years: Greater likelihood of reporting pain (OR 0.118, 95% CI 0.01–0.42, p=0.04), fatigue (OR 8.27, 95% CI 6.76–9.96, p=0.04), drowsiness (OR 2.15, 95% CI 2.11–3.46, p=0.04), depressive symptoms (OR 2.28, 95% CI 1.23–3.35, p=0.04), and lower anxiety with treatment (OR 0.11, 95% CI 0.02–0.52, p=0.005). 76–86 years: Greater prevalence of drowsiness (OR 20.77, 95% CI 12.14–26.31, p=0.02) and reduced anxiety about the disease (OR 0.13, 95% CI 0.03–0.62, p=0.01). Feeling at peace was less common (OR 0.38, 95% CI 0.002–0.64, p=0.02). 87–97 years: More likely to report pain (OR 11.38, 95% CI 8.11–16.63, p=0.02), anxiety about the disease (OR 9.39, 95% CI 4.11–11.47, p=0.005), and satisfaction with receiving requested information (OR 6.19, 95% CI 3.71–8.42, p=0.04). **Conclusions:** Distinct unmet needs were identified across age groups in older cancer patients receiving outpatient palliative care. Younger older adults (65–75) had higher physical and psychological unmet needs, while the oldest patients (87–97) were more likely to report pain and anxiety about their disease but experienced better communication. Tailored interventions addressing these specific needs are essential to improving patient-centered care. Research Sponsor: None.

12097 **Poster Session**

Disparities in cachexia and anorexia in hospitalized female patients with breast cancer: A national population-based study. First Author: Amro Awad, Hennepin County Medical Center, Minneapolis, MN

Background: Breast cancer is the most common cancer in females in the US. Cachexia and anorexia are common complications from either the disease itself or the treatment regimen. Specific disparities in the prevalence of anorexia and cachexia in female breast cancer patients is not known. This study seeks to address this gap in knowledge by comparing the prevalence of this issue among different demographic factors. **Methods:** The National Inpatient Sample (NIS) databases (2016–2021) of the Healthcare Cost and Utilization Project (HCUP) was used. We applied discharge weight (DISCWT) provided in the database to generate the national estimates. Pearson Chi-square test for categorical variables and Student's t-tests/one-way ANOVA for continuous variables were applied to compare the baseline demographics and hospital characteristics between the groups. The objective of the study was to determine demographic factors associated with increased cachexia, specifically race (African American vs all races), income (lowest quarterlies vs highest), Insurance type (private vs all types) and age (older than 65 years old vs younger). Multivariate linear and logistic regression models were used to adjust for confounders such as demographics, tobacco use, hypertension, COPD, Ischemic heart disease, prior CVA, and prior diagnosis of anorexia nervosa. **Results:** Anorexia, cachexia or malnutrition were documented in 12% of 1,037,185 hospitalizations of females with breast cancer. After adjusting for confounders, there were higher odds of anorexia and cachexia in patients of the African American race (aOR:1.28; CI 1.11 - 1.52; p-value $<$ 0.001) and patients who are 65 years old or older (aOR:1.18; CI 1.06 - 1.35; p-value 0.015). Having a private insurance was associated with lower odds of anorexia and cachexia (aOR:0.69; CI 0.62 - 0.78; p-value $<$ 0.001). There were no significant differences between patients of different levels of income. **Conclusions:** Female breast cancer patients of certain demographics have higher odds of developing cachexia or anorexia, a very common complication of breast cancer. Further considerations for these vulnerable populations should be studied and focused efforts should be made to ensure adequate healthcare access for all demographics. Research Sponsor: None.

Demographic studied	Prevalence of anorexia/cachexia (aOR, P-value, CI)
African American race vs all races	1.28, $<$0.001*, 1.11 - 1.52
Age ≥ 65 vs <65	1.18, 0.015*, 1.06 - 1. 35
Private insurance vs all insurance types	0.69, $<$0.001*, 0.62 - 0.78
Income (lowest quarterile vs highest)	1.05, 0.45, 0.81 - 1.23

*Statistically significant.

12098 Poster Session

Economic outcomes of palliative care in colorectal cancer hospitalizations: A propensity-matched retrospective cohort study on resource utilization. First Author: Elvis Obomanu, Jefferson Einstein Hospital, Philadelphia, PA

Background: The economic burden of colorectal cancer (CRC), a major cause of cancer-related death worldwide, is significant and is fueled by extended hospital stays, intensive treatments, and expensive end-of-life care, with costs expected to rise as the population ages. While clinical research has established the benefits of palliative care (PC) in improving patient outcomes, its economic impact within CRC care pathways remains underexplored. This study employs a large-scale, propensity-matched cohort analysis to evaluate the economic burden of PC integration during CRC hospitalization, addressing knowledge regarding the impact of early palliative interventions on healthcare expenditures and resource utilization. **Methods:** Utilizing data from the Global Collaborative Network-TriNetX, this retrospective cohort analysis evaluated the economic ramifications of early palliative care integration in adults (≥18 years) hospitalized with colorectal cancer. Using ICD-10 codes, we identified patients with malignant colorectal neoplasms, stratifying them into two cohorts: Cohort 1 (n=14,430) comprised individuals receiving palliative care within one month of diagnosis, while Cohort 2 (n=752,405) included those without palliative care exposure. Cohorts were balanced across sociodemographic and clinical variables via propensity score matching. Outcomes using surrogates for healthcare resource utilization and economic burden (inpatient, emergency department, and outpatient visits) were assessed over a 10-year follow-up period (beginning one day post-diagnosis). Results are reported as odds ratios (ORs) with 95% confidence intervals (CIs). **Results:** Following propensity score matching, two balanced cohorts (n=13,991 each) were established, with comparable baseline characteristics. The palliative care cohort had a mean age of 75.8 years, predominantly white—58.7%—and 54.3% males and 45.7% females—while the non-palliative care cohort averaged 76.3 years, predominantly white—59.8%—53.8% males and 46.2% females. Compared to the non-palliative care cohort, the palliative care cohort demonstrated significantly lower risks of inpatient admissions (OR 0.371; 95% CI 0.333–0.413; $p < 0.001$), emergency department visits (OR 0.342; 95% CI 0.311–0.377; $p < 0.001$), and outpatient visits (OR 0.397; 95% CI 0.357–0.441; $p < 0.001$). **Conclusions:** Our study found that early integration of palliative care (PC) in colorectal cancer (CRC) hospitalizations is associated with significant cost savings, achieved through reduced utilization of resource-intensive services, including inpatient, outpatient, and emergency department admissions. These findings suggest that PC could have a positive impact on financial sustainability and end-of-life quality while alleviating the economic burden on healthcare systems and individuals. Research Sponsor: None.

12099 Poster Session

"The telehealth means I get distance from the hospital so I don't feel so much like a patient": A qualitative sub-study examining the acceptability of nurse-led follow-up for ovarian cancer via telehealth using the MOST-S26 to structure consultations. First Author: Rachel Campbell, Faculty of Science, Centre for Medical Psychology and Evidence-Based Decision-Making (CeMPED), Sydney, NSW, Australia

Background: The MOST-S26 is a patient-reported outcome measure that complements follow-up after first-line treatment for ovarian cancer (OC). MOST-S26 enables assessment of physical and psychological symptoms, and well-being. A randomized trial was conducted to evaluate nurse-led follow-up for OC via telehealth using the MOST-S26 to structure consultations vs routine hospital follow-up (ACTRN12620000332921). A qualitative sub-study assessed acceptability of the intervention from patient and nurse perspectives. **Methods:** Semi-structured interviews via video or telephone explored experiences of receiving or delivering nurse-led follow-up. Patients that participated in at least two nurse-led follow-up appointments were eligible. Study nurses delivering the intervention were interviewed at the end of the trial. Interviews were recorded, transcribed and coded using a Framework Approach following five stages: familiarisation, developing a thematic framework, indexing, charting, mapping and interpretation. **Results:** From June 2021, 38 patients were enrolled at 6 Australian sites. The trial closed to acrual in April 2024. Twenty-one participants were interviewed (15 women with OC and 6 study nurses). Analysis identified 3 overarching themes: (1) *key patient-centred benefits* (convenience and flexibility; providing a sense of connection and feeling cared for; enabling personalised, holistic care and prompt management of symptoms; providing dedicated space for patients' to freely express experiences and emotions); (2) *challenges to delivery from nurses' perspectives* (emotional impact of patients' cancers recurring; lack of referral pathways; inability to observe physical cues; difficulties establishing rapport; and, lack of suitability for all patients e.g. non-English speaking or patients with low literacy); and, (3) *Nurse views on usefulness of MOST-S26 to support consultations* (provides a useful tool to guide consultations/referrals, detect recurrence, track symptoms over time, flag symptoms for discussion, and, helps patients' reflect on their symptoms). **Conclusions:** Results confirmed acceptability of this type of follow-up for both OC patients and nurses. Both reported several benefits compared with standard hospital-based follow-up. Challenges that should be considered prior to routine implementation of this follow-up model included: the need to provide support to nurses to cope with the emotional impact of patients' cancers recurring; developing clear referral pathways for symptom management; and considering the characteristics of patients most and least suitable for this type of follow-up. Clinical trial information: ACTRN12620000332921. Research Sponsor: Western Australia Health Translation Network; Australian Government's Medical Research Future Fund; Australia and New Zealand Gynaecological Oncology Group; Jakovich Family; The Ladybird Foundation.

12100 Poster Session

Telemedicine-enabled synchronous medical oncology and home hospice visits. First Author: Sara Dost, Hartford HealthCare Cancer Institute, Hartford, CT

Background: Hospice is underutilized at end-of-life by patients with cancer. Among the barriers to earlier acceptance of hospice may be the perceived loss of the therapeutic alliance and emotional support provided by the oncology team once the hospice team starts care. With the growing utilization of telemedicine, we sought to understand patient, caregiver, hospice nurse, and oncologist perceptions of synchronizing home hospice visits by the hospice nurse with remote telemedicine visits performed by the oncologist in their clinic. **Methods:** Thirty-four newly enrolled hospice patients (age 57-90+; 20 female & 14 male; 28 white non-Hispanic,1 white Hispanic, 3 black/African American, 2 other; 19 married, 3 single, 3 divorced, 1 significant other, 7 widowed, 1 other) and 34 caregivers were consented to an IRB-approved study between 5/14/21-9/9/24. Home hospice nurse visits were coordinated with the oncologist's clinic schedule and telemedicine visits were securely conducted through Epic MyChart functionality. Mixed methodology was utilized with patients, caregivers, hospice nurses and oncologists completing five-point Likert-scale surveys at baseline and subsequent serial surveys for patients and caregivers. **Results:** All groups rated improvement in overall communication. Likert scores for ease and quality of communication improved for oncologists (3.0 to 1.5) and nurses (2.0 to 1.0). Therapeutic alliance scores for patients and caregivers were stable and improved for oncologists (2.5 to 1.5) and nurses (2.0 to 1.5). **Conclusions:** Patients and caregivers expressed highly favorable ratings of hospice experience at baseline and improvement with telemedicine visits. There was no degradation in patient and caregiver therapeutic alliance scores, suggesting preservation of patient experience. Improvement among oncologists and hospice nurses was seen for both communication and therapeutic alliance scores once synchronous telemedicine hospice visits were instituted. These findings suggest that all four groups found value in oncologist-hospice patient telemedicine visits. Qualitative interviews and thematic analysis of caregivers' impressions of the program continue to identify how better to support patients and caregivers during home hospice care. Research Sponsor: None.

Quantitative results.

			Baseline Score Median (IQR)	Improvement in Score Median (IQR)
Patient	Communication	Overall	2.0 (1.25-2.75)	1.0 (0.5-1.0)
	Therapeutic Alliance	Support received from oncologist	2.0 (1-3)	0.0 (-0.5-2.5)
Caregiver	Communication	Overall	2.0 (1.75-3)	1.0 (0.0-1.0)
	Therapeutic Alliance	Support received from oncologist	1.0 (1-3)	0.0 (0.0-0.0)
Oncologist	Communication	Overall	3.0 (2-4.75)	2.0 (0.0-3.0)
	Therapeutic Alliance	Connection	2.5 (2.0-3.0)	1.0 (0.0-2.0)
Hospice Nurse	Communication	Overall	2.0 (2-2.75)	1.0 (0.0-1.0)
	Therapeutic Alliance	Connection with patient & family	2.0 (1-2)	0.5 (0.0-1.0)

IQR – interquartile range.

12101 Poster Session

Evaluating the feasibility of a peer-support group for patients with cancer (presently). First Author: Brandon Anderson, San Francisco Medical Center, Kaiser Permanente Northern California, San Francisco, CA

Background: Many patients with cancer experience significant mental health challenges (commonly depression, anxiety, and adjustment disorders) which can impair quality of life and treatment adherence. Despite this, few seek mental health care due to barriers such as stigma, limited resources, and lack of suitable programs. We sought to determine the feasibility of "Presently", a novel, trauma-informed, virtual, peer-support program for patients regardless of cancer type or treatment, facilitated by trained cancer survivors. **Methods:** An 8-week pilot was implemented at Kaiser Permanente San Francisco, allowing self-enrollment. Demographic and clinical utilization data were collected from one year prior to the program through its completion (9/1/23–11/1/24). Post-program evaluation included surveys and participant feedback sessions. **Results:** Of 42 self-enrolled patients, 31 (74%) attended at least one session, averaging 4 sessions per participant. Most attendees were female (87%) and white (68%). Mental health comorbidities were prevalent, with 59% having an active diagnosis and 34% prescribed psychotropic medications. Participants represented diverse cancer types: breast (32%), lymphoma (24%), genitourinary (21%), gastrointestinal (10%), leukemia (7%), lung (3%), and pre-cancerous (3%). Disease stages varied: 38% local, 24% locally advanced, and 38% metastatic. Nearly half (48%) were undergoing active treatment. In the year prior, attendees utilized more healthcare services, including 157% more oncology and 10% more primary care visits than non-attendees. Participant feedback was positive: 65% found Presently very effective in providing emotional support and 64% were highly likely to recommend it to others. Most participants (82%) found support from peers meaningful, with 71% appreciating staff facilitation and 59% valuing opportunities to help others. All non-attendees expressed interest in future participation. **Conclusions:** The Presently program demonstrated feasibility in supporting patients with diverse cancer diagnoses, stages, and mental health histories. Positive participant feedback underscores the potential for novel peer-led models to address the increasing mental health needs of patients with cancer. Future research will investigate clinical outcomes and potential reductions in healthcare utilization through larger-scale implementation. Research Sponsor: None.

12102 Poster Session

Quality of life among oncology patients with distinct spiritual well-being profiles. First Author: Kayoll G. Gyan, Dana-Farber Cancer Institute Phyllis F. Cantor Center for Research in Nursing and Patient Care Services, Boston, MA

Background: Individuals undergoing treatment for cancer experience multiple symptoms moderated by stress/resilience that impact quality of life (QOL). Spiritual well-being (SWB) is an understudied QOL component that may influence outcomes. Purpose: Identify SWB profiles and associations with symptoms, stress, resilience, and QOL. **Methods:** Patients with breast, gastrointestinal, gynecologic and lung cancer undergoing chemotherapy were enrolled in a symptom clusters study. Assessments included: SWB subscale of theMultidimensional Quality of Life Scale-Patient Version (MQOLS); Lee Fatigue Scale (LFS), Attentional Function Index (AFI), Spielberger State-Trait Anxiety Inventory (STAI), Center for Epidemiological Studies-Depression scale (CESD), General Sleep Disturbance Scale (GSDS); Perceived Stress Scale (PSS), Connor-Davidson Resilience Scale (CDRS) and MQOLS. Latent profile analysis (LPA) was used to identify the distinct SWB profiles. Differences among latent classes were evaluated using analysis of variance, Kruskal-Wallis, or Chi Square tests with a Bonferroni corrected p-value of <0.008. **Results:** Among 1324 patients, four distinct SWB profiles were identified (Table). Patients in the Low SWB class were older, better educated, and more likely to be male and White compared to other groups (all $p<0.008$). Low SWB patients reported greater fatigue, anxiety, and depression, poorer general health and mental health, and greater stress. Compared to High and Very High classes, patients in the Low and Moderate classes had lower resilience scores. Low SWB patients reported poorer QOL. **Conclusions:** Four distinct SWB profiles were identified. Patients with lower SWB reported higher symptom burden, higher levels of stress and poorer QOL. An evaluation of patients' SWB may assist clinicians to identify a modifiable condition that warrants targeted interventions. Research Sponsor: National Cancer Institute; CA134900.

Differences in symptoms, stress, resilience, and QOL scores among SWB classes.

Characteristics	Low (1) n=188 (14.2%)	Moderate (2) n=450 (34.0%)	High (3) n=421 (31.8%)	Very High (4) n=265 (20.0%)	Statistics
Evening fatigue (>5.6)	5.5 (2.1)	5.4 (2.1)	5.6 (2.0)	4.8 (2.3)	F = 8.61, p <.001 1, 2, and 3 > 4
AFI (<5.0 = Low, 5 to 7.5 = Moderate, >7.5 = High)	6.2 (1.7)	6.3 (1.8)	6.4 (1.8)	6.8 (1.8)	F = 6.40, p <.001 1, 2, and 3 < 4
STAI (>32.2)	38.2 (13.5)	34.4 (12.0)	33.4 (12.4)	30.6 (11.1)	F = 14.51, p <.001 1 > 2, 3, and 4 2 and 3 > 4
CESD (>16.0)	15.4 (10.9)	13.2 (9.8)	12.4 (9.4)	11.0 (8.6)	F = 7.95, p <.001 1 > 3 and 4 2 > 4
GSDS (>43.0)	55.5 (18.6)	54.1 (19.6)	51.0 (20.5)	50.0 (21.4)	F = 4.47, p = .004 1 and 2 > 4
PSS total (0 to 56)	20.8 (8.7)	19.2 (8.3)	18.1 (8.1)	16.3 (7.2)	F = 12.89, p <.001 1, 2, and 3 > 4 1 > 3
CDRS total (0 to 40)	28.1 (6.4)	29.2 (6.4)	30.7 (6.1)	32.0 (6.0)	F = 18.06, p <.001 1 and 2 < 3 and 4
MQOLS: Psychological well-being	4.8 (1.8)	5.4 (1.8)	5.6 (1.9)	6.0 (1.9)	F = 15.50, p <.001 1, 2, and 3 < 4 2 and 3 < 4
MQOLS: Social well-being	5.6 (2.0)	5.9 (2.0)	5.5 (2.0)	5.9 (2.0)	F = 2.60, p = .051

12103 Poster Session

Awareness of gestational surrogacy among female patients treated for cancer: A national survey. First Author: Alexa Steckler, The Warren Alpert Medical School of Brown University, Providence, RI

Background: ASCO and other international guidelines recommend fertility counseling at diagnosis for all reproductive-aged cancer patients. Yet, how commonly gestational surrogacy (GS) is presented as an option remains unclear. To date, there is very little data to inform the question. Our primary objective was to determine the proportion of cancer survivors aware of GS as an option for parenthood. For the purposes of this study, we defined a gestational surrogate as one who carries a pregnancy using an embryo from the intended parents or a donor embryo, and as such, has no genetic link to the fetus. **Methods:** We developed a national survey that covered fertility preservation options, with specific questions regarding GS. Survey validation and usability testing were conducted with 17 cancer survivors, providing input on the final instrument. Following IRB approval, the survey was disseminated online via REDCap in partnership with multiple cancer advocacy organizations between April and November 2024. All respondents had the ability to select multiple responses as appropriate. Frequencies, proportions, and 95% confidence intervals (CI) were calculated using SAS 9.4 (SAS Institute, Cary, NC). **Results:** 519 female participants completed the survey. By cancer type: 60.7% breast, 14.3% hematologic, 8.1% cervical/uterine, 4.4% ovarian, 3.7% GI, and 8.9% other. Mean age (SD) was 31.1 (6.6) at diagnosis and 36.8 (7.4) at survey response; 30% had children at diagnosis. Overall, 75.9% expressed a desire for children post-cancer at the time of their diagnosis. Among respondents, 302 (58.2%; 95% CI 54.0-62.4) reported that they were aware of GS at diagnosis. Among those aware of GS, a similar proportion learned about it through oncologists (32.1%; 95% CI 26.9-37.4) or REI specialists (31.1%; 95% CI 25.9-36.4). However, the majority learned about GS through non-clinical resources (73.2%; 95% CI 68.2-78.2), including internet/social media (46.0%; 95% CI 40.5-51.7). Of those aware, GS was actively considered by 134 (44.5%) participants, of which 20 (14.9%) pursued GS and 16 (11.9%) have had a child using GS. Of those who did not actively consider GS but who were aware, common barriers included cost (45.3%), not ready to build a family (41.4%), preference to carry the pregnancy (29.9%), and using/planning other methods (20.5%). **Conclusions:** GS is a common route to parenthood in the US and internationally. While almost 60% of participants were aware of GS as an option, the primary source of information was through non-clinical resources. These data indicate GS should be routinely included in fertility counseling at diagnosis, especially in cases where cancer treatment compromises the patient's ability to carry a pregnancy. Education is needed to ensure oncologists are equipped to provide access to accurate, patient-centered oncofertility care, including REI referral. Research Sponsor: None.

12104 Poster Session

Inclusion of gestational surrogacy in oncologist-led fertility counseling at cancer diagnosis: A national survey. First Author: Alexa Steckler, The Warren Alpert Medical School of Brown University, Providence, RI

Background: ASCO guidelines recommend that oncologists discuss infertility risks and fertility preservation early with reproductive-aged cancer patients. However, little is known about how often gestational surrogacy (GS) is presented as a parenthood option, or the factors influencing these conversations. GS is defined as someone who carries a pregnancy using an embryo from the intended parents or donor, with no genetic link to the fetus. We sought to assess the frequency and predictors of oncologist-provided GS counseling among a national cohort of female cancer survivors diagnosed at a reproductive age. **Methods:** We developed a REDCap survey on GS counseling experiences and demographic/cancer-related information, incorporating feedback from 17 survivors. The final survey was distributed nationally via multiple cancer advocacy organizations (April–November 2024). Fisher's exact tests, T-tests, and multiple logistic regression identified predictors of GS counseling, with $p < 0.05$ considered significant. **Results:** 519 female cancer survivors completed the survey. By cancer type: 60.7% breast, 14.3% hematologic, 8.1% cervical/uterine, 4.4% ovarian, 3.7% GI, and 8.9% other. Mean age at diagnosis was 31.1 (SD 6.6). 82.1% of patients recalled their doctor discussing the impact of cancer treatment on fertility. Only 18.7% received GS counseling from their oncologist. Patients with cervical/uterine (35.7%) and ovarian (30.4%) cancer were significantly more likely to receive GS counseling from their oncologist compared to breast (19.1%), hematologic (13.5%), GI (5.3%), and other cancers (8.7%) ($p = 0.007$). Patients who were younger age at diagnosis (mean 30.0 vs. 31.4 years, $p = 0.05$), had a younger current age (mean 34.2 vs. 37.4, $p < 0.001$), fewer years since diagnosis (21.3% < 5 years vs. 20.6% 6-10 years vs. 6.0% > 10 years since diagnosis, $p = 0.003$), and were childless at diagnosis (21.3% vs. 12.9% with children, $p = 0.03$) were significantly more likely to receive counseling. GS counseling did not vary by patient race, sexual orientation, relationship status, geographic location, income, or education. Logistic regression showed older current age (aOR 0.90; 95% CI 0.95-0.95) and having children at diagnosis (aOR = 0.56; 95% CI 0.31-0.98) predicted lower odds, while gynecologic cancer increased odds of GS counseling (aOR = 2.21; 95% CI 1.06-4.49). **Conclusions:** Fewer than 1 in 5 survivors received GS counseling from their oncologist, with younger, childless patients with gynecologic cancers more likely to be counseled. These findings highlight potential biases in counseling practices and underscore the need for systematic, equitable fertility discussions at diagnosis, before gonadotoxic treatment. Research Sponsor: None.

12105 Poster Session

Using large language models to assess adherence to ASCO patient-oncologist communication standards. First Author: Joshua Paul Davis, Dana-Farber Cancer Institute, Boston, MA

Background: The American Society of Clinical Oncology (ASCO) convened a multidisciplinary panel resulting in patient-oncologist communication guidelines published in 2017. These guidelines contain recommendations across topics including goals of care, treatment selection, end-of-life care, facilitating family involvement, and clinician training in communication. Ideally, these conversations should be documented in the electronic health record (EHR), so that they can be referred to at future visits as a patient's clinical course evolves. Tracking adherence to these communication guidelines may be beneficial for quality improvement efforts. However, manual chart review of unstructured free text notes is tedious and burdensome. The recent development of Large Language Models (LLMs) may represent a new computational approach that can capture such documentation more efficiently than chart review. To our knowledge, no prior study has used LLMs to capture such documentation in free text notes, validated against gold-standard manual chart review. **Methods:** As part of a larger study on development of LLMs for tracking palliative care quality measures, we randomly selected 30 patients with advanced cancer and clinical notes in the month following navigation to a poor prognosis treatment node. We used *GPT-4o-2024-05-13*, our HIPAA-secure tool, to develop an LLM prompt for identifying 14 ASCO communication domains in clinical text. The LLM prompt required output to generate source text to support identification of a communication domain. A "hallucination score" was calculated for source text, which is a measure of evidence produced by LLMs not found in source text. We then compared to gold standard manual chart review using standard performance metrics. **Results:** Across communication domains, note-level LLM analysis achieved sensitivity ranging from 0.43-1.0, specificity ranging 0.32-0.99, and accuracy ranging 0.51-0.99. Examples of documentation identified by both the LLM and chart review include goals of care and prognosis ("recently informed that her disease had progressed with treatment. Currently on 'last line' of chemotherapy"), treatment options and clinical trials ("her oncologist recommended a potential trial treatment, and she is contemplating involvement in this"), end-of-life care ("if her cancer continues to progress with her current treatment, they will transition her care to home hospice for comfort measures only"), and cost of care ("financial insecurity - referred to resource specialist"). Average hallucination index for documentation identified by the LLM was low. LLM frequently identified information missed by annotators. The LLM extracted information relevant to communication domains in a fraction of the time required by manual chart review. **Conclusions:** LLMs can identify communication domains in EHRs, potentially contributing to quality improvement efforts. Research Sponsor: National Institute on Aging; National Cancer Institute.

12106 Poster Session

The association between emotional distress prior to receiving immune checkpoint inhibitors and overall survival among patients with cancer: A population-based study. First Author: Luciana Beatriz Mendes Gomes Siqueira, Division of Medical Oncology and Hematology, Princess Margaret Cancer Centre, University of Toronto, Toronto, ON, Canada

Background: Immune checkpoint inhibitors (ICIs) are widely used across cancer care. Emerging evidence from smaller studies links pretreatment emotional distress (ED) to poorer outcomes in patients with melanoma and non-small cell lung cancer undergoing ICIs due to changes in inflammatory states but large-scale studies are lacking. We conducted a population-level retrospective cohort study to assess the impact of pre-treatment ED on overall survival (OS) across solid tumor patients treated with ICIs. **Methods:** Using population-level administrative data, a cohort of patients with cancer, age 18 years or older, who received at least one dose of an ICI between June 2012 to October 2018 in Ontario, Canada, were identified using systemic therapy databases. Databases were deterministically linked to obtain socio-demographic, clinical co-variates, pre-treatment ED levels, and overall survival. ED was defined as having the sum of the Edmonton Symptom Assessment Scale (ESAS) anxiety and depression score $\geq$ 4. Multivariable Cox proportional hazard models assessed the association between ED and OS, adjusted for age, sex, body mass index, history of autoimmune conditions, cancer centre facility level, comorbidity score, and hospitalization within 60 days prior to starting ICI. **Results:** Among the 3237 patients who received ICIs and completed the ESAS prior to ICI treatment, most were male (58%), median age 67 years (IQR 59-74), the median combined ESAS anxiety and depression score was 3 (IQR 0-7); 45% had pre-treatment ED. The majority had lung cancer (49%), melanoma (37%) or renal cancer (9%), and were either treated with nivolumab (42%), pembrolizumab (36%) or ipilimumab (19%). Median OS was 330 days. Pre-ICI treatment ED was associated with poorer OS (aHR = 1.23, 95% CI [1.12–1.34] $P < 0.0001$) and when analyzed as a continuous variable, a higher combined ESAS anxiety and depression score was associated with poorer OS (aHR = 1.02 per 1 unit increase, 95% CI [1.01-1.03] $P < 0.0001$). Pre-treatment ED was associated with poorer OS for both males (aHR_{males}= 1.27, 95% CI [1.12–1.43] $P = 0.0001$) and females ($aHR_{females}$= 1.18, 95% CI [1.03–1.36] $P = 0.02$). Among disease sites, ED was associated with reduced OS among patients with lung cancer (aHR = 1.33, 95% CI [1.17–1.51] $P < 0.0001$) and showed a similar but non-significant trend among patients with melanoma (aHR = 1.14, 95% CI [0.98–1.32] $P = 0.09$); while ED not significantly associated OS for patients with renal cancer (aHR = 0.98, $P = 0.89$). Similar results were observed across sexes and disease sites when evaluating the combined ESAS anxiety and depression score and OS. **Conclusions:** Among patients receiving ICIs, pretreatment ED is associated with poorer OS. These findings suggest the importance of screening for and addressing ED as a part of routine cancer care, which may potentially influence ICI treatment outcomes. Research Sponsor: University of Toronto; Conquer Cancer, the ASCO Foundation.

12107 Poster Session

Effect of a single home visit on distress in cancer patients undergoing chemotherapy: A comparative study. First Author: Mila Petrova, MHAT "Nadezhda", Sofia, Bulgaria

Background: This study aimed to investigate whether a home visit after the first chemotherapy can significantly reduce cancer patients' psychological distress levels. **Methods:** The National Comprehensive Cancer Network Distress Thermometer and problem list was used to assess patients' level of distress on a scale from 0 to 10, with scores of 4 or higher considered a high level of distress. Between 01 Mar and 01 Nov 2024 chemotherapy naïve cancer patients were divided into two groups – the study group had a home visit by a medical oncologist within 10 days after the start of their 1st chemotherapy, and the patients in the control group were only seen at the clinic before the start of their 1st and 2nd chemotherapy course. During the home visits, a patient-led discussion was held, in which the oncologist answered various questions about the patient's staging, prognosis, therapy and its anticipated effects. Home visits were offered to all patients, but only those who opted in received them. All patients in both groups had their distress levels assessed at two time points – before the start of 1st chemotherapy course and before the start of the 2nd chemotherapy course. Responses were analysed and compared between the two groups. **Results:** The level of psychological distress was assessed in 126 patients with solid tumours; of them, 88 (69.8%) opted in for a home visit and formed the study group, while 38 refused and were only seen at the clinic and served as the control group. Mean age in the study group was 60.6$\pm$12.4 and 56.9$\pm$14.4 for the controls. In both groups, breast, lung, and colon cancer prevailed. High baseline levels of distress (before the start of chemotherapy) were similarly prevalent in both groups: 72.7% of the home visit group and 65.8% of the control group scored 4 or higher. McNemar's test showed that the number of patients with high levels of distress at the second interview was significantly reduced in the home visit group, from 72.7% to 53.4% ($p < 0.001$), in contrast to the controls, where it remained almost unchanged from 65.8% to 68.4%. In addition, the Wilcoxon test showed that one home visit significantly decreased the level of distress in the study group, from 4.9$\pm$2.6 to 3.4$\pm$2.5 ($p < 0.001$). In contrast, distress levels in the control group, comprising patients who declined home visits, showed no significant improvement, barely dropping from 4.6$\pm$2.8 to 4.2$\pm$2.7 (p = 0.263) between the first and second interviews. **Conclusions:** This study demonstrates that a single home visit by an oncologist after the start of chemotherapy can significantly reduce distress levels in cancer patients and thus enhance overall patient well-being. Research Sponsor: None.

12109 Poster Session

Promoting resilience in stress management within patients with early stage breast cancer. First Author: Gabrielle Betty Rocque, University of Alabama at Birmingham, Division of Hematology and Oncology, Birmingham, AL

Background: Women with breast cancer often experience persistent psychological distress, including fear of recurrence, which can be exacerbated in marginalized populations. Promoting Resilience In Stress Management (PRISM) is an intervention initially developed for adolescents and young adults with serious illness that builds resilience utilizing skills-based coaching, which may be able to be adapted and deployed to address psychological needs of women with breast cancer. **Methods:** This pilot study examined PRISM's feasibility and preliminary effects in women with early-stage breast cancer undergoing chemotherapy. Six PRISM sessions were delivered individually by trained coaches, targeted getting to know participants, stress-management, goal setting, cognitive-reframing, meaning making, and family integration. Feasibility, the primary outcome, was defined as 70% of participants completing the PRISM intervention, baseline, and follow-up surveys. Secondary outcomes were measured using the Acceptability of Intervention Measure, Intervention Appropriateness Measure, Feasibility of Intervention Measure, PROMIS-Global Quality of Life, Post-Traumatic Growth Inventory, Connor-Davidson Resilience scale, Functional Assessment of Chronic Illness Therapy–Spiritual Well-Being, Fear of Cancer Recurrence Inventory, Patient Health Questionnaire Depression Scale, General Anxiety Disorder–Anxiety Scale, and Patient Activation Measure. Pre- and post- results were analyzed using paired t-tests for continuous measures and McNemar's test for categorical measures. Effect sizes were calculated using Cohen's d and Cramer's V. **Results:** From February to September 2024, 30 patients participated in the PRISM intervention pilot. The study population had a median age of 51 years (IQR 47-59), were predominantly Black (57%) and unemployed at the start of the study (37%). Two patients died, two withdrew, and one patient was lost to follow-up, resulting in a completion rate of 83%, meeting the primary feasibility endpoint. Patients reported that the sessions were acceptable (mean 4.6 [SD 0.7]), appropriate (mean 4.5 [SD 0.9]), and feasible (mean 4.6 [SD 0.4]).The largest effect was observed in participants' resilience (mean 4-point increase; d = 0.6). There was also a mean 14-point increase of patient growth and self-improvement (d = 0.5). Modest effect sizes were observed for improvements in overall spiritual well-being and reductions in fear of cancer recurrence (both d = 0.4). Small effects were observed for depression, anxiety symptoms, patient activation, global health, physical health, and mental health (d = range 0.1 to 0.2). **Conclusions:** The PRISM intervention was feasible amongst a diverse group of women with early-stage breast cancer and effect sizes suggest potential benefit, warranting further investigation in a future randomized control trial. Clinical trial information: NCT06133348. Research Sponsor: American Cancer Society.

12110 Poster Session

Systematic screening of perception of curability among patients with advanced cancer: A longitudinal analysis. First Author: Kayley Ancy, The University of Texas MD Anderson Cancer Center, Houston, TX

Background: Clinicians do not routinely assess patients' illness understanding despite its importance in decision making. Systematic screening of illness understanding is a novel approach that normalizes discussion of this sensitive topic, helps identify patients with information needs and allows clinicians to monitor and support their patients' understanding over time. In this study, we examined the changes in perception of curability over time in patients who completed systematic screening at our supportive care clinic (SCC). **Methods:** We implemented universal electronic systematic screening of illness understanding in our SCC using two questions from the Prognosis and Treatment Perception Questionnaire at consultation and every 2 months. We included all advanced cancer patients who completed screening at their consultation and at least one follow-up visit within one year. The primary outcome was patients' perception of curability, which was categorized as accurate if they reported the likelihood of cure as $<$ 25%. Patients were grouped into one of four categories based on responses at their first and last SCC visits: accurate-accurate, accurate-inaccurate, inaccurate-accurate and inaccurate-inaccurate. We examined patient characteristics associated with the inaccurate-inaccurate group versus all others using univariate and multivariate logistic regression analysis. **Results:** 432 patients (mean age 58 [SD 13], female n=248 [57.4%], white n=331 [76.6%]) were included. The mean number of SCC visits was 2.69 [SD 0.9] and the median duration between the first and last SCC visits was 157 days [IQR 129-194]. At visits 1, 2, 3, 4 and 5+, 34% [147/432], 37% [159/432], 36% [71/197], 38% [30/78] and 46% [11/24] of patients had an accurate understanding of their curability (p=0.24), respectively. Comparing the first and last visit, 233 [54%] were inaccurate-inaccurate, 119 [28%] were accurate-accurate, 52 [12%] were inaccurate-accurate and 28 [6%] were accurate-inaccurate. Asian race and greater well-being at baseline were associated with being inaccurate-inaccurate (Table). **Conclusions:** Systematic screening identified that only ~1 in 3 advanced cancer patients had an accurate understanding of their curability at SCC consultation and this did not improve significantly over time. Certain subgroups were more likely to remain inaccurate at last follow-up. Our findings highlight the need to systematically screen for illness understanding and to work towards bridging information gaps with better communication and coping support. Research Sponsor: None.

Multivariate analysis of patient characteristics associated with being in the inaccurate-inaccurate group.

Patient Characteristic	Odds Ratio	95% CI	p-value
Race (versus White)			
Asian	3.92	1.52-12.2	0.009
Black or African American	1.91	0.90-4.26	0.1
Edmonton Symptom Assessment System Well-Being	0.82	0.73-0.93	0.003

12111 Poster Session

A longitudinal analysis of social networks and patient-reported outcomes among young adult cancer survivors. First Author: Katie Darabos, Rutgers School of Public Health, Piscataway, NJ

Background: Nearly 80,000 young adults (YAs; aged 18-39) are diagnosed with cancer each year in the United States with > 80% expected to survive beyond 5 years. Social connectedness (connections/relations with others) is one of the most documented psychosocial factors cited as influencing health and well-being among YA survivors. However, given cancer diagnosis, treatment, and the challenging late effects, the social networks of YA survivors invariably change, including the quantity, quality, and types of relationships. Limited work has focused on identifying the extent of changes within YA survivors' social networks, such as the social network structure (network size) and social network composition (sociodemographic characteristics) that may confer risk. To understand this, we present preliminary data mapping the social networks of YA survivors, analyzing network changes over a 3-month period and associations with depression and anxiety. **Methods:** YAs (N= 25) completed a baseline social network questionnaire capturing social network structure (number of network members), composition (network member characteristics), and types of support each network member provides. YA survivors also completed measures of depression and anxiety at 3 months post baseline. Wilcoxon signed-rank tests assessed changes in social network metrics; correlations examined associations between baseline social network metrics and depression and anxiety at 3 months. **Results:** YA survivors (M_{age}= 27.0, SD= 5.4, range = 18-37) were majority female (56%) and white (56%). YA survivors reported a wide range of cancer diagnoses (leukemia, lymphoma, testicular, thyroid, breast) and were on average 2 years since diagnosis (M= 22 months). On average YA survivors' networks over 3 months contracted by 0.96 people (Z= -2.09, p= 0.036). Social networks changed compositionally over time, with a decrease in second degree relatives (Z= -2.066, p= 0.039) and male network members (Z= -2.17, p= 0.03), but no change in the mean age or in the number of female network members. The types of support that YA survivors received over time also changed, with a decrease in the amount of emotional support (Z= -2.03, p= 0.04). Only the number of parental network members at baseline was positively associated with depression (r= 0.53, p= 0.007) and anxiety (r= 0.51, p= 0.009) at 3 months. There were no other significant associations between baseline social network metrics on depression and anxiety scores at 3 months. **Conclusions:** Despite networks getting smaller and less heterogeneous over time, this was not associated with later depression or anxiety in our preliminary sample. More work is needed to inform the development and delivery of targeted social network interventions focused on intervening upon social network indicators to improve the long-term health and well-being of this vulnerable YA survivor population. Research Sponsor: Pediatric Hematology and Oncology Research Center of Excellence.

12112 Poster Session

Is metastatic cancer curable? A survey of medical oncologists. First Author: Shalini Subramaniam, NHMRC Clinical Trials Center, The University of Sydney, Sydney, Australia

Background: More patients with metastatic cancer are living longer due to treatment advances like immune checkpoint inhibitors and targeted therapies. We aimed to determine oncologists' attitudes about the possibility of cure in metastatic cancer and to understand how they discuss cure with their patients. **Methods:** We invited medical oncologists and medical oncology trainees via a national mailing list and social media to complete a digital 21-question purpose-built survey. Descriptive statistical analyses were conducted. **Results:** Between September and October 2024, 127 respondents completed the survey. Median age was 39 years (IQR 36-45). Most participants worked in an Australian (64%) metropolitan (88%) public practice (56%), and 51% were women. Clinical experience ranged from <5 years (36%), 5 to 10 years (24%) and >10 years (34%) since oncology qualification; 6% were trainees. The most frequently treated cancer types were breast (55% of participants), lung (52%), and colorectal (50%). 82% reported thinking patients with metastatic cancer can be cured. The types of metastatic cancer that participants thought had the highest chance of cure were testicular (81%), melanoma (32%) and colorectal (16%) (Table). At the time of diagnosis, 51% of participants reported they would tell a patient with metastatic cancer that cure is possible. After delivering treatment for metastatic cancer, 29% reported telling some patients that they *have been* cured, while 74% reported telling some patients that they *may have* been cured. During treatment, 1%, 4% and 17% of participants thought a patient had been cured if the cancer had not progressed 1, 2, and 5 years after starting treatment. A greater proportion *thought* cure was a realistic possibility when discussing the benefits of immunotherapy (83%) compared to chemotherapy (40%), but only 44% and 27% respectively reported they would *tell* patients this. When discussing prognosis, most reported using multiple ranges of time with probabilities e.g. best-case, typical-case and worst-case scenarios (68%). **Conclusions:** Although most oncologists in this survey believed metastatic cancer is curable, only a minority would tell a patient with metastatic cancer they have been cured. Research Sponsor: None.

Median cure rates by disease as reported by participants.

Cancer type	Median cure rate (%)	IQR (%)
Testicular	81	71-88
Melanoma	32	20-50
Colorectal	16	9-25
Lung	13	6-21
Genitourinary	8	1-17
Breast	7	4-14
Gynaecological	6	1-12
Head and Neck	5	0-11
Gastroesophageal	2	0-7
Mesothelioma	2	0-7

12113 Poster Session

Sexual health communication and young-onset cancer (YOC): Healthcare practitioners' attitudes and practices. First Author: Louise Kelly, Department of Medical Oncology, Trinity St. James's Cancer Institute, Dublin 8, Ireland

Background: Sexual health-related discussions are often challenging for Healthcare Practitioners (HCPs) and patients, making sexual health communication a frequently neglected aspect of cancer care. HCPs' lack of knowledge regarding LGBTQ+ cancer care contributes to greater unmet survivorship needs.We explored HCPs' attitudes and practices regarding sexual health-related discussions with YOC patients (25yrs–50yrs) to identify barriers and training needs for improving effective communication. **Methods:** A cross-sectional, mixed-methods design was employed. 160 HCPs working with patients with gastrointestinal and head & neck cancers at the Trinity St James Cancer Institute, Dublin, Ireland were invited to complete an anonymised 23-item online questionnaire. Data was analysed using descriptive statistics for quantitative responses, and thematic analysis for qualitative insights. **Results:** 52 respondents included; Medical Oncology (46.2%), Surgical Oncology (36.5%), Radiation Oncology (11.5%), Psych-Oncology (5.8%), and Palliative Care (5.8%). 34.6% (18/52) and 25.0% (13/52) reported 'rarely' and 'never' enquiring about sexual health-related issues during routine consultations. 34.6% (18/52) reported feeling 'somewhat' or 'very' unconfident initiating a sexual health-related discussion, while 5.7% (3/52) reported feeling adequately trained to enquire about sexual health-related issues. 43.1% (22/51) reported feeling 'somewhat' knowledgeable regarding the impact of cancer on sexual health, while 52.9% (27/51) reported they do not have sufficient knowledge regarding LGBTQ+ cancer care needs. Whilst 63.5% (33/52) agreed knowing a patient's sexual orientation and/or gender identity is relevant to their healthcare, 19.2% (10/52) reported asking about sexual orientation in routine practice. Notably, 98.1% (51/52) reported 'rarely' or 'never' enquiring about gender identity. Common identified barriers included: lack of training or knowledge (76.9% (40/52)), inappropriate time/setting (59.6% (31/52)), HCP discomfort (46.2% (24/52)), and patient discomfort (48.1% (25/52)). There was strong interest in receiving formal sexual health-related education and training, and 75.0% (39/52) believed access to a specialist for advice and/or to whom patients could be referred would increase HCPs confidence. **Conclusions:** HCPs acknowledged the importance of sexual health-related communication with YOC patients, yet significant gaps exist in knowledge, confidence, and training, particularly regarding the LGBTQ+ population.These findings underscore the need for targeted training and education to empower HCPs to engage in meaningful sexual health communication. Research Sponsor: None.

12114 Poster Session

Shared decision-making in follow-up care for lung cancer screening. First Author: Nihal Mohamed, Icahn School of Medicine at Mount Sinai Department of Urology and Oncological Sciences, New York, NY

Background: Shared decision-making (SDM) is a critical component of lung cancer screening (LCS) decisions to ensure patients understand the benefits, risks, and follow-up processes. Follow-up discussions on adherence to LCS present unique challenges, including managing patient expectations, addressing concerns about outcomes, and integrating smoking cessation efforts. This study uses The Centers for Disease Control and Prevention (CDC) SHARE model to examine SDM dynamics to identify areas for improvement in patient-provider communication. **Methods:** A thematic content analysis using ATLAS.ti was conducted by four trained coders on transcripts from primary care provider (PCP) visits between September 2022 and May 2024 with 24 patients referred for LCS. Guided by the CDC SHARE model for SDM—Seek, Help, Assess, Reach, and Evaluate—consultations were analyzed to examine how PCP revisited prior screening attempts and results, engaged patients in follow-up screening decisions, and addressed barriers to continued screening and smoking cessation. Inter-rater agreement ranged from 83.8% to 92.3%. Code prevalence was assessed using frequency counts (i.e., groundedness). **Results:** Five themes from the SHARE model were identified: (1) Evaluating prior LCS decisions made in the past (15), (2) Seeking patient participation in the SDM process by explicitly communicating that a choice about LCS adherence still exists (n = 7); (3) Helping patients explore the risks and benefits of LCS, including clarifying potential risks and outcomes (n = 13); (4) Assessing patient values and concerns regarding LCS, such as fears about false positives or financial burden (n = 8); and (5) Reaching a decision about a new LCS, where PCP guided patients through the decision-making process and confirmed next steps (n = 21). In addition to the themes derived from the SHARE model, two new emergent themes were identified: (a) providing supportive talk and reassurance (n = 7) to address patient uncertainty and encourage engagement in LCS; and (b) addressing smoking cessation if patients indicated that they still smoke (n = 6), with discussions initiated primarily by PCP and narrowly focused on pharmacological treatments. Notably, LCS decision aids were not used or discussed in any consultation. **Conclusions:** This study identifies strengths and gaps in PCP communication during LCS discussions. While PCP assessed patient risk factors and facilitated screening decisions, significant gaps in SDM emerged. Smoking cessation discussions were limited, and decision aids were absent, highlighting missed opportunities for patient-centered care. Follow-up consultations for LCS require addressing barriers to adherence to LCS and integration of smoking cessation as a standard component of care. Incorporating decision aids could improve patient engagement and adherence to long-term screening recommendations. Research Sponsor: None.

12115 Poster Session

Temporal trends of suicide among cancer patients: A SEER database analysis from 2000 to 2021. First Author: Ahmed Bashir Sukhera, Texas Tech University Health Sciences Center, Odessa, TX

Background: Cancer is a known cause of morbidity and mortality, with over 2 million new diagnoses and 600,000 deaths projected in 2024. Some of the most common cancers have shown an increased incidence, including breast and prostate cancer. There is an increasing mortality trend towards younger populations, with colorectal cancer becoming the leading and second most common cause of cancer death in men and women younger than 50 years respectively. An estimated 20-25% of cancer patients suffer from depression, which alongside specific cancer diagnoses and demographic factors translates to increased suicidality. Here we attempt to elucidate the relationship between specific cancer diagnoses and suicide. **Methods:** We conducted a population-based cohort study of suicide/self-inflicted injury deaths among cancer patients using the National Cancer Institute Surveillance, Epidemiology and End Results Program (SEER) over the period 2000 through 2021. The SEER data is comprised of 22 different registries across the United States (US) which captures approximately 47.9% of the US population. We applied simple linear regression with total suicides as response variable and year as predictor variable to estimate the rate of change of the annual number of suicides among cancer patients. Subgroup analysis included sex, age group, household income, and the primary site of cancer. Results are reported as counts and percentage and the rates of change are reported as regression slope and 95% confidence interval (β, 95% CI). **Results:** A total of 16,156 suicide mortalities were identified of which 13,520 (83.7%) were male and 2,636 (16.3%) were female. The total number of suicides rose approximately ten-fold from 123 in 2000 to 1,211 in 2021 corresponding to β = 54.6 / year (95% CI 50.6 – 58.7). Male suicides rose from 107 in 2000 to 1,017 in 2021 (β = 44.6 / year (95% CI 41.7 – 47.5)) while Female suicides rose from 16 in 2000 to 194 in 2021 (β = 10.0 / year (95% CI 8.6 – 11.5)). The most common primary cancer sites were prostate 3,624 (22.4%), lung and bronchus 1,699 (10.5%), urinary bladder 1,108 (6.9%), and breast 977 (6.0%). Prostate cancer suicides increased from 16 in 2000 to 283 in 2021 (β = 14.0 / year (95% CI 12.9 - 15.1)). Lung cancer suicides rose from 36 in 2000 to 122 in 2021 (β = 2.6 / year (95% CI 12.9 - 15.1)). Breast cancer suicides rose from 4 in 2000 to 80 in 2021 (β = 4.0 / year (95% CI 3.3 – 4.7)). The distribution of ages among suicides was 14.0% for under 50 years old, 19.3% between 50 and 59, 27.8% between 60 and 69, 26.5% between 70 and 79 and 12.5% for 80 years old or greater, with each age group demonstrating significant increase in annual suicides over the period analyzed. **Conclusions:** A significant and increasing trend of suicide is observed across various cancers. Almost half (47.1%) of suicide attempts were among patients between 50 and 69 years. Males committed suicide more often than females, an exacerbation of the trend seen in the general population. Research Sponsor: None.

12116 Poster Session

Adequacy of immune checkpoint inhibitor-associated thyroid function monitoring following therapy. First Author: Maria Antonia Velez Velez, Department of Medicine, Division of Hematology/Oncology, University of California, Los Angeles, Los Angeles, CA

Background: Immune checkpoint inhibitor (ICI)-induced thyroid dysfunction is the most common endocrine immune-related adverse event. While ICI-induced thyroid dysfunction rates during therapy are well documented, data on post-treatment dysfunction is limited. Describing these rates is important as ICIs are increasingly used in the curative treatment setting. This study aimed to evaluate the rates of post-ICI thyroid dysfunction, evaluate for predictors of post-ICI thyroid dysfunction and assess adequacy of post-ICI thyroid function surveillance. **Methods:** A retrospective analysis of 3626 patients treated with ICIs for various malignancies and cancer stages within a single health system from March 2013 to December 2022 was conducted. Rates of clinically acted upon thyroid dysfunction (diagnosis or thyroid-directed medication) were evaluated before, during, and after ICI therapy, alongside rates of thyroid laboratory surveillance in the post treatment setting. A multivariate analysis evaluated the odds of developing clinically acted upon post-ICI thyroid dysfunction based on patient/treatment characteristics. Rates of clinically acted upon thyroid dysfunction were evaluated based on therapy duration. Statistical analyses were carried out using R V4.1.0. **Results:** Clinically acted upon thyroid dysfunction occurred in 8.1% of patients (294/3626) during treatment and 4.4% (159/3626) after treatment. However, in patients alive two months after ICI cessation, 53.9% (989/1834) had no post-ICI thyroid function tests performed. Among the 1170 patients with post-ICI thyroid labs and no prior dysfunction, 11.6% (136/1170) developed post-ICI thyroid dysfunction. Thirty percent of patients with abnormal TSH values and no clinically acted upon thyroid dysfunction prior to therapy discontinuation subsequently developed clinically acted upon thyroid dysfunction. The rate of post treatment thyroid dysfunction in patients who underwent thyroid test surveillance and received $<$9 months of therapy was 13.3% compared to 6.5% in those who received therapy $>$9 months. The odds ratio for developing post-ICI dysfunction were 1.76 (95% CI, 1.03 to 2.95) for patients with urologic malignancies compared to patients with respiratory malignancies as the reference group. **Conclusions:** Post-ICI thyroid dysfunction is frequent, with 11.6% of patients who undergo thyroid function surveillance being affected. Patients with abnormal TSH before ICI discontinuation and those who received treatment for $<$ 9 months as well as those with urologic malignancies may benefit from more stringent post-ICI surveillance. Research Sponsor: None.

12117 Poster Session

Equivalence of Ina, an AI-based nutrition platform, to human dietitians for counseling patients with cancer. First Author: Marissa Buchan, Savor Health LLC, New York, NY

Background: Addressing nutritional issues in patients with cancer can reduce symptoms, shorten hospitalizations, enhance treatment adherence, and improve quality of life. However, most patients never receive nutrition counseling due to dietitian workforce shortages and healthcare access disparities. Advances in artificial intelligence (AI) and high rates of mobile device utilization among all demographics provide opportunities to expand reach. This study assessed if guidance from an expert-designed AI nutrition platform, "Ina", is equivalent to that of human Oncology-Credentialed Registered Dietitians (RD-CSO). **Methods:** RD-CSOs were recruited from a professional message board and grouped by quartiles of RD experience (yrs). We randomly selected 1 from each quartile as "Responders" (n = 4) and 3 with $>$10 yrs experience as expert "Reviewers" (n = 3). To compare Ina to RD Responders, a list of 20 top oncology nutrition queries was developed and assigned to 10 hypothetical patient profiles representing common cancer types, comorbidities, side effects, food allergies and preferences. Both Ina and RD Responders answered the queries. The Reviewers then blindly rated each answer (n = 100) using a modified version of the validated Quality Assessment of Medical AI (mQAMAI) instrument, which individually scores domains of accuracy, clarity, relevance, completeness, and usefulness yielding a total score between 5-25. Within-query differences between Ina and Responders were expressed as mean differences (SD) and tested for significance using a Signed Rank or two-tailed paired T-test. Equivalence was defined a priori as a mean within-query difference $<$ 5. **Results:** The criteria for equivalence was met and no statistically significant differences were found between the total scores of Ina and each RD Responder. Ina's average total score was superior to the combined RD Responders (19.3 vs 18.3, 95% CI [0.1,1.8]; p = 0.02). A descriptive analysis of individual mQAMAI domains demonstrated higher scores for Ina compared to averaged RD Responder scores (Table). Ina had a 54% faster response time (8.5 vs 18.5 min per 2 queries; CI [-0.21,-0.13]; p $<$ 0.001) and 27% easier readability (Flesch-Kincaid grade level 7.2 vs 9.9; CI [-3.3,-1.9]; p $<$ 0.001). **Conclusions:** Ina provides equivalent nutritional guidance to that of human dietitians for patients with cancer, with greater speed and readability. This technology offers a solution to meet the needs of patients with cancer in settings where access to dietitians is limited. Research Sponsor: Savor Health LLC.

Mean mQAMAI score.

	Total Quality Score	Accuracy	Clarity	Relevance	Completeness	Usefulness
AI-Platform Mean (SD)	19.3 (2.7)	3.9 (0.7)	4.2 (0.5)	4.1 (0.6)	3.3 (0.8)	3.8 (0.7)
RD Responders Mean (SD)	18.3 (3.0)	3.8 (0.7)	3.9 (0.6)	3.9 (0.6)	3.2 (0.8)	3.5 (0.7)
Mean Difference [95% CI]	0.9 [0.1,1.8]	0.1 [-0.1, 0.3]	0.3 [0.1, 0.5]	0.2 [0.0, 0.4]	0.1 [-0.1, 0.3]	0.2 [0.0, 0.4]
P val	0.02	0.06	0.001	0.04	0.36	0.02

12118 Poster Session

Immune profiling to identify predictive biomarkers and highlights the potential efficacy of IL-6R blockade in checkpoint inhibitor–related myocarditis. First Author: Michel Obeid, CHUV, LCIT Center, Lausanne, Switzerland

Background: Immune checkpoint inhibitor–associated myocarditis (ICI-My) is a rare but potentially life-threatening complication. Advancing our understanding of its underlying immunological mechanisms is essential for the development of improved diagnostic tools and treatment strategies, with the aim of minimizing morbidity and mortality. **Methods:** This retrospective single-center study (July 2019–June 2024) identified 33 patients who developed ICI-My. A Comprehensive immuno-profiling was conducted using 49 cytokines, 7 traditional cardiac biomarkers, and 46 mass cytometry markers. These profiles were compared to the baseline levels of a cohort of 97 cancer patients prior to ICI treatment. The analysis assessed the identification of biomarkers for differentiating low and high-grade myocarditis and corticosteroids (CS)-refractory ICI-My. The therapeutic efficacy of tocilizumab was assessed in eight cases of CS-refractory myocarditis. **Results:** ICI-My patients showed marked elevations in IL-6, CXCL9, CXCL10, CXCL13, VEGF-A, and sCD25 compared with baseline cancer patients prior to ICI initiation. High-grade myocarditis was characterized by lower levels of CCL4 and CXCL12, with predictive accuracies of 78.6% and 82.1%, respectively. In contrast, conventional biomarkers (cTnT, cTnI, CK, CK-MB, NT-ProBNP, and d-dimers) failed to differentiate disease severity. Mass cytometry revealed a distinct immune profile in ICI-My, including increased immature neutrophils, reduced switched and unswitched memory B cells, elevated double-positive ($CD38^+$/$HLA\text{-}DR^+$) T cells across $CD4^+$ and $CD8^+$ subsets, decreased $CXCR5^+$ leukocytes, and diminished CXCR3 expression within all memory T-cell subsets. Notably, no complement activation was detected. HGF, CXCL10, and BDNF successfully discriminated patients requiring immunosuppression from those untreated (accuracies of 89%, 79%, and 79%, respectively), while IL-18 and CCL4 predicted the need for tocilizumab (TCZ) therapy (accuracies of 79% and 82%, respectively). This underscores the dual benefit of CCL4. In addition, all cases of corticosteroid (CS)-refractory myocarditis (n = 8), including those unresponsive to mycophenolate mofetil or infliximab, responded effectively to TCZ. **Conclusions:** This study provides the first comprehensive immuno-profile of ICI-My. CCL4 and CXCL12 outperformed some traditional cardiac biomarkers as prognostic tools, while IL-18 and CCL4 emerged as key predictors for tocilizumab therapy, which could offer a personalized therapeutic approach. The absence of complement activation indicates that cytokine-mediated and cellular pathways are central to ICI-My pathogenesis. Notably, the success of anti-IL-6 therapy in CS-refractory cases highlights new therapeutic opportunities, enhancing patient care and guiding future interventions. Research Sponsor: CHUV pôle prioritaire.

12119 Poster Session

Comparison of two electroacupuncture regimens on symptoms and brain structures in breast cancer survivors: A randomized, controlled trial. First Author: Alexandre Chan, University of California, Irvine, Irvine, CA

Background: Although electroacupuncture (EA) has shown usefulness in managing neuropsychiatric symptoms in cancer survivors, a specific acupoint regimen has not been established. We conducted a randomized, controlled, patient- and assessor-blinded pilot trial to compare two EA regimens on neuropsychiatric symptoms and associated brain structural changes in breast cancer survivors. (Clinicaltrials.gov: NCT05283577). **Methods:** Breast cancer survivors who self-reported cognitive impairment, fatigue, insomnia, or psychological distress were randomized (1:1) to receive ten weekly therapeutic EA to target either neuropsychiatric-specific (nEA) or non-neuropsychiatric-specific (sham EA, sEA) acupoints. Outcomes were assessed using patient-reported outcomes (EORTC QLQ-C30, FACT-Cog, MFSI-SF), neurocognitive tests (CANTAB), and neuroimaging (measuring gray matter, white matter, cerebrospinal fluid, diffusion tensor metrics, and volume and mean intensity of the hippocampus) before and after treatment. We computed group-specific treatment effect sizes (Glass's Δ) adjusted for baseline variability using linear mixed models. A Pearson's correlation analysis was performed between the neurocognitive scores and the imaging metrics. Multiple testing was controlled via the Benjamini-Hochberg method, with statistical significance set at P-adjusted < 0.05. Adverse events (AEs) were graded with CTCAE v5. **Results:** Thirty-five participants were recruited, of which five dropped out, leaving 30 (86%) completing all treatment sessions. The average ($\pm$SD) age was 58.2 $\pm$12.2 years, with 66% non-Hispanic White, 77% holding a Bachelor's degree or higher, 94% received systemic treatment and/or radiotherapy for cancer, 86% reporting $\geq$2 neuropsychiatric symptoms. Both groups showed statistically significant pre-post medium-to-large effect sizes in perceived cognitive function, fatigue, and quality of life. nEA group observed significant improvement in cognitive domains of attention (ES=0.708, P-adjusted=0.004), memory (ES=0.488, P-adjusted=0.026), and emotional functioning (ES=0.664, P-adjusted=0.004). Neuroimages showed greater gray matter volume change (P=0.0327) and post-treatment hippocampus mean intensity (P=0.0468) in nEA versus sEA. In the nEA group, correlations were observed between attention and gray matter volume (P=0.0198) and between executive function and hippocampus volume (P=0.0204). All AEs were grade 2 or lower: nEA participants reported pain (n=1) and bleeding (n=1), while sEA participants reported numbness (n=2), bruising (n=1), nausea (n=1), and redness (n=1). **Conclusions:** Ten weeks of electroacupuncture targeting neuropsychiatric-related acupoints, compared to sham acupoints, improves neuropsychiatric symptoms in breast cancer survivors, supported by clinically relevant structural brain changes. Clinical trial information: NCT05283577. Research Sponsor: California Breast Cancer Research Program; UCI Anticancer Challenge.

12120 Poster Session

MOLGEN: Detecting new DPYD variants for the safer delivery of 5FU and capecitabine. First Author: Helen Winter, University Hospitals Bristol and Weston NHS Foundation Trust, Bristol, United Kingdom

Background: Adverse drug reactions (ADRs) pose a significant challenge to healthcare systems, leading to 6.5-15% of NHS hospital admissions costing over £2.2 billion annually. Genetic factors play a crucial role in predisposing patients to ADRs. One notable example is dihydropyrimidine dehydrogenase (DPD) enzyme deficiency, which affects the metabolism of anticancer drugs like 5-fluorouracil (5FU), capecitabine and tegafur. Current genetic testing in the NHS focuses on four DPYD gene variants associated with European populations, potentially leaving non-European populations at greater risk of drug toxicity. This study aims to expand the genetic evidence base by identifying additional DPYD variants. **Methods:** This observational study recruited patients who experienced grade 3 or 4 toxicities after receiving 5FU and capecitabine, despite undergoing standard DPYD genetic testing. Participants include both European and non-European patients meeting specified inclusion criteria. Blood samples were collected for genetic testing using either Sanger or next generation sequencing of exons and intron-exon boundaries. Clinical data, including administered dose and toxicity grade, were recorded. Clinicians received genetic results to inform discussions with patients about future treatment. **Results:** Fifteen patients experienced grade 3-4 toxicity despite standard testing. Of these patients, one patient was heterozygous for c.2846A $>$ T, and therefore predicted to have decreased DPD activity. This patient was wild-type based on NHS standard testing, and was therefore treated with full dose capecitabine, resulting in Grade 3 diarrhoea and vomiting. However, the Clinical Pharmacogenetics Implementation Consortium (CPIC) dosing guideline suggests a 50% dose reduction in the presence of this variant. Three patients were found to be heterozygous for other DPYD variants, including c.771C $>$ A, c.2786T $>$ C, c.2766+1G $>$ A, and c.1757T $>$ C. for which there are no current dosing guidelines. The functional impact of these variants requires further study, currently ongoing. All three patients had severe reactions after 1-2 cycles of capecitabine, including one patient requiring a seven-week ICU admission for Grade 4 neutropenic sepsis. Seven patients have found to be heterozygous for DPYD variants that result in normal predicted DPD enzyme activity according to current knowledge, but again further work is needed. Four patients had no DPYD variants. **Conclusions:** By broadening the genetic analysis of DPD deficiency and identifying new variants, opportunities exist for enhanced patient safety and treatment efficacy. Expanding the variants in DPYD testing in the future, including those found in diverse ancestral populations could lead to improved dosing strategies and reduced the risk of severe ADRs. The findings have the potential to inform future NHS genetic testing protocols and promote equitable healthcare outcomes. Clinical trial information: iras 7086. Research Sponsor: None.

12121 Poster Session

NG11-2 phase-Ib trial to prevent/reduce severe oral mucositis induced by radiotherapy. First Author: Mary Lei, Guy's and St Thomas' NHS Foundation Trust, London, United Kingdom

Background: Radiation-induced oral mucositis (RIOM) affects up to 80% of people undergoing treatment for head and neck cancer (HNC), reaching nearly 100% in altered or accelerated fractional radiation. Current approaches necessitate multiple supportive care pharmacotherapies with no approved preventative pharmaceutical products available for the reduction of RIOM in patients with HNC. To address this unmet medical need an innovative oral topical vasoconstrictor solution (NG11-2) has been developed and a phase-Ib dose escalation study carried out to assess the safety and preliminary efficacy of NG11-2 in preventing/reducing RIOM in patients undergoing treatment for HNC. **Methods:** In this single arm, multi-centre, phase-1b "2+4" dose escalation study (NCT06669390) using NG11-2, 15 participants, with a diagnosis of HNC and scheduled to receive radiotherapy with at least 30Gy exposure to the oral cavity and/or buccal mucosa (with or without chemotherapy) were enrolled, with 2 each into the 0.92mg/mL, 1.83mg/mL, 3.66mg/mL and 5.5mg/mL dose cohorts. An additional 7 patients were enrolled in the 5.5mg/mL cohort as an expansion phase. Safety was the primary endpoint, with secondary endpoints including duration, incidence and time to onset of severe RIOM using World Health Organization [WHO], Radiation Therapy Oncology Group [RTOG], and National Cancer Institute-Common Terminology Criteria for Adverse Events [NCI-CTCAE] V5 grading criteria, with severe levels being Grade 3 or above. Patient Reported Outcome Measurements were also performed. The Kaplan-Meier method was applied to the expanded dose cohort to estimate the median duration, incidence and time to onset of severe RIOM. **Results:** No Dose Limiting Toxicities or Serious Adverse Reactions were observed during the study. The duration and incidence of severe RIOM were reduced in the 5.5mg/mL cohort (15.5 days and 44.4% using WHO criteria respectively, 14 days and 33.3% using RTOG respectively, 17days and 33.3% using NCI-CTCAE respectively), relative to the 0.92mg/mL cohort (18-46 days and 100% respectively using the WHO, RTOG and NCI-CTCAE criteria). **Conclusions:** NG11-2 is well tolerated in the patient population included in this study. NG11-2 shows encouraging preliminary efficacy results which support proceeding to larger scale confirmation studies. Clinical trial information: NCT06669390. Research Sponsor: None.

12122 Poster Session

Examining the link between p16, an aging biomarker, and a clinically meaningful functional outcome in older adults with early breast cancer. First Author: Chaiyaporn Charles Vatanatham, UCLA Internal Medicine, Los Angeles, CA

Background: Chemotherapy is thought to accelerate aging by disrupting fundamental processes of aging such as cellular senescence. Senescence is a state of terminal cell cycle arrest that is linked to increased inflammation, tissue damage, and impaired regeneration. In older adults with early breast cancer, treatment with neo/adjuvant chemotherapy is associated with persistent increases in circulating $p16^{INK4a}$ (p16) expression, an established biomarker of senescence. However, it remains unknown whether higher levels of p16 correlate with clinically meaningful aging outcomes, such as physical function, in older adults with early breast cancer. **Methods:** We analyzed a prospective cohort of 501 adults age $>$65 with stage I-III breast cancer receiving neo/adjuvant chemotherapy. We assessed physical function using the timed up and go test (TUG), at two time points: pre-chemotherapy (T1) and post-chemotherapy (T2). The TUG score was measured as the time (in seconds) a participant takes to stand up from a standard armchair, walk 3 meters, turn around, walk back to the chair, and sit down. We collected blood at T1 and quantified p16 expression levels in circulating CD3+ T lymphocytes. Expression of p16 was determined using TaqMan quantitative reverse-transcription polymerase chain reaction. We calculated the Spearman correlations to examine the relationship between blood p16 levels at T1 with TUG score at T1, at T2, and change in individual TUG score from T1 to T2. **Results:** The median age of participants was 70 years (range 65-86). The majority (64.4%) had stage II/III disease and 58.1% received an anthracycline. Baseline TUG scores were available for 467 participants and baseline p16 data were available for 317 participants. The mean baseline p16 level was 10.2 $\log_2$ p16 units (SD = 0.9). Mean TUG scores were 11.4 sec (SD = 4.6) at T1 and 11.5 sec (SD = 5.3) at T2. The mean change in TUG score from T1 to T2 was 0.3 (SD = 4.2). There was no significant correlation observed between p16 and TUG score at T1 (r = 0.11, p = 0.05), T2 (r = 0.06, p = 0.36), or the change in TUG score from T1 to T2 (r = 0, p = 0.99). **Conclusions:** In this cohort of older adults with early breast cancer treated with neo/adjuvant chemotherapy, we did not find a correlation between pretreatment p16 and physical function as measured by TUG. Future studies are needed to understand the role of biological aging markers in improving precision risk assessment of treatment toxicity in older adults with cancer. Clinical trial information: NCT01472094. Research Sponsor: U.S. National Institutes of Health; R01 AG037037.

12123 Poster Session

Effect of IV magnesium supplementation in reducing adverse cisplatin associated kidney outcomes.

First Author: Ekta Panjrolia, Section of Hospital Medicine, Central Virginia Veterans Affairs Health Care System, Richmond, VA

Background: Cisplatin is a commonly used chemotherapy agent that is associated with significant nephrotoxicity due to renal tubular cell injury. IV magnesium (mg) has emerged as a potential agent for preventing cisplatin-induced kidney injury. This study aims to explore the efficacy of IV mg in reducing cisplatin induced major adverse kidney events (MAKE). **Methods:** This is a retrospective observation cohort study of the TriNetX research network (with NLP) which included 105 Health care organizations (HCOs). Patients who received first dose of IV Cisplatin between 09/30/2004 to 09/30/2024 were included. Cohort further divided into two groups based on IV Mg supplementation during chemotherapy: IV Mg and Control groups. To mitigate potential confounding variables, we conducted 1:1 propensity score matching (PSM) that involved 42 variables covering demographics, comorbidities, medications, and laboratory results. The primary outcome of interest was MAKE, defined as stage 3 AKI, Dialysis or eGFR $<$ 15 ml/min/1.73m2, Death at 30 days. Secondary outcomes were mortality and dialysis needing AKIs at 30 days. Adjusted hazard ratios (AHRs) with 95% CIs and P values were calculated using Cox proportional hazards regression models for all outcomes. The Kaplan-Meier method was used to estimate survival probabilities after PSM, considering 2-sided p $<$ .05 as statistically significant. Sensitivity analyses with different observations and study window and subgroup analysis were done. **Results:** Our analysis consisted of 106,141 adults who received their first dose of IV Cisplatin. After excluding 519 patients with previous ESRD, 23,761(age 60.1+12.6, Male-51.8%, White-75.1%) were in IV Mg group(22.5%) and 81,861 (age 56.2+14.5, Male-58.5%, White-40.9%) in control group(77.5%). After PSM, each group had 20,647 participants. MAKE incidence was 586/20647(2.84%) in IV Mg group vs. 1934/20647(9.37%) in the control (aHR 0.28; 95% CI, 0.26-0.31). The mortality incidence was 274/20,647(1.33%) in the IV Mg group compared to 515/20,647 (2.49%) in the control group (aHR 0.53; 95% CI, 0.45-0.61). Dialysis needing AKIs were 27/20,647(0.13%) in IV Mg group vs. 102/20,647(0.49%) in control group (aHR 0.26; 95% CI, 0.17-0.40). Sensitivity analysis with 90 days observation window and last 5 years of study period (09/30/2019 to 09/30/2024) and different subgroup analysis showed consistent results. **Conclusions:** IV mg supplementation is associated with reduced MAKE and mortality in patients receiving cisplatin. Research Sponsor: None.

Baseline characteristics of patients after propensity score matching.

Characteristic	IV Mg group	Control	Std Diff
Demographic			
Age, mean	59.5(12.9)	59.1 (13.7)	0.035
Male, n (%)	10810 (52.36%)	10724 (51.94%)	0.008
White, n (%)	14834 (71.85%)	15095 (73.11%)	0.028
Hispanic, n (%)	1248 (6.04%)	1478 (7.16%)	0.045
Comorbidities, n (%)			
Malignant neoplasms of ill-defined, other secondary and unspecified sites	10789 (52.26%)	10700 (51.82%)	0.009
Hypertension	8408 (40.72%)	8402 (40.69%)	0.001
Malignant neoplasms of Head and Neck	4844 (23.46%)	4427 (21.44%)	0.0482
Hyperlipidemia	4801 (23.25%)	4670 (22.62%)	0.015
Nicotine dependence	4478 (21.69%)	4445 (21.53%)	0.004
Type 2 diabetes mellitus	3048 (14.76%)	3035 (14.7%)	0.002
Ischemic heart diseases	2554 (12.37%)	2534 (12.27%)	0.003
Chronic obstructive pulmonary disease	2403 (11.64%)	2292 (11.1%)	0.017
Cerebrovascular diseases	1038 (5.03%)	1043 (5.05%)	0.001
Chronic kidney disease	933 (4.52%)	893 (4.33%)	0.009
Heart failure	698 (3.38%)	726 (3.52%)	0.007
Medications, n (%)			
Beta-Blockers	6594 (31.94%)	6655 (32.23%)	0.006
Proton pump inhibitors	6018 (29.15%)	6111 (29.6%)	0.01
Statin	4911 (23.79%)	4949 (23.97%)	0.004
RAS Blockers	4739 (22.95%)	4664 (22.59%)	0.009
Diuretics	4475 (21.67%)	4666 (22.6%)	0.022
NSAIDS	4155 (20.12%)	4348 (21.06%)	0.023
Allopurinol	662 (3.21%)	776 (3.76%)	0.03
Gemcitabine	522 (2.53%)	465 (2.25%)	0.018
Methotrexate	448 (2.17%)	391 (1.89%)	0.02
PD-1/PDL-1 inhibitors	325 (1.57%)	314 (1.52%)	0.004
Doxorubicin	288 (1.4%)	304 (1.47%)	0.007
VEGF/VEGFR inhibitors	226 (1.1%)	208 (1.01%)	0.009
Zoledronic acid	203 (0.98%)	207 (1%)	0.002
Cyclophosphamide	159 (0.77%)	165 (0.8%)	0.003
Pemetrexed	111 (0.54%)	113 (0.55%)	0.001
Ifosfamide	21 (0.1%)	46 (0.22%)	0.03
Laboratory			
Blood Pressure, Systolic	125.8 (20.5)	125.3 (20.5)	0.025
BMI, mean (SD), kg/m2	27.6 (6.5)	27.2 (6.5)	0.059
>= 30 kg/m2, n (%)	5930 (28.72%)	5993 (29.03%)	0.007
Sodium, mean (SD), mmol/L	138.2 (3.2)	137.9 (3.5)	0.075
Potassium, mean (SD), mmol/L	4.2 (0.4)	4.1 (0.5)	0.09
Creatinine, mean (SD), mg/dL	0.87(1.42)	0.85 (0.35)	0.018
Hemoglobin A1c, mean (SD), %	6.5 (2.0)	6.4 (1.5)	0.102
Hemoglobin, mean (SD), g/dL	12.7(2.1)	12.4 (2.1)	0.163
< 10 g/dL, n (%)	4444 (21.52%)	4671 (22.62%)	0.027
Albumin, mean (SD), g/dL	3.9(0.6)	3.8 (0.6)	0.187
< 3 g/dL, n (%)	3175 (15.38%)	3413 (16.53%)	0.031
Magnesium, mean (SD), mg/dL	1.96 (0.25)	1.97 (0.29)	0.039
< 1.7 mg/dL, n (%)	3853 (18.66%)	4065 (19.69%)	0.026

12124 Poster Session

Exploring unmet needs in radiation-induced nausea and vomiting after moderately emetogenic treatment.

First Author: Sarah Arn Lowry, Oregon Health & Science University, Knight Cancer Institute, Portland, OR

Background: Despite their prevalence and clinical significance, interventions to improve radiation-induced nausea and vomiting (RINV) are insufficiently researched and prioritized. The 2020 ASCO Antiemetic guidelines categorize craniospinal radiation therapy (RT) as a moderate risk for RINV requiring 5HT3-RA prophylaxis +/- dexamethasone. Yet, RINV guideline implementation and associated clinical outcomes remain poorly characterized. **Methods:** We performed a retrospective analysis at an NCI-designated comprehensive cancer center. Our primary aim was to determine the proportion of adult patients with guideline-concordant antiemetics prescribed prior to craniospinal RT between 06/2020-10/2023. Patients were excluded if they received concurrent chemotherapy. We selected the first eligible RT regimen. Secondary aims included determining the proportion of consult notes documenting RINV risk, patient report of RINV, and correlating RINV with clinical variables using logistic regression. **Results:** A total of 212 patients met inclusion criteria, with a median age of 67 and 37% were female. The most common malignancies were prostate (27%), breast (14%), and lung (11%). At the start of RT, 44% had a prescription for a 5HT3-RA and 42% had dexamethasone prescribed for pain and/or edema. 41% of radiation oncology consult notes documented RINV as a risk of RT. Overall, 39% of patients reported RINV during or up to 10 days after RT. An increased risk of RINV was associated with a documented history of prior chemotherapy-induced nausea and vomiting (CINV; OR 2.50, p=0.017), younger age (OR 2.28, p=0.018), and a 5HT3-RA prescription prior to the start of RT (OR 1.76, p=0.047). There was no association between RINV and sex, prior chemotherapy, dexamethasone, or 5HT3-RA/dexamethasone combination at the start of RT. **Conclusions:** Despite the prevalence of RINV, standardized prophylaxis remains suboptimal for patients receiving craniospinal RT. A key opportunity exists to enhance patient outcomes by conducting prospective interventional studies to address this unmet clinical need. Research Sponsor: None.

			Outcome: RINV (yes vs. no)	
Patient Characteristics	**Categories**	**N (%)**	**Odds Ratio (95% CI)**	**p-value**
Sex	Male^	133 (62.7)		
	Female	79 (37.3)	1.46 (0.82-2.57)	0.196
Age	≥55 yo^	170 (80.2)42 (19.8)	2.28 (1.15-4.56)	
	<55 yo			**0.018**
Prior exposure to chemotherapy	No^	124 (58.5)		
	Yes	88 (41.5)	1.08 (0.62-1.89)	0.783
Documented history of CINV	No^	179 (84.4)		
	Yes	33 (15.6)	2.50 (1.18-5.41)	**0.017**
5HT3-RA at RT start	No^	119 (56.1)93 (43.9)		
	Yes		1.76 (1.01-3.10)	**0.047**
Dexamethasone (pain, edema) at RT start	No^	123 (58.0)		
	Yes	89 (42.0)	0.75 (0.43-1.32)	0.328
5HT3-RA + dexamethasone at RT start	No^	169 (79.7)		
	Yes	43 (20.3)	0.92 (0.46-1.83)	0.825

^Reference level for logistic regression odds ratio (odds of RINV).

12125 Poster Session

Germline determinants of pneumonitis in patients with cancer treated with antibody drug conjugates.

First Author: Emre Yekeduz, Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA

Background: Antibody-drug conjugates (ADCs) are now essential in the treatment of solid and hematologic cancers. While effective, ADCs can cause adverse events (AEs) requiring careful management. Pneumonitis, a potentially severe AE, may result in treatment discontinuation or mortality. However, its risk factors and underlying mechanisms remain poorly understood. **Methods:** Patients (pts) with solid or hematologic malignancies treated with ADCs at Dana-Farber Cancer Institute up to August 1, 2024, were screened. Only those with available genomic data were included. Pneumonitis was evaluated based on the Common Terminology Criteria for AEs v4.03. A total of 18 candidate single nucleotide polymorphisms (SNPs) linked to drug-related AEs and implicated in ADC metabolism pathways were identified using PharmGKB. SNPs were inferred from targeted panel sequencing using the STITCH pipeline, with 3 SNPs that could not be successfully imputed. The association between the SNPs, as probabilistic dosages, and occurrence of pneumonitis was tested using a multivariable Cox regression model, adjusting for age, sex, race, cancer type, and sequencing panel version. Pts were censored at the end of treatment or death. P-values were adjusted using the Bonferroni correction. **Results:** The study included 1,184 pts with cancer treated with ADCs, encompassing a total of 1,465 ADC treatments, as some pts received multiple lines of ADCs. The median age at treatment initiation was 60 years (interquartile range: 20). Most pts were female (80.7%). Breast cancer was the most common cancer (54.6%), followed by urothelial (13.3%), and ovarian (11.6%) cancers. The most frequently administered ADCs included trastuzumab deruxtecan (33.1%), sacituzumab govitecan (25.1%), and enfortumab vedotin (11.3%). A total of 92 pneumonitis events were observed in 89 pts (Table), among which 54 (58.6%) were grade 2 or higher. The prevalence of pts carrying the minor alleles (intermediate or poor metabolizers) of rs4646437 (CYP3A4) and rs776746 (CYP3A5) was 16.8% and 15.6%, respectively. Multivariable analysis revealed that carriers of the minor allele of rs4646437 (Hazard Ratio [HR]: 3.03, 95% Confidence Interval [CI]: 1.73–5.29, P= 0.001) or rs776746 (HR: 2.43, 95% CI: 1.56–3.81, P= 0.001) had a significantly higher risk of developing pneumonitis, after adjusting for age, sex, race, cancer type, and sequencing panel version. **Conclusions:** Our findings highlight the potential role of inherited genetic factors in modulating treatment-related toxicities of ADCs. Understanding these associations can provide valuable insights into personalized treatment strategies and inform risk assessment to optimize the safety and efficacy of ADCs. Research Sponsor: None.

Rates of pneumonitis.

	% per Group	N
Trastuzumab Deruxtecan	13.1	64
Mirvetuximab Soravtansine	8.4	10
Tisotumab Vedotin	5.0	1
Enfortumab Vedotin	3.6	6
Trastuzumab Emtansine	3.3	6
Sacituzumab Govitecan	1.3	5

12126 Poster Session

CDK4/6 inhibitor toxicity in geriatric subgroups: Evidence from the FAERS database.

First Author: Bahadır Köylü, Koç University School of Medicine, Department of Medical Oncology, Istanbul, Turkey

Background: Despite their widespread use, the safety of cyclin-dependent kinase 4/6 inhibitors (CDK4/6i) in geriatric patients remains underexplored. **Methods:** We conducted a retrospective analysis of cases reported in the FAERS database regarding CDK4/6i in female breast cancer patients from January 1, 2015, to September 30, 2024, focusing on hematological, gastrointestinal (GI), and liver toxicities. The cases were categorized into different age subgroups. **Results:** We identified 46,871 female patients with breast cancer treated with CDK4/6i (abemaciclib, n = 3,987 [8.5%]; palbociclib, n = 37,020 [79.0%]; ribociclib, n = 5,864 [12.5%]). According to multivariate analysis considering age subgroups, CDK4/6i type, and concomitant treatments, 75-84 age group had a lower risk of hematologic toxicity (OR = 0.93 [95% CI 0.86–1.00]; *P*= 0.040), with a similar trend identified in patients aged ≥85 years (OR = 0.88 [0.76–1.01)]; *P*= 0.077). Ribociclib was associated with a higher risk of hematologic toxicity (OR = 1.31 [1.17–1.47]; *P*< 0.0001), whereas palbociclib was associated with a reduced risk (OR = 0.90 [0.82–1.00]; *P*= 0.041). However, only 75-84 age group treated with abemaciclib (OR = 0.57 [0.41–0.77]) and ≥85 years group treated with palbociclib (OR = 0.85 [0.73–0.99]) showed a reduced risk compared to patients younger than 65, while no significant differences were found among age subgroups treated with ribociclib. Despite the overall higher risk of GI toxicity associated with abemaciclib (OR = 7.53 [6.65–8.56]; *P*< 0.0001), ≥85 years group showed a lower risk compared to patients younger than 65 (OR = 0.59 [0.38–0.88]). The overall risk of GI toxicity was also higher in patients treated with palbociclib compared to ribociclib (OR = 1.17 [1.04–1.31]), with no significant differences observed among the age subgroups. Among patients treated with ribociclib, 65–74 (OR = 1.33 [1.03–1.71]) and 75–84 (OR = 1.45 [1.06–1.96]) age groups showed a higher risk of GI toxicity, while no significant difference was observed in ≥85 years group (OR = 1.64 [0.79–3.04]). Ribociclib was associated with a higher risk of liver toxicity (OR = 1.37 [1.20–1.55]; P < 0.0001), whereas palbociclib was associated with a reduced risk (OR = 0.30 [0.27–0.34]; *P*< 0.0001). In both palbociclib- and ribociclib-treated patients, all geriatric age subgroups showed a reduced risk of liver toxicity (Palbociclib; 65-74 y, OR = 0.80 [0.70–0.91]; 75-84 y, OR = 0.49 [0.41–0.58]; ≥85 y, OR = 0.35 [0.23–0.51]; Ribociclib; 65-74 y, OR = 0.80 [0.67–0.96]; 75-84 y, OR = 0.51 [0.38–0.65]; ≥85 y, OR = 0.52 [0.25–0.95]). However, only 75-84 age group treated with abemaciclib (OR = 0.70 [0.49–0.97]) showed a reduced risk of liver toxicity. **Conclusions:** Our findings demonstrated that liver toxicity was lower across all geriatric age subgroups, and hematological toxicity was reduced only in 75-84 age group. There were no significant differences in GI toxicities among the age subgroups. Research Sponsor: None.

12127 Poster Session

Impact of health literacy in cancer outpatients receiving oral anticancer drugs and followed by the ONCORAL multidisciplinary city-hospital educational follow-up: The LITTORAL study. First Author: Chloé Herledan, Clinical Oncology Pharmacy Unit, Lyon Sud Hospital, Hospices Civils De Lyon, Université Lyon 1, Pierre-Benite, France

Background: Multidisciplinary follow-up is crucial to manage drug-related problems (DRP) associated with oral anticancer therapies (OAT). However, these approaches might fail to address social vulnerability determinants, such as a low level of health literacy (HL), which can be a barrier to patient education and contributes to inappropriate self-management of medications. This study aims to assess the impact of HL on relative dose intensity (RDI) of OAT and health-related quality of life (HRQoL) in cancer patients followed by Oncoral, a multidisciplinary program consisting in personalized face-to-face consultations with a pharmacist and nurse after each subsequent oncologist consultation, to prevent and correct DRPs. **Methods:** This prospective cohort study enrolled adult cancer patients who initiated OAT (baseline) from 11/03/2019 to 24/08/2022 and were followed by Oncoral for $\geq$6 months. HL was assessed at baseline using the HLS-EU16 questionnaire. The primary endpoint was RDI at 6 months, defined as the ratio between the prescribed dose of OAT and the optimal dose to be administered according to Summary of Product Characteristics. A RDI $\geq$80% was considered satisfactory, based on the literature. The secondary endpoint was the variation in HRQoL from baseline to 6 months of OAT, measured by the EORTC QLQ C30 questionnaire. **Results:** This study included 182 patients (58.2% male, median [range] age 69 [29-101] years), mostly with hematological malignancies (60.4%, including multiple myeloma 29.7% and chronic lymphocytic leukemia 11.0%) and breast cancer (12.1%). At baseline, the majority (71.8%) lived with a partner, 20.0% had children living at home. Most were retired (67.1%) but 18.2% worked full-time. Household incomes were inferior to French minimum wage for 20.6% of patients, and 20.6% only received elementary education. Mean HL score was 12.1 $\pm$ 3.12, 52.7% of patients having a HL score considered sufficient (13-16), 32.4% problematic (9-12) and 14.8% insufficient (0-8). RDI at 6 months was evaluable for 135 patients (74.2%), 68.9% of which maintained a RDI $\geq$ 80%. Mean RDI was 83.9 $\pm$ 20.4%. HL had no influence on 6-month RDI. Variation of HRQoL was evaluable for 114 patients (62.6%). Patients with inadequate HL showed lower emotional (p = 0.02) and cognitive scores (p = 0.03) at baseline. A significant improvement was shown at 6 months for global health status (+9.83 out of 100, p = 0.001), emotional functioning (+10.73, p $<$ 0.001), insomnia (-14.03, p $<$ 0.001), pain (-11.76, p = 0.02) and fatigue (-11.76, p = 0.005), with no difference in other scales. **Conclusions:** Cancer patients followed by Oncoral globally maintain a 6-month RDI $\geq$ 80% regardless of HL, with a HRQoL maintained or improving in all dimensions, suggesting that this personalized follow-up benefits to all patients and may limit the impact of social vulnerability. Research Sponsor: None.

12128 Poster Session

Impact of proton pump inhibitor (PPI) pharmacogenomics (PGx) on toxicities associated with immune checkpoint inhibitor (ICI) therapy. First Author: Laura Carpin Kennedy, Vanderbilt-Ingram Cancer Center, Nashville, TN

Background: There is evidence for the impact of PPIs on clinical outcomes when given concurrently with ICI therapies. Moreover, CYP2C19 genotype impacts PPI metabolism; poor and intermediate metabolizers having higher PPI effectiveness. Cancer patients routinely receive PPIs for acid suppression; we therefore undertook a PGx analysis to evaluate the impact of PPIs on adverse events (AEs) in patients receiving curative-intent ICI therapy. **Methods:** We performed a retrospective analysis on data from four Roche studies with atezolizumab (A) (NCT03197935, NCT02486718, NCT02450331, NCT03038100) and included patients who had available germline whole-genome sequencing information. PGx variants of the CYP2C19 gene were assessed using PharmCAT which predicted metabolizer phenotypes- normal, rapid/ultra-rapid, and poor/intermediate. Exposure to PPIs was categorized using the ConMedClassify R package. The primary outcome was time to the first Grade $\geq$ 3 AE. We used an extended multivariate Cox proportional hazards model that accounted for delayed entry into the PPI exposure class and stratified by study ID. An interaction term was included between PPI exposure, primary cancer treatment (A containing: yes/no), and CYP2C19 metabolizer phenotype. We adjusted for baseline covariates: race, sex, age, BMI, ECOG status, plasma albumin level, and neutrophil-to-lymphocyte ratio. Missing data were imputed with missRanger. Marginal effect estimates were pooled across the completed datasets using the mice R package. **Results:** This analysis included 816 patients who received A as adjuvant/neoadjuvant therapy in triple negative breast cancer, non-small cell lung cancer, and urothelial cancer, or for stage III/IV ovarian cancer indications; and 775 patients who received non-A based treatment as standard of care across corresponding tumor types. Patients receiving A-containing regimen and having a predicted intermediate/poor metabolizer phenotype [(N = 241 (30%)] were more likely to experience Grade $\geq$ 3 AEs if they were exposed to a PPI versus if they were exposed to H2 blocker (HR = 3.117, 1.319 - 7.368 95% CI, p-value = 0.01, FDR = 0.172, Ns in contrast groups: 46 vs 89). The analysis to evaluate the impact of PPI PGx on ICI efficacy outcomes is ongoing. **Conclusions:** Given the widespread use of PPIs in cancer patients receiving ICI therapies, consideration may be needed regarding CYP2C19 genotype data to guide acid suppression therapy. Where possible, prescribing a lower dose of PPI, considering PPIs with less CYP2C19 metabolism, or substituting with H2 blockers in patients receiving curative ICI therapy may minimize the risk of toxicity in patients with intermediate/poor metabolizer status (30% in our cohort from four A trials). This would be especially important in early disease settings where there may be less risk tolerance for toxicity compared with advanced disease. Research Sponsor: None.

12129 Poster Session

Association of *IL7* germline variants with immune-related adverse events (irAEs) in cancer patients (pts) treated with immune checkpoint inhibitors (ICIs). First Author: Eddy Saad, Dana-Farber Cancer Institute, Boston, MA

Background: Despite the transformative impact of ICIs on cancer treatment, their efficacy remains limited by adverse events (AEs), underscoring the need for reliable biomarkers. Here, we aimed to investigate the effect of a previously identified *IL7* SNP in predicting irAEs across two clinical trials and an East Asian pan-cancer cohort. **Methods:** In this pooled analysis, we included 1,205 pts from the CheckMate-025 trial (CM025, NCT01668784) with renal cell carcinoma (RCC) who received either nivolumab (NIVO) or everolimus (EVE), from the BinTA-0037 (BTA-037, NCT03631706) in non-small cell lung cancer (NSCLC) treated with pembrolizumab (PEMBRO), and from the Asan ICI-treated pan-cancer cohort. The rs7816685 SNP dosages were inferred from blood and/or tumor whole exome sequencing (WES) using STITCH for CM025, and Minimac4 for Asan. For BTA-037, a surrogate SNP (rs16906062, R^2=1.0) was extracted from tumor WES. The association between the SNP carrier status and the time to incident AEs was investigated via multivariable cause-specific Cox regression models. RNA-sequencing (RNA-seq) was performed on blood samples from the Asan cohort collected pre- and post-initiation of ICI. Blood immune cell fractions were estimated from RNA-seq data using ImmucellAI. **Results:** The frequency of the risk allele was 15% in CM025, 17% in BTA-037, and 24% in Asan. *IL7* SNP carriers demonstrated a significantly higher risk of AEs when treated with ICI therapies in all 3 cohorts, but not with EVE (non-ICI control) (SNP´treatment $P_{interaction}$=0.0012 in CM025) (Table). The SNP showed a consistent effect across different tumor types and irAE profiles, with no apparent impact on survival outcomes. RNA-seq data revealed the expression of a novel *IL7* cryptic exon in carriers, and a significant increase in peripheral cytotoxic T-cell post-ICI (q=0.002). Both features were significantly correlated (R=0.29, P=1x10-11), suggesting a potential mechanistic link. **Conclusions:** The *IL7* SNP (rs7816685) is associated with a higher risk of immune toxicity in pts treated with ICI. Overall, our findings support the use of this germline biomarker for irAE risk stratification, and pave the way for future functional studies. Research Sponsor: None.

Adjusted hazard ratios (HRs) from multivariable Cox models adjusting for baseline covariates in each cohort.

Cohort	Cancer type	Treatment	N	SNP	adjusted HR for irAEs
CM025	RCC	NIVO	189	rs7816685	3.01 [1.59-5.68], *P*=0.0007
CM025	RCC	EVE	193	rs7816685	0.65 [0.33-1.28], *P*=0.22
BTA-037	NSCLC	PEMBRO	152	rs16906062	2.3 [1.16-4.6], *P*=0.017
Asan	Pan-cancer	Any ICI	671	rs7816685	1.12 [1.02-1.2], *P*=0.015

12130 Poster Session

Impact of cancer related fatigue on quality of life of 1,262 patients with breast cancer receiving chemotherapy: A URCC NCORP nationwide phase III RCT. First Author: Jeremy McGuire, University of Rochester Medical Center, Rochester, NY

Background: Cancer-related fatigue (CRF) is one of the most common and debilitating symptoms reported by cancer patients, significantly impairing quality of life (QoL) across physical, functional, emotional, and social domains. Despite its prevalence, limited data exist quantifying how rapid changes in CRF after a single chemotherapy cycle influence QoL. We aim to evaluate if rapid clinically meaningful changes in CRF post chemotherapy impact QoL in breast cancer patients. **Methods:** This Phase III RCT (NCT03367572) enrolled chemotherapy-naïve breast cancer patients across 21 NCORP practices receiving high/moderate emetogenic chemotherapy. CRF was assessed at baseline and post chemotherapy cycle 1 (n = 1,262) using a four-day home diary, with maximum fatigue change as the primary outcome. For analysis, the CRF variable was dichotomized into two categories: a clinically significant increase ($\geq$3 points) and less than a 3-point increase. QOL was measured with FACT-G and its subscales: emotional (EWB), functional (FWB), physical (PWB), and social (SWB). ANCOVA and Cohen's d effect size (ES) evaluated whether clinically meaningful CRF changes predicted QOL changes across cycles. **Results:** Among 1,262 patients with valid fatigue scores, 74.8% experienced increased CRF after cycle 1, with 53.2% reporting a $\geq$3-point increase and a mean increase of 2.9 points for the group. Clinically significant increases in CRF strongly impacted quality of life (QOL), as reflected in FACT-G Total Score changes post-cycle 1 ($\geq$3: $-$12.4 vs $<$ 3: $-$4.7; mean difference: 7.7, p $<$ 0.001, ES: 0.74), exceeding the clinically meaningful threshold of $>$ 5 points. Analysis of the subscales revealed PWB with the largest changes of 4.8 ($\geq$3: $-$X vs $<$ 3: $-$X; p $<$ 0.001, ES: 1.00). FWB changes were 2.1 ($\geq$3: $-$X vs $<$ 3: $-$X; p$\leq$0.0001, ES: 0.48) and EWB changes were 0.7 ($\geq$3: $-$X vs $<$ 3: $-$X; p $<$ 0.001, ES: 0.26). CRF did not significantly impact SWB. Notably, many of these subscale changes surpassed the clinically meaningful threshold of $>$ 2 points. **Conclusions:** This study underscores the rapid onset and significant impact of CRF on QoL in breast cancer patients receiving chemotherapy. Clinically meaningful increases in CRF, even after a single chemotherapy cycle, were predictive of substantial declines in QoL, particularly in physical and functional well-being. These results emphasize the urgent need for targeted fatigue management strategies, such as tailored interventions addressing physical and functional domains, to improve patient outcomes. Clinical trial information: NCT03367572. Research Sponsor: National Institutes of Health (NIH) Ruth L. Kirschstein National Research Service Award (NRSA) Institutional Research Training Grant; T32CA102618; RO1; R01CA200579; University of Rochester-NCORP Research Base; NCI UG1CA189961.

12131 **Poster Session**

Virtual yoga (vYOCAS) intervention for psychological distress: A decentralized digital randomized controlled trial with cancer survivors. First Author: Po-Ju Lin, Wilmot Cancer Institute, University of Rochester Medical Center, Rochester, NY

Background: Psychological distress is highly prevalent among cancer survivors, and it interferes with their ability to recover after treatment and resume normal life activities. Yoga is a promising therapy that may reduce psychological distress and facilitate optimal recovery for survivors. However, accessibility can be limited for survivors who have higher risks of infection due to immunosuppression or high travel burden. Virtual delivery of yoga may increase accessibility for survivors. **Methods:** We conducted a decentralized, digital, phase II randomized controlled trial (RCT) examining the efficacy of virtual yoga compared to usual care for improving psychological distress among survivors. Participants were cancer survivors who completed primary treatment (e.g., surgery, chemotherapy, radiation therapy) within the last 2-60 months. Participants were randomized to receive virtual yoga or usual care. The Zoom platform was used to virtually deliver the Yoga for Cancer Survivors (vYOCAS) intervention. vYOCAS is a 4-week intervention based on gentle Hatha and restorative yoga. Each yoga session was delivered by a certified yoga instructor in small groups (2-4 survivors/group) for 75 minutes, twice a week. Psychological distress was assessed via the Profile of Mood States (POMS) at baseline and post-intervention. POMS evaluated tension-anxiety, depression, anger-hostility, fatigue, confusion, and overall mood. T-tests and ANCOVAs with baseline as a covariate were used to evaluate within- and between-group changes, respectively. **Results:** 42 survivors (93% female; mean age 58.5$\pm$11.6 years; 60% breast cancer; 17% residing in small town/underserved areas) were randomized and completed the study. On average, participants attended 6.2 of 8 prescribed yoga sessions. 44% of vYOCAS participants reported additional home practice of 62.8 minutes over 4 weeks. vYOCAS participants reported significant decreases in psychological distress (tension-anxiety: -1.5$\pm$0.6; depression: -1.2$\pm$0.4; fatigue: -2.4$\pm$0.7; overall mood: -7.3$\pm$2.4; all $p < 0.05$) at post-intervention. Usual care participants did not demonstrate similar improvements. ANCOVA results also revealed that vYOCAS participants experienced significantly greater improvements in fatigue (-2.1$\pm$0.8, p = 0.02) and overall mood (-6.4$\pm$3.1, p = 0.04) compared to usual care participants. No intervention-related adverse events were reported and the majority of survivors would recommend virtual yoga to others. **Conclusions:** vYOCAS is safe, feasible, and amenable for cancer survivors. vYOCAS may also significantly improve psychological distress.Clinicians should consider recommending virtual yoga therapy for survivors with psychological distress to overcome barriers related to accessibility. Future phase III decentralized digital RCTs are needed to confirm these findings. Clinical trial information: NCT04458194. Research Sponsor: National Cancer Institute; UG1CA189961, T32CA102618.

12132 **Poster Session**

Immune-related endocrinopathy in cancer patients receiving immune checkpoint inhibitor therapy in the nationwide prospective DIRECT cohort. First Author: Hala Awad, University of Rochester Medical Center, Rochester, NY

Background: Immune checkpoint inhibitors (ICIs) have transformed cancer treatment, extending patient survival. However, side effects such as endocrinopathies are common and have severe, sometimes irreversible outcomes if not managed promptly. Predictive factors for endocrinopathies are poorly understood. We examined whether demographic and clinical characteristics are linked with the development of ICI-induced endocrinopathies. **Methods:** The DiRECT Cohort (URCC21038, NCT05364086) is an ongoing observational trial of cancer patients scheduled to receive anti-PD-(L)1 ICI therapy and enrolled through the URCC NCORP Research Base nationwide network. This analysis was based on 1,525 patients with toxicity data assessed 12/31/2024. Endocrinopathies were graded using the Common Terminology Criteria for Adverse Events (CTCAE) criteria version 5.0. Toxicity data was collected after each infusion of ICI. Demographics (age, sex, BMI, race) and clinical factors (cancer type, cancer stage, treatment agent, autoimmune disease, and significant comorbidities) were collected at baseline. We tested bivariate associations with chi-square tests and multivariable associations with logistic regression; statistical significance was set at a p-value of 0.05. **Results:** Of the 1.525 participants, 533 (35%) had lung cancer, 263 (17.3%) had breast cancer, 812 (53.3%) were aged $\geq$ 65, 1142 (75.4%) White, 828 (54.4%) women, 1009 (66.3%) had BMI $<$ 30, 802 (52.7%) had at least one comorbidity, and 128 (8.4%) had an autoimmune disease, 831 (55.2%) had stage IV cancer, and 930 (61.1%) were on pembrolizumab. 252 (16.5%) developed endocrinopathies of any grade: Hyperthyroidism, 61 (24.2%); Hypothyroidism, 156 (61.9%); Thyrotoxicosis, 7 (2.75%); and Adrenal insufficiency, 11 (4.37%). The most common of these were hypo/hyperthyroidism, of which 9% were grade $\geq$2. In bivariate analyses, grade $>$2 endocrinopathies were associated with younger age (11% age $<$ 65 vs. 7% age $\geq$65, p = 0.012), female sex (10% in women vs. 4% in men, p = 0.001), and obesity (12% of those with BMI $>$30 vs 7% with BMI $<$ 30, p = 0.001). We found no significant associations with other factors evaluated. In multivariable logistic regression analyses, younger age, female sex, and obesity were significant predictors, with higher odds of endocrinopathy for those of age $<$ 65 (OR: 1.58, 95% CI: 1.35-1.85), female sex (OR: 1.75, 95% CI: 1.48-2.08), with BMI $\geq$30 (OR: 1.97, 95% CI: 1.68-2.31). **Conclusions:** In this nationwide observational trial, younger age, female sex, and obesity were associated with a higher likelihood of developing grade $\geq$2 ICI-induced endocrinopathies. Future work will focus on identifying biomarkers predictive of endocrinopathy and developing predictive models for risk stratification. Research Sponsor: National institute of Health (NIH)/ National cancer Institute (NCI); NCI UG1CA189961; UH3CA260602.

12133 **Poster Session**

Glucagon-like peptide-1 receptor agonists and the risk of chemotherapy-induced peripheral neuropathy in patients with diabetes: A real-world study. First Author: Xiaocao Xu, Department of Hematology and Oncology, University of Vermont Medical Center, Burlington, VT

Background: Chemotherapy-induced peripheral neuropathy (CIPN) is a prevalent condition that significantly affects quality of life in patients with cancer. Diabetes and the use of taxane or platinum-based chemotherapy are major risk factors for CIPN. Glucagon-Like Peptide-1 Receptor Agonists (GLP-1RA) have emerged as promising agents for preventing CIPN due to their potent antihyperglycemic and weight-loss effects. However, the effects of GLP-1RA on CIPN are unknown. **Methods:** We conducted a retrospective, propensity score-matched cohort study utilizing the TriNetX Analytics Network database. Adult patients with concurrent diagnoses of cancer and diabetes who were treated with taxane and/or platinum-based chemotherapy and either GLP-1RA or non-GLP-1RA (including Insulin, Dipeptidyl peptidase-4 inhibitors, Sodium-glucose Cotransporter-2 Inhibitors, Metformin, Thiazolidinediones) anti-diabetes agents were included. Patients with a prior history of neuropathy were excluded. The index date was defined as the initiation of chemotherapy. The primary outcome was the occurrence of CIPN, identified using International Classification of Diseases codes, within one year following the index date. Secondary outcomes included the use of neuropathic pain medications, such as gabapentinoids, serotonin and norepinephrine reuptake inhibitors (SNRI), tricyclic antidepressants (TCA), and tramadol. Cohorts were matched on variables such as age, race, sex, hemoglobin A1c, BMI, cancer type, metastatic disease, and underlying comorbidities. **Results:** We identified 39,772 patients eligible for inclusion, among which 1813 received GLP-1RA and 37,959 received non-GLP-1RA. After propensity score matching, cohorts were all well-balanced across variables. We included 1,763 patients in each cohort for the final analysis. The mean BMI for the GLP-1RA and non-GLP-1RA groups are 32.5 $\pm$ 7.5 and 32.2 $\pm$7.7, and the mean HbA1c are 7.7 $\pm$ 1.8 and 7.6 $\pm$ 1.8, respectively. When compared with patients who received non-GLP-1RA, patients who received GLP-1RA had a higher risk of CIPN (13.9 vs 10.9%, HR 1.34 [95% CI: 1.11 - 1.62]) and significantly increased use of gabapentinoids, SNRI, and tramadol (Table). **Conclusions:** GLP-1RAs are associated with a higher risk of CIPN and greater use of neuropathic pain medications than non-GLP-1RA in patients with cancer and diabetes receiving taxane/platinum-based chemotherapy. Further studies are required to elucidate the possible mechanism underlying the increased risk of CIPN associated with GLP-1RAs. Research Sponsor: None.

	GLP-1RA vs. non GLP-1RA HR (95% CI)	P-value
Chemotherapy-induced neuropathy	1.34 (1.11 - 1.62)	0.002
Gabapentinoids (gabapentin/ pregabalin)	1.26 (1.13 - 1.41)	$<$0.001
duloxetine	1.66 (1.30 - 2.12)	$<$0.001
Venlafaxine	1.56 (1.09 - 2.22)	0.010
TCA	1.05 (0.69 - 1.61)	0.70
Tramadol	1.30 (1.16 - 1.54)	$<$0.001

12134 **Poster Session**

Interrogating the interleukin-6 (IL-6)/IL-23/T-helper (Th)17 axis in immunotherapy toxicity: Mechanistic insights and therapeutic implications. First Author: Noha Abdel-Wahab, The University of Texas MD Anderson Cancer Center, Houston, TX

Background: Immune checkpoint inhibitors (ICIs) have transformed cancer therapy, but grade $\geq$ 3 immune-related adverse events (irAEs) affect 60% of patients. The mechanisms driving irAEs remain poorly understood, hindering the development of strategies to mitigate toxicity without compromising efficacy. **Methods:** We analyzed biomarkers from an ongoing phase I/II trial (NCT04940299) evaluating tocilizumab (IL-6R blockade) in two regimens; 162 mg subcutaneously weekly (regular dose, RD) or bi-weekly (dose-dense, DD), combined with ipilimumab (3 mg/kg) and nivolumab (1 mg/kg) up to 12 weeks as front-line therapy for advanced melanoma. Longitudinal analyses of blood, tumor, and inflamed tissue biopsies were performed to identify biomarkers for risk stratification and to elucidate the immunobiology of irAEs and antitumor responses across four patient subgroups, categorized by tumor response and the presence or absence of grade $\geq$ 3 irAEs. **Results:** A total of 35 patients were treated with the triplet and followed for up to 15 months. By week 12 after treatment initiation, grade $\geq$ 3 irAEs occurred in 15 patients (43%), with similar frequencies in the RD (44%) and the DD (40%) cohorts. Within 90 days after last tocilizumab dose, the incidence of grade $\geq$ 3 irAEs increased to 56% in the RD cohort but remained unchanged in the DD cohort, resulting in an overall incidence of 51%. The best overall response rate (ORR) was 66%, with 64% in the RD cohort and 70% in the DD cohort. NanoString analysis of tumor biopsies identified 31 upregulated genes in patients with grade $\geq$ 3 irAEs compared to those without, including RORC, a key regulator of Th17 differentiation, which was significantly elevated in longitudinal biopsies (pre: n = 8; post: n = 6) of patients with high-grade irAEs. IL-17, IL-1, and TNF signaling pathways were significantly decreased after tocilizumab treatment in the subgroup of patients without the grade $\geq$ 3 irAEs (pre: n = 14, post: n = 9). LunaPhore-COMET analysis showed elevated Th17 and $\gamma\delta$ T-cell subsets (CD4+ and CD8+) in inflamed tissues compared to matched healthy or tumor tissues. CyTOF profiling of blood showed higher $\gamma\delta$ T-cell levels at baseline in patients with grade $\geq$ 3 irAEs (n = 6), which remained elevated following tocilizumab treatment. **Conclusions:** These findings underscore the pivotal role of Th17 cells in the development of irAEs and suggest that current tocilizumab regimens may provide insufficient IL-6 blockade or require combination strategies, such as concurrent IL-23 inhibition, to more effectively target Th17 cells expansion and maintenance. Notably, this study is the first to identify $\gamma\delta$ T-cells as potential predictive biomarkers for irAEs, yet their utility requires further validation. A randomized phase II trial exploring these mechanisms is underway. Clinical trial information: NCT04940299. Research Sponsor: National Institute of Allergy and Infectious Diseases (NIAID); K01AI163412.

12135 Poster Session

Association between epigenetic clocks and chemotoxicity in older adults with early breast cancer. First Author: Jingran Ji, UCLA Health Jonsson Comprehensive Cancer Center, Los Angeles, CA

Background: Epigenetic clocks are blood-based biomarkers developed to predict biological age and mortality risk from DNA methylation data. Here, we investigated the association between epigenetic clocks and grade 2+ chemotoxicities, given that low grade toxicity has significant clinical impact in older adults with breast cancer. **Methods:** This was a secondary analysis of a prospective cohort of 394 adults age ≥65 with stage I-III breast cancer who completed treatment with neo/adjuvant chemo. We analyzed peripheral blood DNA methylation to estimate epigenetic age acceleration (EAA) prior to chemo. We estimated EAA using three generations of epigenetic clocks (1st gen: Horvath and Hannum; 2nd gen: PhenoAge and GrimAge; 3rd gen: DunedinPACE). Our outcomes of interest were the five most frequently reported grade 2+ chemotoxicities. Using multivariable logistic regression, we examined the association between EAA (as continuous variables) and the chemotoxicities of interest, adjusting for age, stage, race/ethnicity, education, regimen, organ function, cell composition, and geriatric assessment variables. **Results:** The median (range) chronological age of the participants was 70 (65-85). Most (65%) had stage II/III disease, 38% received anthracycline, and 75% received G-CSF prophylaxis. A total of 334 (84.8%) participants experienced a grade 2+ toxicity. The five most common grade 2+ toxicities were fatigue (34%), anemia (31%), infection (30%), neuropathy (20%), and diarrhea (13%). On multivariable analysis, we observed an association between pretreatment GrimAge and infection (OR=1.35, 95% CI 1.03-1.77, p=0.03) as well as DunedinPACE and diarrhea (OR=1.43, 95% CI 1.01-2.03, p=0.04). **Conclusions:** In this study of older adults with early breast cancer, we saw an association between some measures of EAA and select grade 2+ toxicities. Further research is needed to examine how measures of biological age can guide the care of older adults with early breast cancer. Clinical trial information: NCT01472094. Research Sponsor: U.S. National Institutes of Health; R01 AG037037.

Grade 2+ chemotoxicity in older adults with early breast cancer, odds ratio (95% CI).

Measures of EAA*	Fatigue (n=134)	Anemia (n=121)	Infection (n=120)	Neuropathy (n=77)	Diarrhea (n=53)
First gen					
Horvath	0.86 (0.67-1.10)	0.97 (0.75-1.26)	0.95 (0.75-1.22)	1.22 (0.91-1.65)	1.02 (0.74 -1.41)
Hannum	0.90 (0.69-1.16)	1.14 (0.86-1.50)	1.03 (0.79-1.33)	1.15 (0.84-1.56)	0.81 (0.56-1.17)
Second gen					
PhenoAge	1.13 (0.86-1.48)	1.10 (0.81-1.48)	1.02 (0.77-1.35)	1.22 (0.88-1.69)	1.10 (0.76-1.60)
GrimAge	1.11 (0.86-1.44)	1.17 (0.88-1.56)	**1.35 (1.03-1.77)**	1.04 (0.76-1.43)	1.39 (0.98-1.96)
Third gen					
DunedinPACE	1.24 (0.96-1.61)	1.09 (0.82-1.44)	1.06 (0.81-1.38)	1.14 (0.83-1.56)	**1.43 (1.01-2.03)**

*The first and second gen clocks are in chronologic years and DunedinPACE is in biological year per chronologic year. OR adjusted for age, stage, race/ethnicity, education, regimen, organ function, cell composition, and geriatric assessment variables.

TPS12136 Poster Session

In-bedroom renewed air as anti-inflammatory adjuvant therapy in cancer survivors: BREATHS trial. First Author: Eva Hernandez-Garcia, The Bartlett School of Sustainable Construction, University College London (UCL), London, United Kingdom

Background: Inflammation plays a pivotal role in both cancer progression and adverse cardiovascular (CV) effects of anticancer treatments. Cardio-oncology rehabilitation with inflammatory pathways-targeting therapies is emerging as a promising approach for cancer survivors at high risk of CV toxicity. In-home air filtration interventions effectively lower interleukin-6 levels in high-risk populations for CV and respiratory events and significantly impact C-reactive protein (CRP) levels in patients with atherosclerosis. Evidence indicates that CRP can serve as a reliable clinical indicator of residual inflammatory risk and cardiotoxicity after cancer therapy. Concurrent administration of purified air therapy along with conventional pharmacological agents—including statins, cyclooxygenase inhibitors, and beta-blockers—may potentiate the desired therapeutic effect, yet the underlying interactions are not fully understood. We investigate whether overnight in-bedroom air filtration effectively reduces inflammation and cardiac markers in survivors of adult-onset cancer at high risk of CV toxicity. **Methods:** This is a series of N-of-1 randomized, adaptive, blinded, and placebo-controlled trials conducted in the homes of adult survivors residing in densely populated urban areas of Valencia, Spain, with the poorest air quality levels, as evidenced by particulate matter concentrations exceeding the WHO and EU Directive limits. Inclusion criteria are age ≥ 18 years, prior history of breast, colorectal, prostate, lung, or hematologic cancer, exposure to cardiotoxic cancer therapy, and CRP level ≥ 3 mg/L. Participants will be randomly assigned to three treatment sets, each comprising a 14-day period of active therapy (portable air purifier at 275 m^3/h) and a 14-day period of placebo (sham purification). In-bedroom air filtration treatment and placebo will be administered nightly for a minimum of 7 consecutive hours. The blinded sequence will last between 4 and 12 weeks per participant, depending on the clinical efficacy evidenced after each treatment set (CRP < 2 mg/L or CRP reductions ≥ 35%). Participants who fail to achieve the clinically meaningful change in the last treatment set will undergo an open-label phase: 14 days of no treatment and 14 days of active therapy administered nightly and daily (air purifier operating continuously at 275 m^3/h). Participants will be asked to keep a daily in-bedroom time log. The primary endpoint is defined as the change in blood CRP levels after each cycle. Secondary outcomes include changes in D-dimer, serum amyloid A and glycated hemoglobin A1c concentrations, and blood pressure. Exploratory endpoints include the feasibility of at-home point-of-care testing to monitor residual inflammatory toxicity. Ten participants will be enrolled in the trial. No enrolled participants at the time of abstract submission. Clinical trial information: NCT06778122. Research Sponsor: None.

TPS12137 Poster Session

Social genomic mechanisms of health disparities among adolescent/young adult survivors of Hodgkin and non-Hodgkin lymphoma: ECOG-ACRIN EAQ211. First Author: Brad J. Zebrack, University of Michigan School of Social Work, Ann Arbor, MI

Background: Research in human genomics maps molecular pathways through which social and psychological factors regulate gene expression in immune cells and tumor tissue, thus affecting chronic disease progression, symptom development, antiviral resistance, morbidity, and mortality. In many cases, psychosocial factors trigger neural and endocrine responses that regulate expression of genes involved in cancer progression (inflammation, metastasis, treatment resistance) and immune function (stimulating inflammatory genes and suppressing antiviral gene transcription, as observed in the "Conserved Transcriptional Response to Adversity" / CTRA transcriptome signature). However, nothing is known about how such effects impact AYA cancer survivors. This study aims to identify functional genomic pathways through which psychosocial factors influence gene regulation and alter health outcomes in AYA cancer patients; and define the role of such effects in structuring health disparities in post-treatment survivorship. **Methods:** This longitudinal single cohort study is administered through the ECOG-ACRIN Cancer Research Group. Subjects are accrued through the NCI Community Oncology Research Program (NCORP) or self-refer through a broad network of cancer support organizations and clinical programs that serve the AYA population. Accrual goal is 2,000 survivors of Hodgkin or Non-Hodgkin Lymphoma who have achieved complete response to therapy at time of study registration, aged 15-39 years at time of diagnosis, and recruited within three years following completion of treatment. Current accrual is n=117. Upon enrollment, participants complete an online survey of patient-reported outcome measures of social and psychological risk and resilience factors, including quality of life (QOL), social isolation, socioeconomic status, and exposures to childhood trauma. Clinical records are reviewed for medically reported comorbidities and vital status. Data are collected at baseline and repeated every 6 months for two years. Blood specimens also are collected at each time point. The CTRA transcriptome profile will be assayed using an established 53-gene index comprised of a block of 19 pro-inflammatory genes (e.g., *IL1B, IL6, IL8/CXCL8, TNF*) and 34 genes involved in innate antiviral response (e.g., *IFNA/B, IFI-, OAS-*, and *MX*-family genes), with CTRA representing the difference in average expression of those 2 blocks (inflammatory – interferon). CTRA is a biological intermediate state, which is hypothesized to mediate relationships between proposed psychosocial risk and resilience factors and outcomes (morbidity, mortality, QOL). Defining effects of psychosocial conditions on gene expression and their role in structuring disparities for AYA survivors will fill a critical gap in knowledge that informs risk-based models for cancer survivorship care. Research Sponsor: US Department of Health and Human Services, National Institutes of Health, National Cancer Institute; R01CA261752; ECOG-ACRIN Cancer Research Group (Peter J. O'Dwyer, MD and Mitchell D. Schnall, MD, PhD, Group Co-Chairs); UG1CA189828.

TPS12138 Poster Session

Testosterone replacement therapy for fatigue, sexual dysfunction, and quality of life in older men with cancer (TEMEC). First Author: Egidio Del Fabbro, Medical College of Georgia, Augusta, GA

Background: Fatigue is prevalent in men with cancer, affecting 70-100% of survivors. Fatigue impairs quality of life (QOL), increases caregiver burden, and is associated with reduced lean body mass and sexual dysfunction. Muscle loss, fatigue, sexual dysfunction and depressed mood are common in older males with testosterone deficiency, with or without cancer. Testosterone replacement therapy (TRT) in non–cancer patients improves fatigue, body composition and sexual function. However, despite high prevalence of testosterone deficiency in men with cancer (50-90%), no TRT practice guidelines are available. Older age, chronic inflammation, opioids, megestrol acetate, corticosteroids and some anti-neoplastic therapies are implicated in lowering testosterone. A preliminary (n=29) double blind trial comparing 4 weeks of intramuscular (n=13) TRT to placebo (n=16) in men with advanced cancer reported improvement in fatigue and sexual desire scores. Based on these findings, TRT may mitigate fatigue and related symptoms but requires a large, adequately powered trial. **Methods:** Randomized, double-blind, placebo-controlled trial of daily transdermal testosterone or placebo gel for 6-months in men ≥55 years, with solid or hematological cancer. Participants with no evidence of disease or receiving anti-neoplastic therapy are eligible if they report fatigue, have low serum testosterone by mass spectrometry <348 ng/dl or free testosterone <70 pg/ml and the interval from last treatment (chemotherapy, radiation therapy, immunotherapy), is ≤60 months. Ineligibility includes prostate cancer, elevated PSA, hematocrit >48% or recent thromboembolism. Sample size is predicated on 1:1 randomization to two arms, stratified by 3 sites and 90% power to detect relevant effects. Assignment of participants to either testosterone or placebo via permuted block design is known to statistician, study pharmacists, and unblinded study physician responsible for dose-adjustment. By December 2024, 150 of planned 230 participants are enrolled. NCT04301765. Primary outcome is change in fatigue by Functional Assessment of Chronic Illness Therapy fatigue scale (FACIT-Fatigue). Secondary outcomes include Harbor-UCLA 7-day Sexual Function Questionnaire including sexual activity and desire. Additional outcomes include questionnaires of erectile function, positive and negative affect scale (PANAS), Brief Assessment Scale determining Caregiver Burden (BASC) and body composition by dual energy X-ray absorptiometry. Physical performance evaluations include maximal leg press strength, 6-minute walk test and actigraphy. Additionally, lived experiences of 60 participants at baseline and 24 weeks are assessed by semi-structured, qualitative phone interviews with men from testosterone and placebo arms. Clinical trial information: NCT04301765. Research Sponsor: National Institute on Aging; AG061558.

TPS12139 **Poster Session**

Randomized trial of a clinical nurse specialist–led enhanced survivorship and early palliative care intervention for patients with metastatic cancer. First Author: Megha Schmalzle, NYITCOM, Old Westbury, NY

Background: While the benefits of early palliative care and clinician empathy for patients with metastatic cancer are well established, cancer survivorship remains inadequately integrated into the care of patients with distant metastases (Langbaum, N Engl J Med 380: 1300, 2019). Moreover, the optimal model of care delivery is poorly defined. Based on these data, we developed a novel multidisciplinary care model in which the radiation oncology Clinical Nurse Specialist develops therapeutic relationships with survivors with metastatic cancer and identifies and coordinates interventions to address their unmet physical and emotional issues. The goal of this intervention is to improve quality of life and overall survival. **Methods:** Eligible patients are adult patients with metastatic solid tumor malignancy with a predicted median survival of $\geq$1 year using the validated NEAT model. Using block randomization with varying block sizes of 4, 6 and 8, we plan to randomize 100 patients to either usual care or a supplemental Clinical Nurse Specialist led survivorship and palliative care intervention. Patients randomized to the Clinical Nurse Specialist have personalized coordination of services, patient education and referral to supportive care services resulting from additional in-person and phone-based touchpoints. These supplemental interactions address individual needs, such as medication side effects, physical therapy, end-of-life planning and access to community and spiritual resources. The primary endpoint of this trial is patient reported symptom burden using the Edmonton Symptom Assessment System score. Secondary endpoints are patient reported quality of life using the NCCN survivorship assessment and long-term overall survival. To date, 45 patients have been enrolled. Clinical trial information: NCT05947695. Research Sponsor: Good Samaritan Hospital Foundation.

TPS12140 **Poster Session**

Fecal microbiota transplantation (FMT) for opioid-induced constipation (OIC): A prospective, multicenter, single-arm, phase II clinical study. First Author: Xiaoying Wang, Department of Oncology, The Second People's Hospital of Changzhou, the Third Affiliated Hospital of Nanjing Medical University, Changzhou, China

Background: Opioids are the cornerstone of cancer pain management. Opioid-Induced Constipation (OIC) is the most common adverse effect of opioid therapy. OIC significantly impairs patients' quality of life and reduces compliance, making it a major factor in inadequate pain control. Recent studies indicate that opioids cause gut microbiota dysbiosis, with gut microbes playing a role in modulating opioid-mediated analgesia and tolerance, including constipation. Currently, fecal microbiota transplantation (FMT) has been shown to be an effective method for adjusting gut flora by introducing various metabolically active bacteria. Therefore, we initiated this study to evaluate the efficacy of FMT in treating OIC. **Methods:** In this multicenter, single-arm exploratory study, 30 cancer patients aged 18-80 years who receive opioid treatment for manageable pain but suffer from persistent constipation are planned for enrollment. Other inclusion criteria include ECOG status 0-2, expected survival $\geq$3 months, having received opioid therapy for at least two weeks, currently stable opioid dosage, manageable pain with NRS $\leq$4, and ability to undergo standard laxative treatment and anticancer therapy. Patients unable to ingest enteric capsules or requiring antibiotics for infections are excluded. Enrolled patients will receive weekly FMT. The treatment will be administered continuously for 4 weeks, with follow-up until constipation reoccurs or one month after the last dose, whichever comes first. The primary endpoint is the improvement of constipation (assessed by BFI scale), while secondary endpoints include cancer pain before and after treatment (evaluated by NRS scale), quality of life (measured by QLQ-C30 scale), nutritional status improvement, and safety. Blood and fecal samples will be collected during the study for efficacy evaluation. The study is currently in the open recruitment phase, with the first patient enrolled in January 2025. Clinical trial information: ChiCTR2500096421. Research Sponsor: None.

TPS12141 **Poster Session**

A randomized phase III study comparing stereotactic body radiotherapy (SBRT) versus conventional palliative radiotherapy (CRT) for participants with painful non-spine bone metastases (NCT06391242). First Author: Arjun Sahgal, Sunnybrook Health Sciences Center, Toronto, ON, Canada

Background: Stereotactic body radiotherapy (SBRT) is efficacious in the treatment of painful spinal metastases [1]. Data are required regarding the efficacy feasibility, toxicity and clinical outcomes associated with SBRT in patients with painful non-spine bone metastases prior to widespread adoption of this technique. **Methods:** This is a Canadian Cancer Trials Group led multi-centre, phase III randomized controlled trial comparing SBRT to conventional palliative external beam radiotherapy (CRT) in patients with solid tumours and a dominant painful non-spine bone metastasis (worst pain score $>$2). *Treatment arms:* EBRT 20Gy/5fr (control) versus SBRT 35 Gy/5fr or 30Gy/5fr (experimental). *Primary objective*: To compare 3-month complete pain response (CPR) rate and analgesic intake assessed using the International Consensus on Palliative Radiotherapy Endpoints [2]. Secondary objectives evaluate pain response pattern at 1, 3 and 6 months and assess re-irradiation rates, fracture incidence within RT target site, incidence of Grade $>$ 2 adverse events, image-based local control, and patient reported outcomes (EORTC QLQ-C30 and QLQ-BM22). *Statistical design:* The target accrual is 230 patients, randomized 1:1. The trial is powered at 80% with a two-sided alpha of 0.05 to detect an improvement in the CPR rate from 17% (CRT) to 34% (SBRT), accounting for a 15% missing data rate. *Conduct to Date*: Study was activated on June 26, 2024. Supported by CCS grant # 707213. [1] Sahgal, Arjun, et al. "Stereotactic body radiotherapy versus conventional external beam radiotherapy in patients with painful spinal metastases: an open-label, multicentre, randomised, controlled, phase 2/3 trial." *The Lancet Oncology* 22.7 (2021): 1023-1033. [2] Chow E, Hoskin P, Mitera G, Zeng L, Lutz S, Roos D, Hahn C, van der Linden Y, Hartsell W, Kumar E; International Bone Metastases Consensus Working Party. Update of the international consensus on palliative radiotherapy endpoints for future clinical trials in bone metastases. Int J Radiat Oncol Biol Phys. 2012 Apr 1;82(5):1730-7. doi: 10.1016/j.ijrobp.2011.02.008. Epub 2011 Apr 12. PMID: 21489705. Clinical trial information: NCT06391242. Research Sponsor: Canadian Cancer Society (CCS); 707213.

TPS12142 **Poster Session**

A phase 1b dose escalation study of AV-380 (anti-GDF15 monoclonal antibody) in combination with standard-of-care therapy in cancer patients with cachexia. First Author: Eric Roeland, Knight Cancer Institute, Oregon Health & Science University, Portland, OR

Background: Cachexia is a complex and common cancer comorbidity associated with a high risk of death. Despite its significant impact, no FDA-approved therapies exist to treat cancer cachexia, and current off-label treatments are limited and increase the risk of side effects. Circulating GDF-15, an inflammatory cytokine involved in the stress response and body weight regulation, has emerged as a main modulator implicated in the pathogenesis of cachexia. Further, preclinical models have shown that elevated levels of circulating GDF-15 elicit cachexia, and GDF-15 expression increases in proportion to disease severity. AV-380 is a high-affinity anti-GDF-15 IgG1 monoclonal antibody resulting in circulating GDF-15 elimination. AV-380 has been shown to reverse weight loss and increase muscle recovery in animal cancer models. In a phase 1 healthy volunteer study (in-house data), AV-380 was well-tolerated without serious AEs. **Methods:** This is an open-label, dose-escalation, multicenter phase 1b study to assess the safety, tolerability, PK, and PD of AV-380. Eligible patients must be $\geq$18 years of age, have cancer with cachexia (per international consensus criteria), receive standard-of-care antineoplastic therapy, have a prognosis of $\geq$3 months, and have an ECOG PS $\leq$2. Patients with known brain metastases (unless treated and stable for $\geq$2 weeks), myocardial infarction or grade 3/4 heart failure ($\leq$3 months), uncontrolled third-spacing of fluids (pleural effusion, pericardial effusion, and/or ascites), or non-cancer-related cachexia, are excluded. Primary endpoints will evaluate the safety and tolerability per dose-limiting toxicities, adverse events (NCI CTCAE v5), and laboratory test results. Secondary endpoints include PK analysis, and exploratory endpoints include anti-drug antibodies, weight changes, patient-reported outcomes (Functional Assessment of Anorexia Cachexia Therapy, Patient Global Impression of Severity, Patient's Global Impression of Change, Patient-Reported Outcomes Measurement Information System) physical function (by digital measures), and body composition (Lumbar 3 Skeletal Muscle Index). Escalating dose cohorts of AV-380 consist of 3-6 patients each, following a standard 3+3 design. The treatment is structured into 28-day courses for each cohort. AV-380 will be administered by IV infusion. Patients will remain on AV-380 until they have unacceptable toxicity, complete 4 courses, withdraw consent, or the sponsor terminates the study. Statistical analyses will be completed by cohort and summarized descriptively. Clinical trial information: NCT05865535. Research Sponsor: AVEO Oncology.

TPS12143 **Poster Session**

Supervised home-based exercise in patients with advanced non-small cell lung cancer (NSCLC) on maintenance immune checkpoint inhibitors (ICI). First Author: Justin Wang Shi, Indiana University School of Medicine, Indianapolis, IN

Background: Lung cancer is the leading cause of cancer-related mortality in the US and results in significant morbidities, including fatigue, depression, and decreased quality of life. Exercise has been shown to reduce severity of fatigue and depression while improving cardiorespiratory fitness (CRF) in patients with lung cancer. Past trials have primarily investigated exercise interventions in patients who received surgery and/or chemotherapy; data on the impact of exercise in patients with lung cancer on immune checkpoint inhibitors (ICI) has been sparse. Following the advent of ICI as maintenance therapy in advanced lung cancer, patients have experienced improved survival and more favorable toxicity profile that better positions them to both participate in and derive benefit from an exercise program. In addition, exercise is expected to promote a patient's response to ICI by promoting mobilization of natural killer-cells and T-cells. Already observed in animal and patient derived xenograft models, the combination of exercise and ICI reduced tumor growth by influencing the tumor microenvironment, increasing tumor infiltrating lymphocytes. In this trial, we are investigating the impact of a supervised home-based exercise program on fatigue, depression, CRF, physical function, muscle mass and biomarkers of immune activation in patients with advanced lung cancer on maintenance ICI. **Methods:** This prospective, randomized phase II trial (NCT06513663) aims to enroll 86 patients with advanced NSCLC receiving maintenance ICI. Patients are randomized 1:1 to an exercise intervention or usual care, stratified by baseline frailty as determined by short physical performance battery (SPPB). Eligible patients have locally advanced (stage III) or metastatic (stage IV) NSCLC and are currently receiving maintenance ICI for at least 1 month with plans for at least an additional 3 months of therapy. The trial is targeting an enrollment of 3-4 patients per month over a period of 2 years, and began in June 2024. Patients randomized to exercise participate in 60-minute sessions including aerobic, resistance, and balance exercises, delivered virtually three days per week for 12 weeks by a professional trainer. The primary endpoint is the change in patient-reported fatigue using the Functional Assessment of Cancer Therapy: Fatigue (FACT-F) questionnaire from baseline to post-intervention, compared between the intervention and usual care. Secondary endpoints include changes in patient-reported depression using Hospital Anxiety and Depression Scale (HADS), muscle mass on CT scan, CRF by VO_{2peak} on a ramp treadmill test, objective and subjective physical function, and adherence to exercise intervention. Exploratory analysis will include changes in circulating tumor cells and T-cell subsets. Patients will be followed post-intervention for up to 2 years. Clinical trial information: NCT06513663. Research Sponsor: None.

TPS12144 **Poster Session**

Virtual personalized exercise program for subjects with lung cancer: A feasibility study. First Author: Melissa Francoise Neumann, Zuckerberg Cancer Center, Northwell Health, Lake Success, NY

Background: With improved outcomes, cancer is increasingly viewed as a chronic disease, highlighting the need for exercise programs to enhance the quality of life for survivors. Unlike heart disease, diabetes, and pulmonary disease, where exercise has been recommended for decades, exercise recommendations for cancer patients have been slow to evolve. Exercise and rehabilitation interventions have shown to clearly benefit cancer survivors by improving outcomes, response and tolerability to treatments, delaying progression, and preventing development of new primary cancer. Despite these benefits and strong endorsements from societies such as ASCO, exercise programs are not typically included in lung cancer treatment plans. **Methods:** This is a single-arm, investigator-initiated feasibility study of a virtual exercise platform targeted to patients with non-small cell lung cancer (NSCLC) who receive surgery (+/-) neoadjuvant/adjuvant chemo (+/-) immunotherapy (cohort A); radiation +/- chemo (cohort B); or systemic treatment only (cohort C) at our Cancer Center. This study will assess the feasibility and usability of this program. Potentially eligible subjects are referred to physiatry for evaluation, enrollment, and personalized virtual exercise prescription, which can be accessed by patients using their personal electronic device. Enrollees complete a baseline quality of life FACT-L questionnaire. Pulmonary Function Test (PFT), Six Minute Walk Test (6MWT), and Sit to Stand Test (STS) are also obtained at the start and end of the 12-month program. FACT-L, Patient and Physician Platform Satisfaction questionnaires are collected every three months. We hypothesize that the virtual exercise program is feasible for patients with lung cancer to participate in and will have beneficial outcomes across all cohorts. The primary objective is feasibility, aiming for 50% of those who qualify and enroll to complete the program at 12 months. The secondary objective is satisfaction, as assessed by patient and provider satisfaction questionnaires. Exploratory objectives include improvement in pulmonary function tests and physical endurance as assessed by the PFTs, 6MWT, and STS, as well as improvement or maintenance of quality of life. **Results:** 20 patients are consented and 10 are active. Of the 10 patients who are no longer part of the study, four were screen-fails, and six patients withdrew consent/did not comply with appointments within the study timeline. Patient compliance increased exponentially after the patient navigator was recruited, who started at the end of November. Since this time, six consents were signed and four remain compliant with the study. **Conclusions:** If feasible and acceptable to patients and providers, this program can be practice-changing, leading to the implementation of virtual exercise prescriptions for patients with all cancer types within Northwell and potentially beyond. Clinical trial information: NCT06540495. Research Sponsor: The Northwell Health Cancer Institute; AstraZeneca; Global Initiatives Group at Northwell.

TPS12145 **Poster Session**

An open-label randomized trial of exercise ± creatine supplementation to augment the adaptations of exercise training in cancer survivors. First Author: Darpan Patel, University of Texas Medical Branch at Galveston, Galveston, TX

Background: Breast cancer survivors face a heightened risk of skeletal muscle wasting, which can be worsened by cancer treatments, adversely affecting their ability to perform daily activities. Additionally, lower extremity muscle weakness has been linked to persistent fatigue in survivors. Research on resistance exercise interventions has demonstrated significant improvements in strength, endurance, and body composition among breast cancer survivors. Nonetheless, developing effective strategies to optimize exercise adaptations for this population remains a critical area of focus. Creatine phosphate (CP) supplementation has gained attention in the medical field because of the numerous health and quality of life benefits. CP is crucial to maintaining muscle energetics because of its role in rephosphorylating adenosine diphosphate to adenosine triphosphate (ATP). To date, few studies have examined the use of CP supplementation to augment exercise adaptations in breast cancer survivors. As such, we propose the THRIVE clinical trial to assess the effects of 12-weeks of CP supplementation in combination with home-based resistance exercise on outcomes of strength, body composition, physical function and mechanistic biomarkers. **Methods:** The THRIVE clinical trial is a prospective, open-label, randomized trial aiming to recruit thirty breast cancer survivors that have completed infusion chemotherapy less than 6 months prior to study enrollment. Patients will be randomized (1:1) to either the CP plus exercise group or exercise only group. Participants who are randomized to receive CP will be initially dosed at 20 g per day for 7 days to boost the availability of CP systemically. Thereafter, the dose will be reduced to 5 g per day for maintenance throughout the duration of the 12-week protocol. All participants will engage in 3 virtually supervised, home-based exercise session each week. Each session will last roughly 1 hour and include a 10-minute warm-up and a 50-minute stimulus phase consisting of upper body and lower body resistance exercises. Primary outcomes will be strength, body composition (DXA scan), physical function (6 min walk test) and mechanistic biomarkers (growth factor and inflammatory biomarkers). Secondary objective will be muscle cross-sectional area and intramuscular creatine, phosphocreatine and ATP as measured by magnetic resonance imaging and spectroscopy, respectively. Tertiary outcomes will be patient reported outcomes on quality of life. To date, 11 of the planned 30 patients have been enrolled. This study is registered with clinicaltrials.gov (NCT06395506). Clinical trial information: NCT06395506. Research Sponsor: Thrivewell Cancer Foundation.

TPS12146 **Poster Session**

A pilot study of the ApricityCare program for early detection and management of treatment-related adverse events in patients with metastatic cancer. First Author: Lily Chen, Department of Internal Medicine, McGovern Medical School, The University of Texas Health Science Center at Houston (UTHealth Houston), Houston, TX

Background: Immune checkpoint therapies (ICTs) induce T cell-mediated anti-tumor immunity and can provide long-term survival benefits for cancer patients. However, ICTs may also cause life-threatening immune-related adverse events (irAEs), often requiring treatment discontinuation and high-dose steroids, leading to significant comorbidities. Early detection and intervention in irAEs can reduce steroid use, enable continuation of ICTs, and improve clinical outcomes. To address the need for earlier detection of severe irAEs, we are implementing ApricityCare, a digital health service that integrates remote symptom reporting via smartphone application, telephone, or text message, with telehealth feedback for patients on ICTs. The platform analyzes patient-reported symptoms and alerts triage nurses to intervene based on pre-specified algorithms. Hypothesis: We hypothesize that early detection and intervention in severe irAEs will improve outcomes and enable ICT continuation. **Methods:** This phase IV clinical trial evaluates ApricityCare's impact on treatment outcomes for patients receiving systemic therapies for metastatic cancer. The study includes a 50-patient run-in phase (Part I) focusing on genitourinary metastatic cancers (prostate, kidney, bladder) to assess feasibility, followed by an expansion of up to 1,000 patients (Part II) across three cohorts: investigational immunotherapies (IO), standard-of-care IO, and standard-of-care non-IO. In Part I, the primary objective is to assess patient symptom reporting via ApricityCare, defined as 80% of patients reporting symptoms for at least 80% of the study duration. Part II aims to determine the rate of therapy discontinuation due to toxicity. Exploratory objectives include associations between alerts and diagnoses, corticosteroid use (>2 weeks), and emergency visits/hospitalizations. Futility for each cohort will be evaluated using a Bayesian optimal phase 2 design, monitoring patients without therapy discontinuation over 3 months. The study is open for enrollment. ApricityCare usage will be analyzed by study phase and cohort. Symptom reporting frequency, Net Promoter Score (NPS), corticosteroid dose, and emergency visit/hospitalization rates will be summarized using frequencies, medians, and interquartile ranges. Time from symptom onset to active management will be assessed with Kaplan-Meier methods. Associations between alerts and confirmed diagnoses will be evaluated for sensitivity and specificity, with clinical diagnoses as the gold standard. The modified intention-to-treat (mITT) population includes all patients receiving at least one anticancer regimen dose. Longitudinal data will be used to identify symptom profiles associated with and preceding irAEs, informing future clinical trials. Clinical trial information: NCI-2024-09566 and MDACC 2024-0229. Research Sponsor: None.

TPS12147 **Poster Session**

ACTIVATE: A pilot randomized activity coaching trial to increase vitality and energy during post-operative pelvic radiation therapy for endometrial cancer. First Author: Avani Dholakia Rao, Radiation Oncology Associates of the National Capital Region, Fairfax, VA

Background: The ASCO-Society for Integrative Oncology guidelines strongly recommend exercise as a therapeutic strategy for cancer-related fatigue (CRF), advising that exercise regimens be tailored to each patient's capabilities. Despite this broad endorsement, at least two-thirds of cancer patients are unable to adhere to the recommendation of exercise due to symptoms and barriers, with women being more likely than men to report barriers to adherence to exercise. There is a lack of data on how to effectively integrate exercise into the treatment regimens of pelvic radiation therapy (RT). Most studies focus on other cancer types or male patients, leaving a significant gap in the literature regarding female patients with gynecological malignancies. Given the high prevalence of CRF and its impact on QoL, interventions reducing fatigue are vital. The primary objective of the ACTIVATE pilot trial(NCT06746428)is to evaluate the feasibility and acceptability of conducting a randomized trial with an exercise coaching program as the intervention in this patient population. Secondary objectives include estimating preliminary efficacy of exercise coaching on fatigue and health-related quality of life, quantifying baseline fatigue levels in our patient population, assessing eligibility criteria suitability, and exploring behavioral mechanisms and variables influencing intervention strength. **Methods:** The study methods include randomization of immediate versus delayed intervention with attention-control of 16 women treated with total or modified radical hysterectomy and surgical staging for Stage I-IVA endometrial cancer and are planned to complete pelvic RT as part of their adjuvant treatment. The intervention is an exercise coaching program which will consist of weekly check-ins for 10 weeks with a certified oncology exercise coach with a goal to address readiness for exercise, identify barriers, and develop an individualized plan for exercise for each week with a goal of increasing activity to 150 minutes of moderate activity per week. The immediate-start group begins with the start of RT; the delayed-start group starts at 6-8 weeks post-RT. Participants will be asked to wear an activity monitor to track steps and moderate activity minutes, complete assessments of patient-reported fatigue (FACIT-Fatigue), bowel/urinary toxicity (EPIC), sexual function and satisfaction (PROMIS), and quality of life (PROMIS-29+2 Profile v2.1), and participate in a six-minute walk test (6MWT) at predefined time points throughout the study. Feasibility will be evaluated on a prior goal of 50% provider acceptability, 50% patient acceptability, 50% appropriateness of screening criteria, and 70% adherence to the coaching session and physical activity monitor. Enrollment began in January 2025 and accrual is expected to be complete within 6 months. Clinical trial information: NCT06746428. Research Sponsor: None.

TPS12148 **Poster Session**

A phase II randomized placebo-controlled study of fisetin and exercise to mitigate chemotherapy-related functional decline in postmenopausal women with early breast cancer (PROFFi). First Author: Jingran Ji, UCLA Health Jonsson Comprehensive Cancer Center, Los Angeles, CA

Background: Despite substantial improvements in survival, postmenopausal survivors of breast cancer remain at high risk of functional decline after cancer treatment. One potentially targetable mechanism of chemotherapy-related functional decline is cellular senescence, a state of cell cycle arrest. Senescent cells (Sncs) develop a senescence-associated secretory phenotype (SASP), where they secrete a milieu of inflammatory cytokines that drive functional decline over time. In patients with stage I-III breast cancer treated with chemotherapy, markers of Sncs and SASP sharply increase after treatment and persist over time. Emerging data suggest that senolytics and exercise can decrease Snc burden. Senolytics are novel agents that eliminate Sncs and improve physical function in non-cancer populations. Among the existing senolytics, fisetin is a natural compound that is safe and tolerable in humans. Exercise also reduces Sncs in individuals without cancer and is well-established to improve physical function in survivors of cancer. More recent pre-clinical data shows that senolytics combined with exercise led to a greater reduction in Sncs than either intervention alone. However, no studies have tested whether senolytics and exercise, either alone or in combination, can reduce Sncs and improve physical function in cancer survivors. Therefore, we hypothesize that targeting Sncs with a combination of fisetin and exercise will lead to both independent and synergistic effects to prevent physical function decline in postmenopausal breast cancer survivors. **Methods:** This multicenter phase II randomized, placebo-controlled study will enroll 200 postmenopausal women with stage I-III breast cancer. Key eligibility criteria include completing neo/adjuvant chemotherapy within 12 months with diminished physical function as measured by the 6-minute walk distance (6MWD). Using a 2x2 factorial design, participants will be randomized 1:1:1:1 to exercise with fisetin, exercise alone, fisetin alone, or a control group for a total 16-week course. Fisetin will be dosed at 20mg/kg on days 1-3 every 14 days. Those randomized to the exercise arms will undergo a tailored, supervised remote exercise program led by a qualified exercise physiologist. The primary objective is to determine the effect of fisetin and/or exercise on physical function, as measured by the change in 6MWD from baseline to end of treatment. Secondary objectives include evaluating the effect of exercise and/or fisetin on other measures of physical, cognitive, psychosocial, and cardiometabolic function as well as digital biomarkers. We will also examine the effect of exercise and/or fisetin on markers of Sncs and SASP. Enrollment on this study began July 2024 and is currently ongoing (NCT06113016). Clinical trial information: NCT06113016. Research Sponsor: U.S. National Institutes of Health; R01 CA280088.

TPS12149 **Poster Session**

Epidermal growth factor receptor (EGFR) inhibitor-induced dermal toxicity treated with topical application of a novel Staphylococcus epidermidis compound. First Author: Mary C. Spellman, Panclarity LLC, San Francisco, CA

Background: Agents targeting the EGFR-mediated signaling pathway are used for the treatment of advanced lung, pancreatic, colorectal, and head and neck cancers. Significant dermal toxicities, occurring in up to 90% of patients treated with EGFR inhibitors (EGFRIs) and other medications inhibiting downstream signaling pathways, may be disruptive to a patient's quality of life and adherence to therapy. Inhibition of the EGFR pathway may suppress host defenses and lead to opportunistic pathogenic colonization or infection. Dermal toxicity is associated with elevated levels of Staphylococcus aureus and IL-36γ. ATR04-484 is an S. epidermidis strain isolated from a healthy human volunteer, selected for its ability to reduce S. aureus colonization and inhibit IL-36γ when applied topically. Reconstructed human epidermis (RHE) and ex vivo pig skin were utilized to measure the effect of ATR04-484 on S. aureus in therapeutic and prophylactic settings with S. aureus added prior to or after ATR04-484, respectively. ATR04-484 inhibited growth of both methicillin-resistant (MRSA) and methicillin-sensitive (MSSA) S. aureus in both therapeutic and prophylactic settings. IL-36γ levels were measured on RHE treated with erlotinib alone or in combination with ATR04-484. Application of ATR04-484 reduced erlotinib-induced IL-36γ to a level comparable to non-erlotinib treated RHE. The effect was dose-dependent; application of 10^9CFU/cm^2 of ATR04-484 showed more potent IL-36γ reduction compared to 10^8 CFU/cm^2. ATR04-484 has a promising profile of activities for the treatment of EGFRI-induced dermal toxicity by significantly reducing *S. aureus* growth and completely ameliorating IL-36γ levels. **Methods:** This multicenter, randomized, double-blind, vehicle-controlled Phase 1/2 clinical study is designed to evaluate the safety and tolerability of topical ATR04-484 (10^9 CFU/g) for the treatment of EGFRI associated dermal toxicity affecting the face of adult patients. ATR04-484 or its vehicle (3:1 randomization) will be applied in a stable volume to all patients and may include application to prioritize affected areas of the neck, chest, back, and paronychial areas (using remaining product on unaffected skin in the same areas, as needed). The key objectives of the study are to assess the safety and tolerability of topical ATR04-484 and to evaluate efficacy signals including severity of disease, pruritus, and pain. The bioavailability of ATR04-484 and pharmacodynamic parameters (including IL-36γ) are also studied. This clinical study will establish the basis for continued clinical development of ATR04-484. Clinical trial information: not yet assigned. Research Sponsor: Azitra Inc.

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